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Molecular Diversity via Amino Acid Derived α-Amino Nitriles: Synthesis of Spirocyclic 2,6-Dioxopiperazine Derivatives

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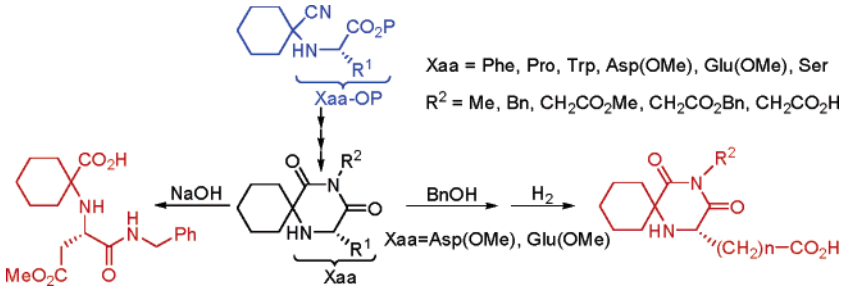

Chiral spirocyclic 2,6-dioxopiperazines were synthesized from amino acid derived α-quaternary α-amino nitriles via H_2SO_4-promoted cyano hydration, followed by base-mediated cyclization and *N*-alkylation. This methodology, requiring the previous preparation of the amino nitrile by a modified Strecker reaction, was applied to Phe, Trp, Pro, Asp, Glu, and Ser derivatives. In the case of the Trp-derived amino nitrile the major product of the treatment with H_2SO_4 was not the expected carboxamide, but a new tetracyclic indoline derivative containing the novel heterocyclic system hexahydropyrrolo[1′,2′,3′:1,9a,9]imidazo[1,2-*a*]indole, as a result of a domino tautomerization. The treatment of this indoline derivative with refluxing 1 N HCl led to a Trp-derived 2,6-dioxopiperazine. The 2,6-dioxopiperazine ring opened under the reaction conditions of methyl ester saponification, giving *N*-(carboxyalkyl)amino acid derivatives. Therefore, the synthesis of 2,6-dioxopiperazines containing free carboxylic acids from the respective methyl esters required transesterification to benzyl esters, followed by hydrogenolysis.

Introduction

Within the past few years, the hit generation step in the drug discovery process has been broadly approached by means of high-throughput screening of diverse collections of small molecules. The most commonly used synthetic strategy to access to these collections involves the appendage of different sets of building blocks to a common molecular skeleton.[1] However, this strategy has led to a limited structural diversity, as the diversity of building blocks upon a common scaffold produces compounds looking rather similar. Now, it is generally accepted that gaining efficiency in the search of the chemical space of small molecules requires access to complex and diverse molecular skeletons via diversity-oriented synthesis.[2] Multicomponent-coupling reactions, complexity-generating reactions (domino and tandem), and branching pathways are the most valuable in this process. Stereoisomerism also contributes to diversity; therefore, chirality is an additional factor to have in mind.[2d]

As part of a wide program aimed to develop methodologies for generating peptidomimetics, we have focused our attention on the potential of amino acid derived α-amino nitriles as a source of diversity of privileged scaffolds,[3] such as piperazine,[4] 1,4-benzodiazepine,[5] and

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(1) (a) Obrecht, D.; Villalgordo, J. M. *Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries*; Pergamon: Oxford, 1998. (b) Terrett, N. K. *Combinatorial Chemistry*; Oxford University Press: New York, 1998.

(2) (a) Schreiber, S. L. *Science* **2000**, *287*, 1964−1968. (b) Burke, M. D.; Berger, E. M.; Schreiber, S. L. *Science* **2003**, *302*, 613−618. (c) Spring, D. R. *Org. Biomol. Chem.* **2003**, *1*, 3867−3870. (d) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46−58.

(3) (a) Patchett, A. A.; Nargund, R. P. In *Annual Reports in Medicinal Chemistry*; Doherty, A. M., Ed.; Academic Press: San Diego, 2000; Vol. 35, pp 289−298. (b) Klabunde, T.; Hessler, G. *ChemBioChem* **2002**, *3*, 928−944. (c) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893−930.

(4) Herrero, S.; García-López, M. T.; Latorre, M.; Cenarruzabeitia, E.; Del Río, J.; Herranz, R. *J. Org. Chem.* **2002**, *67*, 3866−3873.

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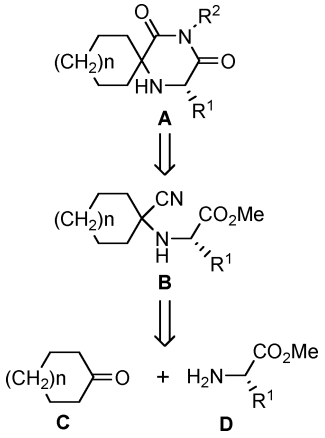
SCHEME 1. Retrosynthesis of Spiro-2,6-dioxopiperazine Derivatives



pyrazino[1,2-*c*]pyrimidine[6] derivatives, via (cyanomethylene)amino pseudopeptides.[7] The construction of these scaffolds takes advantage of the structural and stereochemical diversity of readily accessible amino acid derivatives and of the high reactivity profile of the cyano group combined with that of the functional groups of the starting amino acid derivatives. Now, we have explored the extension of some of these methodologies to the preparation of spirocyclic compounds, particularly to the synthesis of 2,6-dioxopiperazine derivatives (**A**), as shown in the retrosynthetic Scheme 1. This scheme involves the synthesis of amino acid derived α-quaternary α-amino nitriles **B** via a three-component Strecker reaction,[8] followed by cyano hydration, cyclization, and *N*-alkylation. Piperazines and their spiro derivatives are included among the most frequently occurring privileged substructures found in compounds of therapeutic interest.[3b,c] Among them, 1,4-disubstituted piperazine derivatives and 2,5-dioxopiperazines (cyclic dipeptides)[9] have been the main focus of interest, while 2,6-dioxopiperazine derivatives, apart from certain antitumoral bis(2,6-dioxopiperazine) derivatives,[9a,10] have received scarce attention. Bearing in mind that the retrosynthetic Scheme 1 would allow access to diverse highly functionalized chiral spirocyclic 2,6-dioxopiperazine derivatives, we have studied and report herein its application to the synthesis of spirocyclohexane derivatives, using cyclohexanone as a model of cyclic ketone. With respect to the amino acid component, the performance of reactions was first studied with phenylalanine derivatives (**a**), and then the studies were extended to the preparation of Pro (**b**), Trp (**c**), Asp (**d**−**f**), Glu (**g**−**i**), and Ser (**j**) derivatives. Due to our recent interest in the search for new glutamate receptor ligands, special attention was paid to the glutamic and aspartic acid derivatives.

TABLE 1. Optimization of Reaction Conditions for the Synthesis of the Phe-Derived α-Amino Nitrile 4a

		formation of imine **3a** (step a, Scheme 2)[a]			step b[b]	
entry	solvent	catalyst	drying agent[c]	*T* (°C)	catalyst[d]	**4a** yield[e] (%)
1	MeOH	$ZnCl_2$		−20	$ZnCl_2$	0
2	MeOH	$ZnCl_2$		20	$ZnCl_2$	12
3	MeOH			20	$ZnCl_2$	73
4	MeOH			65	$ZnCl_2$	77
5	CH_2Cl_2			20	$ZnCl_2$	77
6	CH_2Cl_2		$MgSO_4$	20	$ZnCl_2$	61
7	THF		$MgSO_4$	20	$ZnCl_2$	10
8	CH_2Cl_2		$MgSO_4$	20	$Yb(OTf)_3$	97
9	CH_2Cl_2			20	$Yb(OTf)_3$	98

[a] Reaction time 3 h. [b] First 1 h at 0 °C, then 20 h at room temperature, except for entries 8 and 9, where this step was carried out stirring 1 h at −20 °C and 20 h at room temperature. [c] It was filtered off before adding TMSCN. [d] 0.1 equiv of $ZnCl_2$ and 0.02 equiv of $Yb(OTf)_3$. [e] Determined by RP-HPLC analysis of the reaction crude.

Results and Discussion

Initially, the synthesis of α-amino nitriles **B** was attempted following the reaction conditions previously developed in our laboratory for the preparation of α-amino aldehyde-derived amino nitriles,[7] which involved the $ZnCl_2$-catalyzed reaction of α-amino aldehydes with a *N*-unprotected amino acids at −20 °C, followed by in situ addition of trimethylsilylcyanide (TMSCN) to the intermediate imine (Table 1, entry 1). However, when these conditions were applied to the reaction of cyclohexanone (**1**) with the methyl ester of phenylalanine (**2a**), the formation of the corresponding amino nitrile derivative **4a** was not observed, and we obtained the cyanohydrin **5** as the only reaction product (Scheme 2). Therefore, it was necessary to ascertain the most favorable reaction conditions for the formation of the intermediate imine **3a** and the subsequent preferential addition of TMSCN to this intermediate, instead of to cyclohexanone. Interestingly, imines **3** were unstable, and their formation could not be detected by TLC nor HPLC. However, the formation of imine **3a**, in equilibrium with cyclohexanone and H-Phe-OMe, was observed by ^{13}C NMR when the reaction was performed in $CDCl_3$ in an NMR tube.

As shown in Table 1, increasing the temperature in the formation of the imine **3a** (step a) from −20 to +20 °C led to the amino nitrile **4a**, although in very low yield (12%). The most significant improvement was obtained by adding the catalyst ($ZnCl_2$) after formation of the imine, at the same time as TMSCN (step b, entry 3).

(5) (a) Herrero, S.; García-López, M. T.; Cenarruzabeitia, E.; Del Río, J.; Herranz, R. *Tetrahedron* **2003**, *59*, 4491−4499. (b) Herrero, S.; García-López, M. T.; Herranz, R. *J. Org. Chem*. **2003**, *68*, 4582−4585.

(6) Herrero, S.; Salgado, A.; García-López, M. T.; Herranz, R. *Tetrahedron Lett*. **2002**, *43*, 4899−4902.

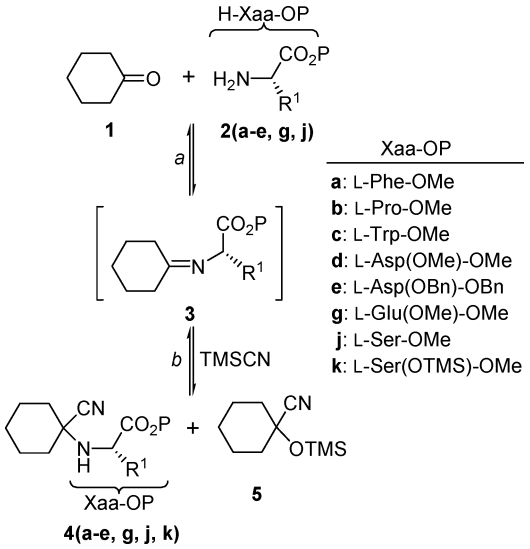
(7) (a) Herranz, R.; Suárez-Gea, M. L.; Vinuesa, S.; García-López, M. T. *J. Org. Chem*. **1993**, *58*, 5186−5191. (b) Suárez-Gea, M. L.; García-López, M. T.; Pérez, C.; Herranz, R. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1491−1496. (c) González-Muñiz, R.; García-López, M. T.; Gómez-Monterrey, I.; Herranz, R.; Jimeno, M. L.; Suárez-Gea, M. L.; Johansen, N. L.; Madsen, K.; Thøgersen, H.; Suzdak, P. *J. Med. Chem.* **1995**, *38*, 1015−1021. (d) Herrero, S.; Suárez-Gea, M. L.; González-Muñiz, R.; García-López, M. T.; Herranz, R.; Ballaz, S.; Barber, A.; Fortuño, A.; Del Río, J. *Bioorg. Med. Chem. Lett*. **1997**, *7*, 855−860.

(8) Some recent reviews on the Strecker reaction: (a) Williams, R. M. *Synthesis of Optically Active* α*-Amino Acids*; Pergamon Press: Oxford, 1989; pp 208−229. (b) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539−1650. (c) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev*. **2000**, *29*, 359−373. (d) Ager, D. J.; Fotheringham, I. G. *Curr. Opin. Drug. Discov. Devel*. **2001**, *4*, 800−807. (e) Gröger, H. *Chem. Rev*. **2003**, *103*, 2795−2827.

(9) Recent reviews on dioxopiperazine derivatives: (a) Witiak, D. T.; Wei, Y. In *Progress in Drug Research*; Jucker, E., Ed.; Birkhäuser Verlag: Basel, 1990; Vol. 35, pp 249−363. (b) Prasad, C. *Peptides* **1995**, *16*, 151−164. (c) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *J. Comput. Aid. Mol. Des*. **2002**, *16*, 415−430. (d) Dinsmore, C. J.; Beshore, D. C. *Tetrahedron* **2002**, *58*, 3297−3312. (e) Fischer, P. M. *J. Peptide Sci.* **2003**, *9*, 9−35.

(10) Andoh, T.; Ishida, R. *Biochim. Biophys. Acta* **1998**, *1400*, 155−171.

SCHEME 2. Synthesis of Cyclohexanone-Derived α-Amino Nitriles[a]



[a] Reagents: (a) H-Xaa-OP·HCl, TEA; (b) $ZnCl_2$ or $Yb(OTf)_3$, TMSCN.

Under these conditions, the increase of temperature to 65 °C (entry 4), or the equivalents of cyclohexanone (from 1 to 2) or TMSCN (from 1.2 to 2), did not produce a significant improvement in the yield of **4a**. Concerning the solvent, MeOH (entry 3) and CH_2Cl_2 (entries 5 and 6) led to very similar results, while in THF (entry 7) the yield was drastically lower. The use of $MgSO_4$ as drying agent, to favor the formation of the imine,[11] did not lead to any improvement either. However, as indicated in entries 8 and 9, the substitution of $ZnCl_2$ by ytterbium triflate, which catalyzes the preferential addition of nucleophiles to imines versus keto compounds,[12] led to a significant improvement and the amino nitrile **4a** was obtained in a yield higher than 90%. Applying the conditions of entry 9, amino nitriles **4a**−**e,g** were isolated in good yields (75−98%). In the case of the serine derivative **2j**, a mixture of the corresponding amino nitrile **4j** (23%) and its *O*-trimethylsilyl derivative **4k** (22%) was obtained, which was chromatographically resolved. It is interesting to note that, although amino nitriles **4** were isolated as analytically pure compounds, they reverted to the starting amino acid derivative and cyclohexanone, particularly in the acid media of the silica gel used for chromatography (TLC and column). A higher instability could account for the lower yield obtained in the serine (**4j**,**k**) and proline (**4b**) derivatives. The instability of α-quaternary amino nitriles had not been previously observed for α-amino aldehyde-derived amino nitriles.

Initially, the cyano hydration of amino nitrile **4a** was attempted in a neutral medium by treatment with MnO_2 in CH_2Cl_2[13] or via oxidative hydration by treatment with H_2O_2 and NaOH, using tetrabutylammonium bisulfate as phase transfer catalyst,[14] but after 2 days under both conditions, **4a** was recovered unchanged along with traces of decomposition products. Eventually, the cyano hydration was achieved by treating a CH_2Cl_2 solution of the amino nitrile with concentrated H_2SO_4 (Scheme 3), which led to the corresponding α-amino carboxamide **6** together with the respective spirocyclic 2,6-dioxopiperazine derivative **7** in a variable ratio depending on the starting amino nitrile (Table 2). The treatment of the α-amino carboxamides **6** with NaH in dry THF at room temperature provided the corresponding 2,6-dioxopiperazine derivative **7** in more than 85% yield, except for the proline derivative **7b**, which was obtained in 60% yield.

SCHEME 3. Acid-Mediated Hydration of Amino Nitriles 4

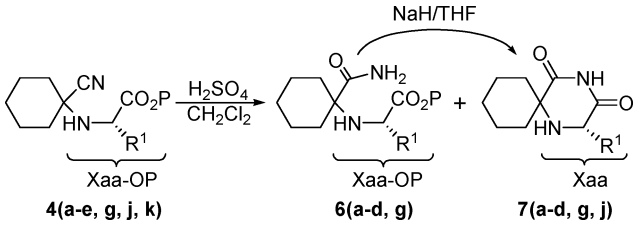


TABLE 2. Hydration of Amino Nitriles 4

		yield (%)	
α-amino nitrile	Xaa-OP	carboxamide **6**	2,6-dioxo-piperazine **7**
4a	L-Phe-OMe	93	5
4b	L-Pro-OMe	25	0
4c	L-Trp-OMe	15	0
4d	L-Asp(OMe)-OMe	24	68
4e	L-Asp(OBn)-OBn	0	0
4g	L-Glu(OMe)-OMe	45	55
4j	L-Ser-OMe	0	20
4k	L-Ser(OTMS)-OMe	0	20[a]

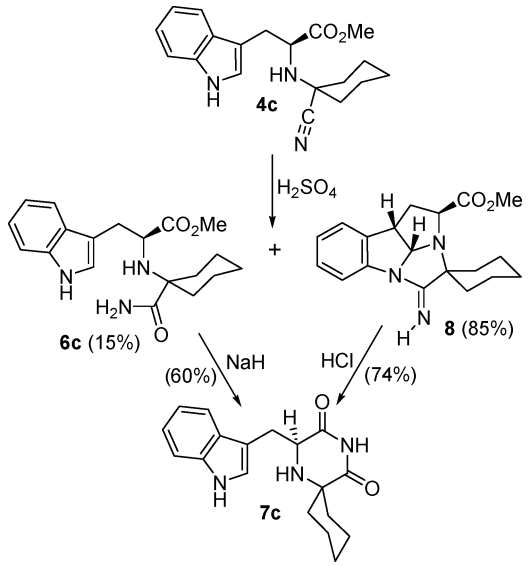
[a] Yield of **7j** because the H_2SO_4 treatment removes the TMS group.

The overall yield of the hydration was higher than 90% for the Phe (**4a**), Asp(OMe) (**4d**), and Glu(OMe) (**4g**) derivatives. Probably due to the hydrolysis of the benzyl ester groups in the hydration reaction medium, the *O*-benzyl-protected aspartic acid derivative **4e** did not provide the corresponding derivatives **6e** or **7e**. In the case of the proline and serine derivatives **4b** and **4j**,**k**, the low yield was due to their previously mentioned instability in acid media, observing the formation of cyclohexanone and their respective amino esters (**2b** and **2j**) in the reaction mixture. On the other hand, the TMS group of the serine derivative **4k** did not survive after treatment with H_2SO_4, which led to the corresponding deprotected 2,6-dioxopiperazine derivative **7j**.

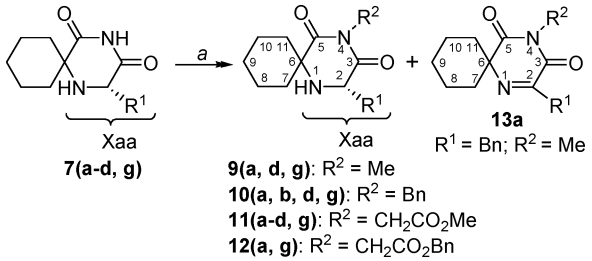
With respect to the tryptophan-derived amino nitrile **2c**, the low yield of hydration to give the amino carboxamide **6c** (15%) was due to the unfavorable competition of this reaction with a tautomerization, as we have recently reported,[15] which involves the formation of an

(11) Basile, T.; Bocoum, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1994**, *59*, 7766−7773.
(12) (a) Kobayashi, S.; Nagayama, S. *J. Org. Chem.* **1997**, *62*, 232−233. (b) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1997**, *119*, 10049−10053.
(13) (a) Gateau-Olesker, A.; Cléophax, J.; Géro, S. D. *Tetrahedron Lett.* **1986**, *27*, 41−44. (b) Herranz, R. *An. Quim.* **1987**, *83*, 318−322.
(14) (a) Herranz, R.; Conde, S.; Fernández-Resa, P.; Arribas, E. *J. Chem. Soc., Perkin Trans. 1* **1988**, 649−655. (b) Suárez-Gea, M. L.; García-López, M. T.; Herranz, R. *J. Org. Chem.* **1994**, *59*, 3600−3603.
(15) González-Vera, J. A.; García-López, M. T.; Herranz, R. *Org. Lett.* **2004**, *6*, 2641−2644.

SCHEME 4. Hydration and Tautomerization of the Trp-Derived Amino Nitrile 4c



SCHEME 5. Alkylation of Dioxopiperazines[a]



[a] Meaning of **a**−**d**, **g** as indicated in Scheme 2. Reagents: (a) R^2-X, Cs_2CO_3 or K_2CO_3, CH_3CN, Δ.

endocyclic amidine within the novel indole-based tetracyclic system of compound **8** (Scheme 4). The treatment of this compound with aqueous 1 N HCl at 100 °C for 48 h led to the 2,6-dioxopiperazine derivative **7c**, which was also prepared by NaH-mediated cyclization of the α-amino carboxamide **6c**.

Further functionalization of dioxopiperazine derivatives **7**, by alkylation with alkyl halides, was first attempted in dry THF, using NaH as base. Under these conditions, the products of selective alkylation at position 4 were obtained in a very low yield within a complex mixture of reaction products. The alkylation was then studied in dry CH_3CN at 50 °C, using 1.5 equiv of alkyl halide and Cs_2CO_3 or K_2CO_3 as base (Scheme 5). In both cases, the alkylation products **9**−**12** were obtained in higher than 85% yield, although when K_2CO_3 was used the reaction was slower. Partial dialkylation at position 4 of the piperazine ring and at position 1 of the indole (∼25%) was observed in the tryptophan derivative **7c**. To minimize the alkylation at the indole ring, the amount of alkyl halide was lowered to 0.95 equiv. Thus, the N^4-monoalkylated product **11c** was obtained in 83% yield along with a 5% yield of the N,$^4N^i$-dialkylation product, which were separated by column chromatography. In the alkylation of all dioxopiperazines **7**, traces (1−4%) of dioxotetrahydropyrazines were obtained, resulting from the slow oxidation of the dioxopiperazine ring in the basic media of the alkylation reaction. Due to the small quantity obtained of these dioxotetrahydropyrazines, only the phenylalanine derivative **13a** was completely characterized. This compound was obtained in 70% yield from piperazine **9a** after 7 days of reflux in CH_3CN in the presence of 1.5 equiv of Cs_2CO_3. The ^1H NMR spectrum of **13a** showed the disappearance of the signal corresponding to the 2-H and a higher than 0.70 ppm deshielding for its 2-CH_2 protons with respect to the starting dioxopiperazine **9a**. Correspondingly, the ^{13}C NMR spectrum of **13a** showed the disappearance of the aliphatic C_2 and its appearance in the zone of quaternary carbons at 157.1 ppm.

In view of the low overall yield of the proline derivatives **10b** and **11b** (∼10%) and the tryptophan derivative **11c** (∼8%) from their respective starting amino acid derivatives **2b** and **2c** in the sequential Strecker reaction−hydration−cyclization−alkylation, we studied their alternative preparation via an Ugi four-component reaction.[2a,16] This reaction was carried out as previously described for the synthesis of other 2,6-dioxopiperazine analogues,[17] which involved the reaction of cyclohexanone with the corresponding amino acid and methyl isocyanoacetate in the presence of TEA. However, this method did not provide any increase in yield over our methodology.

In those dioxopiperazine derivatives containing methyl ester groups, the synthesis of their corresponding free carboxylic acids was initially attempted by means of saponification. However, when this was first tried using the Asp derivative **10d**, by treatment with 1 equiv of 1 N NaOH in (1:9) H_2O/MeOH, the free acid **10f** was obtained as a minor product (29%), along with 47% of **14**, resulting from the simultaneous saponification and opening of the N_4-C_5 bond by the nucleophilic attack of MeOH to the C_5 (Scheme 6). On the other hand, when the saponification was attempted by reaction with 1 equiv of 1 N NaOH in acetonitrile or dioxane containing 10% of H_2O, the only reaction product was **15**, resulting from the nucleophilic attack of H_2O to the C_5. To avoid the opening of the 2,6-dioxopiperazine ring, we considered the transesterification of methyl to benzyl esters followed by hydrogenolysis. As shown in Scheme 7, transesterification was performed for the Pro and Trp derivatives **11b** and **11c** and the Asp and Glu derivatives **9**−**11d**,**g** by treatment of the methyl esters with benzyl alcohol in the presence of 3-chloro-1-hydroxytetrabutyldistannoxane, freshly prepared from Bu_2SnO and Bu_2SnCl_2,[18,19] yielding 65−80% of the benzyl esters **12b**,**c** and (**9**, **10**, and **12**)**e**,**h**. Subsequently, catalytic hydrogenolysis of these benzyl esters and the Phe derivative **12a** led to the corresponding carboxylic acids **9f**,**i**, **10f**,**i**, and **16a**−**c**,**f**,**i**, quantitatively.

Although in previous studies on the chemical manipulation of amino acid derived α-amino nitriles[3−7] we had

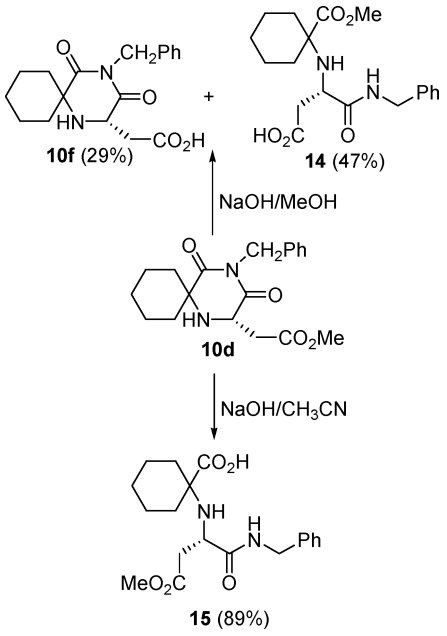
(16) Recent reviews on the Ugi four component reaction: (a) Ugi, I.; Lohberger, S.; Karl, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 1083−1109. (b) Domling, A. *Comb. Chem. High Throughput Screen* **1998**, *1*, 1−22. (c) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3169−3210. (d) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51−80.

(17) Ugi, I.; Hörl, W.; Hanusch-Kompa, C.; Schmid, T.; Herdtweck, E. *Heterocycles* **1998**, *47*, 965−975.

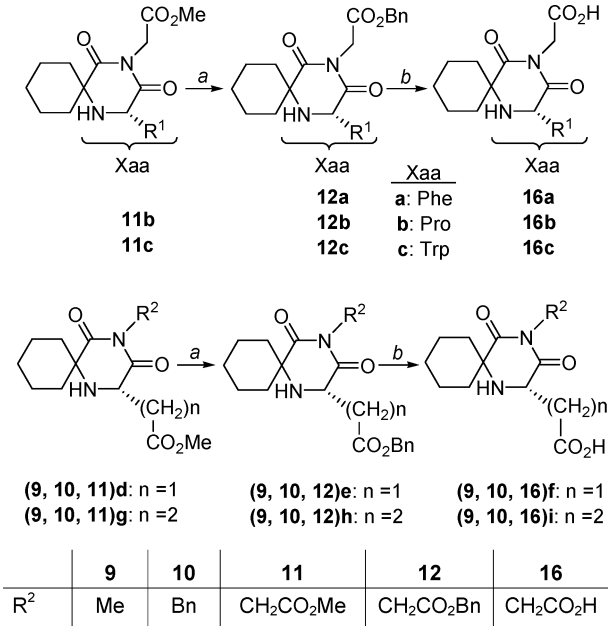
(18) Okawara, R.; Wada, M. *J. Organomet. Chem.* **1963**, *1*, 81−88.

(19) Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307−5311.

SCHEME 6. Reactivity of the Asp-Derived Dioxopiperazine 10d with NaOH



SCHEME 7. Synthesis of Free Carboxylic Acids[a]

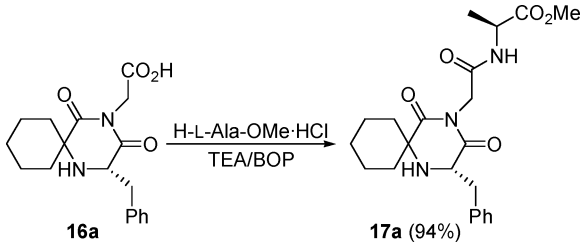


	9	10	11	12	16
R^2	Me	Bn	CH_2CO_2Me	CH_2CO_2Bn	CH_2CO_2H

[a] Reagents: (a) BnOH, ($^nBu_4Sn_2ClOH)_2$, $PhCH_3$; (b) H_2, Pd(C), MeOH.

not observed racemization, taking into account the strong basic media used in the cyclization of α-aminocarboxamides and in the alkylation of the 2,6-dioxopiperazine derivatives, as well as the low values of optical rotation measured for most of these derivatives, a priori, the existence of racemization could not be discarded. This aspect was studied in the phenylalanine derivatives **7a** and **16a**. In the first case, we tried the acylation at positions 1 or 4 of the dioxopiperazine ring with an excess of the chloride of the Mosher acid [(*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride, (*R*)-MTPA]. However, this acylation did not take place, and the starting compound was recovered unaltered. In the

SCHEME 8. Study of the Optical Purity



second case, as shown in Scheme 8, the coupling of the free carboxylic acid **16a** with the methyl ester of L-Ala, using BOP and TEA as coupling reagents, led to the corresponding pseudotripeptide analogue **17a**. The RP HPLC and NMR analyses of the crude reaction products did not show the existence of duplicity of signals. This result indicated the absence of diastereoisomers and, therefore, the absence of racemization.

In conclusion, the studies herein reported show that amino acid derived α-quaternary α-amino nitriles are good starting materials for the synthesis of diverse spirocyclic 2,6-dioxopiperazine derivatives with retention of configuration, by means of H_2SO_4-promoted cyano hydration, followed by base-mediated cyclization and *N*-alkylation. In the case of tryptophan-derived α-amino nitriles a domino tautomerization to the novel heterocyclic ring system hexahydropyrrolo[1′,2′,3′:1,9a,9]imidazo-[1,2-*a*]indole competes favorably with the cyano hydration to the corresponding carboxamide derivative. The treatment of the new tetracyclic indoline derivative with refluxing aqueous 1 N HCl solution leads to the corresponding 2,6-dioxopiperazine derivative. To avoid the reactivity of the 2,6-dioxopiperazine ring under the basic conditions of saponification, the synthesis of 2,6-dioxopiperazines containing free carboxylic acids requires the transesterification of the methyl to benzyl esters and subsequent hydrogenolysis. Finally, the reactivity of the 2,6-dioxopiperazine derivatives herein observed toward nucleophiles in basic media could be used to synthesize *N*-(carboxyalkyl)amino acid derivatives of interest in the field of peptidase inhibitors.[20] Studies in this direction are in progress.

Experimental Section

General Methods. All reagents were of commercial quality. Solvents were dried and purified by standard methods. Analytical TLC were performed on aluminum 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 radial chromatography was performed on 20 cm diameter glass plates coated with a 1-mm layer of silica gel PF_{254}. Analytical RP-HPLC was performed on a Novapak C_{18} (3.9 × 150 mm, 4 μm) column, with a flow rate of 1 mL/min, and 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. Melting points were taken on a micro hot stage apparatus and

(20) (a) Neustadt, B. R.; Smith, E. M.; Tulshian, D. PCT Int. Appl. WO 9403481, 1994; *Chem. Abstr.* **1994**, *122*, 56581. (b) Robinson, R. P.; Cronin, B. J.; Donahue, K. M.; Jones, B. P.; Lopresti-Morrow, L. L.; Mitchell, P. G.; Rizzi, J. P.; Reeves, L. M.; Yocum, S. A. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 1725−1730. (c) Quibell, M.; Johnson, T.; Hart, T. PCT Int. Appl. WO 9742216, 1997; *Chem. Abstr.* **1997**, *128*, 30375. (d) Quibell, M.; Johnson, T.; Hart, T. PCT Int. Appl. WO 9740065, 1997; *Chem. Abstr.* **1997**, *128*, 1461. (e) Robinson, R. P. PCT Int. Appl. US 5854275, 1998; *Chem. Abstr.* **1999**, *130*, 95848.

are uncorrected. ^{1}H NMR spectra were recorded at 200, 300, or 400 MHz, using TMS as reference, and ^{13}C NMR spectra were recorded at 50, 75, or 100 MHz. The NMR spectra assignment was based on COSY and HSQC spectra. ESI-MS spectra were performed, in positive mode, using MeOH as solvent.

General Procedure for the Synthesis of the α-Amino Nitriles 4a−e,g,j−k. TEA (139.2 μL, 1 mmol) was added to a solution of the corresponding amino acid derivative [H-Phe-OMe·HCl (**2a**), H-Pro-OMe·HCl (**2b**), H-Trp-OMe·HCl (**2c**), H-Asp(OMe)-OMe·HCl (**2d**), H-Asp(OBz)-OBz·Tos (**2e**), H-Glu-(OMe)-OMe·HCl (**2g**), H-Ser(OMe)-OH·HCl (**2j**)] (1 mmol) in dry CH_2Cl_2 (20 mL). After 30 min of stirring at room temperature under argon, cyclohexanone (103.6 μL, 1 mmol) was added, and the stirring was maintained for 3 h. Then, the solution was cooled to −23 °C, and ytterbium triflate (13.6 mg, 0.02 mmol) and trimethylsilyl cyanide (TMSCN, 187.7 μL, 1.5 mmol) were added. After being successively 1 h at −23 °C and 20 h at room temperature, the mixture was evaporated to dryness. The residue was dissolved in CH_2Cl_2 (20 mL), and the solution was washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography, using 20−50% gradient of EtOAc in hexane as eluant, to yield the corresponding α-amino nitrile **4a−e**,**g**,**j−k**. Significant analytical and spectroscopic data of these α-amino nitriles are summarized in Table 1 of the Supporting Information.

General Procedure for the Hydration of the α-Amino Nitriles 4(a−e,g,j−k). Synthesis of the α-Amino Carboxamides 6 and the (2*S*)-3,5-Dioxo-1,4-diazaspiro[5.5]-undecane Derivatives 7. Concentrated H_2SO_4 (5 mL) was added to a solution of the corresponding amino nitrile (**4a−e**,**g**,**j−k**) (3 mmol) in CH_2Cl_2 (12 mL), and this mixture was stirred at room temperature for 1 h. Afterward, the reaction mixture was sequentially poured into ice, neutralized with NH_4OH, and extracted with CH_2Cl_2 (20 mL). The organic extracts were successively washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by flash chromatography, using 75−100% gradient of EtOAc in hexane as eluant, to give the spiricyclic 2,6-dioxopiperazines **7a**,**d**,**g**,**j** of higher R_f and the α-amino carboxamides derivatives **6a−d**,**g**. In the case of the tryptophan-derived amino nitrile **4c**, the hexahydropyrrolo[1′,2′,3′:1,9a,9]imidazo[1,2-*a*]indole derivative **8** was the major product of this reaction.[15] Significant analytical and spectroscopic data of these α-amino carboxamides **6a−d**,**g** and of the (2*S*)-3,5-dioxo-1,4-diazaspiro[5.5]undecane derivatives **7a**,**d**,**g**,**j** are summarized in Tables 2 and 3, respectively, and those of the proline derivative **7b** in Table 7 of the Supporting Information.

General Procedure for the Cyclization of the α-Amino Carboxamides 6. Synthesis of the (2*S*)-3,5-Dioxo-1,4-diazaspiro[5.5]undecane Derivatives 7. Method B. NaH (60% dispersion in mineral oil; 6.6 mg, 0.28 mmol) was added to a solution of the corresponding α-amino carboxamide (**6a−d**,**g**) (0.25 mmol) in dry THF (7.5 mL), and this mixture was stirred at room temperature for 1 h. Then, the solvent was evaporated, the residue was dissolved in CH_2Cl_2 (20 mL), and the resulting solution was successively washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by circular chromatography, using 25−40% gradient of EtOAc in hexane as eluant. Significant analytical and spectroscopic data of the resulting dioxopiperazine derivatives **7a−d**,**g** are summarized in Table 3 of the Supporting Information, except for those of the proline derivative **7b** which are summarized in Table 7.

General Procedure for the Alkylation of the Dioxopiperazine Derivatives 7. Synthesis of (2*S*)-2,4-Disubtituted-3,5-dioxo-1,4-diazaspiro[5.5]undecane Derivatives 9a,d,g, 10a,b,d,g, 11a−d,g, and 12a,g. Cs_2CO_3 (122.2 mg, 0.375 mmol) and the corresponding alkylating agent (methyl iodide, benzyl bromide, methyl bromoacetate, or benzyl bromoacetate, 0.375 mmol) were added to a solution of the corresponding dioxopiperazine derivative **7a−d**,**g** (0.25 mmol) in dry CH_3CN (2.5 mL). After 2 h of stirring at 50 °C, the mixture was evaporated, the residue was dissolved in CH_2Cl_2 (20 mL), and the resulting solution was successively washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by circular chromatography, using 15−25% gradient of EtOAc in hexane as eluant. Significant analytical and spectroscopic data of the resulting dioxopiperazine derivatives **9a**,**d**,**g**, **10a**,**b**,**d**,**g**, **11a−d**,**g**, and **12a**,**g** are summarized in Tables 4−7 of the Supporting Information.

Synthesis of 2-Phenylmethyl-4-methyl-3,5-dioxo-1,4-diazaspiro[5.5]undec-1-ene 13a. Cs_2CO_3 (25.59 mg, 0.078 mmol) was added to a solution of **9a** (15 mg, 0.052 mmol) in CH_3CN (3 mL), and this mixture was stirred at 60 °C for 7 days. Afterward, the solvent was evaporated, the residue was dissolved in CH_2Cl_2 (20 mL), and the resulting solution was successively washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by circular chromatography, using 10−12% gradient of EtOAc in hexane as eluant: foam (10.3 mg, 70%); $[\alpha]^{20}_D$ −1.70 (*c* 0.8, MeOH); RP-HPLC [Novapak C_{18} (3,9 × 150 mm, 4μm), (A/B 50:50)] t_R 16.51 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.42−1.94 [m, 10H, (7−11)-H], 2.05−2.11 (m, 2H, 7-H_{ax} and 11-H_{ax}), 3.13 (s, 3H, 4-CH_3), 4.01 (s, 2H, 2-CH_2), 7.29 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 20.5 (C_8 and C_{10}), 25.4 (C_9), 25.6 (4-CH_3), 37.1 (C_7 and C_{11}), 40.5 (2-CH_2), 65.5 (C_6), 126.7, 128.4, 129.4 and 136.3 (Ph), 155.8 (C_3), 157.1 (C_2), 177.0 (C_5); EM-ES *m/z* 285.0 (100) $[M + 1]^+$. Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.75; H, 7.40; N, 9.88.

Reactivity of the Asp-Derived Dioxopiperazine 10d with NaOH. NaOH (1 N, 200 μL, 0.2 mmol) was added to a solution of **10d** (68.9 mg, 0.2 mmol) in 10:1 MeOH/H_2O or 10:1 MeCN/H_2O (3 mL). After 2 h of stirring at room temperature, the mixture was evaporated, the residue was dissolved in H_2O (4 mL), and the resulting solution was washed with CH_2Cl_2 (12 mL). The aqueous solution was acidified with 1 N HCl to pH 3, then the mixture was extracted with EtOAc (3 × 12 mL). The organic extracts were dried over Na_2SO_4 and evaporated to dryness. The residue was purified by radial chromatography using 2−30% gradient of MeOH in CH_2Cl_2 as eluant, yielding the dioxopiperazine derivative **10f** (19.2 mg, 29%) and the opened compound **14** (34.2 mg, 47%) in the case of the reaction in MeOH/H_2O, and **15** (64.4 mg, 89%) in the case of the reaction in MeCN/H_2O.

***N*-[1-(Methoxycarbonyl)cyclohexyl]aspartic acid benzyl amide (14):** amorphous solid (34.2 mg, 47%); $[\alpha]^{20}_D$ +2.75 (*c* 1, MeOH); RP-HPLC [Novapak C_{18} (3.9 × 150 mm, 4μm), (A/B 30:70)] t_R 3.98 min; ^{1}H NMR (200 MHz, DMSO-d_6) δ (ppm) 1.15−1.84 (m, 10H, cyclohexyl), 2.22 [(dd, 1H, J = 7.5 and 14.5 Hz, 3-H (Asp)], 2.38 [(dd, 1H, J = 5 and 14.5 Hz, 3-H(Asp)], 3.33 [dd, 1H, 2-H(Asp)], 3.50 (s, 3H, OCH_3), 4.17 (d, 1H, J = 6 Hz, CH_2−Ph), 4.34 (d, 1H, J = 6 Hz, CH_2−Ph), 7.26 (m, 5H, Ph), 8.70 (bs, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6) δ (ppm) 22.0 and 22.3 [C_3 and C_5 (cyclohexyl)], 25.2 [C_4 (cyclohexyl)], 32.3 and 34.9 [C_2 and C_6 (cyclohexyl)], 40.1 (C_3), 42.0 (CH_2-Ph), 53.6 (C_2), 126.7, 127.2, 128.2 and 139.5 (Ph), 171.0 (C_1), 174.7 (CO_2CH_3); EM-ES *m/z* 363.3(100) $[M + 1]^+$. Anal. Calcd for $C_{19}H_{26}N_2O_5$: C, 62.97; H, 7.23; N, 7.73. Found : C, 63.21; H, 7.44; N, 7.59.

***N*-[1-(Carboxyl)cyclohexyl]-Asp(OMe) benzyl amide (15):** amorphous solid (64.4 mg, 89%); $[\alpha]^{20}_D$ −0.84 (*c* 1, MeOH); RP-HPLC [Novapak C_{18} (3.9 × 150 mm, 4 μm), (A/B 30:70)] t_R 1.85 min; ^{1}H NMR (200 MHz, acetone-d_6) δ 1.18−2.06 (m, 10H, cyclohexyl), 2.63 [dd, 1H, J = 6 and 14.5 Hz, 3-H (Asp)], 2.76 [dd, 1H, J = 5 and 14.5 Hz, 3-H (Asp)], 3.65 [dd, 1H, 2-H (Asp)], 3.51 (s, 3H, OCH_3), 4.33 (d, 1H, J = 6 Hz, CH_2−Ph), 4.43 (d, 1H, J = 6 Hz, CH_2−Ph), 7.24 (m, 5H, Ph), 8.02 (bs, 1H, NH); ^{13}C NMR (50 MHz, acetone-d_6) δ 23.2 (C_3 and C_5 cyclohexyl), 26.6 (C_4 cyclohexyl), 34.0 and 35.1 (C_2 and C_6 cyclohexyl), 38.7 (C_3), 44.2 (CH_2-Ph), 53.9 (C_2), 126.8, 127.4, 128.2 and 139.6

(Ph), 175.5 (C_1), 176.2 (CO_2CH_3); EM-ES *m/z* 363.3(100) $[M + 1]^+$. Anal. Calcd for $C_{19}H_{26}N_2O_5$: C, 62.97; H, 7.23; N, 7.73. Found : C, 63.23; H, 7.38; N, 7.63.

General Procedure for the Transesterification of Methyl to Benzyl Esters in the Dioxopiperazine Derivatives 9−11(a−d,g). Synthesis of the Benzyl Esters 9−10-(e,h) and 12a−c,e,h. Benzyl alcohol (259 μL, 2.5 mmol) and 3-chloro-1-hydroxytetrabutyldistannoxane (13 mg, 0.025 mmol), freshly prepared from Bu_2SnO and Bu_2SnCl_2,[18,19] were added to a solution of the corresponding methyl ester **9**−**11**(**a**−**d**,**g**) (0.25 mmol) in toluene (2 mL), and this mixture was refluxed for 2 h. Afterward, the solvent was evaporated to dryness, and the residue was purified by circular chromatography using 12−15% gradient of EtOAc in hexane as eluant. Significant analytical and spectroscopic data of the benzyl esters **9**−**10**(**e**,**h**) and **12a**−**c**,**e**,**h** are summarized in Tables 4−7 of the Supporting Information.

General Procedure for the Hydrogenolysis of the Benzyl Esters 9−10(e,h) and 12a−c,e,h. Synthesis of the Free Carboxylic Acids 9−10(f,i) and 16a−c,f,i. Pd(C) (10% w/w) was added to a solution of the corresponding benzyl ester [**9**−**10**(**e**,**h**) and **12a**−**c**,**e**,**h**] (0.09 mmol) in MeOH (20 mL), and the resulting suspension was hydrogenated at room temperature and 15 psi of H_2 pressure for 1 h. After filtration of the catalyst, the solvent was evaporated yielding the corresponding free carboxylic acid **9**−**10**(**f**,**i**) and **16a**−**c**,**f**,**i** quantitatively. Significant analytical and spectroscopic data of these free carboxylic acids are summarized in Tables 4−7 of the Supporting Information.

Synthesis of the Pseudotripeptide Derivative 17a. TEA (31 μL, 0.196 mmol) was added to a solution of H-Ala-OMe·HCl (27.4 mg, 0.196 mmol) in dry CH_2Cl_2 (20 mL). After 30 min of stirring at room temperature under argon, the solution was cooled to 0 °C, and **16a** (32.4 mg, 0.098 mmol), BOP (86.8 mg, 0.196 mmol), and TEA (31 μL, 0.196 mmol) were successively added. After stirring successively for 1 h at 0 °C and 24 h at room temperature, the mixture was evaporated to dryness. The residue was dissolved in CH_2Cl_2 (20 mL), and the solution was washed successively with saturated solution of Na_2CO_3 (2 × 5 mL), H_2O (2 × 5 mL), citric acid 10% (2 × 5 mL), and brine (5 mL), dried over Na_2SO_4, and evaporated. The residue was purified by circular chromatography using 50−70% gradient of EtOAc in hexane as eluant, yielding **17a** as a foam (38.2 mg; 94%): $[\alpha]^{20}_D$ −47.87 (*c* 1, MeOH); RP-HPLC [Novapak C_{18} (3.9 × 150 mm, 4 μm), (A/B 50:50)] t_R 4.25 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.11−1.63 [m, 8H, (7−11)-H], 1.41 [d, 3H, J = 7 Hz, CH_3 (Ala)], 1.98 (m, 1H, 7-H_{ec}), 1.83 (bs, 1H, 1-H), 2.09 (dt, 1H, J = 4, 13 Hz, 7-H_{ax}), 2.93 (dd, 1H, J = 9 and 14 Hz, 2-CH_2), 3.38 (dd, 1H, J = 4 and 14 Hz, 2-CH_2), 3.68 (s, 3H, OCH_3), 3.80 (bs, 1H, 2-H), 4.28 [d, 1H, J = 15 Hz, 2-H (Gly)], 4.42 [d, 1H, J = 15 Hz, 2-H (Gly)], 4.51 [q, 1H, J = 7 Hz, 2-H (Ala)], 6.20 (d, 1H, J = 7 Hz, CONH), 7.24 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 18.6 (4-CH_3), 19.9 and 20.5 (C_8 and C_{10}), 25.1 (C_9), 29.5 and 33.9 (C_7 and C_{11}), 37.0 (2-CH_2), 41.9 [C_2 (Gly)], 48.2 [C_2 (Ala)], 52.5 (OCH_3), 54.4 (C_2), 58.1 (C_6), 127.0, 128.7, 129.2 y 137.0 (Ph), 166.1 and 173.2 (CO), 172.5 (C_3), 176.1 (C_5); EM-ES, *m/z* 416.1(100) $[M + 1]^+$. Anal. Calcd for $C_{22}H_{29}N_3O_5$: C, 63.60; H, 7.04; N, 10.11. Found : C, 63.82; H, 7.24; N, 10.03.

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Supporting Information Available: Tables of significant analytical and spectroscopic data of α-quaternary α-amino nitriles **4**, α-amino carboxamides **6**, and 2,6-dioxopiperazine derivatives **7**, **9**−**12**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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