Synthesis of 2,3-Disubstituted Pyrrolidines and Piperidines via One-Pot Oxidative Decarboxylation−*β*-Iodination of Amino Acids

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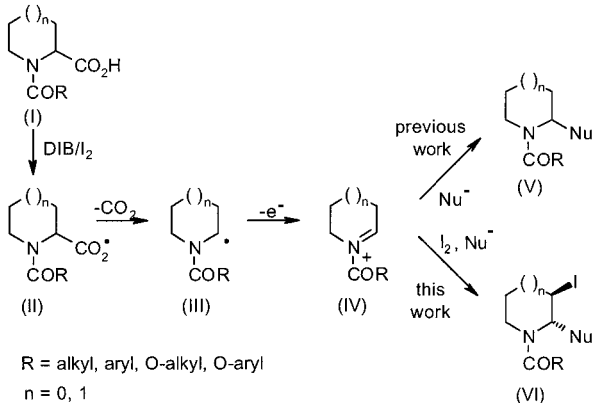
A new synthesis of 2,3-disubstituted pyrrolidines and piperidines is described. This mild procedure is based on the one-pot oxidative decarboxylation−*β*-iodination of α-amino acid carbamates or amides. The iodine is introduced at the previously unfunctionalized 3-position. Different substituents can be introduced at C-2, e.g., hydroxy, alkoxy, allyl, alkyl, etc. A *trans* relationship between the C-2 and C-3 substituents is exclusively obtained. The influence of the solvent and the ring size of the starting amino acid are studied, as well as the nature of the protecting group on the nitrogen. The stereoselectivity of the reaction was also studied using chiral methyl (2*S*,4*S*)-4-acetyloxyproline-1-carboxylate (**8**). The products obtained can be manipulated to give bicyclic systems present in many natural products. By using the tandem decarboxylation−iodination−alkylation reaction, 2-substituted-3-iodopyrrolidines are formed, which are precursors of 2-substituted-2,5-dihydropyrrols.

Introduction

Many natural products present piperidine or pyrrolidine rings in their structures,[1] from simple compounds such as coniine, the active principle in the poison of hemlock,[1a] to complex alkaloids such as those belonging to the Amarillydaceae family.[1b] These natural products have often shown significant biological activity and in many cases have been used as therapeutic agents.[2] Furthermore, these heterocyclic rings are also of interest in synthetic organic chemistry as chiral auxiliaries.[3] These facts have stimulated efforts for the development of the stereocontrolled synthesis of this class of compounds.[4]

We have recently reported our initial results on the synthesis of 2-substituted piperidine and pyrrolidine rings from α-amino acids (Scheme 1) using a tandem radical decarboxylation−oxidation reaction.[5] Thus, treating the α-amino acid (I) with (diacetoxyiodo)benzene (DIB) and iodine,[6] under irradiation with visible light, a carboxyl radical (II) is generated. This radical evolves by loss of CO_2, giving a new C-radical (III).[7] The latter is oxidized by excess reagent, giving a *N*-acyliminium ion (IV), which can be trapped inter- or intramolecularly by nitrogen, oxygen, or carbon nucleophiles.[8] The final products (V) were the 2-substituted piperidines (n = 1) or pyrrolidines (n = 0). This one-pot process used as

Scheme 1. Strategy for the Synthesis of 2,3-Disubstituted Pyrrolidines (n = 0) and Piperidines (n = 1)



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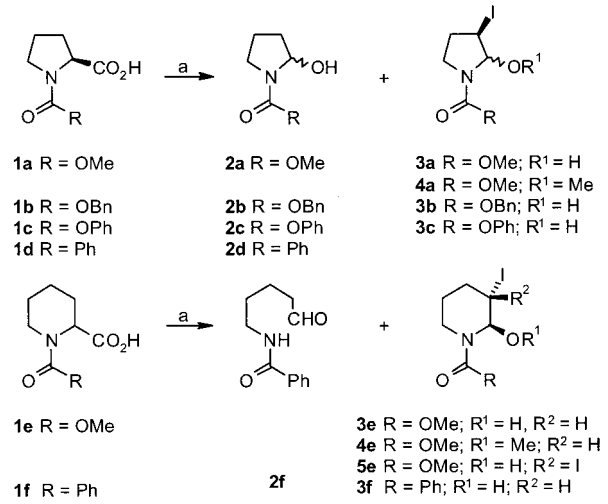
starting material commercially available amino acids or easily formed derivatives and took place under mild conditions, giving good to excellent yields.

In our effort to extend the scope of this interesting reaction, we were pleased to find that under certain conditions a new tandem process of decarboxylation−β-iodination took place, which allowed the synthesis of 2-substituted-3-iodopyrrolidine and piperidine derivatives (VI, Scheme 1).[5a] Since the iodo group can subsequently be replaced by oxygen, nitrogen, and sulfur nucleophiles or by alkyl chains, its introduction in the unfunctionalized 3-position seemed extremely promising. In this article we report on the scope of this reaction, as well as its stereoselectivity.

Results and Discussion

The influence of the solvent, the nitrogen protecting group, and the ring size of the amino acid were studied. In our previous work,[5b−d] the decarboxylation reactions had taken place in dry dichloromethane, and noniodinated products were isolated in good yields. When an excess of iodine was used and dichloromethane was replaced by a more polar solvent such as acetonitrile, the decarboxylation of proline carbamate derivatives **1a**−**c**[5c,9] (Scheme 2) afforded the 3-iodinated pyrrolidines **3a**−**c** as the major products (Table 1). Thus, when *N*-(methyloxycarbonyl)-L-proline **1a**[9d] (Table 1, entry 1) was treated with DIB and iodine in acetonitrile at room temperature, followed by aqueous workup, 2-hydroxy-3-iodopyrrolidine **3a** (Scheme 2) was obtained in good yields, along with noniodinated analogue **2a**.[5c] When the reaction was quenched with dry methanol before workup, 3-iodo-2-methoxypyrrolidine **4a** was obtained as the major product (entry 2). The isolated 2,3-disubstituted product was exclusively *trans* (for a plausible mechanism, see later). Similar results were observed in the decarboxylation of

Scheme 2. Oxidative Decarboxylation−β-Iodination of α-Amino Acids[a]



[a] Key: (a) DIB, I_2, rt, then H_2O or MeOH, rt, 1 h (see Table 1).

Table 1. One-Pot Decarboxylation of α-Amino Acids−Halogenation−Nucleophilic Addition[a]

entry	acid	iodine (equiv)	solvent	*t* (h)	products (%)[b]
1	**1a**	2	MeCN	3	**2a** (15), **3a** (66)
2	**1a**	2	MeCN[c]	3	**3a** (6); **4a** (62)
3	**1b**	2	MeCN	5	**2b** (8); **3b** (54)
4	**1c**	2.5	MeCN	18	**2c** (4); **3c** (69)
5	**1d**	2	MeCN	25	**2d** (35)
6	**1e**	2	MeCN	5	**3e** (9); **5e** (36)
7	**1e**	2	CH_2Cl_2	3	**3e** (35)
8	**1e**	2	CH_2Cl_2[c]	3	**3e** (9); **4e** (62)
9	**1f**	2	CH_2Cl_2	3	**2f** (59); **3f** (8)
10	**1f**	2	MeCN	5	**3f** (19)

[a] The reaction was conducted in dry solvents at room temperature under nitrogen. Two equivalents of DIB were used. After the time noted, the reaction was poured into 10% aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2. [b] Yields are for products isolated after chromatography on silica gel. [c] The reaction was quenched with dry methanol and stirred for 1 h before workup.

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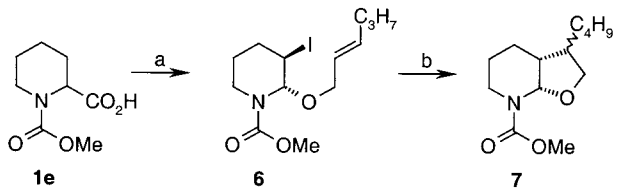
the proline benzyl carbamate **1b**[9e] and the proline phenyl carbamate **1c**[5c] (entries 3 and 4), which gave iododerivatives **3b** and **3c**, together with the minor hemiaminals **2b**[5c] and **2c**,[5c] respectively. However, the iodination of the phenyl carbamate **1c** required longer reaction times. When the amide derivative **1d**[9f] was reacted under similar conditions (entry 5), only the noniodinated product **2d**[5c] was isolated, even after extended reaction times. The results obtained with these proline derivatives suggest that the stronger the electron-withdrawing group on the nitrogen (amides > phenyl carbamates > benzyl or methyl carbamates), the more difficult the iodination.

The influence of the ring size in the reaction results was determined next, using (±)-pipecolinic acid derivatives **1e**−**f** (Scheme 2). To our surprise, when pipecolinic acid methyl carbamate **1e**[9g] was decarboxylated in acetonitrile, followed by aqueous workup (entry 6), a 3,3-diiodinated compound **5e** was formed as the major product, along with the monoiododerivative **3e**. When the reaction was carried out in dichloromethane (entry 7), the major product was the 2-hydroxy-3-iodopiperidine **3e**. The yield of monoiodinated products was doubled when the reaction was quenched with dry methanol (entry 8), giving *trans*-3-iodo-2-methoxypiperidine **4e** as the major product (62%) together with **3e** (9%). A possible explanation for the higher yields will be given later. The reaction was then studied with an amide derivative **1f**[9h] (entries 9 and 10). Interestingly, when the benzamide **1f** was reacted in dichloromethane (entry 9), the 3-iodinated piperidine **3f** was obtained along with noniodinated compound **2f**,[5c] which existed mainly as the aldehyde tautomer.[10] The photolysis in acetonitrile, however, afforded a complex mixture (entry 10), from which iododerivative **3f** could be isolated.

In summary, the decarboxylation−iodination of carbamate derivatives afforded yields better than those of amides. When five-membered rings derived from carbamates were involved, the iodination took place in acetonitrile but not in dichloromethane. No iodination was observed with amides, even in acetonitrile. In the decarboxylation of pipecolinic carbamates, diiodinated products were obtained as the major products in acetonitrile, while monoiodinated ones were formed in dichloromethane. In this way, by choosing the reaction conditions, different non-, mono-, or diiododerivatives can be synthesized.

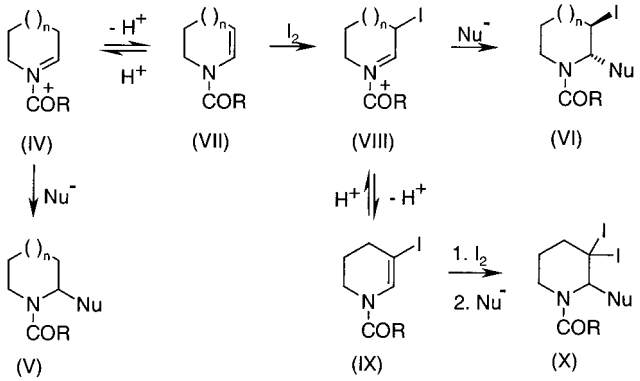
As concluded from the results displayed in Table 1, in the decarboxylation−oxidation of pipecolinic derivative **1e**, the yield of the 2-alkoxypiperidine **4e** (entry 8) is greater than that of 2-hydroxypiperidine **3e** (entry 7). This may indicate that the 2-hydroxy-3-iodopiperidines are less stable than the 2-alkoxy counterparts, and hence, to obtain better yields of the 3-iodopiperidines, the reaction should be quenched with dry alcohols. To check this point, we studied the photolysis of (±)-pipecolinic acid methyl carbamate **1e** in dichloromethane, quenching with dry 2-hexen-1-ol (Scheme 3). To our pleasure, (±)-2-(2′-hexenyloxy)-3-iodo piperidine **6** was obtained in 71% yield after purification by column chromatography. Only the *trans* product was isolated, as in the previous cases.

Scheme 3. Generation of Bicyclic *N,O*-Acetals[a]



[a] Key: (a) DIB (2 equiv), I_2 (1 equiv), CH_2Cl_2, 3 h, rt, then 2-hexen-1-ol, 1.5 h, 71%; (b) Bu_3SnH, AIBN cat., PhH, 80 °C, 4 h, 83%.

Scheme 4. Proposed Mechanism for the Formation of Iodinated Products



This kind of product may be very useful to obtain bicyclic *N,O*-acetals, which are present in natural products such as (±)-physovenine[11a,b] and madindolines A and B.[11c,d] In effect, by treating piperidine **6** with tributyltin hydride and AIBN in benzene,[12] cyclic *N,O*-acetal **7** was obtained in 83% yield and in a 3:1 diastereomeric ratio.

A plausible mechanism for this one-pot decarboxylation−iodination is outlined in Scheme 4. We have seen before (Scheme 1) that an acyliminium intermediate (IV) can be trapped by nucleophiles to give noniodinated piperidines ($n = 1$) or pyrrolidines ($n = 0$) (V). However, in an alternative route (Scheme 4), (IV) could equilibrate with its corresponding enecarbamate (VII), which is subsequently iodinated to give *N*-acyliminium ion (VIII). This intermediate can then be trapped by nucleophiles (e.g., water, alcohols) to afford monoiodinated piperidines or pyrrolidines (VI). Since the bulky iodine group hinders the approach of the nucleophile from the same face, only the 2,3-*trans*-disubstituted products are formed. In the case of six-membered rings, the *N*-acyliminium ion (VIII, $n = 1$) may equilibrate with enecarbamate (IX). The iodination of the latter and subsequent trapping of the resultant acyliminium intermediate with nucleophiles explains the formation of the diiodo compound (X). Each step of the sequence must take place in excellent yields to account for the overall yields obtained.

The *N*-acyliminium−enamide equilibrium has been reported under acid catalysis, usually affording dimeric

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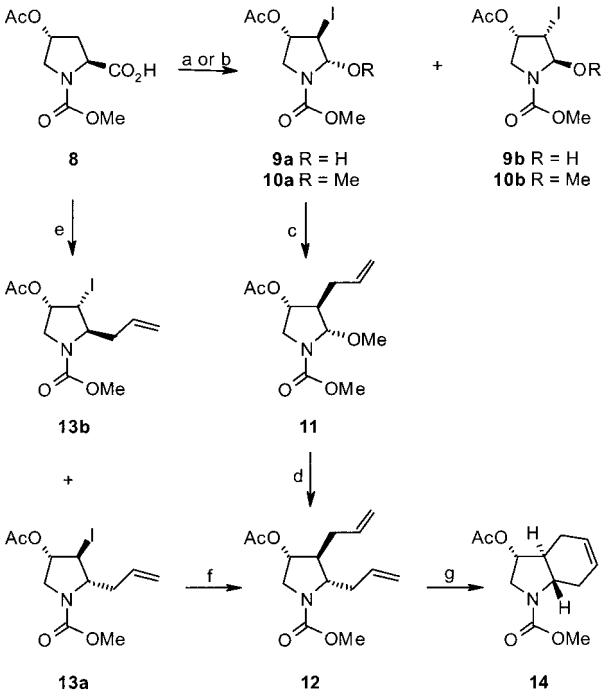
Scheme 5. Synthesis of Chiral 2,3-Disubstituted Pyrrolidines and Derived Bicyclic Systems[a]



[a] Key: (a) DIB (2 equiv), I_2 (2 equiv), MeCN, 5 h, then H_2O, 53% (**9a**:**9b**, 3:2); (b) DIB (2 equiv), I_2 (2 equiv), MeCN, 5 h, then MeOH, TsOH catalytic, 12 h, 56% (**10a**:**10b**, 2:1); (c) allyltributyltin, AIBN cat., PhH, 80 °C, 92%; (d) Allyltrimethylsilane, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 99%; (e) DIB, I_2, MeCN, 3 h, then allyltrimethylsilane, $BF_3{\cdot}Et_2O$, 0 °C, 4 h, 42% (**11a**:**11b**, 10:1); (f) allyltributyltin, AIBN cat., PhH, 80 °C, 99%; (g) Grubbs' catalyst, CH_2Cl_2, reflux, 95%.

side products.[13] The halogenation of enamides and enecarbamates has also been described[14] and applied to the synthesis of natural products such as (±)-mesembrine,[14c] (±)-elsewine,[14c] (−)-sedacrine,[14d] and gelsemine.[14e]

The stereoselectivity of the reaction using chiral substrates was studied next. The starting material used was the readily available *trans*-4-hydroxy-L-proline derivative **8**[9h] (Scheme 5). On treatment with DIB-iodine, followed by aqueous workup, the (2*S*,3*R*,4*S*)- and (2*R*,3*S*,4*S*)-2-hydroxy-3-iodo-4-acetoxypyrrolidines **9a** and **9b** were obtained after 5 h in 53% yield (**9a**:**9b**, 1.5:1). Both diastereomers could be separated by column chromatography on silica gel, and at room temperature each of them was found to be a mixture of two rotamers, which could be observed by NMR at 26 °C. When the temperature of the NMR experiment was increased to 70 °C, a complex mixture was formed. The ^{1}H NMR data at 26 °C of the major rotamer of **9a** support the assigned stereochemistry. Thus, the signal at δ 5.79, corresponding to H−C_2, appears as a broad singlet, due to the *trans* arrangement of H−C_2 and H−C_3. The signal at δ 4.18 (H−C_3) also appears as a broad singlet, confirming a *trans* disposition with respect to H−C_2 and to H−C_4. As for the other diastereomer **9b**, the ^{1}H NMR spectrum for the major rotamer shows a doublet (J = 1.8 Hz) at δ 5.78 (H−C_2), a double doublet at δ 4.43 (J = 5.8, 1.8 Hz, H−C_3), and a dd at δ 4.90 (J = 11.2, 5.8 Hz, H−C_4). These results correspond to a *trans* disposition between H−C_2 and H−C_3 and a *cis* arrangement between H−C_3 and H−C_4. Under similar reaction conditions, but quenching with dry methanol and adding a catalytic amount of TsOH, (2*S*,3*R*,4*S*)- and (2*R*,3*S*,4*S*)-2-methoxy-3-iodo-4-acetoxy compounds **10a** and **10b** were isolated as the major products (**10a**:**10b**, 1:1, 44%), together with the 2-hydroxy-3-iododerivatives **9a** and **9b** (**9a**:**9b**, 4:1, 15%). The diastereomers **10a** and **10b** could be easily separated by column chromatography. As occurred with **9a** and **9b**, each of the 2-methoxy derivatives **10a** and **10b** was obtained as a mixture of two rotamers at room temperature. However, only one rotamer was observed in the NMR spectrum on heating at 70 °C because of the faster rotamer interconversion. Thus, the NMR spectrum at 70 °C for compound **10a** showed a broad singlet at δ 5.46 (H−C_2) and a singlet at δ 4.23 (H−C_3). These signals are assignable to a *trans* disposition between H−C_2 and H−C_3 and between H−C_3 and H−C_4. For compound **10b**, a broad singlet at δ 5.45 (H−C_2), a doublet at δ 4.55 (J = 5 Hz, H−C_3), and a ddd at δ 4.72 (J = 7.6, 7.5, 5.0 Hz, H−C_4) are observed, involving a 2,3-*trans* and a 3,4-*cis* relationships.

The 2-hydroxy or 2-methoxy-3-iodopyrrolidines are useful chiral synthons from which other 2,3-disubstituted pyrrolidines can be easily formed. For instance, using a radical allylation at C-3 the pyrrolidine **11** (Scheme 5) was obtained in excellent yield. Also, when an ionic allylation at C-2 was carried out, the diallylated pyrrolidine **12** was isolated. Both reactions took place with complete stereoselectivity. Thus, the ^{1}H NMR spectrum at 70 °C of product **11** showed a broad singlet at δ 4.96 (H−C_2), involving a *trans* relationship between this proton and H−C_3. A ddd corresponding to H−C_4 was observed at δ 4.89; the $J_{3,4}$ = 2.8 Hz involves a *trans* relationship between H−C_3 and H−C_4. The double resonance experiments also supported the assigned (2*S*,3*R*,4*R*) configuration.

For product **12** the ^{1}H NMR spectrum at 70 °C showed a ddd at δ 4.94 (J = 5.9, 2.8, 2.5 Hz, H−C_4), a multiplet at δ 2.25 (H−C_3), and a multiplet at δ 3.83 (H−C_2). The irradiation of the signal at δ 2.25 (H−C_3) did not affect the signal at δ 3.83 (H−C_2), indicating a *trans* relationship between both protons. The assigned stereochemistry was also supported by 2D-NMR experiments.

The route from **8** to **12** can be shortened even further by a new tandem decarboxylation−β-iodination−allylation reaction. Thus, once the decarboxylation of **8** was completed, allyltrimethylsilane and boron trifluoride were added at 0 °C to the reaction mixture. In this way, products **13a** (2*S*,3*S*,4*S*) and **13b** (2*R*,3*R*,4*S*) were obtained in a remarkable 10:1 diastereomeric ratio (42% overall yield). Both isomers were easily separated by column chromatography.

For each diastereomer **13a** or **13b**, a mixture of two rotamers is observed at room temperature. By heating to 70 °C, the interconversion between rotamers is enhanced, and only one rotamer can be observed by NMR.

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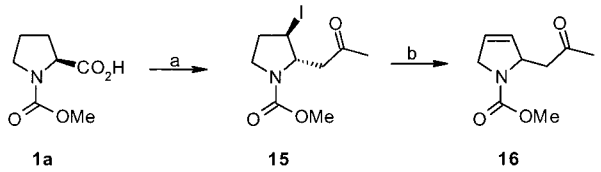
Scheme 6. Expedient Synthesis of 2-Substituted-2,5-Dihydropyrrols[a]



[a] Key: (a) DIB (2 equiv), I_2 (1 equiv), MeCN, 3 h, rt, then CH_2=C(OAc)Me, BF_3·Et_2O, 0 °C, 4 h, 56%; (b) DBU, CH_2Cl_2, rt, 12 h, 99% or $CDCl_3$, 70 °C, 1 h, 99%.

The ^{1}H NMR spectrum and double resonance experiments at 70 °C of the major isomer **13a** permit a *trans* relationship to be established between H−C_3 and H−C_4 ($J_{3,4}$ = 2.3 Hz) and for H−C_3 and H−C_2 ($J_{3,2}$ = 2.1 Hz).

Treating **13a** with allyltributyltin and AIBN in benzene afforded diallyl derivative **12** in 92% yield and 99% stereoselectivity. This compound was transformed via a metathesis reaction[15] into the hexahydroindole derivative **14** in 95% yield. In this way, an easily obtained hydroxyproline derivative was transformed in just three steps and with high stereoselectivity into a highly functionalized bicyclic compound. The polyhydroindole rings are present in Amarillydaceae,[16] Sceletium,[17] Strychnos,[18] and Aspidosperma[19] alkaloids, among others,[20] and peptides such as Aeruginosins.[21]

Moreover, this one-pot decarboxylation−iodination−alkylation process also allows the introduction of a double bond at two previously unfunctionalized positions. Thus, when proline derivative **1a** (Scheme 6) was treated with DIB and iodine followed by addition of isopropenyl acetate and BF_3·Et_2O, the (±)-iodopyrrolidine **15** was obtained in 56% yield. This compound, on treatment with DBU, afforded the 2,5-dihydropyrrol **16** in quantitative yield. The elimination reaction proved to be extremely easy and, to our pleasure, even took place by dissolving **15** in chloroform-*d*; the reaction was completed in hours at room temperature and was accelerated by heating to 70 °C. In this way, in just two steps, 2-substituted 2,5-dihydropyrroles can be obtained from easily available proline derivatives.

In summary, we have developed a promising methodology to obtain 2,3-disubstituted pyrrolidines and piperidines from commercial amino acids, using a one-pot decarboxylation−iodination reaction. The introduction of the substituents in positions 2 and 3 is exclusively *trans*. The influence of the solvent, the ring size, and the protecting group on the nitrogen of the starting amino acid are studied. Thus, by simply changing these features we can obtain mono-, di- or noniodinated pyrrolidines or piperidines. When a chiral C-4 is present in the amino acid, the reaction gives mainly the 2,3-*trans*, 3,4-*trans* 3-iododerivative. The resulting products can be manipulated to give bicyclic systems present in many natural products. Moreover, by a new tandem decarboxylation−iodination−alkylation reaction the *trans* 2-substituted-3-iodopyrrolidines are formed. These can be easily dehydroiodinated to 2-substituted 2,5-dihydropyrrols. In this way a double bond is introduced at two previously unfunctionalized positions. The application of this methodology as the key step in the synthesis of alkaloids is underway and will be reported in due course.

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 room temperature in $CHCl_3$ solutions. IR spectra were recorded in $CHCl_3$ solutions. Mass spectra were determined at 70 eV unless otherwise specified. 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. For most of the compounds described, there is an equilibrium between rotamers at room temperature, causing splitting or broadening of the signals in the NMR experiment. In many cases, the conversion between rotamers was made faster by heating the products to 70 °C, causing the split signals to coalesce. In a few cases, however, the complexity of the spectrum was not reduced on heating, or it was even increased, as for compounds **9a** and **9b**, and hence, the temperature of the experiment is recorded for each case. Merck silica gel 60 PF_{254} and 60 PF (0.063−0.2 mm) were used for thin-layer chromatography and column chromatography, respectively. The TLC analyses were conducted by spraying the layer either with 0.5% vanillin in H_2SO_4/EtOH (4:1) or with 0.25% ninhydrin in EtOH and heating till development of color. The reactions involving air- or moisture-sensitive materials were carried out under a nitrogen atmosphere. Commercially available reagents and solvents were analytical grade or were purified by standard procedures prior to use.[22] All of the starting unprotected amino acids were commercially available.

Oxidative Decarboxylation of α-Amino Acids. General Procedures. Method A. A solution of the acid **1a** (173 mg, 1.0 mmol) in acetonitrile (15 mL) was treated with (diacetoxyiodo)benzene (DIB) (644 mg, 2 mmol) and iodine (308 mg, 2 mmol) under nitrogen. After stirring at room temperature for 3 h, the reaction mixture was poured into 10% aqueous sodium thiosulfate and extracted with dichloromethane. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under vacuum. The residue was immediately purified by column chromatography (hexanes−ethyl acetate, 4:1) yielding

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the iodinated derivative **3a** (173 mg, 0.64 mmol, 64%) and the nonhalogenated hemiaminal **2a** (18 mg, 0.12 mmol, 12%).

Method B. The reaction was performed with **1a** as above, adding dry methanol (1 mL) when TLC analysis showed consumption of the starting material (3 h). Then, the reaction mixture was stirred for 1 h, followed by workup and purification as previously described, yielding compounds **3a** (16 mg, 6%) and **4a** (176 mg, 62%).

Methyl (2*R,3*S**)-2-Hydroxy-3-iodo-1-pyrrolidinecarboxylate (3a).** Two rotamers at 26 °C (2:1); one rotamer at 70 °C; syrup; IR 3586, 3394, 2892, 1691, 1451, 1382 cm^{-1}; ^1H NMR (500 MHz, 70 °C) δ 5.68 (1H, br s), 4.16 (1H, d, J = 5.0 Hz), 3.70 (3H, s), 3.56 (2H, m), 2.52 (1H, m), 2.10 (1H, m); ^{13}C NMR (125.7 MHz, 26 °C) δ major rotamer 155.9 (C), 89.5 (CH), 52.8 (CH_3), 44.6 (CH_2), 33.8 (CH_2), 27.0 (CH); δ minor rotamer 154.8 (C), 89.0 (CH), 52.8 (CH_3), 45.0 (CH_2), 32.8 (CH_2), 28.0 (CH); MS (FAB) m/z (rel intensity) 272 ($M^+ + H$, 5), 254 (39), 154 (100). Anal. Calcd for $C_6H_{10}INO_3$: C 26.59; H 3.72; N 5.17. Found: C, 26.79; H, 3.96; N, 5.12.

Methyl (2*R,3*S**)-3-Iodo-2-methoxy-1-pyrrolidinecarboxylate (4a).** Two rotamers at 26 °C (2:1); one rotamer at 70 °C; syrup; IR 1702, 1447, 1384, 1078 cm^{-1}; ^1H NMR (500 MHz, 70 °C) δ 5.35 (1H, br s), 4.20 (1H, d, J = 5.2 Hz), 3.74 (3H, s), 3.65 (1H, m), 3.46 (1H, dd, J = 9.0, 9.1 Hz), 3.38 (3H, s), 2.50 (1H, m), 2.11 (1H, dd, J = 6.8, 14.3 Hz); ^{13}C NMR (125.7 MHz, 26 °C) δ major rotamer 156.1 (C), 96.5 (CH), 56.3 (CH_3), 52.7 (CH_3), 44.5 (CH_2), 33.7 (CH_2), 25.6 (CH); δ_minor rotamer 155.3 (C), 96.1 (CH), 55.7 (CH_3), 52.8 (CH_3), 44.7 (CH_2), 32.7 (CH_2), 26.3 (CH); MS (EI) m/z (rel intensity) 285 (M^+, 2), 254 ($M^+ - OMe$, 100); HRMS calcd for $C_7H_{12}INO_3$ 284.9862, found 284.9878. Anal. Calcd for $C_7H_{12}INO_3$: C 29.49; H, 4.24; N 4.91. Found: C, 29.63; H, 4.46; N, 4.95.

Methyl (2*R,3*S**)-2-[(2*E*)-2-Hexenyloxy]-3-iodo-1-piperidinecarboxylate (6).** A solution of the acid **1e** (260 mg, 1.4 mmol) in dichloromethane (19 mL) was treated with DIB (895 mg, 2.8 mmol) and iodine (308 mg, 1.2 mmol) under nitrogen. After stirring at room temperature for 3 h, the reaction mixture was quenched with 2-hexen-1-ol and after another 1.5 h, the mixture was poured into 10% aqueous sodium thiosulfate and extracted with dichloromethane. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under vacuum. The residue was immediately purified by column chromatography (hexanes−EtOAc, 4:1) yielding the iodinated derivative **6** (362 mg, 0.99 mmol, 71%): two rotamers at 26 °C (2:1.5); syrup; IR 1694, 1448, 1270 cm^{-1}; ^1H NMR (500 MHz, 26 °C) δ 5.52−5.46 (3H, m), 4.37 (1H, m), 3.93−3.70 (3H, m), 3.65 (3H, s), 2.94 (1H, m), 2.05 (1H, m), 1.90 (3H, m), 1.75 (1H, d, J = 14.6 Hz), 1.40 (1H, m), 1.30 (2H, ddd, J = 7.4, 7.4, 7.4 Hz), 0.81 (3H, dd, J = 7.4, 7.4 Hz); ^{13}C NMR (125.7 MHz, 26 °C) δ major rotamer 135.2 (CH), 125.4 (CH), 84.0 (CH), 68.0 (CH_2), 52.7 (CH_3), 38.1 (CH_2), 34.3 (CH_2), 30.1 (CH), 28.0 (CH_2), 22.0 (CH_2), 20.9 (CH_2), 13.5 (CH_3); δ minor rotamer 135.0 (CH), 125.4 (CH), 84.0 (CH), 68.4 (CH_2), 52.7 (CH_3), 38.5 (CH_2), 34.3 (CH_2), 29.7 (CH), 28.0 (CH_2), 22.0 (CH_2), 21.1 (CH_2), 13.5 (CH_3); the signal of the carbamate carbonyl could not be observed; MS (EI) m/z (rel intensity) 284 ($M^+ - C_6H_{11}$, 1), 268 ($M^+ - C_6H_{11}O$, 100), 188 (30), 141 (98); HRMS calcd for $C_7H_{11}INO_3$ 283.9784, found 283.9809. Anal. Calcd for $C_{13}H_{22}INO_3$: C, 42.52; H, 6.04; N, 3.81. Found: C, 42.26; H, 6.23; N, 3.95.

Methyl (2*R,3a*R**,7a*R**)-3-Butylhexahydrofuro[2,3*b*]-pyridine-7(4*H*)-carboxylate (7).** A solution of methyl carboxylate **6** (160 mg, 0.44 mmol) and a catalytic amount of AIBN (10 mg) in dry benzene (10 mL), under nitrogen, was treated with tributyltin hydride (0.5 mL, 1.8 mmol) at room temperature. Then the reaction was heated to 80 °C for 4 h. The reaction mixture was allowed to cool to room temperature, the solvent was evaporated under vacuum, and the residue was purified by column chromatography (first elution with hexanes to remove the tin reagent, followed by hexanes−EtOAc, 80:20), yielding **7** (86 mg, 83%): two unseparable diastereomers (3:1 at 70 °C); syrup; IR 1694, 1448, 1352, 1018 cm^{-1}; ^1H NMR (500 MHz, 70 °C) δ major diastereomer 5.59 (1H, d, J = 5.1 Hz), 4.02 (1H, dd, J = 8.8, 7.5 Hz), 3.81 (1H, ddd, J = 12.8, 4.3, 4.3 Hz), 3.66 (3H, s), 3.36 (1H, dd, J = 8.8, 4.3 Hz), 2.89 (1H, ddd, J = 11.8, 11.8, 3.4 Hz), 1.85 (1H, m), 1.76 (1H, m), 1.65−1.58 (2H, m), 1.15−1.40 (8H, m), 0.84 (3H, dd, J = 7.1, 6.9 Hz); δ minor diastereomer 5.65 (1H, d, J = 3.4 Hz), 4.06 (1H, dd, J = 7.4, 7.1 Hz), 3.87 (1H, dd, J = 8.0, 8.0 Hz), 3.65 (3H, s), 3.46 (1H, dd, J = 10.5, 7.9 Hz), 2.84 (1H, ddd, J = 12.8, 12.8, 2.8 Hz), 1.84 (1H, m), 1.58−1.65 (3H, m), 1.15−1.40 (8H, m), 0.86 (3H, dd, J = 7.4, 7.3 Hz); ^{13}C NMR (125.7 MHz, 26 °C) δ major isomer 155.6 (C), 83.0 (CH), 70.5 (CH_2), 52.7 (CH_3), 44.6 (CH), 40.7 (CH), 39.4 (CH_2), 33.5 (CH_2), 30.0 (CH_2), 26.1 (CH_2), 22.8 (CH_2), 22.5 (CH_2), 13.9 (CH_3); δ minor isomer 156.6 (C), 84.7 (CH), 70.0 (CH_2), 52.7 (CH_3), 41.9 (CH), 37.7 (CH), 33.5 (CH_2), 30.3 (CH_2), 26.6 (CH_2), 26.1 (CH_2), 22.8 (CH_2), 19.6 (CH_2), 13.4 (CH_3); MS (EI) m/z (rel intensity) 210 ($M^+ - Me$, 3), 149 (100); HRMS calcd for $C_{12}H_{20}NO_2$ 210.1494, found 210.1471. Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.59; H, 9.86; N, 5.66.

Methyl (2*S*,3*R*,4*S*)-4-Acetyloxy-2-hydroxy-3-iodopyrrolidine-1-carboxylate (9a) and Methyl (2*R*,3*S*,4*S*)-4-Acetyloxy-2-hydroxy-3-iodopyrrolidine-1-carboxylate (9b). A solution of the acid **8** (150 mg, 0.65 mmol) in acetonitrile (19 mL) was treated with DIB (410 mg, 1.3 mmol) and iodine (300 mg, 1.2 mmol) under nitrogen. After stirring at room temperature for 5 h, the reaction mixture was poured into saturated sodium bicarbonate and extracted with dichloromethane. The organic layer was washed with sodium thiosulfate and brine, dried (Na_2SO_4), and evaporated under vacuum. Flash column chromatography on silica gel (hexanes−EtOAc, 80:20) afforded 2-hydroxy-3-iododerivatives **9a** (68 mg, 0.2 mmol, 32%) and **9b** (45 mg, 0.13 mmol, 21%). Compound **9a**: two rotamers at 26 °C (1.5:1); syrup; IR 3576, 3444, 1735, 1694 cm^{-1}; ^1H NMR (500 MHz, 26 °C) δ major rotamer 5.79 (1H, br s), 5.32 (1H, d, J = 4.4 Hz), 4.18 (1H, br s), 4.06 (1H, dd, J = 6.0, 12.7 Hz), 3.90 (1H, br s, OH), 3.76 (3H, s), 3.70 (1H, d, J = 11.8 Hz), 2.10 (3H, s); δ minor rotamer, 5.68 (1H, s), 5.36 (1H, d, J = 3.9 Hz), 4.22 (1H, brs), 4.12 (1H, m), 3.79 (3H, s), 3.77 (1H, m), 3.2 (1H, br s, OH), 2.10 (3H, s); ^{13}C NMR (125.7 MHz, 26 °C) δ major rotamer 169.9 (C), 155.4 (C), 90.0 (CH), 79.0 (CH), 52.9 (CH_3), 49.8 (CH_2), 25.0 (CH), 20.8 (CH_3); δ minor rotamer 169.9 (C), 154.6 (C), 89.5 (CH), 78.2 (CH), 53.1 (CH_3), 50.3 (CH_2), 26.0 (CH), 20.8 (CH_3); MS (EI) m/z (rel intensity) 329 (M^+, <1), 328 ($M^+ - H$, 4), 312 (34), 252 (93), 142 (100); HRMS calcd for $C_8H_{12}INO_5$ 328.9760, found 328.9764. Anal. Calcd for $C_8H_{12}INO_5$: C, 29.18; H, 3.68; N, 4.26. Found: C, 29.48; H, 3.88; N, 4.31. Compound **9b**: two rotamers at 26 °C (1.8:1); syrup; IR 3578, 3458, 1702, 1454 cm^{-1}; ^1H NMR (500 MHz, 25 °C) δ major rotamer 5.78 (1H, d, J = 1.8 Hz), 4.90 (1H, ddd, J = 6.1, 6.1, 5.8 Hz), 4.43 (1H, dd, J = 5.8, 1.8 Hz), 3.97 (1H, brs, OH), 3.82 (1H, dd, J = 6.1, 11.1 Hz), 3.76 (3H, s), 3.51 (1H, dd, J = 6.0, 11.1 Hz), 2.1 (3H, s); δ minor rotamer 5.72 (1H, br s), 4.90 (1H, dd, J = 11.2, 5.8 Hz), 4.90 (1H, br s), 4.40 (1H, m), 4.17 (1H, br s, OH), 4.07 (1H, m), 3.78 (3H, s), 3.61 (1H, dd, J = 6.0, 11.0 Hz), 2.08 (3H, s); ^{13}C NMR (125.7 MHz, 25 °C) δ major rotamer 169.8 (C), 157.7 (C), 89.1 (CH), 70.7 (CH), 52.9 (CH_3), 48.4 (CH_2), 29.5 (CH), 20.9 (CH_3); δ minor rotamer 169.8 (C), 155.5 (C), 88.7 (CH), 70.2 (CH), 53.1 (CH_3), 48.5 (CH_2), 30.8 (CH), 20.7 (CH_3); MS (EI) m/z (rel intensity) 329 (M^+, <1), 312 ($M^+ - OH$, 2), 142 (100); HRMS calcd for $C_8H_{11}INO_4$ 311.9733, found 311.9744. Anal. Calcd for $C_8H_{12}INO_5$: C, 29.18; H, 3.68; N, 4.26. Found: C, 29.25; H, 3.93; N, 4.16.

Methyl (2*S*,3*R*,4*S*)-4-Acetyloxy-3-iodo-2-methoxy-1-pyrrolidinecarboxylate (10a) and Methyl (2*R*,3*S*,4*S*)-4-Acetyloxy-3-iodo-2-methoxy-1-pyrrolidinecarboxylate (10b). A solution of the acid **8** (150 mg, 0.65 mmol) in acetonitrile (19 mL) was treated with DIB (410 mg, 1.3 mmol) and iodine (300 mg, 1.2 mmol) under nitrogen. After stirring at room temperature for 5 h, the reaction mixture was quenched with dry methanol. A catalytic amount of TsOH was added, and the reaction mixture was stirred for 2 h. It was then poured into saturated sodium bicarbonate and extracted with dichloromethane. The organic layer was washed with sodium thiosulfate and brine, dried (Na_2SO_4), and evaporated under vacuum. Column chromatography on silica gel (hexanes−EtOAc, 90:10) afforded 2-methoxy-3-iododerivatives **10a** (47 mg, 0.14 mmol, 21%) and **10b** (51 mg, 0.15 mmol, 23%),

together with 2-hydroxy-3-iodo derivatives **9a** (26 mg, 0.08 mmol, 12%) and **9b** (6 mg, 0.02 mmol, 3%) (59% overall yield). Compound **10a**: two rotamers at 26 °C (1.4:1); one rotamer at 70 °C; syrup; $[\alpha]_D$ +3 (c = 0.61); IR 1740, 1714, 1450, 1385 cm^{-1}; ^1H NMR (500 MHz, 70 °C) δ 5.46 (1H, br s), 5.34 (1H, dd, J = 6.0, 1.8 Hz), 4.23 (1H, s), 4.16 (1H, dd, J = 12.6, 6.0 Hz), 3.78 (3H, s), 3.57 (1H, dd, J = 12.6, 1.7 Hz), 3.44 (3H, s), 2.06 (3H, s); ^{13}C NMR (125.7 MHz, 70 °C) δ 170.0 (C), 155.7 (C), 97.3 (CH), 79.4 (CH), 56.6 (CH_3), 52.9 (CH_3), 50.3 (CH_2), 24.9 (CH), 20.7 (CH_3); MS (EI) m/z (rel intensity) 312 (M^+ − OMe, 29), 284 (9), 252 (33), 156 (100), 125 (94); HRMS calcd for $C_8H_{11}INO_4$ 311.9733, found 311.9744. Anal. Calcd for $C_9H_{14}INO_5$: C, 31.50; H, 4.11; N, 4.08. Found: C, 31.55; H, 4.29; N, 4.03. Compound **10b**: two rotamers at 26 °C (1.6:1); one rotamer at 70 °C; syrup; $[\alpha]_D$ −22 (c = 0.42); IR 1748, 1711, 1450, 1387, 1258 cm^{-1}; ^1H NMR (500 MHz, 70 °C) δ 5.45 (1H, br s), 4.72 (1H, ddd, J = 7.6, 7.5, 5.0 Hz), 4.55 (1H, d, J = 5 Hz), 3.78 (3H, s), 3.73 (1H, dd, J = 10.8, 7.5 Hz), 3.5 (1H, m), 3.45 (3H, s), 2.11 (3H, s); ^{13}C NMR (125.7 MHz, 26 °C) δ major rotamer 169.9 (C), 155.9 (C), 95.9 (CH), 70.8 (CH), 56.8 (CH_3), 53.0 (CH_3), 47.6 (CH_2), 30.8 (CH), 20.9 (CH_3); δ minor rotamer 169.9 (C), 155.9 (C), 95.7 (CH), 70.2 (CH), 56.3 (CH_3), 53.0 (CH_3), 47.8 (CH_2), 31.5 (CH), 20.9 (CH_3); MS (EI) m/z (rel intensity) 312 (M^+ − OMe, 21), 284 (12), 252 (13), 156 (100); HRMS calcd for $C_8H_{11}INO_4$ 311.9733, found 311.9730. Anal. Calcd for $C_9H_{14}INO_5$: C, 31.50; H, 4.11; N, 4.08. Found: C, 31.82; H, 3.79; N, 3.91.

Methyl (2*S*,3*R*,4*R*)-4-Acetyloxy-3-allyl-2-methoxy-1-pyrrolidinecarboxylate (11). A solution of 3-iodo-2-methoxy-1-pyrrolidine derivative **10a** (90 mg, 0.26 mmol) and a catalytic amount of AIBN (10 mg) in dry benzene (7 mL), under nitrogen, was treated with allyltributyltin (0.26 mL, 1.23 mmol) at room temperature. Then the reaction was heated to 80 °C for 4 h. The reaction mixture was allowed to cool to room temperature, the solvent was evaporated under vacuum, and the residue was purified by column chromatography (first elution with hexanes to remove the tin reagent and then with hexanes−EtOAc, 4:1), yielding **11** (61 mg, 91%): two rotamers at 26 °C (2.1:1); one rotamer at 70 °C; syrup; $[\alpha]_D$ +12 (c = 0.318); IR 1732, 1707, 1451 cm^{-1}; ^1H NMR (500 MHz, 70 °C) δ 5.78 (1H, m), 5.09 (1H, dd, J = 12.5, 1.2 Hz), 5.08 (1H, dd, J = 15.8, 1.3 Hz), 4.96 (1H, br s), 4.89 (1H, ddd, J = 5.6, 2.8, 2.8 Hz), 3.95 (1H, dd, J = 12.6, 6.3 Hz), 3.72 (3H, s), 3.41 (1H, dd, J = 12.6, 3.2 Hz), 3.36 (3H, s), 2.34 (1H, ddd, J = 7.2, 7.6, 1.5 Hz), 2.13 (1H, m), 2.06 (1H, m), 2.03 (3H, s); ^{13}C NMR (125.7 MHz, 70 °C) δ 170.4 (C), 155.80 (C), 134.8 (CH), 117.5 (CH_2), 92.9 (CH), 76.0 (CH), 55.9 (CH_3), 52.5 (CH_3), 51.1 (CH_2), 50.2 (CH), 34.7 (CH_2), 20.9 (CH_3); MS (EI) m/z (rel intensity) 226 (M^+ − OMe, 2), 197 (29), 166 (100); HRMS calcd for $C_{11}H_{16}NO_4$ 226.1079, found 226.1014. Anal. Calcd for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found: C, 55.89; H, 7.75; N, 5.45.

Methyl (2*S*,3*S*,4*R*)-4-Acetyloxy-2,3-diallyl-1-pyrrolidinecarboxylate (12). A solution of 3-allyl-2-methoxypyrrolidine derivative **11** (30 mg, 0.12 mmol) and allyltrimethylsilane (0.1 mL, 0.6 mmol) in dry acetonitrile (3 mL) was cooled to 0 °C and treated dropwise with $BF_3{\cdot}Et_2O$ (0.05 mL, 0.24 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 18 h; then it was poured into saturated aqueous sodium bicarbonate and extracted with dichloromethane. The organic layer was dried, concentrated under vacuum, and purified by column chromatography (hexanes−EtOAc, 4:1), yielding **12** (31 mg, 99%): two rotamers at 26 °C (2:1); one rotamer at 70 °C; syrup; $[\alpha]_D$ + 29 (c = 0.348); IR 1730, 1689, 1453, 1391 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz, 70 °C) δ 5.79 (1H, dddd, J = 17.3, 10.1, 7.3, 7.3 Hz), 5.65 (1H, dddd, J = 17.3, 10.5, 7.0, 7.0 Hz), 5.10 (1H, dd, J = 17.3, 0.8 Hz), 5.07 (1H, dd, J = 10.0, 0.9 Hz), 5.0 (1H, dd, J = 10.5, 1.1 Hz), 4.99 (1H, dd, J = 17.5, 1.0 Hz), 4.94 (1H, ddd, J = 5.9, 2.8, 2.5 Hz), 3.90 (1H, dd, J = 12.5, 5.9 Hz), 3.83 (1H, m), 3.60 (3H, s), 3.46 (1H, dd, J = 12.6, 2.1 Hz), 2.80 (1H, m), 2.53 (1H, ddd, J = 13.7, 8.5, 8.4 Hz), 2.25 (1H, m), 1.96 (2H, m), 1.73 (3H, s); ^{13}C NMR (125.7 MHz, 70 °C) δ 169.9 (C), 155.3 (C), 134.9 (CH), 134.8 (CH), 117.4 (2 × CH_2), 76.7 (CH), 61.6 (CH), 52.2 (CH_3), 51.4 (CH_2), 46.9 (CH), 38.1 (CH_2), 36.5 (CH_2), 20.8 (CH_3); MS (EI) m/z (rel intensity) 267 (M^+, <1), 236 ($M^+ - OCH_3$, 1), 226 (11) 166 (100); HRMS calcd for $C_{14}H_{21}NO_4$ 267.1471, found 267.1475. Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.76; H, 8.14; N, 5.24.

Methyl (2*S*,3*S*,4*S*)-4-Acetyloxy-2-allyl-3-iodo-1-pyrrolidinecarboxylate (13a) and Methyl (2*R*,3*R*,4*S*)-4-Acetyloxy-2-allyl-3-iodo-1-pyrrolidinecarboxylate (13b). A solution of the acid **8** (106 mg, 0.46 mmol) in acetonitrile (12 mL) was treated with DIB (297 mg, 0.96 mmol) and iodine (130 mg, 0.5 mmol) under nitrogen. After stirring at room temperature for 3.5 h, the reaction was cooled at 0 °C, and an excess of allyltrimethylsilane was added (0.7 mL, 4.6 mmol). Then, $BF_3{\cdot}Et_2O$ (0.18 mL, 0.96 mmol) was added dropwise. The reaction mixture was allowed to reach room temperature (1 h) and stirred for other 2 h. The solution was poured into saturated sodium bicarbonate and extracted with dichloromethane. The organic layer was washed with 10% aqueous sodium thiosulfate and brine, dried (Na_2SO_4), and evaporated under vacuum. Column chromatography on silica gel (hexanes−EtOAc, 90:10) afforded allyl derivatives **13a** (60 mg, 0.17 mmol, 37%) and **13b** (6 mg, 0.017 mmol, 4%) (41% global yield, **13a**:**13b**, 10:1). Compound **13a**: two rotamers at 26 °C (1.5:1); one rotamer at 70 °C; oil; $[\alpha]_D$ +10 (c = 0.71); IR 1744, 1697, 1454, 1385, 1123 cm^{-1}; ^1H NMR (500 MHz, 70 °C) δ 5.80 (1H, m), 5.38 (1H, ddd, J = 5.1, 2.3, 2.3 Hz), 5.15 (1H, d, J = 10.3 Hz), 5.10 (1H, dd, J = 17.1, 1.5 Hz), 4.34 (1H, m), 4.27 (1H, d, J = 2.1 Hz), 4.21 (1H, dd, J = 12.7, 5.8 Hz), 3.75 (3H, s), 3.48 (1H, dd, J = 12.7, 2.1 Hz), 2.67 (1H, m), 2.38 (1H, ddd, J = 14.4, 8.8, 8.5 Hz), 2.07 (3H, s); ^{13}C NMR (125.7 MHz, 26 °C) δ major rotamer 169.5 (C), 155.0 (C), 133.5 (CH), 118.5 (CH_2), 80.3 (CH), 68.2 (CH), 52.7 (CH_3), 50.0 (CH_2), 38.5 (CH_2), 23.5 (CH), 20.8 (CH_3); δ minor rotamer 169.5 (C), 155.0 (C), 133.7 (CH), 118.6 (CH_2), 79.5 (CH), 68.2 (CH), 52.7 (CH_3), 50.4 (CH_2), 39.2 (CH_2), 24.5 (CH), 20.8 (CH_3); MS (EI) m/z (rel intensity) 312 ($M^+ - C_3H_5$, 19), 252 (60), 125 (100); HRMS calcd for $C_8H_{11}INO_4$ 311.9733, found 311.9725. Anal. Calcd for $C_{11}H_{16}INO_4$: C, 37.41; H, 4.57; N, 3.97. Found: C, 37.51; H, 4.41; N, 3.91. Compound **13b**: two rotamers at 26 °C (1.6:1); one rotamer at 70 °C; oil; $[\alpha]_D$ −13 (c = 1.16); IR 1745, 1700, 1453, 1389 cm^{-1}; ^1H NMR (500 MHz, 70 °C) δ 5.76 (1H, m), 5.16 (1H, d, J = 11.4 Hz), 5.15 (1H, d, J = 15.3 Hz), 4.80 (1H, ddd, J = 5.2, 5.2, 5.2 Hz), 4.41 (1H, dd, J = 4.7, 4.7 Hz), 4.32 (1H, m), 3.74 (3H, s), 3.69 (1H, dd, J = 11.7, 4.9 Hz), 3.60 (1H, dd, J = 11.7, 5.8 Hz), 2.53 (2H, m), 2.10 (3H, s); ^{13}C NMR (125.7 MHz, 26 °C) δ major rotamer 169.9 (C), 154.9 (C), 132.4 (CH), 119.4 (CH_2), 71.6 (CH), 66.1 (CH), 52.6 (CH_3), 49.7 (CH_2), 36.0 (CH_2), 27.4 (CH), 21.1 (CH_3); δ minor rotamer 169.9 (C), 155.0 (C), 133.4 (CH), 119.4 (CH_2), 71.3 (CH), 65.8 (CH), 52.6 (CH_3), 50.0 (CH_2), 36.8 (CH_2), 28.0 (CH), 21.1 (CH_3); MS (EI) m/z (rel intensity) 312 ($M^+ - C_3H_5$, 100), 252 ($M^+ - C_3H_5$ − AcOH, 4); HRMS calcd for $C_8H_{11}INO_4$ 311.9733, found: 311.9729. Anal. Calcd for $C_{11}H_{16}INO_4$: C, 37.41; H, 4.57; N, 3.97. Found: C, 37.34; H, 4.20; N, 4.18.

3-Allylation of Methyl (2*S*,3*S*,4*S*)-4-Acetyloxy-2-allyl-3-iodo-1-pyrrolidinecarboxylate (13a). A solution of 2-allyl-3-iodopyrrolidine derivative **13a** (35 mg, 0.1 mmol) and a catalytic amount of AIBN (5 mg) in dry benzene (4 mL), under nitrogen, was treated with allyltributyltin (0.1 mL, 0.5 mmol) at room temperature. The reaction mixture was heated to 80 °C for 4 h and then cooled to room temperature, the solvent was evaporated under vacuum, and the residue was purified by column chromatography (first elution with hexanes to remove the tin reagent and then with hexanes−EtOAc, 5:1), yielding **12** (23 mg, 99%), identical to previously described (vide supra).

Methyl (3*R*,3a*S*,7a*S*)-3-Acetyloxy-2,3,3a,4,7,7a-hexahydro-1*H*-indole-1-carboxylate (14). To a solution of the 2,3-diallylpyrrolidine derivative **12** (13 mg, 0.05 mmol) in dichloromethane (3 mL) was added a catalytic amount of Grubbs' catalyst [$Cl_2(Cy_3P)_2Ru{=}CHPh$] (3 mg, 0.0036 mmol); the reaction was refluxed for 8 h and then stirred at room temperature overnight. The reaction mixture was evaporated under vacuum and purified by chromatography on silica gel (hexanes−EtOAc, 95:5), yielding bicyclic compound **14** (11 mg, 95%): syrup; $[\alpha]_D$ +175 (c = 0.5); IR 1736, 1699, 1454, 1358 cm^{-1}; ^1H NMR (500 MHz, 70 °C) δ 5.68 (2H, m), 4.90 (1H, ddd,

J = 8.2, 8.2, 8.1 Hz), 4.03 (1H, dd, J = 11.1, 7.9 Hz), 3.71 (3H, s), 3.31 (1H, ddd, J = 10.6, 10.6, 5.3 Hz), 3.22 (1H, dd, J = 11.1, 8.1 Hz), 3.04 (1H, brd, J = 16.4 Hz), 2.35 (1H, m), 2.12 (1H, m), 2.05 (3H, s), 2.02 (2H, m); ^{13}C NMR (125.7 MHz, 26 °C) δ 170.8 (C), 156.2 (C, br), 125.9 (CH), 125.7 (CH), 73.8 (CH, br), 57.1 (CH), 52.2 (CH_3), 51.0 (CH_2), 46.0 (CH, br), 32.8 (CH_2, br), 28.7 (CH_2), 20.8 (CH_3); MS (EI) m/z (rel intensity) 240 (M^+ + H, <1), 179 (M^+ − AcOH, 100); HRMS calcd for $C_{12}H_{18}NO_4$ 240.1236, found 240.1265. Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.47; H, 6.94; N, 6.01.

Methyl (2*S,3*R**)-3-Iodo-2-(2-oxopropyl)pyrrolidine-1-carboxylate (15).** A solution of the acid **1a** (230 mg, 1.3 mmol) in acetonitrile (18 mL) was treated with DIB (850 mg, 2.6 mmol) and iodine (335 mg, 1.3 mmol) under nitrogen. After stirring at room temperature for 3 h, the reaction mixture was cooled to 0 °C, and then $BF_3{\cdot}Et_2O$ (0.35 mL, 2.6 mmol) and isopropenyl acetate (0.8 mL, 6.5 mmol) were added. The reaction mixture was allowed to reach room temperature and stirred for 4 h; it was then poured into 10% aqueous sodium thiosulfate and extracted with dichloromethane. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under vacuum. The residue was immediately purified by column chromatography (hexanes−EtOAc, 80:20) yielding the iodinated derivative **15** (229 mg, 56%): two rotamers at 26 °C (2:1); syrup; IR 1694, 1455, 1389 cm^{-1}; ^{1}H NMR (500 MHz, 26 °C) δ major rotamer 4.47 (1H, br d, J = 8.5 Hz), 4.30 (1H, br d, J = 10.5 Hz), 3.69 (3H, s), 3.66 (1H, m), 3.48 (1H, m), 2.95 (1H, d, J = 15.5 Hz), 2.44 (1H, m), 2.26 (1H, m), 2.18 (1H, m), 2.17 (3H, s); δ minor rotamer 4.47 (1H, br d, J = 8.5 Hz), 4.30 (1H, br d, J = 10.5 Hz), 3.69 (3H, s), 3.66 (1H, m), 3.48 (1H, m), 2.76 (1H, d, J = 18 Hz), 2.44 (1H, m), 2.26 (1H, m), 2.18 (1H, m), 2.17 (3H, s); ^{13}C NMR (50.3 MHz, 26 °C) δ major rotamer 206.1 (C), 155.0 (C), 65.6 (CH), 52.5 (CH_3), 46.8 (CH_2), 45.2 (CH_2), 35.4 (CH_2), 30.2 (CH_3), 24.7 (CH); δ minor rotamer 206.1 (C), 155.0 (C), 65.1 (CH), 52.5 (CH_3), 48.0 (CH_2), 45.2 (CH_2), 34.5 (CH_2), 30.2 (CH_3), 25.6 (CH); MS (EI) m/z (rel intensity) 280 (M^+ − OMe, 2), 253 (16), 184 (M^+ − I, 83), 183 (19), 142 (100); HRMS calcd for $C_8H_{11}INO_2$ 279.9835, found 279.9745. Anal. Calcd for $C_9H_{14}INO_3$: C, 34.73; H, 4.54; N, 4.50. Found: C, 34.49; H, 4.62; N, 4.80.

Methyl 2-(2-Oxopropyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (16). A solution of product **15** (100 mg, 0.32 mmol) in dichloromethane (50 mL) was treated with DBU (0.1 mL, 2 equiv) and stirred at room temperature for 12 h. The reaction mixture was poured into 10% HCl and extracted with dichloromethane. After purification by column chromatography (hexanes−EtOAc, 80:20) the dihydropyrrol **16** was obtained (54 mg, 99%): one rotamer at 70 °C; syrup; IR 1716, 1519, 1265 cm^{-1}; ^{1}H NMR (500 MHz, 70 °C) δ 5.92 (1H, d, J = 2.7 Hz), 5.85 (1H, d, J = 2.6 Hz), 4.65 (1H, m), 3.68 (3H, s), 3.45 (1H, d, J = 6.6 Hz), 3.42 (1H, d, J = 6.6 Hz), 2.80 (1H, d, J = 6.5 Hz), 2.78 (1H, d, J = 6.6 Hz), 2.23 (3H, s); ^{13}C NMR (50.3 MHz, 26 °C) δ 107.1 (CH), 106.0 (CH), 52.07 (CH_3), 39.70 (CH_2), 28.66 (CH_2), 13.50 (CH_3); the signals of C-2 and the carbamate and ketone carbonyls could not be observed; MS (EI) m/z (rel intensity) 183 (M^+, 35), 108 (100), 95 (93); HRMS calcd for $C_9H_{13}NO_3$ 183.0895, found 183.0892. Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.91; H, 7.41; N, 7.52.

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Supporting Information Available: Physical properties and spectroscopic data for compounds **3b**, **3c**, **5e**, **3e**, **4e**, and **3f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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