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Regioselective Base-Promoted Nucleophilic Ring Opening of Spirocyclic 2,6-Dioxopiperazines: Synthesis of *N*-(1-Carboxycyclohexyl)amino Acid Derivatives

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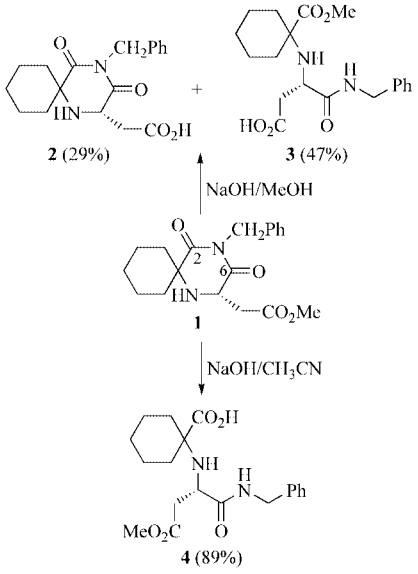
Amino acid derived spirocyclic 2,6-dioxopiperazines are easily and regioselectively opened by base-promoted nucleophilic attack of hydroxide or H_2O on the less crowded carbonyl group at C-6 to give *N*-(1-carbamoylcyclohexyl)amino acid derivatives. However, the imide group of the 2,6-dioxopiperazine ring is rather unreactive toward alcohols, alkoxides, and amines.

Introduction

In the context of a program focused on diversity-oriented synthesis for the search of new potential glutamate receptor ligands, we have recently reported a general method for the synthesis of α-amino acid derived spirocyclic 2,6-dioxopiperazines.[1] In this report, we commented that when we tried to obtain 2,6-dioxopiperazines containing free carboxylic acids by saponification of the corresponding methyl esters, we mainly obtained ring opening products, as shown in Scheme 1 for aspartic acid derived 2,6-dioxopiperazine **1**. This result was a consequence of the known high reactivity of imides toward nucleophiles in basic media, which has been synthetically used for the ring opening of *N*-acyl- or *N*-urethanelactam (hemicyclic imide) derivatives. Thus, the alcoholysis and aminolysis of *N*-Boc β-lactams have been applied to the synthesis of β-amino esters and β-amino amides, including peptides.[2] The intramolecular version of this aminolysis reaction of *N*-Boc β-lactams has been applied to the synthesis of macrocycles.[3] The nucleophilic ring opening of imides has also been applied to *N*-acyl- or *N*-urethanepyrrolidinone derivatives,[4] particularly to pyroglutamate derivatives,[5] to some bicyclic *N*-Boc lactams,[6] and to succinimide[7] and phthalimide[8] derivatives. With these precedents in mind, we considered the study of the nucleophilic ring opening of 2,6-dioxopiperazines as a potential source of diverse *N*-(carboxyalkyl)amino acid derivatives to be screened as potential glutamate receptor ligands. For this purpose, we have studied, and report herein, the reactivity of Phe-, Asp-, Glu-, and Trp-derived 2,6-dioxopiperazine-3-spirocyclohexanes in the presence of NaOH, H_2O, MeOH, EtOH, NaOMe, and NaOEt as O-nucleophiles, and H-Ala-OMe as a model for amine nucleophiles. As the nucleophile could attack either the C-2 or the C-6 positions of the dioxopiperazine ring, special attention was paid to its regioselectivity. The study was first carried out in parallel in 1-(methoxycarbonyl)methyl-substituted phenylalanine- and aspartic acid derived dioxopiperazines, and the reaction conditions that gave the best results were then applied to analogues derived from glutamic acid and tryptophan.



Scheme 1. Nucleophilic ring opening of 2,6-dioxopiperazine **1**.

Results and Discussion

As shown in Scheme 2, the reactivity of Phe-derived dioxopiperazine **5** varies depending on the nucleophile and the solvent. In each case, the disappearance of starting material **5**, and the appearance of reaction products, was fol-

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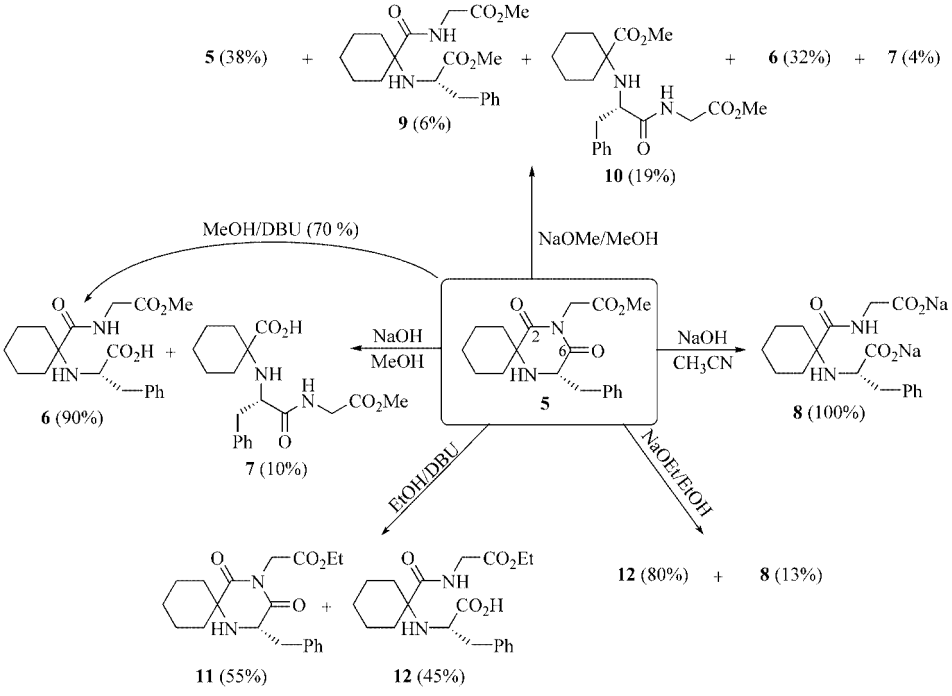
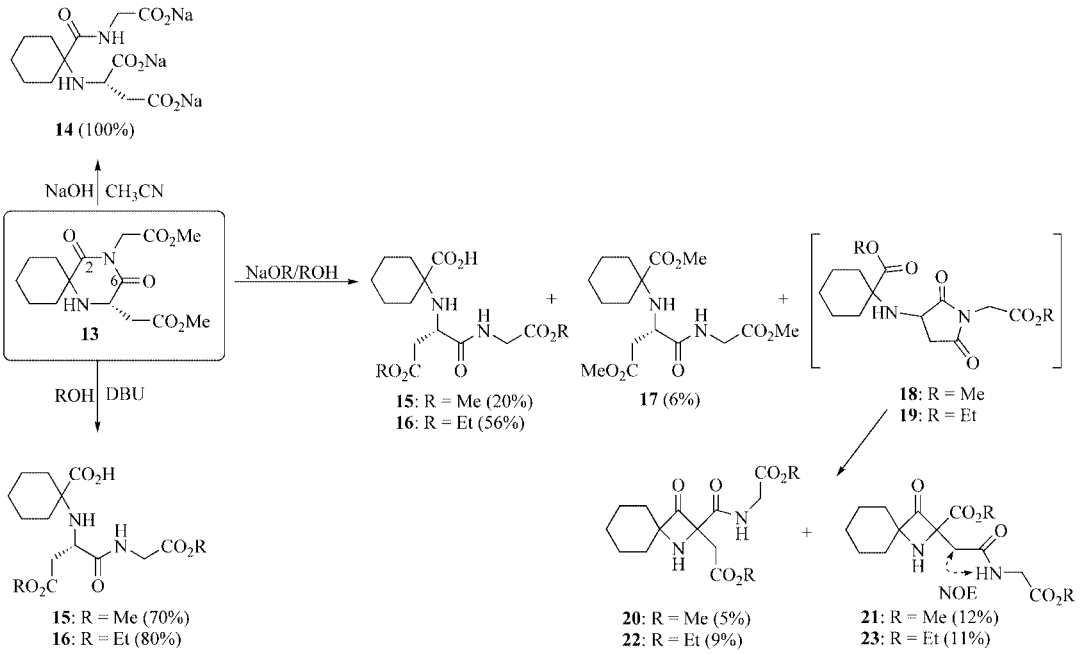
lowed by TLC and RP HPLC. First, under standard saponification conditions such as treatment with 1 equiv. of 1 N NaOH in MeOH/H_2O (9:1), a 9:1 mixture of carboxylic acids **6** and **7**, which result from NaOH nucleophilic attack at the C-6 and C-2 positions, respectively, was obtained after 6 h of reaction followed by neutralization. The replacement of MeOH by CH_3CN required 2 equiv. of 1 N NaOH for complete reaction and exclusively afforded disodium salt **8**, which results from the regioselective ring opening at C-6 by NaOH and simultaneous saponification of the methoxycarbonyl group. In view of the high purity of disodium salt **8** observed in its RP HPLC analysis, and because of the difficulty of extraction of the corresponding dicarboxylic acid from the aqueous phase after neutralization, either with 1 N HCl solution or with acid resin Dowex 50X, **8** was quantitatively obtained from the aqueous phase by lyophilization. Subsequently, to avoid the preferred ring opening by hydroxide and to facilitate the nucleophile attack of MeOH, the nucleophilic base NaOH was replaced by non-nucleophilic 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and by using absolute MeOH as the solvent. However, under these conditions, starting dioxopiperazine **5** opened very slowly (>28 d for complete reaction) to carboxylic acid **6**, by the action of H_2O traces in the reaction medium, and we could not detect any product resulting from a ring opening reaction by MeOH. The treatment of dioxopiperazine **5** with 1 equiv. of NaOMe in dry MeOH for 2 d gave a complex mixture of products, which included carboxylic acids **6** and **7** (32 and 4%, respectively) and the two possible products of ring opening by NaOMe, **9** and **10**, which were chromatographically isolated from the organic extract of the crude reaction mixture in 6 and 19% yield, respectively. Interestingly, the regioselectivity of this ring opening by NaOMe was opposite to the one previously observed for the ring opening by NaOH or H_2O. The treatment of **5** with1 equiv. of DBU in absolute EtOH gave first (24 h) the product of transesterification, **11**, followed by the slow (28 d, 45% of conversion) and regioselective ring opening at C-6 by traces of water in the reaction medium to give carboxylic acid **12**. The results of the treatment with NaOEt/EtOH were similar, except that the ring opening reaction was faster (2 d, total opening) and ring opened and saponified product **8** was obtained in a 13% yield. Finally, the results of the treatment of **5** with 1 equiv. of H-L-Ala-OMe, in the presence of 1 equiv. of DBU in dry CH_3CN either at room temperature or 60 °C, were similar to those obtained in the treatment with DBU/MeOH, which resulted in a 70% yield of carboxylic acid **6** after 28 d. Unfortunately, the ring opening reaction with the amino acid to give any of the two possible pseudotetrapeptides was not observed.

As shown in Scheme 3, the reactivity of aspartic acid derived dioxopiperazine **13** with nucleophiles was in part different to that above described for Phe analogue **5**. Thus, the treatment of **13** with 3 equiv. of 1 N NaOH in CH_3CN/H_2O (9:1) also produced the simultaneous ring opening at the C-6–N bond and saponification of the methoxycarbonyl groups, which quantitatively led to trisodium salt **14**. Also similarly, the treatment of **13** with DBU in absolute MeOH or EtOH led only to the slow ring opening (>28 d) by water traces in the reaction medium, but, differing from **5**, in this case the opening took place exclusively at the N–C-2 bond to give **15** and **16**, respectively. As in Phe-derived dioxopiperazine **5**, treatment with EtOH led to the transesterification of the two methoxycarbonyl groups of **13** prior to the ring opening reaction. Finally, the treatment of this dioxo-



Scheme 2. Reactivity of Phe-derived dioxopiperazine **5** with O-nucleophiles.



Scheme 3. Reactivity of Asp-derived dioxopiperazine **13** with O-nucleophiles.

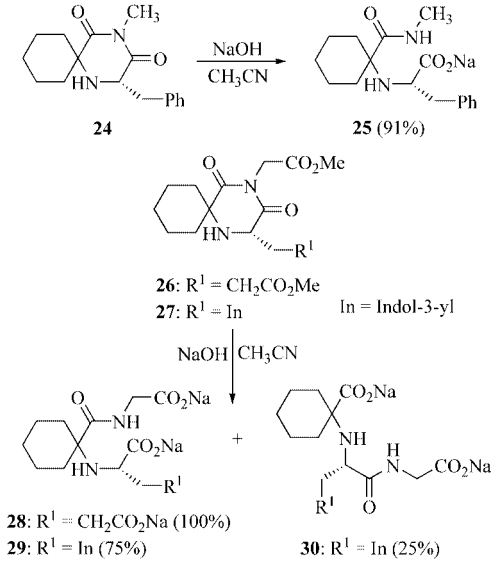
piperazine with NaOMe and NaOEt in the corresponding dry alcohol led to a complex mixture of products of ring opening in both cases. Thus, the treatment with 2 equiv. of NaOMe at room temperature for 2 d gave the mixture of the products of ring opening at the N–C-2 bond by H_2O **15** (20%) and by NaOMe **17** (6%), along with 3-oxoazetidines **20** (5%) and **21** (12%). Although we cannot unequivocally explain the mechanism of the formation of these 3-oxoazetidine derivatives, we assume the formation of an aspartimide intermediate like **18**, in which the base would remove the Asp α-proton, and the resulting carbanion would attack the alkoxycarbonyl group, which would form the C-3′–C-4′ bond of the azetidine ring. Simultaneously, or subsequently, the aspartimide ring would be opened by the alkoxide to give corresponding α-Asp and β-Asp derivatives **20** and **21**. The formation of aspartimide intermediates is very frequent in peptides that contain the sequence Asp-Xaa, particularly when Xaa = Gly,[9] as in **13**, which could be considered as a conformationally restricted analogue of the Asp-Gly dipeptide. Aspartimide derivatives are easily opened in either basic or acidic media to give preferably β-Asp derivatives.[9c] The reactivity of **13** with NaOEt/EtOH was parallel to that observed with NaOMe/MeOH, except for the absence of the OEt analogue of **17**, which would be the product of ring opening by NaOEt.

The structural assignment of 3-oxoazetidine derivatives **20**–**23** was based on their ESMS and NMR spectroscopic data. With respect to starting dioxopiperazine **13**, the ^1H NMR spectra showed the disappearance of the 5-H proton (corresponding to the Asp α-H) and a higher than 1 ppm deshielding for the 5-CH_2 protons (corresponding to the Asp β-H), which appeared as two doublets with a difference in their chemical shift higher than 0.5 ppm. The ^{13}C NMR spectra showed the presence of the 3-oxocarbonylic carbon at 211–213 ppm, the conversion of the tertiary C-5 at 50–52 ppm into a quaternary carbon at 56–58 ppm, and a significant deshielding of ≈ 20 ppm for the Asp C-β. The difference between α-Asp (**20** and **22**) and β-Asp derivatives (**21** and **23**) was based on the NOE effects between the Gly NH and the Asp β-H protons observed in the 1D NOESY spectra of β-Asp derivatives **21** and **23** (shown in Scheme 3).[9b] Furthermore, as it has been described previously,[9a,9b,9d] α-Asp derivatives (**20** and **22**) showed higher t_R in their RP HPLC analysis than the corresponding β-Asp analogues (**21** and **23**).

With the limited number of 3-oxoazetidine derivatives described in the literature in mind, as well as the scarce number of methods for their preparation,[10] we tried to improve the yield of spirocyclic 3-oxoazetidines **20**–**23** by increasing the number of equivalents of sodium alkoxide from 2 to 10 equiv., or the reaction time from 2 to 5 d, but these attempts were unsuccessful.

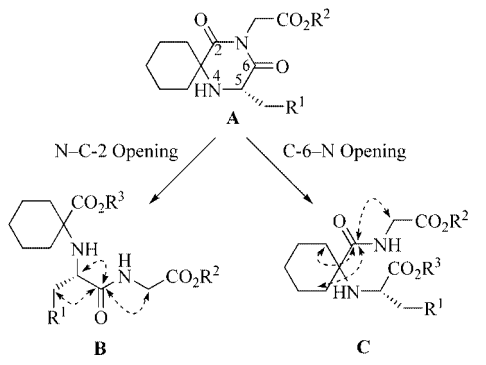
The overall results of the aforementioned studies showed the high reactivity of spirocyclic 2,6-dioxopiperazines **5** and **13** toward hydroxide or H_2O, and its low reactivity toward more voluminous O-nucleophiles, such as alcohols, alkoxides, and amines. For both dioxopiperazines **5** and **13**, nucleophilic attack was regioselective, although the selectivity depended on the amino acid side chain and on the nucleophile. Thus, in Phe-derived dioxopiperazine **5** the C-6 carbonyl group was the most reactive, except for the attack by NaOMe, whereas in Asp-derived analogue **13**, the C-2 carbonyl was more reactive, except for the treatment with NaOH in CH_3CN, where both dioxopiperazines opened exclusively at the C-6–N bond. In view of these results, we decided to apply these last conditions to the ring opening of other dioxopiperazines derived from phenylalanine (**24**), glutamic acid (**26**) and tryptophan (**27**). As shown in

Scheme 4, the treatment of the Phe- and Glu-derived dioxopiperazines (**24** and **26**) in CH_3CN with 2 and 3 equiv. of 1 N NaOH, respectively, after 2 h at room temperature followed by lyophylization, produced the simultaneous ring opening at the C-6–N bond and the saponification of the methoxycarbonyl groups, to give corresponding sodium salts **25** and **28**, with a purity higher than 95% by NMR and RP HPLC analysis. However, in the case of Trp derivative **27**, a similar treatment with 2 equiv. of 1 N NaOH in CH_3CN led to a 3:1 mixture of sodium salts **29** and **30**, which could not be separated.



Scheme 4. NaOH-mediated ring opening of Phe-, Glu-, and Trp-derived dioxopiperazines.

In all cases, the opening position at the 2,6-dioxopiperazine ring was assigned on the basis of the ^1H- and ^{13}C NMR spectroscopic evidence and the multiple bond correlations observed in the HMBC spectra of the resulting *N*-(1-carboxycyclohexyl)amino acid derivatives. Thus, in compounds resulting from the N–C-2 bond opening, we observed correlation of the carbamoyl group carbon with the amino acid α- and β-protons and with the α-protons of glycine (Scheme 5, **B**), whereas in compounds resulting from the C-6–N bond opening, the carbamoyl group carbon correlated with the α-protons of Gly, or the Me group protons of **25**, and in some cases, with 2-H and 6-H protons of the cyclohexyl ring (Scheme 5, **C**). The difference between the free carboxylic acid and the alkoxycarbonyl groups was established by the correlation of the corresponding carbonylic carbon with the alkoxy protons in the ester groups.



Scheme 5. Opening position assignment based on HMBC ^1H- and ^{13}C NMR correlations.

The free carboxylic acids or sodium salts **6**–**8**, **12**, **14**–**16**, **25**, and **28**–**30** were assayed as glutamate receptor ligands by measuring the displacement of L-[^{3}H]glutamate from rat brain synaptic membranes following a described procedure.[11] Unfortunately, no displacement was found with the use of concentrations up to 100 μM.

Conclusions

In conclusion, the overall results herein reported show the high reactivity of spirocyclic 2,6-dioxopiperazines toward low volume O-nucleophiles, such as hydroxide and H_2O, and the high preference for the ring opening by the nucleophilic attack on the less crowded carbonyl group at C-6. The resulting compounds did not show significant affinity for glutamate receptors. However, taking into account the importance of *N*-(carboxyalkyl)amino acids as peptidase inhibitors, the new *N*-(1-carbamoylcyclohexyl)amino acid derivatives herein described could have potential application in that therapeutic field.[12] The steric hindrance around the imide group of the 2,6-dioxopiperazine ring could explain its low or lack of reactivity toward alcohols, alkoxides, and amines.

Experimental Section

General: All reagents were of commercial quality. Solvents were dried and purified by standard methods. Analytical TLC was performed with aluminium sheets coated with a 0.2 mm layer of silica gel 60 F_{254}. Silica gel 60 (230–400 mesh) was used for flash chromatography. Preparative circular chromatography was performed with 20 cm diameter glass plates coated with a 1 mm layer of silica gel PF_{254}. Analytical RP-HPLC was performed with a Novapak C_{18} (3.9 × 150 mm, 4 μm) column, with a flow rate of 1 mL/min, and by using a tunable UV detector set at 214 nm. Mixtures of CH_3CN (solvent A) and 0.05% TFA in H_2O (solvent B) were used as mobile phases. ^1H NMR spectra were recorded at 300, 400 or 500 MHz, using TMS as reference, and ^{13}C NMR spectra were recorded at 75, 100 or 125 MHz. The NMR spectra assignment was based on COSY, HSQC, and HMBC spectra. ESMS spectra were performed in positive mode by using MeOH as the solvent.

Ring Opening of Phe-Derived 2,6-Dioxopiperazine 5 by NaOH/MeOH. Method A: Synthesis of a 9:1 Mixture of Carboxylic Acids 6 and 7: NaOH (1 N 0.2 mL, 0.2 mmol) was added to a solution of dioxopiperazine **5** (68.8 mg, 0.2 mmol) in MeOH/H_2O (9:1, 3 mL). After 6 h of stirring at room temperature, the solution was concentrated under reduced pressure, and the residue was dissolved in H_2O (4 mL). This solution was successively washed with CH_2Cl_2, acidulated with 1 N solution of HCl to pH 3, and extracted with EtOAc. The organic extracts were dried with Na_2SO_4 and the solvents evaporated to dryness to give a 9:1 mixture of carboxylic acids **6** and **7**, which could not be resolved. Carboxylic acid **6** was

isolated and characterized as a pure compound from the treatment of **5** with DBU in MeOH as below described.

Ring Opening of 2,6-Dioxopiperazines 5, 13, 24, 26, and 27 by NaOH/CH_3CN. Method B: General Method for the Synthesis of *N*-(1-Carbamoylcyclohexyl)amino Acid Derivatives 8, 14, 25, and 28–30: NaOH (1 N, 0.4 or 0.6 mmol) was added to a solution of the corresponding dioxopiperazine (0.2 mmol) in CH_3CN/H_2O (9:1, 3 mL). After 2 h of stirring at room temperature, the solution was concentrated under reduced pressure, and the residue was dissolved in H_2O (4 mL). This solution was successively washed with CH_2Cl_2 and lyophilized to give respective sodium salt **8**, **14**, **25**, and **28**–**30**, with a purity higher than 95% according to their NMR and RP HPLC analysis.

***N*-(1-Carboxymethylcarbamoyl)cyclohexyl-L-phenylalanine Disodium Salt (8):** Amorphous white solid (69.6 mg, 100%). ^{1}H NMR (500 MHz, D_2O): δ = 1.05-1.71 [m, 10 H, cyclohexyl], 2.51 [dd, J = 8.0 and 13.5 Hz, 1 H, β-H (Phe)], 2.70 [dd, J = 9.0 and 13.5 Hz, 1 H, β-H (Phe)], 2.84 [d, J = 17.0 Hz, 1 H, α-H (Gly)], 2.92 [dd, J = 8.0 and 9.0 Hz, 1 H, α-H (Phe)], 3.36 [d, J = 17.0 Hz, 1 H, α-H (Gly)], 7.12 [m, 5 H, Ph] ppm. ^{13}C NMR (125 MHz, D_2O): δ = 21.4 and 21.6 [C-3′ and C-5′], 24.9 [C-4′], 30.0 and 35.9 [C-2′ and C-6′], 41.6 [C-β (Phe)], 43.1 [C-α (Gly)], 61.9 [C-α (Phe)], 62.0 [C-1′], 126.8, 128.8, 129.7 and 138.9 [Ph], 176.5 [CO_2Na (Gly)], 178.8 [CO-NH], 183.6 [CO_2Na] ppm. ESMS: m/z = 349.2 [M + 1]$^+$. RP HPLC [Novapak C_{18} (3.9 × 150 mm, 4 μm), (A:B, 25:75)]: t_R = 1.85 min. According to NMR and RP HPLC analysis, the purity of **8** was higher than 95%.

***N*-(1-Carboxymethylcarbamoyl)cyclohexyl-L-aspartic Acid Trisodium Salt (14):** Solid (63.2 mg, 100%). Mp >350 °C. ^{1}H NMR (500 MHz, D_2O): δ = 1.10-1.69 [m, 10 H, cyclohexyl], 2.08 [dd, J = 4.0 and 14.0 Hz, 1 H, β-H (Asp)], 2.21 [dd, J = 10.0 and 14.0 Hz, 1 H, β-H (Asp)], 3.14 [dd, J = 4.0 and 10.0 Hz, 1 H, α-H (Asp)], 3.45 [d, J = 17.0 Hz, 1 H, α-H (Gly)], 3.56 [d, J = 17.0 Hz, 1 H, α-H (Gly)] ppm. ^{13}C NMR (125 MHz, D_2O): δ = 21.4 and 21.5 [C-3′ and C-5′], 25.0 [C-4′], 31.5 and 34.3 [C-2′ and C-6′], 43.3 [C-β (Asp)], 43.6 [C-α (Gly)], 57.1 [C-α (Asp)], 61.7 [C-1′], 177.3 [CO_2Na (Gly)], 179.2 [CO-NH], 180.1 [β-CO_2Na (Asp)], 183.6 [α-CO_2Na (Asp)] ppm. ESMS: m/z = 317.1 [M + 1]$^+$. RP HPLC [Novapak C_{18} (3.9 × 150 mm, 4 μm), (A:B, 25:75)]: t_R = 1.20 min. According to NMR and RP HPLC analysis, the purity of **14** was higher than 95%.

***N*-(1-Methylcarbamoyl)cyclohexyl-L-phenylalanine Sodium Salt (25):** Amorphous white solid (55.4 mg, 91%). ^{1}H NMR (400 MHz, D_2O): δ = 1.04–1.70 [m, 10 H, cyclohexyl], 2.41 [d, J = 4.0 Hz, 3 H, CH_3], 2.81 [dd, J = 4.5 and 13.5 Hz, 1 H, β-H (Phe)], 3.05 [dd, J = 9.0 and 13.5 Hz, 1 H, β-H (Phe)], 3.50 [dd, J = 4.5 and 9.0 Hz, 1 H, α-H (Phe)], 7.22 [m, 5 H, Ph] ppm. ^{13}C NMR (100 MHz, D_2O): δ = 21.9 and 22.0 [C-3′ and C-5′], 24.9 [C-4′], 26.2 [CH_3], 30.8 and 34.5 [C-2′ and C-6′], 39.6 [C-β (Phe)], 58.9 [C-α (Phe)], 63.3 [C-1′], 127.0, 128.6, 129.6 and 136.9 [Ph], 173.1 [CO-NH], 176.0 [CO_2Na] ppm. ESMS: m/z = 305.2 [M + 1]$^+$. RP HPLC [Novapak C_{18} (3.9 × 150 mm, 4 μm), (A:B, 25:75)]: t_R = 5.39 min. According to NMR and RP HPLC analysis, the purity of **25** was higher than 95%.

***N*-(1-Carboxymethylcarbamoyl)cyclohexyl-L-glutamic Acid Trisodium Salt (28):** Amorphous white solid (66.0 mg, 100%). ^{1}H NMR (400 MHz, D_2O): δ = 1.11–1.82 [m, 10 H, cyclohexyl], 1.58–1.82 [m, 2 H, β-H (Glu)], 1.94–2.08 [m, 2 H, γ-H (Glu)], 2.91 [dd, J = 5.0 and 6.0 Hz, 1 H, α-H (Glu)], 3.59 [s, 2 H, α-H (Gly)] ppm. ^{13}C NMR (100 MHz, D_2O): δ = 21.8 and 21.9 [C-3′ and C-5′], 24.9 [C-4′], 31.4 and 34.3 [C-2′ and C-6′], 31.4 [C-β (Glu)], 34.3 [C-γ (Glu)], 43.5 [C-α (Gly)], 58.8 [C-α (Glu)], 62.6 [C-1′], 176.8 [α-CO_2Na (Glu)], 177.1 [γ-CO_2Na (Glu)], 182.2 [CO-NH], 182.9 [CO_2Na (Gly)] ppm. ESMS: m/z = 331.0 [M + 1]$^+$. RP HPLC [Novapak C_{18} (3.9 × 150 mm, 4 μm), (A:B, 20:80)]: t_R = 1.30 min. According to NMR and RP HPLC analysis, the purity of **28** was higher than 95%.

Mixture (3:1) of *N*-(1-Carboxymethylcarbamoyl)cyclohexyl-L-tryptophan Disodium Salt (29) and *N*-(1-Carboxy)cyclohexyl-L-Trp-Gly-OH Disodium Salt (30): Amorphous white solid (77.5 mg, 100%). ^{1}H NMR (500 MHz, D_2O): δ = 1.04–1.70 [m, 10 H, cyclohexyl], 2.06 [d, J = 17.0 Hz, 0.75 H, α-H (Gly)], 2.67 [dd, J = 10.5 and 14.0 Hz, 0.75 H, β-H (Trp)], 2.92–2.96 [dd, J = 6.0 and 13.5 Hz, 0.25 H, β-H (Trp)], 2.94 [dd, J = 4.0 and 14.0 Hz, 0.75 H, β-H (Trp)], 3.01 [dd, J = 8.0 and 13.5 Hz, 0.25 H, β-H (Trp)], 3.09 [dd, J = 4.0 and 10.5 Hz, 0.75 H, α-H (Trp)], 3.09 [d, J = 17.0 Hz, 0.75 H, α-H (Gly)], 3.36 [d, J = 18.0 Hz, 0.25 H, α-H (Gly)], 3.36 [dd, J = 6.0 and 8.0 Hz, 0.25 H, α-H (Trp)], 3.42 [d, J = 18.0 Hz, 0.25 H, α-H (Gly)], 6.99-7.03 [m, 2 H, 2-H and 6-H (indol)], 7.08 [t, J = 6.5 Hz, 1 H, 5-H (indol)], 7.32 [d, J = 8.0 Hz, 1 H, 7-H (indol)], 7.50 [d, J = 8.0 Hz, 0.25 H, 4-H (indol)], 7.55 [d, J = 8.0 Hz, 0.75 H, 4-H (indol)] ppm. ^{13}C NMR (125 MHz, D_2O): δ = 21.3, 21.5 and 22.8 [C-3′ and C-5′], 24.9 and 25.3 [C-4′], 29.9 and 32.4 [C-β (Trp)], 31.2, 35.8 and 35.9 [C-2′ and C-6′], 42.3 and 43.2 [C-α (Gly)], 58.0 and 60.3 [C-α (Trp)], 61.8 and 62.1 [C-1′], 111.2 and 111.8 [C-3 (indol)], 118.8 [C-6 (indol)], 119.3 and 119.4 [C-4 (indol)], 121.9 and 122.1 [C-5 (indol)], 124.7 [C-2 (indol)], 127.0 [C-3a (indol)], 136.2 and 136.5 [C-7a (indol)], 176.3 [CO_2Na (Gly)], 182.6 [CO-NH], 184.4 [CO_2Na] ppm. ESMS: m/z = 388.3 [M + 1]$^+$. RP HPLC [Novapak C_{18} (3.9 × 150 mm, 4 μm), (A:B, 25:75)]: t_R = 2.11 (75%, **29**) and 2.39 (25%, **30**) min;

General Procedure for the Study of Reactivity of Phe- and Asp-Derived 2,6-Dioxopiperazines 5 and 13 toward Alcohols and Alkoxides. Method C: Synthesis of 6, 9–12, and 15–23: DBU and NaOMe or NaOEt (0.4–4 mmol) were added to a solution of corresponding 2,6-dioxopiperazine **5** or **13** (0.2 mmol) in the appropriate dry alcohol (MeOH or EtOH, 3 mL), and the solution was stirred at room temperature (in all cases) and at 60 °C (in the studies of reactivity toward ROH/DBU) for a variable time (2–28 d), until complete conversion of the starting material or nonprogression of reaction (determined by TLC and RP HPLC analysis of the crude reaction mixture). After removal of the solvent to dryness, the residue was dissolved in H_2O (4 mL), and this solution was extracted with CH_2Cl_2. The organic extracts were dried with Na_2SO_4, evaporated to dryness, and the residue was resolved by circular chromatography, with the use of 20–100% gradient of EtOAc in hexane as the eluent, to obtain **9**–**11** (from **5**), **17**, and 3-oxoazetidine derivatives **20**–**23** (from **13**). The aqueous phase was either acidulated with 1 N HCl or lyophilized and processed as in method A or method B, respectively, to obtain respective carboxylic acids **6**, **12**, **15**, and **16**, and disodium salt **8**, as shown in Schemes 2 and 3.

***N*-(1-Methoxycarbonylmethylcarbamoyl)cyclohexyl-L-phenylalanine (6):** Foam (50.7 mg, 70%, from the treatment of **5** with MeOH/DBU). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 1.22-1.76 [m, 10 H, cyclohexyl], 2.75 [dd, J = 5.0 and 13.5 Hz, 1 H, β-H (Phe)], 2.85 [dd, J = 7.0 and 13.5 Hz, 1 H, β-H (Phe)], 3.04 [dd, J = 5.0 and 7.0 Hz, 1 H, α-H (Phe)], 3.53 [s, 3 H, OCH_3], 3.56 [s, 2 H, α-H (Gly)], 7.20 [m, 5 H, Ph], 8.07 [br. s, 1 H, CO-NH] ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 21.5 and 22.0 [C-3′ and C-5′], 25.4 [C-4′], 33.0 and 33.8 [C-2′ and C-6′], 40.1 [C-β (Phe)], 43.3 [C-α (Gly)], 51.6 [OCH_3], 59.5 [C-α (Phe)], 61.0 [C-1′], 125.7, 127.7, 129.9 and 140.1 [Ph], 170.3 [CO_2CH_3 (Gly)], 173.3 [CO-NH], 177.1 [CO_2H (Phe)] ppm. ESMS: m/z = 363.3 [M + 1]$^+$. RP HPLC [Novapak C_{18} (3.9 × 150 mm, 4 μm), (A:B, 25:75)]: t_R = 3.07 min.

$C_{19}H_{26}N_2O_5$ (362.18): calcd. C 62.97, H 7.23, N 7.73; found C 62.96, H 7.49, N 7.44.

Mixture (1:3) of *N*-(1-Methoxycarbonylmethylcarbamoyl)cyclohexyl-L-phenylalanine Methyl Ester (9) and *N*-(1-Methoxycarbonyl)-cyclohexyl-L-Phe-Gly-OMe (10): Foam (19.0 mg, 25%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.08–1.98 [m, 10 H, cyclohexyl], 2.78 [dd, J = 5.0 and 14.0 Hz, 0.25 H, β-H (Phe)], 2.82 [dd, J = 5.0 and 14.0 Hz, 0.75 H, β-H (Phe)], 2.91 [dd, J = 9.0 and 14.0 Hz, 0.25 H, β-H (Phe)], 2.94 [dd, J = 9.0 and 14.0 Hz, 0.75 H, β-H (Phe)], 3.41 [s, 3 H, OCH_3 (Gly)], 3.37 [dd, J = 9.0 and 14.0 Hz, 0.25 H, α-H (Phe)], 3.52 [dd, J = 9.0 and 14.0 Hz, 0.75 H, α-H (Phe)], 3.75 [s, 3 H, OCH_3], 3.99 [dd, J = 5.5 and 18.5 Hz, 1 H, α-H (Gly)], 4.09 [dd, J = 5.5 and 18.5 Hz, 1 H, α-H (Gly)], 7.24 [m, 5 H, Ph], 7.71 [t, J = 5.5 Hz, 1 H, CO-NH] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.9 and 22.3[C-3′ and C-5′], 25.3 [C-4′], 25.6 [C-4′], 31.3 and 36.6 [C-2′ and C-6′], 32.4 and 36.0 [C-2′ and C-6′], 39.9 [C-β (Phe)], 41.3 [C-α (Gly)], 41.9 [C-α (Gly)], 52.1 [OCH_3 (Gly)], 52.4 [OCH_3], 58.1 [C-α (Phe)], 58.5 [C-α (Phe)], 62.1 [C-1′], 62.4 [C-1′], 127.2, 129.0, 130.3 and 137.9 [Ph], 170.6 [CO_2CH_3 (Gly)], 174.5 [CO_2CH_3], 175.2 [CO-NH] ppm. ESMS: m/z = 377.2 [M + 1]$^+$. RP HPLC [Novapak C_{18} (3.9 × 150 mm, 4 μm), (A:B, 50:50)]: t_R = 2.69 (24%, **9**) and 2.29 (76%, **10**) min.

(5*S*)-1-Ethoxycarbonylmethyl-2,6-dioxo-5-phenylmethylpiperazine-3-spirocyclohexane (11): Foam (39.4 mg, 55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 [t, J = 7.0 Hz, 3 H, CH_3 (Et)], 1.12–1.62 (m, 8 H, cyclohexyl), 1.86 [m, 1 H, 2-H_{ec} (cyclohexyl)], 1.98 [m, 1 H, 6-H_{ax} (cyclohexyl)], 2.92 (dd, J = 8.0 and 14.0 Hz, 1 H, 5-CH_2), 3.33 (dd, J = 4.0 and 14.0 Hz, 1 H, 5-CH_2), 3.77 (dd, J = 4.0 and 8.0 Hz, 1 H, 5-H), 4.07 [q, J = 7.0 Hz, 2 H, CH_2 (Et)], 4.35 (s, 2 H, 1-CH_2), 7.19 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.4 [CH_3 (Et)], 19.8, 20.3, 25.0, 29.2, 33.6, and 36.8 (cyclohexyl), 40.4 (1-CH_2), 54.2 (C-5), 57.8 (C-3), 60.7 [CH_2 (Et)], 126.3, 127.7, 128.6 and 136.2 (Ph), 167.2 (CO_2Et), 172.3 (C-6), 175.7 (C-2) ppm. ESMS: m/z = 359.1 [M + 1]$^+$. RP HPLC [Novapak C_{18} (3.9 × 150 mm, 4 μm), (A:B, 50:50)]: t_R = 12.58 min. $C_{20}H_{26}N_2O_4$ (358.19): calcd. C 67.02, H 7.31, N 7.82; found C 67.26, H 7.39, N 7.62.

***N*-(1-Ethoxycarbonylmethylcarbamoyl)cyclohexyl-L-phenylalanine Methyl Ester (12):** Foam (33.9 mg, 45%, from the treatment of **5** with EtOH/DBU; 60.2 mg, 80%, from the treatment of **5** with NaOEt/EtOH). ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 1.22 [t, J = 7.0, 3 H, CH_3 (Et)], 1.24–2.04 [m, 10 H, cyclohexyl], 2.94 [d, J = 7.0 Hz, 2 H, β-H (Phe)], 3.50 [t, J = 7.0 Hz, 1 H, α-H (Phe)], 3.59 [d, J = 7.0 Hz, 1 H, α-H (Gly)], 3.64 [d, J = 7.0 Hz, 1 H, α-H (Gly)], 4.17 [q, J = 7.0 Hz, 2 H, CH_2 (Et)], 7.26 [m, 5 H, Ph] ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 14.5 [CH_3 (Et)], 23.2 and 23.6 [C-3′ and C-5′], 26.5 [C-4′], 32.5 and 37.3 [C-2′ and C-6′], 42.0 [C-β (Phe) and C-α (Gly)], 58.9 [C-α (Phe)], 61.7 [CH_2 (Et)], 62.2 [C-1′], 127.8, 129.4, 130.5 and 139.0 [Ph], 170.9 [CO_2Et (Gly)], 176.5 [CO-NH], 177.1 [CO_2H (Phe)] ppm. ESMS: m/z = 377.2 [M + 1]$^+$. RP HPLC [Novapak C_{18} (3.9 × 150 mm, 4 μm), (A:B, 25:75)]: t_R = 4.67 min. $C_{20}H_{28}N_2O_5$ (376.20): calcd. C 63.81, H 7.50, N 7.44; found C 63.57, H 7.64, N 7.66.

***N*-(1-Carboxy)cyclohexyl-L-Asp(OMe)-Gly-OMe (15):** Foam (48.2 mg, 70%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.26–1.96 [m, 10 H, cyclohexyl], 2.47–2.60 [m, 2 H, β-H (Asp)], 3.59 [s, 3 H, OCH_3], 3.74 [m, 1 H, α-H (Asp)], 4.32 [s, 2 H, α-H (Gly)] ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 20.2 and 21.5 [C-3′ and C-5′], 25.2 [C-4′], 32.6 and 33.6 [C-2′ and C-6′], 38.0 [C-β (Asp)], 40.7 [C-α (Gly)], 52.1 [OCH_3], 57.4 [C-α (Asp)], 61.1 [C-1′], 168.3 [CO-NH], 170.5 [CO_2Me (Gly)], 173.5 [CO_2Me (Asp)], 176.1 [CO_2H] ppm. ESMS: m/z = 345.2 [M + 1]$^+$. RP HPLC [Novapak C_{18} (3.9 × 150 mm, 4 μm), (A:B, 25:75)]: t_R = 1.64 min. $C_{15}H_{24}N_2O_7$ (344.16): calcd. C 52.32, H 7.02, N 8.13; found C 52.46, H 7.21, N 7.98.

***N*-(1-Carboxy)cyclohexyl-L-Asp(OEt)-Gly-OEt (16):** Foam (60.0 mg, 80%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.24 and 1.30 [t, J = 7 Hz, 3 H, CH_3 (Et)], 1.21–2.09 [m, 10 H, cyclohexyl], 2.75–3.06 [m, 2 H, β-H (Asp)], 3.79 [m, 1 H, α-H (Asp)], 4.01 [s, 2 H, α-H (Gly)], 4.13 and 4.21 [q, J = 7 Hz, 4 H, CH_2 (Et)], 9.07 [br. s, 1 H, CO-NH] ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 14.1 [CH_3 (Et)], 21.7 and 24.7 [C-3′ and C-5′], 25.8 [C-4′], 33.0 and 33.8 [C-2′ and C-6′], 40.6 [C-β (Asp)], 41.3 [C-α (Gly)], 55.1 [C-α (Asp)], 61.4 and 61.7 [CH_2 (Et)], 61.3 [C-1′], 168.4 [CO-NH], 170.2 [CO_2Et (Gly)], 173.4 [CO_2Et (Asp)], 178.4 [CO_2H] ppm. ESMS: m/z = 273.2 [M + 1]$^+$. RP HPLC [Novapak C_{18} (3.9 × 150 mm, 4 μm), (A:B, 25:75)]: t_R = 2.20 min. $C_{17}H_{28}N_2O_7$ (372.19): calcd. C 54.83, H 7.58, N 7.52; found C 55.01, H 7.68, N 7.62.

***N*-(1-Methoxycarbonyl)cyclohexyl-L-Asp(OMe)-Gly-OMe (17):** Foam (5 mg, 6%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24–2.03 [m, 10 H, cyclohexyl], 2.53 [dd, J = 6.0 and 13.0 Hz, 1 H, β-H (Asp)], 2.93 [dd, J = 6.0 and 13.0 Hz, 1 H, β-H (Asp)], 3.58 [t, J = 6.0 Hz, 1 H, α-H (Asp)], 3.66 [s, 3 H, OCH_3 (Asp)], 3.67 [s, 3 H, OCH_3], 3.75 [s, 3 H, OCH_3 (Gly)], 3.98 [dd, J = 5.0 and 18.0 Hz, 1 H, α-H (Gly)], 4.05 [dd, J = 6.0 and 18.0 Hz, 1 H, α-H (Gly)], 7.99 [br. s, 1 H, CO-NH] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.0 and 22.3 [C-3′ and C-5′], 25.4 [C-4′], 31.5 and 35.8 [C-2′ and C-6′], 36.2 [C-β (Asp)], 41.2 [C-α (Gly)], 51.8 [OCH_3 (Asp)], 51.9 [OCH_3], 52.3 [OCH_3 (Gly)], 52.4 [C-α (Asp)], 170.2 [CO_2Me (Gly)], 172.0 [CO_2Me (Asp)], 173.7 [CO-NH], 176.0 [CO_2Me] ppm. ESMS: m/z = 359.2 [M + 1]$^+$. RP HPLC [Novapak C_{18} (3.9 × 150 mm, 4 μm), (A:B, 50:50)]: t_R = 2.32 min. $C_{16}H_{26}N_2O_7$ (358.17): calcd. C 53.62, H 7.31, N 7.82; found C 53.64, H 7.54, N 7.72.

(*R*,*S*)-4′-Methoxycarbonylmethyl-4′-(methoxycarbonylmethyl)carbamoyl-3′-oxocyclohexanespiro-2′-azetidine (20): Foam (3.3 mg, 5%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24–1.76 [m, 10 H, cyclohexyl], 3.75 [s, 3 H, OCH_3 (Gly)], 3.79 [s, 3 H, OCH_3], 3.81 [d, J = 6.0 Hz, 1 H, 4′-CH_2], 4.02 [dd, J = 6.0 and 14.0 Hz, 1 H, α-H (Gly)], 4.12 [dd, J = 6.0 and 14.0 Hz, 1 H, α-H (Gly)], 4.38 [d, J = 6.0 Hz, 1 H, 4′-CH_2], 7.71 [br. s, 1 H, NH] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3 and 21.5 [C-3 and C-5], 25.0 [C-4], 32.7 and 33.1 [C-2 and C-6], 41.1 [C-α (Gly)], 52.4 [OCH_3 (Gly)], 53.1 [OCH_3], 55.8 [4′-CH_2], 58.4 [C-4′], 66.0 [C-2′], 168.2 [CO_2Me], 169.9 [CO_2Me (Gly)], 172.0 [CO-NH], 211.2 [C-3′] ppm. ESMS: m/z = 327.1 [M + 1]$^+$. RP HPLC [Novapak C_{18} (3.9 × 150 mm, 4 μm), (A:B, 25:75)]: t_R = 1.99 min. We did not obtain sufficient quantity for elemental analysis.

(*R*,*S*)-4′-Methoxycarbonyl-4′-(methoxycarbonylmethyl)carbamoylmethyl-3′-oxocyclohexanespiro-2′-azetidine (21): Foam (7.8 mg, 12%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23–1.76 [m, 10 H, cyclohexyl], 3.55 [d, J = 8.0 Hz, 1 H, 4′-CH_2], 3.75 [s, 3 H, OCH_3 (Gly)], 3.79 [s, 3 H, OCH_3], 4.02 [dd, J = 5.0 and 14.0 Hz, 1 H, α-H (Gly)], 4.10 [dd, J = 5.0 and 14.0 Hz, 1 H, α-H (Gly)], 4.23 [d, J = 8.0 Hz, 1 H, 4′-CH_2], 6.96 [br. s, 1 H, NH] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.0 and 21.4 [C-3 and C-5], 25.0 [C-4], 31.2 and 33.2 [C-2 and C-6], 41.4 [C-α (Gly)], 52.4 [OCH_3 (Gly)], 52.8 [OCH_3], 56.1 [4′-CH_2 and C-4′], 65.9 [C-2′], 164.9 [CO-NH], 169.7 [CO_2Me (Gly)], 173.0 [CO_2Me], 212.7 [C-3′] ppm. ESMS: m/z = 327.1 [M + 1]$^+$. RP HPLC [Novapak C_{18} (3.9 × 150 mm, 4 μm), (A:B, 25:75)]: t_R = 1.72 min. $C_{15}H_{22}N_2O_6$ (326.15): calcd. C 55.21, H 6.79, N 8.58; found C 55.56, H 6.89, N 8.77.

(*R*,*S*)-4′-Ethoxycarbonylmethyl-4′-(ethoxycarbonylmethyl)carbamoyl-3′-oxocyclohexanespiro-2′-azetidine (22): Foam (6.4 mg, 9%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 [t, J = 7.0 Hz, 3 H, OEt (Gly)],

1.29 [t, J = 7.0 Hz, 3 H, CH_3 (OEt)], 1.20-1.75 [m, 10 H, cyclohexyl], 3.77 [d, J = 5.5 Hz, 1 H, 4′-CH_2], 3.99 [dd, J = 5.5 and 18.0 Hz, 1 H, α-H (Gly)], 4.08 [dd, J = 7.0 and 18.0 Hz, 1 H, α-H (Gly)], 4.19 [q, J = 7.0 Hz, 2 H, OEt (Gly)], 4.22 [q, J = 7.0 Hz, 2 H, CH_2 (OEt)], 4.36 [d, J = 5.5 Hz, 1 H, 4′-CH_2], 7.71 [br. s, 1 H, NH] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0 [OEt (Gly)], 14.1 [CH_3 (OEt)], 21.3 and 21.5 [C-3 and C-5], 25.0 [C-4], 32.7 and 33.0 [C-2 and C-6], 41.3 [C-α (Gly)], 56.0 [4′-CH_2], 58.4 [C-4′], 61.6 [OEt (Gly)], 62.2 [CH_2 (OEt)], 65.9 [C-2′], 167.7 [CO_2Et], 169.5 [CO_2Et (Gly)], 172.0 [CO-NH], 211.1 [C-3′] ppm. ESMS: m/z = 355.2 [M + 1]$^+$. RP HPLC [Novapak C_{18} (3.9 × 150 mm, 4 μm), (A:B, 25:75)]: t_R = 4.29 min. $C_{17}H_{26}N_2O_6$ (354.18): calcd. C 57.61, H 7.39, N 7.90; found: C 57.82, H 7.61, N 8.12.

(*R*,*S*)-4′-Ethoxycarbonyl-4′-(ethoxycarbonylmethyl)carbamoylmethyl-3′-oxocyclohexanespiro-2′-azetidine (23): Foam (7.8 mg, 11%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 [t, J = 7.0 Hz, 3 H, OEt (Gly)], 1.28 [t, J = 7.0 Hz, 3 H, CH_3 (OEt)], 1.19–1.59 [m, 10 H, cyclohexyl], 3.57 [d, J = 5.5 Hz, 1 H, 4′-CH_2], 4.00 [dd, J = 5.0 and 18.5 Hz, 1 H, α-H (Gly)], 4.06 [dd, J = 5.0 and 18.5 Hz, 1 H, α-H (Gly)], 4.19 [q, J = 7.0 Hz, 2 H, OEt (Gly)], 4.23 [q, J = 7.0 Hz, 2 H, CH_2 (Et)], 4.50 [d, J = 5.5 Hz, 1 H, 4′-CH_2], 6.89 [br. s, 1 H, NH] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 [CH_3], 21.1 and 21.4 [C-3 and C-5], 25.1 [C-4], 31.3 and 33.1 [C-2 and C-6], 41.6 [C-α (Gly)], 56.2 [4′-CH_2], 56.4 [C-4′], 61.6 [OEt (Gly)], 61.9 [CH_2 (OEt)], 65.9 [C-2′], 165.0 [CO-NH], 169.3 [CO_2Et], 172.6 [CO_2Et (Gly)], 213.0 [C-3] ppm. ESMS: m/z = 355.2 [M + 1]$^+$. RP HPLC [Novapak C_{18} (3.9 × 150 mm, 4 μm), (A:B, 25:75)]: t_R = 3.79 min. $C_{17}H_{26}N_2O_6$ (354.18): calcd. C 57.61, H 7.39, N 7.90; found C 57.72, H 7.31, N 8.07.

Study of the Reactivity of Phe-Derived 2,6-Dioxopiperazine 5 toward H-L-Ala-OMe. Method D: A solution of H-L-Ala-OMe·HCl (27.9 mg, 0.2 mmol) and TEA (32 μL, 0.2 mmol) in dry CH_3CN (2 mL) was added to a solution of 2,6-dioxopiperazine **5** (68.8 mg, 0.2 mmol) and DBU (60.8 mg, 0.4 mmol) in dry CH_3CN (2 mL), and the solution was stirred at 60 °C for 28 d. The resulting reaction mixture was processed as in method C to yield 70% of carboxylic acid **6**.

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