HETEROCYCLES, Vol. 57, No. 3, 2002, pp. 501 - 513, Received, 19th November, 2001

AMINO ACID-DERIVED 4-ALKYL-4-CARBOXY-2-AZETIDINONES. NEW INSIGHTS INTO β-LACTAM RING FORMATION AND *N*-DEPROTECTION

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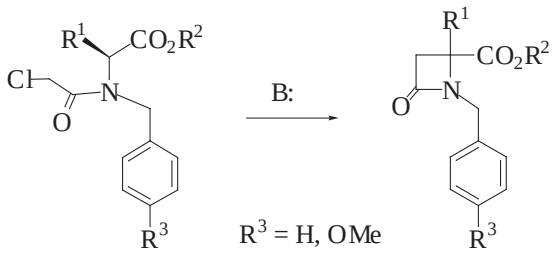
Abstract- The preparation and *N*-deprotection of a series of phenylalanine-derived 2-azetidinones incorporating 2,4-dimethoxybenzyl (Dmb), 2,3,4-, 2,4,6- and 3,4,5-trimethoxybenzyl (Tmb) groups at 1 position are described. The base-promoted cyclization of the corresponding methoxy-substituted N^{α}-benzyl-N^{α}-chloroacetyl derivatives to the 1,4,4-trisubstituted azetidinones proceeded with moderate to good yields, except for the 2,4,6-Tmb analogue. In spite of the number and position of the OMe groups, *N*-unsubstituted β-lactams were obtained by oxidative debenzylation using potassium peroxodisulfate. Alternatively, debenzylation of Pmb, Dmb and Tmb 2-azetidinones with TFA/anisole resulted in concomitant β-lactam opening to α-benzylaspartic acid derivatives.

In addition to the utility of monocyclic β-lactams as antibiotic agents (such as norcardicines, and monobactams),[1] their value in designing new enzyme inhibitors justifies a renewed interest in these compounds.[2] Moreover, 2-azetidinones have served as important synthetic intermediates for the construction of highly functionalized natural and unnatural products. Thus, monocyclic 2-azetidinones have been used as precursors of β-amino acids, as building blocks for peptides containing non-proteinogenic amino acids and for the preparation of secondary structure mimetics.[3-6] The use of azetidinone derivatives as structural units for incorporating conformational restraints into peptides has also gained importance in recent years.[7-15] In a similar way, conveniently substituted 2-azetidinones have served as precursors of different type of heterocyclic compounds, such as γ-lactones and pyrrolizidines.[16,17]

In connection with our current interest in conformationally constrained amino acids, we recently reported the first preparation of 3-unsubstituted 4-alkyl-4-carboxy-2-azetidinone derivatives, that either by themselves or after transformation into the corresponding azetidines, can be considered as new conformationally constrained amino acids with fixed ϕ dihedral angles. Our synthetic strategy involves, as the key step, the formation of the C_3-C_4 bond of the β-lactam ring.[18,19] This was achieved through base-promoted intramolecular alkylation of the corresponding easily available N^{α}-benzyl- or N^{α}-(*p*-methoxy)benzyl-N^{α}-chloroacetyl-derived amino acid alkyl esters (Scheme 1). These *N*-benzyl groups are required for constraining the amide moiety to a *cis*-rotamer, the conformation that allows the amino acid

derivative to cyclize, and can be subsequently removed either with lithium in liquid ammonia or with potassium peroxodisulfate in buffered media.[18,19] Although it has been reported that *p*-methoxybenzyl (Pmb) substituted amides and lactams may be cleaved with TFA,[20,21] our 1-Pmb-2-azetidinones were completely stable to the treatment with this strong organic acid at room temperature.[18,19] It was expected that the incorporation of electron donating substituents into the benzyl group could facilitate the acid promoted deprotection. In fact, cleavage of several 2,4-dimethoxybenzyl (Dmb) protected amides and lactams could be easily performed employing TFA.[22-26] 2,4,6-Trimethoxybenzyl, 2-hydroxy-4-methoxybenzyl, and related groups have also been used as reversible backbone protection in the synthesis of peptide difficult sequences.[27-30] In addition, mild oxidative deprotection of Pmb, including *N*-substituted 2-azetidinones, and Dmb could be achieved using CAN.[31-39] Based on these facts, we decided to investigate whether the incorporation of additional methoxy substituents into the *N*-benzyl group of the N^{α}-chloroacetyl amino acid derivatives could affect the four-membered ring formation and the subsequent *N*-debenzylation reactions. This paper deals with the synthesis and *N*-deprotection, using different methods, of a series of phenylalanine-derived 2-azetidinones incorporating 2,4-dimethoxybenzyl (Dmb), 2,3,4-, 2,4,6-, and 3,4,5-trimethoxybenzyl (Tmb) groups at 1 position.



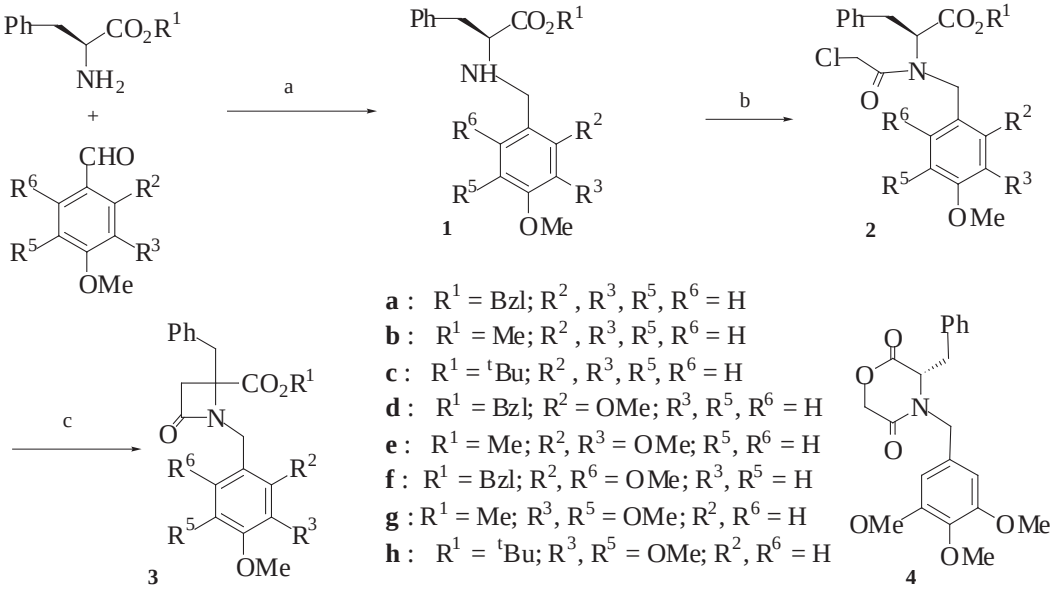
Scheme 1.

RESULTS AND DISCUSSION

As shown in Scheme 2, *N*-benzyl derivatives (**1**) were prepared by reaction of phenylalanine alkyl esters with the corresponding substituted benzaldehydes, followed by reduction of the imine intermediate with $NaBH_4$. In this reaction, the presence of a methoxy group at position 2 (or both in 2 and 6) of the aldehyde decreased the yield of the reductive amination. In all cases, *N*-benzyl-*N*-chloroacetyl derivatives (**2**) were obtained, in almost quantitative yield, by treatment of compounds (**1**) with chloroacetyl chloride, using propylene oxide as HCl scavenger.

The Cs_2CO_3-promoted cyclization of compounds (**2d**, **2e** and **2g**) gave 2-azetidinones (**3d**, **3e** and **3g**) in yields that were comparable to those obtained from the corresponding *p*-methoxybenzyl analogues (**2a**) and (**2b**) (Table 1). In general, longer reaction times were required for the complete disappearance of the starting chloroacetyl derivatives when the cyclization was carried out in MeCN, but yields were higher than in DMF. In comparison with the cyclization of the monomethoxy analogue (**2c**), a marked decrease in the β-lactam formation was observed from the *tert*-butoxycarbonyl 3,4,5-trimethoxybenzyl-substituted derivative (**2h**). In this case, the azetidinone (**3h**) was obtained along with the corresponding 2,5-dioxomorpholine (**4**) (15-30%), resulting from the intramolecular *O*-alkylation of the corresponding enolate intermediate (Table 1). The high tendency of the chloromethyl derivative (**2h**) to the *O*-alkylation

could not be related either to the trimethoxy substitution or to the relative position of the methoxy groups at the benzyl moiety, since no morpholine side products were formed during the β-lactamization of the trimethoxy analogues (**2e**) and (**2g**). As previously found for related compounds,[18,19] the formation of the undesired side product (**4**) became more important in DMF than in MeCN (Table 1).



a : R^1 = Bzl; R^2 , R^3, R^5, R^6 = H
b : R^1 = Me; R^2 , R^3, R^5, R^6 = H
c : R^1 = ^{t}Bu; R^2 , R^3, R^5, R^6 = H
d : R^1 = Bzl; R^2 = OMe; R^3, R^5, R^6 = H
e : R^1 = Me; R^2, R^3 = OMe; R^5, R^6 = H
f : R^1 = Bzl; R^2, R^6 = OMe; R^3, R^5 = H
g : R^1 = Me; R^3, R^5 = OMe; R^2, R^6 = H
h : R^1 = ^{t}Bu; R^3, R^5 = OMe; R^2, R^6 = H

Scheme 2. Reagents and conditions: (a) 1. MeOH, rt, 2 h; 2. $NaBH_4$, rt, 2 h. (b) $ClCH_2COCl$/propylene oxide/THF, rt, 1 h. (c) Cs_2CO_3/MeCN or DMF, rt (see Table 1).

Table 1. Influence of *N*-Substituents on the Generation of 2-Azetidinones (**3**).

Starting Compd	Rotamers *trans:cis*[a]	R^1	R^2	R^3	R^5	R^6	Solvent	Time (days)	(**3**) (%)
2a[b]	10:1	Bzl	H	H	H	H	MeCN	7	75
2a[b]							DMF	2	68
2b[b]	9:1	Me	H	H	H	H	MeCN	6	74
2b[b]							DMF	1	68
2c[b]	10:1	^{t}Bu	H	H	H	H	MeCN	7	71
2d	6.4:1	Bzl	OMe	H	H	H	MeCN	4	65
2d							DMF	3	60
2e	5:1	Me	OMe	OMe	H	H	MeCN	5	73
2f	1:0	Bzl	OMe	H	H	OMe	MeCN	6	3[c]
2f							DMF	15	20[d]
2g	4.6:1	Me	H	OMe	OMe	H	MeCN	7	76
2h	4.2:1	^{t}Bu	H	OMe	OMe	H	MeCN	11	45[e]
2h							DMF	7	36[f]

[a] Measured by ^{1}H NMR spectrometry, based on the integrals of α-CH, and/or *N*-CH_2 protons. [b] From ref. 19. [c] Unaltered (**2f**) (71%) recovered. [d] Unaltered (**2f**) (39%). [e] Morpholine (**4**) (15%) isolated. [f] Morpholine (**4**) (30%) .

The presence of methoxy groups at both position 2 and 6 of the benzyl moiety, as in **2f**, dramatically reduced the rate of the intramolecular cyclization to azetidinone (**3f**). Thus, only a 3% of compound (**3f**) could be isolated after 6 days of reaction in MeCN, while most of the chloroacetyl derivative (**2f**) was recovered unaltered. In a similar way, merely a 60% of conversion was obtained after 15 days of reaction

in DMF, where the expected azetidinone (**3f**) was obtained in 20% yield (Table 1). The different reactivity found for the 2,4,6-trimethoxy derivative (**2f**) and the corresponding 2,4-dimethoxy analogue (**2d**) could be related to the behaviour of these compounds in solution. Thus, while the ^{1}H NMR spectra of compound (**2d**) in $CDCl_3$ showed the presence of both *trans* and *cis* rotamers (6.4:1 ratio) around the tertiary amide bond, only the *trans* rotamer could be observed for the trimethoxy derivative (**2f**). Considering that the cisoid conformation of the amide moiety in compounds (**2**) is required to allow the amino acid derivative to cyclize, the dramatic decrease in reactivity observed for **2f** could be explained through destabilization of the *cis*-(**2f**) rotamer, probably due to unfavorable electrostatic interaction between the oxygen atoms of the carbonyl and 2(6)-methoxy groups (Figure 1).

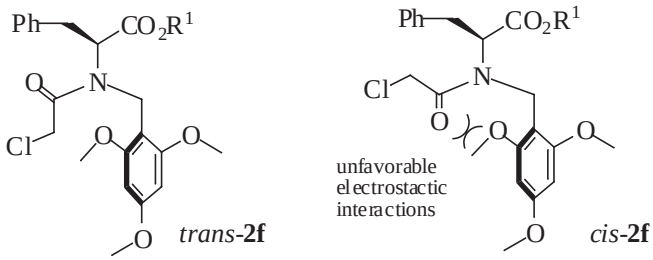
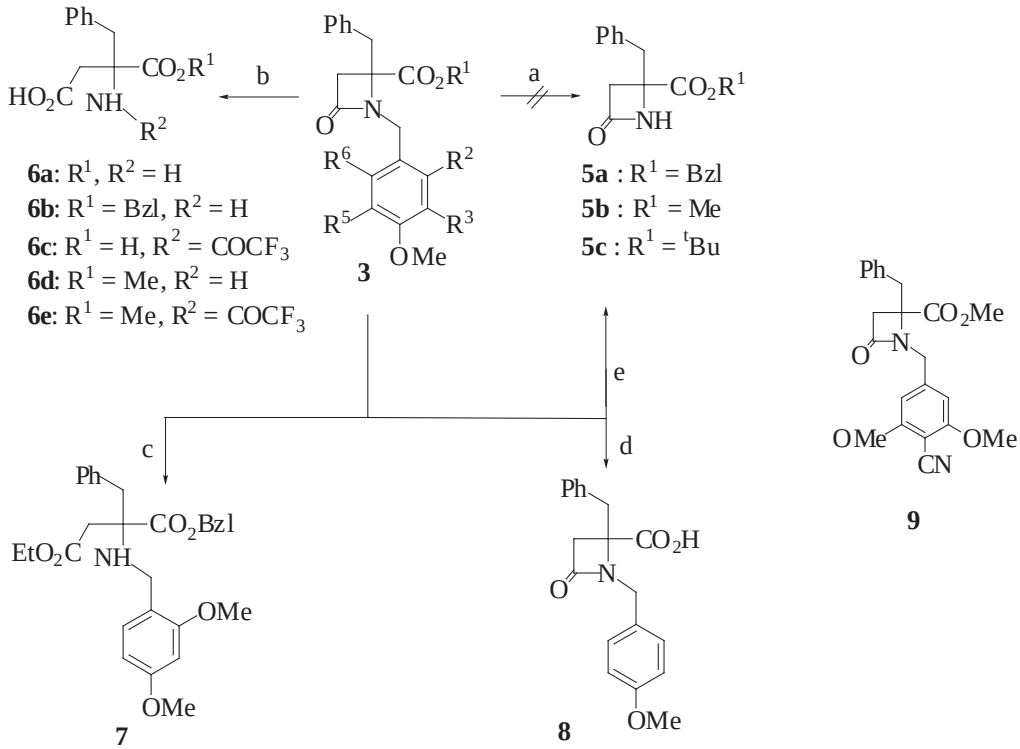


Figure 1. Amide rotamers for *N*-chloroacetyl derivative (**2f**)

With the 1,4,4-trisubstituted 2-azetidinones (**3**) in hands, the next question we addressed was the selective removal of the *N*-protecting groups (Scheme 3). Several methods for the cleavage of the substituted benzyl groups were tested. Oxidation with CAN led, in all cases, to the formation of complex mixtures of products, which could not be identified. Similar over-oxidation of 1-Pmb-3,4-disubstituted β-lactams with CAN has been described.[38] No appreciable reaction was observed by treatment of **3a**, **3b**, and **3d-g** with either neat TFA, TFA/anisole or TFA/H_2O (19:1) at room temperature for two days. In the case of compound (**3f**), the opening of the β-lactam ring and removal of the 2,4,6-Tmb group took place under these conditions, providing a mixture of the α-benzylaspartic acid (**6a**) and its corresponding benzyl ester (**6b**) (Table 2). Removal of Pmb, Dmb and Tmb groups was also achieved by treatment of **3b**, **3d-e** and **3g** with anhydrous TFA at reflux, in the presence of anisole as the carbocation scavenger, to give the corresponding open α-benzylaspartic acid derivatives (**6a**) or (**6d**), along with variable amounts of the trifluoroacetyl derivatives (**6c**) or (**6e**). The concomitant *N*-trifluoroacetylation of the amino group was especially important when the debenzylation reaction promoted by TFA was performed without addition of the carbocation scavenger, as demonstrated by the formation of compound (**6e**) in 81% yield from **3b** in refluxing TFA.

The use of saturated HCl in EtOAc also resulted in β-lactam opening, leading to the ethoxycarbonyl derivative (**7**) in which the Dmb group remained attached. From the above results, it seems that under acidic conditions these 2-azetidinones have a great tendency to the ring opening, and that the elimination of benzyl groups presumably takes place after the cleavage of the 4-membered ring. On the other hand, the Dmb and Tmb groups became more resistant to the acidic hydrolysis in these β-lactam derivatives than in other lactams.[22-26] Probably, the presence of the electron-withdrawing group CO_2R^1 in position 4

attenuates the basicity of the amide carbonyl oxygen and thus prevents the debenzylation reaction, as previously found for a series of 2,4-dimethoxybenzylmaleimides.[22]



Scheme 3. Reagents and conditions: (a) TFA or TFA/H_2O, rt. (b) TFA or TFA/anisole, 80°C, 48 h. (c) HCl/EtOAc, rt, 13 days. (d) $AlCl_3$/anisole, 65°C, 1 h. (e) $K_2S_2O_8$/K_2HPO_4/MeCN-H_2O, 75°C, 3-5 h.

Table 2. *N*-Debenzylation Reactions.

Starting Compd	Method[a]	Final Compd	Yield (%)
3b	A	**6d**	75
3b[b]	A	**6e**	81
3d	A	**6a**+**6c**	40+42
3e	A	**6d**+**6e**	80+3
3f[c]	A	**6a**+**6b**	58+15
3g	A	**6d**	79
3d	B	**7**	55
3a	C	**8**	61
3b[d]	D	**5b**	67
3c[d]	D	**5c**	65
3d	D	**5a**	50
3e	D	**5b**	41
3g	D	**5b** (**9**)	36 (9)
3h	D	**5c**	57

[a] Method A: TFA/anisole/Δ. Method B: HCl/EtOAc, rt. Method C: $AlCl_3$/anisole/Δ. Method D: $K_2S_2O_8$/ MeCN:H_2O/Δ. [b] Reaction performed without anisole. [c] Reaction performed at room temperature. [d] From reference 19.

Attempts to remove the Pmb group from (**3ª**) using $AlCl_3$/anisole[40] resulted unsuccessful, but the benzyl ester was affected leading to the free carboxylic acid (**8**).[19] Similarly to Pmb derivatives, removal of the di- and trimethoxybenzyl groups to the corresponding *N*-unsubstituted 2-azetidinones was readily

achieved by oxidation with potassium peroxodisulfate in buffered media. The expected compounds H-α-Bn-Azn-OBn (**5a**), H-α-Bn-Azn-OMe (**5b**)[19] and H-α-Bn-Azn-O^{t}Bu (**5c**),[19] keeping the α-carboxy protection, were obtained. Compared to Pmb derivatives, slightly lower yields were found for the oxidative removal of Dmb and Tmb groups (Table 2). Regarding trimethoxy derivatives, the 3,4,5-Tmb analogue (**3g**) gave the lowest yield of the corresponding deprotected β-lactam (**5b**), due to formation of different side products, among which the *p*-cyano derivative (**9**) could be identified.

From the results reported in this paper, we can conclude that the intramolecular N^{α}-C^{α}-cyclization of *N*-benzyl-*N*-chloroacetyl phenylalanine derivatives to 1,4,4-trisubstituted 2-azetidinones was, in general, independent on the number and position of the OMe groups at the phenyl ring of the benzyl group. The only remarkable exception was the 2,4,6-Tmb derivative, which led to the corresponding azetidinone in low yield, due to unfavourable electrostatic interaction between the oxygen atoms of the 2(6)-OMe and NCO groups, which prevented the *cis*-amide conformation required for the intramolecular cyclization. Concerning the debenzylation reactions, oxidative removal of Pmb, Dmb and Tmb groups with potassium peroxodisulfate in buffered media led to the corresponding 4,4-disubstituted 2-azetidinones, while treatment with TFA resulted in a direct entry to valuable α-benzylaspartic acid derivatives.

EXPERIMENTAL

All reagents were of commercial quality. Solvents were dried and purified by standard methods. Amino acid derivatives were obtained from Bachem AG or Neosystem. ^{1}H NMR spectra were recorded with a Varian Gemini 200 or a Varian Unity 300 spectrometers operating at 200 and 300 MHz, respectively, using TMS as internal standard. ^{13}C NMR spectra were registered on a Varian Gemini 200 (50 MHz) or a Varian Unity 300 (75 MHz). Electospray MS (positive mode) were recorded with a Hewlett Packard 1100SD spectrometer. Elemental analyses were obtained on a CHN-O-RAPID instrument. Analytical TLC was performed on aluminium sheets coated with a 0.2 mm layer of silica gel 60 F_{254} (Merck). Silica gel 60 (230-400 mesh, Merck) was used for flash column chromatography. Analytical HPLC was performed on a Waters Nova-pak C_{18} (3.9 x 150 mm, 4 μm) column, with a flow rate of 1 mL/min, using a tuneable UV detector set at 214 nm. Mixtures of MeCN (solvent A) and 0.05% TFA in H_2O (solvent B) were used as mobile phase.

General procedure for the synthesis of *N*-benzylphenylalanine derivatives (1): A solution of H-L-phenylalanine-OR^1.HCl (13.9 mmol) in MeOH (28 mL) was successively treated with TEA (1.93 mL, 13.9 mmol) and the corresponding benzaldehyde (20.8 mmol). After stirring at rt for 2 h, $NaBH_4$ (2.1 g, 55.6 mmol) was added in portions, and the stirring continued for 2 h. Then, the solvent was evaporated to dryness, the residue was extracted with EtOAc and the extract was washed with H_2O and brine. The organic layer was dried over Na_2SO_4 and, after evaporation, the residue was purified on a silica gel column as specified in each case.

Benzyl *N*-(2,4-Dimethoxy)benzyl-L-phenylalaninate (1d): Yield: 52%. Syrup. Eluent: EtOAc/hexane (1:20). HPLC: t_R = 4.76 min (A:B= 50:50). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-6.89 (m, 11H), 6.28 (m, 2H), 4.94 (s, 2H), 3.71 (s, 3H), 3.66 (d, 1H, *J* = 13.2), 3.55 (d, 1H, *J* = 13.2), 3.54 (s, 3H), 3.47 (t, 1H, *J* = 7.1), 2.89 (d, 1H, *J* = 7.1). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.50, 160.23, 158.10, 137.04, 130.20,

129.22, 128.93, 128.85, 128.15, 128.08, 126.31, 121.66, 119.45, 103.54, 98.15, 61.55, 60.65, 55.01, 51.03, 51.31, 46.93, 39.17. Anal. Calcd for $C_{25}H_{27}NO_4$: C, 74.05; H 6.71; N, 3.45. Found: C, 73.81; H, 6.95; N, 3.34.

Methyl *N*-(2,3,4-Trimethoxy)benzyl-L-phenylalaninate (1e): Yield: 68%. Syrup. Eluent: EtOAc/hexane (1:6). HPLC: t_R = 3.91 min (A:B= 40:60). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13 (m, 5H), 6.77 (d, 1H, *J* = 8.4), 6.49 (d, 1H, *J* = 8.4), 3.76 (s, 3H), 3.69 (s, 3H), 3.64 (d, 1H, *J* = 12.8), 3.55 (s, 3H), 3.52 (d, 1H, *J* = 12.8), 3.48 (m, 1H), 2.88 (m, 2H), 1.96 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.81, 152.90, 151.95, 141.90, 137.25, 129.02, 128.24, 126.49, 125.24, 123.92, 106.66, 62.17, 60.76, 60.57, 55.82, 51.48, 46.98, 39.57. Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.84; H 7.01; N, 3.90. Found: C, 66.59; H, 7.15; N, 3.71.

Benzyl *N*-(2,4,6-Trimethoxy)benzyl-L-phenylalaninate (1f): Yield: 25%. mp = 75-77°C. Eluent: EtOAc/hexane (1:6). mp = 75-77°C (EtOAc-hexane). HPLC: t_R = 20.02 min (A:B= 35:65). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.11 (m, 10H), 5.93 (s, 2H), 4.87 (m, 2H), 3.70 (s, 3H), 3.52 (s, 6H), 3.45 (dd, 1H, *J* = 7.2, 6.8), 2.86 (m, 2H), 2.15 (br s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.26, 160.13, 159.03, 137.30, 135.62, 128.91, 128.14, 127.92, 126.18, 107.82, 89.86, 65.96, 61.63, 55.14, 55.03, 39.56, 39.45. Anal. Calcd for $C_{26}H_{29}NO_5$: C, 71.70; H 6.71; N, 3.22. Found: C, 71.66; H, 6.82; N, 3.30.

Methyl *N*-(3,4,5-Trimethoxy)benzyl-L-phenylalaninate (1g): Yield: 86%. Syrup. Eluent: EtOAc/hexane (1:5). HPLC: t_R = 8.21 min (A:B= 40:60). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 (m, 5H), 6.44 (s, 2H), 3.82 (s, 3H), 3.79 (d, 1H, *J* = 13.3), 3.78(s, 6H), 3.68 (s, 3H), 3.56 (d, 1H, *J* = 13.3), 3.54 (dd, 1H, *J* = 7.7, 6.1), 3.00 (dd, 1H, *J* = 13.5, 6.1), 2.92 (dd, 1H, *J* = 13.5, 7.7), 1.84 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.05, 153.53, 137.36, 136.67, 135.30, 129.18, 128.30, 126.62, 104.61, 61.82, 60.75, 55.91, 52.03, 51.65, 39.71. Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.84; H 7.01; N, 3.90. Found: C, 66.73; H, 7.11; N, 3.71.

***tert*-Butyl *N*-(3,4,5-Trimethoxy)benzyl-L-phenylalaninate (1h):** Yield: 85%. Syrup. Eluent: EtOAc/hexane (1:5). HPLC: t_R = 7.18 min (A:B= 35:65). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 (m, 5H), 6.46 (s, 2H), 3.81 (s, 3H), 3.78 (s, 6H), 3.77 (d, 1H, *J* = 13.3), 3.56 (d, 1H, *J* = 13.3), 3.40 (dd, 1H, *J* = 7.2, 7.0), 2.90 (m, 2H), 1.87 (br s, 1H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.85, 152.95, 137.56, 136.30, 135.50, 129.28, 128.04, 126.33, 104.58, 80.98, 62.23, 60.65, 55.81, 51.89, 39.74, 27.89. Anal. Calcd for $C_{23}H_{31}NO_5$: C, 68.80; H 7.78; N, 3.49. Found: C, 68.77; H, 7.94; N, 3.35.

General procedure for the synthesis of *N*-benzyl-*N*-chloroacetylphenylalanine derivatives (2): A solution of the corresponding phenylalanine derivative (**1**) (11.4 mmol) in THF (38 mL) was treated with propylene oxide (12 mL, 171 mmol) and chloroacetyl chloride (1.09 mL, 13.7 mmol). After stirring at rt for 1-2 h, the solvents were evaporated and the resulting residue was purified on a silica gel column, using the solvent system specified in each case.

Benzyl *N*-(2,4-Dimethoxy)benzyl-*N*-chloroacetyl-L-phenylalaninate (2d): Yield: 99%. Syrup. Eluent: EtOAc/hexane (1:8). HPLC: t_R = 14.72 min (A:B= 50:50). ^{1}H NMR (300 MHz, $CDCl_3$): rotamers ratio (6.4:1) δ major rotamer 7.14 (m, 10H), 6.73 (d, 1H, *J* = 8.3), 6.18 (d, 1H, *J* = 8.3), 6.15 (s, 1H), 4.91 (m, 2H), 4.25 (d, 1H, *J* = 15.7), 4.22 (d, 1H, *J* = 12.4), 4.09 (d, 1H, *J* = 12.4), 3.98 (dd, 1H, *J* = 9.5, 5.2), 3.68 (s, 3H), 3.42 (d, 1H, *J* = 15.7), 3.39 (s, 3H), 3.32 (dd, 1H, *J* = 14.0, 5.2), 3.16 (dd, 1H, *J* = 14.0, 9.6). ^{13}C NMR (75 MHz, $CDCl_3$): major rotamer δ 169.71, 166.42, 161.01, 158.64, 137.99, 135.60, 130.74, 129.38, 128.39, 128.27, 128.23, 127.97, 126.50, 115.12, 103.50, 98.59, 66.79, 60.73, 55.24, 54.74, 49.09,

41.37, 34.59. MS (ES, positive mode): 504.4 (M^++Na). Anal. Calcd for $C_{27}H_{28}NO_5Cl$: C, 67.29; H 5.86; Cl, 7.36; N, 2.91. Found: C, 67.12; H, 5.69; Cl, 7.10; N, 3.05.

Methyl *N*-(2,3,4-Trimethoxy)benzyl-*N*-chloroacetyl-L-phenylalaninate (2e): Yield: 99%. Syrup. Eluent: EtOAc/hexane (1:4). HPLC: t_R = 13.12 min (A:B= 40:60). ^{1}H NMR (300 MHz, $CDCl_3$): rotamers ratio (5:1) δ major rotamer 7.21 (m, 5H), 6.71 (d, 1H, *J* = 8.5), 6.54 (d, 1H, *J* = 8.5), 4.38 (d, 1H, *J* = 16), 4.28 (d, 1H, *J* = 12.4), 4.16 (d, 1H, *J* = 12.4), 4.13 (dd, 1H, *J* = 9.5, 5.3), 3.83 (s, 6H), 3.80 (s, 3H), 3.58 (s, 3H), 3.56 (d, 1H, *J* = 16), 3.39 (dd, 1H, *J* = 14.0, 5.3), 3.20 (dd, 1H, *J* = 14.0, 9.5). ^{13}C NMR (75 MHz, $CDCl_3$): major rotamer δ 170.12, 166.55, 154.02, 151.83, 141.73, 137.83, 129.33, 128.46, 126.63, 123.94, 120.28, 106.41, 60.72, 60.62, 60.44, 55.86, 52.07, 48.57, 41.33, 34.70. MS (ES, positive mode): 458.3 (M^++Na). Anal. Calcd for $C_{22}H_{26}NO_6Cl$: C, 60.62; H 6.01; Cl, 8.13; N, 3.21. Found: C, 60.63; H, 5.87; Cl, 8.11; N, 3.18.

Benzyl *N*-(2,4,6-Trimethoxy)benzyl-*N*-chloroacetyl-L-phenylalaninate (2f): Yield: 90%. mp = 96-98°C Eluent: EtOAc/hexane (1:5). mp = 96-98°C (CH_2Cl_2). HPLC: t_R = 16.36 min (A:B= 50:50). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.11 (m, 10H), 5.84 (s, 2H), 4.87 (m, 2H), 4.32 (m, 2H), 4.16 (d, 1H, *J* = 14.8), 3.88 (dd, 1H, *J* = 9.4, 5.1), 3.71 (d, 1H, *J* = 14.8), 3.69 (s, 3H), 3.46 (s, 6H), 3.33 (dd, 1H, *J* = 14.0, 5.1), 3.16 (dd, 1H, *J* = 14.0, 9.4). ^{13}C NMR (75 MHz, $CDCl_3$): major rotamer δ 170.20, 166.07, 161.16, 159.25, 138.17, 135.74, 129.44, 128.00, 127.88, 127.76, 127.61, 126.02, 103.07, 90.04, 66.33, 60.48, 55.04, 54.96, 42.18, 41.35, 34.35. MS (ES, positive mode): 534.2 (M^++Na). Anal. Calcd for $C_{28}H_{30}NO_6Cl$: C, 65.69; H 5.91; Cl, 6.92; N, 2.74. Found: C, 65.66; H, 5.95; Cl, 7.01; N, 2.55.

Methyl *N*-(3,4,5-Trimethoxy)benzyl-*N*-chloroacetyl-L-phenylalaninate (2g): Yield: 99%. mp = 106-108°C Eluent: EtOAc/hexane (1:2). mp = 106-108°C (EtOAc-hexane). HPLC: t_R = 8.21 min (A:B= 40:60). ^{1}H NMR (300 MHz, $CDCl_3$): rotamers ratio (4.6:1) δ major rotamer 7.22 (m, 5H), 6.41 (s, 2H), 4.39 (d, 1H, *J* = 16.8), 4.17 (dd, 1H, *J* = 10.0, 5.0), 4.00 (m, 2H), 3.80 (s, 3H), 3.77 (s, 6H), 3.72 (s, 3H), 3.57 (d, 1H, *J* = 16.8), 3.39 (dd, 1H, *J* = 14.2, 5.0), 3.26 (dd, 1H, *J* = 14.2, 10.0). ^{13}C NMR (75 MHz, $CDCl_3$): major rotamer δ 169.85, 166.97, 153.39, 137.53, 130.78, 129.21, 128.55, 126.81, 103.75, 61.96, 60.69, 55.93, 53.19, 52.35, 41.22, 34.66. MS (ES, positive mode): 458.3 (M^++Na). Anal. Calcd for $C_{22}H_{26}NO_6Cl$: C, 60.62; H 6.01; Cl, 8.13; N, 3.21. Found: C, 60.45; H, 5.91; Cl, 8.03; N, 3.14.

***tert*-Butyl *N*-(3,4,5-Trimethoxy)benzyl-*N*-chloroacetyl-L-phenylalaninate (2h):** Yield: 96%. Syrup. Eluent: EtOAc/hexane (1:2). HPLC: t_R = 13.40 min (A:B= 45:55). ^{1}H NMR (300 MHz, $CDCl_3$): rotamers ratio (4.2:1) δ major rotamer 7.19 (m, 5H), 6.40 (s, 2H), 4.44 (d, 1H, *J* = 16.9), 4.30 (dd, 1H, *J* = 9.7, 5.3), 3.98 (m, 2H), 3.80 (s, 3H), 3.75 (s, 6H), 3.74 (d, 1H, *J* = 16.9), 3.34 (dd, 1H, *J* = 14.3, 5.3), 3.20 (dd, 1H, *J* = 14.3, 9.7) 1.28 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): major rotamer δ 168.48, 167.12, 153.44, 137.82, 131.19, 129.12, 128.46, 126.64, 104.00, 82.02, 62.12, 60.74, 56.07, 52.68, 41.34, 34.92, 27.82. MS (ES, positive mode): 479.3 (M^++1). Anal. Calcd for $C_{25}H_{32}NO_6Cl$: C, 62.82; H 6.75; Cl, 7.42; N, 2.93. Found: C, 62.95; H, 6.86; Cl, 7.39; N, 2.77.

General procedure for the synthesis of 2-azetidinone derivatives (3)[41]: A solution of the corresponding *N*-benzyl-*N*-chloroacetyl derivative (**2**) (1.6 mmol) in dry MeCN or DMF (20 mL) was treated with Cs_2CO_3 (1.04 g, 3.2 mmol) and stirred at rt until disappearance of the starting material (see Table 1). After evaporation of the solvent, the residue was partitioned between EtOAc and H_2O and the

phases separated. The organic layer was dried over Na_2SO_4 and evaporated, leaving a residue, mainly containing the corresponding 2-azetidinone (**3**), which was purified on a silica gel column as specified in each case (Yields are recorded in Table 1).

4-Benzyl-1-(2,4-dimethoxy)benzyl-4-benzyloxycarbonyl-2-azetidinone (Dmb-α-Bn-Azn-OBn, 3d): Eluent: EtOAc/hexane (1:2). mp = 103-105°C (EtOAc-hexane). HPLC: t_R = 9.14 min (A:B= 50:50). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25-6.89 (m, 11H), 6.34 (dd, 1H, *J* = 8.3, 2.3), 6.31 (s, 1H), 4.88 (d, 1H *J* = 12.3), 4.77 (d, 1H *J* = 12.3), 4.35 (m, 2H), 3.68 (s, 3H), 3.65 (s, 3H), 3.21 (d, 1H, *J* = 14.3), 3.05 (d, 1H, *J* = 14.5), 2.90 (d, 1H, *J* = 14.3), 2.76 (d, 1H, *J* = 14.5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.96, 166.15, 160.63, 158.18, 134.88, 131.88, 131.29, 129.83, 128.47, 128.41, 128.31, 128.10, 127.00, 116.23, 103.99, 98.16, 67.13, 62.50, 55.26, 55.06, 45.25, 38.99, 38.05. MS (ES, positive mode): 446.3 (M^++1). Anal. Calcd for $C_{27}H_{27}NO_5$: C, 72.79; H 6.11; N, 3.14. Found: C, 72.81; H, 5.90; N, 3.00.

4-Benzyl-1-(2,3,4-trimethoxy)benzyl-4-methoxycarbonyl-2-azetidinone (2,3,4-Tmb-α-Bn-Azn-OMe,3e): Syrup. Eluent: EtOAc/hexane (1:2). HPLC: t_R = 7.32 min (A:B= 40:60). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21-6.60 (m, 7H), 4.42 (s, 2H), 3.90 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.50 (s, 3H), 3.28 (d, 1H, *J* = 14.2), 3.15 (d, 1H, *J* = 14.6), 2.99 (d, 1H, *J* = 14.2), 2.86 (d, 1H, *J* = 14.6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.32, 166.08, 153.47, 151.66, 141.85, 134.79, 129.71, 128.44, 127.08, 124.63, 121.50, 106.93, 62.55, 60.77, 60.65, 55.90, 52.18, 45.26, 39.06, 38.61. MS (ES, positive mode): 400.2 (M^++1). Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H 6.31; N, 3.51. Found: C, 65.86; H, 5.99; N, 3.61.

4-Benzyl-1-(2,4,6-trimethoxy)benzyl-4-benzyloxycarbonyl-2-azetidinone (2,4,6-Tmb-α-Bn-Azn-OBn, 3f): Syrup. Eluent: EtOAc/hexane (1:5). HPLC: t_R = 9.46 min (A:B= 50:50). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (m, 10H), 5.96 (s, 2H), 4.87 (d, 1H, *J* = 12.6), 4.60 (d, 1H, *J* = 12.6), 4.49 (d, 1H, *J* = 14.2), 4.40 (d, 1H, *J* = 14.2), 3.69 (s, 3H), 3.64 (s, 6H), 3.23 (d, 1H, *J* = 14.6), 2.97 (d, 1H, *J* = 14.6), 2.86 (d, 1H, *J* = 14.2), 2.64 (d, 1H, *J* = 14.2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.70, 165.81, 161.35, 159.59, 135.51, 135.28, 130.21, 128.45, 128.34, 128.14, 127.72, 126.86, 103.70, 90.14, 66.97, 61.49, 55.48, 55.27, 45.23, 36.58, 32.65. MS (ES, positive mode): 476.2 (M^++1). Anal. Calcd for $C_{28}H_{29}NO_6$: C, 70.72; H 6.15; N, 2.95. Found: C, 70.80; H, 6.45; N, 2.58.

4-Benzyl-1-(3,4,5-trimethoxy)benzyl-4-methoxycarbonyl-2-azetidinone (3,4,5-Tmb-α-Bn-Azn-OMe, 3g): Syrup. Eluent: EtOAc/hexane (1:2). HPLC: t_R = 5.48 min (A:B= 40:60). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24-6.98 (m, 5H), 6.52 (s, 2H), 4.37 (s, 2H), 3.83 (s, 6H), 3.81 (s, 3H), 3.52 (s, 3H), 3.28 (d, 1H, *J* = 14.0), 3.26 (d, 1H, *J* = 14.8), 3.00 (d, 1H, *J* = 14.0), 2.93 (d, 1H, *J* = 14.8). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.21, 166.27, 153.19, 137.25, 134.43, 131.83, 129.62, 128.52, 127.24, 105.47, 62.87, 60.76, 56.07, 52.25, 45.38, 45.14, 39.36. MS (ES, positive mode): 400.3 (M^++1), 422.4 (M^++Na). Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H 6.31; N, 3.51. Found: C, 66.09; H, 6.55; N, 3.40.

4-Benzyl-1-(3,4,5-trimethoxy)benzyl-4-*tert*-butoxycarbonyl-2-azetidinone (3,4,5-Tmb-α-Bn-Azn-O^{t}Bu, 3h): Syrup. Eluent: EtOAc/hexane (1:5). HPLC: t_R = 8.10 min (A:B= 45:55). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21-6.97 (m, 5H), 6.52 (s, 2H), 4.41 (d, 1H, *J* = 15.5), 4.29 (d, 1H, *J* = 15.5), 3.81 (s, 3H), 3.78 (s, 6H), 3.25 (d, 1H, *J* = 14.6), 3.22 (d, 1H, *J* = 14.0), 2.93 (d, 1H, *J* = 14.0), 2.90 (d, 1H, *J* = 14.6), 1.26 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.59, 166.72, 153.20, 137.21, 134.74, 132.48, 129.61, 128.37, 127.10, 105.27, 82.71, 63.63, 60.72, 56.01, 45.59, 44.93, 39.58, 27.56. MS (ES, positive mode): 442.3 (M^++1), 464.2 (M^++Na). Anal. Calcd for $C_{25}H_{31}NO_6$: C, 68.01; H 7.08; N, 3.17. Found: C, 67.93; H, 6.90; N, 3.10.

3(S)-Benzyl-4-(3,4,5-trimethoxy)benzyl-2,5-dioxomorpholine (4g): Foam. HPLC: t_R = 5.75 min (A:B= 35:65). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.11 (m, 5H), 6.45 (s, 2H), 5.33 (d, 1H, *J* = 14.6), 4.38 (m, 1H), 4.32 (d, 1H, *J* = 16.2), 3.79 (d, 1H, *J* = 14.6), 3.84 (s, 9H), 3.22 (m, 2H), 3.16 (d, 1H, *J* = 16.2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.63, 163.88, 153.58, 137.89, 137.44, 129.91, 129.59, 129.18, 128.27, 105.52, 66.43, 58.42, 56.07, 55.88, 47.24, 36.83. MS (ES, positive mode): 386.2 (M^++1). Anal. Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H 6.01; N, 3.63. Found: C, 65.50; H, 5.79; N, 3.45.

Attempts to remove the *N*-benzyl groups from compounds (3): *Method A.*– The corresponding 1-benzyl-2-azetidinone (**3**) (0.73 mmol) and anisole (0.16 mL, 1.46 mmol) were treated with TFA (4 mL) and heated to reflux for 48 h. After evaporation of TFA, Et_2O (10 mL) was added and the solid was filtered and dried. When necessary, the solid was purified on a silica gel column as indicated. *Method B.*– Compound (**3d**) (0.2 g, 0.45 mmol) was treated with a s aturated solution of HCl in EtOAc (4 mL), and stirred for 13 days. After evaporation to dryness, the resulting residue was purified on a silica gel column, using EtOAc-hexane (1:2) as eluent, to give 0.118 g (55%) of compound (**9**), along with a 3% of the unaltered starting azetidinone (**3d**). *Method C.*– A solution of $AlCl_3$ (0.47 g, 3.54 mmol) in anisole (1.7 mL) was added to **3a** (0.2 g, 0.48 mmol) under Ar atmosphere, and the mixture heated to 65°C for 1 h. 1M HCl (10 mL) was added to the reaction mixture. The aqueous layer was washed with Et_2O and concentrated in vacuum to leave a residue which was purified on a silica gel column, using CH_2Cl_2/MeOH (10:1) as eluent, to give 0.095 g (61%) of the carboxylic acid (**7**). *Method D*– A solution of the corresponding 1-substituted 2-azetidinone (**3**) (0.98 mmol) in MeCN/H_2O (1:1, 30 mL) was treated with K_2HPO_4 (1.46 g, 8.4 mmol) and $K_2S_2O_8$ (2.95 g, 10.9 mmol), and heated to 75°C under Ar atmosphere for 3-5 h. After evaporation of the MeCN, the aqueous layer was extracted with EtOAc, and the organic extract was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated. The resulting residue was purified on a silica gel column, as indicated.

4-Benzyl-4-benzyloxycarbonyl-2-azetidinone (H-α-Bn-Azn-OBn, 5a): Yield: 50% (from **3d**, method D). Eluent: EtOAc/CH_2Cl_2 (1:15). mp = 77-79°C (EtOAc-hexane). HPLC: t_R = 2.93 min (A:B= 50:50). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-6.97 (m, 10H), 6.49 (br s, 1H), 5.06 (s, 2H), 3.34 (d, 1H, *J* = 13.5), 3.08 (d, 1H, *J* = 15.0), 2.92 (d, 1H, *J* = 13.5), 2.92 (d, 1H, *J* = 15.0). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.54, 165.59, 134.77, 134.70, 129.27, 128.56, 128.52, 128.42, 127.27, 67.38, 58.86, 47.58, 42.29. MS (ES, positive mode): 318.2 (M^++Na). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 72.89; H, 6.10; N, 4.60.

3-Amino-3-carboxy-4-phenylbutyric Acid (H-α-Bn-Asp-OH, 6a): Yield 58% (from **3f**, method A, but at rt for 15 days), 40% (from **3d**, method A, 6 h of reaction). mp = 241°C (EtOAc). HPLC: t_R = 2.68 min (A:B= 10:90). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.22 (m, 5H), 3.07 (d, 1H, *J* = 14.2), 2.96 (d, 1H, *J* = 14.2), 2.80 (d, 1H, *J* = 16.7), 2.52 (d, 1H, *J* = 16.7). ^{13}C NMR (50 MHz, DMSO-d_6): δ 171.54, 170.12, 133.50, 130.02, 128.19, 127.10, 59.92, 41.12, 40.70. MS (ES, positive mode): 224.2 (M^++1).

3-Amino-3-benzyloxycarbonyl-4-phenylbutyric Acid (H-α-Bn-Asp-OBn, 6b): Yield 15% (from **3f**, method A, but at rt for 15 days). Foam. HPLC: t_R = 17.80 min (A:B= 10:90). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.26 (m, 10H), 5.10 (m, 2H), 3.01 (m, 3H), 2.56 (d, 1H, *J* = 16.9). ^{13}C NMR (50 MHz, DMSO-d_6): δ 171.45, 170.12, 135.5, 133.50, 129.34, 130.14, 128.19, 127.87, 127.10, 67.00, 59.90, 43.50, 40.73. MS (ES, positive mode): 314.2 (M^++1).

3-Trifluoroacetylamino-3-carboxy-4-phenylbutyric Acid (CF_3CO-α-Bn-Asp-OH, 6c): Yield 42% (from **3d**, method A, 6 h of reaction). Foam. HPLC: t_R = 9.92 min (A:B= 25:77). ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 7.75 (s, 1H), 7.19 (m, 5H), 3.61 (d, 1H, *J* = 13.5), 3.57 (d, 1H, *J* = 16.7), 3.30 (d, 1H, *J* = 13.5), 3.26 (d, 1H, *J* = 16.7). ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 172.15, 171.00, 156.00 (J_{C-F} = 37.0), 135.41, 130.58, 129.12, 128.20, 114.50 (J_{C-F} = 286.5), 63.18, 40.37, 39.01. MS (ES, positive mode): 320.1 (M^++1).

3-Amino-3-methoxycarbonyl-4-phenylbutyric Acid (H-α-Bn-Asp-OMe, 6d): Yield 75% (from **3b**, method A), 80% (from **3e**, method A), 79% (from **3g**, method A). Foam. HPLC: t_R = 7.50 min (A:B= 10:90). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.60 (m, 3H), 7.26 (m, 5H), 3.67(s, 3H), 3.08 (m, 3H), 2.75 (d, 1H, *J* = 17.8). ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.60, 169.84, 132.20, 129.96, 128.07, 127.24, 59.67, 52.47, 41.10, 39.00. MS (ES, positive mode): 238.1 (M^++1), 260.0 (M^++Na).

3-Trifluoroacetylamino-3-methoxycarbonyl-4-phenylbutyric Acid (CF_3CO-α-Bn-Asp-OMe, 6e): Yield 81% (from **3b**, method A, but without anisole), 3% (from **3e**, method A). Eluent: EtOAc/hexane (1:2). Foam. HPLC: t_R = 12.80 min (A:B= 30:70). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.26 (s, 1H), 7.25 (s, 1H), 7.19-6.86 (m, 5H), 3.79 (d, 1H, *J* = 17.2), 3.74 (s, 3H), 3.63 (d, 1H, *J* = 13.7), 3.11 (d, 1H, *J* = 17.2), 3.01 (d, 1H, *J* = 13.7). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.65, 174.50, 170.94, 156.41 (J_{C-F} = 37.0), 133.50, 129.34, 128.53, 127.74, 115.49 (J_{C-F} = 286.5), 63.03, 53.41, 40.10, 38.94. MS (ES, positive mode): 334.2 (M^++1), 356.1 (M^++Na). Anal. Calcd for $C_{14}H_{14}NO_5F_3$: C, 50.46; H 4.23; N, 4.20. Found: C, 50.27; H, 4.44; N, 4.08.

Ethyl 3-(2,4-Dimethoxybenzyl)amino-3-benzyloxycarbonyl-4-phenylbutyrate (Dmb-α-Bn-Asp(OEt)-OBn, 7): Yield 55% (from **3d**, method B). Eluent: EtOAc/hexane (1:1). Syrup. HPLC: t_R = 8.64 min (A:B= 50:50). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-6.43 (m, 13H), 5.12 (m, 2H), 4.13 (q, 2H, *J* = 6.7), 3.80 (m, 5H), 3.76 (s, 3H), 3.33 (d, 1H, *J* = 13.7), 3.19 (d, 1H, *J* = 13.7), 2.85 (d, 1H, *J* = 15.6), 2.76 (d, 1H, *J* = 15.6), 2.29 (br s, 1H), 1.24 (t, 3H, *J* = 6.7). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.58, 170.61, 159.93, 158.32, 136.06, 135.51, 130.33, 130.16, 128.34, 128.09, 127.99, 126.61, 120.41, 103.79, 98.28, 66.64, 64.55, 60.29, 55.20, 54.99, 42.11, 40.76, 38.56, 13.10. MS (ES, positive mode): 492.3 (M^++1). Anal. Calcd for $C_{29}H_{33}NO_6$: C, 70.86; H 6.77; N, 2.85. Found: C, 70.70; H, 6.55; N, 2.68.

4-Benzyl-1-(4-cyano-3,5-dimethoxy)benzyl-4-methoxycarbonyl-2-azetidinone (9): Yield 9% (from **3h**, method D). Eluent: EtOAc/hexane (1:3). Syrup. HPLC: t_R = 12.30 min (A:B= 35:65). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (m, 5H), 6.38 (s, 2H), 4.30 (s, 2H), 3.78 (s, 6H), 3.48 (s, 3H), 3.21 (d, 1H, *J* = 15.0), 3.17 (d, 1H, *J* = 14.0), 3.02 (d, 1H, *J* = 14.0), 2.92 (d, 1H, *J* = 15.0). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.17, 166.56, 162.59, 144.33, 134.13, 129.54, 128.67, 127.45, 113.87, 103.38, 90.5, 63.24, 56.26, 52.48, 45.78, 45.43, 39.76. MS (ES, positive mode): 395.1 (M^++1). Anal. Calcd for $C_{22}H_{22}N_2O_5$: C, 66.99; H 5.62; N, 7.10. Found: C, 66.75; H, 5.65; N, 6.84.

ACKNOWLEDGEMENTS

We thank the Comisión Interministerial de Ciencia y Tecnología (SAF 2000-0147) for financial support. G. G.-N. and M.A.B. are predoctoral fellows from the Ministerio de Ciencia y Tecnología (Spain) and Fundación Ramón Areces (Spain), respectively.

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41. Compounds (**3**) were formed as enantiomeric mixtures. It has been described that derivatives (**3a-c**) are obtained with moderate enantioselectivity, due to the recently described process of the memory of chirality (see ref. 19).