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Memory of chirality in the stereoselective synthesis of β-lactams: importance of the starting amino acid derivative

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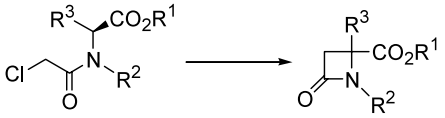
Abstract—The enantioselectivity of the base-promoted cyclization of *N*-alkyl-*N*-chloroacetyl amino acid derivatives to β-lactams is dependent on the substituents on the starting material. While ᵗBu esters are preferred over Me esters, and *N*-Bzl-, *N*-Pmb, *N*-Nph and *N*-Mom groups gave similar e.e. values, only amino acid derivatives with branched side-chains at the γ-position were able to show a good memory of chirality.

1. Introduction

In recent years some chemical transformations have been described to proceed in a selective manner without using any external chiral source, a phenomenon that has been explained in terms of a new asymmetric concept known as 'memory of chirality'.[1] Most of these transformations are found in the chemistry of α-amino acids,[2–16] although a few examples involve α-alkoxycarbonyl derivatives and axially chiral *o*-haloacrylanilides.[17–19] Although the initial stereogenic center (or chiral axis) is destroyed during the generation of the corresponding reactive intermediates (radicals, carbenium cations, enolates), these intermediates are able to 'remember' the configuration of their precursors to transfer the chirality to the final compounds. The alkylation of a number of α-amino acid derivatives has been extensively studied by Fuji's group, and determined to proceed with a high degree of asymmetric induction.[12–16] A chiral non racemic enolate with restricted rotation around the C–N axis has been proposed as the crucial intermediate.[13] We used a similar rationale to explain the stereoselectivity found in the intramolecular alkylation of several *N*-benzyl-*N*-chloroacetyl amino acids I to the corresponding 2-azetidinones II.[20,21] From the initial results, we envisaged a certain dependence of the enantioselectivity on the amino acid side-chain and on the base and solvent.[21] Focused on the search for the appropriate reaction conditions, we have recently performed a more detailed study, which has allowed us to determine the critical importance of the base and solvent for the final enantiomer distribution.[22]



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Now, to gain further insight into the factors governing the phenomenon of the memory of chirality, herein we have investigated the influence of R^1, R^2 and R^3 substituents on the selectivity of the β-lactam ring formation.

2. Results and discussion

As shown in Scheme 1, the starting chloroacetyl derivatives **20–38** were conveniently prepared by reaction of chloroacetyl chloride with the R^2-substituted compounds **1–8**, and **10–19**, previously synthesized by reductive amination of commercially available α-amino esters and the appropriate aldehyde.[21] In the particular case of compound **28**, the sequence of reactions was reversed to allow the incorporation of the

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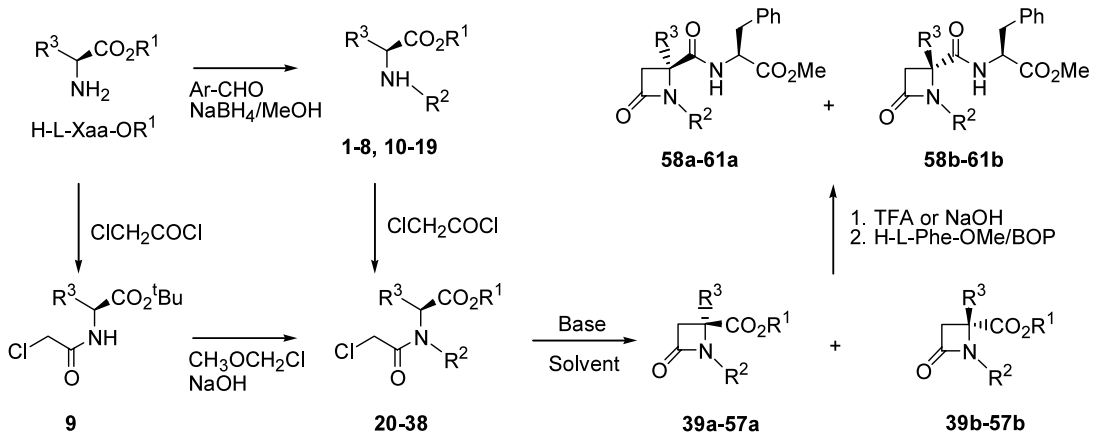


Compd.	R^1	R^2	R^3	Compd.	R^1	R^2	R^3
1, 20, 39	^{t}Bu	Pmb	CH_2Ph	**10, 29, 48**	Me	Pmb	$CH_2C_6H_4$(p-O-di-Cl-Bzl)
2, 21, 40	Me	Pmb	CH_2Ph	**11, 30, 49**	^{t}Bu	Pmb	CH_2In(*N*-Boc)
3, 22, 41	Bzl	Pmb	CH_2Ph	**12, 31, 50**	^{t}Bu	Bzl	CH_2In
4, 23, 42	Bzl	2,4-Dmb	CH_2Ph	**13, 32, 51**	Me	Pmb	$(CH_2)_3$-NHZ
5, 24, 43	Me	2,3,4-Tmb	CH_2Ph	**14, 33, 52**	Me	Pmb	$(CH_2)_4$-NHZ
6, 25, 44	Bzl	2,4,6-Tmb	CH_2Ph	**15, 34, 53, 58**	Me	Pmb	$CH_2CO_2{}^t$Bu
7, 26, 45	Me	3,4,5-Tmb	CH_2Ph	**16, 35, 54,59**	Me	Pmb	$(CH_2)_2CO_2{}^t$Bu
8, 27, 46	^{t}Bu	Nph	CH_2Ph	**17, 36, 55, 60**	Me	Pmb	$CH_2CH(CH_3)_2$
9, 28, 47	^{t}Bu	Mom	CH_2Ph	**18, 37, 56, 60**	^{t}Bu	Pmb	$CH_2CH(CH_3)_2$
				19, 38, 57, 61	^{t}Bu	Bzl	CH_3

Scheme 1.

methoxymethyl (Mom) group by *N*-alkylation of the chloroacetyl derivative **9**.[23]

To assess the contribution of the nature of the carboxylic ester on the observed enantioselectivity, the cyclization of *tert*-butyl, methyl and benzyl esters derived from phenylalanine derivatives **20**–**22** was checked on a series of defined reaction conditions, and the enantiomeric ratio of the resulting 2-azetidinones was then measured by chiral HPLC (Table 1).[22] With

Table 1. Influence of the R^1 group on the selectivity of the cyclization of L-Phe derivatives.

Entry	Starting compd	R^1	Base	Solvent	Final compd	Yield (%)[a]	**a**:**b**[b]	e.e.
1	**20**	^{t}Bu	Cs_2CO_3	MeCN	**39**	71	78:22[c]	56
2	**21**	Me	Cs_2CO_3	MeCN	**40**	74	78:22[d]	56
3	**22**	Bzl	Cs_2CO_3	MeCN	**41**	75	79:21[e]	58
4	**20**	^{t}Bu	BTPP	MeCN	**39**	73	76:24[c]	52
5	**21**	Me	BTPP	MeCN	**40**	68	67:33[d]	34
6	**22**	Bzl	BTPP	MeCN	**41**	58	57:43[e]	14
7	**20**	^{t}Bu	BEMP	MeCN	**39**	81	76:24[c]	52
8	**20**	^{t}Bu	BTPP	DCM	**39**	58	74:26[c]	48
9	**21**	Me	BTPP	DCM	**40**	65	67:33[d]	34
10	**20**	^{t}Bu	BEMP	DCM	**39**	65	75:25[c]	50
11	**21**	Me	BEMP	DCM	**40**	68	68:32[d]	36
12	**20**	^{t}Bu	BTPP	NMP	**39**	56	43:57[c]	14[f]
13	**21**	Me	BTPP	NMP	**40**	79	34:66[d]	32[f]
14	**20**	^{t}Bu	BEMP	NMP	**39**	52	51:49[c]	2
15	**21**	Me	BEMP	NMP	**40**	81	43:57[d]	14[f]

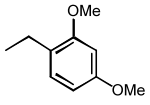
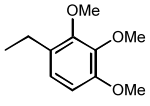
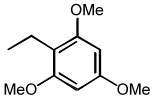
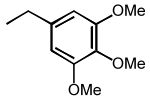
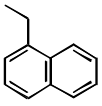
[a] Isolated yield.
[b] Measured by chiral HPLC (Column: OL-389).
[c] Hexane/acetone (96:4), 1.5 ml/min.
[d] Hexane/EtOH (95:5), 1 ml/min.
[e] OL-321, hexane/EtOH (97:3), 1 ml/min.
[f] Major isomer has *R* configuration.

the hindered phosphazene bases in MeCN or in DCM, the (*S*)-selectivity was higher for the bulky *tert*-butyl derivative than for the methyl ester, with a 13–18% increase in e.e. for both BTPP and BEMP. Still lower selectivity was found in the BTPP-assisted cyclization of the Bzl derivative **22**, which afforded β-lactam **41** in only 14% e.e. In contrast, the type of alkyl ester did not have any influence in the reactions carried out with cesium carbonate, probably as a consequence of similar *E*/*Z* enolate distribution and/or to close aggregate species in all cases. As previously observed,[22] the sense of the asymmetric induction was reversed when NMP was used as solvent, and better results were obtained for the methyl ester derivative. The enhancement in (*R*)-selectivity (Me versus ^{t}Bu) was independent of the sterical hindrance of the organic base, BTPP or BEMP.

Phenylalanine derivatives **23**–**28**, bearing a 2,4-dimethoxybenzyl group (2,4-Dmb), different trimethoxybenzyls (Tmb), a 1-naphthylmethyl group (Nph), and a methoxymethyl moiety (Mom) have been prepared to gain further information about the influence of the R^2 substituent on the degree of stereocontrol (Table 2).[24] Previously, we had observed that Bzl and Pmb groups give similar asymmetric inductions, indicating that the *p*-methoxy group has not any effect on the selectivity.[21] However, the appendage of an additional methoxy group in *ortho*-position of the phenyl ring, as in **23** and **24**, gave to remarkable decreases in the e.e.'s of the resultant β-lactams **42** and **43**. In agreement with these results, the decrease in selectivity was particularly marked for the 2,4,6-Tmb derivative **44**, with two *o*-methoxy groups, which was obtained in almost racemic form. The presence of OMe groups in *meta*-position had minor influence on the selectivity (compare Table 1: entry 2 with Table 2: entry 5). From these results, it could be rationalized that the *o*-methoxy groups at the benzyl substituent contribute to destabilize the anionic intermediates responsible for the preservation of the information of chirality of the starting amino acid. The detrimental effect of this ortho group does not seem to be related to its steric hindrance, since an increase in the volume of the benzyl moiety, as in the 1-Nph derivative **46**, resulted in a slight increase in the selectivity. Surprisingly, a clearly different group, as Mom, was also able to induce good selectivities, comparable to those previously obtained for the Pmb substituted derivative **39** under the indicated conditions.[22] Mom has previously been found to be a good stereodirecting element in the intermolecular α-alkylation of amino acid derivatives.[13]

In our preliminary studies,[20,21] Trp, Phe and Leu derivatives gave the β-lactam ring stereoselectively, while racemic azetidinones were obtained from Ala analogues. To extend this study, the enantiomeric ratio obtained in the cyclization of representative amino acid derivatives, such as Tyr, Trp(Boc), Orn, Lys, Asp, and Glu, was measured (Table 3). In those cases where the efforts to determine the e.e.'s by chiral HPLC were

Table 2. Influence of R^2 substituents on the selectivity of the cyclization of L-Phe chloroacetyl derivatives

Entry	Starting compd.	R^1	R^2	Base	Solvent	Final compd.	Yield (%)[a]	**a:b**[b]	*e.e.*
1	**23**	Bzl		Cs_2CO_3	MeCN	**42**	75	59:41[c]	18
2	**23**	Bzl			DMF	**42**	68	63:37	26
3	**24**	Me		Cs_2CO_3	MeCN	**43**	73	62:38[d]	24
4	**25**	Bzl		Cs_2CO_3	DMF	**44**	20	48:51[d]	3
5	**26**	Me		Cs_2CO_3	MeCN	**45**	76	73:27[e]	46
6	**27**	^{t}Bu		BTPP	MeCN	**46**	70	77:23[f]	54
7	**28**	^{t}Bu		Cs_2CO_3	MeCN	**47**	36	74:26[g]	48
8	**28**	^{t}Bu		NaOH	DCM	**47**	64	62:38	24

[a] Isolated compounds [b] Measured by chiral HPLC (Column: OL-389). [c] Hexane/acetone/EtOH (95:4:1), 1.2 ml/min. [d] Hexane/EtOH (96:4), 1 ml/min. [e] Hexane/EtOH (95:5), 1 ml/min. [f] Hexane/acetone (96:4), 1.5 ml/min. [g] Hexane/acetone (98:2), 1.5 ml/min.

Table 3. Influence of the amino acid side-chain (R^3) on the selectivity of the corresponding β-lactam (MeCN as solvent)

Entry	Starting compd	R^1	R^2	R^3	Base	Final compd	Yield (%)[a]	a:b[b]	e.e.
1	**29**	Me	Pmb	$CH_2C_6H_4$(*p*-O-di-Cl-Bzl)	Cs_2CO_3	**48**	77	74:28[c]	46
2	**29**	Me	Pmb	$CH_2C_6H_4$(*p*-O-di-Cl-Bzl)	BTPP	**48**	68	63:37	26
3	**30**	^{t}Bu	Pmb	CH_2In(N-Boc)	BTPP	**49**	90	71:29[d]	42
4	**31**	^{t}Bu	Bzl	CH_2In	BTPP	**50**	24	65:35[d]	30
5	**32**	Me	Pmb	$(CH_2)_3$-NHZ	Cs_2CO_3	**51**	81	57:43[e]	14
6	**32**	Me	Pmb	$(CH_2)_3$-NHZ	BTPP	**51**	76	55:45	10
7	**33**	Me	Pmb	$(CH_2)_4$-NHZ	Cs_2CO_3	**52**	82	54:46[f]	8
8	**34**	Me	Pmb	$CH_2CO_2{}^t$Bu	Cs_2CO_3	**53**	46	77:23[g,h]	54
9	**34**	Me	Pmb	$CH_2CO_2{}^t$Bu	Cs_2CO_3	**53**	61	40:60[g,h,i]	20
10	**35**	Me	Pmb	$(CH_2)_2CO_2{}^t$Bu	Cs_2CO_3	**54**	65	50:50[g]	0
11	**36**	Me	Pmb	$CH_2CH(CH_3)_2$	Cs_2CO_3	**55**	19	71:29[g]	42
12	**37**	^{t}Bu	Pmb	$CH_2CH(CH_3)_2$	BTPP	**56**	42	78:22[g]	56
13	**38**	^{t}Bu	Bzl	CH_3	Cs_2CO_3	**57**	69	50:50[g]	0
14	**38**	^{t}Bu	Bzl	CH_3	BTPP	**57**	53	50:50[g]	0

[a] Isolated compounds.
[b] Measured by chiral HPLC (Column: OL-389).
[c] Hexane/acetone/EtOH (95:4:1), 1.2 ml/min.
[d] Hexane/acetone (96:4), 1.2 ml/min.
[e] Hexane/EtOH (90:10), 1 ml/min.
[f] Hexane/EtOH (94:6), 1 ml/min.
[g] Diastereoisomeric excesses measured after derivatization to the corresponding Azn-L-Phe-OMe dipeptide derivatives (Refs. 21 and 22).
[h] Major compound **a** has *R* configuration.
[i] Reaction in THF.

unproductive, the diastereoisomeric ratio was measured after derivatization to dipeptide derivatives.[21,22] All aromatic amino acid derivatives tested were able to induce memory of chirality effects with the selectivity following the order Phe>Tyr≈Trp. Compared to Phe-OMe-derived β-lactam **40**, Tyr-OMe analogue **48** was obtained with slightly lower selectivity when both Cs_2CO_3 and BTPP were used as base. For Trp derivatives, the incorporation of a Boc group at position 1 of the indole ring resulted in a 12% increase in the e.e. value with respect to the NH analogue (compare entries 3 and 4). Concerning amino acids with basic side-chains, only marginal enantioselectivities were found for Orn and Lys derivatives. In contrast, a good asymmetric induction was found in the Cs_2CO_3-assisted intramolecular alkylation of the Asp derivative **34**,[†] although a lot of non-identified side products were also formed in this reaction, probably due to competition between α- and β-enolate formation. In good agreement with this, the yield in the β-lactam **53** was increased by lowering the polarity of the solvent (THF versus MeCN), but as expected the selectivity decreased in this solvent.[22] In the acidic amino acid series, lengthening the side-chain (Glu derivative **54**), had a detrimental effect on the selectivity leading to the complete loss of the asymmetric induction. For aliphatic amino acids, the alkylation of ramified Leu derivatives resulted in good selectivities, comparable to those found for Phe analogues, while not branched Ala derivative gave racemic products.

From these results, it seems that the presence of amino acids with branched side chains at the γ position is crucial for the stereoselectivity. Aromatic (Phe, Tyr) and heteroaromatic (Trp) rings, aliphatic chains (Leu), as well as carboxylate groups (Asp) can be considered as useful branched moieties at this point. All these results can be rationalized in terms of the existence of enolate intermediates possessing axial chirality, by restricted rotation around the C^{α}–N^{α} bond (Fig. 1). From our previous results,[25] and those reported by Fuji,[1b,13] the pro-*S* *Z*-enolate is supposed to be the main responsible of the observed selectivity. This proposal is in agreement with the increase in selectivity observed for bulky *tert*-butyl esters versus methyl esters, and for large Trp(Boc) derivative **49** compared with Trp analogue **50**. The need for enolates with restricted mobility about C–N bond is in concordance with the lack of memory of chirality in Ala and Glu derivatives, and with the marginal selectivity in Orn and Lys analogues, all possessing linear side-chains that facilitate free rotation of the C–N bond and, therefore,

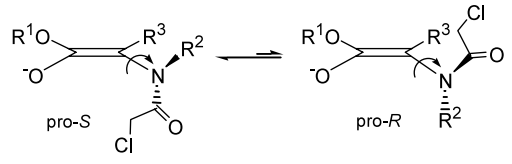


Figure 1. Proposed enolate intermediates (*Z*-geometry).

[†] Taking into account that the 4-$CH_2CO_2{}^t$Bu group has preference over the CH_2CON branch of the β-lactam ring, major diastereoisomer **53a** has *R* configuration, and the corresponding dipeptide derivative **58a** is heterochiral.

the formation of the corresponding racemic mixtures. The complete lack of asymmetry found for Glu and Ala derivatives also discards the involvement of complex intermediates consisting of achiral enolates and remaining optically active starting materials.

In conclusion, we have demonstrated that the stereoselectivity, due to memory of chirality, in the cyclization of amino acid derivatives to β-lactams is highly dependent on the substituents of the starting *N*-chloroacetyl amino acid derivative. Among these substituents, the amino acid side-chain (R^3) appears the principal stereodirecting element, offering additional support for the explanation that the memory of chirality is caused by a hindered rotation around the C–N bond.

3. 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). Electrospray mass spectra (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 aluminum sheets coated with a 0.2 mm layer of silica gel 60 F254 (Merck). Silica gel 60 (230–400 mesh, Merck) was used for column chromatography. Analytical HPLC was performed on a Waters Nova-pak C_{18} (3.9×150 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. Trp, Phe, Leu and Ala derivatives not described below were prepared as described.[20,21,24]

3.1. Synthesis of *N*-Benzyl-type amino acids

General procedure: A solution of H-Xaa-OR^1·HCl (19.4 mmol) in MeOH (30 ml) was treated with TEA (2.7 ml, 19.40 mmol) and the corresponding aldehyde (29.09 mmol). The reaction was stirred at rt for 1.5 h, cooled to 0°C, and $NaBH_4$ (1.47g, 38.79 mmol) was added in portions. After stirring at rt for additional 2 h, the solvent was evaporated to dryness, and the residue was extracted with EtOAc and 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.

3.1.1. *N*-(1-Naphthyl)methyl-L-Phe-O^{t}Bu 8. Syrup. Yield: 75%. Eluent EtOAc:hexane (1:8). HPLC: t_R = 6.13 min (A:B = 45:55). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12–7.22 (m, 12H, Ar), 4.31 (d, 1H, J = 12.9, N-CH_2), 3.57 (d, 1H, J = 12.9, N-CH_2), 3.57 (t, 1H, J = 6.9, α-CH), 2.97 (m, 2H, β-CH_2), 1.97 (br s, 1H, α-NH), 1.44 (s, 9H, CH_3, ^{t}Bu). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.30 (COO), 137.97–124.27 (16C, Ar), 81.46 (C, ^{t}Bu), 63.50 (α-CH), 50.32 (N-CH_2), 40.17 (β-CH_2), 28.32 (CH_3, ^{t}Bu). Anal calcd for $C_{24}H_{27}NO_2$: C, 79.74; H, 7.53; N, 3.87. Found: C, 79.76; H, 7.65; N, 3.99.

3.1.2. *N*-(*p*-Methoxybenzyl)-L-Tyr(O-di-Cl-Bzl)-OMe 10. Syrup. Yield: 71%. Eluent AcOEt:hexano (1:9). HPLC: t_R = 8.91 min (A:B = 40:60). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–6.76 (m, 11H, C_6H_5 and C_6H_4), 5.20 (s, 2H, CH_2, OBzl), 3.73 (s, 3H, OMe), 3.70 (d, 1H, J = 13.0, N-CH_2), 3.61 (s, 3H, OMe), 3.53 (d, 1H, J = 13.0, N-CH_2), 3.46 (t, 1H, J = 7.0, α-CH), 2.87 (d, 2H, J = 7.0, β-CH_2), 1.78 (br s, 1H, α-NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.53 (COO), 159.08 (4-C, C_6H_4), 158.12 (4-C, Pmb), 137.41–114.13 (16C, Ar), 65.68 (CH_2, OBzl), 62.42 (α-CH), 55.65 (OMe), 52.04 (OMe), 51.81 (N-CH_2), 39.23 (β-CH_2). Anal calcd for $C_{25}H_{25}Cl_2NO_4$: C, 63.30; H, 5.31; N, 2.95; Cl, 14.95. Found: C, 63.25; H, 5.33; N, 2.88; Cl, 14.87.

3.1.3. *N*-(*p*-Methoxybenzyl)-L-Orn(Z)-OMe 13. Syrup. Yield: 90%. Eluent EtOAc:hexane (2:1). HPLC: t_R = 6.59 min (A:B = 30:70). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (s, 5H, C_6H_5), 7.22 (d, 2H, J = 8.7, C_6H_4), 6.82 (d, 2H, J = 8.7, C_6H_4), 5.25 (br s, 1H, δ-NH), 5.09 (s, 2H, CH_2, Z), 3.78 (s, 3H, OMe), 3.72 (d, 1H, J = 12.6, N-CH_2), 3.71 (s, 3H, OMe), 3.54 (d, 1H, J = 12.6, N-CH_2), 3.24 (m, 1H, α-CH), 3.17 (m, 2H, δ-CH_2), 1.85 (br s, 1H, α-NH) , 1.64 (m, 4H, β-CH_2 and γ-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.63 (COO), 158.64 (4-C, Pmb), 156.30 (CO, Z), 136.57–113.67 (11C, Ar), 66.45 (CH_2, Z), 60.09 (α-CH), 55.14 (OMe), 51.69 (N-CH_2), 51.46 (OMe), 40.64 (δ-CH_2), 30.63 (β-CH_2), 26.31 (γ-CH_2). Anal calcd for $C_{22}H_{28}N_2O_5$: C, 65.98; H, 7.08; N, 7.00. Found: C, 65.90; H, 7.00; N, 6.82.

3.1.4. *N*-(*p*-Methoxybenzyl)-L-Lys(Z)-OMe 14. Syrup. Yield: 65%. Eluent AcOEt:hexano (1:2). HPLC: t_R = 4.11 min (A:B = 35:65). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (s, 5H, C_6H_5), 7.23 (d, 2H, J = 8.6, C_6H_4), 6.85 (d, 2H, J = 8.6, C_6H_4), 5.09 (s, 2H, CH_2, Z),4.91 (br s, 1H, δ-NH), 3.78 (s, 3H, OMe), 3.73 (d, 1H, J = 12.7, N-CH_2), 3.72 (s, 3H, OMe), 3.55 (d, 1H, J = 12.7, N-CH_2), 3.24 (t, 1H, J = 6.6, α-CH), 3.16 (m, 2H, ε-CH_2), 1.81 (br s, 1H, α-NH), 1.62 (m, 2H, β-CH_2), 1.42 (m, 4H, γ-CH_2 and δ-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.84 (COO), 158.59 (4-C, Pmb), 156.26 (CO, Z), 136.52–113.62 (11C, Ar), 66.44 (CH_2, Z), 60.17 (α-CH), 55.13 and 51.60 (OMe), 51.43 (N-CH_2), 40.68 (ε-CH_2), 32.92 (δ-CH_2), 29.49 (β-CH_2), 22.80 (γ-CH_2). Anal calcd for $C_{23}H_{30}N_2O_5$: C, 66.65; H, 7.30; N, 6.76. Found: C, 66.75; H, 7.55; N, 6.98.

3.1.5. *N*-(*p*-Methoxybenzyl)-L-Asp(O^{t}Bu)-OMe 15. Syrup. Yield: 79%. Eluent AcOEt:hexano (1:8). HPLC: t_R = 4.00 min (A:B = 35:65). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 (d, 2H, J = 8.4, C_6H_4), 6.83 (d, 2H, J = 8.4, C_6H_4), 3.79 (d, 1H, J = 12.7, N-CH_2), 3.77 (s, 3H, OMe), 3.72 (s, 3H, OMe), 3.64 (d, 1H, J = 12.7, N-CH_2), 3.60 (t, 1H, J = 4.8, α-CH), 2.60 (dd, 2H, J = 4.8, 6.0, β-CH_2), 2.00 (br s, 1H, α-NH), 1.40 (s, 9H, CH_3, ^{t}Bu). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.20 (COO), 169.92 (COO), 158.61 (4-C, Pmb), 131.65–

113.62 (5C, Ar), 80.89 (C, ^{t}Bu), 56.94 (α-CH), 55.13 and 51.85 (OMe), 51.24 (N-CH_2), 39.27 (β-CH_2), 27.92 (CH_3, ^{t}Bu). Anal calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.00; H, 7.55; N, 4.51.

3.2. Synthesis of *N*-alkyl-*N*-chloroacetyl amino acids

General procedure: A solution of the corresponding *N*-alkyl amino acid derivative (4 mmol) in THF (20 ml) was treated with propylene oxide (4.2 ml, 60 mmol) and chloroacetyl chloride (0.47 ml, 6 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.

3.2.1. *N*-Chloroacetyl-*N*-(1-naphthyl)methyl-L-Phe-O^{t}Bu 27. Foam. Yield: 92%. Eluent EtOAc:hexane (1:8). HPLC: $t_R = 17.41$ min (A:B = 60:40). $[\alpha]_D = -117.1$ (*c* 1.05, $CHCl_3$). Rotamer ratio 6.3:1. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90–7.18 (m, 12H, Ar), 4.93 (d, 1H, $J = 18.0$, N-CH_2), 4.42 (d, 1H, $J = 18.0$, N-CH_2), 4.34 (t, 1H, $J = 6.3$, α-CH), 3.98 (s, 2H, CH_2Cl), 3.30 (m, 2H, β-CH_2), 1.46 (s, 9H, CH_3, ^{t}Bu). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.58 (COO) 167.31 (CON), 137.79–121.71 (16C, Ar), 82.06 (C, ^{t}Bu), 62.92 (α-CH), 49.82 (CH_2Cl), 41.15 (N-CH_2), 35.18 (β-CH_2), 27.84 (CH_3, ^{t}Bu). EM (ES positive mode): 460.1 $(M+Na)^+$. Anal calcd for $C_{26}H_{28}ClNO_3$: C, 71.30; H, 6.44; N, 3.20; Cl, 8.09. Found: C, 71.35; H, 6.48; N, 3.15; Cl, 8.15.

3.2.2. *N*-Chloroacetyl-*N*-(*p*-methoxybenzyl)-L-Tyr(O-di-Cl-Bzl)-O^{t}Bu 29. Syrup. Yield: 92%. Eluent AcOEt:hexano (1:2). HPLC: $t_R = 16.03$ min (A:B = 50:50). $[\alpha]_D = -43.4$ (*c* 1.47, $CHCl_3$). Rotamer ratio 9.5:1. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–6.82 (m, 11H, C_6H_4, C_6H_3 and C_6H_4), 5.31 (s, 2H, CH_2, OBzl), 4.45 (d, 1H, $J = 16.4$, N-CH_2), 4.19 (m, 1H, α-CH), 4.15 (d, 1H, $J = 16.4$, N-CH_2), 4.09 (d, 1H, $J = 12.4$, CH_2Cl), 4.03 (d, 1H, $J = 13.9$, β-CH_2), 3.81 (m, 4H, N-CH_2 and OMe), 3.70 (s, 3H, OMe), 3.35 (dd, 1H, $J = 5.5$, 13.9, β-CH_2), 3.25 (dd, 1H, $J = 9.7$, 13.9, β-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.67 (COO), 167.33 (CON), 159.77 (4-C, C_6H_5), 158.20 (4-C, Pmb), 137.38–115.74 (16C, Ar), 65.83 (CH_2, OBzl), 61.91 (α-CH), 55.69 (OMe), 52.97 (CH_2Cl), 52.66 (OMe), 41.92 (N-CH_2), 34.44 (β-CH_2). EM (ES positive mode): 550.1 $(M+1)^+$. Anal calcd for $C_{27}H_{26}Cl_3NO_5$: C, 58.87; H, 4.76; N, 2.54; Cl, 19.31. Found: C, 59.05; H, 4.51, N, 2.75; Cl, 19.65.

3.2.3. *N*-Chloroacetyl-*N*-(*p*-methoxybenzyl)-L-Orn(Z)-OMe 32. Syrup. Yield: 98%. Eluent EtOAc:hexane (1:1). HPLC: $t_R = 16.53$ min (A:B = 35:65). $[\alpha]_D = -32.9$ (*c* 2.19, $CHCl_3$). Rotamer ratio 3.2:1. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–6.77 (m, 9H, Ar), 5.08 (s, 2H, CH_2, Z), 4.82 (br s, 1H, δ-NH), 4.60 (d, 1H, $J = 16.2$, N-CH_2), 4.50 (d, 1H, $J = 16.2$, N-CH_2), 4.41 (t, 1H, $J = 7.8$, α-CH), 4.08 (m, 2H, CH_2Cl), 3.79 (s, 3H, OMe), 3.62 (s, 3H, OMe), 3.10 (m, 2H, δ-CH_2), 2.03 (m, 1H, β-CH_2), 1.77 (m, 1H, β-CH_2), 1.48 (m, 2H, γ-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.73 (COO), 167.44 (CON), 159.39 (4-C, Pmb), 156.32 (CO, Z), 129.51–114.28 (11C, Ar), 66.55 (CH_2, Z), 58.48 (α-CH), 55.24 (OMe), 52.19 (OMe), 50.83 (N-CH_2), 41.56 (CH_2Cl), 40.42 (δ-CH_2), 26.81 (β-CH_2), 26.33 (γ-CH_2). EM (ES positive mode): 477.3 $(M+1)^+$. Anal calcd for $C_{24}H_{29}ClN_2O_6$: C, 60.44; H, 6.13; N, 5.87; Cl, 7.43. Found: C, 60.55; H, 6.10; N, 5.75; Cl, 7.65.

3.2.4. *N*-Chloroacetyl-*N*-(*p*-methoxybenzyl)-L-Lys(Z)-OMe 33. Syrup. Yield: 87%. Eluent AcOEt:hexano (2:1). HPLC: $t_R = 12.20$ min (A:B = 40:60). $[\alpha]_D = -35.3$ (*c* 1.04, $CHCl_3$). Rotamer ratio 2.7:1. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (s, 5H, C_6H_5), 7.17 (d, 2H, $J = 8.6$, C_6H_4), 6.85 (d, 2H, $J = 8.6$, C_6H_4), 5.05 (s, 2H, CH_2, Z), 4.88 (br s, 1H, δ-NH), 4.51 (m, 2H, N-CH_2), 4.44 (t, 1H, $J = 7.1$, α-CH), 4.05 (d, 1H, $J = 12.3$, CH_2Cl), 3.99 (d, 1H, $J = 12.3$, CH_2Cl), 3.76 (s, 3H, OMe), 3.58 (s, 6H, OMe), 3.09 (m, 2H, ε-CH_2), 1.97 (m, 1H, β-CH_2), 1.73 (m, 1H, β-CH_2), 1.34 (m, 4H, δ-CH_2 and γ-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.83 (COO), 167.40 (CON), 159.23 (4-C, Pmb), 156.27 (CO, Z), 136.49–113.52 (11C, Ar), 66.38 (CH_2, Z), 58.39 (α-CH), 55.17 and 52.05 (OMe), 50.50 (N-CH_2), 41.57 (CH_2Cl), 40.47 (ε-CH_2), 29.31 (δ-CH_2), 28.57(β-CH_2), 23.36 (γ-CH_2). EM (ES positive mode): 513.2 $(M+Na)^+$. Anal calcd for $C_{25}H_{31}ClN_2O_6$: C, 61.16; H, 6.36; N, 5.71; Cl, 7.22. Found: C, 61.35; H, 6.06; N, 5.83; Cl, 7.05.

3.2.5. *N*-Chloroacetyl-*N*-(*p*-methoxybenzyl)-L-Asp(O^{t}Bu)-OMe 34. Syrup. Yield: 98%. Eluent AcOEt:hexano (1:4). HPLC: $t_R = 8.69$ min (A:B = 40:60). $[\alpha]_D = -62.3$ (*c* 1.96, $CHCl_3$). Rotamers ratio 4.2:1. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, 2H, $J = 8.5$, C_6H_4), 6.86 (d, 2H, $J = 8.5$, C_6H_4), 4.64 (d, 1H, $J = 14.4$, N-CH_2), 4.46 (t, 1H, $J = 6.7$, α-CH), 4.44 (d, 1H, $J = 14.4$, N-CH_2), 4.09 (d, 1H, $J = 12.7$, CH_2Cl), 4.01 (d, 1H, $J = 12.7$, CH_2Cl), 3.77 (s, 6H, OMe), 3.68 (s, 3H, OMe), 3.16 (dd, 1H, $J = 6.7$, 16.9, β-CH_2), 2.58 (dd, 1H, $J = 6.7$, 16.9, β-CH_2), 1.39 (s, 9H, CH_3, ^{t}Bu). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.11 (COO), 169.70 (COO), 166.74 (CON), 159.31 (4-C, Pmb), 128.68–114.11 (5C, Ar), 81.00 (C, ^{t}Bu), 56.87 (α-CH), 55.13 (OMe), 52.52 (N-CH_2), 52.29 (OMe), 41.27 (CH_2Cl), 35.37(β-CH_2), 27.83 (CH_3, ^{t}Bu). EM (ES positive mode): 422.1 $(M+Na)^+$. Anal calcd for $C_{19}H_{26}ClNO_6$: C, 57.07; H, 6.55; N, 3.50; Cl, 8.87. Found: C, 57.35; H, 6.88; N, 3.15; Cl, 8.55.

3.2.6. *N*-Chloroacetyl-L-Phe-O^{t}Bu 9. A solution of H-L-Phe-O^{t}Bu (3 g, 11.64 mmol) in dry THF (48 ml) was treated with TEA (1.62 ml, 11.64 mmol), and cooled to 0°C. Then, propylene oxide (12.2 ml, 174.6 mmol) and chloroacetyl chloride (1.11 ml, 13.9 mmol) was added. After stirring at rt for 1–2 h, the solvents were evaporated and the resulting residue was purified on a silica gel column using EtOAc:hexane (1:10). Foam. Yield: 86%. Eluent EtOAc:hexane (1:10). HPLC: $t_R = 4.78$ min (A:B = 45:55). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.90–7.18 (m, 5H, C_6H_5), 7.03 (d, 1H, $J = 7.1$, α-NH), 4.76 (m, 1H, α-CH), 4.05 (s, 2H, CH_2Cl), 3.13 (d, 2H, $J = 5.8$, β-CH_2), 1.46 (s, 9H, CH_3, ^{t}Bu). ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.98 (COO), 165.52 (CON), 135.84–127.22 (6C, Ar), 82.81 (C, ^{t}Bu), 53.90 (α-CH), 42.54 (CH_2Cl), 38.03 (β-CH_2), 28.01 (CH_3, ^{t}Bu). EM (ES

positive mode): 320.1 $(M+Na)^+$. Anal calcd for $C_{15}H_{23}ClNO_3$: C, 67.90; H, 8.74; N, 5.28; Cl, 11.91. Found: C, 67.85; H, 8.70; N, 5.35; Cl, 11.75.

3.2.7. *N*-Chloroacetyl-*N*-methoxymethyl-L-Phe-O^{t}Bu 28. A solution of **9** (0.2 g, 0.67 mmol) in CH_2Cl_2 (2 ml) was treated with tetrabutylammonium bromide (43.2 mg, 0.13 mmol), and cooled to 0°C. Then, a solution of 50% NaOH (0.19 ml, 2.37 mmol) and chloromethylmethyl ether (0.61 ml, 0.80 mmol) were added dropwise. After stirring at rt for 4.5 h, the solvents were evaporated and the resulting residue was partitioned between CH_2Cl_2 and H_2O (1:1) and the phases were separated. The organic layer was washed with brine and dried over Na_2SO_4. After evaporation, the resulting residue was purified on a silica gel column using EtOAc:hexane (1:5). Syrup. Yield: 59%. Eluent EtOAc:hexane (1:5). HPLC: $t_R = 7.17$ min (A:B = 45:55). $[\alpha]_D = -65.85$ (*c* 0.56, $CHCl_3$). Rotamer ratio 10.8:1. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.24–7.16 (m, 5H, C_6H_5), 4.53 (d, 1H, $J = 11.5$, N-CH_2), 4.07 (s, 2H, CH_2Cl), 4.00 (d, 1H, $J = 11.5$, N-CH_2), 3.25 (m, 5H, β-CH_2 and OCH_3), 1.42 (s, 9H, CH_3, ^{t}Bu). ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.27 (COO), 167.46 (CON), 138.18–127.07 (6C, Ar), 82.45 (N-CH_2), 80.64 (C, ^{t}Bu), 62.59 (OMe) 56.12 (α-CH), 41.32 (CH_2Cl), 35.49 (β-CH_2), 28.28 (CH_3, ^{t}Bu). EM (ES positive mode): 364.1 $(M+Na)^+$. Anal calcd for $C_{17}H_{24}ClNO_4$: C, 59.73; H, 7.08; N, 4.10; Cl, 10.37. Found: C, 59.65; H, 6.89; N, 4.00; Cl, 10.15.

3.3. Synthesis of 2-azetidinones

General procedure: The corresponding chloroacetyl derivative (0.38 mmol) was dissolved in the appropriate solvent (1.5 ml) and treated, at rt and under Ar atmosphere, with the base (0.56 mmol). The reaction was monitored by TLC or HPLC until complete disappearance of the starting material. The solution or suspension was evaporated, redissolved in EtOAc, washed with H_2O, and dried over Na_2SO_4. After evaporation, the resulting residue was purified on a silica gel column. The obtained 2-azetidinone was directly evaluated by chiral HPLC, or transformed into the corresponding dipeptide derivatives, as previously described.[21]

3.3.1. 4-Benzyl-4-*tert*-butoxycarbonyl-1-(1-naphthyl)-methyl-2-azetidinone 46. Foam. Yield: 70%. Eluent EtOAc:hexane (1:8). HPLC: $t_R = 13.52$ min (A:B = 50:50). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25–6.86 (m, 12H, Ar), 5.14 (d, 1H, $J = 15.3$, 1-CH_2), 4.78 (d, 1H, $J = 15.3$, 1-CH_2), 3.27 (d, 1H, $J = 14.8$, 3-H), 3.10 (d, 1H, $J = 13.9$, 4-CH_2), 2.91 (d, 1H, $J = 14.8$, 3-H), 2.62 (d, 1H, $J = 13.9$, 4-CH_2), 1.22 (s, 9H, CH_3, ^{t}Bu). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.73 (COO), 166.79 (CON), 135.09–123.93 (16C, Ar), 82.86 (C, ^{t}Bu), 64.22 (4-C), 45.92 (1-CH_2), 42.85 (3-C), 39.41 (4-CH_2), 27.74 (CH_3, ^{t}Bu). EM (ES positive mode): 402.3 $(M+1)^+$. Anal calcd for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49. Found: C, 77.56; H, 6.76; N, 3.20.

3.3.2. 4-Benzyl-4-*tert*-butoxycarbonyl-1-methoxymethyl-2-azetidinone 47. Foam. Yield: 36% (*Method A*). Eluent EtOAc:hexane (1:6). HPLC: $t_R = 5.31$ min (A:B = 45:55). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.27–7.17 (m, 5H, C_6H_5), 4.61 (s, 2H, N-CH_2), 3.39 (d, 1H, $J = 14.3$, 3-H), 3.34 (s, 3H, OMe), 3.25 (d, 1H, $J = 15.0$, 4-CH_2), 3.11 (d, 1H, $J = 14.3$, 3-H), 2.93 (d, 1H, $J = 15.0$, 4-CH_2), 1.38 (s, 9H, CH_3, ^{t}Bu). ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.89 (COO), 167.19 (CON), 137.90–126.80 (6C, Ar), 82.17 (C, ^{t}Bu), 80.36 (N-CH_2) 62.32 (4-C), 55.84 (OMe), 41.03 (3-C), 35.22 (4-CH_2), 28.00 (CH_3, ^{t}Bu). EM (ES positive mode): 328.1 $(M+Na)^+$. Anal calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.75; H, 7.38, N, 4.32.

3.3.3. 1-(*p*-Methoxybenzyl)-4-methoxycarbonyl-4-(p-2,6-dichlorobenzyloxy)benzyl-2-azetidinone 48. Syrup. Eluent AcOEt:hexano (1:2). HPLC: $t_R = 12.69$ min (A:B = 50:50). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–6.77 (m, 13H, C_6H_5, and C_6H_4), 5.15 (s, 2H, CH_2, OBzl), 4.32 (m, 2H, 1-CH_2), 3.71 (s, 3H, OMe), 3.45 (s, 3H, OMe), 3.18 (d, 1H, $J = 14.7$, 3-H), 3.14 (d, 1H, $J = 14.1$, 4-CH_2), 2.84 (d, 1H, $J = 14.7$, 3-H), 2.81 (d, 1H, $J = 14.1$, 4-CH_2).^{13}C NMR (75 MHz, $CDCl_3$): δ 171.29 (COO), 166.26 (CON), 159.07 (4-C C_6H_5), 158.03 (4-C, Pmb), 136.96–113.89 (16C, Ar), 65.14 (CH_2, OBzl), 62.96 (4-C), 55.24 (OMe), 52.28 (OMe), 45.32 (1-CH_2), 44.36 (3-C), 38.75 (4-CH_2), 40.36 (3′-C), 30.38. EM (ES positive mode): 514.1 $(M^+ + 1)$. Anal calcd for $C_{27}H_{25}Cl_2NO_5$: C, 63.04; H, 4.90; N, 2.72; Cl, 13.78. Found: C, 63.35; H, 4.92; N, 2.52; Cl, 13.87.

3.3.4. 1-(*p*-Methoxybenzyl)-4-methoxycarbonyl-4-[3-(benzyloxycarbonyl)amino]propyl-2-azetidinone 51. Syrup. Yield: 81%. Eluent EtOAc:hexane (2:1). HPLC: $t_R = 10.45$ min (A:B = 35:65). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (s, 5H, C_6H_5), 7.18 (d, 2H, $J = 8.1$, C_6H_4), 6.80 (d, 2H, $J = 8.1$, C_6H_4), 5.06 (s, 2H, CH_2, Z), 4.74 (m, 1H, 3′-NH), 4.43 (d, 1H, $J = 15.3$, 1-CH_2), 4.24 (d, 1H, $J = 15.3$, 1-CH_2), 3.73 (s, 3H, OMe), 3.58 (s, 3H, OMe), 3.19 (d, 1H, $J = 14.7$, 3-H), 2.98 (m, 2H, 3′-H), 2.83 (d, 1H, $J = 14.7$, 3-H), 1.89 (m, 1H, 1′-H), 1.58 (m, 1H, 1′-H), 1.34 (m, 2H, 2′-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.64 (COO), 165.89 (CON), 159.02 (4-C, Pmb), 156.19 (CO, Z), 136.38–113.82 (11C, Ar), 66.49 (CH_2, Z), 62.04 (4-C), 55.09 (OMe), 52.31 (OMe), 45.46 (1-CH_2), 44.10 (3-C), 40.36 (3′-C), 30.38 (1′-C), 24.22 (2′-C). EM (ES positive mode): 441.3 $(M^+ + 1)$. Anal calcd for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36. Found: C, 65.35; H, 6.29; N, 6.15.

3.3.5. 1-(*p*-Methoxybenzyl)-4-methoxycarbonyl-4-[4-(benzyloxycarbonyl)amino]butyl-2-azetidinone 52. Syrup. Eluent AcOEt:hexano (2:1). HPLC: $t_R = 8.04$ min (A:B = 40:60). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (s, 5H, C_6H_5), 7.11 (d, 2H, $J = 8.7$, C_6H_4), 6.75 (d, 2H, $J = 8.7$, C_6H_4), 5.00 (s, 2H, CH_2, OBzl), 4.69 (br s, 1H, 3′-NH), 4.37 (d, 1H, $J = 15.3$, 1-CH_2), 4.17 (d, 1H, $J = 15.3$, 1-CH_2), 3.68 (s, 3H, OMe), 3.51 (s, 3H, OMe), 3.13 (d, 1H, $J = 14.6$, 3-H), 2.97 (m, 2H, 4′-H), 2.75 (d, 1H, $J = 14.6$, 3-H), 1.81 (m, 1H, 1′-H), 1.48 (m, 1H, 1′-H), 1.19 (m, 2H, 3′-H), 1.05 (m, 2H, 2′-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.78 (COO), 166.06 (CON), 159.00 (4-C, Pmb), 156.12 (CO, Z), 136.50–113.82 (11C, Ar), 66.51 (CH_2, OBzl), 62.30 (4-C), 55.17 and 52.32 (OMe), 45.48 (1-CH_2) 44.12 (3-C), 40.42 (4′-C), 33.00

(3′-C), 27.63 (1′-C). 20.94 (2′-C). EM (ES positive mode): 455.1 $(M+1)^+$. Anal calcd for $C_{25}H_{30}N_2O_6$: C, 66.06; H, 6.65; N, 6.16. Found: C, 66.45; H, 6.75; N, 6.25.

3.3.6. 1-(*p*-Methoxybenzyl)-4-methoxycarbonyl-4-(*tert*-butoxycarbonyl)methyl-2-azetidinone 53. Solid. Eluent AcOEt:hexano (1:2). HPLC: $t_R = 5.63$ min (A:B = 40:60). $[\alpha]_D = -2.3$ (*c* 1.33, $CHCl_3$ for 20% e.e.). ^1H NMR (300 MHz, $CDCl_3$): δ 7.11 (d, 2H, $J = 8.1$, C_6H_4), 6.75 (d, 2H, $J = 8.7$, C_6H_4), 4.31 (d, 1H, $J = 15.1$, 1-CH_2), 4.23 (d, 1H, $J = 15.1$, 1-CH_2), 3.71 (s, 3H, OMe), 3.50 (s, 3H, OMe), 3.28 (d, 1H, $J = 14.8$, 3-H), 2.93 (d, 1H, $J = 14.8$, 3-H), 2.78 (d, 1H, $J = 16.6$, 4-CH_2), 2.56 (d, 1H, $J = 16.6$, 4-CH_2), 1.31 (s, 9H, CH_3, ^{t}Bu). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.36 (COO), 168.92 (COO), 166.19 (CON), 159.62 (4-C, Pmb), 130.12–114.44 (5C, Ar), 82.14 (C, ^{t}Bu), 59.63 (4-C), 55.63 and 52.76 (OMe), 48.00 (1-CH_2) 44.85 (3-C), 40.82 (4-CH_2), 28.31 (CH_3, ^{t}Bu). EM (ES positive mode): 364.2 $(M+1)^+$. Anal calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.45; H, 7.15; N, 3.95.

3.4. Synthesis of dipeptide derivatives

General procedure: A solution of the corresponding 4-alkoxycarbonyl 2-azetidinone (0.24 mmol) was hydrolyzed with TFA (1 ml) in CH_2Cl_2 (2 ml), for tert-butyl esters, or with 2N NaOH (0.18 ml, 0.36 mmol) in MeOH (3 ml), for methyl esters, and worked up normally. A solution of the obtained 4-carboxy derivative and H-L-Phe-OMe (0.48 mmol) in dry THF (4 ml) was successively treated at rt with BOP (0.21 g, 0.48 mmol) and TEA (0.13 ml, 0.96 mmol). The stirring was continued until complete disappearance of the starting material (1–2 days). The isomers ratio was determined by HPLC or by ^1H NMR on the crude reaction mixtures. To characterize the obtained dipeptide derivatives, the solvent was evaporated, the residue was dissolved in EtOAc and washed with citric acid (10%), $NaHCO_3$ (10%) and brine. The organic layer was dried (Na_2SO_4) and evaporated leaving a residue that was purified on a silica gel column as specified in each case.

3.4.1. 1-(*p*-Methoxybenzyl)-4-[*N*-(1′-methoxycarbonyl-2′-phenyl)ethyl]carbamoyl-4-(*tert*-butoxycarbonyl)-methyl-2-azetidinone 58. Isomer 4*R*,1′*S* **58a**: Syrup. Eluent AcOEt:hexano (2:1). HPLC: $t_R = 29.92$ min (A:B = 35:65). $[\alpha]_D = +73.5$ (*c* 1.07, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.13 (m, 7H, C_6H_5 and C_6H_4), 6.74 (d, 2H, $J = 8.7$, C_6H_4), 6.41 (d, 1H, $J = 7.8$, α-NH), 4.63 (m, 1H, α-CH), 4.29 (d, 1H, $J = 14.9$, 1-CH_2), 4.16 (d, 1H, $J = 14.9$, 1-CH_2), 3.70 (s, 3H, OMe), 3.58 (s, 3H, OMe), 3.01 (m, 2H, 3-H), 2.89 (dd, 1H, $J = 6.4$, 13.9, β-Phe), 2.87 (d, 1H, $J = 16.9$ 4-CH_2), 2.80 (dd, 1H, $J = 6.4$, 13.9, β-Phe), 2.54 (d, 1H, $J = 16.9$ 4-CH_2), 1.33 (s, 9H, CH_3, ^{t}Bu). EM (ES positive mode): 533.2 $(M+Na)^+$. Anal calcd for $C_{28}H_{34}N_2O_7$: C, 65.87; H, 6.71; N, 5.49. Found: C, 65.45; H, 6.40; N, 5.75. Isomer 4*S*,1′*S* **58b**: Syrup. Eluent AcOEt:hexano (2:1). HPLC: $t_R = 25.84$ min (A:B = 35:65). $[\alpha]_D = -24.5$ (*c* 0.69, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.21–6.74 (m, 9H, C_6H_5 and C_6H_4), 6.26 (d, 1H, $J = 7.5$, α-NH), 4.58 (m, 1H, α-CH), 4.37 (s, 2H, 1-CH_2), 3.74 (s, 3H, OMe), 3.64 (s, 3H, OMe), 3.03 (dd, 1H, $J = 5.6$, 14.1, β-Phe), 2.96 (d, 1H, $J = 16.2$, 3-H), 2.80 (d, 1H, $J = 16.8$, 4-CH_2), 2.67 (dd, 1H, $J = 8.1$, 13.1, β-Phe), 2.63 (d, 1H, $J = 16.2$ 3-H), 2.57 (d, 1H, $J = 16.8$, 4-CH_2), 1.33 (s, 9H, CH_3, ^{t}Bu). EM (ES positive mode): 533.2 $(M+Na)^+$. Anal calcd for $C_{28}H_{34}N_2O_7$: C, 65.87; H, 6.71; N, 5.49. Found: C, 65.95; H, 6.50; N, 5.65.

3.4.2. 1-(*p*-Methoxybenzyl)-4-[*N*-(1′-methoxycarbonyl-2′-phenyl)ethyl]carbamoyl-4-(2-*tert*-butoxycarbonyl)-ethyl-2-azetidinone 59. Isomer 4*S*,1′*S* **59a**: Foam. Eluent AcOEt:hexano (2:1). HPLC: $t_R = 52.21$ min (A:B = 30:70). $[\alpha]_D = -4.8$ (*c* 1.20, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.30–6.81 (m, 9H, C_6H_5 and C_6H_4), 6.14 (d, 1H, $J = 8.3$, α-NH), 4.68 (m, 1H, α-CH), 4.27 (s, 2H, 1-CH_2), 3.76 (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.08 (dd, 1H, $J = 5.2$, 13.9, β-Phe), 2.81 (d, 1H, $J = 15.1$, 3-H), 2.71 (dd, 1H, $J = 8.3$, 13.9, β-Phe), 2.67 (d, 1H, $J = 15.1$, 3-H), 2.18 (m, 2H, 2′CH_2), 1.97 (m, 2H, 1′CH_2), 1.38 (s, 9H, CH_3, ^{t}Bu). EM (ES positive mode): 547.2 $(M+Na)^+$. Anal calcd for $C_{29}H_{36}N_2O_7$: C, 66.39; H, 6.92; N, 5.34. Found: C, 66.75; H, 6.40; N, 5.15. Isomer 4*R*,1′*S* 59b: Syrup. Eluent AcOEt:hexano (2:1). HPLC: $t_R = 47.84$ min (A:B = 30:70). $[\alpha]_D = +22.8$ (*c* 1.04, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.32–6.80 (m, 9H, C_6H_5 and C_6H_4), 6.28 (d, 1H, $J = 7.9$, α-NH), 4.71 (m, 1H, α-CH), 4.35 (d, 1H, $J = 15.3$, 1-CH_2), 4.07 (d, 1H, $J = 15.3$, 1-CH_2), 3.76 (s, 3H, OMe), 3.70 (s, 3H, OMe), 3.06 (dd, 1H, $J = 6.0$, 13.9, β-Phe), 2.98 (d, 1H, $J = 14.9$, 3-H), 2.84 (d, 1H, $J = 14.9$, 3-H), 2.81 (dd, 1H, $J = 7.6$, 13.9, β-Phe), 2.01 (m, 4H, 1′CH_2 and 2′CH_2), 1.38 (s, 9H, CH_3, ^{t}Bu). EM (ES positive mode): 547.3 $(M+Na)^+$. Anal calcd for $C_{29}H_{36}N_2O_7$: C, 66.39; H, 6.92; N, 5.34. Found: C, 66.25; H, 6.90; N, 5.55.

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References

1. (a) Fuji, K.; Kawabata, T. *Chem. Eur. J.* **1998**, *4*, 373–376; (b) Kawabata, T.; Fuji, K. *Top. Stereochem.* **2003**, *23*, 175–205.
2. Sauer, S.; Schumacher, A.; Barbosa, F.; Giese, B. *Tetrahedron Lett.* **1998**, *39*, 3685–3688.
3. Giese, B.; Wettstein, P.; Stähelin, C.; Barbosa, F.; Neuburger, M.; Zehnder, M.; Wessig, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 2586–2587.
4. Matsumura, Y.; Shirakawa, Y.; Satoh, Y.; Umino, M.; Tanaka, T.; Maki, T.; Onomura, O. *Org. Lett.* **2000**, *2*, 1689–1691.

5. Wanyoike, G. N.; Onomura, O.; Maki, T.; Matsumura, Y. *Org. Lett.* **2002**, *4*, 1875–1877.
6. Griesbeck, A. G.; Kramer, W.; Lex, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 577–579.
7. Griesbeck, A. G.; Kramer, W.; Lex, J. *Synthesis* **2001**, 1159–1166.
8. Griesbeck, A. G.; Kramer, W.; Bartoschek, A.; Schmickler, H. *Org. Lett.* **2001**, *3*, 537–539.
9. Brewster, A. G.; Frampton, C. S.; Jayatissa, J.; Mitchell, M. B.; Stoodley, R. J.; Vohra, S. *Chem. Commun.* **1998**, 299–300.
10. Betts, M. J.; Pritchard, R. G.; Schofield, A.; Stoodley, R. J.; Vohra, S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1067–1072.
11. Brewster, A. G.; Jayatissa, J.; Mitchell, M. B.; Schofield, A.; Stoodley, R. J. *Tetrahedron Lett.* **2002**, *43*, 3919–3922.
12. Kawabata, T.; Wirth, T.; Yahiro, K.; Suzuki, H.; Fuji, K. *J. Am. Chem. Soc.* **1994**, *116*, 10809–10810.
13. Kawabata, T.; Suzuki, H.; Nagae, Y.; Fuji, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2155–2157.
14. Kawabata, T.; Chen, J.; Suzuki, H.; Nagae, Y.; Kinoshita, T.; Chancharunee, S.; Fuji, K. *Org. Lett.* **2000**, *2*, 3883–3885.
15. Kawabata, T.; Kawakami, S.; Fuji, K. *Tetrahedron Lett.* **2002**, *43*, 1465–1467.
16. Kawabata, T.; Kawakami, S.; Shimada, S.; Fuji, K. *Tetrahedron* **2003**, *59*, 965–974.
17. Kawabata, T.; Yahiro, K.; Fuji, K. *J. Am. Chem. Soc.* **1991**, *113*, 9694–9696.
18. Buckmelter, A. J.; Kim, A. I.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2000**, *122*, 9386–9390.
19. Curran, D. P.; Liu, W.; Chen, C. H.-T. *J. Am. Chem. Soc.* **1999**, *121*, 11012–11013.
20. Gerona-Navarro, G.; Bonache, M. A.; Herranz, R.; García-López, M. T.; González-Muñiz, R. *Synlett* **2000**, 1249–1252.
21. Gerona-Navarro, G.; Bonache, M. A.; Herranz, R.; García-López, M. T.; González-Muñiz, R. *J. Org. Chem.* **2001**, *66*, 3538–3547.
22. Bonache, M. A.; Gerona-Navarro, G.; Martín-Martínez, M; García-López, M. T.; López, P.; Cativiela, C.; González-Muñiz, R. *Synlett* **2003**, 1007–1011.
23. Chiron, S.; Abian, J.; Ferrer, M.; Sánchez-Baeza, F.; Messeguer, A.; Barceló, D. *Environ. Toxicol. Chem.* **1995**, *14*, 1287–1298.
24. Gerona-Navarro, G.; Bonache, M. A.; Reyero, N.; García-López, M. T.; González-Muñiz, R. *Heterocycles* **2002**, *57*, 501–513.
25. Gerona-Navarro, G.; García-López, M. T.; González-Muñiz, R. *J. Org. Chem.* **2002**, *67*, 3953–3956.