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Quaternary α,α-2-Oxoazepane α-Amino Acids: Synthesis from Ornithine-Derived β-Lactams and Incorporation into Model Dipeptides

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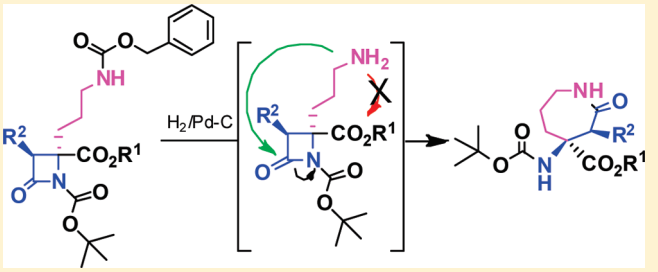
Supporting Information

ABSTRACT: To explore further the chemistry of amino acid-derived β-lactams, their conversion to α,α-heterocyclic quaternary amino acid derivatives is investigated. The latter derivatives, containing 2-oxoazepane as the α,α-substituent, are synthesized by a simple Pd−C-catalyzed hydrogenolysis of Orn(Z)-derived 2-azetidinones. The rearrangement from four- to seven-membered lactam ring is driven by the key intramolecular opening of the 1-Boc-β-lactam, initiated by 7-exotrig ring closure from the NH_2 of the Orn side chain. The synthetic route is applied to the stereoselective preparation of enantiomerically pure 4-amino-3-methyl-2-oxoazepane-4-carboxylate derivatives, for which the structure and configuration is confirmed by X-ray diffraction. Molecular modeling and NMR experiments indicate that these quaternary amino acids are able to drive the adoption of β-turn secondary structures when incorporated in model dipeptide derivatives.



INTRODUCTION

The design of peptides and proteins with defined conformations and specific properties often relies on the incorporation of non-natural amino acid derivatives.[1] Among them, α,α-disubstituted (quaternary) α-amino acids have received considerable attention because they have been shown to affect the conformation, biological activity, and stability of peptides.[2] Because they are a subject of interest in biological chemistry as peptide α-helix-inducing elements, quaternary amino acids have attracted great attention in the medicinal chemistry field. In fact, these types of amino acids can be recognized within the structure of biologically active natural products, such as antibiotics,[3] enzyme inhibitors,[4] ion-channel blockers,[5] and agonists or antagonists of different receptors.[6]

Due to this interest, the preparation of optically pure α, α-disubstituted amino acids constitutes a challenge,[7] which, up to date, relies either on the optical resolution of racemic forms[8] or on asymmetric transformations. These transformations are mainly based on the alkylation of enolates from bislactim, oxazinones, and imidazolidinones,[9] and more recently on catalytic processes,[10] among other procedures.[11]

Within quaternary amino acids, special attention has been paid to cyclic derivatives because they provide greater conformational restriction compared with their linear analogues.[12] In the case of carbocycles, the preference for stabilizing β-turn, 3_{10}- and α-helical conformations is highly dependent on the ring size.[13] However, the synthesis and conformational studies of α, α-heterocyclic α-amino acids are much scarcer. Some α,α-pyrrolidine amino acids have been stereoselectively prepared as glutamate receptor ligands,[14] while dithiolane and tetrahydrofuran analogues have been found to induce β-turn conformations when incorporated into small peptides.[15] With regard to six-membered ring derivatives, 3,3- and 4,4-disubstituted piperidine, pyrane, and thiopyrane amino acid derivatives have been used as synthetic intermediates for bioactive compounds[16] and as inducers of different peptide secondary structures.[17] Among them, the 2,2,6,6-tetramethylpiperidine-1-oxyl-4-amino-4-carboxylic acid has been shown to be an effective β-turn and 3_{10}/α-helix inducer in peptides and an excellent rigid EPR probe due to the nitroxide spin-labeling moiety.[18] The examples of quaternary amino acids bearing seven-membered or larger heterocycles are still rarer. Thus, only a few 3-amino-2-oxoazepane-3-carboxylate derivatives, patented as caspase inhibitors and brain function improvers,[19] and some 4,4-disubstituted azepanes as antimicrobial agents are found in the literature.[20] In addition, the stereoselective synthesis of related 6-amino-3-azabicyclo[3.2.1]-octane-6-carboxylic acid has recently been reported.[21]

Following our interest in the chemistry of amino acid-derived β-lactams,[22] in a previous paper, we studied the controlled opening,

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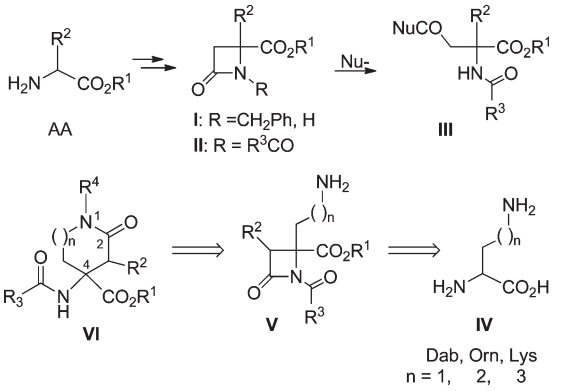

Figure 1. Intermolecular nucleophile opening of β-lactams and retrosynthetic analysis of the intramolecular conversion to heterocyclic quaternary amino acids.

by O- and N-nucleophiles, of the N1−C2 bond of 1-carbamate-substituted 2-azetidinones **II** to provide access to orthogonally protected α-alkyl aspartic acid and asparagines derivatives **III** (Figure 1).[23] Considering the importance of quaternary amino acids, we now focus our attention on exploring the intramolecular version of this opening as a potential approach to α,α-azaheterocyclic disubstituted α-amino acids **VI** (2-oxopiperidine, n = 1; 2-oxoazepane, n = 2; 2-oxoazocane, n = 3), with the basic amino acid-derived β-lactams **V** as the key intermediates (Figure 1).

Quaternary amino acids represented by **VI** possess many sites of reactivity and hence opportunities for further chemical modifications, a feature that enhances their potential usefulness in the study of peptide conformations. Thus, they could allow the incorporation of different substituents at positions 1 (R^4) and 3 (R^2) of the ring, which could facilitate additional transformations within peptides (click chemistry,[24] stapled methodologies,[25] etc.), participate in molecular recognition processes, or serve to modulate solubility. In addition, α,α-heterocyclic amino acids **VI** contain a carbonyl group in the heterocyclic ring, which could further contribute to stabilizing peptide secondary structures. All these aspects prompted us to explore the synthesis of quaternary heterocyclic amino acid derivatives **VI** as described in this paper. The incorporation of one example of **VI** (n = 2) into model dipeptides and the evaluation of their ability to induce turn-like secondary structures are also reported.

RESULTS AND DISCUSSION

Exploratory Chemistry to Heterocyclic Quaternary Amino Acids from β-Lactams. To investigate the scope and limitations of the intramolecular opening of β-lactams, we first attempted to prepare racemic 2-azetidinones derived from the basic amino acids Dab, Orn, and Lys. Following our described method,[22] the first step was the reductive amination of the conveniently protected amino acid derivatives. Thus, starting from H-Dab-(Z)-OMe, H-Orn(Z)-OMe, H-Orn(Z)-O^{t}Bu, H-Lys(Z)-OMe, and H-Lys(Z)-O^{t}Bu, the reaction with *p*-methoxy- or *o*,*p*-dimethoxybenzaldehyde, followed by reduction of the corresponding imine intermediates with $NaBH_4$, afforded the expected *N*-benzyl derivatives **1**−**5** in high yield (Scheme 1). Next, treatment of the latter compounds with chloroacetyl chloride, in the presence of propylene oxide as acid scavenger, gave compounds **6**−**10** almost in a quantitative manner.

As expected, the cyclization under basic media of Dab-, Orn-, and Lys-derived chloroacteyl compounds **6**−**10** proceeded with formation of the 2-azetidinone ring in all cases. However, while for Orn and Lys derivatives **12**−**15** the protected side chain remained unaltered, in the case of the Dab analogue **6** the 1,6-diazaspiro[3.4]octane-2,5-dione **11** was the only isolated product. This spiro derivative should result from the concomitant formation of β-lactam and pyrrolidinone rings, this latter due to a 5-exotrig ring closure between the ZNH group and the carboxylic ester,[26] followed by Z-protecting group removal.

Oxidation of the 2-azetidinones **12**−**15** with $K_2S_2O_8$/K_2HPO_4 in CH_3CN/H_2O at 75 °C under bubbled Ar[27] yielded the expected 1-unsubstituted analogues **16**−**19** in moderate yield (30−60%). No big differences were found in the oxidation of the 1-Pmb Orn derivative **12** and its Dmb analogue **13**; therefore the Pmb group was selected, due to better yields in the cyclization to the β-lactam derivatives. Unfortunately, attempts to cause benzyl group removal by oxidation with CAN or by acidic hydrolysis with TFA were unsuccessful, resulting in overoxidation[27a] and β-lactam-ring-opening, respectively. As previously described for related 2-azetidinones,[23] the next step was the acylation with di-*tert*-butyldicarbonate at the β-lactam 1-position, to provide derivatives **20**−**23**, which could facilitate the controlled opening of the 2-azetidinone ring through the N1−C2 bond. Finally, the catalytic hydrogenation of Orn-derived *N*-Boc-substituted β-lactams, in the presence of Pd−C as catalyst, led to the anticipated 2-oxoazepanes Boc-Oaz-OMe (**24**) and Boc-Oaz-O^{t}Bu (**25**) (81 and 83% yield, respectively). The Pd−C catalyzed hydrogenolysis process allowed the removal of the Z-protecting group, and then, in the reaction media, the intramolecular nucleophilic attack of the free NH_2 to the carbonyl of the azetidinone ring resulted in the 7-exotrig closure to the 2-oxoazepane derivatives. Although a 6-exotrig cyclization to a pyrrolidinone spirolactam system might be expected (analogous to the 5-exotrig cyclization that gave rise to the five-membered spirolactam in the Dab-derived **11**), no traces of spirocyclic compound were observed in the crude reaction mixtures, which could have been detected either by MS spectrometry (MW of the spirolactam would be 254.28) or by ^{1}H NMR through the disappearance of the signals corresponding to methyl and *tert*-butyl esters. Similar attempts to obtain the corresponding eight-membered 2-oxoazocane derivatives from Lys-derived 1-Boc-azetidinones **22** and **23** (n = 3) resulted in very complex mixtures of quite insoluble products, probably polymeric. Also, no traces of the possible spirocyclic azepinone byproduct (analogous to spirocyclic compounds **11**) were detected in the crude reaction mixtures, which could have originated from a 7-exotrig ring closure between the liberated amino group and the ester carbon. Such spirolactam could easily have been detected by MS.

In spite of the marked difference in the course of reaction with Lys-derived **22** and **23** (n = 3), as compared with the Orn-derived **20** and **21** (n = 2), the β-lactam in both instances (n = 3 or n = 2) is activated for cleavage, either thermodynamically by the release of the β-lactam ring strain or kinetically by the Thorpe−Ingold effect caused by the β-lactam C4 quaternary center.[28] Thus, the successful and high-yielding formation of the seven-membered ring in Orn-derived **24** and **25** has evidently resulted from the favorable kinetics of the 7-exotrig ring closure, as compared with the other possible competing reactions, which possibly could include the intermolecular attack of the β-lactam or ester functions, leading to polymer formation, and intramolecular attack on the ester, leading to spirocyclic products (des-3-methyl

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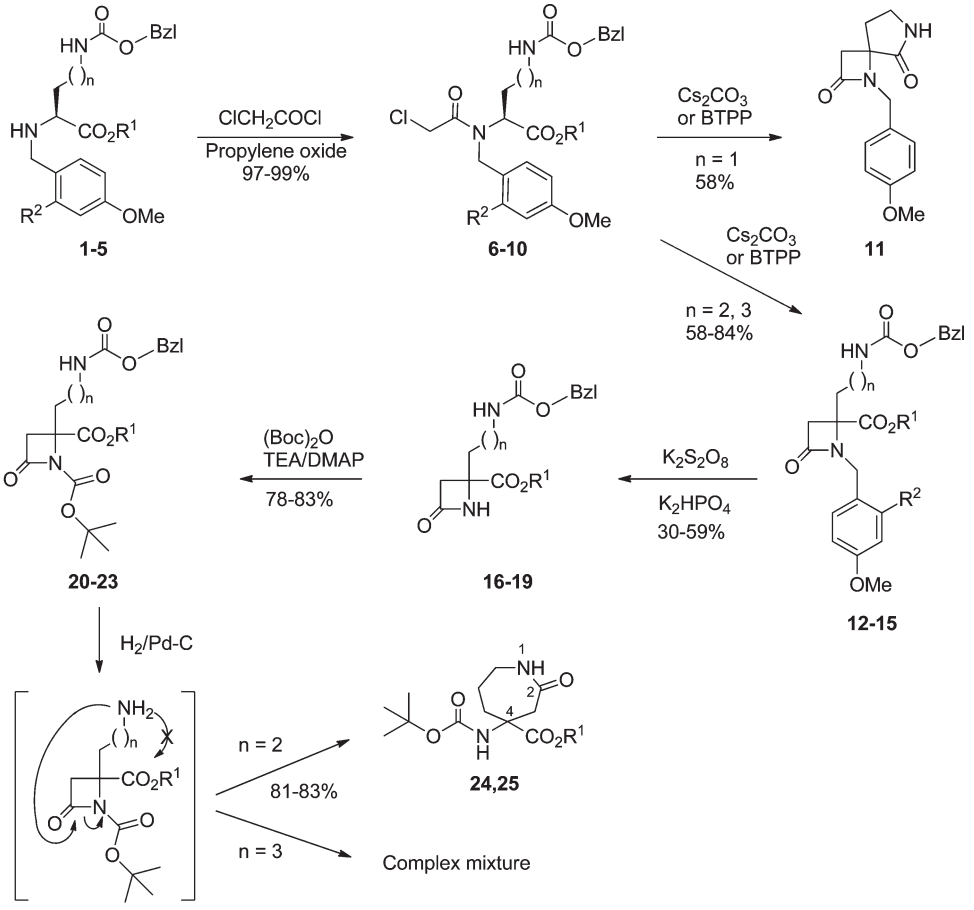
Scheme 1. Exploratory Attempts on the Formation of Hetrocyclic Quaternary Amino Acids from β-Lactams



Compd	n	R^1	R^2
1,6	1	Me	H
2, 7, 12	2	Me	H
3, 8, 13	2	^{t}Bu	OMe
4, 9, 14	3	Me	H
5, 10, 15	3	^{t}Bu	H
16, 20, 24	2	Me	–
17, 21, 25	2	^{t}Bu	–
18, 22	3	Me	–
19, 23	3	^{t}Bu	–

analogs of **35c**). On the contrary, the analogous but unsuccessful 8-exotrig ring closure from **22** and **23** evidently was kinetically less favorable than one or more of the possible side reactions.

The structural characterization of compounds **24** and **25** was performed on the basis of their ^{1}H and ^{13}C NMR data. Thus, the presence in the ^{1}H NMR spectra of the signal corresponding to methyl and *tert*-butyl esters in **24** and **25**, respectively, showed that these groups remained unaltered in the final compounds. Furthermore, in the ^{13}C NMR spectra, the amide carbonyl carbon resonates at considerably lower field than in the starting derivative ($\Delta\delta \geq 10.5$ ppm), indicating that the β-lactam carbonyl is not retained in the final products. Definite support for the 2-oxoazepane structure came from the HMBC heteronuclear experiment performed for compound **25**, in which the correlation between both 7-H and 3-H protons (δ 3.20 and 2.91 ppm, respectively) and the amide carbonyl carbon (δ 173.6 ppm) confirmed the formation of the seven-membered ring.

Stereoselective Synthesis of 2-Oxoazepane-Derived Amino Acids. After determining that the 2-azetidinones derived from Orn (**20**, **21**, $n = 2$) were the only suitable intermediates to the target α,α-heterocyclic quaternary amino acids (**24**, **25**), we decided to explore the preparation of the 3-substituted analogs of

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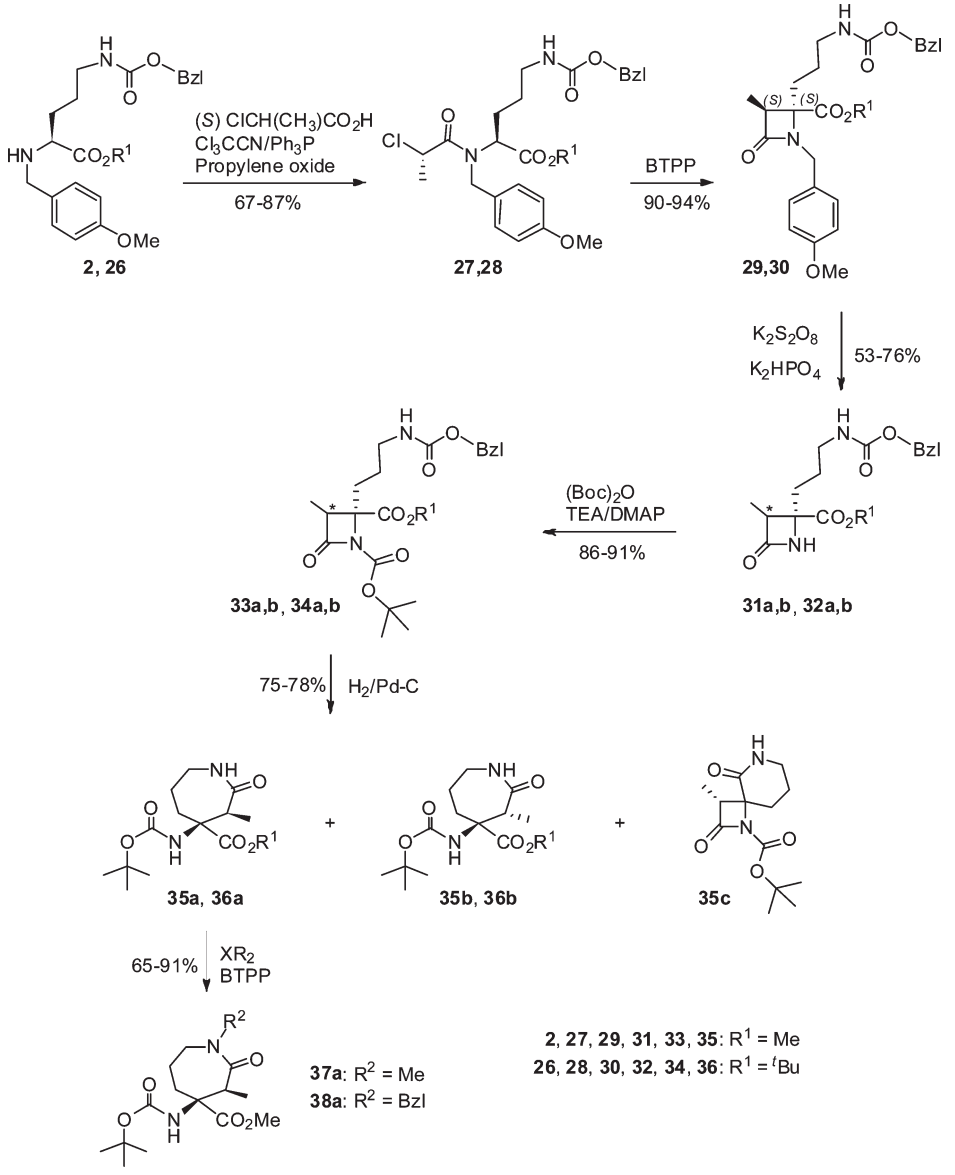
Scheme 2. Diastereoselective and Enantiospecific Synthesis of 3-Methyl-2-oxoazepane-Derived Amino Acids



these amino acid derivatives, and to do so in enantiopure form. In a recent publication,[29] we described a highly stereoselective synthesis of 1,3,4,4-tetrasubstituted β-lactams from simple amino acids (Ala, Phe, Lys, Glu). In this process, the stereochemical control of the cyclization to the β-lactam ring was exclusively directed by the configuration of the *N*-2-chloropropionyl group. Application of this procedure to Orn derivatives **2** and **26** allowed the preparation, after two steps, of the desired 3*S*-methyl-2-azetidinones **29** and **30** in high yield (Scheme 2). It is worth noting that the synthesis of intermediates **27** and **28** required strict neutral conditions to avoid racemization of the enantiomerically pure 2*S*-chloropropionic acid.[30] For this reason, 2*S*-chloropropionyl chloride was generated in situ from the 2*S*-chloropropionic acid with the chlorinating agent trichloroacetonitrile and triphenyl phosphine[31] and then reacted with compounds **2** and **26** in the presence of excess of propylene oxide as HCl scavenger.

Removal of the *p*-methoxybenzyl group by oxidation, as indicated,[27a] afforded the 1-NH unprotected compounds **31** and **32** in moderate/good yield (50−70%) and approximately 20−25% epimerization at C-3. Suitable activation of mixtures **31a,b** and **32a,b** with di-*tert*-butyldicarbonate gave the corresponding *N*-Boc-2-oxoazetidines **33a,b** and **34a,b**, in the same ratio of inseparable diastereoisomers as their precursors. After hydrogenation, compounds **33a,b** and **34a,b** rearranged to the expected 3-methyl-2-oxoazepane derivatives **35a,b** and **36a,b**. Fortunately, these mixtures of epimers could be separated by column chromatography. The structure of compound **35a** was established by single-crystal X-ray diffraction study[32] as shown in Figure 2, thus confirming the ring size and configuration of the new quaternary amino acid derivatives **35** and **36** in the present study.

It should be noted that during the hydrogenolysis of **33a,b**, along with the diastereomeric quaternary amino acids **35a** and

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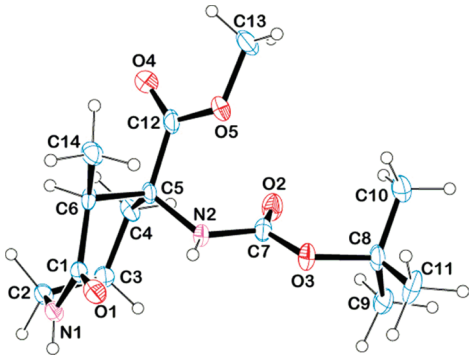


Figure 2. Molecular structure of quaternary 2-oxoazepane derivative **35a** as determined by single-crystal X-ray diffraction, showing the atomic numbering scheme. Ellipsoids are drowning at the 50% probability level of non-H atoms, and the H atoms are denoted as spheres of 0.1 Å radius.

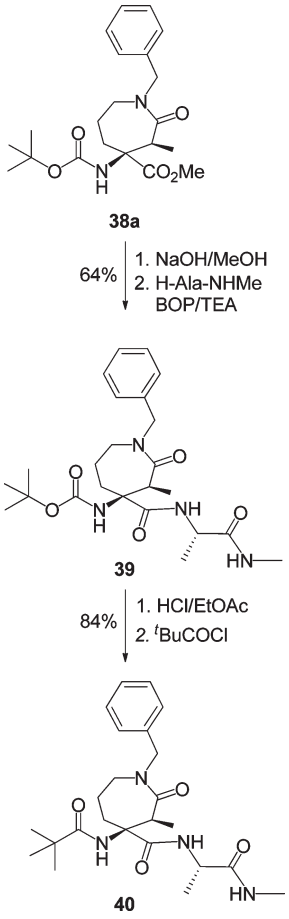
35b, the spiro-derivative **35c** was also formed and isolated as a single isomer. Considering the ratio of diastereoisomers in **33a,b** (3.6:1), and the relative amount of final compounds **35a**:**35b**:**35c** (13.3:1:2.6), it appears that the spiro derivative is exclusively formed from the minor 3*R*,4*S*-**33b** isomer. This result seems to indicate that the formation of the α-oxoazepane quaternary amino acid (7-exotrig ring closure) is preferred for the 3*S*, 4*S*-configured *β*-lactam, while the four to seven ring rearrangement of the corresponding 3*R*,4*S* isomer is more difficult, thus competing with the spirocyclization (6-exotrig cyclization). The fact that the Me group in the 3*R*,4*S* isomer is situated at the same face of the four-membered ring as the reactive aminopropyl side chain could account for this behavior. Compound **35c** was not detected in the transformation of **34a,b** (**a**/**b** = 4.2:1), for which the expected compounds **36a** and **36b** were formed along with the Z-deprotected *β*-lactam derivative (detected by HPLC-MS). This could be explained because the *tert*-butyl ester is less prone to undergo the intramolecular cyclization to the spiro compound than the corresponding OMe derivative.

Finally, the possibility of incorporating substituents to the azepane NH was investigated. In particular, compounds **37a** and **38a** were obtained from **35a** by using MeI and BnBr as the alkylating agents and BTPP as base under microwave irradiation.

Synthesis and Conformational Analysis of Model Dipeptides. To demonstrate the use of these quaternary amino acids in peptide synthesis, and to gain insight into their possible significance as inducers of peptide secondary structures, model dipeptide derivatives **39** and **40** were synthesized and studied. Dipeptide **39** was prepared in satisfactory yield from the aminoester **38a** through saponification and subsequent coupling with H-Ala-NHMe in the presence of BOP/TEA (Scheme 3). Compound **39** was transformed into its pivaloyl analogue **40** by removal of the N-terminal Boc-protecting group with TFA and reaction with pivaloyl chloride in the presence of TEA and propylene oxide.

The temperature coefficient values ($\Delta\delta/\Delta T$) and the chemical shifts in $CDCl_3$ and DMSO-d_6 for amide NH protons of compounds **39** and **40** could be indicative of the possible involvement of these NH's in hydrogen bonds (Table 1). For small peptides in DMSO solution, $\Delta\delta/\Delta T$ values below 3 ppb K^{-1} (in absolute value) are indicative of solvent-shielded NH protons that usually participate in intramolecular H-bonds.[33] According to this criterion, both N- and C-terminal NH's in **39** and **40** are protected from the solvent, thus indicating the existence of intramolecular H-bonds for these amide protons (Table 1). Contrastingly, the

Scheme 3. Synthesis of 2-Oxoazepane-Containing Dipeptide Models



central Ala NH is totally exposed to solvent ($\Delta\delta/\Delta T$ > 4 ppb K^{-1}). As for related dipeptide derivatives containing quaternary amino acids at the i + 1 position,[2] the protection of the C-terminal NHMe amide proton could be attributed to the formation of a H-bond with the carbonyl group of residue i (Boc or ^{t}BuCO), stabilizing *β*-turn-like conformations. The low $\Delta\delta/\Delta T$ values for the N-terminal NH could also be attributed to a hydrogen-bonded state, probably in this case with the oxygen of the 2-oxoazepane carbonyl group. Although this hydrogen bond cannot be seen in solution for the amino acid derivatives **35a** and **38a** ($\Delta\delta/\Delta T$ > 4 ppb K^{-1}, Table 1), the spatial disposition between the 2-CO and the Boc-NH amide proton in the solid structure of compound **35a** (Figure 2) seems close to that expected for H-bond stabilization through the formation of a six-membered pseudocycle (CO···HN distance, 2.4 Å; H···O=C angle, 71.6°; and N−H···O angle, 136.7°), although the H···O=C angle is slightly lower than the accepted value.[33]

A chemical shift >7.0 ppm in chloroform, and a small variation of this shift when the solvent is changed to DMSO, could also confirm the possible participation of the corresponding amide proton in an H-bond.[33] Application of these criteria to our compounds indicates that the *C*-terminal NHMe proton of dipeptides **39** and **40**, but not the Ala NH proton, is solvent-shielded, which reinforces their involvement in an intramolecular H-bond. For the N-terminal amide protons, the $\Delta\delta_{DMSO-CDCl_3}$ are very low (∼0.2 ppm), also proving the existence of H-bonded

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Table 1. Temperature Coefficients for the NH Amide Protons of 2-Oxoazepane Derivatives

	$\Delta\delta/\Delta T$ (ppb/K)[a]			δ ($CDCl_3$)[b]			δ (DMSO)[b,c]		
compd	*N*-term.	Ala	*C*-term.	*N*-term.	Ala	*C*-term.	*N*-term.	Ala	*C*-term.
35a	−7.6			4.86			5.87 (1.01)		
38a	−5.9			4.98			5.80 (0.82)		
39	−1.1	−4.8	−1.6	5.31	6.37	7.12	5.51 (0.20)	8.00 (1.63)	7.46 (0.34)
40	−0.8	−5.1	−1.1	6.58	6.08	7.03	6.35 (0.23)	7.67 (1.59)	7.47 (0.44)

[a] $\Delta\delta$ measured in DMSO-d_6, 30−45 °C (each 5 °C for a total of 4 points); samples at 7−10 mM concentration. [b] ppm. [c] $\Delta\delta_{DMSO-CDCl_3}$ are indicated in parentheses.

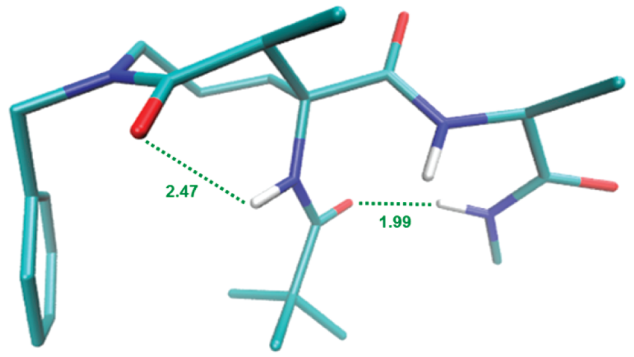

Figure 3. Theoretical structure of the absolute minimum energy conformer of compound **40**. For simplicity, hydrogen atoms are not shown, except for the amide NH's.

conformations. In this case the chemical shifts below 7 ppm can be attributed to the urethane character of these NH's.

The ability of dipeptide derivative **40** to adopt specific conformations was also examined by molecular dynamics. From this study, it can be concluded that all minimum energy conformers, within a 3 kcal/mol window from the global minimum, adopt type I β-turn conformations, as deduced from the ϕ and ψ dihedral angle values, as well as the $CO^{i}-NH^{i+3}$ distance and H-bond angles (Figure 3, Table 2). Among all the conformers, more than 56% also showed a correct distance between the 2-CO and the Boc-NH amide proton to be in a hydrogen-bonded state, d(2-CO−NH^{i+1}) < 2.5 Å,[33] in agreement with previous obtained NMR data. The H···O═C angle, though, is again a bit smaller than the standard values,[33] as it was the case in the X-ray structure of compound **35a**.

CONCLUSIONS

In conclusion, we have developed an operationally simple method for the preparation of 2-oxoazepane-containing quaternary amino acid derivatives by easy manipulation of Orn-derived β-lactams. The key step of this synthesis relies on the facile 7-exotrig ring closure and concomitant intramolecular opening of the activated 1-Boc-β-lactams by the NH_2 of the Orn side chain, after catalytic Z-removal. The potential of the procedure, initially developed in a racemic version, has now been realized for the synthesis of the enantiomerically pure 3-substituted analog, 3*S*,4*S*-amino-3-methyl-2-oxoazepane-4-carboxylate, as the methyl and *tert*-butyl esters. A preliminary experiment, aimed at ascertaining the utility of these novel quaternary heterocyclic amino acids as peptide secondary structure inducers, indicated that the incorporation of one of these 2-oxoazapane amino acids at the i + 1 position of model dipeptides forced the adoption of β-turn-like conformations. Therefore, these compounds can be considered new tools to be incorporated in the peptidomimetic design toolbox. Further work to explore the usefulness of these new disubstituted amino acids is currently in progress.

EXPERIMENTAL SECTION

Abbreviations. BOP: benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphoniumhexafluorophosphate. BTPP: phosphazene base P1-t-Bu-tris-(tetramethylene). Dab: 2,4-diaminobutyric acid. Md: major diastereoisomer. md: minor diastereoisomer. Mr: major rotamer. mr: minor rotamer. Oaz: (3*S*,4*S*)-4-amino-3-methyl-2-oxoazepane-4-carboxylic acid. Oaz(Bn): (3*S*,4*S*)-4-amino-1-benzyl-3-methyl-2-oxoazepane-4-carboxylic acid. TEA: triethylamine.

General Information. All reagents were of commercial quality. Solvents were dried and purified by standard methods. ^{1}H NMR spectra were recorded on a 300 MHz instrument, using TMS as internal standard. ^{13}C NMR spectra were registered at 75 MHz. Analytical TLC was performed on aluminum sheets with a 0.2 mm layer of silica gel F254. Silica gel 60 (230−400 mesh) was used for column chromatography. Analytical HPLC was performed on a Novapak C_{18} (3.9 × 150 mm, 4 μm) or on a Deltapak C_{18} (3.9 × 150 mm, 4 μm) column, with a flow rate of 1 mL/min, using a tunable UV detector set at 214 nm. Mixtures of MeCN (solvent A) and 0.05% TFA in H_2O (solvent B) were used in the mobile phase. Electrospray mass spectra were recorded in the positive mode directly in an LC−MS apparatus with an X-bridge C_{18} column (2.1 × 100 mm, 3.5 μm). Microwave irradiations were performed in a microwave oven. *N*-(*p*-methoxy)benzyl-, *N*-chloroacetyl-, and 2-azetidinone-amino acid derivatives **2**, **7**, **12**, **4**, **9**, and **14** were prepared as previously described.[34]

General Prodedure for the Synthesis of *N*-Benzyl Amino Acid Derivatives. A solution of H-L-Dab(Z)-, H-L-Orn(Z)-, or H-L-Lys(Z)-OR^1 HCl (13.9 mmol) in MeOH (28 mL) was successively treated with TEA (1.93 mL, 13.9 mmol) and the corresponding benzaldehyde (20.8 mmol). After the mixture was stirred at room temperature for 2 h, $NaBH_4$ (2.1 g, 55.6 mmol) was added in portions, and the stirring continued for 2 h. Then the solvent was evaporated to dryness, the residue was extracted with EtOAc, and the extract was washed with H_2O and brine. The organic layer was dried over Na_2SO_4, and after evaporation the residue was purified on a silica gel column as specified in each case.

***N*-(*p*-Pmb)-L-Dab(Z)-OMe (1).** Syrup: yield, 55%; eluent, EtOAc/hexane (2:1); HPLC t_R = 5.45 min (A/B = 30:70); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (s, 5H), 7.21 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 5.82 (br s, 1H), 5.09 (s, 2H), 3.76 (s, 3H), 3.72 (m, 4H), 3.54 (d, J = 12.4 Hz, 1H), 3.40 (m, 1H), 3.29 (m, 2H), 1.91 (m, 1H), 1.69 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 158.7, 156.2, 131.4, 129.5, 128.4, 128.0, 127.9, 113.7, 66.4, 59.2, 55.2, 51.9, 51.5, 39.0, 32.3 ppm. Elemental analysis calcd (%) for $C_{21}H_{26}N_2O_5$: C 65.27, H 6.78, N 7.25. Found: C 65.30, H 6.75, N 7.25.

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Table 2. Relevant Topographical Parameters of Minimum Energy Families of Conformers for Piv-Oaz(Bn)-Ala-NHMe 40 (within a 3 kcal/mol Window from the Global Minimum)

conf family	ΔE^a	$d(CO^i-NH^{i+3})^b$	$d(2\text{-}CO-NH^{i+1})^b$	H-bond angles[c] (CO^i-NH^{i+3})	H-bond angles[c] $(2\text{-}CO-NH^{i+1})$	ϕ_{i+1}	ψ_{i+1}	ϕ_{i+2}	ψ_{i+2}	%
40-1	0	1.99	2.47	167.0 (119.8)	133.9 (68.8)	−54.10	−16.11	−134.33	17.11	29
40-2	0.27	1.96	2.47	168.1 (136.8)	133.5 (70.8)	−54.03	−18.83	−67.00	−17.56	27
40-3	2.42	1.95	4.70	165.1 (132.0)	77.6 (47.8)	−50.52	−30.77	−66.15	−14.62	30
40-4	2.69	2.03	4.71	167.3 (111.8)	77.7 (47.4)	−50.87	−27.30	−131.41	21.22	14

[a] kcal/mol. [b] Å. [c] N—H···O and H···O═C angles; the latter is in parentheses.

***N*-(*o*,*p*-Dmb)-L-Orn(Z)-O^{t}Bu (3).** Syrup: yield, 77%; eluent, EtOAc/hexane (1:2); HPLC t_R = 4.27 min (A/B = 50:50); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (s, 5H), 7.11 (d, J = 8.1 Hz, 1H), 6.43−6.37 (m, 2H), 5.41 (br s, 1H), 5.08 (s, 2H), 3.78 (s, 3H), 3.77 (s, 3H), 3.70 (d, J = 12.9 Hz, 1H), 3.60 (d, J = 12.9 Hz, 1H), 3.17 (m, 1H), 3.10 (m, 2H), 2.06 (br s, 1H), 1.60 (m, 4H), 1.44 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 159.9, 158.5, 156.2, 136.6, 130.3, 128.3, 127.9, 127.8, 120.3, 103.6, 98.3, 80.7, 66.2, 61.0, 55.1, 55.1, 46.8, 40.6, 30.6, 27.9, 26.1 ppm. Elemental analysis calcd (%) for $C_{26}H_{36}N_2O_6$: C 66.08, H 7.68, N 5.93. Found: C 66.00, H 7.55, N 5.98.

***N*-(*p*-Pmb)-L-Lys(Z)-O^{t}Bu (5).** Syrup: yield, 90%; eluent, EtOAc/hexane (1:3); HPLC t_R = 6.05 min (A/B = 35:65); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28−7.23 (m, 5H), 7.16 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 8.7 Hz, 2H), 5.01 (s, 2H), 4.81 (br s, 1H), 3.71 (s, 3H), 3.66 (d, J = 12.5 Hz, 1H), 3.47 (d, J = 12.5 Hz, 1H), 3.09 (m, 1H), 3.02 (t, J = 6.6 Hz, 2H), 1.74 (br s, 1H), 1.40 ppm (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 158.5, 156.0, 136.5, 131.9, 129.3, 128.4, 127.9, 113.6, 80.9, 66.4, 60.9, 55.1, 51.3, 40.7, 33.0, 29.5, 28.0, 22.8 ppm. Elemental analysis calcd (%) for $C_{26}H_{36}N_2O_5$: C 68.40, H 7.95, N 6.14. Found: C 68.45, H 7.85, N 5.95.

***N*-(*p*-Pmb)-L-Orn(Z)-O^{t}Bu (26).** Syrup: yield, 73%; eluent, EtOAc/hexane (1:4); HPLC t_R = 12.32 min (gradient A/B from 95:5 to 20:80 over 20 min); $[\alpha]_D$ = −7.7 (c = 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.32 (m, 5H), 7.24 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 5.24 (br s, 1H), 5.09 (s, 2H), 3.78 (s, 3H), 3.73 (d, J = 12.5 Hz, 1H), 3.56 (d, J = 12.5 Hz, 1H), 3.19 (m, 2H), 3.11 (t, J = 5.7 Hz, 1H), 1.95 (br s, 1H), 1.60 (m, 4H), 1.48 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 159.0, 156.5, 136.9, 131.7, 129.8, 128.7, 128.3, 128.2, 114.0, 81.5, 66.7, 61.0, 55.4, 51.7, 41.0, 30.9, 28.3, 26.5 ppm; MS (ESI) m/z = 443.2 $[M + H]^+$. Elemental analysis calcd (%) for $C_{25}H_{34}N_2O_5$: C 67.85, H 7.74, N 6.33. Found: C 68.55, H 7.82, N 5.99.

General Procedure for the Synthesis of *N*-Chloroacetyl Amino Acid Derivatives. A solution of the corresponding *N*-benzyl 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 room temperature for 1−2 h, the solution was evaporated, and the resulting residue was purified on a silica gel column, using the solvent system specified in each case.

***N*-Chloroacetyl-*N*-(*p*-Pmb)-L-Dab(Z)-OMe (6).** Syrup: yield, 99%; eluent, EtOAc/hexane (2:1); HPLC t_R = 6.35 min (A/B = 42:58); $[\alpha]_D$ = −46.9 (c = 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, two rotamers, Mr/mr = 6:1) δ 7.25 (s, 5H), 7.10 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 8.8 Hz, 2H, Mr), 6.78 (d, J = 8.8 Hz, 2H, mr), 5.00 (s, 2H), 4.80 (br s, 1H), 4.40 (m, 2H), 4.30 (m, 1H), 4.00 (m, 2H), 3.70 (s, 3H), 3.50 (s, 3H, Mr), 3.42 (s, 3H, mr), 3.20 (m, 1H), 3.00 (m, 1H), 2.10 (m, 1H), 1.90 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 167.6, 159.4, 156.3, 136.5, 128.6, 128.4, 128.0, 127.0, 114.3, 66.5, 56.3, 55.2, 52.2, 51.0, 41.4, 37.7, 29.4 ppm; MS (ESI) m/z = 463.4 $[M + H]^+$. Elemental analysis calcd (%) for $C_{23}H_{27}ClN_2O_6$: C 59.67, H 5.88, Cl 7.66, N 6.05. Found: C 59.75, H 5.85, Cl 7.75, N 6.10.

***N*-(*o*,*p*-Dmb)-*N*-chloroacetyl-L-Orn(Z)-O^{t}Bu (8).** Syrup: yield, 97%; eluent, EtOAc/hexane (1:2); HPLC t_R = 9.74 min (A/B = 50:50); $[\alpha]_D$ = −16.7 (c = 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, two rotamers, Mr/mr = 5.1:1) δ 7.34 (s, 5H), 7.13 (d, J = 8.8 Hz, 2H), 6.45 (d, J = 8.8 Hz, 2H), 5.06 (s, 2H), 4.72 (br s, 1H), 4.54 (d, J = 16.3 Hz, 1H), 4.40 (d, J = 16.3 Hz, 1H), 4.25 (d, J = 12.2 Hz, 1H), 4.17 (d, J = 12.2 Hz, 1H), 3.98 (m, 1H), 3.78 (s, 6H, Mr), 3.75 (s, 6H, mr), 3.01 (m, 2H), 1.96 (m, 1H), 1.64 (m, 1H), 1.40 (s, 9H, Mr), 1.36 (s, 9H, mr), 1.27 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, two rotamers) δ 169.3, 166.8, 161.0, 158.4, 156.1, 136.5, 129.9, 128.4, 127.9, 116.1, 103.8, 98.5, 81.5, 66.4, 59.7, 55.3, 55.1, 52.1, 48.0, 41.4, 40.4, 30.6, 27.8, 26.2 ppm; MS (ESI) m/z = 571.5 $[M + Na]^+$. Elemental analysis calcd (%) for $C_{28}H_{37}ClN_2O_7$: C 61.25, H 6.79, N 5.10, Cl 6.46. Found: C 61.20, H 6.80, N 5.05, Cl 6.40.

***N*-Chloroacetyl-*N*-(*p*-Pmb)-L-Lys(Z)-O^{t}Bu (10).** Syrup: yield, 99%; eluent, EtOAc/hexane (1:2); HPLC t_R = 8.98 min (A/B = 50:50); $[\alpha]_D$ = −45.1 (c = 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, two rotamers, Mr/mr = 3:1) δ 7.20 (m, 5H), 7.11 (d, J = 8.8 Hz, 2H), 6.77 (d, J = 8.8 Hz, 2H, Mr), 6.68 (d, J = 8.8 Hz, 2H, mr), 4.96 (m, 3H), 4.51 (d, J = 16.7 Hz, 1H), 4.34 (d, 1H, J = 16.7 Hz, 1H), 4.14 (m, 1H), 3.90 (s, 2H), 3.67 (s, 3H, Mr), 3.61 (s, 3H, mr), 2.94 (m, 2H, Mr), 2.90 (m, 2H, mr), 1.85 (m, 1H), 1.56 (m, 1H), 1.31 (s, 9H, Mr), 1.26 (s, 9H, mr), 1.16 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, two rotamers) δ 169.4, 167.1, 159.2, 156.3, 136.5, 129.2, 128.3, 128.2 (Mr), 127.9 (mr), 114.1 (Mr), 113.6 (mr), 82.6 (mr), 81.69 (Mr), 66.3, 59.7, 55.1, 50.8, 41.5, 40.5, 29.4, 28.8, 27.7 (Mr), 27.6 (mr), 23.6 (Mr), 23.3 (mr) ppm; MS (ESI) m/z = 533.3 $[M + H]^+$. Elemental analysis calcd (%) for $C_{25}H_{31}ClN_2O_6$: C 61.16, H 6.36, Cl 7.22, N 5.71. Found: C 61.25, H 6.45, Cl 7.15, N 5.85.

General Procedure for the Synthesis of *N*-Chloropropionyl Amino Acid Derivatives. PPh_3 (7.615 g, 29.03 mmol) was added to a solution of (*S*)-2-chloropropionic acid (1.9 mL, 22.02 mmol) and Cl_3CCN (2.9 mL, 28.98 mmol) in THF (50 mL) at 0 °C, and the reaction mixture was stirred for 30 min. Then a solution of *N*-Pmb-L-Orn(Z)-OR[1] (14.49 mmol) and propylene oxide (15.2 mL, 217.32 mmol) in THF (2 mL) was added dropwise to the reaction mixture. After stirring for 48 h, the solvent was evaporated under vacuum and the resultant residue was dissolved in Et_2O, filtered over Celite, and concentrated under vacuum. The residue was purified by column chromatography on silica gel using the solvent system specified.

***N*-[(*S*)-2-Chloropropionyl]-*N*-(*p*-Pmb)-L-Orn(Z)-OMe (27).** Syrup: yield, 87%; eluent, acetone/CH_2Cl_2 (1:30); $[\alpha]_D^{20}$ = −16.4 (c = 0.5 in $CHCl_3$); HPLC t_R = 7.36 min (A/B = 50:50); ^{1}H NMR (300 MHz, $CDCl_3$, two rotamers, Mr/mr = 6.7:1) δ 7.35 (m, 5H), 7.19 (d, J = 8.5 Hz, 2H, mr), 7.13 (d, J = 8.6 Hz, 2H, Mr), 6.87 (d, J = 8.6 Hz, 2H, Mr), 6.79 (d, J = 8.5 Hz, 2H, mr), 5.08 (br s, 2H), 4.73 (m, 3H), 4.51 (m, 2H), 3.79 (s, 3H, Mr), 3.74 (s, 3H, mr), 3.58 (s, 3H, mr), 3.53 (s, 3H, Mr), 3.14 (q, J = 6.7 Hz, 2H, Mr), 3.05 (q, partially overlapped, J = 6.7 Hz, 2H, mr), 2.02 (m, 1H), 1.74 (m, 1H), 1.63 (d, J = 6.5 Hz, 3H), 1.47 (quint, J = 6.7 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 171.0 (Mr), 170.4 (mr), 159.4 (Mr), 158.9 (mr), 156.5, 136.7, 131.5, 129.7, 128.6, 128.2, 128.1 (Mr), 128.0 (mr), 114.4 (Mr), 113.9 (mr), 66.7, 60.2, 57.5, 55.4, 52.2 (Mr), 51.9 (mr), 50.2 (Mr), 49.4 (mr), 40.8 (mr), 40.6 (Mr), 30.7, 26.7 (Mr), 26.6 (mr), 21.0 ppm; MS (ESI) m/z = 513.35 $[M + Na]^+$. Elemental analysis calcd (%) for

$C_{25}H_{31}N_2O_6Cl$: C 61.16, H 6.36, N 5.71. Found (%): C 60.98, H 6.54, N 5.85.

***N*-[(*S*)-2-Chloropropionyl]-*N*-(*p*-Pmb)-L-Orn(Z)-O^{t}Bu (28).** Syrup: yield, 67%; eluent, EtOAc/hexane (1:6); $[\alpha]_D^{20} = -18.9$ (c = 1.3 in $CHCl_3$); HPLC t_R = 12.99 min (A/B = 50:50); ^{1}H NMR (400 MHz, $CDCl_3$, two rotamers, Mr/mr = 4.3:1) δ 7.34 (m, 5H), 7.20 (d, J = 7.8 Hz, 2H), 6.88 (d, J = 7.8 Hz, 2H), 6.79 (d, J = 8.2 Hz, 2H, mr), 5.08 (s, 2H), 4.78 (br s, 1H), 4.64 (m, 1H), 4.56 (m, 2H), 4.28 (t, J = 7.2, 1H), 3.79 (s, 3H, Mr), 3.73 (s, 3H, mr), 3.10 (q, J = 6.4 Hz, 2H, Mr), 3.01 (q, partially overlapped, J = 6.8 Hz, 2H, mr), 2.04 (m, 1H), 1.66 (m, 1H), 1.64 (d, J = 6.0 Hz, 3H), 1.45 (m, 2H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1 (mr), 169.6 (Mr), 169.4, 159.3, 156.3, 136.6, 129.4, 128.5, 128.3, 128.1, 128.0, 114.2 (Mr), 113.8 (mr), 82.7 (mr), 81.9 (Mr), 66.6 (mr), 66.5 (Mr), 61.3 (mr), 59.2 (Mr), 55.3 (Mr), 55.2 (mr), 50.3, 50.1, 40.5 (Mr), 40.2 (mr), 27.7, 26.9, 26.9, 21.0 (mr), 20.9 (Mr) ppm; MS (ESI) m/z = 533.51 $[M + H]^+$. Elemental analysis calcd (%) for $C_{28}H_{37}N_2O_6Cl$: C 63.09, H 7.00, N 5.26. Found (%): C 62.85, H 7.08, N 5.46.

General Procedure for the Synthesis of 2-Oxoazetidine Derivatives. A solution of the corresponding *N*-benzyl-*N*-chloroalkyl derivative (1.6 mmol) in dry CH_3CN (20 mL) was treated with Cs_2CO_3 (1.04 g, 3.2 mmol, method A) or BTPP (1.09 mL, 2.4 mmol, method B) and stirred at room temperature until disappearance of the starting material. After evaporation of the solvent, the 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 that was purified on a silica gel column, using the solvent system specified in each case.

(4*R*,*S*)-1-(*p*-Methoxy)benzyl-1,6-diazaspiro[3.4]octane-2,5-dione (11). Syrup: yield (method B), 58%; eluent, MeOH/CH_2Cl_2 (1:20); HPLC t_R = 4.04 min (A/B = 15:85); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 6.63 (br s, 1H), 4.67 (d, J = 15.1 Hz, 1H), 3.97 (d, J = 15.1 Hz, 1H), 3.78 (s, 3H), 3.30 (m, 2H), 3.23 (d, J = 14.2 Hz, 1H), 2.88 (d, J = 14.2 Hz, 1H), 2.04 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 166.0, 159.0, 129.7, 128.2, 113.8, 58.7, 55.1, 50.1, 44.3, 42.1, 20.7 ppm; MS (ESI) m/z = 261.1 $[M + H]^+$. Elemental analysis calcd (%) for $C_{14}H_{16}N_2O_3$: C 64.60, H 6.20, N 10.76. Found: C 64.65, H 6.25, N 10.70.

(4*R*,*S*)-1-(*o*,*p*-Dimethoxy)benzyl-4-*tert*-butoxycarbonyl-4-[3-(benzyloxycarbonyl)amino]propyl-2-oxoazetidine (13). Solid: mp 89−90 °C; yield (method A) , 84%; eluent, EtOAc/hexane (1:2); HPLC t_R = 6.04 min (A/B = 50:50); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (s, 5H), 7.13 (d, J = 8.0 Hz, 2H), 6.38 (d, J = 8.0 Hz, 2H), 5.03 (s, 2H), 4.70 (m, 1H), 4.47 (d, J = 15.1 Hz, 1H), 4.20 (d, J = 15.1 Hz, 1H), 3.71 (s, 6H), 3.03 (d, J = 14.4 Hz, 1H), 2.94 (m, 2H), 2.75 (d, J = 14.4 Hz, 1H), 1.88 (m, 1H), 1.49 (m, 1H), 1.38 (s, 9H), 1.17 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 166.1, 160.5, 157.9, 156.0, 136.4, 131.0, 128.3, 127.9, 116.4, 104.0, 98.0, 82.1, 66.3, 62.5, 55.1, 54.9, 45.2, 40.4, 38.6, 29.7, 27.6, 23.8 ppm; MS (ESI) m/z = 535.4 $[M + Na]^+$. Elemental analysis calcd (%) for $C_{28}H_{36}N_2O_7$: C 65.61, H 7.08, N 5.47. Found: C 65.45, H 7.15, N 5.25.

(4*R*,*S*)-1-(*p*-Methoxy)benzyl-4-[3-(benzyloxycarbonyl)-amino]butyl-4-*tert*-butoxycarbonyl-2-oxoazetidine (15). Syrup: yield (method A), 58%; eluent, EtOAc/hexane (1:2). HPLC t_R = 11.23 min (A/B = 45:55); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 5H), 7.13 (d, J = 8.7 Hz, 2H), 6.75 (d, J = 8.7 Hz, 2H), 5.00 (s, 2H), 4.61 (br s, 1H), 4.50 (d, J = 15.3 Hz, 1H), 4.08 (d, J = 15.3 Hz, 1H), 3.68 (s, 6H), 3.10 (d, J = 14.6 Hz, 1H), 2.95 (m, 2H), 2.71 (d, J = 14.6 Hz, 1H), 1.74 (m, 1H), 1.41 (m, 1H), 1.34 (s, 9H), 1.15 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 166.3, 158.8, 156.1, 136.3, 133.5, 129.5, 128.5, 128.3, 127.9, 113.7, 82.4, 66.4, 63.1, 55.0, 45.3, 43.9, 40.3, 33.2, 29.5, 27.6, 20.9 ppm; MS (ESI) m/z = 497.1 $[M + H]^+$. Elemental analysis calcd (%) for $C_{28}H_{36}N_2O_6$: C 67.72, H 7.31, N 5.64. Found: C 67.65, H 7.25, N 5.85.

(3*S*,4*S*)-4-[3-(Benzyloxycarbonyl)amino]propyl-1-*p*-methoxybenzyl-3-methyl-4-methoxycarbonyl-2-oxoazetidine (29). Syrup: yield (method B), 90%; eluent, EtOAc/hexane (1:1); $[\alpha]_D^{20} = -16.8$ (c = 0.5 in $CHCl_3$); HPLC t_R = 10.10 min (A/B = 40:60); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (s, 5H), 7.19 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 5.05 (s, 2H), 4.77 (d, J = 15.4 Hz, 1H), 4.31 (br s, 1H), 4.07 (d, J = 15.4 Hz, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 3.12 (q, J = 7.5 Hz, 1H), 2.85 (m, 2H), 1.73 (m, 2H), 1.27 (m, 2H), 1.14 (d, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 169.2, 159.1, 156.2, 136.5, 129.7, 128.8, 128.5, 128.1, 114.0, 68.4, 66.6, 55.2, 53.0, 52.1, 44.5, 40.4, 31.5, 24.5, 10.1 ppm; MS (ESI) m/z = 477.45 $[M + Na]^+$. Elemental analysis calcd (%) for $C_{25}H_{30}N_2O_6$: C 66.06, H 6.65, N 6.16. Found (%): C 65.87, H 6.72, N 6.15.

(3*S*,4*S*)-4-[3-(Benzyloxycarbonyl)amino]propyl-4-*tert*-butoxycarbonyl-1-*p*-methoxybenzyl-3-methyl-2-oxoazetidine (30). Syrup: yield (method B), 94%; eluent, EtOAc/hexane (1:1); $[\alpha]_D^{20} = -10.7$ (c = 0.7 in $CHCl_3$); HPLC t_R = 8.83 min (A/B = 50:50); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 5H), 7.19 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 5.03 (s, 2H), 4.79 (d, J = 16.2 Hz, 1H), 4.21 (br s, 1H), 4.04 (d, J = 16.2 Hz, 1H), 3.69 (s, 3H), 3.07 (q, J = 7.5 Hz, 1H), 2.81 (m, 2H), 1.67 (m, 2H), 1.53 (m, 2H), 1.47 (s, 9H), 1.19 (d, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 169.6, 159.1, 156.2, 136.5, 129.6, 129.1, 128.5, 128.1, 114.0, 82.9, 68.4, 66.6, 55.2, 53.0, 44.4, 40.5, 32.1, 28.1, 24.5, 10.5 ppm; MS (ESI) m/z = 497.47 $[M + H]^+$. Elemental analysis calcd (%) for $C_{28}H_{36}N_2O_6$: C 67.72, H 7.31, N 5.64. Found (%): C 67.43, H 7.50, N 5.39.

General Procedure for the Removal of *N*-Benzyl Groups. A solution of the corresponding 1-substituted 2-oxoazetidine (0.69 mmol) in CH_3CN/H_2O (1:1, 22 mL) was treated with K_2HPO_4 (5.93 mmol) and $K_2S_2O_8$ (7.66 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 $NaHCO_3$ (10%) and brine, dried over Na_2SO_4, and evaporated. The resulting residue was purified on a silica gel column, as indicated.

(4*R*,*S*)-4-Methoxycarbonyl-4-[3-(benzyloxycarbonyl)-amino]propyl-2-oxoazetidine (16). Syrup: yield, 53%; eluent, EtOAc/hexane (2:1); HPLC t_R = 6.24 min (A/B = 25:75); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (s, 5H), 6.95 (br s, 1H), 5.15 (br s, 1H), 5.08 (s, 2H), 3.75 (s, 3H), 3.18 (m, 3H), 2.89 (d, J = 15.0 Hz, 1H), 2.04 (m, 1H), 1.81 (m, 1H), 1.50 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 166.4, 156.4, 136.3, 128.4, 128.1, 128.0, 66.6, 58.0, 52.1, 47.6, 40.4, 33.5, 25.1 ppm; MS (ESI) m/z = 321.1 $[M + H]^+$. Elemental analysis calcd (%) for $C_{16}H_{20}N_2O_5$: C 59.99, H 6.29, N 8.74. Found: C 59.68, H 6.35, N 8.53.

(4*R*,*S*)-4-*tert*-Butoxycarbonyl-4-[3-(benzyloxycarbonyl)-amino]propyl-2-oxoazetidine (17). Syrup: yield, 59%; eluent, EtOAc/hexane (1:1); HPLC t_R = 3.24 min (A/B = 45:55); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (s, 5H), 6.89 (br s, 1H), 5.18 (br s, 1H), 4.98 (s, 2H), 3.09 (m, 2H), 2.99 (d, J = 15.0 Hz, 1H), 2.73 (d, J = 15.0 Hz, 1H), 2.04 (m, 1H), 1.67 (m, 1H), 1.42 (m, 2H), 1.36 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 166.8, 156.4, 136.4, 128.4, 128.1, 82.6, 66.6, 58.5, 47.4, 40.5, 33.6, 27.8, 25.1 ppm; MS (ESI) m/z = 385.1 $[M + Na]^+$. Elemental analysis calcd (%) for $C_{19}H_{26}N_2O_5$: C 62.97, H 7.23, N 7.73. Found: C 62.90, H 7.35, N 7.57.

(4*R*,*S*)-4-[3-(Benzyloxycarbonyl)amino]butyl-4-methoxycarbonyl-2-oxoazetidine (18). Syrup: yield, 38%; eluent, EtOAc/hexane (3:1); HPLC t_R = 3.42 min (A/B = 35:65); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 5H), 6.38 (br s, 1H), 5.02 (s, 2H), 4.77 (br s, 1H), 3.69 (s, 3H), 3.10 (m, 3H), 2.83 (d, J = 15.5 Hz, 1H), 1.99 (m, 1H), 1.75 (m, 1H), 1.46 (m, 2H), 1.25 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 166.5, 156.4, 136.4, 128.4, 128.0, 66.5, 58.3, 52.7, 47.6, 40.4, 36.0, 29.5, 21.7 ppm; MS (ESI) m/z = 357.1 $[M + Na]^+$. Elemental analysis calcd (%) for $C_{17}H_{22}N_2O_5$: C 61.07, H 6.63, N 8.38. Found: C 61.15, H 6.45, N 8.47.

(4*R*,*S*)-4-[3-(Benzyloxycarbonyl)amino]butyl-4-*tert*-butoxycarbonyl-2-oxoazetidine (19). Syrup: yield, 30%; HPLC t_R = 3.50 min (A/B = 45:55); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (m, 5H), 6.92 (br s, 1H), 5.18 (br s, 1H), 4.97 (s, 2H), 3.05 (m, 2H), 2.97 (d, J = 14.9 Hz, 1H), 2.71 (d, J = 14.9 Hz, 1H), 1.90 (m, 1H), 1.62 (m, 1H), 1.27 ppm (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 166.9, 156.3, 136.4, 128.3, 127.9, 82.3, 66.3, 58.6, 47.3, 40.3, 35.9, 29.4, 27.6, 21.5 ppm; MS (ESI) m/z = 399.3 $[M + Na]^+$. Elemental analysis calcd (%) for $C_{20}H_{28}N_2O_5$: C 63.81, H 7.50, N 7.44. Found: C 63.95, H 7.45, N 7.37.

(3*RS*,4*S*)-4-[3-(Benzyloxycarbonyl)amino]propyl-4-methoxycarbonyl-3-methyl-2-oxoazetidine (31a,b). Diastereoisomeric ratio (3*S*,4*S*/3*R*,4*S*), Md/md = 3.2:1. Syrup: yield, 76%; eluent, EtOAc/hexane (1:2); HPLC t_R = 15.98 min (md), 16.53 min (Md) (A/B = 25:75); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 5H), 6.54 (s, 1H, md), 6.49 (s, 1H, Md), 5.09 (s, 2H), 4.89 (br s, 1H), 3.76 (s, 3H, OCH_3, Md), 3.75 (s, 3H, OCH_3, md), 3.34 (qd, J = 7.6 Hz, J = 1.9 Hz, 1H, md), 3.20 (q, J = 6.5 Hz, 2H), 3.11 (q, J = 7.6 Hz, 1H, Md), 2.20 (m, 1H, Md), 2.01 (m, 1H, md), 1.71 (m, 1H), 1.47 (m, 2H), 1.26 (d, J = 7.6 Hz, 3H, md), 1.16 (d, J = 7.6 Hz, 3H, Md) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4 (md), 172.0 (Md), 170.5 (md), 170.1 (Md), 156.6, 136.6, 128.6, 128.3, 128.2, 66.8, 64.1 (Md), 61.7 (md), 55.4 (Md), 53.8 (md), 52.8 (md), 52.5 (Md), 40.6, 34.1 (Md), 29.7 (md), 25.7 (Md), 25.2 (md), 10.7 (Md), 8.8 (md) ppm; MS (ESI) m/z = 357.37 $[M + Na]^+$. Elemental analysis calcd (%) for $C_{17}H_{22}N_2O_5$: C 61.07, H 6.63, N 8.38. Found (%): C 61.36, H 6.51, N 8.13.

(3*RS*,4*S*)-4-[3-(Benzyloxycarbonyl)amino]propyl-4-*tert*-butoxycarbonyl-3-methyl-2-oxoazetidine (32a,b). Diastereoisomeric ratio (3*S*,4*S*/3*R*,4*S*), Md/md = 4.7:1. Solid: yield, 53%; eluent, EtOAc/hexane (1:1); HPLC t_R = 6.50 min (both diastereomers) (A/B = 40:60); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (s, 5H), 6.26 (s, partially overlapped, 1H, md), 6.22 (s, 1H, Md), 5.09 (s, 2H), 4.83 (s, 1H), 3.29 (q, partially overlapped, J = 7.2 Hz, 1H, Md), 3.20 (m, 2H), 3.06 (q, J = 7.7 Hz, 1H, Md), 2.01 (m, 2H, Md), 1.98 (m, 2H, md), 1.67 (m, 2H), 1.48 (s, 9H), 1.25 (d, partially overlapped, J = 7.2 Hz, 3H, md), 1.22 (d, J = 7.7 Hz, 3H, Md) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 170.1, 156.4, 136.4, 128.6, 128.2, 128.1, 82.9 (Md), 82.6 (md), 66.8, 63.8 (Md), 61.9 (md), 55.0 (Md), 53.4 (md), 40.6, 34.5, 28.1 (Md), 27.9 (md), 25.6, 10.9 (Md), 8.8 (md) ppm; MS (ESI) m/z = 399.40 $[M + Na]^+$. Elemental analysis calcd (%) for $C_{20}H_{28}N_2O_5$: C 63.81, H 7.50, N 7.44. Found (%): C 63.48, H 7.64, N 7.16.

General Procedure for the Synthesis of *N*-Boc-oxoazetidine Derivatives. A solution of the corresponding 1-NH oxoazetidine (0.36 mmol) in dry CH_2Cl_2 (7 mL) was successively treated with TEA (50 L, 0.36 mmol), DMAP (4 mg, 0.036 mmol), and di-*tert*-butyldicarbonate (87 mg, 0.39 mmol), and stirring continued for 5 h. Then the solvent was evaporated to dryness, and the residue was purified on a silica gel column as specified in each case.

(4*R*,*S*)-1-*tert*-Butoxycarbonyl-4-methoxycarbonyl-4-[3-(benzyloxycarbonyl)amino]propyl-2-oxoazetidine (20). Syrup: yield, 83%; eluent, EtOAc/hexane (1:1); HPLC t_R = 5.63 min (A/B = 40:60); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (s, 5H), 5.10 (s, 2H), 4.85 (br s, 1H), 3.79 (s, 3H), 3.27 (m, 2H), 3.10 (d, J = 15.9 Hz, 1H), 2.95 (d, J = 15.9 Hz, 1H), 2.14 (m, 2H), 1.71 (m, 1H), 1.54 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 163.1, 156.7, 147.5, 136.9, 128.9, 128.6, 128.5, 84.3, 67.1, 61.1, 53.3, 46.2, 41.2, 30.1, 28.3, 24.8 ppm; MS (ESI) m/z = 443.3 $[M + Na]^+$. Elemental analysis calcd (%) for $C_{21}H_{28}N_2O_7$: C 59.99, H 6.71, N 6.66. Found: C 59.66, H 6.70, N 6.45.

(4*R*,*S*)-1,4-di-*tert*-Butoxycarbonyl-4-[3-(benzyloxycarbonyl)amino]propyl-2-oxoazetidine (21). Syrup: yield, 83%; eluent, EtOAc/hexane (1:3); HPLC t_R = 12.83 min (A/B = 45:55); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (s, 5H), 5.02 (s, 2H), 4.77 (br s, 1H), 3.18 (m, 2H), 2.95 (d, J = 15.7 Hz, 1H), 2.83 (d, J = 15.7 Hz, 1H), 2.01 (m, 2H), 1.55 (m, 2H), 1.43 (s, 9H), 1.40 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 163.1, 156.3, 147.2, 136.4, 128.5, 128.1, 83.7, 82.9, 66.7, 61.0, 45.7, 40.8, 29.5, 28.0, 27.8, 24.5 ppm; MS (ESI) m/z = 485.2 $[M + Na]^+$. Elemental analysis calcd (%) for $C_{24}H_{34}N_2O_7$: C 62.32, H 7.41, N 6.06. Found: C 62.50, H 7.30, N 6.25.

(4*R*,*S*)-4-[3-(Benzyloxycarbonyl)amino]butyl-1-*tert*-butoxycarbonyl-4-methoxycarbonyl-2-oxoazetidine (22). Syrup: yield, 78%; HPLC t_R = 5.87 min (A/B = 45:55); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 5H), 5.02 (s, 2H), 4.74 (br s, 1H), 3.71 (s, 3H), 3.15 (m, 2H), 3.00 (d, J = 15.9 Hz, 1H), 2.88 (d, J = 15.9 Hz, 1H), 2.04 (m, 2H), 1.40 ppm (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 162.8, 156.3, 147.0, 136.6, 128.4, 127.9, 83.6, 66.5, 60.8, 52.7, 45.5, 40.5, 31.7, 29.8, 27.9, 20.6 ppm; MS (ESI) m/z = 457.1 $[M + Na]^+$. Elemental analysis calcd (%) for $C_{22}H_{30}N_2O_7$: C 60.82, H 6.96, N 6.45. Found: C 60.75, H 6.95, N 6.67.

(4*R*,*S*)-4-[3-(Benzyloxycarbonyl)amino]butyl-1,4-di-*tert*-butoxycarbonyl-2-oxoazetidine (23). Syrup: yield, 78%; eluent, EtOAc/hexane (1:3); HPLC t_R = 9.05 min (A/B = 45:55); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (s, 5H), 4.97 (s, 2H), 4.91 (br s, 1H), 3.12 (m, 2H), 2.89 (d, J = 15.9 Hz, 1H), 2.80 (d, J = 15.9 Hz, 1H), 1.95 (m, 2H), 1.39 (s, 9H), 1.37 (s, 9H), 1.32 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 163.3, 156.3, 147.0, 136.5, 128.4, 128.0, 83.4, 82.6, 66.4, 61.2, 45.4, 40.4, 31.5, 29.8, 27.9, 27.7, 20.7 ppm; MS (ESI) m/z = 499.3 $[M + Na]^+$. Elemental analysis calcd (%) for $C_{25}H_{36}N_2O_7$: C 63.01, H 7.61, N 5.88. Found: C 63.15, H 7.45, N 5.97.

(3*RS*,4*S*)-4-[3-(Benzyloxycarbonyl)amino]propyl-1-*tert*-butoxycarbonyl-4-methoxycarbonyl-3-methyl-2-oxoazetidine (33a,b). Diastereoisomeric ratio (3*S*,4*S*/3*R*,4*S*), Md/md = 3.6:1. Syrup: yield, 86%; eluent, EtOAc/hexane (1:2); HPLC t_R = 31.68 min (md), 33.76 min (Md) (A/B = 40:60); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5H), 5.08 (s, 2H), 4.95 (s, 1H, Md), 4.84 (s, 1H, md), 3.77 (s, 3H, Md), 3.76 (s, 3H, md), 3.37 (q, J = 7.8 Hz, 1H, md), 3.22 (m, 3H), 2.12 (m, 2H), 1.77 (m, 1H), 1.55 (m, 1H), 1.48 (s, 9H), 1.25 (d, J = 7.8 Hz, 3H, md), 1.15 (d, J = 7.5 Hz, 3H, Md) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4 (md), 170.3 (Md), 166.5, 156.5, 147.6 (md), 147.5 (Md), 136.6, 128.6, 128.2, 128.2, 83.9 (md), 83.8 (Md), 66.6, 66.4, 53.6 (md), 52.9 (md), 52.5 (Md), 52.2 (Md), 41.2 (md), 40.9 (Md), 30.3, 28.1, 25.7 (md), 24.6 (Md), 9.3 (Md), 8.9 (md) ppm; MS (ESI) m/z = 457.3 $[M + Na]^+$. Elemental analysis calcd (%) for $C_{22}H_{30}N_2O_7$: C 60.82, H 6.96, N 6.45. Found (%): C 60.71, H 6.79, N 6.36.

(3*RS*,4*S*)-4-[3-(Benzyloxycarbonyl)amino]propyl-1,4-di-*tert*-butoxycarbonyl-3-methyl-2-oxoazetidine (34a,b). Diastereoisomeric ratio (3*S*,4*S*/3*R*,4*S*), Md/md = 4.2:1. Solid: yield, 91%; eluent, EtOAc/hexane (1:3); HPLC t_R = 27.41 min (both diastereomers) (A/B = 50:50). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 5.05 (br s, 3H), 3.26 (q, J = 7.5 Hz, 1H, md), 3.13 (m, 2H), 3.13 (q, J = 7.5 Hz, 1H, Md), 2.03 (m, 2H), 1.70 (m, 2H), 1.46 (s, 9H, Md), 1.45 (s, 9H), 1.43 (s, 9H, md), 1.15 (d, J = 7.5 Hz, 3H, Md), 1.11 (d, J = 7.5 Hz, 3H, md) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8 (Md), 168.7 (md), 166.9, 156.5 (md), 156.5 (Md), 147.5, 136.6, 128.7, 128.3, 128.2, 83.7 (md), 83.5 (Md), 83.3 (Md), 82.9 (md), 66.8, 66.4, 53.5 (md), 52.1 (Md), 41.2, 30.7, 28.2 (Md), 28.2 (Md), 28.0 (md), 28.0 (md), 24.8, 9.5 (Md), 9.0 (md) ppm; MS (ESI) m/z = 499.5 $[M + Na]^+$. Elemental analysis calcd (%) for $C_{25}H_{36}N_2O_7$: C 63.01, H 7.61, N 5.88. Found (%): C 62.78, H 7.91, N 5.89.

General Procedure for the Synthesis of the 2-Oxoazepane Derivatives. A solution of the corresponding 1-*N*-Boc-2-oxoazetidine (0.71 mmol) in EtOAc or MeOH (55 mL) was treated with Pd/C (10% w/w). The suspension was hydrogenated at room temperature and atmospheric pressure for 4−6 h. After filtration of the catalyst, the solvent was evaporated. Purification by column chromatograhy was required in some instances.

(4*R*,*S*)-4-(*tert*-Butoxycarbonyl)amino-4-methoxycarbonyl-perhydro-2-oxoazepane (24). Solid: mp 179−180 °C (EtOAc/cyclohexane); yield, 81%; eluent, MeOH/CH_2Cl_2 (1:15); ^{1}H NMR

(300 MHz, MeOD) δ 3.71 (s, 3H), 3.29 (m, 3H, including d at 3.20 ppm, J = 13.8 Hz), 3.09 (d, J = 13.8 Hz, 1H), 1.92 (m, 4H), 1.43 ppm (s, 9H); ^{13}C NMR (75 MHz, MeOD) δ 176.3, 176.2, 157.2, 80.6, 58.5, 52.9, 49.2, 42.3, 38.9, 28.7, 25.4 ppm; MS (ESI) m/z = 287.2 $[M + H]^+$. Elemental analysis calcd (%) for $C_{13}H_{22}N_2O_5$: C 54.53, H 7.74, N 9.78. Found: C 54.29, H 7.59, N 9.65.

(4*R*,*S*)-4-(*tert*-Butoxycarbonyl)amino-4-*tert*-butoxycarbonylperhydro-2-oxoazepane (25). Solid: mp 214−215 °C (EtOAc/cyclohexane); yield, 83%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (br s, 1H), 5.08 (br s, 1H), 3.20 (m, 2H), 2.91 (m, 2H), 2.50 (m, 1H), 2.04 (m, 1H), 1.75 (m, 2H), 1.43 ppm (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 173.6, 154.6, 81.7, 79.7, 57.1, 43.0, 42.0, 35.0, 28.2, 27.7, 24.6 ppm; MS (ESI) m/z = 351.2 $[M + Na]^+$. Elemental analysis calcd (%) for $C_{16}H_{28}N_2O_5$: C 58.52, H 8.59, N 8.53. Found: C 58.37, H 8.60, N 8.40.

4-(*tert*-Butoxycarbonyl)amino-4-methoxycarbonyl-3-methyl-2-oxoazepane (35). *(3S,4S)-**35a***. Solid: mp 138−140 °C (EtOAc/cyclohexane); yield, 72%; eluent, EtOAc/hexane (1:2); $[\alpha]_D^{20}$ = −40.2 (c = 0.7 in $CHCl_3$); HPLC t_R = 3.28 min (A/B = 40:60); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.29 (s, 1H), 4.86 (s, 1H), 3.73 (s, 3H), 3.32 (m, 1H), 3.22 (m, 1H), 3.11 (q, J = 7.0 Hz, 1H), 3.05 (m, 1H), 2.18 (m, 1H), 1.73 (m, 2H), 1.41 (s, 9H), 1.04 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 172.7, 155.2, 79.8, 61.3, 52.3, 43.7, 42.0, 35.8, 28.2, 24.8, 12.8 ppm; MS (ESI) m/z = 323.3 $[M + Na]^+$. Elemental analysis calcd (%) for $C_{14}H_{24}N_2O_5$: C 55.98, H 8.05, N 9.33. Found (%): C 55.73, H 8.18, N 9.11.

*(3R,4S)-**35b** (md).* Solid: mp 132−134 °C (EtOAc/cyclohexane); yield, 6%; eluent, EtOAc/hexane (2:1); $[\alpha]_D^{20}$ = −18.0 (c = 0.8 in $CHCl_3$); HPLC t_R = 8.80 min (gradient A/B from 95:5 to 20:80 over 20 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11 (s, 1H), 5.30 (s, 1H), 3.73 (s, 3H), 3.27 (m, 3H), 2.70 (m, 1H), 2.16 (m, 1H), 1.83 (m, 2H), 1.42 (s, 9H), 1.21 (d, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 173.0, 154.6, 80.3, 61.4, 52.7, 47.6, 41.7, 31.1, 28.4, 25.2, 11.4 ppm; MS (ESI) m/z = 301.2 $[M + H]^+$, 323.1 $[M + Na]^+$. Elemental analysis calcd (%) for $C_{14}H_{24}N_2O_5$: C 55.98, H 8.05, N 9.33. Found (%): C 55.73, H 8.18, N 9.11.

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-1,6-diazaspiro[3.5]nonane-2,5-dione (35c). Syrup: yield, 14%; eluent, EtOAc/hexane (2:1); HPLC t_R = 8.58 min (gradient A/B from 95:5 to 20:80 over 20 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (br s, 1H), 3.45 (q, J = 7.7 Hz, 1H), 3.35 (m, 2H), 2.38 (td, J = 13.4 Hz, J = 3.1 Hz, 1H), 2.16 (m, 1H), 2.02 (m, 1H), 1.70 (m, 1H), 1.49 (s, 9H), 1.29 (d, J = 7.7 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 167.4, 154.5, 83.3, 60.4, 53.1, 42.4, 28.0, 26.0, 21.0, 8.6 ppm; MS (ESI) m/z = 291.0 $[M + Na]^+$.

4-*tert*-Butoxycarbonyl-4-(*tert*-butoxycarbonyl)amino-3-methyl-2-oxoazepane (36). *(3S,4S)-**36a***. Solid: mp 132−135 °C (EtOAc/cyclohexane); yield, 70%; eluent, MeOH/CH_2Cl_2 (1:60); $[\alpha]_D^{20}$ = −46.6 (c = 1.4 in $CHCl_3$); HPLC t_R = 4.91 min (A/B = 50:50); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.60 (s, 1H), 4.84 (s, 1H), 3.31 (m, 1H), 3.19 (m, 1H), 3.08 (q, J = 7.0, Hz, 1H), 2.98 (m, 1H), 2.11 (m, 1H), 1.65 (m, 2H), 1.44 (s, 9H), 1.38 (s, 9H), 1.09 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 171.3, 154.8, 82.2, 79.3, 60.9, 43.7, 42.1, 35.9, 28.3, 27.9, 24.9, 12.7 ppm; MS (ESI) m/z = 365.4 $[M + Na]^+$. Elemental analysis calcd (%) for $C_{17}H_{30}N_2O_5$: C 59.63, H 8.83, N 8.18. Found (%): C 59.48, H 9.12, N 8.10.

*(3R,4S)-**36b** (md).* Syrup: yield, 5%; eluent, MeOH/CH_2Cl_2 (1:120); $[\alpha]_D^{20}$ = −1.5 (c = 1.3 in $CHCl_3$); HPLC t_R = 13.15 min (gradient A/B from 95:5 to 20:80 over 20 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.31 (s, 1H), 5.36 (s, 1H), 3.27 (m, 3H), 2.71 (m, 1H), 2.07 (m, 1H), 1.83 (m, 2H), 1.45 (s, 9H), 1.42 (s, 9H), 1.18 (d, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 171.3, 154.5, 82.9, 79.8, 61.5, 46.9, 41.9, 32.1, 28.6, 28.0, 25.8, 11.5 ppm; MS (ESI) m/z = 365.2 $[M + Na]^+$. Elemental analysis calcd (%) for $C_{17}H_{30}N_2O_5$: C 59.63, H 8.83, N 8.18. Found (%): C 59.58, H 9.02, N 8.10.

(3*S*,4*S*)-4-(*tert*-Butoxycarbonyl)amino-1,3-dimethyl-4-methoxycarbonyl-2-oxoazepane (37a). A solution of the corresponding 2-oxoazepane derivative (0.64 mmol) in CH_3CN (9 mL) was treated with BTPP (0.59 mL, 1.93 mmol) and stirred at room temperature for 1 h. MeI (0.32 mL, 1.93 mmol) was then added to the reaction mixture. After stirring for 48 h, the solvent was evaporated under vacuum and the residue was extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure, leaving a residue that was purified by chromatography on silica gel using EtOAc/hexane (1:1). Solid: mp 76−79 °C (EtOAc/cyclohexane); yield, 21% (68% of starting material recovered); $[\alpha]_D^{20}$ = −37.8 (c = 0.7 in $CHCl_3$); HPLC t_R = 5.57 min (A/B = 40:60); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.92 (s, 1H), 3.72 (s, 3H), 3.72 (m, 1H), 3.19 (q, J = 6.9 Hz, 1H), 3.15 (m, 1H), 3.01 (s, 3H), 2.97 (m, 1H), 2.21 (m, 1H), 1.70 (m, 2H), 1.41 (s, 9H), 1.04 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 172.8, 172.7, 155.3, 79.6, 61.4, 52.1, 50.5, 43.3, 36.2, 35.3, 28.2, 24.8, 12.8 ppm; MS (ESI) m/z = 337.4 $[M + Na]^+$. Elemental analysis calcd (%) for $C_{15}H_{26}N_2O_5$: C 57.31, H 8.34, N 8.91. Found (%): C 57.18, H 8.07, N 9.04.

(3*S*,4*S*)-1-Benzyl-4-(*tert*-butoxycarbonyl)amino-4-methoxycarbonyl-3-methyl-2-oxoazepane (38a). BTPP (0.53 mL, 1.72 mmol) and BnBr (0.21 mL, 1.72 mmol) were added to a solution of 2-oxoazepane derivative (0.57 mmol) in CH_3CN (4 mL). After microwave heating at 120 °C for 45 min, the solvent was evaporated to dryness, and the residue was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel using EtOAc/hexane (1:2). Syrup: yield, 91%; $[\alpha]_D^{20}$ = −78.6 (c = 0.5 in $CHCl_3$); HPLC t_R = 11.23 min (A/B = 50:50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.31 (m, 5H), 4.98 (s, 1H), 4.80 (d, J = 14.7 Hz, 1H), 4.44 (d, J = 14.7 Hz, 1H), 3.72 (s, 3H), 3.57 (m, 1H), 3.23 (q, J = 6.9 Hz, 1H), 3.21 (m, 1H), 2.92 (m, 1H), 2.14 (m, 1H), 1.57 (m, 2H), 1.42 (s, 9H), 1.09 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 172.6, 155.1, 137.2, 128.5, 128.4, 127.5, 79.5, 61.5, 52.2, 51.7, 48.0, 43.7, 35.2, 28.3, 23.4, 13.6 ppm; MS (ESI) m/z = 391.5 $[M + H]^+$, 413.3 $[M + Na]^+$. Elemental analysis calcd (%) for $C_{21}H_{30}N_2O_5$: C 64.59, H 7.74, N 7.17. Found (%): C 64.36, H 7.53, N 6.89.

Boc-Oaz(Bn)-Ala-NHMe (39). A solution of compound **38a** (0.132 g, 0.34 mmol) in MeOH (2 mL) was treated with 2 N NaOH (1.014 mL, 2.03 mmol) and stirred at room temperature for 5 days. Then, the solvent was evaporated to dryness, and the residue was dissolved in H_2O and washed with EtOAc. The aqueous phase was acidified with 1 M HCl to pH 3 and extracted with EtOAc. The organic phase was separated and dried over Na_2SO_4, evaporated to dryness, and dissolved in dry CH_2Cl_2 (7 mL). This solution was treated with H-Ala-NHMe·HCl (0.067 g, 0.49 mmol), BOP (0.215 g, 0.49 mmol), and TEA (0.135 mL, 0.97 mmol). After being stirred for 24 h at room temperature, the solution was washed successively with citric acid (10%), $NaHCO_3$ (10%), H_2O, and brine. The organic phase was dried over Na_2SO_4 and evaporated to dryness. The residue was purified by chromatography on silica gel using MeOH/CH_2Cl_2 (1:40). Solid: mp 104−107 °C (EtOAc/cyclohexane); yield, 64%; $[\alpha]_D^{20}$ = −70.8 (c = 1.0 in $CHCl_3$); HPLC t_R = 4.33 min (gradient A/B from 90:10 to 0:100 over 10 min); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (s, 1H), 7.44 (s, 1H), 7.26−7.33 (m, 5H), 5.51 (s, 1H), 4.79 (d, J = 14.5 Hz, 1H), 4.30 (d, J = 14.5 Hz, 1H), 4.22 (quint, J = 7.2 Hz, 1H), 3.66 (m, 1H), 3.41 (q, J = 7.0 Hz, 1H), 3.21 (m, 1H), 2.56 (d, J = 4.6 Hz, 3H), 2.42 (m, 1H), 2.14 (m, 1H), 1.47 (m, 1H), 1.40 (s, 9H), 1.23 (d, J = 7.2 Hz, 3H), 1.08 (m, 1H), 1.01 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.3, 172.3, 171.1, 154.5, 138.0, 128.3, 128.1, 127.2, 79.2, 60.6, 50.8, 48.6, 47.0, 42.7, 33.5, 28.0, 25.5, 23.2, 17.6, 13.2 ppm; MS (ESI) m/z = 461.3 $[M + H]^+$, 483.3 $[M + Na]^+$. Elemental analysis calcd (%) for $C_{24}H_{36}N_4O_5$: C 62.59, H 7.88, N 12.16. Found (%): C6 2.27, H 7.95, N 12.05.

Piv-Oaz(Bn)-Ala-NHMe (40). Dipeptide derivative **39** (0.046 g, 0.10 mmol) was dissolved in a solution of HCl/EtOAc (2.5 mL, 3.2 M), and the solution was stirred at room temperature for 4 h. After evaporation of the solvent, the crude mixture was dissolved in dry CH_2Cl_2 (6 mL) and TEA (0.014 mL, 0.10 mmol), propylene oxide (0.111 mL, 1.59 mmol) and pivaloyl chloride (0.014 mL, 0.11 mmol) were added. The solution was stirred for 18 h at room temperature, the solvent was evaporated to dryness, and the residue was purified by chromatography on silica gel using MeOH/CH_2Cl_2 (1:30). Syrup: yield, 84%; $[\alpha]_D^{20} = -5.5$ ($c = 0.4$ in $CHCl_3$); HPLC $t_R = 11.72$ min (gradient A/B from 95:5 to 20:80 over 20 min); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (d, $J = 7.2$ Hz, 1H), 7.47 (q, $J = 4.6$ Hz, 3H), 7.24−7.34 (m, 5H), 6.36 (s, 1H), 4.68 (d, $J = 14.5$ Hz, 1H), 4.41 (d, $J = 14.5$ Hz, 1H), 4.25 (quint, $J = 7.2$ Hz, 1H), 3.71 (m, 1H), 3.43 (q, $J = 6.9$ Hz, 1H), 3.25 (m, 1H), 2.59 (m, 1H), 2.56 (d, $J = 4.6$ Hz, 3H,), 2.22 (m, 1H), 1.59 (m, 1H), 1.24 (d, $J = 7.2$ Hz, 3H), 1.15 (m, 1H), 1.09 (s, 9H), 1.03 (d, $J = 6.9$ Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 178.5, 173.6, 172.2, 170.2, 137.6, 128.4, 128.2, 127.2, 60.5, 50.5, 48.3, 47.1, 42.4, 32.8, 30.7, 26.8, 25.6, 23.1, 17.6, 13.5 ppm; MS (ESI) $m/z = 445.3$ $[M + H]^+$, 467.3 $[M + Na]^+$. Elemental analysis calcd (%) for $C_{24}H_{36}N_4O_4$: C 64.84, H 8.16, N 12.60. Found (%): C 64.66, H 7.89, N 8.21.

Preparation of Single Crystals for X-ray Diffraction Analysis. Pure compound **35a** (5 mg) was dissolved in CH_2Cl_2 (4 mL), and the mixture was put in a crystallizing dish, resulting in spontaneous crystallization after 4 days at room temperature in a closed jar.

Molecular Modeling Studies. Molecular dynamic simulations were carried out using the Amber 10 suite of programs,[35] with the ff99SB force field. Antechamber was used to assign atom types to model dipeptide **40** and to calculate a set of point charges using the AM1-BCC charge model. The Hawkins−Cramer−Truhlar pairwise generalized Born model was used. The molecule was relaxed by energy minimization, and then a molecular dynamic simulation was carried out over 40 ps at constant temperature (300 K). Then the system was heated to 1000 K over 350 ps and allowed to stay at this temperature for 100 ps. The structures were subsequently cooled slowly to 300 K in steps. In each step the temperature was lowered by 100 K, and the system was allowed to stay at the new temperature for 100 ps, with 200 ps extra at 300 K. The final conformation obtained was energy-refined using steepest descent followed by conjugate gradient algorithm, with a final gradient of 0.001 kcal/mol as the convergence criteria. The conformer was stored and used to start a new simulation at high temperature. This procedure afforded samples of 100 energy-minimized conformations, which were compared to each other to eliminate the identical ones. The resulting structures were visually inspected using the computer program VMD[36] and analyzed using the ptraj analysis program within Amber.

■ ASSOCIATED CONTENT

Supporting Information. X-ray packing of compound **35a**, NMR spectra for all new compounds, and crystal data. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ DEDICATION

Dedicated to the memory of Professor Rafael Suau.

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