Entry to New Conformationally Constrained Amino Acids. First Synthesis of 3-Unsubstituted 4-Alkyl-4-carboxy-2-azetidinone Derivatives via an Intramolecular N^{α}-C^{α}-Cyclization Strategy

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A systematic study on the base-assisted intramolecular alkylation of *N*-benzyl-*N*-chloroacetyl amino acid derivatives is described. This study resulted in the first concise and versatile route to the preparation of 3-unsubstituted 4-alkyl-4-carboxy-2-azetidinones, to be included into the scarce family of β-lactams with quaternary centers at the C_4 position. Particularly noteworthy is that the intramolecular N^{α}-C^{α}-cyclization of Phe and Leu derivatives afforded the corresponding β-lactam derivatives with moderate enantioselectivity (up to 56%). It is suggested that, in these particular cases, the cyclization reaction proceeds by way of planar enolate intermediates, which possess dynamic chirality. The described sequence of reactions, that is compatible with commonly used protecting moieties for the α-carboxy group, cannot be applied to dipeptides, since the cyclization to the six-membered 2,5-diketopiperazine ring occurrs preferentially.

Introduction

The interaction of peptides with macromolecular receptors is fundamental for many biological processes. The successful transfer of information which occurs during these events is highly dependent on the three-dimensional conformation of peptides. Consequently, much efforts have been directed toward the preparation of locally or globally constrained peptide analogues.[1] At the local level this target can be achieved by modification of individual residues via N-, α-, and β-alkylation of natural amino acids and/or different cyclizations.[2] However, due to the difficulty to determine a priori the most appropriate conformational restriction for a given peptide, procedures leading to structurally diversified nonproteinogenic amino acids, from easily available starting materials, could prove to be of great value.

In connection with our current interest in turn mimetics,[3] we were interested in conformationally constrained amino acid derivatives, having the ϕ torsion angle restricted to values near to those found in standard β-turns. The restriction of the ϕ dihedral angle could be achieved through N^{α}-C^{α}-cyclizations,[1] but scarce attention has been paid to this kind of restricted amino acid derivatives, and only some α-alkylprolines have been studied in detail.[2e,4] The small ring of the azetidine **1** (α-alkyl-Aze) or azetidinone **2** (α-alkyl-Azn)[5] should lead to ϕ dihedral angle values of approximately 70 or −70°, depending on the relative configuration of the respective C_2 or C_4 stereogenic center. To the best of our knowledge, only three references in the literature deal with the synthesis of α-substituted azetidine- or azetidinone-α-carboxylic acids, related to **1** and **2**. Thus, Seebach group reported the stereoselective synthesis of compounds **3a** and **3b** (α-Et-Aze), by hydroxyalkylation of enantiopure azetidine-2-carboxylic acid derivatives and N^{α}-C^{γ}-cyclization of chiral amino acids, respectively.[6,7] Compounds **4** and **5**, prepared by asymmetric construction of the quaternary C_4 center via [2 + 2] cycloaddition reaction of ketenes with ketimines,[8] constitute the sole example of 4-alkyl-4-carboxy-substituted β-lactams. In this pioneering approach, Palomo et al.[8] used pyruvate imines

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(5) For easy of naming, the symbol Aze is generally accepted to describe azetidine-2-carboxylic acid. Here we propose the symbol Azn to describe 2-azetidinone-4-carboxylic acids, in a similar way to the incorporation of a final "n" letter in Asn and Gln, that serves to distinguish asparagine and glutamine, with a carboxamide side chain, from Asp and Glu.

(6) Seebach, D.; Vettiger, T.; Müller, H.M.; Plattner, D. A.; Petter, W. *Liebigs Ann. Chem.* **1990**, 687−695.

(7) Seebach, D.; Dziadulewicz, E.; Behrendt, L.; Cantoreggi, S.; Fitzi, R. *Liebigs Ann. Chem.* **1989**, 1215−1232.

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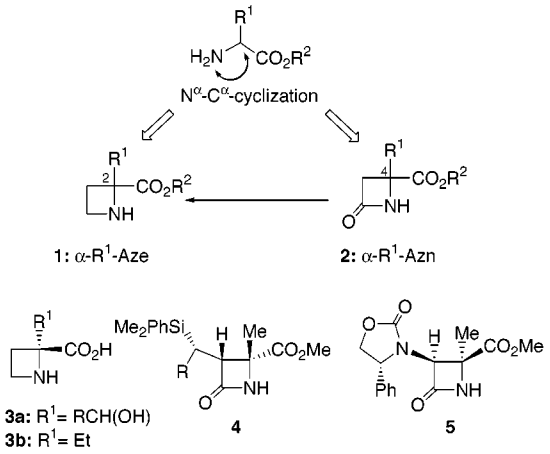
and chiral ketenes, required for the asymmetric induction, to obtain the 3,4,4-trisubstituted 2-azetidinones **4** and **5** with moderate to good diastereoselectivity. However, methods for the synthesis of 3-unsubstituted 4-alkyl-4-carboxy-2-azetidinones **2** could not be found in the literature, and therefore their preparation constitutes a synthetic challenge. Apart from our particular interest in compounds **1** and **2** as conformationally restricted amino acid derivatives, the multiple chemical transformations described for β-lactams[9] suggested that Azn derivatives **2** could also be useful building blocks to create molecular diversity. In close connection with our work, the use of azetidine and azetidinone derivatives as structural units for incorporating conformational restraints into peptides,[10] and as synthetic intermediates in the preparation of secondary structure mimetics,[11] has gained importance in recent years.

To address the possibility of the synthesis of 3-unsubstituted 4,4-disubstituted 2-azetidinones **2**, we recently reported the preparation of new conformationally constrained tryptophan derivatives (**2**, $R^1 = CH_2In$) and their ulterior transformation into the corresponding azetidines **1**.[12] For such purpose, we designed a synthetic strategy involving, as the key step, the formation of the C_3-C_4 bond of the β-lactam ring.[13] This was achieved through base-promoted intramolecular alkylation of the corresponding easily available N^{α}-benzyl-N^{α}-chloroacetyl-substituted Trp derivatives. To evaluate the versatility of this new synthetic strategy, we have next undertook a systematic study on the intramolecular alkylation of different *N*-benzyl-*N*-chloroacetyl-derived amino acids. This paper deals with the scope and limitation of this new synthetic procedure toward 4,4-disubstituted 2-azetidinones, derived from representative aromatic (Phe), aliphatic (Ala, Leu), acidic (Glu), and basic (Orn) amino acids. The preparation of 4-carboxy-2-azetidinones from Gly derivatives, the compatibility of different α-carboxy derivatives (O^{t}Bu, OMe, OBzl, NHR) with the proposed sequence of reactions, and the selective *C*- and *N*-deprotection have also been investigated.

Chart 1. Conformationally Restricted Amino Acids by Cyclization to Azetidine or Azetidinone Rings



Results and Discussion

Although *N*-unsubstituted 2-azetidinones were our final goal, N^{α}-benzyl- or N^{α}-(*p*-methoxy)benzyl-N^{α}-chloroacetyl amino acid derivatives **7**, that would provide 1-substituted 2-azetidinones **8**, were initially selected for two reasons: an *N*-alkyl group should constrain the amide moiety of **7** to a cisoid conformation that might allow the amino acid derivative to cyclize easily,[14,15] and these *N*-benzyl protecting groups can be readily removed from azetidinones.[16] As shown in Scheme 1, the starting derivatives **7** were prepared, in almost quantitative yield, by reaction of the corresponding N^{α}-benzyl- or N^{α}-(*p*-methoxy)benzyl amino acid alkyl ester **6** with chloroacetyl chloride, using propylene oxide as HCl scavenger.

On the basis of the previous result with Trp,[12] NaH and Cs_2CO_3 were chosen as bases to promote the cyclization of the N^{α}-chloroacetyl derivatives **7** to the β-lactams **8**. Independently on the starting amino acid, Cs_2CO_3 worked better than NaH, especially for methyl ester derivatives in which the last base induced a considerable extent of saponification (Table 1).[17] In general, using Cs_2CO_3 longer reaction times were required for the complete disappearance of the starting chloroacetyl derivatives than with NaH. The described sequence of reactions is compatible with most of the protecting moieties commonly used for the α-carboxy group, and similar yields were obtained in the generation of the *tert*-butyl, methyl, and benzyl ester Phe derivatives **8c**, **8d**, and **8e**. Regarding the starting amino acid, Phe-, Ala-, Glu-, and Orn-derived compounds afforded satisfactory yields of the corresponding 2-azetidinones. However, for the Gly and Leu analogues incomplete or complex reactions were found, the yields being higher for methyl ester derivatives

(9) For some selected reviews, see: (a) Ojima, I. In *The Organic Chemistry of β-Lactams*; Georgs, G. I., Ed; VCH: New York, 1992; pp 197−255. (b) Palomo, C.; Aizpurua, J. M.; Gamboa, I. In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1996, pp 279−357.

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(14) For recent examples on the effect of the *N*-substitution in promoting cyclizations, see: (a) Ehrlich, A.; Heyne, H.U.; Winter, R.; Beyermann, M.; Haber, H.; Carpino, L. A.; Bienert, M. *J. Org. Chem.* **1996**, *61*, 8831−8838. (b) El Mahdi, O.; Lavergne, J.P.; Vialefont, P.; Martinez, J.; Riche, C. *Synth. Commun.* **1997**, *27*, 3539−3545. (c) El Mahdi, O.; Lavergne, J.P.; Martinez, J.; Vialefont, P.; Essassi, E. M.; Riche, C. *Eur. J. Org. Chem.* **2000**, 251−255.

(15) In our hands, attempts to cyclize N^{α}-chloroacetyl-L-Phe-O^{t}Bu by using NaH or Cs_2CO_3 either in MeCN or DMF resulted unsuccessful.

(16) Wild, H. In *The Organic Chemistry of β-Lactams*; Georgs, G. I., Ed; VCH: New York, 1992; pp 1−48.

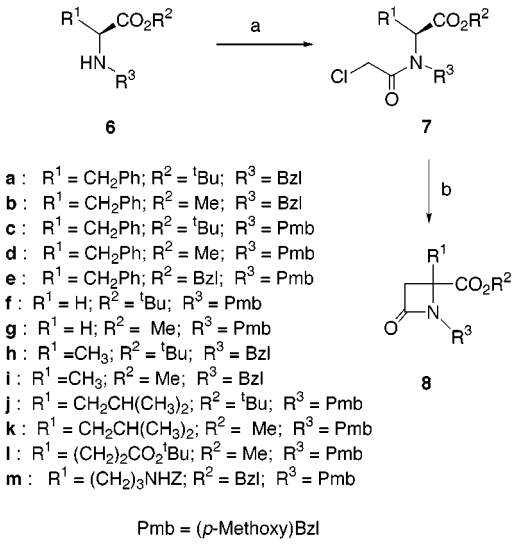
(17) Hydrolysis of the chloroacetyl group in compounds **7** to the starting *N*-benzyl derivatives **6** was observed in reactions performed with NaH, but not with Cs_2CO_3. The extent of this hydrolysis range from 10 to 30%.

Table 1. Synthesis of 1,4,4-Trisubstituted 2-Azetidinones 8 Derived from Different Amino Acids.

start. compd	R^1	R^2	R^3	base	solvent	time (days)	**8**[a] (**9**)[a] (%)
7a	CH_2Ph	tBu	Bzl	NaH	MeCN	1	62
7b	CH_2Ph	Me	Bzl	NaH	MeCN	1	30[b]
7c	CH_2Ph	tBu	Pmb	NaH	MeCN	1	53
7c	CH_2Ph	tBu	Pmb	Cs_2CO_3	MeCN	7	71
7d	CH_2Ph	Me	Pmb	Cs_2CO_3	MeCN	6	74
7d	CH_2Ph	Me	Pmb	Cs_2CO_3	DMF	1	68 (6)
7e	CH_2Ph	Bzl	Pmb	Cs_2CO_3	MeCN	7	75
7e	CH_2Ph	Bzl	Pmb	Cs_2CO_3	DMF	2	68 (7)
7f	H	tBu	Pmb	NaH	MeCN	1	32 (10)[c]
7f	H	tBu	Pmb	Cs_2CO_3	MeCN	10	23 (18)[d]
7g	H	Me	Pmb	Cs_2CO_3	MeCN	10	54 (19)
7h	CH_3	tBu	Bzl	NaH	MeCN	1	60
7i	CH_3	Me	Bzl	NaH	MeCN	1	38[e]
7i	CH_3	Me	Bzl	Cs_2CO_3	MeCN	8	69
7j	$CH_2(CH_3)_2$	tBu	Pmb	NaH	MeCN	10	38 (11)[f]
7j	$CH_2(CH_3)_2$	tBu	Pmb	Cs_2CO_3	MeCN	20	19 (16)[g]
7k	$CH_2(CH_3)_2$	Me	Pmb	Cs_2CO_3	MeCN	15	35 (16)
7l	$(CH_2)_2CO_2{}^tBu$	Me	Pmb	NaH	MeCN	1	11[h]
7l	$(CH_2)_2CO_2{}^tBu$	Me	Pmb	Cs_2CO_3	MeCN	4	65
7m	$(CH_2)_3NHZ$	Bzl	Pmb	Cs_2CO_3	MeCN	1	72

[a] Yield of isolated compounds. [b] Compound **10a** (30%) was also isolated. [c] Unaltered **7f** (6%) was recovered. [d] Unaltered **7f** (41%) was recovered. [e] Compound **10g** (15%) was also isolated. [f] Unaltered **7j** (7%) was recovered. [g] Unaltered **7j** (12%) was recovered. [h] Hydrolysis of the methyl ester was observed (≈24%, estimated by HPLC).

Scheme 1. Synthesis of 4-Alkyl-4-carboxy-2-azetidinones from Amino Acids[a]

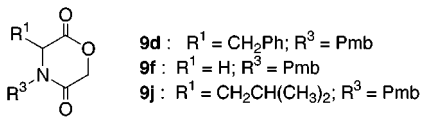


[a] Reagents and conditions: (a) $ClCH_2COCl$/propylene oxide/THF, rt, 1−2 h. (b) Base/solvent (see Table 1)

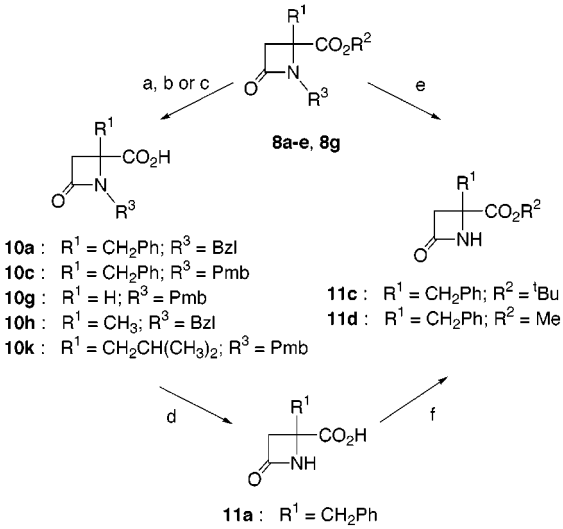
than for *tert*-butyl esters. In both cases, the respective azetidinones were obtained along with the corresponding 2,5-dioxoperhydrooxazines **9f** (10−19%) and **9j** (11−16%), resulting from the intramolecular *O*-alkylation of the corresponding enolate intermediate (Table 1). However, in the case of Phe, Ala, Glu, and Orn derivatives, this *O*-alkylation was not especially significant using MeCN as solvent. The competing oxazine formation become higher when the cyclization was carried out in DMF, as observed in the reaction of the Phe *N*-chloroacetyl derivatives **7d** and **7e** (Compound **9d**, Chart 2, Table 1).

With the 1,4,4-trisubstituted 2-azetidinones **8** in hand, the next question we addressed was the selective removal of *C*- and *N*-protecting groups (Scheme 2). As demonstrated for compounds **8a**−**e**, **8g**, **8h**, and **8k**, the corresponding free carboxylic acid derivatives **10** can be easily obtained by using conventional hydrolysis procedures, such as acid treatment (R^2 = ^{t}Bu) or saponification (R^2 = Me), and hydrogenolysis (R^2 = Bzl). With regard to the *N*-deprotection, H-α-Bzl-Azn-OH (**11a**) was prepared from **10a** in 60% yield by reductive debenzylation using Li in NH_3.[18] In this method, the free carboxylic acid was required in order to avoid carboxamide formation. Removal of the *p*-methoxybenzyl group in **8c** and **8d** was readily achieved by treatment with $K_2S_2O_8$,[19] to give H-α-Bzl-Azn-O^{t}Bu (**11c**) and H-α-Bzl-Azn-OMe (**11d**), keeping the α-carboxy protection.

Chart 2. Products Resulting from Intramolecular *O*-Alkylation



Scheme 2. Selective *C*- and *N*-Deprotection Reactions[a]



[a] Reagents and conditions: (a) TFA/CH_2Cl_2, rt, 2 h. (b) 1. 2 N NaOH/MeOH, rt, overnight. (c) H_2/Pd−C/EtOAc, rt, 7 h. (d) Li/NH_3, −78 °C, 5 min. (e) $K_2S_2O_8$/K_2HPO_4/MeCN−H_2O, 75 °C, 3−5 h. (f) CH_2N_2/Et_2O, 0 °C, 30 min

To evaluate the enantioselectivity, if any, of the intramolecular alkylation reaction, 2-azetidinone-4-carboxylic acids **10a**, **10c**, **10h**, and **10k**, obtained after hydrolysis of the corresponding alkyl esters **8a**, **8c** (**8d**), **8h**, and **8k**, were transformed into the dipeptide derivatives **12** and **13** (Scheme 3, Table 2).[20,21] Since NOE experiments performed with **12** and **13** resulted inconclusive, the tentative assignment of the configuration at C_4 position in these compounds was based on the chemical shifts of the β-H protons of the aliphatic residue,[22,23] and on their respective retention times in the HPLC

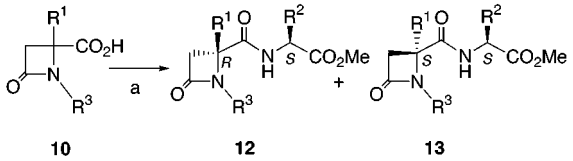
(18) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3783−3786.

(19) Podlech, J.; Linder, M. R. *J. Org. Chem.* **1997**, *62*, 5873−5883.

(20) Optical rotation values of zero for Ala- (**8h**, **8i**), Glu- (**8l**), and Orn-derived (**8m**) azetidinones indicated no enantioselectivity in the cyclization reactions affording these compounds.

(21) To avoid kinetic resolution, the coupling reactions were conducted with large excesses of the amino acid and of the coupling agent (BOP), until complete disappearance of the azetidinone derivative **10** (quantified by HPLC).

Scheme 3. Synthesis of Dipeptide Derivatives[a]



10 **12** **13**

a: $R^1 = CH_2Ph$; $R^2 = CH_3$; R^3 = Bzl
c: $R^1 = CH_2Ph$; $R^2 = CH_3$; R^3 = Pmb
h: $R^1 = CH_3$; $R^2 = CH_2Ph$; R^3 = Bzl
k: $R^1 = CH_2CH(CH_3)_2$; $R^2 = CH_2Ph$; R^3 = Pmb

[a] Reagents and conditions: (a) H-L-Ala-OMe or H-L-Phe-OMe/BOP/TEA/THF, rt

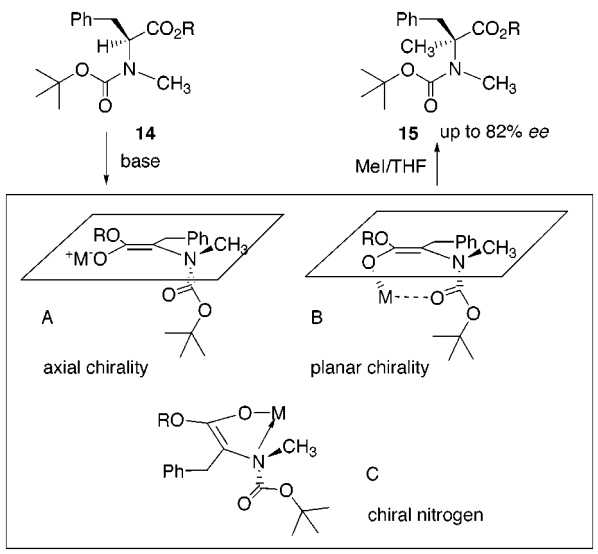
Table 2. Stereoselectivity in the Formation of 1,4,4-Trisubstituted 2-Azetidinones

entry	starting compd	yield (%)[a] **12**+**13**	**12**:**13**[b] ratio	de
1	**10a**[c]	83	67:33	34
2	**10c**[c]	89	67:33	34
3	**10c**[d]	86	78:22	56
4	**10c**[e]	82	78:22	56
5	**10c**[f]	88	65:35	30
6	**10h**[f]	82	50:50	0
7	**10k**[g]	86	71:29	42

[a] Yield of isolated compounds. [b] Measured by HPLC. [c] Obtained from the corresponding ^{t}Bu-substituted azetidinone, previously generated with NaH in MeCN. [d] Obtained from the *tert*-butoxycarbonyl derivative **8c**, previously generated with Cs_2CO_3 in CH_3CN. [e] Obtained from the methoxycarbonyl derivative **8d**, previously generated with Cs_2CO_3 in CH_3CN. [f] Obtained from compound **8d**, previously generated with Cs_2CO_3 in DMF. [g] Obtained from compound **8k**, previously generated with Cs_2CO_3 in CH_3CN.

chromatograms.[24] As shown in Table 2, coupling of Phe-derived compounds **10a** and **10c**, coming from the corresponding *tert*-butoxycarbonyl derivative and NaH-induced cyclization, with enantiomerically pure H-L-Ala-OMe, led to the formation of dipeptides **12a** and **12c**, respectively, in 34% de, independently of the 1-substituent. In the Cs_2CO_3-promoted cyclizations, the ratio of diastereoisomeric dipeptide derivative **12c** was the same when **10c** came from the methyl ester derivative **8d** than when it arose from the *tert*-butyl ester analogue **8c** (Table 2, entries 3 and 4). By contrast, the stereoselectivity was much higher when CH_3CN was used as solvent than in the case of DMF (compare entries 4 and 5). The diastereomeric excess was increased by 22% when the formation of the starting 4-benzyl-2-azetidinone was induced by Cs_2CO_3 (entry 4), compared to NaH (entry 2), showing the importance of the countercation on the observed stereoselectivity. Concerning the effects of the R^1 substituent, Leu-derived dipeptides **12k** and **13k** were obtained in a 71:29 ratio (42% de, entry 7), lower than that found for their corresponding Phe analogues (entry 3). Diastereoisomeric excesses up to 47% were previously found in the formation Trp-derived 2-azetidinones.[12] On the contrary, reaction of **10h** with H-L-Phe-OMe led to the corresponding dipeptides **12h** and **13h** in a ratio of 50:50, indicating that the formation of the precursor Ala-derived azetidinone **8h** proceeded without stereoselection.

Scheme 4. Memory of Chirality: Asymmetric Methylation of (*S*)-Phe Derivatives and Proposed Chiral Intermediates



14 **15** up to 82% *ee*

base MeI/THF

A axial chirality B planar chirality C chiral nitrogen

It has been described that *N*-methyl-*N*-Boc-(*S*)-phenylalanine alkyl esters **14** can be converted into enantiomerically enriched α-methyl derivatives **15** by direct alkylation, without employing any external chiral source (Scheme 4).[25] This enantioselectivity can be ascribed to the preservation of the information on chirality of the starting material in the intermediate anionic species for a limited time.[26] Taking into account that *N*-benzyl-*N*-chloroacetyl amino acid derivatives **7** share certain structural features of **14**, our results imply that the stereochemical course of the intramolecular alkylation of **7a**, **7c**, and **7k**, leading to the 2-azetidinones **8a**, **8c**, and **8k**, is similar to that reported for the asymmetric methylation of **14** to give **15**, according to this recently proposed concept of the *memory of chirality*. The stereoselectivity observed in the case of Phe, Leu, and Trp derivatives could be explained in terms of the existence of chiral enolate intermediates, such as those proposed by Fuji et al. and depicted in Scheme 4.[26] In our case, the implication of enolate B as intermediate in the *β*-lactam formation can be discarded because the intramolecular alkylation of **7** to **8** requires an amide *cis*-rotamer, while the coordination of the metal cation by the carbonyl oxygen in B fixes the amide bond in a transoid conformation, incompatible with the creation of the four-membered ring.

To evaluate the possible preparation of 2-azetidinones from dipeptides, the cyclization of Phe-Ala dipeptide derivative **17** was finally investigated (Scheme 5). Under the general conditions previously used for amino acid

(22) ^{1}H NMR studies on stereoisomeric dipeptides composed by one aromatic amino acid and one aliphatic amino acid, showing that the methyl or methylene protons of the aliphatic residue are more shielded in the D-L and L-D dipeptides than in the L-L and D-D analogues: (a) Deber, C. M.; Joshua, M. *Biopolymers* **1972**, *11*, 2493−2503. (b) García-López, M. T.; González-Muñiz, R.; Molinero, M. T. Del Río, J. *J. Med. Chem.* **1988**, *31*, 295−300. (c) González-Muñiz, R.; Cornille, F.; Bergeron, F.; Ficheux, D.; Pothier, J.; Durieux, C.; Roques, B. P. *Int J. Pept. Protein Res.* **1991**, *37*, 331−340.

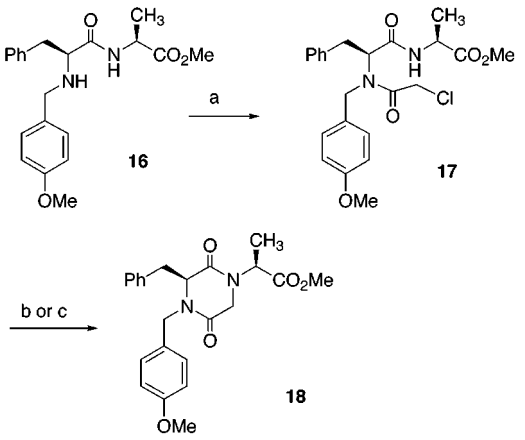
(23) Taking into account that the CH_2CO branch of the *β*-lactam ring has preference over the benzyl, isobutyl, or methyl groups, 4*R*-isomers show the same spatial disposition as in L-amino acids, while 4*S*-isomers correspond to D-configured amino acids.

(24) In dipeptides and retrodipeptides, it was shown that heterochiral (L-D or D-L) derivatives are more retained than homochiral (L-L or D-D) analogues: Fournié-Zaluski, M. C.; Lucas-Soroca, E.; Devin, J.; Roques, B. P. *J. Med. Chem.* **1986**, *29*, 751−757.

(25) Kawabata, T.; Wirth, T.; Yahiro, K.; Suzuki, H.; Fuji, K. *J. Am. Chem. Soc.* **1994**, *116*, 10809−10810.

(26) For a general review on the memory of chirality, see: Fuji, K.; Kawabata, T. *Chem. Eur. J.* **1998**, *4*, 373−376.

Scheme 5. Base-Assisted Cyclization of an *N*-Chloroacetyl Dipeptide Derivative[a]



[a] Reagents and conditions: (a) $ClCH_2COCl$/propylene oxide/THF, rt, 1 h. (b) NaH/MeCN, rt, 20 min. (c) Cs_2CO_3/MeCN, rt, 2 h.

derivatives (Cs_2CO_3, CH_3CN), compound **17** mainly afforded diasteromerically pure 2,5-diketopiperazine **18**,[27] indicating that cyclization to the six-membered ring is much faster than competing ring closure to β-lactams **14c** and **15c** (**14c** + **15c** ≈ 2%, determined by HPLC). In our previous communication on Trp-derived 2-azetidinones, we found that the β-lactam formation did not compete with the cyclization to a seven-membered diazepine ring.[12]

Conclusions

In the present study, we have demonstrated that 3-unsubstituted 4-alkyl-4-carboxy-2-azetidinones can be readily prepared via intramolecular alkylation of *N*-benzyl-*N*-chloroacetyl amino acid derivatives. This approach provides for the first time a wide variety of 4-alkyl-4-carboxy-2-azetidinones, that by themselves, or after transformation into the corresponding azetidines,[12] could be considered as new conformationally constrained amino acids with fixed ϕ dihedral angles. Additional attractive features of this approach include an expanded scope of β-lactam chemistry and the potential use of these 2-azetidinones to create molecular diversity, after appropriate chemical transformations. Of particular interest in this synthesis is the observed enantioselectivity during the β-lactam ring formation in Trp, Phe, and Leu derivatives (up to 56%), constituting novel examples of asymmetry due to the memory of chirality.[14] This selectivity was dependent on the R^1 group, and on the base and solvent used. Although the enantioselectivity was only moderate, it is expected that application of other asymmetric protocols, such as chiral auxyliaries of chiral phase-transfer catalysts, to this convenient procedure could result in more enantioselective ways to this kind of 4,4-disubstituted 2-azetidinones. Work in this direction is ongoing in our laboratories.

Experimental Section

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 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. *N*-Benzyl and *N*-(*p*-methoxy)-benzyl derivatives **6** were obtained by reaction of the corresponding amino acid alkyl ester and benzaldehyde or *p*-methoxybenzaldehyde, followed by reduction with $NaBH_4$.[28]

Synthesis of *N*-Chloroacetyl Amino Acid Derivatives 7. General Procedure. A solution of the corresponding *N*-benzyl or *N*-(*p*-methoxybenzyl) amino acid derivative **6** (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 room temperature 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.

***N*-Benzyl-*N*-chloroacetyl-L-Phe-O^{t}Bu (7a).** Yield: 97%. Eluent: EtOAc/hexane (1:30). HPLC: t_R = 15.36 min (A:B = 50:50). $[\alpha]_D$ = −126.2 (c = 1.11, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): rotamers ratio[29] (7:1) δ major rotamer 7.33−7.13 (m, 10H), 4.49 (d, 1H, J = 16.8), 4.10 (m, 1H), 3.98 (m, 2H), 3.73 (d, 1H, J = 16.8), 3.34 (dd, 1H, J = 14.0, 5.6), 3.24 (dd, 1H, J = 14.0, 9.5), 1.43 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): major rotamer δ 168.53, 166.62 137.95, 135.41, 129.32, 128.59, 128.52, 127.81, 127.33, 126.63, 81.84, 62.54, 52.89, 41.29 34.85, 27.81. MS (ES, positive mode): 388.3 (M^+ + 1). Anal. Calcd for $C_{22}H_{26}ClNO_3$: C, 68.12; H, 6.76; Cl, 9.14; N, 3.61. Found: C, 67.92; H, 6.91; Cl, 9.08; N, 3.47.

***N*-Benzyl-*N*-chloroacetyl-L-Phe-OMe (7b).** 90%. Eluent: gradient from 8 to 30% of EtOAc in hexane. HPLC: t_R = 9.58 min (A:B = 45:55). $[\alpha]_D$ = −126.7 (c = 0.45, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): rotamers ratio (7:1) δ major rotamer 7.35−7.15 (m, 10H), 4.50 (d, 1H, J = 16.7), 4.24 (dd, 1H, J = 9.5, 5.7), 4.01 (m, 2H), 3.80 (d, 1H, J = 16.7), 3.68 (s, 3H), 3.38 (dd, 1H, J = 14.0, 5.7), 3.27 (dd, 1H, J = 14.0, 9.5). ^{13}C NMR (75 MHz, $CDCl_3$): major rotamer δ 170.09, 167.02, 137.68, 135.31, 129.50, 128.91, 128.79, 128.11, 127.41, 126.99, 61.68, 52.76, 52.30, 41.43, 34.85. MS (ES, positive mode): 346.2 (M^+ + 1). Anal. Calcd for $C_{19}H_{20}ClNO_3$: C, 65.99; H, 5.83; Cl, 10.25; N, 4.05. Found: C, 65.88; H, 5.71; Cl, 9.98; N, 3.85.

***N*-(*p*-Methoxybenzyl)-*N*-chloroacetyl-L-Phe-O^{t}Bu (7c).** Yield: 99%. Eluent: EtOAc/hexane (1:3). HPLC: t_R = 13.92 min (A:B = 50:50). $[\alpha]_D$ = −111.6 (c = 1.15, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): rotamers ratio (10:1) δ major rotamer 7.28−6.74 (m, 9H), 4.37 (d, 1H, J = 16.2), 4.01 (m, 1H), 3.98 (m, 2H), 3.73 (s, 3H), 3.59 (d, 1H, J = 16.2), 3.25 (m 2H), 1.40 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): major rotamer δ 168.35, 166.20, 158.98, 137.90, 129.10, 128.69, 128.27, 126.89, 126.37, 113.67, 81.41, 62.06, 54.95, 52.39, 41.15, 34.52, 27.60. MS (ES, positive mode): 440.1 (M^+ + Na). Anal. Calcd for $C_{23}H_{28}ClNO_4$: C, 66.10; H 6.75; Cl, 8.48; N, 3.35. Found: C, 66.01; H, 6.95; Cl, 8.44; N, 3.26.

***N*-(*p*-Methoxybenzyl)-*N*-chloroacetyl-L-Phe-OMe (7d).** Yield: 99%. Eluent: EtOAc/hexane (1:4). HPLC: t_R = 8.43 min

(27) Using NaH as base, compound **18** was obtained as an epimeric mixture at C_3, in an 84:16 3*S*/3*R* ratio. In the ^{1}H NMR spectrum of the epimeric mixture, the 1′-methyl group of minor 3*R*-isomer appeared as a doublet at 0.87 ppm, while in the 3*S*-epimer the chemical shift of these protons was 1.09 ppm.

(28) Weygand, F.; Steglich, W.; Bjarnarsson, J.; Akhtar, R.; Chytill, N. *Chem. Ber.* **1968**, *101*, 3623−3641.

(29) Rotamers ratio was measured by ^{1}H NMR. In general, main differences between major and minor rotamers were found for α-CH, *N*-CH_2, and O^{t}Bu or OMe protons.

(A:B = 45:55). $[\alpha]_D = -131.1$ ($c = 1.11$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): rotamers ratio (9:1) δ major rotamer 7.27−6.75 (m, 9H), 4.36 (d, 1H, $J = 16.3$), 4.12 (m, 1H), 4.00 (m, 2H), 3.71 (s, 3H), 3.66 (d, 1H, $J = 16.3$), 3.61 (s, 3H), 3.29 (m 2H). ^{13}C NMR (75 MHz, $CDCl_3$): major rotamer δ 169.73, 166.44, 158.92, 137.33, 128.98, 128.52, 128.21, 126.48, 126.39, 113.66, 60.99, 55.08, 52.44, 52.08, 41.46, 34.61. MS (ES, positive mode): 398.1 ($M^+ + Na$). Anal. Calcd for $C_{20}H_{22}ClNO_4$: C, 63.91; H, 5.90; Cl, 9.43; N, 3.73. Found: C, 64.05; H, 5.64; Cl, 9.29; N, 3.57.

***N*-(*p*-Methoxybenzyl)-*N*-chloroacetyl-L-Phe-OBzl (7e)**. Yield: 83%. Eluent: gradient from 6 to 15% of EtOAc in hexane. HPLC: $t_R = 12.91$ min (A:B = 50:50). $[\alpha]_D = -124.0$ ($c = 1.12$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): rotamers ratio (10:1) δ major rotamer 7.27−6.56 (m, 14H), 5.01 (m, 2H), 4.31 (d, 1H, $J = 16.4$), 4.04, (m, 1H), 3.92 (m, 2H), 3.65 (s, 3H), 3.50 (d, 1H, $J = 16.4$), 3.27 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): major rotamer δ 169.27, 166.59, 159.16, 137.63, 135.36, 129.28, 128.77, 128.49, 128.32, 128.10, 126.67, 113.88, 67.06, 61.65, 55.06, 52.62, 41.23, 34.63. MS (ES, positive mode): 474.1 ($M^+ + Na$). Anal. Calcd for $C_{26}H_{26}ClNO_4$: C, 69.10; H, 5.80; Cl, 7.84; N, 3.10. Found: C, 68.86; H, 5.90; Cl, 7.73; N, 2.95.

***N*-(*p*-Methoxybenzyl)-*N*-chloroacetyl-Gly-O^{t}Bu (7f)**. Yield: 85%. Eluent: EtOAc/hexane (1:8). HPLC: $t_R = 10.94$ min (A:B = 41:59). ^1H NMR (300 MHz, $CDCl_3$): rotamers ratio (1.4:1) δ major rotamer 7.13−6.78 (m, 4H), 4.55 (m, 2H), 4.14 (m, 2H), 3.85 (m, 2H), 3.74 (s, 3H), 1.39 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): major rotamer δ 167.50, 166.90, 159.22, 128.31, 126.81, 114.15, 81.74, 55.06, 51.64, 49.51, 40.90, 27.76. MS (ES, positive mode): 328.1 ($M^+ + 1$). Anal. Calcd for $C_{16}H_{22}ClNO_4$: C, 58.62; H, 6.76; Cl, 10.82; N, 4.27. Found: C, 58.66; H, 6.54; Cl, 10.74; N, 4.15.

***N*-(*p*-Methoxybenzyl)-*N*-chloroacetyl-Gly-OMe (7g)**. Yield: 99%. Eluent: EtOAc/hexane (1:1). HPLC: $t_R = 6.43$ min (A:B = 30:70). ^1H NMR (300 MHz, $CDCl_3$): rotamers ratio (2.3:1) δ major rotamer 7.06−6.80 (m, 4H), 4.50 (m, 2H), 4.13 (s, 2H), 3.92 (s, 2H), 3.70 (s, 3H), 3.60 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): major rotamer δ 169.02, 167.34, 159.36, 128.40, 126.55, 114.26, 55.15, 52.08, 51.82, 46.64, 40.85. MS (ES, positive mode): 286.2 ($M^+ + 1$). Anal. Calcd for $C_{13}H_{16}ClNO_4$: C, 54.65; H, 5.64; Cl, 12.41; N, 4.90. Found: C, 54.38; H, 5.31; Cl, 12.39; N, 4.85.

***N*-Benzyl-*N*-chloroacetyl-L-Ala-O^{t}Bu (7h)**. Yield: 99%. Eluent: gradient from 3 to 30% of EtOAc in hexane. HPLC: $t_R = 5.60$ min (A:B = 50:50). $[\alpha]_D = -54.2$ ($c = 1.13$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): rotamers ratio (3.5:1) δ major rotamer 7.39−7.20 (m, 5H), 4.71 (d, 1H, $J = 17.6$), 4.54 (d, 1H, $J = 17.6$), 4.47 (m, 1H), 4.08 (m, 2H), 1.44 (s, 9H), 1.34 (d, 1H, $J = 8.7$). ^{13}C NMR (75 MHz, $CDCl_3$): major rotamer δ 170.04, 167.17, 136.37, 128.89, 127.80, 126.33, 81.75, 55.69, 50.64, 41.39, 27.85, 14.40. MS (ES, positive mode): 334.2 ($M^+ + Na$). Anal. Calcd for $C_{16}H_{22}ClNO_3$: C, 61.63; H, 7.11; Cl, 11.37; N, 4.49. Found: C, 61.62; H, 6.95; Cl, 11.09; N, 4.18.

***N*-Benzyl-*N*-chloroacetyl-L-Ala-OMe (7i)**. Yield: 90%. Eluent: gradient from 8 to 15% of EtOAc in hexane. HPLC: $t_R = 9.24$ min (A:B = 30:70). $[\alpha]_D = -49.7$ ($c = 1.28$, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): rotamers ratio (6:1) δ major rotamer 7.41−7.23 (m, 5H), 4.65 (m, 3H), 4.04 (m, 2H), 3.69 (s, 3H), 1.40 (d, 3H, $J = 7.2$). ^{13}C NMR (75 MHz, $CDCl_3$): major rotamer δ 171.51, 167.21, 136.30, 129.02, 127.97, 126.66, 55.08, 52.30, 50.85, 41.82, 14.51. MS (ES, positive mode): 270.2 ($M^+ + 1$). Anal. Calcd for $C_{13}H_{16}ClNO_3$: C, 57.89; H, 5.98; Cl, 13.14; N, 5.19. Found: C, 57.67; H, 5.77; Cl, 12.80; N, 4.85.

***N*-(*p*-Methoxybenzyl)-*N*-chloroacetyl-L-Leu-O^{t}Bu (7j)**. Yield: 73%. Eluent: EtOAc/hexane (1:10). HPLC: $t_R = 8.18$ min (A:B = 41:59). $[\alpha]_D = -59.9$ ($c = 1.59$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): rotamers ratio (2.8:1) δ major rotamer 7.19−6.86 (m, 4H), 4.65 (d, 1H, $J = 17.0$), 4.43 (d, 1H, $J = 17.0$), 4.23 (m, 1H), 3.98 (s, 2H), 3.78 (s, 3H), 1.84 (m, 1H), 1.51 (m, 2H), 1.40 (s, 9H), 0.87 (d, 3H, $J = 6.3$), 0.77 (d, 3H, $J = 6.3$). ^{13}C NMR (75 MHz, $CDCl_3$): major rotamer δ 169.95, 167.29, 159.16, 128.19, 127.93, 114.14, 81.59, 57.79, 55.21, 50.13, 41.68, 38.35, 27.81, 25.19, 22.36, 22.25. MS (ES, positive mode): 384.5 ($M^+ + 1$). Anal. Calcd for $C_{20}H_{30}ClNO_4$: C, 62.57; H, 7.88; Cl, 9.23; N, 3.65. Found: C, 62.68; H, 7.84; Cl, 9.03; N, 3.28.

***N*-(*p*-Methoxybenzyl)-*N*-chloroacetyl-L-Leu-OMe (7k)**. Yield: 100%. Eluent: EtOAc/hexane (1:4). HPLC: $t_R = 12.05$ min (A:B = 40:60). $[\alpha]_D = -55.5$ ($c = 1.09$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): rotamers ratio (3.2:1) δ major rotamer 7.11−6.80 (m, 4H), 4.66 (m, 1H), 4.55 (d, 1H, $J = 17.1$), 4.42 (d, 1H, $J = 17.1$), 3.97 (s, 2H), 3.71 (s, 3H), 3.54 (s, 3H), 1.78 (m, 1H), 1.51 (m, 2H), 0.81 (d, 3H, $J = 6.1$), 0.73 (d, 3H, $J = 6.2$). ^{13}C NMR (75 MHz, $CDCl_3$): major rotamer δ 171.43, 167.53, 159.21, 129.21, 127.99, 114.18, 56.52, 55.23, 52.06, 49.91, 41.77, 38.06, 24.98, 22.51, 22.09. MS (ES, positive mode): 364.3 ($M^+ + Na$). Anal. Calcd for $C_{17}H_{24}ClNO_4$: C, 59.73; H, 7.08; Cl, 10.37; N, 4.10. Found: C, 59.57; H, 7.23; Cl, 9.98; N, 4.00.

***N*-(*p*-Methoxybenzyl)-*N*-chloroacetyl-L-Glu(O^{t}Bu)-OMe (7l)**. Yield: 82%. Eluent: EtOAc/hexane (1:10). HPLC: $t_R = 16.60$ min (A:B = 41:59). $[\alpha]_D = -53.36$ ($c = 1.02$, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): rotamers ratio (3.2:1) δ major rotamer 7.24−6.87 (m, 4H), 4.57 (m, 2H), 4.36 (m, 1H), 4.06 (m, 2H), 3.79 (s, 3H), 3.62 (s, 3H), 2.29−1.85 (m, 4H), 1.40 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): major rotamer δ 171.99, 170.41, 167.17, 159.25, 128.37, 127.29, 114.12, 80.48, 58.20, 55.15, 52.08, 50.97, 41.51, 31.72, 27.92, 24.19. MS (ES, positive mode): 436.2 ($M^+ + Na$). Anal. Calcd for $C_{20}H_{28}ClNO_6$: C, 58.04; H, 6.82; Cl 8.57; N, 3.38. Found: C, 58.00; H, 6.61; Cl, 8.29; N, 3.29.

***N*-(*p*-Methoxybenzyl)-*N*-chloroacetyl-L-Orn(Z)-OBzl (7m)**. Yield: 99%. Eluent: EtOAc/hexane (2:1). HPLC: $t_R = 13.72$ min (A:B = 50:50). $[\alpha]_D = -39.1$ ($c = 1.0$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): rotamers ratio (5:1) δ major rotamer 7.24−6.66 (m, 14H), 5.19 (br s, 1H), 4.97 (m, 4H), 4.51 (d, 1H, $J = 17.0$), 4.33 (d, 1H, $J = 17.0$), 4.20 (m, 1H), 3.94 (m, 2H), 3.66 (s, 3H), 3.00 (m, 2H), 1.97 (m, 1H), 1.71 (m, 1H), 1.42 (m 2H). ^{13}C NMR (75 MHz, $CDCl_3$): major rotamer δ 169.98, 167.25, 159.34, 156.29, 135.24, 129.49, 128.42, 128.26, 127.15, 127.10, 114.16, 67.10, 58.96, 55.18, 51.26, 41.46, 40.39, 30.57, 26.28. MS (ES, positive mode): 553.3 ($M^+ + 1$). Anal. Calcd for $C_{30}H_{33}ClN_2O_6$: C, 65.15; H, 6.01; Cl, 6.41; N, 5.07. Found: C, 64.88; H, 5.98; Cl, 6.44; N, 4.76.

General Procedures for the Synthesis of 2-azetidinone Derivatives 8. Cyclization Promoted by NaH. A solution of the corresponding *N*-benzyl-*N*-chloroacetyl derivative **7** (0.7 mmol) in dry CH_3CN (5 mL) was treated with NaH (36 mg, 1.5 mmol) and stirred at room temperature until disappearance of the starting material (see Table 1). The reaction mixture was acidified to pH 3 and evaporated. The resulting residue was partitioned between EtOAc and H_2O, and the phases were separated. The organic layer was dried over Na_2SO_4 and evaporated, leaving a residue which was purified on a silica gel column, using the solvent system specified in each case.

Cyclization Promoted by Cs_2CO_3. A solution of the corresponding *N*-benzyl-*N*-chloroacetyl derivative **7** (1.6 mmol) in dry CH_3CN or DMF (20 mL) was treated with Cs_2CO_3 (1.04 g, 3.2 mmol) and stirred at room temperature 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 were separated. The workup was continued as above.

1,4-Dibenzyl-4-*tert*-butoxycarbonyl-2-azetidinone (Bzl-α-Bzl-Azn-O^{t}Bu, 8a). Eluent: gradient from 15 to 50% of EtOAc in hexane. HPLC: $t_R = 10.80$ min (A:B = 50:50). ^1H NMR (300 MHz, $CDCl_3$): δ 7.35−7.01 (m, 10H), 4.56 (d, 1H, $J = 15.5$), 4.38 (d, 1H, $J = 15.5$), 3.32 (d, 1H, $J = 14.5$), 3.23 (d, 1H, $J = 14.0$), 2.94 (d, 1H, $J = 14.5$), 2.89 (d, 1H, $J = 14.0$), 1.30 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.53, 166.72, 136.83, 134.90, 129.58, 128.57, 128.42, 128.31, 127.51, 127.11, 82.77, 63.83, 45.65, 44.78, 39.97, 27.63. MS (ES, positive mode): 352.2 ($M^+ + 1$). Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 75.02; H, 7.33; N, 3.76.

1,4-Dibenzyl-4-methoxycarbonyl-2-azetidinone (Bzl-α-Bzl-Azn-OMe, 8b). Eluent: EtOAc/hexane (1:3). HPLC: $t_R = 6.44$ min (A:B = 45:55). ^1H NMR (300 MHz, $CDCl_3$): δ 7.35−

7.01 (m, 10H), 4.51 (d, 1H, J = 15.4), 4.41 (d, 1H, J = 15.4), 3.45 (s, 3H), 3.29 (d, 1H, J = 14.8), 3.28 (d, 1H, J = 14.0), 2.97 (d, 1H, J = 14.0), 2.96 (d, 1H, J = 14.8). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.91, 166.17, 136.03, 134.43, 129,45, 128.46, 128.43, 128.35, 127.47, 127.13, 62.78, 52.08, 45.24, 44.76, 39.35. MS (ES, positive mode): 310.3 ($M^+ + 1$). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.81; H, 6.11; N, 4.54.

4-Benzyl-1-(*p*-methoxybenzyl)-4-*tert*-butoxycarbonyl-2-azetidinone (**Pmb-α-Bzl-Azn-O^{t}Bu**, **8c**). Eluent: gradient from 20 to 30% of EtOAc in hexane. HPLC: t_R = 9.67 min (A:B = 50:50). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.28−6.85 (m, 9H), 4.54 (d, 1H, J = 15.4), 4.29 (d, 1H, J = 15.4), 3.79 (s, 3H), 3.27 (d, 1H, J = 14.6), 3.21 (d, 1H, J = 13.9), 2.91 (d, 1H, J = 14.6), 2.83 (d, 1H, J = 13.9), 1.32 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.56, 166.66, 159.01, 134.94, 129.70, 128.59, 128.86, 128.41, 127.10, 113.92, 82.75, 63.78, 55.23, 45.55, 44.20, 40.01, 27.67. MS (ES, positive mode): 382.2 ($M^+ + 1$). Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.44; H, 7.30; N, 3.88.

4-Benzyl-1-(*p*-methoxybenzyl)-4-methoxycarbonyl-2-azetidinone (**Pmb-α-Bzl-Azn-OMe**, **8d**). Eluent: EtOAc/hexane (1:5). HPLC: t_R = 5.70 min (A:B = 45:55). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25−6.82 (m, 9H), 4.38 (m, 2H), 3.74 (s, 3H), 3.47 (s, 3H), 3.24 (d, 1H, J = 14.0), 3.22 (d, 1H, J = 14.7), 2.92 (d, 1H, J = 14.0), 2.89 (d, 1H, J = 14.7). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.85, 165.85, 158.75, 134.42, 129.61, 129.35, 128.29, 127.98, 126.95, 113.58, 62.52, 54.90, 51.97, 45.03, 44.19, 39.37. MS (ES, positive mode): 340.1 ($M^+ + 1$), 362.2 ($M^+ + Na$). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.54; H, 6.26; N, 4.17.

4-Benzyl-1-(*p*-methoxybenzyl)-4-benzyloxycarbonyl-2-azetidinone (**Pmb-α-Bzl-Azn-OBzl**, **8e**). Eluent: EtOAc/hexane (1:4). HPLC: t_R = 9.21 min (A:B = 50:50). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29−6.75 (m, 14H), 4.88 (s, 2H), 4.38 (d, 1H, J = 15.3), 4.27 (d, 1H, J = 15.3), 3.71 (s, 3H), 3.24 (d, 1H, J = 14.7), 3.19 (d, 1H, J = 14.0), 2.88 (d, 1H, J = 14.7), 2.85 (d, 1H, J = 14.0). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.44, 166.14, 158.97, 134.68, 134.53, 129.81, 129.52, 128.53, 128.50, 128.37, 128.19, 127.15, 113.83, 67.28, 63.01, 55.14, 45.37, 44.29, 39.69. MS (ES, positive mode): 438.1 ($M^+ + Na$). Anal. Calcd for $C_{26}H_{25}NO_4$: C, 75.16; H, 6.06; N, 3.37. Found: C, 74.97; H, 5.89; N, 3.15.

1-(*p*-Methoxybenzyl)-4-*tert*-butoxycarbonyl-2-azetidinone (**Pmb-Azn-O^{t}Bu**, **8f**). Eluent: EtOAc/hexane (1:6). HPLC: t_R = 7.12 min (A:B = 41:59). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.19−6.90 (m, 4H), 4.56 (d, 1H, J = 14.8), 4.09 (d, 1H, J = 14.8), 3.86 (dd, 1H, J = 5.6, 2.4), 3.77 (s, 3H), 3.15 (dd, 1H, J = 14.3, 5.6), 2.86 (dd, 1H, J = 14.3, 2.4), 1.41 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.45, 165.81, 159.14, 129.78, 126.86, 114.07, 82.39, 55.17, 50.45, 44.80, 41.50, 27.83. MS (ES, positive mode): 314.3 ($M^+ + Na$). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.26; N, 4.81. Found: C, 66.01; H, 7.12; N, 5.11.

1-(*p*-Methoxybenzyl)-4-methoxycarbonyl-2-azetidinone (**Pmb-Azn-OMe**, **8g**). Eluent: EtOAc/hexane (1:1). HPLC: t_R = 3.79 min (A:B = 30:70). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.05−6.75 (m, 4H), 4.56 (d, 1H, J = 14.8), 4.01 (d, 1H, J = 14.8), 3.82 (dd, 1H, J = 5.6, 2.6), 3.69 (s, 3H), 3.59 (s, 3H), 3.07 (dd, 1H, J = 14.5, 5.6), 2.90 (dd, 1H, J = 14.5, 2.6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.72, 165.47, 159.12, 129.74, 126.63, 114.00, 55.11, 52.23, 49.54, 44.87, 41.59. MS (ES, positive mode): 250.2 ($M^+ + 1$). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.50; H, 6.11; N, 5.55.

1-Benzyl-4-*tert*-butoxycarbonyl-4-methyl-2-azetidinone (**Bzl-α-Me-Azn-O^{t}Bu**, **8h**). Eluent: gradient from 20 to 50% of EtOAc in hexane. HPLC: t_R = 4.24 min (A:B = 50:50). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (m, 5H), 4.57 (d, 1H, J = 15.3), 4.26 (d, 1H, J = 15.3), 3.21 (d, 1H, J = 14.4), 2.79 (d, 1H, J = 14.4), 1.38 (s, 9H), 1.31 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.04, 166.08, 136.21, 128.55, 128.51, 127.59, 82.29, 59.67, 48.79, 44.61, 27.71, 20.80. MS (ES, positive mode): 276.2 ($M^+ + 1$). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.54; H, 7.55; N, 4.91.

1-Benzyl-4-methoxycarbonyl-4-methyl-2-azetidinone (**Bzl-α-Me-Azn-OMe**, **8i**). Eluent: EtOAc/hexane (1:4). HPLC: t_R = 5.44 min (A:B = 30:70). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (m, 5H), 4.47 (d, 1H, J = 15.2), 4.32 (d, 1H, J = 15.2), 3.54 (s, 3H), 3.24 (d, 1H, J = 14.5), 2.81 (d, 1H, J = 14.5), 1.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.25, 165.60, 135.69, 128.54, 128.46, 127.59, 58.76, 52.23, 48.89, 44.63, 20.49. MS (ES, positive mode): 234.2 ($M^+ + 1$). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.73; H, 6.67; N, 5.81.

1-(*p*-Methoxybenzyl)-4-*tert*-butoxycarbonyl-4-isobutyl-2-azetidinone (**Pmb-α-^{i}Bu-Azn-O^{t}Bu**, **8j**). Eluent: EtOAc/hexane (1:7). HPLC: t_R = 7.04 min (A:B = 55:45). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.14−6.76 (m, 4H), 4.39 (d, 1H, J = 15.5), 4.19 (d, 1H, J = 15.5), 3.71 (s, 3H), 3.33 (d, 1H, J = 14.8), 2.74 (d, 1H, J = 14.8), 1.92 (dd, 1H, J = 13.4, 5.1), 1.48 (m, 1H), 1.31 (s, 9H), 1.19 (dd, 1H, J = 13.4, 8.8), 0.77 (d, 6H, J = 6.7). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.81, 166.91, 158.78, 129.17, 113.72, 82.35, 63.37, 55.10, 46.14, 43.43, 42.91, 27.64, 25.15, 23.79, 22.30. MS (ES, positive mode): 370.4 ($M^+ + Na$). Anal. Calcd for $C_{20}H_{29}NO_4$: C, 69.14; H, 8.41; N, 4.03. Found: C, 68.98; H, 8.20; N, 4.20.

1-(*p*-Methoxybenzyl)-4-methoxycarbonyl-4-isobutyl-2-azetidinone (**Pmb-α-^{i}Bu-Azn-OMe**, **8k**). Eluent: EtOAc/hexane (1:4). HPLC: t_R = 7.81 min (A:B = 40:60). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10−6.73 (m, 4H), 4.26 (m, 2H), 3.68 (s, 3H), 3.43 (s, 3H), 3.34 (d, 1H, J = 14.6), 2.77 (d, 1H, J = 14.6), 1.95 (dd, 1H, J = 13.7, 5.1), 1.46 (m, 1H), 1.25 (dd, 1H, J = 13.7, 8.5), 0.73 (d, 6H, J = 6.6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.25, 166.51, 158.76, 129.31, 128.62, 113.68, 62.38, 55.09, 52.04, 46.15, 43.51, 42.44, 25.03, 23.58, 22.38. MS (ES, positive mode): 306.3 ($M^+ + 1$). Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.91; H, 7.52; N, 4.60.

1-(*p*-Methoxybenzyl)-4-methoxycarbonyl-4-(2-*tert*-butoxycarbonyl)ethyl-2-azetidinone (**8l**). Eluent: EtOAc/hexane (1:4). HPLC: t_R = 8.04 min (A:B = 41:59). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21−6.83 (m, 4H), 4.43 (d, 1H, J = 16.0), 4.29 (d, 1H, J = 16.0), 3.78 (s, 3H), 3.58 (s, 3H), 3.22 (d, 1H, J = 15.0), 2.84 (d, 1H, J = 15.0), 2.15 (m, 2H), 1.98 (m, 2H), 1.39 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.50, 171.28, 165.80, 159.09, 129.96, 127.79, 113.93, 80.79, 61.68, 55.17, 52.46, 45.55, 44.23, 29.88, 28.28, 27.93. MS (ES, positive mode): 400.4 ($M^+ + Na$). Anal. Calcd for $C_{20}H_{27}NO_6$: C, 63.65; H, 7.21; N, 3.71. Found: C, 63.47; H, 6.97; N, 3.63.

1-(*p*-Methoxybenzyl)-4-benzyloxycarbonyl-4-[3-(benzyloxycarbonyl)amino]propyl-2-azetidinone (**8m**). Eluent: EtOAc/hexane (1:1). HPLC: t_R = 6.79 min (A:B = 50:50). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24−6.69 (m, 14H), 4.97 (m, 3H), 4.94 (s, 2H), 4.38 (d, 1H, J = 15.3), 4.06 (d, 1H, J = 15.3), 3.63 (s, 3H), 3.11 (d, 1H, J = 14.6), 2.85 (m, 2H), 1.84 (m, 1H), 1.48 (m, 1H), 1.16 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.08, 165.86, 159.10, 156.16, 136.45, 134.89, 129.82, 128.63, 128.57, 128.43, 128.29, 128.06, 128.01, 113.90, 67.22, 66.52, 62.27, 55.12, 45.56, 44.22, 40.39, 30.57, 24.28. MS (ES, positive mode): 517.0 ($M^+ + 1$). Anal. Calcd for $C_{30}H_{32}N_2O_6$: C, 69.75; H, 6.24; N, 5.42. Found: C, 70.01; H, 6.18; N, 5.33.

3-Benzyl-4-(*p*-methoxybenzyl)-2,5-dioxoperhydrooxazine (**9d**). HPLC: t_R = 3.94 min (A:B = 45:55). $[\alpha]_D = -3.9$ (c = 0.26, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29−6.82 (m, 9H), 5.26 (d, 1H, J = 14.6), 4.27 (m, 1H), 4.22 (d, 1H, J = 16.1), 3.83 (d, 1H, J = 14.6), 3.75 (s, 3H), 3.12 (m, 2H), 3.05 (d, 1H, J = 16.1). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.79, 163.52, 159.76, 134.02, 130.04, 129.74, 129.31, 128.33, 126.36, 114.54, 66.60, 58.25, 55.34, 46.39, 36.90. MS (ES, positive mode): 326.3 ($M^+ + 1$), 348.2 ($M^+ + Na$). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 69.89; H, 5.73; N, 4.22.

4-(*p*-methoxybenzyl)-2,5-dioxoperhydrooxazine (**9f**). HPLC: t_R = 2.75 min (A:B = 30:70). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17−6.86 (m, 4H), 4.78 (s, 2H), 4.52 (s, 2H), 3.97 (s, 2H), 3.78 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.67, 163.09, 159.66, 129.86, 126.19, 114.41, 67.54, 55.26, 48.64, 46.46. MS (ES, positive mode): 236.2 ($M^+ + 1$), 258.2 ($M^+ + Na$). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.15; H, 5.49; N, 5.78.

4-(*p*-Methoxybenzyl)-3-isobutyl-2,5-dioxoperhydrooxazine (9j). HPLC: t_R = 2.46 min (A:B = 55:45). $[\alpha]_D$ = +17.3 (c = 0.88, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.17−6.87 (m, 4H), 5.13 (d, 1H, J = 14.7), 4.86 (d, 1H, J = 16.1), 4.76 (d, 1H, J = 16.1), 3.98 (d, 1H, J = 14.7), 3.97 (m, 1H), 3.80 (s, 3H), 1.73 (m, 2H), 1.53 (m, 1H), 0.93 (d, 6H, J = 6.3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.70, 163.80, 159.93, 130.05, 126,91, 114.73, 67.50, 55.68, 55.56, 47.28, 40.33, 24.74, 23.26, 21.73. MS (ES, positive mode): 314.2 (M^+ + Na). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.26; N, 4.81. Found: C, 65.97; H, 7.20; N, 4.61.

Removal of *C*-terminal alkyl groups from compounds 8. Method A. A solution of the corresponding 4-*tert*-butoxycarbonyl derivative (1.42 mmol) and TFA (1 mL) in CH_2Cl_2 (2 mL) was stirred at room temperature for 2 h, and the solvents were evaporated to dryness. The resulting residue was purified on a silica gel column, as specified.

Method B. A solution of the corresponding 4-methoxycarbonyl derivative (0.24 mmol) in MeOH (3 mL) was treated with 2 N NaOH (0.18 mL, 0.36 mmol), and the mixture was stirred overnight at room temperature. After evaporation of the MeOH the remaining aqueous mixture was diluted with H_2O (5 mL), acidified with 1 N HCl to pH 3, and extracted with EtOAc. The extract was dried (Na_2SO_4) and evaporated. The resulting residue was purified on a silica gel column, as specified.

Method C. A solution of the corresponding 4-benzyloxycarbonyl derivative (0.2 mmol) in EtOAc (17 mL) was hydrogenated at room temperature and 15 psi of pressure for 7 h, using 10% Pd−C as catalyst. After filtration of the catalyst, the solvent was evaporated, and the resulting residue was purified on a silica gel column, as specified.

4-Carboxy-1,4-dibenzyl-2-azetidinone (Bzl-α-Bzl-Azn-OH, 10a). Yield: 91% (from **8a**, method A), 89% (from **8b**, method B). Eluent: CH_2Cl_2/MeOH (50:1). HPLC: t_R = 11.79 min (A:B = 30:70). ^1H NMR (300 MHz, DMSO-d_6): δ 7.32−7.10 (m, 10H), 4.48 (d, 1H, J = 15.8), 4.26 (d, 1H, J = 15.8), 3.20 (d, 1H, J = 13.8), 3.09 (d, 1H, J = 14.4), 3.04 (d, 1H, J = 13.8), 2.93 (d, 1H, J = 14.4). ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.34, 165.99, 137.07, 135.39, 129.86, 128.32, 128.28, 127.99, 127.17, 126.87, 62.66, 44.59, 44.49, 38.46. MS (ES, positive mode): 296.2 (M^+ + 1). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.01; H, 6.13; N, 4.56.

4-Benzyl-1-(*p*-methoxybenzyl)-4-carboxy-2-azetidinone (Pmb-α-Bzl-Azn-OH, 10c). Yield: 85% (from **8c**, method A), 87% (from **8d**, method B), 92% (from **8e**, method C).Eluent: CH_2Cl_2/MeOH (50:1). HPLC: t_R = 6.03 min (A:B = 35:65). ^1H NMR (300 MHz, $CDCl_3$): δ 8.40 (br s, 1H), 7.22−6.76 (m, 9H), 4.51 (d, 1H, J = 15.4), 4.22 (d, 1H, J = 15.4), 3.70 (s, 3H), 3.19 (d, 1H, J = 14.8), 3.15 (d, 1H, J = 14.0), 2.87 (d, 1H, J = 14.8), 2.83 (d, 1H, J = 14.0). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.43, 167.17, 159.11, 134.45, 130.13, 129.67, 128.57, 128.05, 127.27, 113.91, 63.39, 55.21, 45.13, 44.83, 39.52. MS (ES, positive mode): 326.2 (M^+ + 1). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.02; H, 6.09; N, 4.34.

1-(*p*-Methoxybenzyl)-4-carboxy-2-azetidinone (Pmb-Azn-OH, 10g). Yield: 89% (from **8g**, method B). Eluent: CH_2Cl_2/MeOH (50:1). HPLC: t_R = 2.05 min (A:B = 30:70). ^1H NMR (300 MHz, $CDCl_3$): δ 7.10−6.80 (m, 4H), 6.41 (br s, 1H), 4.69 (d, 1H, J = 14.8), 4.02 (d, 1H, J = 14.8), 3.87 (dd, 1H, J = 5.6, 2.2), 3.73 (s, 3H), 3.16 (dd, 1H, J = 14.6, 5.6), 3.00 (dd, 1H, J = 14.6, 2.2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.23, 166.23, 159.32, 129.96, 126.45, 114.23, 55.26, 49.46, 45.07, 41.58. MS (ES, positive mode): 236.2 (M^+ + 1). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.02; H, 5.60; N, 5.85.

1-Benzyl-4-carboxy-4-methyl-2-azetidinone (Bzl-α-Me-Azn-OH, 10h). Yield: 99% (from **8h**, method A). Eluent: CH_2Cl_2/MeOH (50:1). HPLC: t_R = 4.46 min (A:B = 30:70). ^1H NMR (300 MHz, $CDCl_3$): δ 8.15 (br s, 1H), 7.23 (m, 5H), 4.65 (d, 1H, J = 15.1), 4.15 (d, 1H, J = 15.1), 3.21 (d, 1H, J = 14.6), 2.79 (d, 1H, J = 14.6), 1.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.57, 166.82, 135.59, 128.65, 128.61, 127.81, 59.43, 48.67, 45.09, 20.79. MS (ES, positive mode): 220.1 (M^+ + 1), 242.1 (M^+ + Na). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.35; H, 6.21; N, 6.20.

1-(*p*-Methoxybenzyl)-4-carboxy-4-isobutyl-2-azetidinone (Pmb-α-^{i}Bu-Azn-OH, 10k). Yield: 91% (from **8k**, method B). Eluent: CH_2Cl_2/MeOH (50:1). HPLC: t_R = 3.04 min (A:B = 40:60). ^1H NMR (300 MHz, $CDCl_3$): δ 10.08 (br s, 1H), 7.16−6.75 (m, 4H), 4.51 (d, 1H, J = 15.4), 4.18 (d, 1H, J = 15.4), 3.69 (s, 3H), 3.36 (d, 1H, J = 15.0), 2.84 (d, 1H, J = 15.0), 1.90 (dd, 1H, J = 13.7, 4.6), 1.52 (m, 1H), 1.24 (dd, 1H, J = 13.7, 8.9), 0.75 (d, 6H, J = 6.5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.40, 167.89, 158.91, 129.62, 128.41, 113.78, 63.32, 55.14, 45.93, 44.13, 42.63, 25.07, 23.79, 22.31. MS (ES, positive mode): 292.2 (M^+ + 1). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.26; N, 4.81. Found: C, 66.01; H, 7.37; N, 4.69.

Removal of *N*-1 Protecting Groups from Compounds 8. Method A. Compound **10a** (0.36 g, 1.2 mmol) was added to a solution of Li (0.1 g, 14.6 mmol) in liquid NH_3 (21 mL), THF (6 mL), and ^{t}BuOH (0.6 mL), at −78 °C. After 5 min of reaction at −78 °C, the solvents were evaporated, and the resulting residue was dissolved in H_2O and acidified to pH 3. The aqueous layer was extracted with EtOAc, and the organic extract was washed with $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated. The resulting residue was purified on a silica gel column, using CH_2Cl_2/MeOH (30:1) as eluent.

Method B. A solution of the corresponding 1-(*p*-methoxybenzyl)-2-azetidinone (0.98 mmol) in CH_3CN/H_2O (1:1, 30 mL) was treated with K_2HPO_4 (8.4 mmol) and $K_2S_2O_8$ (10.9 mmol), and heated to 75 °C, under Ar atmosphere, for 3−5 h. After evaporation of the CH_3CN, the aqueous layer was extracted with EtOAc, and the organic extract was washed with $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated. The resulting residue was purified on a silica gel column, as specified.

4-Benzyl-4-carboxy-2-azetidinone (H-α-Bzl-Azn-OH, 11a). Yield: 60% (from **10a**, method A). HPLC: t_R = 12.14 min (A:B = 10:90). ^1H NMR (300 MHz, $CDCl_3$): δ 7.53 (br s, 1H), 7.18 (m, 5H), 6.81 (br s, 1H), 3.32 (d, 1H, J = 13.9), 3.07 (d, 1H, J = 14.9), 2.92 (d, 1H, J = 13.9), 2.85 (d, 1H, J = 14.9). ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 174.00, 165.50, 137.00, 130.18, 128.48, 127.10, 59.83, 39.71, 38.51. MS (ES, positive mode): 206.1 (M^+ + 1), 228.1 (M^+ + Na). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.11; H, 5.81; N, 6.65. This compound was also obtained (87%) from **11c**, upon treatment with TFA.

4-Benzyl-4-*tert*-butoxycarbonyl-2-azetidinone (H-α-Bzl-Azn-O^{t}Bu, 11c). Yield: 65% (from **8c**, method B). Eluent: gradient from 10 to 25% of EtOAc in hexane. HPLC: t_R = 2.79 min (A:B = 50:50). ^1H NMR (300 MHz, $CDCl_3$): δ 7.32−6.80 (m, 5H), 6.35 (br s, 1H), 3.34 (d, 1H, J = 13.7), 3.05 (dd, 1H, J = 14.9, 2.6), 2.91 (d, 1H, J = 13.7), 2.89 (d, 1H, J = 14.9), 1.33 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.83, 166.18, 135.18, 129.44, 128.50, 127.29, 82.73, 59.13, 47.65, 42.34, 27.74. MS (ES, positive mode): 262.1 (M^+ + 1), 284.2 (M^+ + Na). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.75; H, 7.08; N, 5.24.

4-Benzyl-4-methoxycarbonyl-2-azetidinone (H-α-Bzl-Azn-OMe, 11d). Yield: 67% (from **8d**, method B). Eluent: gradient from 25 to 50% of EtOAc in hexane. HPLC: t_R = 2.20 min (A:B = 40:60). ^1H NMR (300 MHz, $CDCl_3$): δ 7.27−7.05 (m, 5H), 6.28 (br s, 1H), 3.66 (s, 3H), 3.38 (d, 1H, J = 13.7), 3.12 (dd, 1H, J = 14.9, 2.5), 2.95 (dd, 1H, J = 14.9, 0.8), 2.94 (d, 1H, J = 13.7). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.24, 165.58, 134.91, 129.32, 128.71, 127.47, 58.93, 52.64, 47.72, 42.45. MS (ES, positive mode): 220.1 (M^+ + 1). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.82; H, 6.10; N, 6.10. This compound was also obtained by treatment of compound **11a** with diazomethane.

Synthesis of dipeptide derivatives. General Procedure. A solution of the corresponding 4-carboxy derivative 10 (0.33 mmol) and H-L-Ala-OMe or H-L-Phe-OMe (0.66 mmol) in dry THF (4 mL) was successively treated with BOP (0.29 g, 0.66 mmol) and TEA (0.18 mL, 1.32 mmol) at room temperature. The stirring was continued until complete disappearance of the starting material 10 (1−2 days). The isomers ratio was determined by HPLC on the crude reaction mixtures. To characterize the obtained dipeptide derivatives, the solvent

was evaporated, and 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 which was purified on a silica gel column as specified in each case.

Bzl-α-Bzl-Azn-L-Ala-OMe (**12a** and **13a**). Yield: 83% (from **10a**, and H-L-Ala-OMe), **12a**:**13a** = 67:33. Eluent: EtOAc/hexane (1:4). Isomer (*R*,*S*) **12a**: HPLC: t_R = 19.11 min (A:B = 30:70). $[\alpha]_D = -32.9$ (c = 0.67, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34−7.15 (m, 10H), 5.78 (d, 1H, J = 7.0), 4.68 (d, 1H, J = 15.3), 4.28 (m, 1H), 4.11 (d, 1H, J = 15.3), 3.70 (s, 3H), 3.39 (d, 1H, J = 14.3), 3.22 (d, 1H, J = 14.3), 3.03 (m, 2H), 0.93 (d, 3H, J = 7.2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.40, 171.07, 166.68, 136.73, 135.24, 130.06, 129.32, 129.11, 128.81, 128.21, 127.48, 64.72, 52.45, 48.09, 47.84, 45.39, 39.77, 16.95. MS (ES, positive mode): 381.4 (M^+ + 1), 403.3 (M^+ + Na). Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.29; H, 6.19; N, 7.17. Isomer (*S*,*S*) **13a**: HPLC: t_R = 20.66 min (A:B = 30:70). $[\alpha]_D = +46.7$ (c = 0.38, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36−7.16 (m, 10H), 5.86 (d, 1H, J = 7.2), 4.79 (d, 1H, J = 15.2), 4.25 (m, 1H), 3.92 (d, 1H, J = 15.2), 3.65 (s, 3H), 3.56 (d, 1H, J = 14.5), 3.27 (d, 1H, J = 14.5), 3.10 (d, 1H, J = 14.8), 2.99 (d, 1H, J = 14.8), 0.81 (d, 3H, J = 7.2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.39, 171.17, 167.10, 136.89, 135.50, 130.10, 129.35, 129.20, 128.92, 128.32, 127.54, 64.66, 52.45, 48.42, 47.90, 45.20, 38.66, 16.98. MS (ES, positive mode): 381.4 (M^+ + 1). Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.35; H; 6.41; N, 7.16.

Pmb-α-Bzl-Azn-L-Ala-OMe (**12c** and **13c**).Yield: 89% (from **10c**, and H-L-Ala-OMe), **12c**:**13c** = 67:33 or 65:35, see Table 2. Eluent: gradient from 6 to 12% of EtOAc in hexane. Isomer (*R*,*S*) **12c**: HPLC: t_R = 9.58 min (A:B = 35:65). $[\alpha]_D = -20.6$ (c = 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33−6.80 (m, 9H,), 5.87 (d, 1H, J = 6.9), 4.62 (d, 1H, J = 15.3), 4.29 (m, 1H), 4.04 (d, 1H, J = 15.3), 3.76 (s, 3H), 3.61 (s, 3H), 3.37 (d, 1H, J = 14.4), 3.21 (d, 1H, J = 14.4), 3.00 (m, 2H), 0.97 (d, 3H, J = 7.3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.30, 171.12, 166.52, 159.46, 135.19, 130.42, 129.99, 129.62, 128.72, 128.56, 127.38, 114.32, 64.36, 55.28, 52.35, 48.25, 48.16, 44.91, 39.87, 17.15. MS (ES, positive mode): 433.1 (M^+ + 1). Anal. Calcd for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.38; N, 6.82. Found: C, 67.50; H, 6.06; N, 6.85. Isomer (*S*,*S*) **13c**: HPLC: t_R = 10.28 min (A:B = 35:65). $[\alpha]_D = +30.5$ (c = 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33−6.80 (m, 9H), 5.93 (d, 1H, J = 7.3), 4.71 (d, 1H, J = 15.1), 4.29 (m, 1H), 3.88 (d, 1H, J = 15.1), 3.76 (s, 3H), 3.70 (s, 3H), 3.53 (d, 1H, J = 14.5), 3.24 (d, 1H, J = 14.5), 3.07 (d, 1H, J = 15.0), 2.97 (d, 1H, J = 15.0), 0.88 (d, 3H, J = 7.2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.30, 171.12, 166.92, 159.51, 135.41, 130.42, 130.17, 129.72, 128.78, 128.44, 127.38, 114.51, 64.52, 55.27, 52.35, 48.59, 48.10, 44.69, 38.88, 17.15. MS (ES, positive mode): 433.1 (M^+ + 1). Anal. Calcd for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.38; N, 6.82. Found: C, 67.24; H, 6.16; N, 6.57.

Bzl-α-Me-Azn-L-Phe-OMe (**12h** and **13h**). Yield: 82% (from **10h**, and H-L-Phe-OMe), **12h**:**13h** = 50:50. Eluent: gradient from 50 to 65% of EtOAc in hexane. Isomer (*R*,*S*) **12h**: HPLC: t_R = 19.12 min (A:B = 30:70). $[\alpha]_D = -18.1$ (c = 0.84, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33−6.98 (m, 10H), 6.13 (d, 1H, J = 8.0), 4.69 (m, 1H), 4.36 (d, 1H, J = 15.1), 4.29 (d, 1H, J = 15.1), 3.71 (s, 3H), 3.09 (dd, 1H, J = 13.9, 5.4), 2.77 (m, 2H), 2.73 (dd, 1H, J = 13.9, 7.9), 1.38 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.42, 171.14, 166.32, 136.20, 135.80, 128.68, 128.45, 128.40, 128.21, 127.56, 126.75, 59.80, 52.72, 52.03, 49.84, 44.52, 36.89, 19.70. MS (ES, positive mode): 381.2 (M^+ + 1). Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.31; H, 6.15; N, 7.22. Isomer (*S*,*S*) **13h**: HPLC: t_R = 20.50 min (A:B = 30:70). $[\alpha]_D = +75.7$ (c = 0.68, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34−7.03 (m, 10H), 6.26 (d, 1H, J = 7.8), 4.69 (m, 1H), 4.35 (d, 1H, J = 15.3), 4.02 (d, 1H, J = 15.3), 3.69 (s, 3H), 3.15 (d, 1H, J = 14.8), 3.01 (dd, 1H, J = 14.0, 6.2), 2.83 (d, 1H, J = 14.8), 2.78 (dd, 1H, J = 14.0, 7.3), 1.35 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.47, 171.44, 166.80, 136.19, 135.82, 129.03, 128.97, 128.70, 128.63, 128.01, 127.30, 60.23, 53.17, 52.39, 50.26, 44.80, 37.37, 19.92. MS (ES, positive mode): 381.2 (M^+ + 1). Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.40; H, 6.27; N, 7.09.

Bzl-α-^{i}Bu-Azn-L-Phe-OMe (**12k** and **13k**). Yield: 86% (from **10k**, and H-L-Phe-OMe), **12k**:**13k** = 71:29. EtOAc/hexane (1:3). Isomer (*R*,*S*) **12k**: HPLC: t_R = 65.55 min (A:B = 25:75). $[\alpha]_D = -3.5$ (c = 1.03, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23−6.76 (m, 9H), 5.91 (d, 1H, J = 7.9), 4.59 (m, 1H), 4.31 (d, 1H, J = 15.4), 4.12 (d, 1H, J = 15.4), 3.71 (s, 3H), 3.63 (s, 3H), 2.96 (dd, 1H, J = 13.9, 5.5), 2.82 (d, 1H, J = 14.9), 2.69 (d, 1H, J = 14.9), 2.60 (dd, 1H, J = 13.9, 8.2), 1.85 (dd, 1H, J = 14.0, 4.4), 1.51 (m, 1H), 1.47 (dd, 1H, J = 14.0, 8.0), 0.78 (d, 3H, J = 6.2), 0.73 (d, 3H, J = 6.6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.38, 171.08, 167.01, 159.32, 135.63, 130.05, 128.92, 128.66, 128.51, 127.24, 114.23, 63.95, 55.27, 52.99, 52.36, 47.26, 44.19, 41.69, 37.34, 24.57, 24.49, 22.75. MS (ES, positive mode): 453.3 (M^+ + 1). Anal. Calcd for $C_{26}H_{32}N_2O_5$: C, 69.01; H, 7.13; N, 6.19. Found: C, 68.88; H, 6.15; N, 5.95. Isomer (*S*,*S*) **13k**: HPLC: t_R = 65.55 min (A:B = 25:75). $[\alpha]_D = +27.3$ (c = 0.21, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22−6.75 (m, 9H), 5.91 (d, 1H, J = 7.0), 4.66 (m, 1H), 4.60 (m, 2H), 3.71 (s, 3H), 3.64 (s, 3H), 3.06 (d, 1H, J = 14.8), 2.95 (dd, 1H, J = 14.0, 6.2), 2.85 (d, 1H, J = 14.8), 2.76 (dd, 1H, J = 14.0, 6.8), 1.78 (dd, 1H, J = 13.8, 4.4), 1.46 (m, 1H), 1.34 (dd, 1H, J = 14.0, 6.8), 0.72 (d, 3H, J = 6.8), 0.70 (d, 3H, J = 7.3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.47, 170.56, 166.96, 159.20, 135.54, 129.75, 129.00, 128.68, 128.63, 127.29, 114.20, 63.84, 55.28, 52.97, 52.45, 46.86, 43.90, 42.32, 37.44, 24.73, 24.34, 22.69. MS (ES, positive mode): 453.3 (M^+ + 1). Anal. Calcd for $C_{26}H_{32}N_2O_5$: C, 69.01; H, 7.13; N, 6.19. Found: C, 68.97; H, 6.03; N, 5.90.

Pmb-L-Phe-L-Ala-OMe (**16**). A solution of H-L-Phe-L-Ala-OMe.CF_3CO_2H (0.93 g, 2.55 mmol) in MeOH (4 mL) was treated with TEA (0.35 mL, 2.55 mmol) and *p*-methoxybenzaldehyde (0.46 mL, 3.83 mmol). After stirring at room temperature for 1.5 h, the solution was cooled to 0 °C and treated with $NaBH_4$ (0.19 g, 5.1 mmol). The reaction was allowed to warm to room temperature and stirred for 1 h. The MeOH was evaporated and the residue extracted with EtOAc and washed with H_2O. The organic layer was dried (Na_2SO_4) and evaporated, leaving a residue (0.52 g, 56%) which was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, 1H, J = 8.1), 7.32−6.94 (m, 9H), 4.59 (m, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 3.64 (d, 1H, J = 12.7), 3.40 (d, 1H, J = 12.7), 3.31 (dd, 1H, J = 9.7, 3.9), 3.12 (dd, 1H, J = 13.9, 3.9), 2.63 (dd, 1H, J = 13.9, 9.7), 1.67 (br s, 1H), 1.33 (d, 3H, J = 7.2. MS (ES, positive mode): 271.2 (M^+ + 1).

Pmb-*N*-chloroacetyl-L-Phe-L-Ala-OMe (**17**). A solution of compound **16** (0.51 g, 1.37 mmol) in THF (10 mL) was treated with propylene oxide (1.45 mL, 20.6 mmol) and chloroacetyl chloride (0.13 mL, 1.65 mmol). After stirring at room temperature for 1 h, the solvents were evaporated, and the resulting residue was purified on a silica gel column, using EtOAc/hexane (1:3), yielding 0.5 g (76%) of the title compound. HPLC: t_R = 25.54 min (A:B = 35:65). $[\alpha]_D = +8.05$ (c = 0.97, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): rotamers ratio (9:1) δ major rotamer 7.35−6.80 (m, 9H), 6.72 (d, 1H, J = 7.1), 4.84 (m, 1H), 4.60 (d, 1H, J = 16.0), 4.45 (m, 1H), 4.22 (d, 1H, J = 16.0), 3.99 (m, 2H), 3.79 (s, 3H), 3.71 (s, 3H), 3.24 (m 2H), 1.34 (d, 3H, J = 7.2). ^{13}C NMR (75 MHz, $CDCl_3$): major rotamer δ 172.77, 166.77, 163.53, 159.73, 136.92, 134.00, 130.01, 129.72, 129.28, 128.30, 114.52, 58.24, 55.28, 53.26, 52.37, 46.36, 41.71, 36.86, 16.02. MS (ES, positive mode): 447.1 (M^+ + 1), 469.1 (M^+ + Na). Anal. Calcd for $C_{23}H_{27}ClN_2O_5$: C, 61.81; H, 6.09; Cl, 7.93; N, 6.27. Found: C, 62.05; H, 5.93; Cl, 7.77; N, 6.12.

(3*S*,1′*S*)-3-Benzyl-4-(*p*-methoxybenzyl)-1-(1′methoxycarbonyl)ethyl-2,5-dioxopiperazine (**18**). A solution of compound **17** (0.195 g, 0.44 mmol) in CH_3CN (4 mL) was treated with NaH (21 mg, 0.88 mmol) or Cs_2CO_3 (0.28 g, 0.88 mmol) and stirred at room temperature for 20 min and 2 h, respectively. Then, each reaction was acidified to pH 6, the CH_3CN was evaporated and the aqueous solution was extracted with EtOAc. The organic layer was dried (Na_2SO_4) and evaporated, leaving a resulting residue was purified on a silica gel column, using EtOAc/hexane (1:4), to give 118 mg (66%) and 120 mg (67%, 84:16 3*S*,1′*S*/3*R*,1′*S* epimeric mixture),

respectively, of the title compound. HPLC: $t_R = 12.98$ min (A:B = 35:65). $[\alpha]_D = -31.6$ ($c = 1.09$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.27−6.83 (m, 9H), 5.33 (d, 1H, $J = 14.6$), 5.14 (q, 1H, $J = 7.5$), 4.17 (m, 1H), 3.94 (d, 1H, $J = 14.6$), 3.75 (s, 3H), 3.63 (s, 3H,), 3.42 (d, 1H, $J = 16.7$), 3.10 (m, 2H), 2.42 (d, 1H, $J = 16.7$), 1.09 (d, 3H, $J = 7.5$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.73, 165.64, 164.19, 159.34, 134.64, 129.99, 129.77, 129.65, 128.69, 127.78, 114.36, 59.72, 55.14, 52.35, 50.37, 46.36, 45.48, 36.68, 13.33. MS (ES, positive mode): 411.1 ($M^+ + 1$), 433.2 ($M^+ + Na$). Anal. Calcd for $C_{23}H_{26}N_2O_5$: C, 67.30;H, 6.38; N, 6.82 Found: C, 67.18; H, 6.44; N, 6.65.

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