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An Unconventional Redox Cross Claisen Condensation-Aromatization of 4-Hydroxyprolines with Ketones

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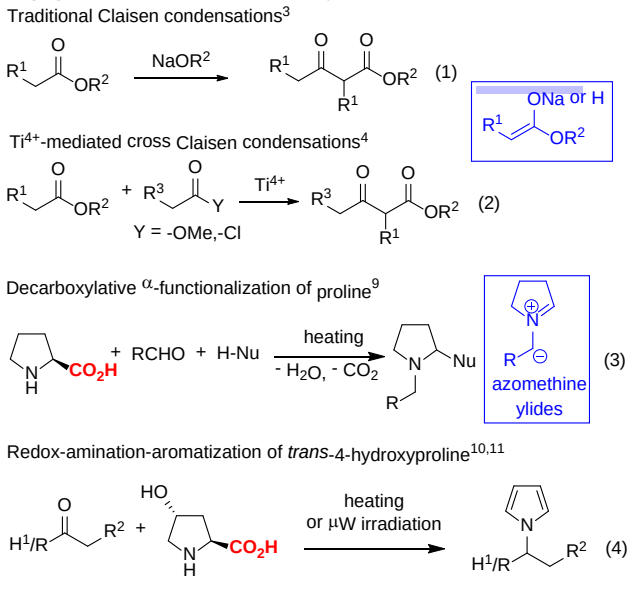
ABSTRACT: Reaction of α-amino acids particularly prolines and their derivatives with carbonyl compounds via decarboxylative redox process is a viable strategy for synthesis of structurally diverse nitrogen centered heterocyclics. In these processes, the decarboxylation is the essential driving force for the processes. The realization of the redox process without decarboxylation may offer an opportunity to explore new reactions. Herein, we report the discovery of an unprecedented redox Claisen type condensation aromatization cascade reaction of 4-substituted 4-hydroxyproline and its esters with unreactive ketones. We found that the use of propionic acid as a catalyst and a co-solvent can change the reaction course. The commonly observed redox decarboxylation and aldol condensation reactions are significantly minimized. Moreover, unreactive ketones can effectively participate in the Claisen condensation reaction. The new reactivity enables a redox cyclization via an unconventional Claisen-type condensation reaction of *in situ* formed enamine intermediates from ketone precursors with 4-substituted 4-hydroxyproline and its esters as electrophilic acylation partners. Under the reaction conditions, the cascade process proceeds highly regio- and stereoselectively to afford highly synthetically and biologically valued *cis*-2,3-dihydro-1*H*-pyrrolizin-1-ones with a broad substrate scope in efficient 'one-pot' operation, whereas such structures generally require multiple steps.

Introduction

Since its discovery in 1887, the Claisen condensation[1] has been established as a viable strategy for the construction of carbon–carbon bonds.[2] In a typical procedure, self-condensation of esters or cross-condensation of esters and carbonyl compounds is carried out in the presence of a strong base such as $NaOR^2$ to deliver 1,3-dicarbonyls (eq 1).[3] Alternative Lewis acids such as Ti(IV)-mediated cross Claisen condensations by esters and/or active acid chlorides were also reported (eq 2).[4] In these processes, formation of essential nucleophilic enolates or enols by a respective strong base or acid from corresponding ester precursors is required for effective transformations. On the other hand, enamines are considered to be the equivalent of enols and could potentially serve as alternative reactive species for the Claisen condensation reactions. However, to the best of our knowledge, such a process has not been reported despite extensive studies using amines as catalysts for aldol reactions.[5] Furthermore, more active esters and acid chlorides are generally used as electrophile for the Claisen condensation reactions. Nonetheless, employment of less reactive carboxylic acids remains a challenge because of less reactivity, serious aldol condensation side reactions, incompatibility with a base and inevitable decomposition of Lewis acid catalysts or side reactions under acidic conditions.[6]

Scheme 1. Conventional Claisen condensation and proline engaged decarboxylation reactions



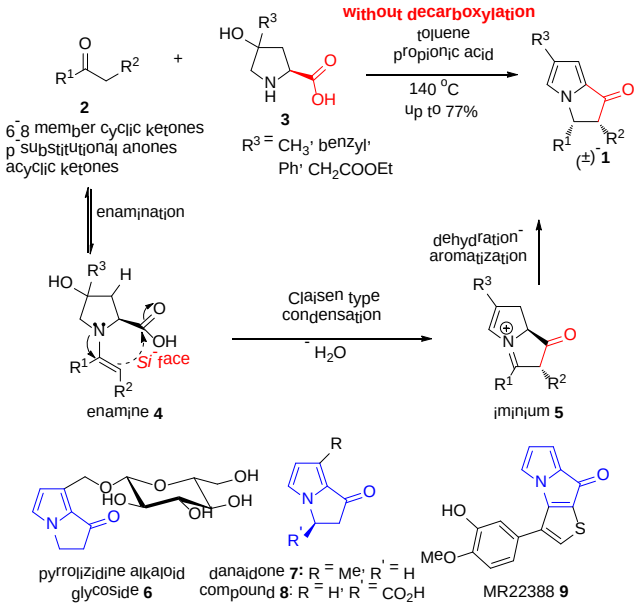
Decarboxylation reaction of α-amino acids particularly prolines and their derivatives with carbonyl compounds, also known as the Strecker degradation,[7] has been demonstrated as a viable strategy for synthesis of structurally diverse nitrogen heterocyclics.[8] Impressively, the strategy re-

cently has been explored in α-functionalization of amino acids (Scheme 1, Eq. 3).[9] Furthermore, the decarboxylative process has been implemented for the synthesis of *N*-alkyl pyrroles via a redox amination-aromatization sequence from *trans*-4-hydroxyproline and carbonyl compounds (Eq. 4).[10,11] Critically, the decarboxylation is the driving force for these essential redox reactions. It is therefore believed that the condensation of α-amino acids with carbonyls without decarboxylation is highly difficult, especially under the harsh reaction conditions (such as high temperature and microwave irradiation). Nonetheless, challenging the dogma may offer an opportunity to explore new reactions for distinct bond connections.

Herein, we wish to report an unconventional Claisen condensation reaction of 4-substituted 4-hydroxyprolines with ketones (Scheme 2). Combining the two classic Claisen condensation and the Strecker degradation reaction leads to an unpredecented Claisen condensation-aromatization cascade. We uncovered that the use of propionic acid as a catalyst and a co-solvent can change the reaction course. The commonly observed redox decarboxylation and aldol condensation reactions are significantly minimized. The reactivity enables *in situ* formed enamines from corresponding 4-substituted 4-hydroxyprolines and ketones as nucleophiles to undergo an unprecedented Claisen type condensation with the less reactive carboxylic acid. Furthermore, we observe an spontaneous aromatization takes place. The cascade process serves as a new efficient disconnection for complex molecule construction. Synthetically and biologically valued, complex molecular architecures *cis*-2,3-dihydro-1*H*-pyrrolizin-1-ones (**1**) are facilely assembled (Scheme 2).

The pyrrolizinone scaffold is featured in many natural products such as pyrrolizidine alkaloid glycoside (**6**),[12] danaidone (**7**),[13] compound (**8**) (Scheme 2).[14] Furthermore, it is also the 'privileged' structure of numerous synthetic substances with a broad spectrum of biological properties such as anti-tumor such as a FLT3-ITD kinase inhibitor MR22388 (**9**),[15,16] antipyretic,[17] anti-inflammatory and analgesic activities.[18] In addition, they are versatile synthetic building blocks for pyrrolizidine alkaloids[19] and serve as the models for the study of radical cyclization reaction.[20] Despite their important synthetic and biological values, limited methods are available for their synthesis. The general methods for their synthesis started from the pyrrole-containing substrates *via* multistep transformations.[20,21] Nag and Madapa recently disclosed a four-step synthesis of the pyrrolizinones scaffold starting with the Baylis-Hillman adducts.[22] The molecular architecture can also be accessed from thiolactams involving thioimidation, cycloaddition, oxidation and elimination 4-step transformations.[23]

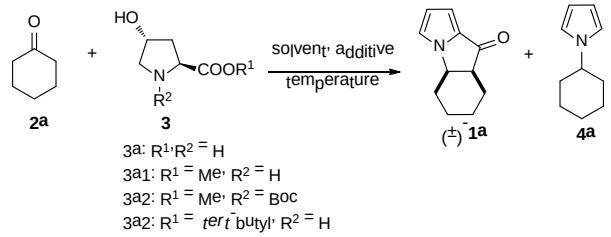
Scheme 2. An unconventional redox cross Claisen condensation-aromatization reaction of 4-hydroxyprolines with ketones serving as a new disconnection for efficient synthesis of 'privileged' pyrrolizinone scaffold.



Results and Discussion

Our initial investigation started with cyclohexanone **2a** and 4-hydroxyprolines (**3a**) in the presence of benzoic acid as a catalyst (0.5 equiv.) in toluene at 120 ºC (Table 1, entry 1). Unfortunately, the expected product **1a** was not detected. Instead, a significant amount of *N*-alkyl pyrrole **4a**, resulting from a decarboxylative-redox-amination-aromatization process was obtained.[10a-c,24] The same results were obtained by other acid additives (entries 1-3) and reaction media (entries 4-5). Increasing the amount of acid to 1.0 equiv. did not change the outcome (entry 6). However, when more acetic acid (AcOH: toluene= 1:4, AcOH as a co-solvent) was used in toluene, 32% of the desired product **1a** was obtained (entry 7). It is believed that the acid as a reaction co-solvent slows down the undesired decarboxylation while facilitating the Claisen type condensation reaction of the enamine with the carboxylate. It is noteworthy that the condensation of α-amino acids with carbonyl compounds without decarboxylation remains a major challenge.[25] To the best of our knowledge, such a process has not been reported. The yield could reach 42% with propionic acid (entry 8). The co-solvent has pronounced influence on the process (entries 8-11). Elevating reaction temperature and increasing the amount of propionic acid are beneficial to the cascade process (entries 12-14). Under the reaction conditions, we did not observe the self aldol condensation reaction. Incomplete conversion of ketone **2a** was observed. Therefore, an excess amount of amino acid **3a** was used to drive the complete conversion. When 4.0 equiv. of **3a** were employed, **2a** could react completely with the yield of 76% in the mixture of toluene and propionic acid (2 : 1, v/v) (entry 14). Notably, the process proceeded highly stereoselectively with the *cis* configuration. Microwave irradiation has limited influence on the reaction process (entry 15). Additionally, *N*-protected and ester derivatives of **3a** are equally effective with this protocol (entries 16-18).

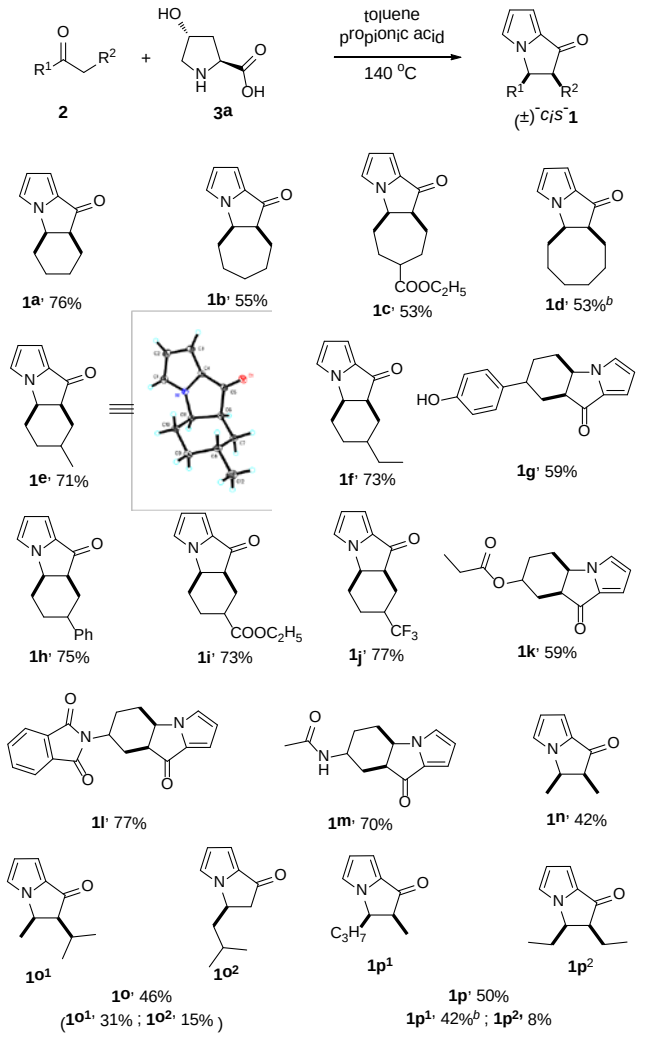
Table 1. Optimization of Reaction Conditions[a]



entry	solvent	additive	Temp (°C)	Time (h)	yield (%)[b]
1	toluene	$PhCO_2H$ (0.5 equiv.)	120	12	ND[c]
2	toluene	CH_3CO_2H (0.5 equiv.)	120	12	ND[c]
3	toluene	$EtCO_2H$ (0.5 equiv.)	120	12	ND[c]
4	DMF	$PhCO_2H$ (0.5 equiv.)	120	12	ND[c]
5	CH_3CN	$PhCO_2H$ (0.5 equiv.)	120	12	ND[c]
6	toluene	$MeCO_2H$ (1.0 equiv)	120	12	ND[c]
7	toluene	$MeCO_2H$ (0.5 mL)	120	12	32
8	toluene	$EtCO_2H$ (0.5 mL)	120	12	42
9	DMF	$EtCO_2H$ (0.5 mL)	120	12	ND[c]
10	DCE	$EtCO_2H$ (0.5 mL)	120	12	ND[c]
11	1,4-dioxane	$EtCO_2H$ (0.5 mL)	120	12	ND[c]
12	toluene	$EtCO_2H$ (0.5 mL)	130	12	52
13	toluene	$EtCO_2H$ (0.5 mL)	140	12	61
14	toluene	$EtCO_2H$ (1.0 mL)	140	12	76[d]
15	toluene	$EtCO_2H$ (1.0 mL)	140	2	70[e]
16	toluene	$EtCO_2H$ (1.0 mL)	140	12	54[f]
17	toluene	$EtCO_2H$ (1.0 mL)	140	12	56[g]
18	toluene	$EtCO_2H$ (1.0 mL)	140	12	69[h]

[a] Reaction conditions: unless otherwise specified, ketone **2a** (0.5 mmol), 4-hydroxyproline **3a** (2.0 mmol, 4.0 equiv), and solvent (2.0 mL), oil temperature. [b] Isolated yields. [c] ND: not detected. Decarboxylaion products observed. [d] 5 .0 equiv. of **3a** was used. [e] The reaction was carried out under μW irradiation. DMF: *N*,*N*-dimethylformamide. DCE: 1,2-dichloroethane. [f] Methyl 4-hydroxypyrrolidine-2-carboxylate used. [g] *N*-Boc-methyl 4-hydroxypyrrolidine-2-carboxylate used. [h] *tert*-butyl 4-hydroxypyrrolidine-2-carboxylate used.

Scheme 3. The Scope of Ketones.[a]



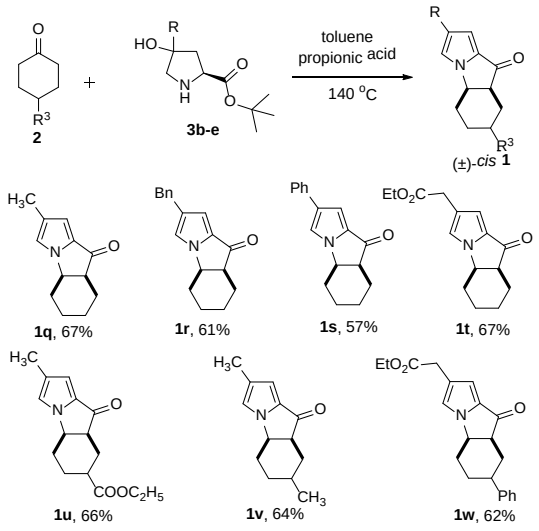
[a] Reactions were carried out using ketones (0.5 mmol, 1.0 equiv.) and *trans*-4-hydroxyproline (2 mmol, 4.0 equiv) or its ester in the mixture of toluene and propionic acid (2 : 1, toluene 2.0 mL) at 140 °C for 12 h. Isolated yield. [b] A small amount of diastereomer observed.

Having optimized conditions in hand, we examined the scope of the protocol with an assortment of substrates (Scheme 3). The one-pot cascade sequence of Claisen type condensation-aromatization proved to be a general approach to the structurally diverse *cis*-2,3-dihydro-1*H*-pyrrolizin-1-oneproducts (**1**). Significant structural variation of cyclic and acyclic ketones effectively engaged in the process (**1a-1p**). Various cyclic ketones ranging from 6

to 8 could be tolerated (**1a-1d**). Furthermore, the reaction conditions could accommodate a wide array of functionalities such as ester (**1c, 1i, 1k**), phenol (**1g**), imide (**1l**), and amide (**1m**). Besides cyclic ketones, acyclic ketones also worked well with the protocol (**1n-1p**). It is noted that in some cases (e.g., **1o** and **1p**), two regioisomers were produced. It appears that the reactions took place at more substituted site. It is understandable that under the thermodynamic reaction conditions, more substituted thermodynamically controlled products were formed favorably. The *cis* configuration of the products is determined by X-ray crystallography with **1e**.[26]

In addition to *trans*-4-hydroxyproline, a wide range of 4-substituted hydroxyprolines are compatible with this cascade transformation, giving an opportunity to synthesize substituted pyrroles (Scheme 4). For the sake of synthesis convenience, *t*-butyl esters of prolines were directly used (see Table 1, entry 18). The protocol is applicable to various 4-substituted hydroxyproline*t*-butyl esters including alkyl (methyl, benzyl), aryl (phenyl) and ester groups (**1q-1t**). Moreover, the combination of 4-substituted hydroxyproline esters and substituted cyclohexanones enabled to generate more structurally diverse *cis*-2,3-dihydro-1*H*-pyrrolizin-1-ones (**1u-1w**).

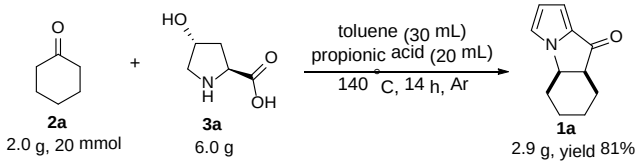
Scheme 4. The Scope of Amino Acids[a]



[a] Reactions were carried out using ketones (0.5 mmol, 1.0 equiv) and amino-acid ester (2 mmol, 4.0 equiv) in the mixture of toluene and propionic acid (2 : 1, toluene 2 mL) at 140 °C for 12 h. Isolated yield.

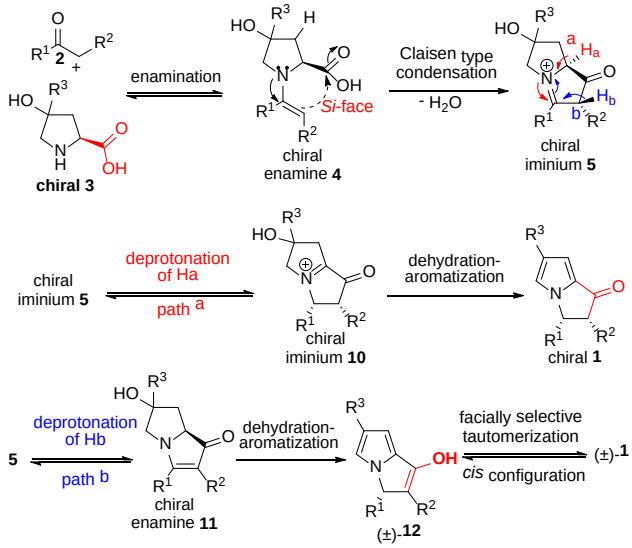
To further test the synthetic practicality of the reaction, gram-scale synthesis of 2,3-dihydro-1*H*-pyrrolizin-1-one (**1a**) were performed, and the desired products **1a** was obtained in 81% yield (Scheme 5).

Scheme 5. Gram Scale Synthesis



While a precise understanding of the reaction mechanism awaits further study, a plausible pathway is proposed in Scheme 6. The condensation of ketone **2** with 4-hydroxyproline or its derivatives **3** gives a more stable *trans*-enamine **4** under thermodynamic control. The intramolecular Claisen condensation occurs between the enamine and carboxylic acid/ester functionalities facilitated by propionic acid and critically a decarboxylation is suppressed. Although the enamine involved Claisen type condensation reaction with an acid has not been reported, precedent studies with relevant acid chlorides and activated ketone are well documented.[3,4] The stereoselective *Si* face attack from the less hindered side leads to *trans*-iminium ion **5**. Two possible pathways could be responsible for the formation of attended *cis*-2,3-dihydro-1*H*-pyrrolizin-1-ones (**1**). In path a, initial deprotonation of H_a followed by reprotonatoin leads to chiral *cis*-iminium ion **10**, which undergoes spontaneous dehydration and aromatization to deliver chiral product *cis*-**1**. A deprotonation of H_b could also occur to create a new chiral enamine **11**. The subsequent dehydration-aromatization gives achiral pyrrole **12**, which undergoes tautomerization to form racemic *cis*-**1.** The observed *cis*-stereochemistry can be rationalized by the protonation of the enol tautomer **12** precursor from the less hindered side, which has been demonstrated experimentally. The observed racemic products **1** suggest path b may be operative.

Scheme 6. Proposed Pathways.



Conclusion

In conclusion, in contrast to the widely studied typical Claisen condensations involving enols or enolates, we have developed an unconventional direct cross Claisen type condensation of 4-hydroxyproline or its derivatives with ketones via enamine intermediates. Propionic acid as co-solvent and promoter can effectively inhibit decarboxylation, which is often observed in the Strecker degradation and aldol condensation reaction. The preparative power of the process is demonstrated for one-

pot synthesis of synthetically and biologically important 2,3-dihydro-1*H*-pyrrolizin-1-one derivatives with broad substrate scopes. The process displays high stereoselectivity and good regioselectivity. The further study of the reaction mechanism, new organic transformations of the activation mode and the biological application of these compounds are under investigation.

Experimental Section

General Methods Commercial reagents were purchased from TCI, Acros, Accela and Adamas and used without further purification unless otherwise stated. Nuclear Magnetic Resonance (NMR) spectra were acquired on a Bruker Avance spectrometer, running at 400 MHz or 500 MHz for ^{1}H and 101 MHz or 126 MHz for ^{13}C, respectively, and chemical shifts are reported in parts permillion (ppm) downfield from TMS, using residual $CDCl_3$ or DMSO-d_6 as an internal standard. Chromatography was carried out with silica gel (300-400 mesh) using mixtures of petroleum ether (m.p. 60-90 °C) and ethyl acetate as eluents. Analytical thin layer chromatography was performed on glass-backed silica gel plates containing ultraviolet-active phosphor and the compounds were visualized either by UV illumination (254 nm), or by means of lime or ink powder. The steric configuration of products was detected on HPLC (Shimadzu LC-Lab Solutions). HRMS were carried out on GCT Premier mass spectrometer (OA- TOF Mass analyzer) or XEVO G2 TOF mass spectrometer.

General Procedures for Synthesis of Products 1

trans-4-Hydroxyproline or its ester as reactants:

Ketones (0.5 mmol, 1.0 equiv) and trans-4-hydroxyproline (2 mmol, 4.0 equiv) or its (*N*-Boc-protected) ester were placed in the mixture of toluene and propionic acid (2 : 1, toluene 2 mL) in a Schlenk-tube with a reflux condenser. The reaction vessel was evacuated and filled with Argon, and then placed into a pre-heated oil bath (140 °C) for 12 h. Upon completion of the reaction, the resulting mixture was allowed to cool to room temperature and neutralized with saturated sodium bicarbonate, and then extracted with ethyl acetate (20 mL × 3). The combined organics were dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel with petroleum/ethyl acetate as the eluent to give the corresponding product.

4-Substituted-4-hydroxyl-L-proline derivatives as reactants:

A 10 mL Schlenk-tube was charged with 4- substituted-4-hydroxyl- L-proline derivatives (**3b-e**) (2 mmol, 4.0 equiv), trifluoroacetic acid (1 mL) and dry dichloromethane (2.0 mL) and stirred for 0.5 h at room temperature. The crude mixture was dried under reduced pressure. Then this crude was charged with ketones (0.5 mmol, 1.0 equiv) and the mixture of toluene and propionic acid (2 : 1, toluene 2 mL). The reaction vessel was equipped with reflux condenser and exchanged with Argon, and then placed into a pre-heated oil bath (140 °C) for 12 h. Upon completion of the reaction, the resulting mixture was allowed to cool to room temperature and neutralized with saturated sodium bicarbonate, and then extracted with ethyl acetate (20 mL × 3). The combined organics were dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel with petroleum/ethyl acetate as the eluent to give the corresponding product.

Compound Characterization

*cis-6,7,8,8a-Tetrahydro-4aH-pyrrolo[1,2-a]indol-9(5H)-one (**1a**).* Petroleum/ethyl acetate (10:1) for column chromatography. Light yellow oil (66 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 – 7.00 (m, 1H), 6.70 (d, *J* = 3.9 Hz, 1H), 6.49 (dd, *J* = 3.9, 2.3 Hz, 1H), 4.59 (dd, *J* = 12.8, 7.0 Hz, 1H), 3.12 (dd, *J* = 11.9, 7.0 Hz, 1H), 2.24 – 2.04 (m, 2H), 1.86 – 1.73 (m, 1H), 1.53 (m, 2H), 1.48 – 1.31 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.9, 131.8, 121.7, 116.1, 107.5, 54.1, 50.2, 30.1, 22.5, 20.8, 19.5. HRMS (ESI) m/z calcd for $C_{11}H_{13}NO$ ($M+H^+$): 175.0997, found: 175.0995.

*cis-5,6,7,8,9,9a-Hexahydrocyclohepta[b]pyrrolizin-10(4H)-one (**1b**).* Petroleum/ethyl acetate (10:1) for column chromatography. Light yellow oil (52 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.71 (d, J = 3.9 Hz, 1H), 6.53 (dd, *J* = 3.6, 2.4 Hz, 1H), 4.69 (td, *J* = 8.7, 3.6 Hz, 1H), 3.34 – 3.19 (m, 1H), 2.18 (m, 1H), 2.13 – 1.82 (m, 3H), 1.70 (m, 2H), 1.46 (d, *J* = 9.8 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.05, 132.63, 121.24, 116.78, 107.11, 59.42, 55.76, 32.93, 30.80, 27.77, 27.63, 24.89. HRMS (ESI) m/z calcd for $C_{12}H_{15}NO$ ($M+H^+$): 190.1232, found: 190.1228.

*cis-Ethyl 10-oxo-4a,5,6,7,8,9,9a,10-octahydrocyclohepta[b]pyrrolizine-7-carboxylate (**1c**).* Petroleum/ethyl acetate (10:1) for column chroma-tography. Light yellow solid (69 mg, 53%), m.p. 67-71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (s, 1H), 6.72 (d, *J* = 3.8 Hz, 1H), 6.53 (d, *J* = 14.5 Hz, 1H), 4.71 – 4.61 (m, 1H), 4.19 – 4.10 (q, *J* = 7.1 Hz, 2H), 3.31 – 3.20 (m, 1H), 2.47 – 2.28 (m, 3H), 2.25 – 2.15 (m, 1H), 2.11 – 2.00 (m, 1H), 1.81 (m, 2H), 1.72 – 1.63 (m, 2H), 1.27 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.05, 175.14, 132.08, 121.40, 117.07, 107.56, 60.55, 59.34, 55.81, 46.90, 30.78, 30.60, 27.69, 25.49, 14.22. HRMS (ESI) m/z calcd for $C_{15}H_{19}NO_3$ ($M+H^+$): 262.1443, found: 262.1439.

*cis-6,7,8,9,10,10a-Hexahydro-4aH-cycloocta[b]pyrrolizin-11(5H)-one (**1d**).* Petroleum/ethyl acetate (10:1) for column chromatography. Light yellow oil (53 mg, 53%, mixture of diastereomers). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 7.8 Hz, 1H), 6.69 (d, *J* = 3.6 Hz, 1H), 6.54 – 6.50 (m, 1H), 4.38 – 4.28 (m, 1H), 2.99 – 2.87 (m, 1H), 2.49 (m, 1H), 2.40 – 2.25 (m, 1H), 1.92 – 1.82 (m, 3H), 1.68 (m, 2H), 1.61 – 1.39 (m, 5H). ^{13}C NMR (101 MHz, CDCl3) δ 191.7, 131.8, 120.9, 116.6, 107.3, 60.7, 56.5, 35.7, 30.0, 27.2, 26.8, 23.6 (2C). HRMS (ESI) m/z calcd for $C_{13}H_{17}NO$ ($M+H^+$): 204.1388, found: 204.1385.

*cis-7-methyl-6,7,8,8a-tetrahydro-4aH-pyrrolo[1,2-a]indol-9(5H)-one (**1e**).* Petroleum/ethyl acetate (10:1) for column chromatography. Colorless solid (67 mg, 71%), m.p. 58-61 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (d, *J* = 1.4 Hz, 1H), 6.58 (d, *J* = 3.9 Hz, 1H), 6.37 (dd, *J* = 3.8, 2.3 Hz, 1H), 4.48 (dd, *J* = 15.2, 6.8 Hz, 1H), 3.10 (td, *J* = 6.9, 2.2 Hz, 1H), 2.27 (dd, *J* = 18.2, 6.1 Hz, 1H), 2.23 – 2.10 (m, 1H), 1.40 (M, 1H), 1.33 – 1.07 (m, 3H), 0.99 – 0.86 (m, 1H), 0.84 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.9, 131.9, 121.1, 116.0, 108.2, 53.3, 50.6, 33.0, 28.6, 27.95, 26.5, 22.34. HRMS (ESI) m/z calcd for $C_{12}H_{15}NO$ ($M+H^+$): 190.1232, found: 190.1225.

*cis-7-Ethyl-6,7,8,8a-tetrahydro-4aH-pyrrolo[1,2-a]indol-9(5H)-one (**1f**).* Petroleum/ethyl acetate (10:1) for column chromatography. Colorless solid (74 mg, 73%), m.p. 61-67 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 1.3 Hz, 1H), 6.70 (d, *J* = 3.9 Hz, 1H), 6.48 (dd, *J* = 3.9, 2.3 Hz, 1H), 4.59 (dd, *J* = 13.9, 7.5 Hz, 1H), 3.21 (td, *J* = 7.0, 2.6 Hz, 1H), 2.38 (d, *J* = 13.8 Hz, 1H), 2.25 (m, 1H), 1.61 – 1.48 (m, 1H), 1.40 – 1.15 (m, 5H), 1.08 – 0.96 (m, 1H), 0.88 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 191.6, 131.6, 121.9, 116.0, 107.4, 54.4, 50.5, 34.0, 31.3, 29.6, 28.5, 26.5, 11.3. HRMS (EI) m/z calcd for $C_{13}H_{17}NO$ (M^+): 203.1310, found: 203.1311.

*cis-7-(4-Hydroxyphenyl)-6,7,8,8a-tetrahydro-4aH-pyrrolo[1,2-a]indol-9(5H)-one (**1g**).* Petroleum/ethyl acetate (2:1) for column chromatography. Off-white solid (79 mg, 59%), m.p. 128-131°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (s, 1H), 7.40 (s, 1H), 7.01 (d, *J* = 8.2 Hz, 2H), 6.69 (d, *J* = 8.2 Hz, 2H), 6.63 (d, *J* = 3.7 Hz, 1H), 6.49 (d, *J* = 1.3 Hz, 1H), 4.76 (dd, *J* = 15.0, 7.1 Hz, 1H), 3.37 (m, 1H), 2.42 (m, 1H), 2.31 – 2.18 (m, 2H), 1.74 (m, 1H), 1.49 (m, 2H), 1.20 – 1.12 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 195.8, 160.8, 141.9, 135.9, 132.6 (2C), 128.5, 120.8, 120.3 (2C), 111.9, 58.5, 55.7, 43.5, 37.9, 35.5, 34.0. HRMS (ESI) m/z calcd for $C_{17}H_{17}NO_2$ ($M+H^+$): 268.1338, found: 268.1334.

*cis-7-Phenyl-6,7,8,8a-tetrahydro-4aH-pyrrolo[1,2-a]indol-9(5H)-one, (**1h**).* Petroleum/ethyl acetate (10:1) for column chromatography. Colorless solid (94 mg, 75%), m.p. 98-102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 7.23 – 7.16 (m, 3H), 7.06 (d, *J* = 1.3 Hz, 1H), 6.74 (d, *J* = 3.7 Hz, 1H), 6.50 (dd, *J* = 3.8, 2.3 Hz, 1H), 4.66 (dd, *J* = 15.3, 6.9 Hz, 1H), 3.31 (td, *J* = 7.0, 1.5 Hz, 1H), 2.66 – 2.59 (m, 1H), 2.53 – 2.47 (m, 1H), 2.45 – 2.38 (m, 1H), 1.84 – 1.69 (m, 2H), 1.64 – 1.54 (m, 1H), 1.44 – 1.33 (m, 1H). ^{13}C NMR (101 MHz, CDCl3) δ 190.9, 146.2, 131.4, 128.5 (2C), 126.8 (2C), 126.4, 122.2, 116.2, 107.7, 53.9, 51.0, 39.2, 32.8, 30.5, 28.4. HRMS (ESI) m/z calcd for $C_{17}H_{17}NO$ ($M+H^+$): 252.1388, found: 252.1382.

*cis-Ethyl 9-oxo-5,6,7,8,8a,9-hexahydro-4aH-pyrrolo[1,2-a]indole-7-carboxylate (**1i**).* Petroleum/ethyl acetate (7:1) for column chromatography. Light yellow oil (90 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J* = 1.2 Hz, 1H), 6.72 – 6.67 (m, 1H), 6.50 (dd, *J* = 3.9, 2.3 Hz, 1H), 4.68 (dd, *J* = 13.0, 7.2 Hz, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.27 (m, 1H), 2.52 – 2.44 (m, 1H), 2.42 – 2.33 (m, 1H), 2.32 – 2.23 (m, 1H), 1.92 (m, 1H), 1.64 (dt, *J* = 12.1, 4.5 Hz, 2H), 1.53 – 1.42 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.5, 175.2, 131.6, 122.0, 116.5, 107.8, 60.6, 53.5, 49.1, 37.1, 29.3, 24.2, 22.1, 14.2. HRMS (ESI) m/z calcd for$C_{14}H_{17}NO_3$ ($M+H^+$): 248.1287, found: 248.1284.

*cis-7-(Trifluoromethyl)-6,7,8,8a-tetrahydro-4aH-pyrrolo[1,2-a]indol-9(5H)-one (**1j**).* Petroleum/ethyl acetate (10:1) for column chromatography. Light yellow oil (93 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (s, 1H), 6.74 (d, *J* = 3.9 Hz, 1H), 6.56 – 6.47 (m, 1H), 4.73 (dd, *J* = 12.8, 6.0 Hz, 1H), 3.37 – 3.25 (m, 1H), 2.50 (m, 1H), 2.31 – 2.11 (m, 2H), 1.86 – 1.71 (m, 1H), 1.63 – 1.43 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.8, 131.7, 127.7 (q, *J* = 278.6 Hz, CF_3), 122.2, 117.0, 108.0, 53.3, 48.3, 35.7 (q, *J* = 27.1 Hz), 28.5, 20.3 (d, J = 2.9 Hz), 18.0 (d, J = 2.5 Hz). HRMS (ESI) m/z calcd for $C_{12}H_{12}F_3NO$ ($M+H^+$): 244.0949, found: 244.0943.

*cis-9-Oxo-5,6,7,8,8a,9-hexahydro-4aH-pyrrolo[1,2-a]indol-7-yl propionate (**1k**).* Petroleum/ethyl acetate (10:1) for column chromatography. Light yellow oil (72 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (t, *J* = 6.6 Hz, 1H), 6.74 (dd, *J* = 3.9, 0.8 Hz, 1H), 6.52 (dd, *J* = 3.9, 2.3 Hz, 1H), 4.92 (m, 1H), 4.64 (m, 1H), 3.30 (q, *J* = 6.9 Hz, 1H), 2.35 – 2.28 (m, 3H), 2.27 – 2.22 (m, 1H), 2.01 (m, 1H), 1.90 – 1.77 (m, 1H), 1.69 – 1.60 (m, 1H), 1.51 (m, 1H), 1.14 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.7, 173.6, 131.6, 121.8, 116.7, 108.1, 67.7, 53.2, 48.0, 27.8, 27.6, 26.7, 25.8, 9.1. HRMS (ESI) m/z calcd for $C_{14}H_{17}NO_3$ ($M+H^+$): 248.1287, found: 248.1287.

*2-(cis-9-Oxo-5,6,7,8,8a,9-hexahydro-4aH-pyrrolo[1,2-a]indol-7-yl)isoindoline-1,3-dione (**1l**).* Petroleum/CH_2Cl_2/ethyl acetate (6:3:1) for column chromatography. Light yellow solid (123 mg, 77%), m.p. 202-208 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dt, *J* = 7.0, 3.5 Hz, 2H), 7.65 – 7.60 (m, 2H), 7.00 (d, *J* = 1.2 Hz, 1H), 6.65 (d, *J* = 3.7 Hz, 1H), 6.44 (dd, J = 3.9, 2.2 Hz, 1H), 4.71 (dd, *J* = 12.9, 7.0 Hz, 1H), 4.20 – 4.07 (m, 1H), 3.34 (m, 1H), 2.59 – 2.42 (m, 2H), 2.37 – 2.25 (m, 1H), 2.03 – 1.90 (m, 1H), 1.60 – 1.41 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.0, 168.0 (2C), 134.0 (2C), 131.8 (2C), 131.6, 123.2 (2C), 122.2, 116.7, 107.9, 53.2, 49.8, 44.4, 30.1, 24.7, 24.1. HRMS (ESI) m/z calcd for $C_{19}H_{16}N_2O_3$ ($M+H^+$): 321.1239, found: 321.1237.

*N-(cis-9-Oxo-5,6,7,8,8a,9-hexahydro-4aH-pyrrolo[1,2-a]indol-7-yl)acetamide (**1m**).* CH_2Cl_2/CH_3OH (10:1) for column chromatography. Light yellow solid (81 mg, 70%), m.p. 202-205 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 7.21 (s, 1H), 6.70 (d, *J* = 3.9 Hz, 1H), 6.58 – 6.48 (m, 1H), 4.71 (dd, *J* = 13.7, 7.0 Hz, 1H), 3.67 (m, 1H), 3.36 (m, 1H), 2.48 – 2.30 (m, 2H), 1.94 (s, 3H), 1.73 (m, 2H), 1.47 – 1.34 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 193.0, 172.5, 132.3, 124.6, 117.9, 109.4, 54.8, 51.1, 45.3, 30.8, 29.0, 28.2, 23.2. HRMS (ESI) m/z calcd for $C_{13}H_{16}N_2O_2$ ($M+H^+$): 233.1290, found: 233.1285.

*cis-2,3-Dimethyl-2,3-dihydro-1H-pyrrolizin-1-one (**1n**).* Petroleum/ethyl acetate (10:1) for column chromatography. Light yellow oil (31 mg, 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 1.3 Hz, 1H), 6.71 (d, *J* = 3.9 Hz, 1H), 6.52 (dd, *J* = 3.9, 2.3 Hz, 1H), 4.17 – 4.06 (m, 1H), 2.69 (qd, *J* = 7.4, 4.8 Hz, 1H), 1.62 (d, *J* = 6.5 Hz, 3H), 1.35 (d, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 191.9, 132.1, 120.9, 116.7, 107.7, 58.2,

53.9, 20.3, 14.1. HRMS (ESI) m/z calcd for $C_9H_{11}NO$ ($M+H^+$): 150.0919, found: 150.0914.

*cis-2-Isopropyl-3-methyl-2,3-dihydro-1H-pyrrolizin-1-one (**1o¹**).* Petroleum/ethyl acetate (10:1) for column chromatography. Light yellow oil (27 mg, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 1.3 Hz, 1H), 6.68 (dd, *J* = 4.0, 0.9 Hz, 1H), 6.51 (dd, *J* = 3.9, 2.3 Hz, 1H), 4.36 (qd, *J* = 6.5, 3.8 Hz, 1H), 2.62 (t, *J* = 3.9 Hz, 1H), 2.48 – 2.37 (m, 1H), 1.57 (d, *J* = 6.5 Hz, 3H), 1.08 – 1.06 (m, 3H), 0.89 (d, *J* = 6.8 Hz, 3H). 13C NMR (101 MHz, $CDCl_3$) δ 191.4, 133.0, 121.1, 116.7, 107.3, 64.7, 52.2, 28.9, 22.8, 20.7, 17.7. HRMS (ESI) m/z calcd for $C_{11}H_{15}NO$ ($M+H^+$): 177.1154, found: 177.1154.

*cis-2-Methyl-3-propyl-2,3-dihydro-1H-pyrrolizin-1-one (**1p¹**).* Petroleum/ethyl acetate (10:1) for column chromatography. Light yellow oil (37 mg, 42%, mixture of diastereomers). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 1.4 Hz, 1H), 6.75 – 6.67 (m, 1H), 6.54 – 6.49 (m, 1H), 4.26 – 4.03 (m, 1H), 2.82 – 2.66 (m, 1H), 2.08 – 1.86 (m, 2H), 1.83 – 1.71 (m, 1H), 1.57 – 1.43 (m, 1H), 1.37 (d, *J* = 7.4 Hz, 3H), 1.01 (t, *J* = 8.4, 3H). 13C NMR (101 MHz, $CDCl_3$) δ 192.2, 132.1, 121.5, 116.7, 107.5, 62.4, 51.7, 37.7, 18.5, 15.7, 14.0. HRMS (ESI) m/z calcd for $C_{11}H_{15}NO$ ($M+H^+$): 178.1232, found: 178.1128.

*cis-3-Methyl-2-propyl-2,3-dihydro-1H-pyrrolizin-1-one (**1p²**).* Petroleum/ethyl acetate (10:1) for column chromatography. Light yellow oil (7 mg, 8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, *J* = 1.2 Hz, 1H), 6.62 (d, *J* = 3.9 Hz, 1H), 6.44 (dd, *J* = 3.9, 2.3 Hz, 1H), 4.17 (m, 1H), 2.57 (m, 1H), 1.85 (m, 1H), 1.58 – 1.47 (m, 4H), 1.44 – 1.33 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H). 13C NMR (101 MHz, CDCl3) δ 191.7, 132.3, 121.0, 116.8, 107.5, 58.9, 56.5, 32.6, 21.8, 20.5, 14.1. HRMS (ESI) m/z calcd for $C_{11}H_{15}NO$ ($M+H^+$): 178.1232, found: 178.1230.

*cis-2-Methyl-6,7,8,8a-tetrahydro-4aH-pyrrolo[1,2-a]indol-9(5H)-one (**1q**).* Petroleum/ethyl acetate (10:1) for column chromatography. Light yellow oil (63 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 1H), 6.52 (s, 1H), 4.53 (dd, *J* = 12.8, 6.8 Hz, 1H), 3.08 (dd, *J* = 12.0, 6.7 Hz, 1H), 2.17 (s, 3H), 2.15 – 2.03 (m, 2H), 1.87 – 1.69 (m, 2H), 1.59 – 1.48 (m, 2H), 1.44 – 1.38 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.8, 131.5, 127.4, 120.8,107.9, 54.1, 49.7, 29.9, 22.6, 20.7, 19.4, 12.5. HRMS (ESI) m/z calcd for $C_{12}H_{15}NO$ ($M+H^+$): 190.1232, found: 190.1229.

*cis-2-Benzyl-6,7,8,8a-tetrahydro-4aH-pyrrolo[1,2-a]indol-9(5H)-one (**1r**).* Petroleum/ethyl acetate (10:1) for column chromatography. Light yellow solid (81 mg, 81%), m.p. 92-98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 2H), 7.19 (m, 3H), 6.78 (s, 1H), 6.53 (s, 1H), 4.48 (dd, *J* = 12.9, 6.7 Hz, 1H), 3.86 (s, 2H), 3.03 (dd, *J* = 12.1, 6.6 Hz, 1H), 2.13 – 2.01 (m, 2H), 1.82 – 1.69 (m, 1H), 1.55 – 1.43 (m, 2H), 1.41 – 1.30 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.9, 141.1, 131.6, 131.5, 128.6(2C), 128.4(2C), 126.0, 120.6, 107.3, 54.1, 49.7, 33.8, 29.9, 22.5, 20.7, 19.4. HRMS (ESI) m/z calcd for $C_{18}H_{19}NO$ ($M+H^+$): 266.1545. found: 266.1542.

*cis-2-Phenyl-6,7,8,8a-tetrahydro-4aH-pyrrolo[1,2-a]indol-9(5H)-one (**1s**).* Petroleum/ethyl acetate (10:1) for column chromatography. Light yellow solid (71 mg, 57%), m.p. 108-111 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.31 (s, 1H), 7.23 (dd, *J* = 13.5, 6.2 Hz, 1H), 6.97 (s, 1H), 4.58 (dd, *J* = 13.0, 6.7 Hz, 1H), 3.10 (dd, *J* = 12.0, 6.6 Hz, 1H), 2.28 – 2.03 (m, 2H), 1.87 – 1.70 (m, 1H), 1.63 – 1.49 (m, 2H), 1.47 – 1.31 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.2, 134.7, 132.5, 132.4, 128.9 (2C), 126.6, 125.4 (2C), 118.8, 104.3, 54.5, 49.9, 30.1, 22.6, 20.8, 19.6. HRMS (ESI) m/z calcd for $C_{17}H_{17}NO$ ($M+H^+$): 252.1388, found: 252.1385.

*Ethyl 2-(cis-9-oxo-5,6,7,8,8a,9-hexahydro-4aH-pyrrolo[1,2-a]indol-2-yl)acetate (**1t**).* Petroleum/ethyl acetate (10:1) for column chromatography. Light yellow oil (87 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 1H), 6.63 (s, 1H), 4.56 (dd, *J* = 12.9, 6.9 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.54 (s, 2H), 3.08 (dd, *J* = 12.0, 6.8 Hz, 1H), 2.18-2.06 (m, 2H), 1.82-1.76 (m, 1H), 1.56-1.49 (m, 2H), 1.45-1.33 (m, 3H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.9, 171.7, 131.5, 123.6, 121.1, 107.8, 60.9, 54.3, 49.8, 33.4, 30.0, 22.5, 20.8, 19.5, 14.2. HRMS (ESI) m/z calcd for $C_{15}H_{19}NO_3$ ($M+H^+$): 262.1443, found: 262.1440.

*cis-Ethyl 2-methyl-9-oxo-5,6,7,8,8a,9-hexahydro-4aH-pyrrolo[1,2-a]indole-7-carboxylate (**1u**).* Petroleum/ethyl acetate (10:1) for column chromatography. White solid (86 mg, 66%), m.p. 82-87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 1H), 6.53 (s, 1H), 4.60 (dd, *J* = 12.9, 6.8 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.23 (m, 1H), 2.43 (m, 2H), 2.23 (m, 1H), 2.17 (s, 3H), 1.91 (m, 1H), 1.63 (m, 2H), 1.54 – 1.43 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.2, 175.4, 131.3, 127.8, 121.2, 108.1, 60.6, 53.4, 48.6, 37.0, 29.1, 24.2, 21.9, 14.2, 12.4. HRMS (ESI) m/z calcd for $C_{15}H_{19}NO_3$ ($M+H^+$): 262.1443, found: 262.1439.

*cis-2,7-Dimethyl-6,7,8,8a-tetrahydro-4aH-pyrrolo[1,2-a]indol-9(5H)-one (**1v**).* Petroleum/ethyl acetate (10:1) for column chromatography. White solid (65 mg, 64%), 66-71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.50 (s, 1H), 4.50 (dd, *J* = 14.5, 7.0 Hz, 1H), 3.20 – 3.13 (m, 1H), 2.35 (d, *J* = 13.5 Hz, 1H), 2.23 (m, 1H), 2.16 (s, 3H), 1.55 – 1.46 (m, 1H), 1.45 – 1.36 (m, 1H), 1.35 – 1.24 (m, 3H), 0.93 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.2, 131.1, 127.2, 121.1, 107.8, 54.0, 50.2, 31.7, 30.8, 29.2, 27.6, 22.3, 12.4. HRMS (ESI) m/z calcd for $C_{13}H_{17}NO$ ($M+H^+$): 204.1388, found: 204.1383.

Ethyl 2-(cis-9-oxo-7-phenyl-5,6,7,8,8a,9-hexahydro-4aH-pyrrolo[1,2-a]indol-2-yl)acetate (1w). Petroleum/ethyl acetate (7:1) for column chromatography. White solid (104 mg, 62%), m.p 114-120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 2H), 7.21 – 7.17 (m, 3H), 7.08 (s, 1H), 6.66 (s, 1H), 4.65 (dd, *J* = 15.0, 7.0 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.55 (s, 2H), 3.31-3.27 (m, 1H), 2.64 – 2.59 (m, 1H), 2.56 – 2.39 (m, 2H), 1.84-1.73 (m, 2H), 1.64-1.55 (m, 1H), 1.46-1.37 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.7, 171.6, 146.1, 131.0, 128.5 (2C), 126.7 (2C), 126.3, 123.7, 121.5, 107.9, 60.9, 54.0, 50.5, 39.1, 33.4, 32.6, 30.4, 28.2, 14.2. HRMS (ESI) m/z calcd for $C_{21}H_{23}NO_3$ ($M+H^+$): 338.1756, found: 338.1751.

ASSOCIATED CONTENT

Supporting Information

Spectroscopic characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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REFERENCES

(1) Claisen, L. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 655-657.

(2) For reviews about biological Claisen condensation reactions, see: Heath, R. J.; Rock, C. O. *Nat. Prod. Rep*. **2002**, *19*, 581-596.

(3) Smith, M. B.; March, J., March's advanced organic chemistry: reactions, mechanisms, and structure (5th ed.). John Wiley & Sons, 2007, p 279.

(4) Selected examples of Tanabe's pioneering work on cross-Claisen condensation, see: (a) Tanabe, Y. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1917-1924. (b) Yoshida, Y.; Hayashi, R.; Sumihara, H.; Tanabe, Y. *Tetrahedron Lett.* **1997**, *38*, 8727-8730. (c) Tanabe, Y.; Makita, A.; Funakoshi, S.; Hamasaki, R.; Kawakusu, T. *Adv. Synth. Catal.* **2002**, *344*, 507-510. (d) Misaki, T.; Nagase, R.; Matsumoto, K.; Tanabe, Y. *J. Am. Chem. Soc.* **2005**, *127, 2854-2855.* (e) Nakatsuji, H.; Nishikado, H.; Ueno, K.; Tanabe, Y. *Org. Lett.* **2009**, *11*, 4258-4261. (f) Nagase, R.; Oguni, Y.; Ureshino, S.; Mura, H.; Misaki, T.; Tanabe, Y. *Chem. Commun.* **2013**, *49*, 7001-7003.

(5) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471-5569.

(6) Nishimoto, Y.; Okita, A.; Yasuda, M.; Baba, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8623-8625.

(7) (a) Strecker, A. *Liebigs Ann. Chem.* **1862**, *123*, 363-365.

(8) For a recent review about the Strecker degradation, see: Wang, Y.; Ho, C.-T. *Chem. Soc. Rev.* **2012**, *41*, 4140-4149.

(9) For reviews of redox amine α-functionalizations: (a) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed*. **2009**, *48*, 2854-2867. (b) Peng, B.; Maulide, N. *Chem. Eur. J.* **2013**, *19,* 13274-13287. (c) Haibach, M. C.; Siedel, D. *Angew. Chem., Int. Ed*. **2014**, *53*, 5010-5036.

(10) For synthesis of *N*-alkylpyrroles from aldehydes, see: (a) Deb, I.; Coiro, D. J.; Seidel, D. *Chem*. *Commun*. **2011**, *47*, 6473-6475. (b) Kumar, A. V.; Rao, K. R. *Tetrahedron Lett*. **2011**, *52*, 3237-3239. Studies from our laboratories, see: (c) Zou, Z.-Q.; Deng, Z.-J.; Yu, X.-H.; Zhang, M.-M.; Zhao, S.-H.; Luo, T.; Yin, X.; Xu, H.; Wang, W. *Sci*. *China-Chem*. **2012**, *55*, 43-49. (d) Wu, S.-C.; Liu, N.; Dong, G.-Q.; Ma, L.; Wang, S.-Z.; Shi, W.-C.; Fang, K.; Chen, S.-Q.; Li, J.; Zhang, W.-N.; Sheng, C.-Q.; Wang, W. *Chem. Commun.* **2016**, *52*, 9593-9596.

(11) For synthesis of *N*-alkylpyrroles from activated α-carbonyl ketones, see: (a) Aly, M. F.; Ardill, H.; Grigg, R.; Leongling, S.; Rajviroongi, S.; Surendrakumar, S. *Tetrahedron Lett*. **1987**, *28*, 6077-6080. (b) Azizian, J.; Karimi, A. R.; Kazemizadeh, Z.; Mohammadi, A. A.; Mohammadizadeh, M. R. *J. Org. Chem*. **2005**, *70*, 1471-1473. (c) Yadav, J. S.; Reddy, B. V. S.; Jain, R.; Reddy, C. S. *Tetrahedron Lett*. **2007**, *48*, 3295-3298. (d) Sridhar, R.; Srinivas, B.; Kumar, V. P.; Reddy, V. P.; Kumar, A. V.; Rao, K. R. *Adv. Synth. Catal*. **2008**, *350*, 1489. (e) Karimi, A. R.; Behzadi, F.; Amini, M. M. *Tetrahedron Lett*. **2008**, *49*, 5393-5396. (f) Kumar, M. A.Krishna, A. B.; Babu, B. H.; Reddy, C. B.; Reddy, C. S. *Synth. Commun*. **2008**, *38*, 3456-3464. (g) Meshram, H. M.; Prasad, B. R. V.; Kumar, D. A. *Tetrahedron Lett*. **2010**, *51*, 3477-3480.

(12) Liu, C.-M.; Wang, H.-X.; Wei, S.-L.; Gao, K. *Helv. Chim. Acta.* **2008**, *91*, 308-316.

(13) Schulz, S.; Beccaloni, G.; Brown, K. S., Jr.; Boppré, M.; Freitas, A. V. L.; Ockenfels, P.; Trigo, J. R. *Biochem. Syst. Ecol.* **2004**, *32*, 699-713.

(14) Box, S. J.; Corbett, D. F. *Tetrahedron Lett.* **1981**, *22*, 3293-3296.

(15) Lisowski, V.; Léonce, S.; Kraus-Berthier, L.; Sopkova-de Oliveira Santos, J.; Pierré, A.; Atassi, G.; Caignard, D. H.; Renard, P.; Rault, S. *J. Med. Chem.* **2004**, *47*, 1448-1464.

(16) (a) Jourdan, J.-P.; Rochais, C.; Legay, R.; Sopkova de Oliveira Santos, J.; Dallemagne, P. *Tetrahedron Lett.* **2013**, *54*, 1133-1136. (b) Sechi, M.; Derudas, M.; Dallocchio, R.; Dessì, A.; Cosseddu, A.; Paglietti, G. *Lett. Drug Des. Discov.* **2009**, *6*, 56-62. (c) Grande, F.; Yamada, R.; Cao, X.; Aiello, F.; Garofalo, A.; Neamati, N. *Expert Opin. Inv. Drug.* **2009**, *18*, 555-568.

[17] Zemribo, R.; Fotins, J.; Abel, U.; Kubas, H.; Meyer, U.; Wolter, F. E.; Hechenberger, M. Patent **2012**, WO2012172093A1.

(18) Zhang, S.; Zhao, X.; Kao, W.; Wang, J. Patent **1997**, US5616604A.

(19) (a) Culvenor, C. C. J.; Edgar, Smith, J. A. L. W.; Tweeddale, H. J. *Aust. J. Chem.* **1970**, *23*, 1853-1867. (b) Karchesy, J. J.; Arbogast, B.;. Deinzer, M. L. *J. Org. Chem.* **1987**, *52***,** 3867-3872. (c) Sayah, B.; Pelloux-Leon, N.; Vallée, Y. *J. Org. Chem.,* **2000**, *65***,** 2824-2826. (d) Sayah, B.; Pelloux-Léon, N.; Milet, A. J.; Pardillos-Guindet, Y. V. *J. Org. Chem.* **2001**, *66***,** 2522-2525.

(20) (a) Miranda, L. D.; Cruz-Almanza, R.; Alvarez-García, A.; Muchowski, J. M. *Tetrahedron Lett.* **2000**, *41*, 3035-3038. (b) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett.* **2001**, *42*, 7887-7890. (c) Reddy, P. V.; Veyron, A.; Koos, P.; Bayle, A.; Greene, A. E.; Delair, P. *Org. Biomol. Chem.* **2008**, *6*, 1170-1172. (*d*) Allin, S. M.; Barton, W. R. S.; Russell Bowman, W.; Bridge, E.; Elsegood, M. R. J.; McInally, T.; McKee, V. *Tetrahedron* **2008**, *64*, 7745-7758.

(21) (a) Gabel, N. W. *J. Heterocycl. Chem.* **1967**, *4*, 627-627. (b) Schnekenburger, J.; Breit, E. *Arch. Pharm.* **1977**, *310*, 152-160. (c) Flitsch, W.; Koszinowski, J.; Witthake, P. *Chem. Ber.* **1979**, *112*, 2465-2471.

(22) Nag, S.; Madapa, S.; Batra, S. *Synthesis* **2008**, 101-109.

(23) O'Gorman, P. A.; Chen, T.; Cross, H. E.; Naeem, S.; Pitard, A.; Qamar, M. I.; Hemming, K. *Tetrahedron Lett.* **2008**, *49*, 6316-6319.

(24) Tang, M.; Tong, L.; Ju, L.; Zhai, W.; Hu, Y.; Yu, X. *Org. Lett.* **2015**, *17*, 5180-5183. .

(25) To the best of our knowledge, only the study without the releasing of CO_2 was carried out in the presence of (*D*)-amino acid oxidase for oxidization of *trans*-4-hydroxyproline to 1*H*-pyrrole-2-carboxylic acid: Radhakrishnan, A. N.; Meister, A. *J. Biol. Chem.* **1957**, *226*, 559-571. Besides, forming an enamine without concomitant decarboxylation was reported when hydroxyproline used as asymmetric organocatalysts in the catalytic system: McIntosh, A. I.; Watson, D. J.; Burton, J. W.; Lambert, R. M. *J. Am. Chem. Soc.*, **2006**, *128*, 7329–7334; Luna, L. E.; Seoane, G.; Cravero, R. M. *Eur J. Org. Chem.*, **2008**, *7*, 1271-1277; Bock, D. A.; Lehmann, C. W.; List, B. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20618-20619.

(26) The structure of compound **1e** was determined by X-ray crystal analysis (see cif and checkcif files in SI). CCDC-1520346 contains the supplementary crystallographic data for this paper.

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