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Biomimetic Approach toward the Total Synthesis of *rac*-2-(Acylmethylene)pyrrolidine Alkaloids

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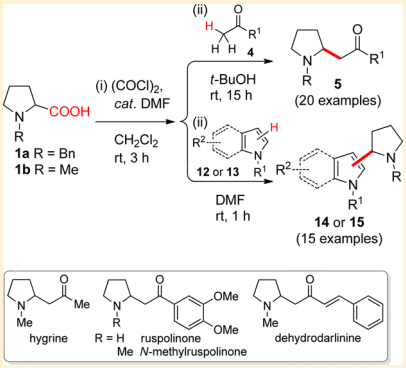
Supporting Information

ABSTRACT: 2-(Acylmethylene)pyrrolidine derivatives were synthesized via intermolecular decarbonylative Mannich reaction from various methyl ketones and 1-alkyl-1-pyrroliniums, generated *in situ* from 1-alkylprolines. This approach mimics the biosynthetic pathway and provides a direct access to a series of 2-(acylmethylene)-pyrrolidine alkaloids, including hygrine, *N*-methylruspolinone, dehydrodarlinine, and ruspolinone.



INTRODUCTION

Pyrrolidine represents a heterocyclic C4N skeleton existing in a wide variety of natural products. These pyrrolidine-containing alkaloids exhibit immense structural diversities and a broad range of biological activities, which makes these alkaloids attractive targets for total synthesis.[1] 2-(Acylmethylene)-pyrrolidines belong to the simplest family of pyrrolidine alkaloids (Figure 1),[2−4] of which the pyrrolidine nucleus is

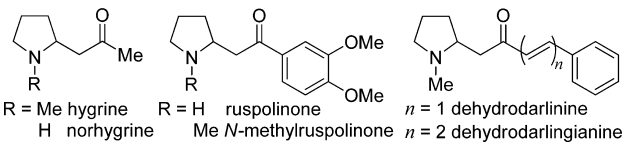
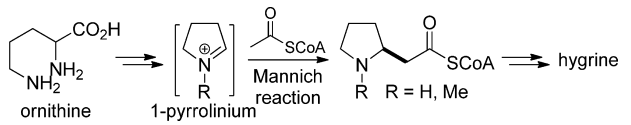


Figure 1. Naturally occurring 2-(acylmethylene)pyrrolidine alkaloids.

biogenetically derived from ornithine. The biosynthesis involves decarboxylation of ornithine, followed by oxidative cyclization, to form 1-pyrrolinium as a reactive intermediate. Subsequently, the Mannich-type reactions with carbon nucleophiles take place to provide the 2-substituted pyrrolidine skeletons[5] (Scheme 1). These 2-substituted pyrrolidines can be further derived into various pyrrolidine, indolizidine, and tropane alkaloids.[5−8]

Scheme 1. Proposed Biosynthesis of Hygrine



Proline is the most abundant naturally occurring pyrrolidine-containing compound and frequently used as the C4N+C pyrrolidine precursor for the synthesis of 2-substituted pyrrolidine derivatives. Proline supplies its pyrrolidine unit and the carboxylic carbon that is incorporated into the substituent at the 2-position of the pyrrolidine. Alternatively, proline can also be utilized as C4N pyrrolidine synthon for 2-substituted pyrrolidines, of which the pyrrolidine ring was abstracted from proline via decarbonylation or decarboxylation and the 2-substituents were introduced by C−C bond formation reaction.

This strategy was first demonstrated by Rapoport et al. in their syntheses of several pyrrolidine alkaloids and only applicable to intramolecular reactions. The *N*-alkylprolines equipped with suitable side chains at N1 or C5 were converted to the acid chloride, followed by thermal decarbonylation, to afford the pyrrolinium intermediates. Subsequently, intramolecular Mannich or Friedel−Crafts reaction with unactivated C-H nucleophiles took place to furnish the pyrrolidine-containing skeletons (Scheme 2, A).[9,10] Based on the same approach, an intermolecular vinylogous Mannich reaction with triisopropylsilyloxyfuran was applied to the total synthesis of croomine by Martin and Barr (Scheme 2, B).[11]

Hernández et al. reported that *N*-acylprolines underwent the oxidative radical decarboxylation in the presence of hypervalent iodobenzene oxidants, followed by the reaction with vinylogous nucleophiles, to furnish the 2-substituted pyrrolidines (Scheme 2, C).[12] It is noteworthy that the intermolecular reactions required the use of vinylogous nucleophiles, including 2-

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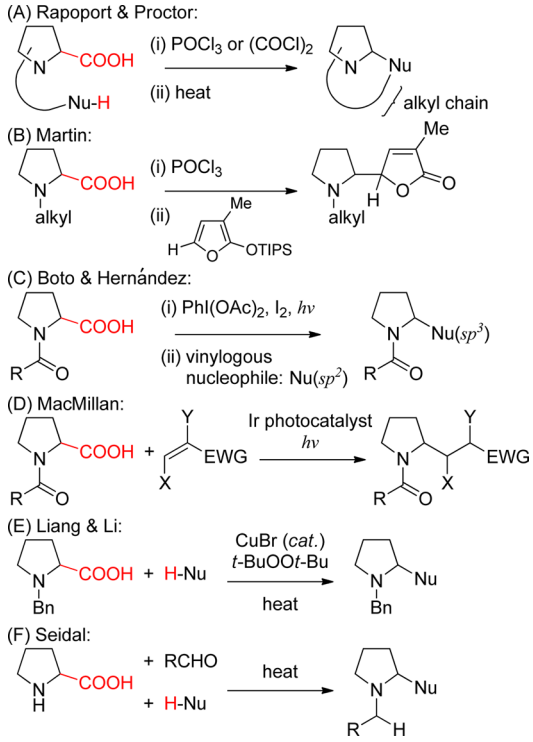
Scheme 2. Decarboxylative and Decarbonylative C−C Bond Formation of Proline Derivatives

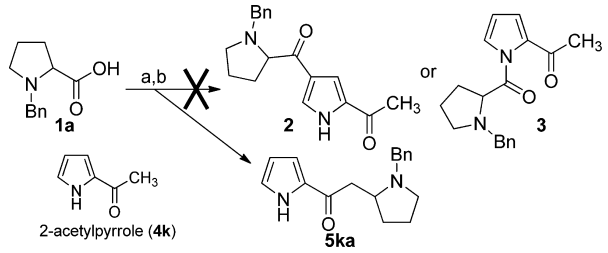


silyloxyfuran, silyl enol ethers, and allylsilanes, as activated carbon nucleophiles. MacMillan et al. further demonstrated that the carbon radical generated by the photon-induced radical decarboxylation of *N*-acylprolines could be directly trapped by radical conjugated addition reaction with electron-deficient olefins (Scheme 2, D).[13]

Li et al. reported an intermolecular decarboxylative coupling reaction of *N*-alkylprolines with terminal alkynes or π-electron-excess (hetero)arenes in the presence of Cu or Fe catalysts with *tert*-butyl peroxide as the oxidant. The proposed mechanism involves oxidative decarboxylation of *N*-alkylprolines, followed by metal-ion-mediated cross-coupling reaction with unactivated C-H nucleophiles (Scheme 2, E).[14] Zhang and Seidel reported a three-component decarboxylative coupling reaction of proline, arylaldehydes, and unactivated C-H nucleophiles, which involved the formation of the azomethine ylide intermediate in the reaction. Subsequently, protonation of the azomethine ylide afforded the iminium intermediate to undergo the C−C bond formation with terminal alkynes or π-electron-excess (hetero)arenes to afford the 2-substituted *N*-alkylpyrrolidines (Scheme 2, F).[15]

In our attempt to carry out the Friedel−Crafts acylation of 2-acetylpyrrole (**4k**), 1-benzylproline (**1a**) was treated with thionyl chloride, which was intended to convert **1a** to the corresponding acid chloride. The presumable acid chloride immediately reacted with 2-acetylpyrrole (**4k**), but neither the Friedel−Crafts nor the *N*-acylated adduct (**2** and **3**, respectively) was obtained. Instead, the only product isolated from the reaction in a minuscule yield was 2-(2-(1-benzylpyrrolidin-2-yl)acetyl)pyrrole (**5ka**) (Scheme 3). We postulated that 1-benzyl-1-pyrrolinium as the reactive intermediate was formed from the decarbonylation of 1-benzylproline acid chloride and reacted with the enol-form of 2-acetylpyrrole (**4k**) via a Mannich-type reaction to afford **5ka**. The C−C bond

Scheme 3. Reaction of 1-Benzylproline (1a) with 2-Acetylpyrrole (4k)



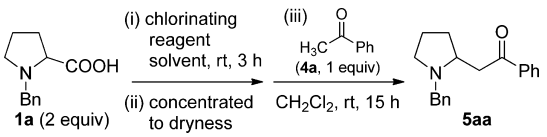
[a]Reagents and conditions: (a) $SOCl_2$, 0 °C to rt, 8 h; (b) 2-acetylpyrrole (**4k**), DIPEA, DMF, rt, 1 h.

formation step closely resembles the hypothetical biosynthetic pathway of pyrrolidine-containing alkaloids from ornithine (Scheme 1),[8,16] which suggested the potential application of this reaction to the synthesis of 2-(acylmethylene)pyrrolidine alkaloids.

RESULTS AND DISCUSSION

Our study focused on the conversion of 1-alkylprolines to the acid chlorides, followed by the decarbonylative C−C bond formation with methyl ketones. The reaction of 1-benzylproline (**1a**) and acetophenone (**4a**) was chosen for our initial evaluation. 1-Benzylproline (**1a**) was first dissolved and reacted in $SOCl_2$ at room temperature. After removal of $SOCl_2$, the reaction mixture was dissolved in dichloromethane; then, acetophenone (**4a**) was added. The reaction proceeded to give 41% yield of desired 2-(benzoylmethylene)pyrrolidine (**5aa**, entry 1 in Table 1). The preliminary success confirmed that the reaction is amenable for the C−C bond formation between the proline C4 and the acetyl α-carbon of acetophenone (**4a**).

Table 1. Examination of Various Chlorinating Reagents



entry	reagent (3 equiv)	solvent (0.5 M)	result[a] (%)
1		$SOCl_2$	41
2	$SOCl_2$	CH_2Cl_2	27
3	$POCl_3$	CH_2Cl_2	40
4	$(COCl)_2$ with one drop of DMF	CH_2Cl_2	52
5	ClCOOEt	CH_2Cl_2	0

[a]The yields were determined by ^{1}H NMR analysis of the crude products after workup using 1,3,5-trimethoxybenzene as an internal standard.

Several chlorinating reagents for converting 1-benzylproline (**1a**) to its acid chloride, as shown in Table 1, were first tested. Oxalyl chloride with a catalytic amount of DMF was found to be the most effective chlorinating condition and was adopted for the following investigation (entry 4 in Table 1). Subsequently, different solvents for the reaction with acetophenone (**4a**) were tested in order to optimize the C−C bond formation step (entries 1−9 in Table 2). It was beyond our expectation that alcoholic solvents were superior, while most of the polar aprotic solvents gave only poor to moderate yields. In particular, *t*-butyl alcohol gave the best yield and was used for further investigation (entry 9 in Table 2). In addition,

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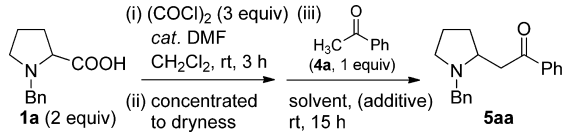
Table 2. Optimization for the C−C Bond Formation



entry	additive (1 equiv)	solvent (0.5 M)	result[a] (%)
1		CH_2Cl_2	52
2		MeCN	24
3		DMF	34[b] (32)[b,c]
4		THF	0
5		toluene	14
6		MeOH	39
7		EtOH	60
8		*i*-PrOH	53
9		*t*-BuOH	78[b] (69)[b,c]
10		TFE[d]	48[b]
11	Et_3N[e]	*t*-BuOH	0
12	NMM[e]	*t*-BuOH	0
13	DIPEA[e]	*t*-BuOH	0
14	DBU[e]	*t*-BuOH	0
15	*t*-BuOLi[e]	*t*-BuOH	0
16	Na_2CO_3[e]	*t*-BuOH	41
17	TMSCl[f,g]	*t*-BuOH	0
18	$BF_3{\cdot}OEt_2$[f,g]	*t*-BuOH	0
19	AcCl[f,g]	*t*-BuOH	0
20	$TsOH{\cdot}H_2O$[f]	*t*-BuOH	0

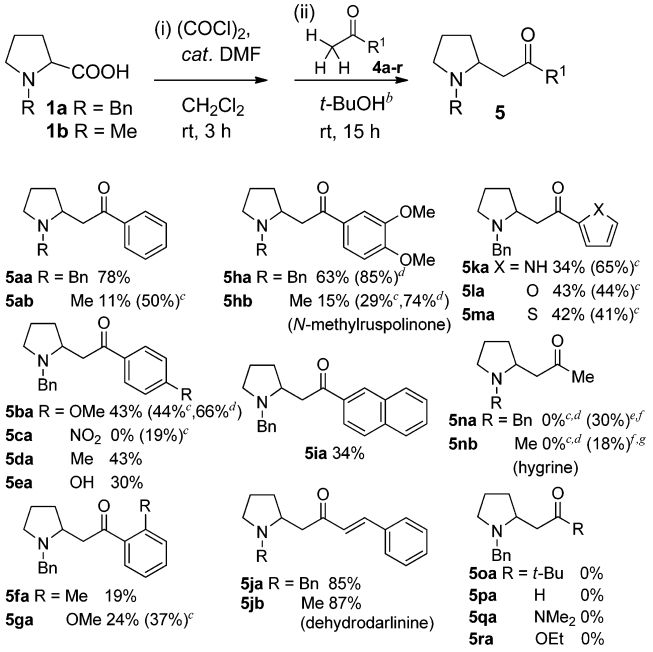
[a]Unless specified otherwise, the yields were determined by ^{1}H NMR analysis of the crude products after workup using 1,3,5-trimethoxybenzene as an internal standard. [b]Isolated yield. [c]The reaction time in step (iii) was changed to 1 h. [d]TFE = 2,2,2-trifluoroethanol. [e]The base was added in prior to acetophenone. [f]The acid was added after acetophenone was added. [g]Both 0.1 and 1 equiv were tested.

during our investigation with alcoholic solvents, 1-alkylproline esters were not observed in the reaction mixture.

The effects of basic and acidic additives were also examined. The addition of base was intended to neutralize HCl generated from the reaction. Nevertheless, when a series of bases were applied to the C−C bond formation step, except that the less soluble Na_2CO_3 gave 41% yield, the rest of the reactions did not result in any desired product. Meanwhile, protic or Lewis acids were anticipated to facilitate the keto−enol tautomerization of acetophenone (**4a**) and, therefore, were also screened. Our investigations revealed that these acidic additives inhibited the C−C bond formation and the reactions did not afford the desired product (entries 10−19 in Table 2).

Under the established reaction sequence and the optimized conditions, the reaction of 1-alkylprolines (**1a−b**) with a series of methyl ketones (**4a−n**) were surveyed to establish the scope and generality of the reaction. Our investigation showed that 1-alkylprolines (**1a−b**) could react with (hetero)aryl methyl ketones (**4a−i**, **4k−m**) to give moderate to good yields of the targeted 2-(acylmethylene)pyrrolidines (**5**). The reaction condition was also applicable to methyl 2-phenylethylene ketone (**4j**) to afford the corresponding products (**5ja** and **5jb**) in good yields. We demonstrated that this methodology provided a facile and concise synthesis of (±)-*N*-methylruspolinone[3,17,18] (**5hb**) and (±)-dehydrodarlinine[2,17,19] (**5jb**). A series of alkyl methyl ketones (**4n−o**) and other acetyl derivatives (**4p−r**) were also tested. However, none of these nucleophilic counterparts could proceed to the desired products under the optimized conditions. Notably, the desired 2-(acetylmethylene)pyrrolidines (**5na** and **5nb**) could be obtained in moderate yields from the reaction of 1-alkylprolines **1a−b** with acetone (**4n**) only when a large excess of acetone (**4n**) was used as the cosolvent and reactant, which allowed the completion of the synthesis of (±)-hygrine[4,20] (**5nb**) (Scheme 4).

Scheme 4. Reaction of 1-Alkylprolines (1a−b) with Methyl Ketones (4a−n) or Acetyl Derivatives (4o−r)[a]



[a]Isolated yields. [b]Unless specified otherwise, *t*-BuOH was used as the solvent. [c]Solvent = DMF. [d]Solvent = CH_2Cl_2. [e]Solvent = acetone/*t*-BuOH (v/v = 1:1). [f]The yield was based on the 1-alkylproline. [g]Solvent = acetone/DMF (v/v = 1:1).

Moreover, a series of α-mono- or α,α-disubstituted methyl ketones (**6a−c**) as well as 1,3-dicarbonyl compounds (**6d−g**) were also subjected to the reaction with 1-benzylproline (**1a**) under the optimized condition. The reaction of the α-branched methyl ketones (**6a−c**) and the acyclic 1,3-dicarbonyl compounds (**6d−e**) gave no desired products. However, surprisingly, the reaction of cyclic 1,3-dicarbonyl compounds, such as 5,5-dimethyl-1,3-cyclohexanedione (**6f**) and 1,3-dimethylbarbituric acid (**6g**), afforded the desired C−C bond formation products (**7fa** and **7ga**, respectively) in moderate yields (Scheme 5).

Survey of the substrate scope reflected that the differences in reactivities among these ketones were mainly attributed to the keto−enol tautomerism. (Hetero)aryl methyl ketones (**4a−i** and **4k−m**) as well as α,β-unsaturated methyl ketone (**4j**) are more enolizable than alkyl methyl ketones (**4n−o**) and acetyl derivatives (**4p−r**) and, therefore, allowed to undergo the Mannich-type reaction. Besides, both steric and electronic effects of the nucleophilic ketone counterparts played important roles. The acyclic 1,3-dicarbonyl compounds (**6d−e**), although readily enolizable, along with the α-branched methyl ketones (**6a−c**) were too hindered for the Mannich reaction with 1-pyrrolinium. Remarkably, cyclic 1,3-dicarbonyl compounds (**6f−g**) are conformationally restricted and their enol-forms are sufficiently nucleophilic and less hindered to undergo the Mannich reaction.

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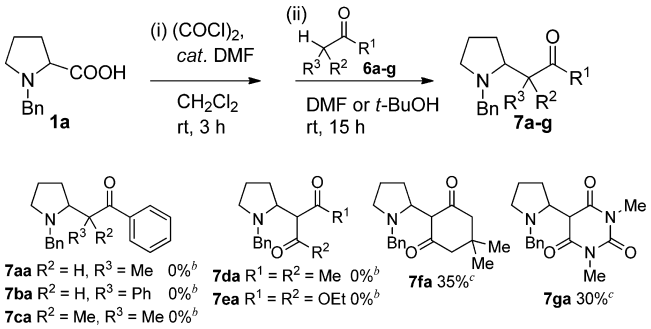
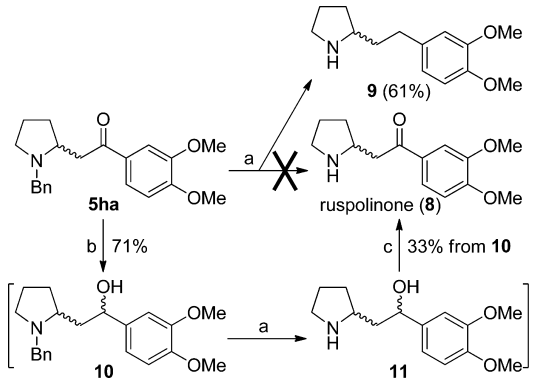
Scheme 5. Reaction of 1-Benzylproline (1a) with α-Substituted Methyl Ketones (6a−c) or 1,3-Dicarbonyl Compounds (6d−g)[a]



[a]Isolated yields. [b]Both *t*-BuOH and DMF as solvents were tested. [c]Solvent = *t*-BuOH.

In an endeavor to pursue the synthesis of the *N*-unsubstituted pyrrolidine alkaloids, the removal of the *N*-benzyl group from 1-benzyl-2-(acylmethylene)pyrrolidines was also attempted. Our initial trials by catalytic hydrogenolysis of **5ha** not only removed the benzyl group, but also reduced the carbonyl functionality to methylene (**9** in Scheme 6). While

Scheme 6. Concise Total Synthesis of (±)-Ruspolinone (8) (Unoptimized)

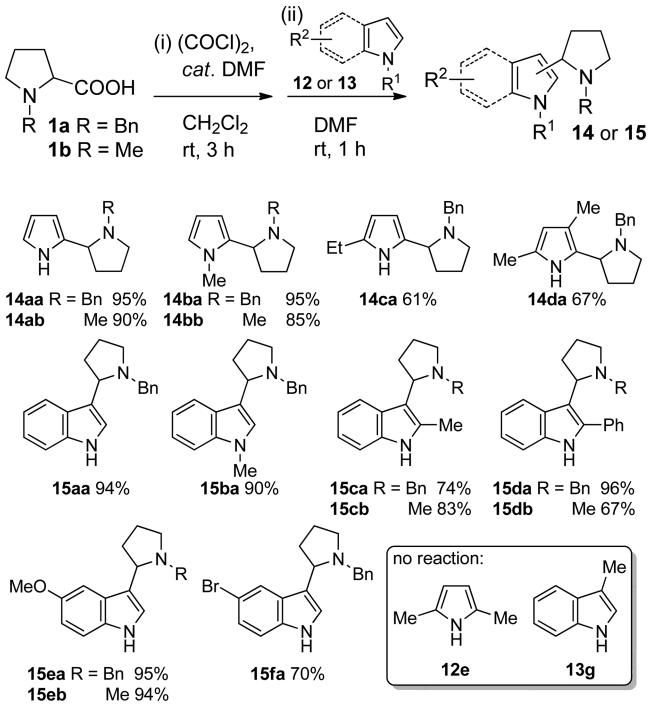


[a]Reagents and conditions: (a) H_2, 10% Pd/C, MeOH, rt, 12 h; (b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, rt, 6 h, 61%; (c) PCC, CH_2Cl_2, rt, 12 h, 33% from **10**.

introducing the protecting group for the ketone functionality encountered unforeseen difficulty, the carbonyl group was temporarily protected by reduction, which resulted in a mixture of two diastereomeric alcohols **10**. Subsequently, catalytic hydrogenolysis to remove the *N*-benzyl group, followed by oxidation of the secondary alcohols, afforded the targeted ruspolinone[3,16,21−23] (**8**) (Scheme 6). Direct removal of the benzyl group from **5ha** or the choice of other suitable alkyl protecting groups to facilitate the synthesis of ruspolinone (**8**) still remains to be further investigated.

The success in the decarbonylative C−C bond formation of 1-alkylprolines (**2**) with methyl ketones (**4**) prompted us to further expand the scope of nucleophilic counterparts to π-electron-excess aromatic nucleophiles. A series of pyrrole (**12**) and indole (**13**) derivatives were subjected to the reactions with 1-alkylprolines (**1a−b**) under the optimized conditions, and the reactions gave the corresponding 1-alkyl-2-heteroarylpyrrolidines (**14** and **15**, respectively) in very good yields. The reactions took place exclusively at the C2-position of pyrroles and C3-position of indoles. The regiostructure of pyrrole adducts (**14**) was deduced based on the X-ray crystal structure of **14aa** as a representative compound, while the regiostructure of indole adducts (**15**) was established by comparing the NMR spectra with several known compounds previously reported in the literature.[14,15] Furthermore, both 2,5-dimethylpyrrole (**12e**) and 3-methylindole (**13g**) showed no reaction under the same reaction conditions, which confirmed the regioselectivities unambiguously (Scheme 7).

Scheme 7. Reaction of 1-Alkylprolines (1a−b) with Pyrrole and Indole Derivatives (12a−e and 13a−g, Respectively)



CONCLUSION

In summary, we have developed a facile and practical synthesis for 2-(acylmethylene)pyrrolidine derivatives. This methodology, although sensitive to steric effects, features the advantages that direct formation of pyrrolinium intermediates from 1-alkylprolines and subsequent intermolecular Mannich reactions with aromatic methyl ketones, pyrroles, or indoles could both be carried out under simple and mild conditions without the use of metal catalysts and other additives. We have demonstrated that the synthesis of several *N*-methyl 2-(acylmethylene)pyrrolidine alkaloids, including (±)-hygrine (**5nb**), (±)-*N*-methylruspolinone (**5hb**), and (±)-dehydrodarlinine (**5jb**), could be accomplished in only three steps from proline and corresponding methyl ketones, albeit a few in lower yields. The investigation could illuminate the understanding of the biological formation of these pyrrolidine alkaloids.[7,8] Further application of this methodology may be amenable to the synthesis of versatile pyrrolidine, indolizidine, and phenanthroindolizidine alkaloids.[21,23,24]

EXPERIMENTAL SECTION

General Chemical Procedures. The chemical shift values are reported in δ values (parts per million, ppm) relative to the standard

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chemical shift for the hydrogen residue peak and carbon-13 peak in the deuterated solvent, $CDCl_3$, or DMSO-d_6.[25] The coupling constant (J) values are expressed in hertz (Hz). The numbers of protons directly attached to the individual carbons were determined by ^{13}C NMR DEPT experiments. Thin-layer chromatography (TLC) was performed on silica gel plates. Compounds on TLC were visualized by illumination under UV light (254 nm), or dipped into 10% phosphomolybdic acid in ethanol, followed by charring on a hot plate. Solvent systems are expressed as a percentage of the more polar component with respect to total volume (v/v%). Silica gel (230−400 mesh) was used for flash column chromatography, and this technique has been described by Still et al.[26] Evaporations were carried out under reduced pressure (water aspirator or vacuum pump) with the bath temperature below 50 °C unless specified otherwise. Materials obtained from commercial suppliers were used without further purification.

[General Procedure A] Chlorination of 1-Benzylproline (1a). To a mixture of 1-benzylproline (0.2053 g, 1.00 mmol) in CH_2Cl_2 (2.0 mL, 0.5 M) was added one drop of DMF and oxalyl chloride (0.1904 g, 0.130 mL, 1.50 mmol). The mixture was stirred at room temperature for 3 h. The solution was concentrated to dryness under reduced pressure. The resulting residue (containing 1-benzylpyrrolinium) was used for the subsequent reaction without further purification.

[General Procedure B] Chlorination of 1-Methylproline (1b). To a mixture of 1-methylproline (0.2583 g, 2.00 mmol) in CH_2Cl_2 (10.0 mL, 0.2 M) was added one drop of DMF and oxalyl chloride (0.5077 g, 0.344 mL, 4.00 mmol). The mixture was stirred at room temperature for 3 h. The solution was concentrated to dryness under reduced pressure. The resulting residue (containing 1-methylpyrrolinium) was used for the subsequent reaction without further purification.

[General Procedure C] Preparation of N-Substituted 2-(Acylmethylene)pyrrolidines (5). To a mixture of the crude product from *General procedure A or B* (prepared from 2.0 mmol of 1-alkylproline **1a** or **1b**) in *t*-BuOH (2.0 mL, alternatively, DMF or CH_2Cl_2) was added the methyl ketone (**4**, 1.0 mmol). The solution was stirred at room temperature for 15 h. The solvent was removed under reduced pressure. The residue was partitioned between CH_2Cl_2 and saturated aqueous Na_2CO_3 solution. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated to dryness under reduced pressure. The resulting residue was purified by flash column chromatography to give the product **5**.

2-(1-Benzylpyrrolidin-2-yl)-1-phenylethanone[27] ***(5aa)***. Compound **5aa** was prepared from 1-benzylproline (**2a**) and acetophenone (**4a**) by *General procedures A and C*. The product was purified by flash column chromatography (Hex/EtOAc = 8.5:1.5) to give **5aa** (brown oil, 0.1084 g, 0.78 mmol, 78%, R_f = 0.13, Hex/EtOAc = 8:2). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.93 (d, 2 H, J = 7.5 Hz), 7.55 (t, 1 H, J = 7.3 Hz), 7.45 (t, 2 H, J = 7.6 Hz), 7.35−7.23 (m, 5 H), 3.99 (d, 1 H, J = 13.0 Hz), 3.37 (d, 1 H, J = 12.8 Hz), 3.31 (d, 1 H, J = 3.3 Hz), 3.15−3.09 (m, 1 H), 3.06−2.93 (m, 2 H), 2.24 (q, 1 H, J = 7.8 Hz), 2.20−2.11 (m, 1 H), 1.80−1.70 (m, 2 H), 1.59−1.51 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.8, 137.4, 133.2 (CH), 129.1 (CH), 128.8 (CH), 128.5 (CH), 128.3 (CH), 127.2 (CH), 60.9 (CH), 59.2 (CH_2), 54.2 (CH_2), 44.3 (CH_2), 31.5 (CH_2), 22.6 (CH_2); MS (ESI) m/z 280 (100) (M + 1); HRMS (ESI, TOF) calcd for $C_{19}H_{22}NO$ (M + H): 280.1701. Found: 280.1700.

2-(1-Methylpyrrolidin-2-yl)-1-phenylethanone[17,23] ***(5ab)***. Compound **5ab** was prepared from 1-methylproline (**2b**) and acetophenone (**4a**) by *General procedures B and C*. The product was purified by flash column chromatography (CH_2Cl_2/MeOH = 9:1, R_f = 0.18) to give **5ab** (yellow oil, 0.0375 g, 0.19 mmol, 37%). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.95 (t, 2 H, J = 4.2 Hz), 7.55 (t, 1 H, J = 7.3 Hz), 7.45 (t, 2 H, J = 7.6 Hz), 3.38 (dd, 1 H, J = 4.0 and 16.7 Hz), 3.17−3.12 (m, 1 H), 3.07−3.00 (m, 1 H), 2.88−2.81 (m, 1 H), 2.40 (s, 3 H), 2.29 (q, 1 H, J = 9.3 Hz), 2.22−2.13 (m, 1 H), 1.89−1.70 (m, 2 H), 1.56−1.46 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.1, 137.0, 133.2 (CH), 128.7 (CH), 128.1 (CH), 62.4 (CH), 56.7 (CH_2), 43.0 (CH_2), 40.4 (CH_3), 31.5 (CH_2), 22.1 (CH_2); MS (ESI) m/z 204 (100) (M + 1); HRMS (ESI, TOF) calcd for $C_{13}H_{18}NO$ (M + H): 204.1388. Found: 204.1383.

2-(1-Benzylpyrrolidin-2-yl)-1-(4-methoxyphenyl)ethanone ***(5ba)***. Compound **5ba** was prepared from 1-benzylproline (**2a**) and 4′-methoxyacetophenone (**4b**) by *General procedures A and C*. The product was purified by flash column chromatography (Hex/EtOAc = 6:4, R_f = 0.16) to give **5ba** (brown oil, 0.1017 g, 0.3287 mmol, 66%). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.91 (d, 2 H, J = 8.8 Hz), 7.35−7.29 (m, 4 H), 7.25−7.22 (m, 1 H), 6.92 (d, 2 H, J = 8.9 Hz), 3.99 (d, 1 H, J = 13.0 Hz), 3.85 (s, 3 H), 3.34 (d, 1 H, J = 13.0 Hz), 3.28 (dd, 1 H, J = 3.9 and 15.8 Hz), 3.12−3.07 (m, 1 H), 2.99−2.92 (m, 2 H), 2.22 (dd, 1 H, J = 9.2 and 17.3 Hz), 2.16−2.09 (m, 1 H), 1.80−1.67 (m, 2 H), 1.57−1.50 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.1, 163.3, 139.4, 130.32, 130.28 (CH), 128.8 (CH), 128.1 (CH), 126.8 (CH), 113.6 (CH), 60.7 (CH), 58.9 (CH_2), 55.3 (CH_3), 53.9 (CH_2), 43.7 (CH_2), 31.2 (CH_2), 22.3 (CH_2); MS (ESI) m/z 310 (100) (M + 1); HRMS (ESI, TOF) Calcd for $C_{20}H_{24}NO_2$ (M + H): 310.1807. Found 310.1804.

2-(1-Benzylpyrrolidin-2-yl)-1-(4-nitrophenyl)ethanone ***(5ca)***. Compound **5ca** was prepared from 1-benzylproline (**2a**) and 4′-nitroacetophenone (**4c**) by *General procedures A and C*. The product was purified by flash column chromatography (Hex/EtOAc = 7.5:2.5 to 6:4) to give **5ca** (yellow oil, 0.0303 g, 0.09 mmol, 19%, R_f = 0.15, Hex/EtOAc = 8:2). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.28 (d, 2 H, J = 8.8 Hz), 8.01 (d, 2 H, J = 8.8 Hz), 7.32−7.25 (m, 5 H), 3.93 (d, 1 H, J = 13.0 Hz), 3.46 (d, 1 H, J = 13.3 Hz), 3.35−3.29 (m, 1 H), 3.15 (m, 1 H), 3.06−3.00 (m, 1 H), 2.31 (q, 1 H, J = 8.8 Hz), 2.21−2.11 (m, 1 H), 1.80−1.74 (m, 2 H), 1.62 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.2, 150.5, 141.7, 129.3 (CH), 129.1 (CH), 128.6 (CH), 127.4 (CH), 124.0 (CH), 60.7 (CH), 59.3 (CH_2), 54.4 (CH_2), 45.0 (CH_2), 31.6 (CH_2), 22.7 (CH_2); MS (ESI) m/z 191 (38), 325 (100) (M + 1); HRMS (ESI, TOF) Calcd for $C_{19}H_{21}N_2O_3$ (M + H): 325.1552. Found: 325.1562.

2-(1-Benzylpyrrolidin-2-yl)-1-(p-tolyl)ethanone ***(5da)***. Compound **5da** was prepared from 1-benzylproline (**2a**) and 4′-methylacetophenone (**4d**) by *General procedures A and C*. The product was purified by flash column chromatography ($CHCl_3$/MeOH = 10:0 to 99:1) to give **5da** (brown oil, 0.0623 g, 0.21 mmol, 43%, R_f = 0.20 (Hex/EtOAc = 7:3)). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.83 (d, 2 H, J = 8.2 Hz), 7.35−7.29 (m, 5 H), 7.25 (d, 2 H, J = 8.2 Hz), 3.99 (d, 1 H, J = 12.9 Hz), 3.36 (d, 1 H, J = 13.0 Hz), 3.31 (dd, 1 H, J = 15.8 and 3.7 Hz), 3.14−3.07 (m, 1 H), 3.02−2.93 (m, 2 H), 2.41 (s, 3 H), 2.24 (q, 1 H, J = 9.0 Hz), 2.18−2.09 (m, 1 H), 1.82−1.66 (m, 2 H), 1.58−1.50 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.3, 143.8, 139.4, 134.8, 129.3 (CH), 128.9 (CH), 128.30 (CH), 127.0 (CH), 60.8 (CH), 59.0 (CH_2), 54.0 (CH_2), 44.0 (CH_2), 31.3 (CH_2), 22.4 (CH_2), 21.7 (CH_3); MS (ESI) m/z 294 (100) (M + 1); HRMS (ESI, TOF) Calcd for $C_{20}H_{24}NO$ (M + H): 294.1858. Found: 294.1850.

2-(1-Benzylpyrrolidin-2-yl)-1-(4-hydroxyphenyl)ethanone ***(5ea)***. Compound **5ea** was prepared from 1-benzylproline (**2a**) and 4′-hydroxyacetophenone (**4e**) by *General procedures A and C*. The product was purified by flash column chromatography ($CHCl_3$/MeOH = 10:0 to 95:5) to give **5ea** (brown oil, 0.0449 g, 0.15 mmol, 30%, R_f = 0.23 (Hex/EtOAc = 0:10)). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, 2 H, J = 8.6 Hz), 7.36−7.24 (m, 5 H), 6.78 (d, 2 H, J = 8.6 Hz), 6.22 (br, 1 H), 4.07 (d, 1 H, J = 12.8 Hz), 3.46 (d, 1 H, J = 12.8 Hz), 3.33 (dd, 1 H, J = 3.9 and 16.0 Hz), 3.27−3.20 (m, 1 H), 3.10−3.00 (m, 2 H), 2.36 (q, 1 H, J = 8.9 Hz), 2.21−2.12 (m, 1 H), 1.80−1.17 (m, 2 H), 1.61−1.52 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.0, 163.0, 137.3, 131.1 (CH), 129.7 (CH), 128.7 (CH), 127.8 (CH), 116.3 (CH), 61.5 (CH), 58.8 (CH_2), 53.8 (CH_2), 42.5 (CH_2), 31.2 (CH_2), 22.1 (CH_2); MS (ESI) m/z 296 (100) (M + 1); HRMS (ESI, TOF) Calcd for $C_{19}H_{22}NO_2$ (M + H): 296.1651. Found: 296.1642; HRMS (ESI, TOF) Calcd for $C_{19}H_{20}NO_2$ (M − 1): 294.1494. Found: 294.1510.

2-(1-Benzylpyrrolidin-2-yl)-1-(o-tolyl)ethanone ***(5fa)***. Compound **5fa** was prepared from 1-benzylproline (**2a**) and 2′-methylacetophenone (**4f**) by *General procedures A and C*. The product was purified by flash column chromatography ($CHCl_3$/MeOH = 10:0 to 99:1) to give **5fa** (oil, 0.0278 g, 0.10 mmol, 19%, R_f = 0.25 (Hex/EtOAc = 7:3)). ^1H

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NMR ($CDCl_3$, 400 MHz) δ 7.58 (d, 1 H, J = 7.3 Hz), 7.38−7.23 (m, 8 H), 3.97 (d, 1 H, J = 12.9 Hz), 3.35 (d, 1 H, J = 12.9 Hz), 3.27 (dd, 1 H, J = 3.6 and 15.8 Hz), 3.05 (m, 1 H), 2.96 (d, 1 H, J = 9.0 Hz), 2.92 (d, 1 H, J = 8.8 Hz), 2.22 (q, 1 H, J = 8.9 Hz), 2.17−2.08 (m, 1 H), 1.77−1.67 (m, 2 H), 1.59−1.50 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.0, 139.4.5, 138.5, 138.1, 132.1 (CH), 131.4 (CH), 129.1 (CH),128.8 (CH), 128.5 (CH), 127.2 (CH), 125.9 (CH), 61.1 (CH), 59.1 (CH_2), 54.1 (CH_2), 47.2 (CH_2), 31.4 (CH_2), 22.5 (CH_2), 21.4 (CH_3); MS (ESI) m/z 294 (M + 1); HRMS (ESI, TOF) Calcd for $C_{20}H_{24}NO$ (M + H): 294.1858. Found: 294.1838.

2-(1-Benzylpyrrolidin-2-yl)-1-(2-methoxyphenyl)ethanone (**5ga**). Compound **5ga** was prepared from 1-benzylproline (**2a**) and 2′-methoxyacetophenone (**4g**) by *General procedures A and C*. The product was purified by flash column chromatography (Hex/Ether = 5:5 to 4:6) to give **5ga** (oil, 0.0566 g, 0.1829 mmol, 37%, R_f = 0.15 (Hex/Ether = 5:5)). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.68 (dd, 1 H, J = 1.7 and 7.7 Hz), 7.50−7.46 (m, 1 H), 7.36−7.31 (m, 4 H), 7.28−7.25 (m, 1 H), 7.02 (t, 1 H, J = 7.5 Hz), 6.98 (d, 1 H, J = 8.4 Hz), 4.05 (d, 1 H, J = 12.9 Hz), 3.90 (s, 3 H), 3.45 (dd, 1 H, J = 2.8 and 15.8 Hz), 3.31 (d, 1 H, J = 13.0 Hz), 3.11−3.01 (m, 2 H), 2.96−2.92 (m, 1 H), 2.22−2.10 (m, 2 H), 1.78−1.68 (m, 2 H), 1.60−1.53 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.9, 158.3, 139.5, 133.3 (CH), 130.1 (CH), 128.9 (CH), 128.8, 128.1 (CH), 126.8 (CH), 120.6 (CH), 111.4 (CH), 60.7 (CH), 58.8 (CH_2), 55.4 (CH_3), 53.8 (CH_2), 49.2 (CH_2), 31.1 (CH_2), 22.2 (CH_2); MS (ESI) m/z 160 (16), 310 (100) (M + 1); HRMS (ESI, TOF) Calcd for $C_{20}H_{24}NO_2$ (M + H): 310.1807. Found 310.1803.

2-(1-Benzylpyrrolidin-2-yl)-1-(3,4-dimethoxyphenyl)ethanone (**5ha**). Compound **5ha** was prepared from 1-benzylproline (**2a**) and 3′,4′-dimethoxyacetophenone (**4h**) by *General procedures A and C*. The product was purified by flash column chromatography (Hex/EtOAc = 7.5:2.5) to give **5ha** (oil, 0.1236 g, 0.4472 mmol, 89%, R_f = 0.16 (Hex/EtOAc = 7:3)). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.57 (dd, 1 H, J = 2.1 and 8.4 Hz), 7.53 (d, 1 H, J = 2.0 Hz), 7.37−7.31 (m, 4 H), 7.28−7.24 (m, 1 H), 6.90 (d, 1 H, J = 8.4 Hz), 4.01 (d, 1 H, J = 12.9 Hz), 3.97 (s, 3 H), 3.95 (s, 3 H), 3.38 (d, 1 H, J = 13.0 Hz), 3.30 (dd, 1 H, J = 3.8 and 15.8 Hz), 3.15−3.09 (m, 1 H), 3.03−2.95 (m, 2 H), 2.25 (dd, 1 H, J = 9.2 and 17.4 Hz), 2.19−2.12 (m, 1 H), 1.81−1.70 (m, 2 H), 1.59−1.52 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.2, 153.2, 149.0, 139.4, 130.5, 128.9 (CH), 128.2 (CH), 126.9 (CH), 122.8 (CH), 110.1 (CH), 110.0 (CH), 60.9 (CH), 59.0 (CH_2), 56.0 (CH_3), 55.9 (CH_3), 54.0 (CH_2), 43.6 (CH_2), 31.2 (CH_2), 22.3 (CH_2); MS (ESI) m/z 160 (21), 340 (100) (M + 1); HRMS (ESI, TOF) Calcd for $C_{21}H_{26}NO_3$ (M + H): 340.1913. Found: 340.1914.

2-(1-Methylpyrrolidin-2-yl)-1-(3,4-dimethoxyphenyl)-ethanone[3,17,18] (**5hb**, *N-Methylruspolinone*). Compound **5hb** was prepared from 1-methylproline (**2b**) and 3′,4′-dimethoxyacetophenone (**4h**) by *General procedures B and C*. The product was purified by flash column chromatography (Hex/EtOAc = 7.5:2.5) to give **5hb** (oil, 0.1236 g, 0.4472 mmol, 89%, R_f = 0.16 (Hex/EtOAc = 7:3)). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63 (dd, 1 H, J = 2.0 and 8.4 Hz), 7.51 (d, 1 H, J = 1.9 Hz), 6.89 (d, 1 H, J = 8.4 Hz), 3.93 (s, 3 H), 3.92 (s, 3 H), 3.49 (dd, 1 H, J = 4.1 and 16.6 Hz), 3.38−3.34 (m, 1 H), 3.20 (dd, 1 H, J = 8.6 and 16.6 Hz), 3.15−3.09 (m, 1 H), 2.52 (s, 3 H), 2.47 (dd, 1 H, J = 9.0 and 18.6 Hz), 2.29−2.21 (m, 1 H), 2.00−1.81 (m, 2 H), 1.70−1.63 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.8, 153.6, 149.1, 129.9, 123.1 (CH), 110.13 (CH), 110.07 (CH), 63.3 (CH), 56.5 (CH_2), 56.1 (CH_3), 56.0 (CH_3), 41.3 (CH_2), 40.1 (CH_3), 31.2 (CH_2), 22.0 (CH_2); MS (ESI) m/z 264 (100) (M + 1); HRMS (ESI, TOF) Calcd for $C_{15}H_{22}NO_3$ (M + H): 264.1600. Found: 264.1590.

2-(1-Benzylpyrrolidin-2-yl)-1-(naphthalen-2-yl)ethanone (**5ia**). Compound **5ia** was prepared from 1-benzylproline (**2a**) and 2-acetonaphthone (**4i**) by *General procedures A and C*. The product was purified by flash column chromatography ($CHCl_3$/MeOH = 10:0 to 99:1) to give **5ia** (yellow oil, 0.0558 g, 0.17 mmol, 34%, R_f = 0.25 (Hex/EtOAc = 7:3)). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.44 (s, 1 H), 8.02 (d, 1 H, J = 1.6 Hz), 8.00 (d, 1 H, J = 1.6 Hz), 7.97 (s, 1 H), 7.95 (s, 1 H), 7.62−7.54 (m, 2 H), 7.38−7.30 (m, 4 H), 7.27−7.23 (m, 1 H), 4.04 (d, 1 H, J = 13.0 Hz), 3.45 (d, 1 H, J = 12.2 Hz), 3.41 (d, 1 H, J = 13.0 Hz), 3.22−3.12 (m, 2 H), 3.01−2.96 (m, 1 H), 2.27 (q, 1 H, J = 9.1 Hz), 2.22−2.13 (m, 1 H), 1.85−1.69 (m, 2 H), 1.64−1.55 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.8, 139.6, 135.7, 134.8, 132.7, 130.0 (CH), 129.8 (CH), 129.1 (CH), 128.6 (CH), 128.4 (CH), 127.9 (CH), 127.1 (CH), 126.9 (CH), 124.0 (CH), 61.0 (CH), 59.2 (CH_2), 54.2 (CH_2), 44.4 (CH_2), 31.5 (CH_2), 22.6 (CH_2); MS (ESI) m/z 330 (100) (M + 1); HRMS (ESI, TOF) Calcd for $C_{23}H_{24}NO$ (M + H): 330.1858. Found 330.1839.

(E)-1-(1-Benzylpyrrolidin-2-yl)-4-phenylbut-3-en-2-one (**5ja**). Compound **5ja** was prepared from 1-benzylproline (**2a**) and *trans*-4-phenyl-3-buten-2-one (**4j**) by *General procedures A and C*. The product was purified by flash column chromatography (Hex/EtOAc = 8:2 to 7:3) to give **5ja** (yellow oil, 0.1293 g, 0.42 mmol, 85%, R_f = 0.28 (Hex/EtOAc = 0:10)). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54−7.24 (m, 11 H), 6.75 (d, 1 H, J = 16.2 Hz), 4.00 (d, 1 H, J = 13.0 Hz), 3.35 (d, 1 H, J = 13.0 Hz), 3.07−2.99 (m, 2 H), 2.97−2.92 (m, 1 H), 2.78−2.71 (m, 1 H), 2.22 (q, 1 H, J = 9.1 Hz), 2.16−2.07 (m, 1 H), 1.81−1.66 (m, 2 H), 1.61−1.52 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.6, 142.7 (CH), 139.5, 134.5, 130.5 (CH), 129.0 (CH), 128.9 (CH), 128.3 (CH), 127.0 (CH), 126.8 (CH), 60.7 (CH), 58.9 (CH_2), 54.0 (CH_2), 46.1 (CH_2), 31.2 (CH_2), 22.3 (CH_2); MS (ESI) m/z 306 (100) (M + 1); HRMS (ESI, TOF) Calcd for $C_{21}H_{24}NO$ (M + H): 306.1858. Found 306.1857.

(E)-1-(1-Methylpyrrolidin-2-yl)-4-phenylbut-3-en-2-one[2,17,19] (**5jb**, *Dehydrodarlinine*). Compound **5jb** was prepared from 1-methylproline (**2b**) and *trans*-4-phenyl-3-buten-2-one (**4j**) by *General procedures B and C*. The product was purified by flash column chromatography ($CHCl_3$/MeOH = 9:1) to give **5jb** (brown oil, 0.2002 g, 0.87 mmol, 87%, R_f = 0.22 ($CHCl_3$/MeOH = 95:5)). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.56 (d, 1 H, J = 16.3 Hz), 7.53−7.55 (m, 2 H), 7.39−7.40 (m, 3 H), 6.74 (d, 1 H, J = 16.2 Hz), 3.09 (ddd, 1 H, J = 2.1, 7.8, 8.7 Hz), 3.03 (dt, 1 H, J = 6.8, 12.8 Hz), 2.69 (ddd, 2 H, J = 6.0, 7.8, 10.4 Hz), 2.36 (s, 3 H), 2.24 (dd, 1 H, J = 9.5, 17.7 Hz), 2.08−2.14 (m, 1 H), 1.77−1.83 (m, 1 H), 1.70−1.76 (m, 1 H), 1.46−1.52 (m, 1 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 199.3, 142.9 (CH), 134.4, 130.5 (CH), 128.9 (CH), 128.3 (CH), 126.7 (CH), 62.3 (CH), 56.8 (CH_2), 45.3 (CH_2), 40.5 (CH_3), 31.4 (CH_2), 22.1 (CH_2); MS (EI, 20 eV) m/z 84 (100), 229 (20) (M^+); HRMS (EI, magnetic sector) Calcd for $C_{15}H_{19}NO$ (M^+): 229.1467. Found 229.1466.

2-(1-Benzylpyrrolidin-2-yl)-1-(pyrrol-2-yl)ethanone (**5ka**). Compound **5ka** was prepared from 1-benzylproline (**2a**) and 2-acetylpyrrole (**4k**) by *General procedures A and C*. The product was purified by flash column chromatography (Hex/EtOAc = 8.5:1.5 to 7.5:2.5) to give **5ka** (brown oil, 0.0868 g, 0.65 mmol, 65%, R_f = 0.10, Hex/EtOAc = 7:3). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.87 (br, 1 H), 7.34−7.23 (m, 5 H), 7.02 (s, 1 H), 6.91 (s, 1 H), 6.28−6.26 (m, 1 H), 4.03 (d, 1 H, J = 12.8 Hz), 3.33 (d, 1 H, J = 12.8 Hz), 3.13−3.02 (m, 2 H), 2.96−2.91 (m, 1 H), 2.88−2.83 (m, 1 H), 2.22 (q, 1 H, J = 8.8 Hz), 2.08−1.99 (m, 1 H), 1.78−1.66 (m, 2 H), 1.65−1.57 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.7, 139.3, 132.6 129.0 (CH), 128.3 (CH), 127.0 (CH), 124.8 (CH), 116.7 (CH), 110.7 (CH), 61.3 (CH), 58.9 (CH_2), 53.9 (CH_2), 43.5 (CH_2), 30.9 (CH_2), 22.3 (CH_2). MS (ESI) m/z 160 (33), 269 (100) (M + 1); HRMS (ESI, TOF) Calcd for $C_{17}H_{21}N_2O$ (M + H): 269.1654. Found: 269.1658.

2-(1-Benzylpyrrolidin-2-yl)-1-(furan-2-yl)ethanone (**5la**). Compound **5la** was prepared from 1-benzylproline (**2a**) and 2-acetylfuran (**4l**) by *General procedures A and C*. The product was purified by flash column chromatography ($CHCl_3$/MeOH = 10:0 to 99:1) to give **5la** (brown oil, 0.0584 g, 0.22 mmol, 43%, R_f = 0.13 (Hex/EtOAc = 7:3)). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (s, 1 H), 7.32−7.22 (m, 5 H), 7.14 (d, 1 H, J = 3.5 Hz), 6.51 (dd, 1 H, J = 2.1 and 3.1 Hz), 4.00 (d, 1 H, J = 13.0 Hz), 3.33 (d, 1 H, J = 13.0 Hz), 3.15 (dd, 1 H, J = 4.1 and 15.0 Hz), 3.10−3.03 (m, 1 H), 2.95−2.85 (m, 2 H), 2.21 (q, 1 H, J = 8.8 Hz), 2.12−2.03 (m, 1 H), 1.78−1.68 (m, 2 H), 1.63−1.55 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 188.6, 153.1, 146.6 (CH), 139.4, 129.0 (CH), 128.3 (CH), 127.0 (CH), 117.4 (CH), 112.3 (CH), 60.8 (CH), 58.9 (CH_2), 54.0 (CH_2), 43.9 (CH_2), 31.1 (CH_2), 22.4 (CH_2); MS (EI, 20 eV) m/z 91 (19), 160 (100), 178 (40), 269 (17) (M^+); HRMS (EI, magnetic sector) Calcd for $C_{17}H_{19}NO_2$ (M^+): 269.1416. Found: 269.1418.

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*2-(1-Benzylpyrrolidin-2-yl)-1-(thiophen-2-yl)ethanone (**5ma**).* Compound **5ma** was prepared from 1-benzylproline (**2a**) and 2-acetylthiophene (**4m**) by *General procedures A and C*. The product was purified by flash column chromatography ($CHCl_3$/MeOH = 10:0 to 99:1) to give **5ma** (brown oil, 0.0595 g, 0.21 mmol, 42%, R_f = 0.13 (Hex/EtOAc = 7:3)). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (dd, 1 H, J = 0.9 and 3.9 Hz), 7.62 (dd, 1 H, J = 0.7 and 4.9 Hz), 7.34−7.24 (m, 5 H), 7.11 (dd, 1 H, J = 4.0 and 4.7 Hz), 3.99 (d, 1 H, J = 13.0 Hz), 3.37 (d, 1 H, J = 13.0 Hz), 3.24 (dd, 1 H, J = 4.1 and 15.2 Hz), 3.15−3.08 (m, 1 H, J = 4.9 Hz), 2.98−2.92 (m, 2 H), 2.24 (q, 1 H, J = 9.1 Hz), 2.16−2.06 (m, 1 H), 1.83−1.66 (m, 2 H), 1.64−1.55 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.5, 145.0, 139.4, 133.8(CH), 132.2(CH), 129.0 (CH), 128.4 (CH), 128.2 (CH), 127.1 (CH), 61.0 (CH), 59.1 (CH_2), 54.1 (CH_2), 44.9 (CH_2), 31.3 (CH_2), 22.5 (CH_2); MS (EI, 20 eV) m/z 91 (26), 160 (100), 194 (58), 285 (10) (M^+); HRMS (EI, magnetic sector) Calcd for $C_{17}H_{19}NOS$ (M^+): 285.1187. Found: 285.1185.

*1-(1-Benzylpyrrolidin-2-yl)propan-2-one[28] (**5na**).* To a mixture of 1-benzylproline (**2a**, 0.2053 g, 1.00 mmol) in CH_2Cl_2 (2.0 mL, 0.5 M) was added one drop of DMF and oxalyl chloride (0.1904 g, 0.130 mL, 1.50 mmol). The mixture was stirred at room temperature for 3 h. The solution was concentrated to dryness under reduced pressure. The resulting residue (containing 1-benzylpyrrolinium) was dissolved in a mixture of *t*-BuOH (1.0 mL) and acetone (1.0 mL). The mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure. The residue was partitioned between $CHCl_3$ and H_2O. The organic layer was washed with saturated aqueous Na_2CO_3 solution and brine, dried over anhydrous $MgSO_4$, and then concentrated to dryness under reduced pressure. The product was purified by flash column chromatography (Hex/EtOAc = 8:2 to 6:4) to give **5na** (yellow oil, 65.2 mg, 0.30 mmol, 30%, R_f = 0.13 (Hex/EtOAc = 0:10)). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27−7.18 (m, 5 H), 3.88 (d, 1 H, J = 13.0 Hz), 3.24 (d, 1 H, J = 13.0 Hz), 2.88−2.81 (m, 1 H), 2.73 (dd, 1 H, J = 3.9 and 16.2 Hz), 2.47−2.41 (m, 1 H), 2.16−2.00 (m, 2 H), 2.10 (s, 3 H), 1.70−1.62 (m, 2 H), 1.47−1.38 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.1, 139.3, 128.8 (CH), 128.2 (CH), 126.9 (CH), 60.1 (CH), 58.8 (CH_2), 53.8 (CH_2), 48.9 (CH_2), 31.0 (CH_2), 30.8 (CH_3), 22.2 (CH_2); MS (ESI) m/z 218 (100) (M + 1); HRMS (ESI, TOF) Calcd for $C_{14}H_{20}NO$ (M + H): 218.1545. Found: 218.1543.

*1-(1-Methylpyrrolidin-2-yl)propan-2-one[20] (**5nb**, Hygrine).* To a mixture of 1-methylproline (**2b**, 0.2583 g, 2.00 mmol) in CH_2Cl_2 (10.0 mL, 0.2 M) was added one drop of DMF and oxalyl chloride (0.34 mL, 0.5077 g, 4.00 mmol). The mixture was stirred at room temperature for 3 h. The solution was concentrated to dryness under reduced pressure. The resulting residue (containing 1-methylpyrrolinium) was dissolved in a mixture of DMF (10 mL) and acetone (10 mL). The mixture was stirred at room temperature for 15 h. The solvent was removed under reduced pressure. The resulting residue was purified by flash column chromatography (CH_2Cl_2/MeOH = 9:1, R_f = 0.15) to give **5nb** (oil, 0.0504 g, 0.3569 mmol, 18%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.39−3.34 (m, 1 H), 3.07 (dd, 1 H, J = 4.7 and 17.0 Hz), 3.04−2.96 (m, 1 H), 2.72 (dd, 1 H, J = 7.6 and 17.1 Hz), 2.51−2.44 (m, 1 H), 2.50 (s, 3 H), 2.23−2.15 (m, 1 H), 2.17 (s, 3 H), 1.99−1.78 (m, 2 H), 1.64−1.54 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.5, 62.7 (CH), 56.3 (CH_2), 46.2 (CH_2), 40.1 (CH_3), 30.8 (CH_2), 30.5 (CH_3), 21.9 (CH_2); MS (ESI) m/z 130 (6), 142 (100) (M + 1); HRMS (ESI, TOF) Calcd for $C_8H_{16}NO$ (M + H): 142.1232. Found: 142.1229.

*2-(1-Benzylpyrrolidin-2-yl)-5,5-dimethylcyclohexane-1,3-dione (**7fa**).* Compound **7fa** was prepared from 1-benzylproline (**2a**) and 5,5-dimethylcyclohexane-1,3-dione (**6f**) by *General procedures A and C*. The product was purified by flash column chromatography (CH_2Cl_2/MeOH = 95:5, R_f = 0.38) to give **7fa** (oil, 0.1048 g, 0.35 mmol, 35%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.41−7.36 (m, 3 H), 7.35−7.32 (m, 2 H), 4.35 (t, 1 H, J = 8.6 Hz), 4.16 (d, 1 H, J = 12.8 Hz), 3.49 (d, 1 H, J = 13.2 Hz), 3.16 (dd, 1 H, J = 6.2 and 11.4 Hz), 2.67 (dd, 1 H, J = 5.0 and 13.8 Hz), 2.36−2.28 (m, 1 H), 2.25−2.22 (m, 4 H), 1.95−1.88 (m, 2 H), 1.86−1.76 (m, 1 H), 0.96 (s, 6 H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 188.8, 133.4, 129.7 (CH), 128.7 (CH), 129.3 (CH), 129.2 (CH), 129.0 (CH), 128.3, 104.6, 65.7 (CH), 57.2 (CH_2), 51.1 (CH_2), 49.0 (CH_2), 32.3, 3.08 (CH_2), 28.7 (2 × CH_3), 22.5 (CH_2); MS (ESI) m/z 300 (100) (M + 1); HRMS (ESI, TOF) Calcd for $C_{19}H_{26}NO_2$ (M + H): 300.1964. Found: 300.1951.

*5-(1-Benzylpyrrolidin-2-yl)-1,3-dimethylpyrimidine-2,4,6-trione (**7ga**).* Compound **7ga** was prepared from 1-benzylproline (**2a**) and 1,3-dimethylbarbituric acid (**6g**) by *General procedures A and C*. The product was purified by flash column chromatography ($CHCl_3$/MeOH = 99:1 to 98:2) to give **7ga** (yellow oil, 0.0472 g, 0.15 mmol, 30%, R_f = 0.47 (CH_2Cl_2/MeOH = 9:1)). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.93 (br, 1 H), 7.42−7.39 (m, 3 H), 7.32−7.30 (m, 2 H), 4.6 (t, 1 H, J = 6.6 Hz), 4.37 (d, 1 H, J = 10.4 Hz), 3.70 (d, 1 H, J = 10.4 Hz), 3.32−3.28 (m, 1 H), 3.31 (s, 6 H), 2.98−2.92 (m, 1 H), 2.42−2.37 (m, 1 H), 2.10−2.02 (m, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.6, 153.0, 130.7, 129.7 (CH), 129.53 (CH), 129.45 (CH), 78.4, 67.5 (CH), 56.3 (CH_2), 50.8 (CH_2), 29.6 (CH_2), 27.2 (CH_3), 21.8 (CH_2); MS (ESI) m/z 314 (100) (M − 1); HRMS (ESI, TOF) Calcd for $C_{17}H_{20}N_3O_3$ (M − 1): 314.1505. Found: 314.1520; HRMS (ESI, TOF) Calcd for $C_{17}H_{22}N_3O_3$ (M + H): 316.1661. Found: 316.1659.

*2-(1-Benzylpyrrolidin-2-yl)-1-(3,4-dimethoxyphenyl)ethanol (**10**).* To a mixture of 2-(1-benzylpyrrolidin-2-yl)-1-(3,4-dimethoxyphenyl)-ethanone (**5ha**, 0.1185 g, 0.3491 mmol, 1 equiv) in methanol (0.70 mL) was added sodium borohydride (0.02641 g, 0.6982 mmol, 2 equiv) and cerium(III) chloride heptahydrate (0.2601 g, 0.6982 mmol, 2 equiv). The reaction was stirred at 20 °C for 12 h. After the reaction completed, the mixture was acidified with aqueous 1 N HCl and extracted with dichloromethane. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to dryness under reduced pressure. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH = 98:2) to give the yellow oil products as a diastereomeric mixture (**10**, 0.0727 g, 0.213 mmol, 61%, R_f = 0.14 and 0.10 (CH_2Cl_2/MeOH = 96:4)). The less polar diastereomer was further purified for spectroscopic analysis (oil): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32−7.37 (m, 4 H), 7.25−7.28 (m, 1 H), 6.99 (d, 1 H, J = 1.8 Hz), 6.91 (dd, 1 H, J = 1.8, 8.2 Hz), 6.83 (d, 1 H, J = 8.2 Hz), 5.06 (dd, 1 H, J = 2.2, 10.6 Hz), 4.23 (d, 1 H, J = 12.6 Hz), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.19 (d, 1 H, J = 12.8 Hz), 2.94−2.99 (m, 2 H), 2.18 (dt, 1 H, J = 7.1, 9.7 Hz), 2.00−2.09 (m, 3 H), 1.76−1.88 (m, 2 H), 1.67−1.72 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.0, 148.0, 138.3, 138.2, 129.1 (CH), 128.5, (CH), 127.3, (CH), 117.8 (CH), 111.1 (CH), 109.2 (CH), 71.0 (CH), 63.3 (CH), 59.0 (CH_2), 56.0 (CH), 55.9 (CH), 53.9 (CH_2), 38.6 (CH_2), 28.4 (CH_2), 23.5 (CH_2); MS (EI, 70 eV) 91 (44), 160 (100), 341 (10) (M^+); HRMS (EI, magnetic sector) Calcd for $C_{21}H_{27}NO_3$ (M^+): 341.1991. Found 341.1986.

*2-(Pyrrolidin-2-yl)-1-(3,4-dimethoxyphenyl)ethanol (**11**).* To a mixture of 2-(1-benzylpyrrolidin-2-yl)-1-(3,4-dimethoxyphenyl)-ethanol (**10**, 0.1919 g, 0.562 mmol) in methanol (11 mL) under an Ar atmosphere was added 10% palladium on charcoal (29.9 mg, 0.0281 mmol, 0.05 equiv). Then, the reaction was stirred under a hydrogen atmosphere for 24 h. The mixture was filtered through a pad of Celite and washed with methanol. The resulting solution was concentrated to dryness under reduced pressure to give the crude product **11**. The crude product was used for the subsequent reaction without further purification.

*2-(3,4-Dimethoxyphenethyl)pyrrolidine (**9**).* A solution of **5ha** (0.3130 g, 0.9221 mmol) in MeOH (9.0 mL) was purged with Ar, followed by the addition of 10% palladium on charcoal (0.2453 g, 0.2305 mmol, 0.25 equiv). The resulting slurry was stirred under a hydrogen atmosphere for 11 h. The mixture was then filtered through a Celite pad to remove the catalyst. The pad was washed with methanol, and the filtrate was combined and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography ($CHCl_3$/MeOH = 97:3 to 95:5) to give **9** (oil, 0.1327 g, 0.5639 mmol, 61%, R_f = 0.19 ($CHCl_3$/MeOH = 95:5)). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.91 (d, 1 H, J = 1.9 Hz), 6.86 (dd, 1 H, J = 1.9 and 8.2 Hz), 6.79 (d, 1 H, J = 8.2 Hz), 3.88 (s, 3 H), 3.85 (s, 3 H), 3.68 (dd, 1 H, J = 3.6 and 10.1 Hz), 3.15−3.10 (m, 1 H), 2.86−2.80 (m, 1 H), 1.96−1.90 (m, 1 H), 1.84−1.65 (m, 6 H), 1.63−1.56 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.9, 147.8, 139.6, 118.3 (CH), 111.0 (CH), 109.7 (CH), 64.8 (CH), 55.89 (CH_3), 55.85 (CH_3), 48.3

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(CH_2), 39.0 (CH_2), 30.6 (CH_2), 26.7 (CH_2), 26.1 (CH_2); MS (ESI) m/z 236 (100) (M + 1); HRMS (ESI, TOF) Calcd for $C_{14}H_{22}NO_2$ (M + H): 236.1651. Found: 236.1646.

1-(3,4-Dimethoxyphenyl)-2-(pyrrolidin-2-yl)ethanone[3,16,21−23] ***(8, Ruspolinone).*** To a mixture of the crude product **11** (obtained from the hydrogenolysis of **10**, 0.562 mmol) and silica gel (0.2725 g) in CH_2Cl_2 (5.6 mL) was added PCC (0.2725 g, 1.2641 mmol, 2.25 equiv). The mixture was stirred at 20 °C for 24 h. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH = 95:5) to give **8** (ruspolinone, yellow oil, 0.0465 g, 0.187 mmol, 33% from **10**, R_f = 0.25 (CH_2Cl_2/MeOH = 9:1)). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.55 (dd, 1 H J = 1.4, 8.3 Hz), 7.47 (s, 1 H), 6.78 (d, 1 H, J = 8.4 Hz), 5.76 (bs, 1 H), 4.00−4.04 (m, 1 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.75 (dd, 1 H, J = 4.0, 11.0 Hz), 3.38 (dd, 1 H, J = 4.1, 11.8 Hz), 3.28 (t, 2 H, J = 7.2 Hz), 2.22−2.27 (m, 1 H), 1.99−2.03 (m, 1 H), 1.93−1.98 (m, 1 H), 1.67−1.74 (m, 1 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 196.0, 153.6, 149.0, 129.3, 123.2 (CH), 110.04 (CH), 110.03 (CH), 56.1 (CH), 56.0 (OCH_3), 55.8 (OCH_3), 45.2 (CH_2), 40.9 (CH_2), 30.7 (CH_2), 23.8 (CH_2); MS (EI, 20 eV) m/z 70 (100), 165 (70), 180 (60), 249 (50) (M^+); HRMS (EI, magnetic sector) Calcd for $C_{14}H_{19}NO_3$ (M^+): 249.1365. Found 249.1359.

[General Procedure D] Preparation of N-Substituted 2-Heteroarylpyrrolidines (14 or 15). To a mixture of the crude product from *General procesure A or B* (prepared from 2.0 mmol of 1-alkylproline **1a** or **1b**) in DMF (2.0 mL) was added the pyrrole or indole derivative (**12** or **13**, 1.0 mmol). The solution was stirred at room temperature for 1 h. The solvent was removed under reduced pressure. The residue was partitioned between CH_2Cl_2 and saturated aqueous Na_2CO_3 solution. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated to dryness under reduced pressure. The resulting residue was purified by flash column chromatography to give the product **14** or **15**.

1-Benzyl-2-(pyrrol-2-yl)pyrrolidine ***(14aa).*** Compound **14aa** was prepared from 1-benzylproline (**2a**) and pyrrole (**12a**) by *General procedures A and D*. The product was purified by flash column chromatography (Hex/EtOAc = 9:1 to 8.5:1.5) to give **14aa** (brown solid, 0.1215 g, 1.00 mmol, 95%, R_f = 0.25, Hex/EtOAc = 7:3). An analytical sample was obtained by recrystallization from EtOAc and MeOH. mp 58−59 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.59 (br, 1 H), 7.35−7.24 (m, 5 H), 6.78 (s, 1 H), 6.19−6.18 (m, 1 H), 6.15 (s, 1 H), 3.92 (d, 1 H, J = 13.1 Hz), 3.59 (t, 1 H, J = 7.5 Hz), 3.15 (d, 1 H, J = 13.1 Hz), 3.08 (t, 1 H, J = 8.3 Hz), 2.27−2.21 (m, 1 H, CH_2), 2.20−2.11 (m, 1 H, CH_2), 1.92−1.76 (m, 3 H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.6, 133.3, 128.9 (CH), 128.3 (CH), 127.0 (CH), 117.1 (CH), 108.1 (CH), 106.6 (CH), 62.7 (CH), 58.4 (CH_2), 53.2 (CH_2), 33.3 (CH_2), 22.5 (CH_2); MS (EI, 20 eV) m/z 91 (100), 93 (23), 107 (55), 225 (20), 226 (63) (M^+); HRMS (EI, magnetic sector) Calcd for $C_{15}H_{18}N_2$ (M^+): 226.1470. Found 226.1466.

1-Methyl-2-(pyrrol-2-yl)pyrrolidine[29,30] ***(14ab).*** Compound **14ab** was prepared from 1-methylproline (**2b**) and pyrrole (**12a**) by *General procedures B and D*. The product was purified by flash column chromatography ($CHCl_3$/MeOH = 9:1, R_f = 0.16) to give **14ab** (oil, 0.1732 g, 1.04 mmol, 90%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.63 (bs, 1 H), 6.73 (dd, 1 H, J = 2.3, 4.3 Hz), 6.12 (dd, 1 H, J = 2.8, 5.8 Hz), 6.05−6.04 (m, 1 H), 3.22 (t, 1 H, J = 8.2 Hz), 3.18−3.15 (m, 1 H), 2.28−2.22 (m, 1 H), 2.20 (s, 3 H), 2.13−2.09 (m, 1 H), 1.94−1.86 (m, 1 H), 1.85−1.81 (m, 1 H), 1.78−1.70 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 132.6, 117.1 (CH), 107.8 (CH), 106.4 (CH), 64.5, 56.6 (CH_2), 40.6, 33.3 (CH_2), 22.3 (CH_2); MS (EI, 20 eV) m/z 93 (42), 150 (100) (M^+); HRMS (EI, magnetic sector) Calcd for $C_9H_{14}N_2$ (M^+): 150.1157. Found: 150.1152.

1-Benzyl-2-(1-methylpyrrol-2-yl)pyrrolidine ***(14ba).*** Compound **14ba** was prepared from 1-benzylproline (**2a**) and 1-methylpyrrole (**12b**) by *General procedures A and D*. The product was purified by flash column chromatography (Hex/EtOAc = 10:0 to 9.8:0.2) to give **14ba** (oil, 0.1452 g, 1.00 mmol, 95%, R_f = 0.38, Hex/EtOAc = 7:3). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.24 (m, 5 H), 6.61 (dd, 1 H, J = 2.1, 2.1 Hz), 6.18 (dd, 1 H, J = 3.2, 1.9 Hz), 6.12 (t, 1 H, J = 3.0 Hz), 4.00 (d, 1 H, J = 13.1 Hz), 3.78 (s, 3 H), 3.56 (t, 1 H, J = 7.7 Hz), 3.10−3.07 (m, 1 H), 3.09 (d, 1 H, J = 12.8 Hz), 2.21−2.14 (m, 2 H), 1.96−1.88 (m, 2 H), 1.85−1.80 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.0, 133.0, 128.8 (CH), 128.3 (CH), 126.8 (CH), 123.0 (CH), 108.1 (CH), 106.8 (CH), 62.7 (CH), 58.4 (CH_2), 53.3 (CH_2), 34.5 (CH_3), 31.7 (CH_2), 22.4 (CH_2); MS (EI, 20 eV) m/z 91 (75), 120 (31), 121 (100), 240 (26) (M^+); HRMS (EI, magnetic sector) Calcd for $C_{16}H_{20}N_2$ (M^+): 240.1626. Found 240.1622.

1-Methyl-2-(1-methylpyrrol-2-yl)pyrrolidine ***(14bb).*** Compound **14bb** was prepared from 1-methylproline (**2b**) and 1-methylpyrrole (**12b**) by *General procedures B and D*. The product was purified by flash column chromatography ($CHCl_3$/MeOH = 9:1, R_f = 0.24) to give **14bb** (oil, 0.1260 g, 0.767 mmol, 85%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.55 (t, 1 H, J = 2.3 Hz), 6.08−6.06 (m, 2 H), 3.66 (s, 3 H), 3.27 (t, 1 H, J = 8.2 Hz), 3.19−3.15 (m, 1 H), 2.31−2.25 (m, 1 H), 2.23 (s, 3 H), 2.18−2.11 (m, 1 H), 1.99−1.78 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 132.8, 122.4 (CH), 107.0 (CH), 106.6 (CH), 63.6, 56.6 (CH_2), 40.5, 34.1, 32.2 (CH_2), 22.2 (CH_2); MS (EI, 20 eV) m/z 84 (65), 121 (21), 164 (100) (M^+); HRMS (EI, magnetic sector) Calcd for $C_{10}H_{16}N_2$ (M^+): 164.1313. Found: 164.1328.

1-Benzyl-2-(5-ethylpyrrol-2-yl)pyrrolidine ***(14ca).*** Compound **14ca** was prepared from 1-benzylproline (**2a**) and 2-ethylpyrrole (**12c**) by *General procedures A and D*. The product was purified by flash column chromatography (Hex/EtOAc = 8.5:1.5 to 8.2:1.8) to give **14ca** (oil, 0.0779 g, 0.31 mmol, 61%, R_f = 0.38, Hex/EtOAc = 5:5). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.39 (br, 1 H), 7.32−7.22 (m, 5 H), 6.00 (t, 1 H, J = 2.8 Hz), 5.85 (d, 1 H, J = 2.6 Hz), 3.90 (d, 1 H, J = 12.8 Hz), 3.48 (t, 1 H, J = 7.6 Hz), 3.11 (d, 1 H, J = 13.1 Hz), 3.04 (t, 1 H, J = 7.6 Hz), 2.64 (q, 2 H, J = 7.6 Hz), 2.28 (dd, 1 H, J = 17.7, 8.8 Hz), 2.18−2.12 (m, 1 H), 1.97−1.76 (m, 3 H), 1.29 (t, 3 H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.6, 134.3, 130.2, 129.2 (CH), 128.3 (CH), 127.1 (CH), 107.2 (CH), 103.7 (CH), 63.2 (CH), 57.9 (CH_2), 52.9 (CH_2), 32.7 (CH_2), 22.0 (CH_2), 21.1 (CH_2), 13.7 (CH_3); MS (ESI) m/z 148 (35), 255 (100) (M + 1); HRMS (ESI, TOF) Calcd for $C_{17}H_{23}N_2$ (M + H): 255.1861. Found 255.1845.

1-Benzyl-2-(3,5-dimethylpyrrol-2-yl)pyrrolidine ***(14da).*** Compound **14da** was prepared from 1-benzylproline (**2a**) and 2,4-dimethylpyrrole (**12d**) by *General procedures A and D*. The product was purified by flash column chromatography (Hex/EtOAc = 7:3) to give **14da** (oil, 0.0851 g, 0.34 mmol, 67%, R_f = 0.35, Hex/EtOAc = 5:5). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (s, 1 H), 7.35−7.24 (m, 5 H), 5.70 (d, 1 H, J = 2.4 Hz), 3.92 (d, 1 H, J = 13.1 Hz), 3.52 (t, 1 H, J = 8.1 Hz), 3.11 (d, 1 H, J = 13.0 Hz), 3.07 (d, 1 H, J = 7.6 Hz), 2.27 (s, 3 H), 2.21 (dd, 1 H, J = 17.7, 8.8 Hz), 2.15−2.12 (m, 1 H, CH_2), 2.08 (s, 3 H), 1.92−1.73 (m, 3 H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.6, 129.0 (CH), 128.3 (CH), 126.9 (CH), 126.5, 126.0, 116.0, 107.9 (CH), 60.8 (CH), 58.4 (CH_2), 53.3 (CH_2), 32.5 (CH_2), 22.4 (CH_2), 13.2 (CH_3), 10.8 (CH_3); MS (EI, 20 eV) m/z 91 (100), 121 (14), 135 (10), 146 (9), 175 (28), 254 (8) (M^+); HRMS (EI, magnetic sector) Calcd for $C_{17}H_{22}N_2$ (M^+): 254.1783. Found 254.1778.

1-Benzyl-2-(indol-3-yl)pyrrolidine[15,31] ***(15aa).*** Compound **15aa** was prepared from 1-benzylproline (**2a**) and indole (**13a**) by *General procedures A and D*. The product was purified by flash column chromatography (Hex/EtOAc = 7:3, R_f = 0.13) to give **15aa** (oil, 0.1299 g, 0.47 mmol, 94%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (bs, 1 H), 7.94 (d, 1 H, J = 7.8 Hz), 7.37 (d, 1 H, J = 8.0 Hz), 7.31−7.22 (m, 7 H), 7.20−7.16 (m, 1 H), 4.05 (d, 1 H, J = 13.0 Hz), 3.73 (t, 1 H, J = 8.3 Hz), 3.18−3.13 (m, 1 H), 3.10 (d, 1 H, J = 13.0 Hz), 2.30−2.20 (m, 2 H), 2.12−1.92 (m, 2 H), 1.89−1.80 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.1, 136.8, 128.8 (CH), 128.0 (CH), 126.7, 126.5 (CH), 121.97 (CH), 121.92 (CH), 120.1 (CH), 119.1 (CH), 118.1, 111.1 (CH), 62.3 (CH), 58.4 (CH_2), 53.4 (CH_2), 33.0 (CH_2), 22.2 (CH_2); MS (EI, 20 eV) m/z 120 (24), 157 (35), 276 (100) (M^+); HRMS (EI, magnetic sector) Calcd for $C_{19}H_{20}N_2$ (M^+): 276.1626. Found: 276.1624.

1-Benzyl-2-(1-methylindol-3-yl)pyrrolidine[15] ***(15ba).*** Compound **15ba** was prepared from 1-benzylproline (**2a**) and 1-methylindole (**13b**) by *General procedures A and D*. The product was purified by flash column chromatography (Hex/EtOAc = 8:2, R_f = 0.17) to give **15ba** (oil, 0.1394 g, 0.4505 mmol, 90%). ^{1}H NMR ($CDCl_3$, 500 MHz)

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δ 7.98 (d, 1 H, J = 7.9 Hz), 7.39−7.26 (m, 7 H), 7.23−7.20 (m, 1 H), 7.16 (s, 1 H), 4.11 (d, 1 H, J = 13.1 Hz), 3.82 (s, 3 H), 3.75 (t, 1 H, J = 8.3 Hz), 3.21−3.18 (m, 1 H), 3.13 (d, 1 H, J = 13.1 Hz), 2.32−2.23 (m, 2 H), 2.15−1.98 (m, 2 H), 1.92−1.85 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.1, 137.5, 128.7 (CH), 128.0 (CH), 127.1, 126.7 (CH), 126.4 (CH), 121.5 (CH), 120.2 (CH), 118.6 (CH), 116.4, 109.2 (CH), 62.2 (CH), 58.4 (CH_2), 53.4 (CH_2), 33.2 (CH_2), 32.6 (CH_3), 22.2 (CH_2); MS (ESI) *m*/*z* 291 (100) (M + 1).

1-Benzyl-2-(2-methylindol-3-yl)pyrrolidine[14,15] ***(15ca)***. Compound **15ca** was prepared from 1-benzylproline (**2a**) and 2-methylindole (**13c**) by *General procedures A and D*. The product was purified by flash column chromatography (Hex/EtOAc = 8.25:1.75) to give **15ca** (oil, 0.1143 g, 0.3694 mmol, 74%, R_f = 0.19 (Hex/EtOAc = 8:2)). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.02 (d, 1 H, J = 7.3 Hz), 7.73 (bs, 1 H), 7.31−7.27 (m, 5 H), 7.23−7.13 (m, 3 H), 3.94 (d, 1 H, J = 13.0 Hz), 3.63 (t, 1 H, J = 8.6 Hz), 3.17−3.13 (m, 1 H), 2.99 (d, 1 H, J = 13.0 Hz), 2.50 (s, 3 H), 2.21−1.96 (m, 4 H), 1.89−1.82 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.4, 135.5, 132.2, 128.7 (CH), 127.9 (CH), 127.7, 126.3 (CH), 120.8 (CH), 120.0 (CH), 118.9 (CH), 111.9, 110.0 (CH), 61.9 (CH), 58.2 (CH_2), 53.4 (CH_2), 31.4 (CH_2), 22.3 (CH_2), 12.0 (CH_3); MS (ESI) *m*/*z* 291 (100) (M + 1).

1-Methyl-2-(2-methylindol-3-yl)pyrrolidine[31] ***(15cb)***. Compound **15cb** was prepared from 1-methylproline (**2b**) and 2-methylindole (**13c**) by *General procedures B and D*. The product was purified by flash column chromatography ($CHCl_3$/MeOH = 8:2, R_f = 0.16) to give **15cb** (solid, 0.1777 g, 0.829 mmol, 83%). mp 170−172 °C (dec); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.40 (bs, 1 H), 7.75 (d, 1 H, J = 7.6 Hz), 7.25 (d, 1 H, J = 7.4 Hz), 7.11−7.03 (m, 2 H), 3.53 (t, 1 H, J = 8.4 Hz), 3.35−3.30 (m, 1 H), 2.39−2.35 (m, 1 H), 2.37 (s, 3 H), 2.32−2.25 (m, 1 H), 2.19 (s, 3 H), 2.16−2.07 (m, 2 H), 1.94−1.90 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.4, 133.2, 127.3, 120.7 (CH), 119.3 (CH), 119.0 (CH), 110.3 (CH), 109.6, 63.6, 56.8 (CH_2), 40.0, 30.6 (CH_2), 22.6 (CH_2), 11.8; MS (EI, 20 eV) *m*/*z* 157 (20), 171 (73), 185 (22), 199 (32), 214 (100) (M^+); HRMS (EI, magnetic sector) Calcd for $C_{14}H_{18}N_2$ (M^+): 214.1470. Found: 214.1467.

1-Benzyl-2-(2-phenylindol-3-yl)pyrrolidine ***(15da)***. Compound **15da** was prepared from 1-benzylproline (**2a**) and 2-phenylindole (**13d**) by *General procedures A and D*. The product was purified by flash column chromatography (Hex/EtOAc = 92:8, R_f = 0.19) to give **15da** (oil, 0.3383 g, 0.96 mmol, 96%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.26 (d, 1 H, J = 7.9 Hz), 8.01 (bs, 1 H), 7.59−7.58 (m, 2 H), 7.49 (t, 2 H, J = 7.9 Hz), 7.43−7.38 (m, 2 H), 7.24−7.21 (m, 1 H), 7.19−7.12 (m, 6 H), 3.88 (d, 1 H, J = 12.9 Hz), 3.75 (t, 1 H, J = 8.6 Hz), 3.10−3.06 (m, 1 H), 2.89 (d, 1 H, J = 12.9 Hz), 2.32−2.24 (m, 1 H), 2.18−2.11 (m, 1 H), 2.09−1.95 (m, 2 H), 1.85−1.78 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.1, 136.3, 136.2, 133.1, 128.8 (CH), 128.7 (CH), 128.5 (CH), 127.73 (CH), 127.66 (CH), 127.5, 126.3 (CH), 122.1 (CH), 121.9 (CH), 119.2 (CH), 113.5, 110.7 (CH), 61.7 (CH), 58.0 (CH_2), 53.2 (CH_2), 31.8 (CH_2), 22.4 (CH_2); MS (EI, 20 eV) *m*/*z* 233 (47), 261 (100), 262 (43), 309 (50), 352 (78) (M^+); HRMS (EI, magnetic sector) Calcd for $C_{25}H_{24}N_2$ (M^+): 352.1939. Found 352.1932.

1-Methyl-2-(2-phenylindol-3-yl)pyrrolidine ***(15db)***. Compound **15db** was prepared from 1-methylproline (**2b**) and 2-phenylindole (**13d**) by *General procedures B and D*. The product was purified by flash column chromatography (Hex/EtOAc = 8:2, R_f = 0.13) to give **15db** (solid, 0.1343 g, 0.671 mmol, 67%). mp 137 °C (dec); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (d, 1 H, J = 7.8 Hz), 8.03 (bs, 1 H), 7.54 (d, 2 H, J = 7.4 Hz), 7.46 (t, 2 H, J = 7.4 Hz), 7.41−7.37 (m, 1 H), 7.33−7.31 (m, 1 H), 7.20 (t, 1 H, J = 7.4 Hz), 7.15−7.11 (m, 1 H), 3.51 (t, 1 H, J = 8.4 Hz), 3.26 (t, 1 H, J = 8.2 Hz), 2.34−2.24 (m, 1 H), 2.22−2.05 (m, 3 H), 2.13 (s, 3 H), 1.96−1.80 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.3, 136.2, 133.2, 128.9 (CH), 128.5 (CH), 127.7 (CH), 127.4, 122.0 (CH), 121.5 (CH), 119.3 (CH), 113.3, 110.7 (CH), 63.5, 57.1 (CH_2), 40.5, 32.0 (CH_2), 22.7 (CH_2); MS (EI, 20 eV) *m*/*z* 198 (30), 233 (18), 247 (34), 261 (100), 276 (39) (M^+); HRMS (EI, magnetic sector) Calcd for $C_{19}H_{20}N_2$ (M^+): 276.1626. Found: 276.1623.

1-Benzyl-2-(5-methoxyindol-3-yl)pyrrolidine[15] ***(15ea)***. Compound **15ea** was prepared from 1-benzylproline (**2a**) and 5-methoxyindole (**13e**) by *General procedures A and D*. The product was purified by flash column chromatography (Hex/EtOAc = 6:4, R_f = 0.13) to give **15ea** (oil, 0.2910 g, 0.95 mmol, 95%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.03 (bs, 1 H), 7.39 (d, 1 H, J = 2.5 Hz), 7.31−7.27 (m, 5 H), 7.23−7.19 (m, 2 H), 6.89 (dd, 1 H, J = 2.5, 8.5 Hz), 4.03 (d, 1 H, J = 13.1 Hz), 3.91 (s, 3 H), 3.67 (t, 1 H, J = 8.2 Hz), 3.15−3.12 (m, 1 H), 3.07 (d, 1 H, J = 13.1 Hz), 2.25−2.17 (m, 2 H), 2.08−2.00 (m, 1 H), 1.99−1.90 (m, 1 H), 1.87−1.79 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.4, 139.9, 132.0, 128.7 (CH), 127.9 (CH), 126.9, 126.4 (CH), 123.0 (CH), 117.0, 111.9 (CH), 111.8 (CH), 102.0 (CH), 62.2, 58.2 (CH_2), 55.9, 53.2 (CH_2), 32.7 (CH_2), 22.0 (CH_2); MS (EI, 20 eV) *m*/*z* 120 (17), 173 (27), 187 (47), 306 (100) (M^+); HRMS (EI, magnetic sector) Calcd for $C_{20}H_{22}N_2O$ (M^+): 306.1732. Found 306.1739.

1-Methyl-2-(5-methoxyindol-3-yl)pyrrolidine[31] ***(15eb)***. Compound **15eb** was prepared from 1-methylproline (**2b**) and 5-methoxyindole (**13e**) by *General procedures B and D*. The product was purified by flash column chromatography ($CHCl_3$/MeOH = 8:2, R_f = 0.18) to give **15eb** (oil, 0.2181 g, 0.947 mmol, 94%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.12 (bs, 1 H), 7.24 (d, 1 H, J = 8.8 Hz), 7.18 (d, 1 H, J = 2.5 Hz), 7.14 (d, 1 H, J = 2.5 Hz), 6.85 (dd, 1 H, J = 2.5, 8.8 Hz), 3.86 (s, 3 H), 3.38 (t, 1 H, J = 8.2 Hz), 3.27−3.24 (m, 1 H), 2.32−2.29 (m, 1 H), 2.27 (s, 3 H), 2.24−2.19 (m, 1 H), 2.03−1.96 (m, 2 H), 1.88−1.83 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.8, 131.7, 127.5, 122.5 (CH), 117.2, 111.9 (CH), 111.8 (CH), 101.6 (CH), 63.5, 57.1, 56.0 (CH_2), 40.8, 33.1 (CH_2), 22.3 (CH_2); MS (EI, 20 eV) *m*/*z* 173 (45), 187 (57), 202 (31), 230 (100) (M^+); HRMS (EI, magnetic sector) Calcd for $C_{14}H_{18}N_2O$ (M^+): 230.1419. Found: 230.1415.

1-Benzyl-2-(5-bromoindol-3-yl)pyrrolidine[14,15] ***(15fa)***. Compound **15fa** was prepared from 1-benzylproline (**2a**) and 5-bromoindole (**13f**) by *General procedures A and D*. The product was purified by flash column chromatography (Hex/EtOAc = 6:4, R_f = 0.3) to give **15fa** (oil, 0.1214 g, 0.70 mmol, 70%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.16 (bs, 1 H), 8.06 (d, 1 H, J = 1.5 Hz), 7.29−7.26 (m, 4 H), 7.25−7.18 (m, 4 H), 3.95 (d, 1 H, J = 13.1 Hz), 3.62 (t, 1 H, J = 8.1 Hz), 3.13−3.09 (m, 1 H), 3.05 (d, 1 H, J = 13.1 Hz), 2.22−2.14 (m, 2 H), 2.02−1.89 (m, 2 H), 1.83−1.77 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.7, 135.4, 128.7 (CH), 128.3 (CH), 128.0, 126.6 (CH), 124.6 (CH), 123.3 (CH), 122.6 (CH), 117.5, 112.6 (CH), 112.3, 62.0 (CH), 58.3 (CH_2), 53.3 (CH_2), 33.0 (CH_2), 22.1 (CH_2); MS (EI, 20 eV) *m*/*z* 91 (71), 120 (63), 160 (51), 237 (34), 265 (33), 354 (84) (M^+), 356 (100) (M + 2); HRMS (EI, magnetic sector) Calcd for $C_{19}H_{19}BrN_2$ (M^+): 354.0732. Found 354.0735.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of all the synthesized compounds and X-ray structural data (CIF) of compound **14aa**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00836.

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Notes

The authors declare no competing financial interest.

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