Tandem Radical Decarboxylation−Oxidation of Amino Acids: A Mild and Efficient Method for the Generation of *N*-Acyliminium Ions and Their Nucleophilic Trapping

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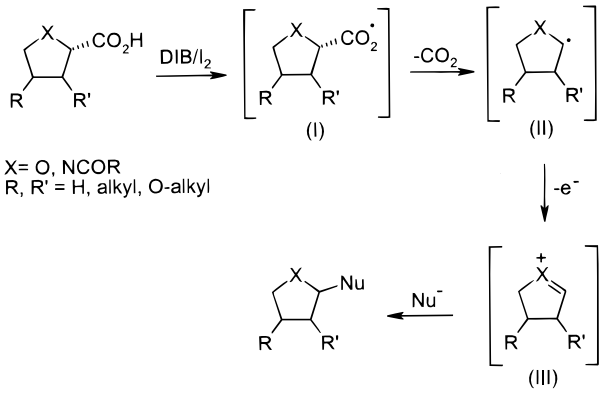
A convenient methodology for the synthesis of 2-substituted pyrrolidines from α-amino acids is described. A number of cyclic and acyclic α-amino acid derivatives have been prepared in order to test the scope and diastereoselectivity of this method. These substrates were treated with iodosylbenzene or (diacetoxyiodo)benzene (DIB) and iodine in order to generate the corresponding carboxyl radical, which evolves by loss of carbon dioxide to produce a carbon radical which in turn undergoes oxidation to an *N*-acyliminium ion. This postulated intermediate could be trapped inter- or intramolecularly by oxygen, nitrogen and carbon nucleophiles. In the case of carbon nucleophiles, a Lewis acid is required for the concomitant carbon−carbon bond formation. High yields and modest diastereoselectivities were obtained. The present methodology was applied to the synthesis of *ω*-amino aldehydes or hemiaminals **8**−**14**, 2-aminopyrrolidine derivative **15**, aminolactone derivative **16**, and *azasugar* analogues **17** and **18**. When carbon nucleophiles were used, alkaloid precursors such as 2-allyl- or 2-alkylpyrrolidines **19**−**23** and **25** were obtained.

Introduction

The radical decarboxylation of acids is a useful and selective procedure for the synthesis of a great variety of organic compounds. The reaction can be effected either under reductive or oxidative conditions.[1] In the latter case, when the resultant C-radical is contiguous to an oxygen or nitrogen substituent, it may be oxidized to a cation. As a continuation of our studies on the oxidative decarboxylation process in organic synthesis,[2] we have recently reported on an interesting application of this reaction to the synthesis of chiral polyhydroxylated rings using uronic or ulosonic acids as substrates[2b] (Scheme 1, X = O). Thus, by treatment with (diacetoxyiodo)-benzene (DIB) and iodine, most probably a carboxyl radical (I) is formed, which evolves by loss of CO_2 generating an alkyl radical (II). The latter, being α-located to an oxygenated function, can be easily oxidized by excess reagent to an oxycarbenium ion (III), which can be trapped by nucleophiles from the reaction mixture (e.g., acetate from DIB).

Scheme 1. Strategy for the Synthesis of 2-Substituted Pyrrolidines



It seemed reasonable to expect that the decarboxylation of suitable *N*-substituted amino acids using this methodology would take place by a similar mechanism.[3] Thus, the resulting radical α-located to a nitrogen atom would evolve to an *N*-acyliminium ion (Scheme 1, X = NCOR), that could be trapped inter- or intramolecularly by nucleophiles.[2a] The synthetic utility of *N*-acyliminium ions is widely recognized,[4] and their trapping by nucleophiles has been used in the synthesis of many biologically active products.[5] Accordingly, several methodologies have been developed to generate these ions,[4−7] such as acid

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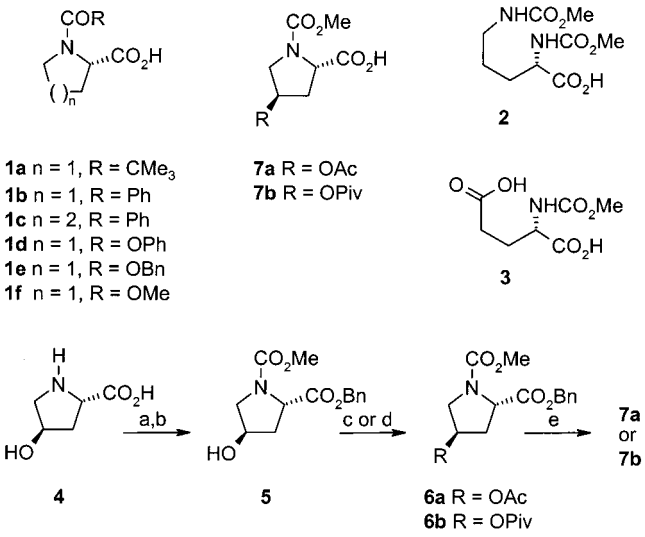
treatment of *N*-acylated *N*,*O*-acetals or hemiaminals,[4] treatment of imines with acyl chlorides,[6] or electrochemical oxidation of amino or amido derivatives.[7] The method we report here is a mild and operationally simple procedure, compatible with the most usual functional groups[8] and can be carried out under neutral conditions and at room temperature. We consider that it is a valuable addition to previous methodologies.

Results and Discussion

Synthesis of Substrates. The substrates used in the present study are shown in Scheme 2. To determine the scope of the reaction, both cyclic and acyclic amino acids were considered, their nitrogen atom protected either as the amide or carbamate derivatives. The synthesis of amides **1a**−**c** and carbamates **1d**−**f** was carried out according to standard procedures.[9] The 4-acetyloxy-L-proline derivative **7a** was synthesized as described in Scheme 2. The synthesis of the 4-pivaloyloxyproline derivative **7b** from **5** took place in a similar way, in 82% overall yield.

Scheme 2. Starting Material for the Decarboxylation−Oxidation Reactions[a]



[a] Key: (a) MeO_2CCl, $NaHCO_3$ aq, THF, 0 °C to room temperature, 16 h; (b) BnBr, NaI, K_2CO_3, CH_3CN, 0 °C to room temperature, 17 h; (c) Ac_2O, Py, rt, overnight (for **6a**); (d) PivCl, CH_2Cl_2, Et_3N, 0 °C to room temperature, overnight (for **6b**); (e) H_2, 10% $Pd(OH)_2$/C, EtOAc, rt, 16 h.

Table 1. Conditions for the Decarboxylation−Oxidation Reaction of Amino Acids[a]

entry	acid	reagent	iodine	solvent	*t* (h)	products (%)[b]
1	**1a**	PhIO	0	CH_2Cl_2	12	**8a** (21)
2	**1a**	PhIO	0.5	CH_2Cl_2	3	**8a** (82)
3	**1a**	PhIO	1	CH_2Cl_2	3	**8a** (60)
4	**1a**	PhIO	0.5	MeCN	2	**8a** (81)
5	**1a**	DIB	0.5	CH_2Cl_2	2	**8a** (83)
6	**1a**	DIB	0.5	MeCN	1	**8a** (84)
7	**1b**	DIB	0.5	CH_2Cl_2	4	**9a:b** (66, 1.3:1)[c]
8	**1c**	DIB	0.5	CH_2Cl_2	4	**10a** (61)
9	**1d**	DIB	0.5	CH_2Cl_2	3	**11** (95)
10	**1e**	DIB	0.5	CH_2Cl_2	3	**12** (54)
11	**1f**	DIB	0.5	CH_2Cl_2	2	**13** (99)
12[d]	**1f**	DIB	0.5	CH_2Cl_2	3	**13** (16) **14** (80)
13	**2**	DIB	0.5	CH_2Cl_2	4	**15** (89)
14	**3**	DIB	0.5	MeCN	1	**16** (66)
15	**7a**	DIB	0.5	CH_2Cl_2	3	**17a:18a** (86, 1:1)[c]
16[d]	**7a**	DIB	0.5	CH_2Cl_2	3	**17b:18b** (84, 1:1)[c,e]

[a] All reactions were conducted in dry solvents (15 mL) at room temperature under nitrogen containing PhIO (2 mmol) or (diacetoxyiodo)benzene (DIB) (2 mmol) and iodine per mmol of acid. The reactions with PhIO were irradiated with a 100 W tungsten filament lamp. [b] Yields of compounds after purification. [c] Ratios determined by ^{1}H NMR. [d] The reaction was quenched with methanol before workup. [e] Hemiaminals **17a:18a** (9%, 1:1) were also obtained.

Study of the Reaction Conditions and Trapping of the Generated *N*-Acyliminium Ion with Oxygen and Nitrogen Nucleophiles. The conditions for the generation of the postulated *N*-acyliminium ions and their subsequent trapping by nucleophiles were studied with *N*-(pivaloyl)-L-proline (**1a**) (Table 1, entries 1−6). In all cases, the reaction of **1a** in the presence of iodosylbenzene (PhIO) or (diacetoxy)iodobenzene (DIB) and iodine, in dichloromethane or acetonitrile, gave only the γ-amino aldehyde **8a** (Scheme 3), in good yields. The bulkiness of the pivaloyl group shifts the equilibrium between the cyclic and acyclic forms toward the open-chain tautomer.[4g−j,10a] To rule out the possibility that the decarboxylative oxidation could be due to DIB or PhIO

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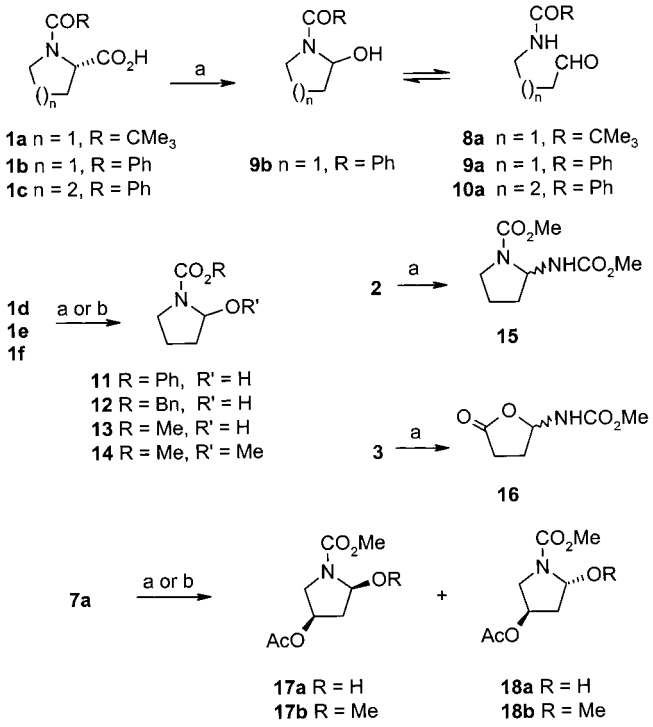
Scheme 3. *N*-Acyliminium Ion Generation−Trapping with Heteroatomic Nucleophiles[a]



[a] Key: (a) DIB, I_2, CH_2Cl_2, rt; (b) DIB, I_2, CH_2Cl_2, rt, then MeOH, rt, 45 min.

alone, a reaction was carried out without iodine (entry 1). The reaction also proceeded but only in 21% yield after 12 h. When iodine was added (entries 2−6), the photolysis proceeded quickly in good yields. Remarkably, a stoichiometric amount of iodine was not necessary (entry 2). Unlike the case of oxycarbenium ions,[2b] acetonitrile did not react with the postulated *N*-acyliminium intermediate in a Ritter-type reaction.[11]

When the decarboxylation was tried with a less bulky amide, *N*-benzoyl-L-proline **1b**, a mixture of the aldehyde **9a** and the hemiaminal **9b** was obtained in 1:1.3 ratio with 66% yield (entry 7). Besides the ring-chain tautomerism, there is an equilibrium between *syn*/*anti* carbamate rotamers which originates signal splitting in the ^{1}H and ^{13}C NMR spectra of **9a/b** at 26 °C. On heating to 70 °C this splitting disappeared, although the mixture aldehyde−hemiaminal was still observed, but shifted to a 1:1 ratio. In the case of the six-membered ring, pipecolinic acid derivative **1c** gave (entry 8) exclusively the acyclic tautomer, the aldehyde **10a**, in 61% yield. However, when the decarboxylation was carried out with carbamates **1d**−**f**, only the cyclic hemiaminal tautomers **11**−**13** were formed[12] (entries 9−11). As before, at 26 °C the ^{1}H and ^{13}C NMR spectra showed an equilibrium between the *cis*- and *trans*-carbamate rotamers, but on heating to 70 °C the signals coalesced.

The *ω*-amino aldehydes and hemiaminals are useful synthons, as precursors of *ω*-amino acids present in pseudopeptidic drugs.[13] Their formation is rationalized by intramolecular trapping of the *N*-acyliminium intermediate with water during the aqueous workup. However, other nucleophiles can be used instead. For instance, when the reaction of the L-proline derivative **1f** was quenched with methanol, 2-methoxypyrrolidine **14** was obtained in good yield (Table 1, entry 12).

The existence of the *N*-acyliminium ion was corroborated by intramolecular trapping with nitrogen or oxygen nucleophiles, using L-ornithine and L-glutamic acid derivatives **2** and **3** as starting substrates (Scheme 3). Thus, decarboxylation of *N*,*N*′-(dimethyloxycarbonyl)-L-ornithine (**2**) afforded the interesting 2-aminopyrrolidine derivative **15** as the sole product, in excellent yield, while that of *N*-(methyloxycarbonyl)-L-glutamic acid (**3**) (entry 14) proceeded with absolute regioselectivity decarboxylation only in the α-position to give aminolactone **16**. Since neither compound **15** nor **16** showed optical rotation, complete racemization should occur during the decarboxylation reaction.

This methodology allows the generation of more complex chiral molecules. For example, decarboxylation of *trans*-hydroxy-L-proline derivatives as **7a** would allow the synthesis of chiral pyrrolidines related to *azasugars*, many of which are biologically active as glycosidase inhibitors.[14] Thus, photolysis of 4-acetyloxyproline **7a** (entry 15) gave hydroxy derivatives **17a** and **18a** in 86% yield and 1:1 ratio. These diastereomers could be separated by fast chromatography and were individually characterized. However, both of them equilibrate with time to a 1:1 mixture of **17a**/**18a**. When the reaction was quenched with dry methanol before the workup, methyl *N*,*O*-acetals **17b** and **18b** were obtained in 1:1 ratio and 84% yield, besides 9% of the 1:1 mixture of hemiaminals **17a**/**18a**. The stereochemistry of **17a** and **18a** was determined on the basis of their spectroscopic data and comparison with those of the precursor **7a** and of compounds **22** and **23** (vide infra).

Trapping of the *N*-Acyliminium Ion with Carbon Nucleophiles. The 2-methoxypyrrolidines such as **14** have been used by other authors to obtain 2-allyl-, 2-aryl-, or 2-alkylpyrrolidines and other cyclic nitrogen derivatives in reactions catalyzed by Lewis acids.[15] Since these heterocycles form a part of many products with biological activity (such as alkaloids),[16] this reaction is of great interest. As an example (Scheme 4), 2-methoxypyrrolidine **14**, obtained from L-proline derivative **1f** using our methodology, was treated with allyltrimethylsilane and

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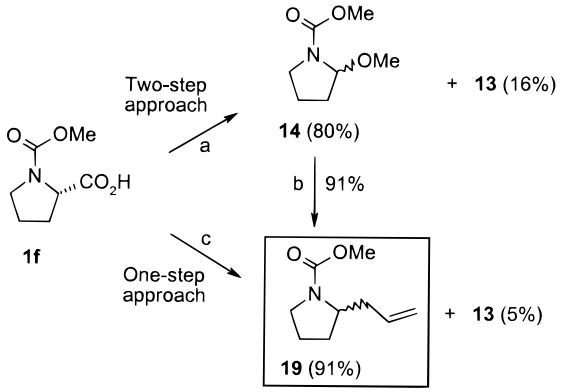
Scheme 4. One-Pot *N*-Acyliminium Ion Generation−Trapping with Carbon Nucleophiles[a]



[a] Key: (a) DIB, I_2, CH_2Cl_2, rt then MeOH, rt, 45 min; (b) allyltrimethylsilane, $BF_3{\cdot}OEt_2$, 0 °C to room temperature, 4 h; (c) DIB, I_2, CH_2Cl_2, rt, 3 h, then allyltrimethylsilane, $BF_3{\cdot}OEt_2$, 0 °C to room temperature, 4 h.

Table 2. Decarboxylation−Oxidation Trapping with Carbon Nucleophiles[a]

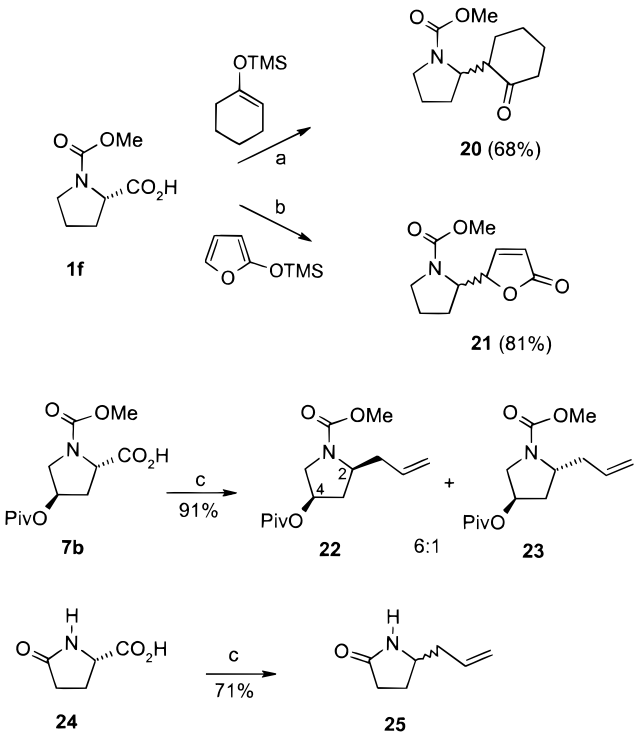
entry	acid	I_2 (eq)	t_1 (h)	$BF_3{\cdot}OEt_2$ (equiv)	nucleophile[b] (equiv)	t_2 (h)	products (%)[c]
1	**1f**	0.5	3	0	A (10)	12	**13** (89)
2	**1f**	0.5	3	2	A (5)	4	**19** (91), **13** (5)
3	**1f**	0.5	3	0	B (10)	12	**13** (89)
4	**1f**	0.5	3.5	2	B (5)	4	**20** (68)
5	**1f**	0.5	3.5	2	C (5)	4	**21** (81)
6	**7b**	1.0	3	2	A (5)	4	**22** (78), **23** (13)
7	**24**	1.0	3	2	A (5)	4	**25** (71)

[a] All reactions were conducted in dry dichloromethane (see general procedure for details). [b] A = allyltrimethylsilane; B = (trimethylsilyloxy)cyclohexane; C = (trimethylsilyloxy)furan. [c] Given yields are for products purified by column chromatography.

boron trifluoride etherate, giving allylpyrrolidine **19**[17] in 91% yield. It occurred to us that this two-step sequence could be shortened by adding allyltrimethylsilane to our decarboxylation reaction (Table 2). However, in the absence of a Lewis acid (Table 2, entry 1) the allylation did not take place, and only hydroxypyrrolidine **13** was isolated in 89% yield. On addition of boron trifluoride etherate, the allylation worked in excellent yields (91%) to give allyl proline derivative **19** (entry 2).

This one-step decarboxylation−oxidation−alkylation methodology also worked very well with other carbon nucleophiles, as shown in Table 2. For instance, decarboxylation of acid **1f** followed by treatment with boron trifluoride etherate and (trimethylsilyloxy)cyclohexene (entry 4) gave pyrrolidine−cyclohexanone **20** as a mixture of diastereomers in 68% yield after purification by chromatography on silica gel (Scheme 5).[15b] When (trimethylsilyloxy)furan (entry 5) was used as nucleophile, the interesting pyrrolidine−furanone **21** was obtained in 81% yield, again as a mixture of diastereomers, with a *threo:erythro* ratio of 6:1.[18]

Scheme 5. One-Pot *N*-Acyliminium Ion Generation−Trapping with Carbon Nucleophiles[a]



[a] Key: (a) DIB, I_2, CH_2Cl_2, rt 3.5 h, then (trimethylsilyloxy)cyclohexane, $BF_3{\cdot}OEt_2$, 0 °C to room temperature, 4 h; (b) DIB, I_2, CH_2Cl_2, rt 3.5 h, then (trimethylsilyloxy)furan, $BF_3{\cdot}OEt_2$, 0 °C to room temperature, 4 h; (c) DIB, I_2, CH_2Cl_2, rt 3 h, then allyltrimethylsilane, $BF_3{\cdot}OEt_2$, 0 °C to room temperature, 4 h.

These results demonstrate that with carbon nucleophiles the addition of the Lewis acid was necessary for the reaction to proceed. Contrarily, acid catalysis was unnecessary when stronger heteroatomic nucleophiles were used.[19] Thus, a possible role for the Lewis acid is to coordinate with the carboxyamido group of the substrate, increasing the electronic deficiency of the *N*-acyliminium intermediate and facilitating its attack by weaker nucleophiles. However, Yoshida[17] has recently reported on the trapping of an electrogenerated *N*-acyliminium ion by carbon nucleophiles without Lewis acid assistance. Thus, another possible role may be to regenerate the *N*-acyliminium ion in the event of its trapping with iodide present in the reaction mixture. Although we have not isolated any compound to support this, we cannot exclude this hypothesis. In any case, whatever the nature of the heteroatomic nucleophile present in the reaction medium, addition of a Lewis acid may regenerate the *N*-acyliminium ion.

To study the stereoselectivity of the reaction, 4-(trimethylacetyloxy)-L-proline derivative **7b** was treated under the previous conditions (entry 6), giving 78% of the (2*S*,4*R*) diastereomer **22**, versus 13% of the 2*R* epimer **23** (91% overall yield, dr 6:1). Their structure and stereochemistry were determined on the basis of their spectroscopic data, including COSY, HMQC, and double resonance experiments. Molecular modeling[20] of compound **22** demonstrated that it may exist in two well-

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(18) For closely related compounds, see: (a) Martin, S. F.; Corbett, J. W. *Synthesis* **1992**, 55−57. (b) Rassu, G.; Carta, P.; Pinna, L.; Battistini, L.; Zanardi, F.; Acquotti, D.; Casiraghi, G. *Eur. J. Org. Chem*. **1999**, 1395−1400. For reviews of trialkylsilyloxyfurans, see: (c) Casiraghi, G.; Rassu, G. *Synthesis* **1995**, 607−626. (d) Rassu, G.; Zanardi, F.; Battistini, L.; Cashiraghi, G. *Synlett*, **1999**, 1333−1350. For other reviews with related strategies, see: (e) Hanessian, S. *Tetrahedron* **1997**, *53*, 12789−12854. (f) Sardina, F. J.; Rapoport, H. *Chem. Rev*. **1996**, *96*, 1825−1872.

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(20) MMX force field as implemented in PCMODEL (v. 4.0), Serena Software, Bloomington IN, 47402-3076.

defined conformations, with the two 2,4-*cis*-substituents either in pseudodiequatorial or diaxial orientation, the latter being the more stable by 1.7 kcal mol^{-1}. This somewhat surprising result has been attributed to the presence of interactions between the 2,4-substituents and the carbamate group in the pseudodiequatorial conformation. A similar situation has been recently reported by Moloney for a derivative of pyroglutamic acid (**24**).[21] The observed coupling constants between protons at 2-C, 3-C, and 4-C, extracted by double resonance from the ^{1}H NMR spectrum of **22** at 70 °C ($J_{2,3\alpha} = 8.5$, $J_{2,3\beta} < 1$, $J_{3\alpha,4} = 6.1$, $J_{3\beta,4} < 1$ Hz) are in good agreement with those calculated over a minimized structure in diaxial conformation by using the Karplus−Altona equation[22] implemented in the PCMODEL program ($J_{2,3\alpha} = 7.9$, $J_{2,3\beta} = 1.2$, $J_{3\alpha,4} = 5.3$, $J_{3\beta,4} = 1.5$ Hz). This confirms that the major diastereomer **22** has the *cis*-configuration, opposite to that present in the starting material.[23] Thus, our one-pot methodology is complementary to the elaboration of the allyl substituent from the lateral chain of the amino acid, which would give **23**.

Even more notably, the reaction also proceeded in good yields with monosubstituted amides, such as pyroglutamic acid (**24**) (entry 7) which gave 5-allyl-2-pyrrolidinone **25** in 71% yield. Possible side reactions due to the formation of *N*-radical intermediates were not observed.[24] This indicates that the decarboxylation and the oxidation of the resultant α-amido radical are considerably faster than other possible competing reactions. The amide group could be used to introduce other functionalities on the pyrrolidone ring, offering great versatility to our methodology.

In summary, a mild, high-yielding methodology has been developed for the decarboxylation of α-amino acids and the subsequent nucleophilic substitution. The intermediacy of an *N*-acyliminium cation may be invoked through its inter- and intramolecular trapping with different heteroatom nucleophiles. The electrophilic *N*-acyliminium ion postulated also can be trapped by weaker carbon nucleophiles, under the influence of Lewis acid, in a one-pot sequence. The application of the present methodology to the synthesis of alkaloids is in progress and will be reported elsewhere.

Experimental Section

General Methods. Melting points were determined with a hot-stage apparatus and are uncorrected. Optical rotations were measured at the sodium line at ambient temperature in $CHCl_3$ solutions. IR spectra were recorded in $CHCl_3$ solutions. NMR spectra were determined at 500 MHz for ^{1}H and 50.3 or 125.7 MHz for ^{13}C in $CDCl_3$ unless otherwise stated, in the presence of TMS as internal standard. Mass spectra were determined at 70 eV unless otherwise specified. Merck silica gel 60 PF_{254} and 60 (0.063−0.2 mm) were used for preparative thin-layer chromatography and column chromatography, respectively. Circular layers of 1 mm of Merck silica gel 60 PF254 were used on a Chromatotron for centrifugally assisted chromatography. Commercially available reagents and solvents were analytical grade or were purified by standard procedures prior to use.[25] All reactions involving air- or moisture-sensitive materials were carried out under a nitrogen atmosphere. The spray reagents for TLC analysis were conducted with 0.5% vanillin in H_2SO_4−EtOH (4:1) or 0.25% ninhydrin in EtOH and further heating until development of color. The starting unprotected amino acids were all commercially available.

Synthesis of Starting Materials. General Procedure for the Preparation of Amides 1a−c. To a solution of L-proline (1.15 g, 10 mmol) in dry CH_2Cl_2 (15 mL) and triethylamine (5 mL) cooled to 0 °C was added dropwise the acyl chloride (12.5 mmol). The solution was allowed to reach rt and was stirred overnight; then the reaction mixture was acidified with 2 M HCl and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by column chromatography, giving the *N*-acyl-L-proline derivatives. Benzoyl-L-proline[9g] (**1b**) and (2*S*)-benzoyl-2-piperidinecarboxylic acid[9h] (**1c**) obtained in 76% and 71% yield, respectively, have been previously described.

***N*-Pivaloyl-L-proline (1a).** Obtained in 68% yield from L-proline; one rotamer at 26 °C; mp 138−139 °C (white crystal from EtOAc); $[\alpha]_D$ −15 ($c = 0.36$); IR 3500−3000 (br b), 1749, 1723, 1413 cm^{-1}; ^{1}H NMR (500 MHz, 26 °C) δ 9.84 (1H, br s), 4.60 (1H, dd, $J = 3.8$, 8.1 Hz), 3.72 (2H, m), 2.20 (1H, m), 2.07 (1H, m), 2.0 (1H, m), 1.96 (1H, m), 1.28 (9H, s); ^{13}C NMR (125.7 MHz, 26 °C) δ 178.6 (C), 175.1 (C), 61.4 (CH), 48.4 (CH_2), 38.9 (C), 27.1 (3 × CH_3), 26.9 (CH_2), 25.8 (CH_2); MS (EI) *m*/*z* (rel intensity) 154 ($M^+ - CO_2H$, 76), 114 (6), 85 (88), 57 (100); HRMS calcd for $C_9H_{16}NO$ 154.1232, found 154.1295. Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.14; H, 8.62; N, 7.34.

Synthesis of Starting Materials. General Procedures for the Preparation of Carbamates 1d−f, 2, and 3. To a solution of L-proline (1.17 g, 10 mmol) in THF (15 mL) and aqueous saturated sodium bicarbonate (15 mL) cooled to 0 °C was added dropwise the alkyl or phenyl chloroformate (20 mmol). The solution was allowed to reach rt and was stirred overnight. The reaction mixture was carefully acidified with 2 M HCl and then extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by column chromatography, giving alkyl or phenyl oxycarbonylproline derivatives. *N*-(Benzyloxy)carbonyl-L-proline[9i] (**1e**) and *N*-methoxycarbonyl-L-proline[9j] (**1f**) obtained in 82% and 89% yield, respectively, have been previously described.

***N*-Phenoxycarbonyl-L-proline (1d).** Obtained in 86% yield from L-proline; two rotamers at 26 °C (1:1); one rotamer at 50 °C; syrup; $[\alpha]_D$ −86 ($c = 0.44$); IR 3500−2800 (br b), 1720, 1393, 1220 cm^{-1}; ^{1}H NMR (500 MHz, 50 °C) δ 8.59 (1H, br s), 7.29 (2H, m), 7.14 (3H, m), 4.50 (1H, m), 3.69 (1H, m), 3.63 (1H, m), 2.27 (1H, m), 2.18 (1H, m), 2.02 (1H, m), 1.95 (1H, m); ^{13}C NMR (125.7 MHz, 26 °C) δ 177.7/176.5 (C/C), 153.9/152.8 (C/C), 151.0 (C/C), 129.2/129.1 (2 × CH/2 × CH), 125.4/125.3 (CH/CH), 121.5 (2 × CH/2 × CH), 59.3/59.0 (CH/CH), 47.0 (CH_2/CH_2), 30.9/29.5 (CH_2/CH_2), 24.3/23.9 (CH_2/CH_2); MS (EI) *m*/*z* (rel intensity) 235 (M^+, 1), 190 (7), 94 (100); HRMS calcd for $C_{12}H_{13}NO_4$ 235.0845, found 235.0839. Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.11; H, 5.84; N, 5.95.

***N,N*-Bis(methoxycarbonyl)-L-ornithine (2).** Obtained in 86% yield from L-ornithine; two rotamers at 26 °C (2:1); one rotamer at 70 °C; mp 90−91 °C (white crystal from EtOAc); $[\alpha]_D$ +36 ($c = 0.49$); IR 3500−3000 (br b), 3448, 3335, 2956, 1718, 1517 cm^{-1}; ^{1}H NMR (500 MHz, 70 °C) δ 7.10 (1H, br b), 5.05 (1H, br b), 5.45 (1H, br b), 4.36 (1H, dd, $J = 13.2$, 7.6

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Hz), 3.71 (3H, s), 3.69 (3H, s), 3.23 (2H, m), 1.93 (1H, m), 1.76 (1H, m), 1.64 (2H, m); ^{13}C NMR (50.3 MHz, 26 °C) major rotamer δ 175.4 (C), 157.6 (C), 157.0 (C), 53.4 (CH), 52.4 (CH_3), 52.2 (CH_3), 40.4 (CH_2), 29.4 (CH_2), 25.7 (CH_2); minor rotamer δ 175.4 (C), 157.6 (C), 157.0 (C), 53.7 (CH), 52.7 (CH_3), 52.4 (CH_3), 40.7 (CH_2), 29.3 (CH_2), 25.5 (CH_2); MS (EI) *m*/*z* (rel intensity) 230 ($M^+ - H_2O$, 9), 198 (13), 128 (100); HRMS calcd for $C_9H_{14}N_2O_5$ 230.0903, found 230.0912. Anal. Calcd for $C_9H_{16}N_2O_6$: C, 43.55; H, 6.50; N, 11.28. Found: C, 43.67; H, 6.58; N, 11.15.

***N*-Methoxycarbonyl-L-glutamic Acid (3).** Obtained in 61% yield from L-glutamic acid; mp 88−90 °C (white crystals from $CDCl_3$); $[\alpha]_D$ +22 (*c* = 0.58); IR 3251−2832 (br b), 1706, 1356 cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz, 26 °C) δ 4.10 (1H, dd, *J* = 8.6, 5.3 Hz), 3.30 (3H, s), 2.06 (2H, dd, *J* = 7.8, 7.3 Hz), 1.80 (1H, m), 1.56 (1H, m); ^{13}C NMR (CD_3OD, 50.3 MHz, 26 °C) δ 175.4 (C), 176.4 (C), 159.2 (C), 54.6 (CH), 52.7 (CH_3), 31.1 (CH_2), 27.9 (CH_2); MS (EI) *m*/*z* (rel intensity) 204 (M^+ − H, 1), 160 (87), 142 (89), 114 (100); HRMS calcd for $C_6H_{10}NO_4$ 160.0610, found 160.0654. Anal. Calcd for $C_7H_{11}NO_6$: C, 40.98; H, 5.40; N, 6.83. Found: C, 40.74; H, 5.35; N, 7.01.

2-Benzyl 1-Methyl (2*S*,4*R*)-4-Hydroxy-1,2-pyrrolidinedicarboxylate (5). To a solution of *trans*-4-hydroxy-L-proline (**4**) (3 g, 22.8 mmol) in a mixture of THF−saturated aqueous $NaHCO_3$ (30 mL, 1:1) cooled to 0 °C was added dropwise methyl chloroformate (3.5 mL, 45 mmol). The reaction mixture was stirred for 16 h and then acidified with 2 M HCl and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and concentrated under vacuum to give an oily residue (3.8 g) which was dissolved in dry acetonitrile (30 mL). Anhydrous sodium iodide (270 mg) and potassium carbonate (5 g) were then added. Finally, the solution was cooled to 0 °C, and benzyl bromide (8.2 mL, 69 mmol) was added slowly. The reaction mixture was allowed to reach rt and stirred for 17 h. Then it was diluted with water (100 mL) and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and concentrated under vacuum, and the residue was purified by column chromatography on silica gel (hexanes−EtOAc, 1:1) to give **5** as a colorless oil (3.96 g, 62%); two rotamers at 26 °C (1:1); one rotamer at 70 °C; $[\alpha]_D$ −65 (*c* = 0.56); IR 3609, 3452, 1744 1698, 1456, 1394 cm^{-1}; ^{1}H NMR (500 MHz, 70 °C) δ 7.30 (5H, m), 5.16 (1H, d, *J* = 12.5 Hz), 5.13 (1H, d, *J* = 12.4 Hz), 4.49 (1H, dd, *J* = 7.4, 7.4 Hz), 4.27 (1H, brs, OH), 3.63 (1H, m), 3.61 (3H, s), 3.52 (1H, m), 2.25 (1H, m), 2.2 (1H, OH), 2.07 (1H, ddd, *J* = 13.4, 7.1, 5.1 Hz); ^{13}C NMR (125.7 MHz, 26 °C) δ 172.5/172.4 (C/C), 155.7/155.3 (C/C), 135.5 (2 × C), 128.5 (2 × CH), 128.5 (2 × CH), 128.3/128.2 (CH)/(CH), 128.1 (2 × CH), 128.0 (2 × CH), 69.9/69.1 (CH/CH), 66.8/66.7 (CH_2/CH_2), 57.9/57.7 (CH/CH), 55.1/54.5 (CH_2/CH_2), 52.7/52.6 (CH_3/CH_3), 39.0/38.3 (CH_2/CH_2); MS (EI) *m*/*z* (rel intensity) 279 (M^+, <1), 261 (1), 144 (100), 91 (28). Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.18; H, 6.27; N, 4.99.

2-Benzyl 1-Methyl (2*S*,4*R*)-4-Acetoxy-1,2-pyrrolidinedicarboxylate (6a). To a solution of 2-benzyl 1-methyl (2*S*,4*R*)-4-hydroxy-1,2-pyrrolidinedicarboxylate (**5**) (1.4 g, 5 mmol) in dry pyridine (6 mL) was added acetic anhydride (3 mL), and the reaction mixture was stirred overnight at room temperature. Then it was poured into 2 M HCl and extracted with CH_2Cl_2. The organic layer was dried and concentrated as usual, and the residue was purified by column chromatography (hexanes−EtOAc, 85:15) to give **6a** as a syrup (1.51 g, 89%); two rotamers at 26 °C (1:1); one rotamer at 70 °C; $[\alpha]_D$ −49 (*c* = 0.62); IR ($CDCl_3$) 1742, 1703, 1455, 1399 cm^{-1}; ^{1}H NMR (500 MHz, 70 °C) δ 7.34 (5H, m), 5.25 (1H, m), 5.17 (1H, d, *J* = 12.4 Hz), 5.14 (1H, d, *J* = 12.4 Hz), 4.47 (1H, m), 3.72 (1H, dd, *J* = 12.1, 5.0 Hz), 3.62 (3H, brs), 3.60 (1H, m), 2.36 (1H, m), 2.21 (1H, m), 1.99 (3H, s); ^{13}C NMR (50.3 MHz, 26 °C) δ 171.7/171.6 (C/C), 170.0 (2 × C), 154.9 (2 × C), 135.2 (2 × C), 128.3 [2(2 × CH)], 128.1 (2 × CH), 128.0 (2 × CH), 127.8 (2 × CH), 72.4/71.5 (CH/CH), 66.7/66.6 (CH_2/CH_2), 57.8/57.5 (CH/CH), 52.6/52.5 (CH_3/CH_3), 52.4/52.0 (CH_2/CH_2), 36.4/35.4 (CH_2/CH_2), 19.9 (2 × CH_3); MS (EI) *m*/*z* (rel intensity) 320 (M^+ − H, <1), 261 (4), 186 (6), 126 (100), 91 (44); HRMS calcd for $C_{16}H_{18}NO_6$ 320.1134, found 320.1102. Anal. Calcd for $C_{16}H_{19}NO_6$: C, 59.81; H, 5.96; N, 4.36. Found: C, 59.84; H, 5.84; N, 4.34.

2-Benzyl 1-Methyl (2*S*,4*R*)-4-[(2,2-Dimethylpropanoyl)oxy]-1,2-pyrrolidinedicarboxylate (6b). To a solution of **5** (0.7 g, 2.5 mmol) in dry CH_2Cl_2 (10 mL) containing triethylamine (4 mL) and cooled to 0 °C was added 2,2-dimethylpropanoyl chloride (0.6 mL, 5 mmol). The reaction was allowed to reach rt and stirred overnight. Then it was poured into 2 M HCl and extracted with CH_2Cl_2. The organic layer was dried and concentrated as usual, and the residue was purified by column chromatography (hexanes−EtOAc, 90:10) to give **6b** (0.78 g, 86%): syrup; two rotamers at 26 °C (1:1); one rotamer at 70 °C; $[\alpha]_D$ −44 (*c* = 0.37); IR 1738, 1725, 1703, 1456, 1394 cm^{-1}; ^{1}H NMR (500 MHz, 70 °C) 7.32 (5H, m), 5.24 (1H, m), 5.18 (1H, d, *J* = 12.4 Hz), 5.15 (1H, d, *J* = 12.3 Hz), 4.47 (1H, m), 3.73 (1H, dd, *J* = 12.2, 4.9 Hz), 3.63 (3H, br s), 3.60 (1H, m), 2.33 (1H, m), 2.22 (1H, m), 1.16 (9H, s); ^{13}C NMR (125.7 MHz, 26 °C) 177.6/177.5 (C/C), 171.8/171.6 (C/C), 155.2/154.6 (C/C), 135.3 (2 × C), 128.5/128.4 (2 × CH/2 × CH), 128.3 (2 × CH), 128.1/127.9 (2 × CH/2 × CH), 72.2/71.4 (CH/CH), 66.8/66.7 (CH_2/CH_2), 57.8/57.5 (CH/CH), 52.6/52.4 (CH_3/CH_3), 52.3/51.9 (CH_2/CH_2), 38. (2 × C), 36.4/35.3 (CH_2/CH_2), 26.82 [2 × (3 × CH_3)]; MS (EI) *m*/*z* (rel intensity) 363 (M^+, <1), 261 (2), 228 (2), 170 (5), 126 (100), 91 (46); HRMS calcd for $C_{19}H_{25}NO_6$ 363.1682, found 363.1667. Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.92; H, 7.14; N, 3.95.

(2*S*,4*R*)-4-(Acetyloxy)-1-(methoxycarbonyl)-2-pyrrolidinecarboxylic Acid (7a). To a solution of benzyl 4-acetyloxy-1-methoxycarbonyl-L-proline (**6a**) (1.5 g, 4.4 mmol) in EtOAc was added 10% $Pd(OH)_2$/C (200 mg), and the reaction mixture was stirred under hydrogen (1 atm) for 16 h. Then it was filtered through Celite, affording pure **7a** (1.0 g, 99%): syrup; two rotamers at 26 °C (2:1); one rotamer at 70 °C; $[\alpha]_D$ −58 (*c* = 0.33); IR 3600−3000 (br b), 1739, 1703, 1456, 1396 cm^{-1}; ^{1}H NMR (500 MHz, 70 °C) δ 10.29 (1H, br s), 5.23 (1H, m), 4.33 (1H, m), 3.77 (3H, s), 3.70 (2H, m), 2.29 (2H, m), 2.01 (3H, s); ^{13}C NMR (50.3 MHz, 26 °C) major rotamer δ 176.2 (C), 170.4 (C), 155.1 (C), 71.8 (CH), 57.6 (CH), 52.7 (CH_3), 52.4 (CH_2), 36.4 (CH_2), 20.9 (CH_3); minor rotamer δ 176.0 (C), 170.4 (C), 155.8 (C), 72.6 (CH), 58.3 (CH), 52.9 (CH_3), 52.1 (CH_2), 35.3 (CH_2), 20.9 (CH_3); MS (EI) *m*/*z* (rel intensity) 231 (M^+, <1), (1), 200 (2), 171 (14), 126 (100); HRMS calcd for $C_9H_{13}NO_6$ 231.0743, found 231.0737. Anal. Calcd for $C_9H_{13}NO_6$: C, 46.75; H, 5.67; N, 6.06. Found: C, 46.95; H, 5.88; N, 5.89.

(2*S*,4*R*)-4-[(2,2-Dimethylpropanoyl)oxy]-1-(methoxycarbonyl)-2-pyrrolidinecarboxylic Acid (7b). Hydrogenolysis of **6b** (1.2 g, 3.3 mmol) took place as for **6a**, affording pure **7b** (857 mg, 95%): syrup; two rotamers at 26 °C (2:1); one rotamer at 70 °C; $[\alpha]_D$ −46 (*c* = 0.24); IR 3480−3000 (br b), 1727, 1703, 1456, 1394 cm^{-1}; ^{1}H NMR (500 MHz, 70 °C) δ 6.65 (1H, br b), 5.26 (1H, m), 4.48 (1H, dd, *J* = 7.3, 7.2 Hz), 3.72 (3H, s), 3.70 (1H, dd, *J* = 12.3, 4.8 Hz), 3.62 (1H, d, *J* = 12.0 Hz), 2.38 (2H, m), 1.17 (9H, s); ^{13}C NMR (125.7 MHz, 70 °C) δ 177.8 (C), 170.4 (C), 155.5 (C), 72.0 (CH), 58.0 (CH), 53.0 (CH_3), 52.3 (CH_2), 38.7 (C), 35.4 (CH_2, br b), 27.1 (3 × CH_3); MS (EI) *m*/*z* (rel intensity). 274 (M^+ + H, <1), 242 (2), 228 (1), 171 (12), 126 (100); HRMS calcd for $C_{12}H_{19}NO_6$ 273.1212, found 273.1235. Anal. Calcd for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.51; H, 7.04; N, 4.88.

Oxidative Decarboxylation of α-Amino Acids and Trapping with Oxygen and Nitrogen Nucleophiles. General Procedures. Method A. A solution of the acid (1 equiv) in CH_2Cl_2 (15 mL) was treated with DIB (2 equiv) or PhIO (2 equiv) and iodine (0.5 equiv) under nitrogen. After stirring at room temperature for the time noted in Table 1 (the reactions with PhIO were irradiated with a 100 W tungsten filament lamp), the reaction was poured into 10% $Na_2S_2O_3$ solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under vacuum. The residue was immediately purified by column chromatography on silica gel (hexanes−EtOAc), yielding the corresponding 2-hydroxy derivatives **8**−**13**, **15**, **16**, **17a**, and **18a**. Methyl 2-hydroxy-1-pyrrolidinecarboxylate[14a] (**13**), obtained in 99% yield from **1f**, has been previously prepared using a different methodology.

Method B. The decarboxylation was performed as above, and when TLC analysis showed consumption of the starting

material, MeOH (1 mL) was added. After stirring for 45 min at room temperature, the reaction mixture was poured into 10% aqueous $Na_2S_2O_3$ and extracted, dried, and evaporated as before. The reaction products were purified by chromatography on silica gel, giving the corresponding 2-methoxy derivatives **14, 17b**, and **18b**. Methyl 2-methoxy-1-pyrrolidinecarboxylate[14b] (**14**), obtained in 80% yield from **1f**, has been previously prepared using a different methodology.

2,2-Dimethyl-*N*-(4-oxobutyl)propanamide (8a). Obtained in 82% yield from **1a**; only the acyclic tautomer was observed: syrup; IR 3467, 2831, 2728, 1724, 1653 cm^{-1}; ^1H NMR (500 MHz) δ 9.76 (1H, s), 5.82 (1H, br s), 3.26 (2H, dd, J = 6.8, 6.7 Hz), 2.53 (1H, dd, J = 7.0, 6.9 Hz), 2.52 (1H, dd, J = 6.9, 6.9 Hz), 1.85 (2H, dddd, J = 6.9, 6.9, 6.8, 6.8 Hz), 1.16 (9H, s); ^{13}C NMR (50.3 MHz) δ 202.1 (C), 178.7 (C), 41.5 (CH_2), 39.0 (CH_2), 38.6 (C), 27.6 (3 × CH_3), 21.8 (CH_2); MS (EI) m/z (rel intensity) 171 (M^+, 6), 154 (36), 142 (20), 57 (100); HRMS calcd for $C_9H_{17}NO_2$ 171.1259, found 171.1293. Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 63.02; H, 10.10; N, 8.43.

***N*-(4-Oxobutyl)benzamide/1-Benzoyl-2-pyrrolidinol (9a/9b).** Obtained in 66% yield from **1b**; tautomeric equilibrium mixture aldehyde/hemiaminal, [1/1.3 (two rotamers at 26 °C (7:1)]; [1/1 (one rotamer at 70 °C)]: syrup; IR 3450, 3362, 2830, 1700, 1653, 1525 cm^{-1}; ^1H NMR (500 MHz, 70 °C) δ 9.42 (1H, s), 7.81 (2H, d, J = 8.3 Hz), 7.72 (2H, d, J = 8.4 Hz), 7.47 (1H, dd, J = 7.4, 7.4 Hz), 7.44 (1H, dd, J = 7.4, 7.4 Hz), 7.42 (2H, dd, J = 7.5, 7.4 Hz), 7.34 (2H, dd, J = 7.8, 7.7 Hz), 6.70 (1H, br s), 6.64 (1H, dd, J = 7.5, 7.4 Hz), 6.44 (1H, br s), 3.54 (2H, dd, J = 6.5, 6.5 Hz), 3.53 (2H, dd, J = 6.4, 6.4 Hz), 2.65 (2H, dd, J = 6.0, 6.0 Hz), 2.59 (1H, dd, J = 7.5, 7.5 Hz), 2.58 (1H, dd, J = 7.0, 7.0 Hz), 1.92 (2H, ddd, J = 7.0, 7.0, 6.9 Hz), 1.44 (2H, br s); ^{13}C NMR (125.7 MHz, 70 °C) δ 202.1 (CH), 170.9 (C), 167.6 (C), 135.7 (C), 134.3 (C), 131.2 (CH), 130.3 (CH), 128.4 (2 × CH), 128.3 (2 × CH), 127.1 (2 × CH), 126.7 (2 × CH), 82.3 (CH), 49.1 (CH_2), 41.4 (CH_2), 39.3 (CH_2), 32.1 (CH_2), 23.6 (CH_2), 21.7 (CH_2); MS (EI) m/z (rel intensity) 191 (M^+, 6), 173 (105 (100), 77 (35); HRMS calcd for $C_{11}H_{13}NO_2$ 191.0946, found 191.0956. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.13; H, 6.87; N, 7.25.

***N*-(5-Oxopentyl)benzamide (10a).** Obtained in 61% yield from **1c**; only the acyclic tautomer was observed; syrup; IR 3451, 3369, 2726, 1722, 1653, 1625, 1522, 1429, 1277, 998 cm^{-1}; ^1H NMR (500 MHz) 9.75 (1H, s), 7.76 (1H d, J = 7.2 Hz), 7.48 (1H, dd, J = 7.4, 7.3 Hz), 7.39 (2H, dd, J, = 7.5, 7.4 Hz), 6.66 (1H, br s), 3.42 (2H, dd, J = 12.9, 6.6 Hz), 2.49 (2H, dd, J = 6.0, 6.0 Hz), 1.68 (2H, m), 1.63 (2H, m); ^{13}C NMR (125.7 MHz) 202.3 (CH), 167.6 (C), 135.5 (C), 131.3 (CH), 128.4 (2 × CH), 126.8 (2 × CH), 43.3 (CH_2), 39.4 (CH_2), 28.9 (CH_2), 18.5 (CH_2); MS (EI) m/z (rel intensity) 188 (M^+ − OH, 46), 105 (100), 77 (33); HRMS calcd for $C_{12}H_{14}NO$ 188.1075, found 188.1080. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.20; H, 7.54; N, 6.87.

Phenyl 2-Hydroxy-1-pyrrolidinecarboxylate (11). Obtained in 95% yield from **1d**; two rotamers at 26 °C (2:1); one rotamer at 70 °C; syrup; IR 3594, 1709, 1595, 1385 cm^{-1}; ^1H NMR (500 MHz, 70 °C) δ 7.36 (2H, m), 7.17 (3H, m), 5.62 (1H, br b), 3.73 (1H, br b), 3.53 (1H, br b), 3.52 (1H, m), 2.16 (1H, m), 2.09 (1H, m), 1.99 (1H, m), 1.91 (1H, m); ^{13}C NMR (125.7 MHz, 26 °C) δ major rotamer 169.9 (C), 150.9 (C), 129.3 (2 × CH), 125.4 (CH), 121.6 (2 × CH), 82.3 (CH), 46.2 (CH_2), 32.7 (CH_2), 22.8 (CH_2); δ minor rotamer 169.9 (C), 153.8 (C), 129.3 (2 × CH), 125.5 (CH), 121.7 (2 × CH), 81.6 (CH), 46.4 (CH_2), 33.8 (CH_2), 22.0 (CH_2); MS (EI) m/z (rel intensity) 207 (M^+, 12), 189 (15), 114 (2), 94 (100); HRMS calcd for $C_{11}H_{13}NO_3$ 207.0921, found 207.0885. Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.73; H, 6.19; N, 6.53.

Benzyl 2-Hydroxy-1-pyrrolidinecarboxylate (12). Obtained in 54% yield from **1e**; two rotamers at 26 °C (2.5:1); one rotamer at 70 °C; syrup; IR 3590, 3451, 1693, 1416 cm^{-1}; ^1H NMR (500 MHz, 70 °C) δ 7.37−7.29 (5H, m), 5.52 (1H, d, J = 4.4 Hz), 5.18 (2H, s), 3.60 (1H, m), 3.39 (1H, m), 2.07 (1H, m), 2.02 (1H, m), 1.94 (1H, m), 1.83 (1H, m), 1.46 (1H, br s); ^{13}C NMR (125.7 MHz, 26 °C) δ major rotamer 155.4 (C), 136.5 (C), 128.5 (2 × CH), 128.0 (CH), 127.8 (2 × CH), 82.1 (CH), 66.8 (CH_2), 45.7 (CH_2), 32.7 (CH_2), 22.7 (CH_2); minor rotamer 154.1 (C), 136.4 (C), 128.6 (2 × CH), 128.2 (CH), 127.8 (2 × CH), 81.3 (CH), 67.1 (CH_2), 46.2 (CH_2), 33.6 (CH_2), 22.0 (CH_2); MS (EI) m/z (rel intensity) 221 (M^+, 1), 203 (42), 91 (100); HRMS calcd for $C_{12}H_{15}NO_3$ 221.1052, found: 221.1060. Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.99; H, 6.97; N, 6.30.

Methyl 2-[(Methoxycarbonyl)amino]-1-pyrrolidinecarboxylate (15). Obtained in 89% yield from **2**; two rotamers at 26 °C; one rotamer at 70 °C; mp 130−131.5 °C (white crystal from EtOAc); IR 3443, 1719, 1697, 1508, 1450, 1383 cm^{-1}; ^1H NMR (500 MHz, 70 °C) δ 5.37 (1H, ddd, J = 6.3, 3.2, 3.1 Hz), 5.0 (1H, br s), 3.65 (3H, s), 3.61 (3H, s), 3.45 (1H, ddd, J = 10.7, 7.8, 3.9 Hz), 3.31 (1H, ddd, J = 10.5, 7.8, 7.8 Hz), 2.02 (2H, m), 1.91 (1H, m), 1.82 (1H, m); ^{13}C NMR (125.7 MHz, 70 °C) δ 155.6 (C), 155.3 (C), 66.3 (CH), 52.3 (CH_3), 51.7 (CH_3), 46.3 (CH_2), 33.2 (CH_2), 22.6 (CH_2); MS (EI) m/z (rel intensity) 202 (M^+, <1), 187 (3), 143 (81), 127 (100); HRMS calcd for $C_8H_{14}N_2O_4$: 202.0954, found 202.0959. Anal. Calcd for $C_8H_{14}N_2O_4$: C, 47.52; H, 6.98; N, 13.85. Found: C, 47.69; H, 6.92; N, 13.47.

Methyl 5-Oxo-tetrahydro-2-furanylcarbamate (16). Obtained in 66% yield from **3**; syrup; IR 3437, 1772, 1735, 1510 cm^{-1}; ^1H NMR (500 MHz) δ 5.99 (2H, br s), 3.72 (3H, s), 2.67 (1H, dd, J = 13.0, 9.8 Hz), 2.55 (2H, m), 2.08 (1H, m); ^{13}C NMR (50.3 MHz) δ 175.7 (C), 155.8 (C), 83.7 (CH), 52.7 (CH_3), 28.6 (CH_2), 27.8 (CH_2); MS (EI) m/z (rel intensity) 159 (M^+, 3), 115 (100); HRMS calcd for $C_6H_9NO_4$ 159.0532, found 159.0535. Anal. Calcd for $C_6H_9NO_4$: C, 45.28; H, 5.70; N, 8.80. Found: C, 45.33; H, 6.04; N, 8.70.

Methyl (2*S*,4*R*)-4-Acetoxy-2-hydroxy-1-pyrrolidinecarboxylate (17a) and Methyl (2*R*,4*R*)-4-Acetoxy-2-hydroxy-1-pyrrolidinecarboxylate (18a). Obtained in 86% yield (1:1) from **7a**; separable mixture (hexanes−EtOAc, 80:20). Compound **17a**: two rotamers at 26 °C (1.3:1); syrup; $[\alpha]_D$ −31 (c = 0.2); IR 3580, 1737, 1694, 1456, 1283, 1245 cm^{-1}; ^1H NMR (500 MHz, 26 °C) δ major rotamer 5.58 (1H, d, J = 6.0 Hz), 5.30 (1H, m), 4.10 (1H, br b), 3.75 (1H, m), 3.72 (3H, s), 3.65 (1H, m), 2.29 (1H, dd, J = 6.0, 6.0 Hz), 2.12 (1H, m), 2.07 (3H, s); minor rotamer 5.62 (1H, dd, J = 5.5, 5.4 Hz), 5.49 (1H, d, J = 4.9 Hz), 5.25 (1H, m), 3.77 (3H, s), 3.47 (1H, d, J = 12.1 Hz), 3.45 (1H, br b), 2.25 (1H, dd, J = 6.0 6.0 Hz), 2.12 (1H, m), 2.03 (3H, s); ^{13}C NMR (125.7 MHz, 26 °C) δ major rotamer 170.4 (C), 155.6 (C), 81.3 (CH), 71.8 (CH), 51.7 (CH_3), 39.6 (CH_2), 38.4 (CH_2), 21.1 (CH_3); minor rotamer 170.6 (C), 155.9 (C), 81.2 (CH), 72.3 (CH), 50.8 (CH_3), 39.6 (CH_2), 38.6 (CH_2), 20.9 (CH_3); MS(EI) m/z (rel intensity) 202 (M^+ − H, 12), 188 (2), 186 (5), 142 (20), 126 (100); HRMS calcd for $C_8H_{12}NO_5$ 202.0715, found 202.0717. Anal. Calcd for $C_8H_{13}NO_5$: C, 47.29; H, 6.89; N, 6.89. Found: C, 47.08; H, 6.65; N, 6.88. Compound **18a**: two rotamers at 26 °C (4:1); syrup; $[\alpha]_D$ −19.5 (c = 0.22); IR 3581, 3454, 1737, 1692 cm^{-1}; ^1H NMR (500 MHz, 26 °C) δ major rotamer 5.63 (1H, dd, J = 5.6, 5.5 Hz), 5.29 (1H, m), 4.07 (1H, br s), 3.76 (1H, m), 3.71 (3H, s), 3.46 (1H, d, J = 12.2 Hz), 2.10 (1H, dd, J = 5.3, 4.0 Hz), 2.13 (1H, dd, J = 5.3, 5.3 Hz), 2.02 (3H, s); minor rotamer 5.57 (1H, m), 5.29 (1H, m), 3.76 (1H, m), 3.76 (3H, s); 3.57 (1H, d, J = 8.8 Hz), 3.30 (1H, br s), 2.10 (1H, dd, J = 5.3, 4.0 Hz), 2.16 (1H, dd, J = 3.9, 3.8 Hz), 2.02 (3H, s); ^{13}C NMR (125.7 MHz, 26 °C) δ major rotamer 170.4 (C), 155.8 (C), 81.3 (CH), 71.8 (CH), 52.5 (CH_3), 50.8 (CH_2), 38.6 (CH_2), 21.0 (CH_3); δ minor rotamer 170.4 (C), 155.8 (C), 80.6 (CH), 71.3 (CH), 52.8 (CH_3), 51.1 (CH_2), 39.6 (CH_2), 21.0 (CH_3); MS (EI) m/z (rel intensity) 202 (M^+ − H, 6), 186 (4), 143 (26), 126 (100); HRMS calcd for $C_8H_{12}NO_5$ 202.0715, found 202.0709. Anal. Calcd for $C_8H_{13}NO_5$: C, 47.29; H, 6.45; N, 6.89. Found: C, 47.39; H, 6.42; N, 6.81.

Methyl (2*S*,4*R*)-4-Acetoxy-2-methoxy-1-pyrrolidinecarboxylate (17b) and Methyl (2*R*,4*R*)-4-Acetoxy-2-methoxy-1-pyrrolidinecarboxylate (18b). Obtained in 84% yield (1:1) from **7a**; separable mixture (hexanes−EtOAc, 95:5). Product **17b**: two rotamers at 26 °C (2:1); one rotamer at 70 °C; syrup; $[\alpha]_D$ +1.3 (c = 0.45); IR 1737, 1704, 1459, 1391, 1247, 1089 cm^{-1}; ^1H NMR (500 MHz, 70 °C) δ 5.24 (2H, m), 3.89 (1H, dd, J = 12.6, 6.5 Hz), 3.74 (3H, s), 3.48 (1H, dd, J = 12.6, 2.6 Hz), 3.39 (3H, s), 2.21 (1H, ddd, J = 14.8, 6.7, 5.9 Hz), 2.12 (1H,

dd, J = 14.8, 0.8 Hz), 2.03 (3H, s); ^{13}C NMR (125.7 MHz, 26 °C) δ major rotamer 170.7 (C), 155.8 (C), 88.6 (CH), 72.3 (CH), 56.1 (CH_3), 52.6 (CH_3), 50.3 (CH_2), 38.2 (CH_2), 20.9 (CH_3); minor rotamer 170.7 (C), 155.8 (C), 88.1 (CH), 71.3 (CH), 55.7 (CH_3), 52.6 (CH_3), 51.9 (CH_2), 38.5 (CH_2), 21.03 (CH_3); MS (EI) m/z (rel intensity) 157 (M^+ − AcOH, 18), 126 (100); HRMS calcd for $C_7H_{11}NO_3$ 157.0739, found 157.07132. Anal. Calcd for $C_9H_{15}NO_5$: C, 49.76, H, 6.96; N, 6.45. Found: C, 49.49; H, 7.20; N, 6.40. Product **18b**: two rotamers at 26 °C (2:1); one rotamer at 70 °C; syrup; $[\alpha]_D$ +19 (c = 0.25); IR 1735, 1706, 1449, 1389, 1248, 1088 cm^{-1}; ^{1}H NMR (500 MHz, 70 °C) δ 5.36 (2H, m), 5.32 (1H, m), 3.75 (3H, s), 3.55 (1H, m), 3.35 (3H, m), 2.31 (1H, dd, J = 13.7, 6.4 Hz), 2.08 (1H, m), 2.02 (3H, s); ^{13}C NMR (125.7 MHz, 26 °C) δ major rotamer 170.5 (C), 155.9 (C), 88.0 (CH), 72.5 (CH), 56.1 (CH_3), 52.6 (CH_3), 50.3 (CH_2), 38.2 CH_2), 20.9 (CH_3); δ minor rotamer 170.5 (C), 155.9 (C), 87.6 (CH), 71.8 (CH), 55.2 (CH_3), 52.6 (CH_3), 50.5 (CH_2), 39.0 (CH_2), 20.9 (CH_3); MS (EI) m/z (rel intensity) 185 (M^+ − MeOH, 13), 157 (45), 126 (100); HRMS calcd for $C_8H_{11}NO_4$ 185.0688, found 185.0784. Anal. Calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.92; H, 6.74; N, 6.39.

Methyl 2-Allyl-1-pyrrolidinecarboxylate (19). A solution of methyl 2-methoxy-1-pyrrolidinecarboxylate (**14**) (160 mg, 1 mmol) in dry CH_2Cl_2 (5 mL) was cooled to 0 °C and treated with allyltrimethylsilane (0.8 mL, 5 mmol). Then $BF_3{\cdot}OEt_2$ (0.25 mL, 2 mmol) was added dropwise. The reaction was allowed to reach rt and was stirred for 4 h before being poured into aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated under vacuum. The residue was purified by chromatography on silica gel yielding methyl 2-allyl-1-pyrrolidinecarboxylate[17] (**19**) (151 mg, 91%).

Oxidative Decarboxylation of α-Amino Acids and Trapping with Carbon Nucleophiles. General Procedure. The substrate in CH_2Cl_2 was treated with DIB (2 equiv) and iodine (see Table 2) and stirred at room temperature for the time noted. Then the reaction was cooled to 0 °C, and the nucleophile (5 equiv) was added. Finally, $BF_3{\cdot}OEt_2$ (2 equiv) was added dropwise. The reaction was allowed to reach rt and the stirring continued for the time noted in Table 2 before being poured into aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic layer was washed with 10% $Na_2S_2O_3$ solution and water, dried (Na_2SO_4), and evaporated under vacuum. The reaction products were purified by column chromatography on silica gel. Methyl 2-allyl-1-pyrrolidinecarboxylate[17] (**19**) and methyl 2-(2-oxocyclohexyl)-1-pyrrolidinecarboxylate[15b] (**20**) obtained from **1f** in 91% and 68% yield, respectively, have been previously described.

Methyl 2-(5-Oxo-2,5-dihydro-furanyl)-1-pyrrolidinecarboxylate (21). Obtained from **1f** in 81% yield; diastereomeric inseparable mixture (*threo*/*erythro*, 6:1, each one rotamer); syrup; IR 1759, 1691, 1572, 1452, 1385 cm^{-1}; ^{1}H NMR (500 MHz) δ major diastereoisomer 7.46 (1H, d, J = 4.7 Hz), 6.04 (1H, d, J = 5.6 Hz), 5.24 (1H, m), 4.32 (1H, m), 3.66 (3H, s), 3.43 (1H, m), 3.28 (1H, m), 2.0 (1H, m), 1.93 (1H, m), 1.80 (2H, m); δ minor diastereoisomer 7.42 (1H, dd, J = 5.8, 1.5 Hz), 6.11 (1H, dd, J = 3.7, 2.1 Hz) 5.33 (1H, m), 4.02 (1H, m), 3.71 (3H, s), 3.43 (1H, m), 3.28 (1H, m), 2.0 (1H, m), 1.93 (1H, m), 1.80 (2H, m); ^{13}C NMR (125.7 MHz, 26 °C) δ major diastereoisomer 172.3 (C), 154.3 (C), 153.9 (CH), 121.5 (CH), 84.9 (CH), 58.1 (CH), 52.3 (CH_3), 47.3 (CH_2), 27.2 (CH_2), 24.0 (CH_2); δ minor diastereoisomer 172.3 (C), 154.2 (C), 153.9 (CH), 122.1 (CH), 83.4 (CH), 59.1 (CH), 52.3 (CH_3), 46.8 (CH_2), 27.2 (CH_2), 25.6 (CH_2); MS (EI) m/z (rel intensity) 211 (M^+, <1), 128 ($M^+ - C_4H_3O_2$, 100). Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 57.02; H, 6.24; N, 6.48.

Methyl (2*S*,4*R*)-2-Allyl-4-[(2,2-dimethylpropanoyl)oxy]-1-pyrrolidinecarboxylate (22) and Methyl (2*R*,4*R*)-2-Allyl-4-[(2,2-dimethylpropanoyl)oxy]-1-pyrrolidinecarboxylate (23). Obtained in 91% yield (6:1) from **7b**; diastereomeric separable mixture (hexanes−EtOAc, 90:10). Compound **22**: 78%; two rotamers at 26 °C (15:1); one rotamer at 70 °C; syrup; $[\alpha]_D$ +41 (c = 0.46); IR 3680, 1624, 1722, 1691, 1455, 1391 cm^{-1}; ^{1}H NMR (500 MHz, 70 °C) δ 5.73 (1H, m), 5.20 (1H, m), 5.04 (1H, d, J = 15.5 Hz), 5.03 (1H, d, J = 11.8 Hz), 3.95 (1H, m), 3.77 (1H, dd, J = 12.7, 6.0, Hz), 3.67 (3H, s), 3.34 (1H, d, J = 12.7 Hz), 2.66 (1H, m), 2.27 (1H, ddd, J = 13.7, 8.8, 8.7 Hz), 2.17 (1H, ddd, J = 14.4, 8.5, 8.2 Hz), 1.92 (1H, d, J = 14.3 Hz), 1.18 (9H, s); ^{13}C NMR (125.7 MHz, 70 °C) δ 177.7 (C), 155.3 (C), 135.0 (CH), 117.3 (CH_2), 72.9 (CH), 56.8 (CH), 52.7 (CH_2), 52.1 (CH_3), 38.7 (CH_2), 38.6 (C), 35.1 (CH_2), 27.1 (3 × CH_3); MS (EI) m/z (rel intensity) 270 (M^+ + H, <1), 228 (1), 168 (1), 126 (100); HRMS calcd for $C_{14}H_{24}NO_4$ 270.1705, found 270.1786. Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.51; H, 8.51; N, 5.11. Compound **23**: 13%; two rotamers at 26 °C (1.3:1), one rotamer at 70 °C; syrup; $[\alpha]_D$ −56 (c = 0.11); IR 3081, 1722, 1697, 1625, 1454, 1392 cm^{-1}; ^{1}H NMR (500 MHz, 70 °C) δ 5.71 (1H, m), 5.17 (1H, m), 5.08 (1H, d, J = 16.8 Hz), 5.06 (1H, d, J = 10.4 Hz), 4.05 (1H, m), 3.69 (3H, s), 3.62 (1H, d, J = 12.5 Hz), 3.48 (1H, dd, J = 12.5, 4.8 Hz), 2.53 (1H, m), 2.31 (1H, ddd, J = 14.5, 7.7, 7.6 Hz), 2.07 (1H, m), 1.97 (1H, m), 1.19 (9H, s); ^{13}C NMR (50.3 MHz, 26 °C) δ 177.9 (2 × C), 155.2 (2 × C), 133.4 (2 × CH); 118.0 (2 × CH_2), 72.1/72.0 (CH/CH), 55.6/55.3 (CH/CH), 52.1 [2 × (CH_3 + CH_2)], 38.6/37.7 (CH_2/CH_2), 38.4 (2 × C), 36.5/35.7 (CH_2/CH_2), 26.9 [2 × (3 × CH_3)]; MS (EI) m/z (rel intensity) 228 ($M^+ - C_3H_5$, <1), 168 (1), 166 (6), 142 (5), 126 (100); HRMS calcd for $C_{11}H_{18}NO_4$ 228.1236, found 228.1237. Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.31; H, 8.69; N, 5.25.

5-Allyl-2-pyrrolidinone (25). Obtained from **24** in 71% yield; syrup; IR 3432, 3083, 1691, 1602, 1421 cm^{-1}; ^{1}H NMR (500 MHz) δ 6.82 (1H, br b), 5.73 (1H, dddd, J = 16.7, 9.7, 7.1, 7.0 Hz), 5.10 (1H, d, J = 15.6 Hz), 5.09 (1H, d, J = 11.7 Hz), 3.69 (1H, dddd, J = 6.5, 6.5, 6.4, 6.4 Hz), 2.30 (2H, m), 2.20 (3H, m), 1.73 (1H, m); ^{13}C NMR (50.3 MHz) δ 172.2 (C), 133.6 (CH), 118.3 (CH_2), 53.7 (CH), 40.9 (CH_2), 30.2 (CH_2), 20.5 (CH_2); MS (EI) m/z (rel intensity) 124 (M^+ − H, 6), 110 (16), 97 (24), 84 (100); HRMS calcd for $C_7H_{10}NO$ 124.0762, found 124.0809. Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.29; H, 8.63; N, 10.98.

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