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# Synthesis and Unexpected Oxidization of the Tricyclic Core of Ugibohlin, Isophakellin, and Styloguanidine

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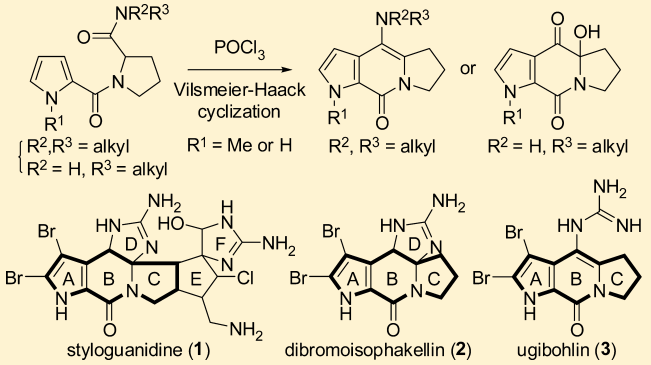
Supporting Information

**ABSTRACT:** A series of 4-substituted 5,6,7,9-tetrahydropyrrolo[2,3-*f*]indolizin-9-ones, representing the tricyclic core skeleton of ugibohlin, isophakellin, and styloguanidine, were synthesized via an intramolecular Vilsmeier−Haack reaction. This reaction allows the chemoselective C−C bond formation between the pyrrole C3 and proline C5 of *N*-[(pyrrol-2-yl)carbonyl]prolinamides to construct the B-ring without the protection of the pyrrole nitrogen. Unexpected oxidizative property of the tricyclic core skeleton was observed, which could illuminate understanding of the biological formation of these marine secondary metabolites.




## INTRODUCTION

A variety of structurally novel secondary metabolites from marine sponges have been identified to contain pyrrole and pyrrolidine ring units.[1] The most intriguing molecules in this family are the isomeric hexacyclic palau'amine[2,3] and styloguanidine[3,4] (**1**). Their A−B−C−D ring units are identical to dibromophakellin[5] and dibromoisophakellin (cantharelline)[6] (**2**), respectively. In addition, ugibohlin[7] (**3**) is the D-ring *seco*-isomer of dibromoisophakellin (**2**) with an aromatized B-ring (Figure 1). These marine alkaloids exhibit interesting biological

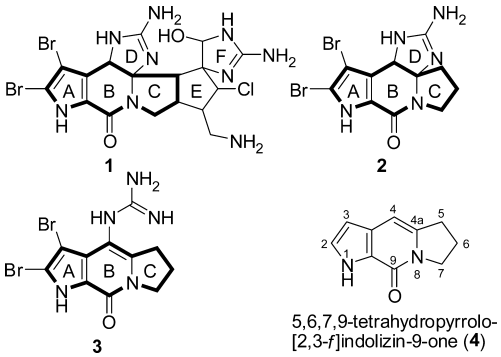


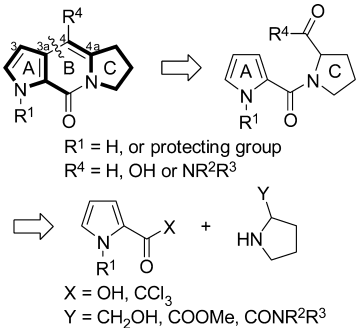

**Figure 1.** Marine natural products possessing tetrahydropyrrolo[2,3-*f*]indolizin-9-one core structure.

properties such as antitumor activities, substantial immunosuppressive activities, and low toxicities.[8] The biological profiles combined with their characteristic structural motifs have made these alkaloids attractive targets for total synthesis.

To date, the total synthesis of phakellin has been accomplished by several research groups.[9,10] Even the challenging synthesis of palau'amine has recently been disclosed in the literature.[11] Nevertheless, the synthesis toward ugibohlin[12] (**3**) and dibromoisophakellin[10,12] (**2**) was achieved only from the chemical conversion of the presynthesized dibromophakellin. Moreover, the total synthesis of styloguanidine (**1**) remains intangible. Since ugibohlin (**3**), dibromoisophakellin (**2**) and styloguanidine (**1**) all possess the same tricyclic core structure (Figure 1), the formation of the tricyclic A−B−C ring skeleton could be a common approach for the synthesis of these marine natural products.

The tricyclic core structure simply consists of pyrrole-2-carboxylic acid and proline skeletons as ring A and C counterparts, respectively. The retrosynthetic analysis, delineated in Scheme 1, suggested that the construction of the tricyclic core could be attained by the *N*-acylation of the proline derivatives with pyrrole-2-carboxylic acid followed by the C−C

**Scheme 1. Retrosynthetic Analysis of the Tricyclic Core**

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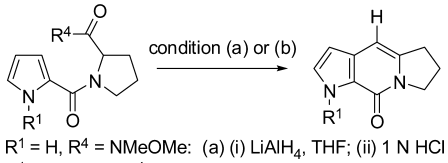
bond formation between pyrrole ring-carbon (C3) and proline carbonyl carbon (C5). Although numerous methods have been developed, the electrophilic aromatic substitution is still one of the most promising reactions for the C−C bond formation at pyrrole ring carbons. Hence, the acid-promoted electrophilic aromatic substitution reaction, Friedel−Crafts acylation, and Vilsmeier−Haack reaction should be the most applicable methods for the preparation of various tricyclic A−B−C ring precursors.

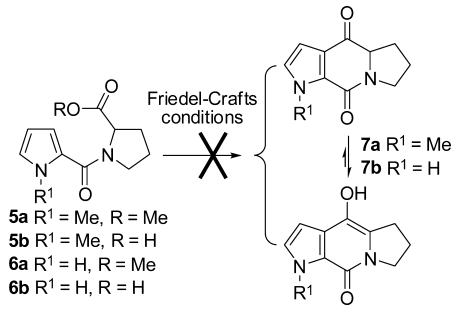
From a literature survey, Al-Mourabit[13] and Lindel[14] both demonstrated that the acid-promoted electrophilic aromatic substitution of *N*-[(pyrrol-2-yl)carbonyl]pyrrolidine-2-carbaldehydes effectively afforded the tricyclic pyrrolo[2,3-*f*]indolizine skeleton (Scheme 2). But their further elaboration at the C4- and C4a-positions of the pyrroloindolizine achieved only limited success.

**Scheme 2. Previous Works by Al-Mourabit[13] and Lindel[14]**




Our study focused on the construction of the tricyclic core and the introduction of functionality at the 4-position on the B ring. In our initial investigation, we recognized that the 4-hydroxy-tricyclic A−B−C ring (**7a,b**) could be presented as its tautomeric keto form, and retrosynthetic disconnection between C-3a and C-4 would provide *N*-[(pyrrol-2-yl)-carbonyl]proline derivatives (**5a,b**, **6a,b**) as the ring A−C adducts (Scheme 3). The C−C bond formation between the

**Scheme 3. Unsuccessful Attempts by Friedel−Crafts Cyclization**

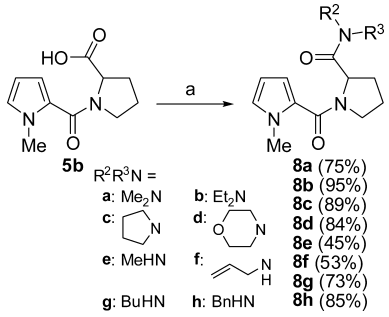



pyrrole C3 and the proline C5 was originally anticipated to be accomplished by Friedel−Crafts acylation reaction. However, attempts to promote the intramolecular Friedel−Crafts acylation of the ring A−C adducts (**5a,b**, **6a,b**)[13,15,16] by various Lewis acids or activating agents were all unsuccessful, which prompted us to investigate other strategies for the ring construction. We report herein the concise synthesis of the tricyclic core structure from pyrrole-2-carboxylic acid and proline via the Vilsmeier−Haack reaction as the key-step reaction and the unexpected oxidizative property of the pyrrolo[2,3-*c*]pyridin-7-one (the A−B ring).

## RESULTS AND DISCUSSIONS

The *N*-[(pyrrol-2-yl)carbonyl]prolinamide substrates for the intramolecular Vilsmeier−Haack reaction were prepared by two different routes. *N*-[(1-Methylpyrrol-2-yl)carbonyl]proline[16] (**5b**), readily prepared from commercially available 1-methylpyrrole and proline, as the acid component was reacted with a series of primary and secondary amines in the presence of EDC and HOBt to afford the corresponding *N*-[(1-methylpyrrol-2-yl)carbonyl]prolinamides (**8a−h**) (Scheme 4).

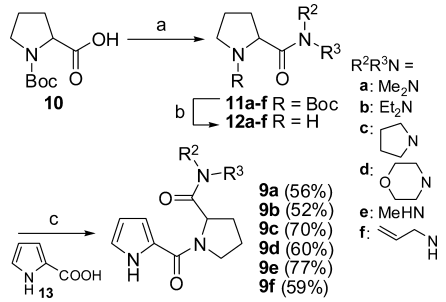
**Scheme 4. Preparation of *N*-[(1-Methylpyrrol-2-yl)carbonyl]prolinamides (8)[a]**




[a]Reagents and conditions: (a) $R^2R^3NH$, EDC, HOBt, $Et_3N$, $CH_2Cl_2$, rt.

The same approach, however, failed to yield the pyrrole-*N*-unsubstituted *N*-[(pyrrol-2-yl)carbonyl]prolinamides (**9a−f**). Alternatively, a series of prolinamides (**12a−f**), prepared from *N*-Boc-proline (**10**), were coupled with pyrrole-2-carboxylic acid (**13**) to form the desired pyrrole-*N*-unsubstituted *N*-[(pyrrol-2-yl)carbonyl]prolinamides (**9a−f**) (Scheme 5).

**Scheme 5. Preparation of *N*-[(Pyrrol-2-yl)carbonyl]prolinamides (9)[a]**




[a]Reagents and conditions: (a) $R^2R^3NH$, EDC, HOBt, $Et_3N$, $CH_2Cl_2$, 0 °C to rt; (b) aq. HCl/1,4-dioxane, rt; (c) EDC, HOBt, $Et_3N$, $CH_2Cl_2$, 0 °C to rt.

In the initial trials, *N*-[(1-methylpyrrol-2-yl)carbonyl]proline dimethylamide (**8a**) was chosen as a model compound to explore the reaction conditions for the Vilsmeier−Haack cyclization. Using a conventional approach, the dimethylamide **8a** was reacted with phosphorus oxychloride in acetonitrile at 65 °C, and the reaction proceeded to give 31% of the product **14a**, which was identified as the desired tricyclic adduct (entry 6 in Table 1). The preliminary success has confirmed that the Vilsmeier−Haack reaction is amenable for the construction of the tetrahydropyrrolo[2,3-*f*]indolizin-9-one ring with a dimethylamino substituent at the C4-position. Subsequently, various


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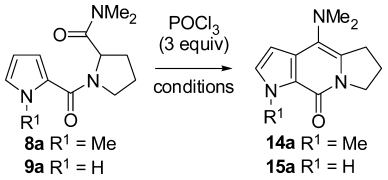
**Table 1. Optimization for the Vilsmeier–Haack Cyclization**



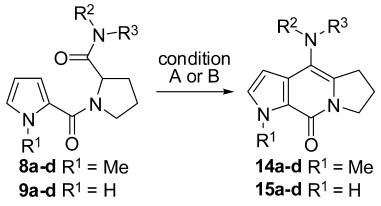

| entry | reactant | base (2 equiv) | solvent | temperature (°C) | time (h)[a] | yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **8a** | | $CH_2Cl_2$ | reflux | 24 | 39 |
| 2 | **8a** | NMM | $CH_2Cl_2$ | reflux | 24 | 21 |
| 3 | **8a** | | THF | reflux | 8 | 59 |
| 4 | **8a** | NMM | THF | reflux | 8 | 15 |
| 5 | **8a** | | $CH_3CN$ | rt | 36 | 4 |
| 6 | **8a** | | $CH_3CN$ | 65 | 2 | 31 |
| 7 | **8a** | $K_2CO_3$ | $CH_3CN$ | 65 | 2 | N.D.[c] |
| 8 | **8a** | DIPEA | $CH_3CN$ | 65 | 3 | 11 |
| 9 | **8a** | DBU | $CH_3CN$ | 65 | 3 | 47 |
| 10 | **8a** | $Et_3N$ | $CH_3CN$ | 65 | 3 | 59 |
| 11 | **8a** | NMM | $CH_3CN$ | 65 | 2 | 68 |
| 12 | **8a** | NMM | $CH_3CN$ | 45 | 24 | 71 |
| 13 | **8a** | NMM | $CH_3CN$ | reflux | 2 | 57 |
| 14 | **9a** | | $CH_2Cl_2$ | reflux | 3 | 39 |
| 15 | **9a** | | THF | rt | 24 | 36 |
| 16 | **9a** | | THF | reflux | 3 | 58 |
| 17 | **9a** | NMM | THF | reflux | 3 | N.D.[c] |
| 18 | **9a** | | DME | 85 | 3 | 39 |
| 19 | **9a** | | $CH_3CN$ | 45 | 3 | 35 |
| 20 | **9a** | | $CH_3CN$ | 65 | 3 | 53 |
| 21 | **9a** | NMM | $CH_3CN$ | 65 | 3 | N.D.[c] |

[a]The reaction time was determined by TLC analysis based on the complete consumption of the reactant (**8a**, **9a**). [b]Isolated yields. [c]N.D. = no desired product.

conditions including different base, solvent, temperature, time and the amount of the reagents were screened in order to optimize the cyclization reaction (Table 1). The optimum condition was to carry out the reaction with 3 equiv of $POCl_3$ and 2 equiv of *N*-methylmorpholine (NMM) in $CH_3CN$ at 65 °C, and the reaction could be completed within 2 h (entry 11 in Table 1). However, when this condition was applied to the pyrrole-*N*-unsubstituted *N*-[(pyrrol-2-yl)carbonyl]proline dimethylamide (**9a**), the reaction did not result in any desired product. Thus, the reaction conditions were screened again, and the best cyclization condition for **9a** was to carry out the reaction with 3 equiv of $POCl_3$ in THF at reflux for 3 h (entry 16 in Table 1). It is noteworthy that the ring closure took place chemoselectively at the C3-position of pyrrole (C3–C5′ bond formation) regardless the pyrrole nitrogen has a substituent.

With the optimized conditions in hand, a series of *N*-[(pyrrol-2-yl)carbonyl]proline dialkylamides (**8a–d**, **9a–d**) were subjected to the Vilsmeier–Haack cyclization conditions, and the corresponding 4-dialkylamino-substituted 5,6,7,9-tetrahydropyrrolo[2,3-*f*]indolizin-9-ones (**14a–d**, **15a–d**) were obtained in good yields (Table 2). When the Vilsmeier–Haack cyclization conditions were applied to *N*-[(pyrrol-2-yl)carbonyl]proline monoalkyl amides (**8e–h**, **9e,f**), the initially formed products from individual reactions were observed on the TLC plates after workup. However, attempts to purify these products by flash column chromatography were unsuccessful, but all the initial products from individual reactions were converted to the same oxidized products, α-hydroxy ketones (**16**, **17**[13] in Table 3), which were purified and characterized by spectroscopic analysis. The α-hydroxy ketones (**16**, **17**) have a higher oxidation state than the natural products at C4-carbon. Attempts to reduce the α-hydroxy ketones (**16**, **17**) to the dihydroxyl functionality were unsuccessful.

**Table 2. Vilsmeier–Haack Cyclization of Dialkylamides 8a–d and 9a–d**




| entry | reactant | $R^1$ | $NR^2R^3$ | condition[a] | time[b] (h) | product (yield, %)[c] |
|---|---|---|---|---|---|---|
| 1[d] | **8a** | Me | $NMe_2$ | A | 2 | **14a** (68) |
| 2 | **8b** | Me | $NEt_2$ | A | 3 | **14b** (48) |
| 3 | **8c** | Me |  | A | 10 | **14c** (34) |
| 4 | **8d** | Me |  | A | 7 | **14d** (62) |
| 5[e] | **9a** | H | $NMe_2$ | B | 3 | **15a** (58) |
| 6 | **9b** | H | $NEt_2$ | B | 3 | **15b** (47) |
| 7 | **9c** | H |  | B | 3 | **15c** (44) |
| 8 | **9d** | H |  | B | 18 | **15d** (13) |

[a]Condition A: $POCl_3$ (3 equiv), NMM (2 equiv), $CH_3CN$, 65 °C. Condition B: $POCl_3$ (3 equiv), THF, reflux. [b]The reaction time was determined by TLC analysis based on the complete consumption of the reactant. [c]Isolated yields. [d]Table 1, entry 11. [e]Table 1, entry 16.

**Table 3. Vilsmeier–Haack Cyclization of Monoalkylamides 8e–h and 9e,f**




| entry | reactant | $R^2$ | condition[a] | time[b] (h) | product(s) (yield, %)[c] |
|---|---|---|---|---|---|
| 1 | **8e** | Me | A | 9 | **16** (59) |
| 2 | **8f** | Allyl | A | 21 | **16** (3) + **18** (15) |
| 3 | **8g** | Bu | A | 3 | **16** (29) |
| 4 | **8h** | Bn | A | 5.5 | **16** (21) |
| 5 | **9e** | Me | B | 12 | **17** (24) |
| 6 | **9f** | Allyl | B | 14 | **17** (21) + **19** (7) |

[a]Condition A: $POCl_3$ (3 equiv), NMM (2 equiv), $CH_3CN$, 65 °C. Condition B: $POCl_3$ (3 equiv), THF, reflux. [b]The reaction time was determined by TLC analysis based on the complete consumption of the reactant. [c]Isolated yields.

The conversion of the initial products, which might be the desired cyclized products, into the oxidized adducts likely involved an autoxidation after the Vilsmeier–Haack cyclization. The unexpected oxidation prompted us to examine the reaction more closely. When *N*-allylamides of *N*-[(pyrrol-2-yl)-carbonyl]prolines (**8f**, **9f**) were subjected to the Vilsmeier–Haack cyclization conditions, 4a-allyl-4,4a,5,6,7,9-hexahydropyrrolo[2,3-*f*]indolizine-4,9-diones (**18**, **19**) were obtained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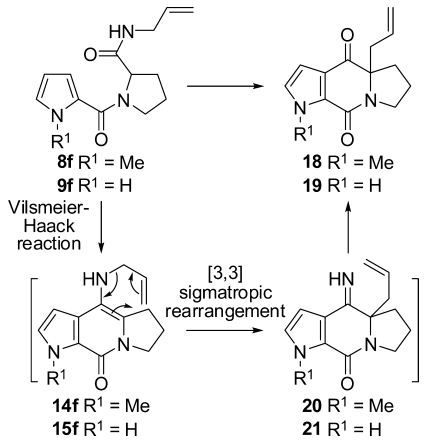
accompanied with the α-hydroxy ketones (**16**, **17**). We rationalized that the α-allyl ketone byproducts (**18**, **19**) were resulted from the aza-Claisen rearrangement of the allylamino adducts (**14f**, **15f**) followed by hydrolysis of the imine intermediates (**20**, **21**). This sequence of putative reactions provided evidence for the formation of the desired products from the Vilsmeier–Haack cyclization (Scheme 6).

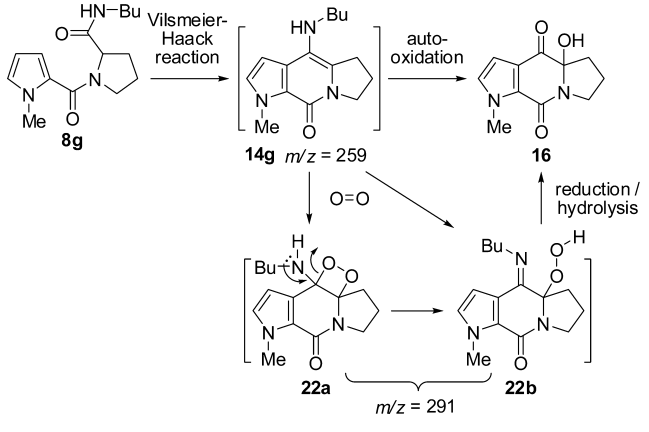
**Scheme 6. Mechanism for the Formation of the α-Allyl Ketones 18 and 19**




Meanwhile, the crude mixture obtained from the reaction of *N*-[(1-methylpyrrol-2-yl)carbonyl]proline butylamide (**8g**) after workup was immediately subjected to mass spectrometric analysis in order to gain insight into the reaction details. The molecular ion ($M^+$, $m/z$ = 259) for the expected Vilsmeier–Haack cyclization adduct was observed if the crude mixture was immediately preserved under argon. Upon exposure to air for an extended time, the appearance of the predominant M+32 ion ($m/z$ = 291), corresponding to a hydroperoxide (**22a**) or a dioxetane (**22b**) intermediate, reflected the immediate autoxidation of the Vilsmeier–Haack cyclization product. The hydroperoxide **22b** was degraded in the slightly acidic silica gel column to form the oxidized product **16** (Scheme 7).

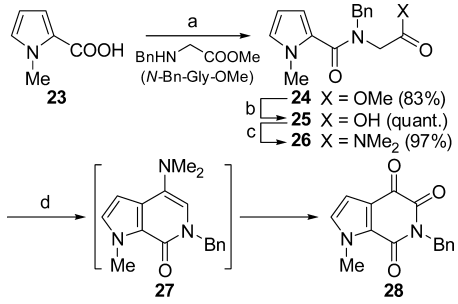
We postulated that the unexpected oxidization was attributed to the oxidizable tendency of the A–B ring unit. Thus, we embarked on the synthesis of the A–B ring unit in order to test whether the amino-substituted pyrrolo[2,3-*c*]pyridine-7-one would be aerobically oxidizable. Analogous to the tricyclic

**Scheme 7. Mechanism for the Formation of the α-Hydroxy Ketones 16 and 17**




system, *N*-methylpyrrole-2-carboxylic acid (**23**) was coupled with *N*-benzylglycine methyl ester, and the resulting ester **24** was saponified followed by coupling with dimethylamine hydrochloride to afford *N*-benzyl-*N*-[(pyrrol-2-yl)carbonyl]-glycine dimethylamide (**26**). The dimethylamide substrate **26** was subjected to the Vilsmeier–Haack cyclization condition, and the $^1$H NMR analysis suggested that the initial product obtained from the reaction immediately after column chromatography was 1-methyl-4-dimethylamino-6-benzyl-pyrrolo[2,3-*c*]pyridin-7-one (**27**). However, upon exposure to the air for a short period of time, the cyclized adduct **27** was oxidized into the corresponding pyrrolo[2,3-*c*]pyridine-4,5,7-trione **28**,[17] the structure of which was confirmed by X-ray crystallographic analysis (Scheme 8). It is notable that even

**Scheme 8. Synthesis and Oxidation of 4-Amino-Substituted Pyrrolo[2,3-*c*]pyridin-7-one**[a]




[a]Reagents and conditions: (a) EDC, HOBt, $Et_3N$, $CH_2Cl_2$, rt, 18 h; (b) (i) aq. NaOH/MeOH, reflux, 3 h; (ii) HCl; (c) $Me_2NH$.HCl, EDC, HOBt, $Et_3N$, $CH_2Cl_2$, rt, 18 h; (d) $POCl_3$, NMM, $CH_3CN$, 65 °C, 20 h, 37% for **28** (from **26**).

though the tricyclic 4-diakylamino-substituted tetrahydro-pyrrolo[2,3-*f*]indolizin-9-ones (**14a–d**, **15a–d**) were stable enough to be purified and characterized, a gradual oxidative degradation of **14a–d** and **15a–d** into **16** and **17**, respectively, and other unidentified decomposition products was observed in a prolonged time period.

To further clarify the role of the 4-amino-substituents in the autoxidation, the 4-unsubstituted tetrahydropyrrolo[2,3-*f*]-indolizin-9-one **29** was prepared by adopting Lindel's approach.[14] *N*-[(1-Methylpyrrol-2-yl)carbonyl]proline methyl ester **5a** was first reduced by lithium borohydride and then oxidized by IBX[18] to form the corresponding aldehyde **5d**. Subsequently, the acid-promoted electrophilic ring-closure afforded the 4-unsubstituted tricyclic core skeleton **29**. Unlike the 4-amino-substituted congeners, the 4-unsubstituted tricyclic core **29** shows substantial stability under aerobic conditions. Therefore, the electron-donating character of the 4-amino-substituents is responsible for the unexpected aerobic oxidation of the pyrrolo[2,3-*c*]pyridin-7-one heterocycle. Furthermore, attempts to carry out the dihydroxylation and epoxidation[13] at the C4–C4a double bond of the tricyclic core **29** were unsuccessful, but interestingly, both resulted in the formation of the α-hydroxyketone adduct **16** (Scheme 9).

## ■ CONCLUSION

In summary, we have developed a facile and practical synthesis for the tricyclic core skeleton, tetrahydropyrrolo[2,3-*f*]-indolizin-9-one, of ugibohlin, isophakellin, and styloguanidine via an intramolecular Vilsmeier–Haack reaction. Our investigation also revealed that the nitrogen-substituent at the 4-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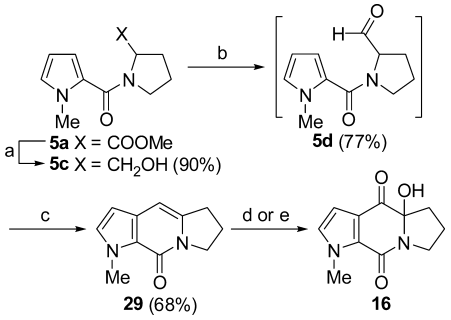
**Scheme 9. Synthesis and Oxidation of the 4-Unsubstituted Tetrahydropyrrolo[2,3-*f*]indolizin-9-one (29)[a]**




[a]Reagents and conditions: (a) $NaBH_4$/LiCl, THF/EtOH, 0 °C to rt, 8 h; (b) IBX, EtOAc, reflux, 3 h; (c) MsOH, $CH_2Cl_2$, rt, 1.5 h; (d) cat. $OsO_4$, NMO, acetone, rt, 3 h, 58%; (e) *m*CPBA, $CH_2Cl_2$, 0 °C to rt, 2 h, 63%.

position of the tricyclic core provoked the aerobic oxidation of the heterocycle. The highly oxidizable tendency of the pyrrolo[2,3-*c*]pyridine-7-one ring unit (A–B ring) could illuminate understanding of the biological formation of these marine secondary metabolites and also present a challenge for the total synthesis of these marine natural products.

## EXPERIMENTAL SECTION

**General Chemical Procedures.** The chemical shift values are reported in $\delta$ values (parts per million, ppm) relative to the standard chemical shift for the hydrogen residue peak and carbon-13 peak in the deuterated solvent, $CDCl_3$, or DMSO-$d_6$.[19] 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. High-resolution mass spectrometry (HRMS) was obtained by the following ionization methods/mass analyzers: EI/magnetic sector, ESI/TOF or FAB/magnetic sector. Thin-layer chromatography (TLC) was performed on silica gel plates. Compounds on TLC were visualized by illumination under UV light (254 nm), or using the following reagents: phosphomolybdic acid reagent, anisaldehyde reagent, ninhydrin reagent or 10% ethanolic sulfuric acid followed by charring on a hot plate. Silica gel (230–400 mesh) was used for flash column chromatography, and this technique has been described by Still et al.[20] 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.

***N*-[(1-Methylpyrrol-2-yl)carbonyl]proline dimethylamide (8a).** A mixture of *N*-[(1-methylpyrrol-2-yl)carbonyl]proline[16] (**5b**) (4.0869 g, 18.39 mmol), EDC (5.1816 g, 27.03 mmol, 1.5 equiv) and HOBt (3.6397 g, 26.94 mmol, 1.5 equiv) in $CH_2Cl_2$ (100 mL) was stirred for 30 min at room temperature under argon. Dimethylammonium chloride (2.9351 g, 36.0 mmol, 2 equiv) and triethylamine (12.6 mL, 89.65 mmol, 5 equiv) were added to the solution. The reaction mixture was stirred for an additional 6 h at ambient temperature under argon and then concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (50 mL), washed with 1 N aqueous HCl solution, saturated aqueous $Na_2CO_3$ solution, and saturated aqueous NaCl solution. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (Hex/EtOAc = 1:9, $R_f$ = 0.1) to give **8a** (amorphous solid, 3.37 g, 13.5 mmol, 75%): mp 125–128 °C; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.84–1.89 (m, 2 H), 1.92–2.24 (m, 2 H), 2.95 (bs, 3 H), 3.15 (bs, 3 H), 3.81 (bs, 3 H), 3.85 (bs, 2 H), 4.99 (bs, 1 H), 6.05 (bs, 1 H), 6.59 (bs, 1 H), 6.64 (bs, 1 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 25.4 ($CH_2$), 28.5 ($CH_2$), 35.9 ($CH_3$), 36.5 ($CH_3$), 37.0 ($CH_3$), 50.0 ($CH_2$), 56.8 (CH), 106.7 (CH), 114.1 (CH), 125.7, 126.7 (CH), 161.7, 172.0; MS (EI, 20 eV) $m/z$ 108 (52), 177 (100), 249 (20) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{13}H_{19}N_3O_2$ 249.1477, found 249.1485.

***N*-[(1-Methylpyrrol-2-yl)carbonyl]proline diethylamide (8b).** Compound **8b** was prepared from **5b** by the method described for **8a**. The reaction was purified by flash column chromatography (Hex/EtOAc = 4:6, $R_f$ = 0.1) to give **8b** (oil, 1.0546 g, 95%): $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.83–0.95 (m, 3 H), 1.07–1.25 (m, 3 H), 1.84–1.90 (m, 2 H), 2.02–2.08 (m, 1 H), 2.10–2.18(m, 1 H), 3.12–3.23 (m, 1 H), 3.23–3.26 (m, 1 H), 3.31–3.33 (m, 1 H), 3.43–3.56 (m, 1 H), 3.76–3.81 (m, 5 H), 4.91 (bs, 1 H), 6.01 (bs, 1 H), 6.53 (bs, 1 H), 6.60 (bs, 1 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 12.8 ($CH_3$), 14.5 ($CH_3$), 25.3 ($CH_2$), 29.2 ($CH_2$), 36.1 ($CH_3$), 40.6 ($CH_2$), 41.8 ($CH_2$), 50.0 ($CH_2$), 56.5 (CH), 106.6 (CH), 113.7 (CH), 125.8, 126.3 (CH), 161.7, 171.5; MS (EI, 20 eV) $m/z$ 108 (50), 177 (100), 277 (17) ($M^+$); MS (EI, 20 eV) $m/z$ 108 (50), 177 (100), 277 (17) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{15}H_{23}N_3O_2$ 277.1790, found 277.1797.

***N*-[(1-Methylpyrrol-2-yl)carbonyl]proline (pyrrolidin-1-yl)-amide (8c).** Compound **8c** was prepared from **5b** by the method described for **8a**. The reaction was purified by flash column chromatography (EtOAc, $R_f$ = 0.1) to give **8c** (colorless oil, 0.5623 g, 89%): $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.76–1.89 (m, 6 H), 2.07–2.14 (m, 2 H), 3.35–3.37 (m, 2 H), 3.47–3.49 (m, 1 H), 3.75–3.78 (m, 9 H), 4.73 (bs, 1 H), 5.99 (bs, 1 H), 6.52 (bs, 1 H), 6.58 (bs, 1 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 23.8 ($CH_2$), 25.3 ($CH_2$), 25.9 ($CH_2$), 28.2 ($CH_2$), 36.2 ($CH_3$), 45.7 ($CH_2$), 45.9 ($CH_2$), 49.9 (CH), 58.1 ($CH_2$), 106.4 (CH), 113.8 (CH), 125.5, 126.4 (CH), 161.5, 170.3; MS (EI, 20 eV) $m/z$ 108 (100), 177 (70), 275 (11) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{15}H_{21}N_3O_2$ 275.1634, found 275.1642.

***N*-[(1-Methylpyrrol-2-yl)carbonyl]proline (morpholin-1-yl)-amide (8d).** Compound **8d** was prepared from **5b** by the method described for **8a**. The reaction was purified by flash column chromatography (EtOAc, $R_f$ = 0.2) to give **8d** (oil, 0.3902 g, 84%): $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.84–1.91 (m, 2 H), 2.09–2.21 (m, 2 H), 3.60–3.83 (m, 13 H), 4.95–4.97 (m, 1 H), 6.04 (bs, 1 H), 6.58 (bs, 1 H), 6.63 (bs, 1 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 25.4 ($CH_2$), 28.8 ($CH_2$), 36.3 ($CH_3$), 42.3 ($CH_2$), 46.0 ($CH_2$), 49.9 ($CH_2$), 56.4 (CH), 66.5 ($CH_2$), 66.7 ($CH_2$), 106.7 (CH), 114.1 (CH), 125.5, 126.8 (CH), 161.7, 170.7; MS (EI, 20 eV) $m/z$ 108 (32), 177 (100), 291 (14) ($M^+$); MS (EI, 70 eV) $m/z$ 108 (33), 177 (100), 291 (13) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{15}H_{21}N_3O_3$ 291.1583, found 291.1589.

***N*-[(1-Methylpyrrol-2-yl)carbonyl]proline methylamide (8e).** Compound **8e** was prepared from **5b** by the method described for **8a**. The reaction was purified by flash column chromatography (EtOAc, $R_f$ = 0.1) to give **8e** (amorphous solid, 1.4702 g, 45%): mp 114–117 °C; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.84–1.92 (m, 1 H), 1.98–2.07 (m, 2 H), 2.30–2.36 (m, 1 H), 2.78 (s, 3 H), 3.66–3.74 (m, 1 H), 3.80–3.87 (m, 4 H), 4.71 (dd, 1 H, $J$ = 4.9 and 7.3 Hz), 6.08 (dd, 1 H, $J$ = 2.6 and 3.8 Hz), 6.54 (bs, 1 H), 6.71 (t, 1 H, $J$ = 1.9 Hz); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 25.2, 26.2, 27.5, 36.7, 50.1, 60.3, 107.1, 114.6, 125.0, 127.6, 163.3, 172.2; MS (EI, 20 eV) $m/z$ 108 (100), 177 (95), 235 (43) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{12}H_{17}N_3O_2$ 235.1321, found 235.1321.

***N*-[(1-Methylpyrrol-2-yl)carbonyl]proline allylamide (8f).** Compound **8f** was prepared from **5b** by the method described for **8a**. The reaction was purified by flash column chromatography (Hex/EtOAc = 2:8, $R_f$ = 0.25) to give **8f** (colorless oil, 0.69 g, 53%): $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.84–1.87 (m, 1 H), 1.97–2.04 (m, 2 H), 2.27–2.28 (m, 1 H), 3.66–3.74 (m, 1 H), 3.77–3.86 (m, 6 H), 4.71 (bs, 1 H), 5.02 (dd, 1 H, $J$ = 1.2 and 10.3 Hz), 5.11 (d, 1 H, $J$ = 17.1 Hz), 5.71–5.78 (m, 1 H), 6.04–6.05 (m, 1 H), 6.51 (bs, 1 H), 6.67 (bs, 1 H), 7.04 (bs, 1 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 25.3, 27.8, 36.7, 41.8, 50.0, 60.5, 107.1, 114.4, 115.9, 125.2, 127.5, 134.1, 163.2, 171.6; MS (EI, 20 eV) $m/z$ 108 (42), 177 (100), 261 (33) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{14}H_{19}N_3O_2$ 261.1477, found 261.1480.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***N*-[(1-Methylpyrrol-2-yl)carbonyl]proline *n*-butylamide (8g).** Compound **8g** was prepared from **5b** by the method described for **8a**. The reaction was purified by flash column chromatography (Hex/EtOAc = 7:3, $R_f$ = 0.1) to give **8g** (pale-yellow oil, 0.7280 g, 73%): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.81 (t, 3 H, $J$ = 7.4 Hz), 1.22−1.28 (m, 2 H), 1.38−1.42 (m, 2 H), 1.83−1.89 (m, 1 H), 1.97−2.02 (m, 2 H), 2.25−2.26 (m, 1 H), 3.15−3.19 (m, 2 H), 3.67−3.69 (m, 1 H), 3.77−3.78 (m, 4 H), 4.64−4.66 (m, 1 H), 6.03−6.04 (m, 1 H), 6.49 (bs, 1 H), 6.66 (m, 1 H), 6.86; $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 13.7, 20.0, 25.2 27.8, 31.5, 36.6, 39.2, 49.9, 60.7, 107.1, 114.4, 125.2, 127.4, 163.2, 171.7; MS (EI, 20 eV) $m/z$ 108 (47), 177 (100), 277 (27) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{15}H_{23}N_3O_2$ 277.1790, found 277.1801.

***N*-[(1-Methylpyrrol-2-yl)carbonyl]proline benzylamide (8h).** Compound **8h** was prepared from **5b** by the method described for **8a**. The reaction was purified by flash column chromatography (Hex/EtOAc = 4:6, $R_f$ = 0.2) to give **8h** (brown amorphous solid, 1.4233 g, 85%): mp 108−111 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.87−1.93 (m, 1 H), 1.98−2.08 (m, 2 H), 2.33−2.36 (m, 1 H), 3.70−3.86 (m, 5 H), 4.44 (dd, 1 H, $J$ = 5.9 and 15.0 Hz), 4.46 (dd, 1 H, $J$ = 5.7 and 14.8 Hz), 4.76−4.78 (m, 1 H), 6.09 (bs, 1 H), 6.55 (bs, 1 H), 6.70 (bs, 1 H), 7.22−7.32 (m, 5 H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 25.1 ($CH_2$), 27.9 ($CH_2$), 36.5 ($CH_3$), 43.2 ($CH_2$), 49.8 ($CH_2$), 60.5 (CH), 106.9 (CH), 114.3 (CH), 125.1, 127.1 (CH), 127.3 (CH), 128.4 (CH), 128.5 (CH), 138.3, 163.1, 171.6; MS (EI, 70 eV) $m/z$ 108 (100), 109 (26), 177 (100), 178 (23), 311 (11) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{18}H_{21}N_3O_2$ 311.1634, found 311.1643.

***N*-[(Pyrrol-2-yl)carbonyl]proline dimethylamide (9a).** To a mixture of pyrrole-2-carboxylic acid (**13**, 1.67 g, 15.0 mmol), EDC (3.45 g, 18.0 mmol, 1.2 equiv) and HOBt (2.43 g, 18.0 mmol, 1.2 equiv) in $CH_2Cl_2$ (75 mL) was added proline dimethylamide hydrochloride salt[21] (**12a**, obtained quantitatively from *N*-Boc-proline dimethylamide[22] (**11a**) by acidic hydrolysis without further purification, 2.68 g, 15.0 mmol, 1.0 equiv) and triethylamine (10.5 mL, 75.0 mmol, 5.0 equiv) at 0 °C. The mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure. The residue was dissolved in $CH_2Cl_2$ (100 mL), washed with $H_2O$ and saturated aqueous NaCl solution. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (Hex/EtOAc = 7:3 to EtOAc) to give **9a** (amorphous solid, 1.99 g, 8.46 mmol, 56%, $R_f$ = 0.10 (EtOAc)): mp 182−183 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 1.72−1.76 (m, 1 H), 1.91−1.97 (m, 1 H), 2.00−2.05 (m, 1 H), 2.11−2.16 (m, 1 H),2.81 (s, 3 H), 3.10 (s, 3 H), 3.76−3.81 (m, 2 H), 4.92−4.95 (m, 1 H), 6.15 (s, 1 H), 6.63 (s, 1 H), 6.90 (s, 1 H), 11.35 (bs, 1 H, NH); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 25.3 ($CH_2$), 28.3 ($CH_2$), 35.7 ($CH_3$), 37.1 ($CH_3$), 48.6 ($CH_2$), 57.6 (CH), 109.3 (CH), 112.5 (CH), 121.9 (CH), 126.0, 159.8, 172.0; MS (EI, 70 eV) $m/z$ 66 (16), 70 (100), 94 (86), 163 (96), 235 (8) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{12}H_{17}N_3O_2$ 235.1321, found 235.1325.

***N*-[(Pyrrol-2-yl)carbonyl]proline diethylamide (9b).** Compound **9b** was prepared from **12b**[21,23] and **13** by the method described for **9a**. The reaction was purified by flash column chromatography (Hex/EtOAc = 4:6 to EtOAc) to give **9b** (amorphous solid, 2.44 g, 52%, $R_f$ = 0.30 (EtOAc)): mp 118−119 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.08 (t, 3 H, $J$ = 7.2 Hz), 1.25 (t, 3 H, $J$ = 7.2 Hz), 1.87−1.99 (m, 2 H), 3.23−3.38 (m, 2 H), 3.48−3.53 (m, 2 H), 3.85−3.97 (m, 2 H), 4.95−4.98 (m, 1 H), 6.17 (s, 1 H), 6.62 (s, 1 H), 6.84 (s, 1 H), 10.51 (bs, 1 H, NH); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 12.9 ($CH_3$), 14.4 ($CH_3$), 25.2 ($CH_2$), 28.8 ($CH_2$), 40.6 ($CH_2$), 41.7 ($CH_2$), 48.6 ($CH_2$), 57.6 (CH), 109.4 (CH), 112.8 (CH), 121.5 (CH), 125.3, 160.4, 171.4; MS (EI, 70 eV) $m/z$ 66 (11), 70 (100), 94 (82), 163 (97), 263 (9) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{14}H_{21}N_3O_2$ 263.1634, found 263.1638.

***N*-[(Pyrrol-2-yl)carbonyl]proline (pyrrolidin-1-yl)amide (9c).** Compound **9c** was prepared from **12c**[21,24] and **13** by the method described for **9a**. The reaction was purified by flash column chromatography (Hex/EtOAc = 5:5 to EtOAc) to give **9c** (amorphous solid, 1.76 g, 70%, $R_f$ = 0.10 (EtOAc)): mp 194−195 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.85−1.88 (m, 2 H), 1.96−2.06 (m, 4 H), 2.14−2.16 (m, 1 H), 2.32−2.34 (m, 1 H), 3.39−3.49 (m, 2 H), 3.58−3.63 (m, 1 H), 3.86−3.91 (m, 2 H), 4.02 (bs, 1 H), 4.82−4.85 (m, 1 H), 6.25 (d, 1 H, 2.2 Hz), 6.66 (s, 1 H), 6.91 (s, 1 H), 9.59 (bs, 1 H, NH); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 24.1 ($CH_2$), 25.4 ($CH_2$), 26.3 ($CH_2$), 28.3 ($CH_2$), 46.0 ($CH_2$), 46.3 ($CH_2$), 48.5 ($CH_2$), 59.2 (CH), 109.9 (CH), 112.6 (CH), 121.1 (CH), 125.6, 160.3, 170.5; MS (EI, 70 eV) $m/z$ 70 (100), 94 (69), 163 (87), 261 (21) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{14}H_{19}N_3O_2$ 261.1477, found 261.1482.

***N*-[(Pyrrol-2-yl)carbonyl]proline (morpholin-1-yl)amide (9d).** Compound **9d** was prepared from **12d**[25,26] and **13** by the method described for **9a**. The reaction was purified by flash column chromatography (Hex/EtOAc = 4:6 to EtOAc) to give **9d** (amorphous solid, 1.95 g, 60%, $R_f$ = 0.10 (EtOAc)): mp 184−185 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.91−1.95 (m, 1 H), 1.99−2.07 (m, 1 H), 2.11−2.19 (m, 1 H), 2.26 (m, 1 H), 3.57−3.72 (m, 7 H), 3.79−3.81 (m, 1 H), 3.89−3.91 (m, 1 H), 3.99−4.00 (m, 1 H), 5.03−5.06 (m, 1 H), 6.24 (d, 1 H, $J$ = 3.0 Hz), 6.66 (s, 1 H), 6.90 (s, 1 H), 9.91 (bs, 1 H, NH); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 25.3 ($CH_2$), 28.5 ($CH_2$), 42.4 ($CH_2$), 46.1 ($CH_2$), 48.4 ($CH_2$), 57.2 (CH), 66.6 ($CH_2$), 66.9 ($CH_2$), 109.9 (CH), 112.7 (CH), 121.4 (CH), 125.4, 160.3, 170.6; MS (EI, 70 eV) $m/z$ 66 (16), 70 (100), 94 (94), 163 (99), 164 (13), 277 (5) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{14}H_{19}N_3O_3$ 277.1426, found 277.1433.

***N*-[(Pyrrol-2-yl)carbonyl]proline methylamide (9e).** Compound **9e** was prepared from **12e**[22,27] and **13** by the method described for **9a**. The reaction was purified by flash column chromatography (Hex/EtOAc = 6:4 to EtOAc) to give **9e** (amorphous solid, 1.93 g, 77%, $R_f$ = 0.13 (EtOAc)): mp 112−113 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.91−2.38 (m, 4 H), 2.74 (d, 3 H, $J$ = 3.6 Hz), 3.75−3.85 (m, 2 H), 4.78 (d, 1 H, $J$ = 4.0 Hz), 6.25 (s, 1 H), 6.66 (s, 1 H), 6.95 (s, 1 H), 7.05 (s, 1 H, NH), 10.29 (s, 1 H, NH); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 25.5 ($CH_2$), 26.2 ($CH_3$), 27.2 ($CH_2$), 48.7 ($CH_2$), 61.1 (CH), 110.3 (CH), 113.3 (CH), 122.1 (CH), 125.0, 161.7, 172.0; MS (EI, 70 eV) $m/z$ 66 (6), 70 (100), 94 (58), 163 (76), 221 (6) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{11}H_{15}N_3O_2$ 221.1164, found 221.1164.

***N*-[(Pyrrol-2-yl)carbonyl]proline allylamide (9f).** Compound **9f** was prepared from **12f**[28] and **13** by the method described for **9a**. The reaction was purified by flash column chromatography (Hex/EtOAc = 7:3 to EtOAc) to give **9f** (amorphous solid, 2.78 g, 59%, $R_f$ = 0.33 (EtOAc)): mp 115−116 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.94−2.44 (m, 4 H), 3.77−3.91 (m, 4 H), 4.83 (d, 1 H, $J$ = 6.6 Hz), 5.06 (d, 1 H, $J$ = 10.2 Hz), 5.15 (d, 1 H, $J$ = 17.2 Hz), 5.79−5.80 (m, 1 H), 6.28 (s, 1 H), 6.68 (s, 1 H), 6.97 (s, 1 H), 7.20 (bs, 1 H, NH), 9.98 (bs, 1 H, NH); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 25.5 ($CH_2$), 27.0 ($CH_2$), 41.7 ($CH_2$), 48.6 ($CH_2$), 61.2 (CH), 110.4 (CH), 113.3 (CH), 115.8 ($CH_2$), 121.9 (CH), 125.0, 134.1 (CH), 161.7, 171.2; MS (EI, 70 eV) $m/z$ 66 (19), 70 (100), 94 (90), 163 (99), 164 (22), 247 (8) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{13}H_{17}N_3O_2$ 247.1321, found 247.1320.

**4-Dimethylamino-1-methyl-5,6,7,9-tetrahydropyrrolo[2,3-*f*]indolizin-9-one (14a).** To a solution of **8a** (0.2501 g, 1.0 mmol) in acetonitrile (20 mL) at 0 °C was added phosphorus oxychloride (0.28 mL, 3.05 mmol, 3 equiv) and *N*-methylmorpholine (0.22 mL, 2.0 mmol, 2 equiv). After the addition was completed, the reaction mixture was heated at 65 °C for 2 h. The solution was cooled to room temperature and then concentrated under reduced pressure. The residue was dissolved in chloroform (25 mL), washed with saturated aqueous $Na_2CO_3$ solution, saturated NaCl solution, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (EtOAc, $R_f$ = 0.5) to give **14a** (pale-yellow amorphous solid, 0.1573 g, 0.68 mmol, 68%): mp 94−97 °C; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 2.08−2.14 (m, 2 H), 2.76 (s, 6 H), 3.05 (t, 2 H, $J$ = 7.2 Hz), 4.08 (t, 2 H, $J$ = 7.3 Hz), 4.11 (s, 3 H), 6.31 (s, 1 H), 6.89 (s, 1 H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 22.4 ($CH_2$), 29.1 ($CH_2$), 35.5 ($CH_3$), 44.0 ($CH_3$), 47.4 ($CH_2$), 100.3 (CH), 123.0, 123.3, 130.5 (CH), 130.9, 135.4, 154.0; MS (EI, 20 eV) $m/z$ 108 (18), 177 (16), 216 (36), 231


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(100) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{13}H_{17}N_3O$ 231.1372, found 231.1372.

**4-Diethylamino-1-methyl-5,6,7,9-tetrahydropyrrolo[2,3-*f*]-indolizin-9-one (14b).** Compound **14b** was prepared from **8b** by the method described for **14a**. The reaction was purified by flash column chromatography (Hex/EtOAc = 1:9 then EtOAc) to give **14b** (brown oil, 86.9 mg, 48%, $R_f$ = 0.25 (EtOAc)): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.89 (t, 6 H, $J$ = 7.1 Hz), 2.04−2.11 (m, 2 H), 3.00−3.06 (m, 6 H), 4.07−4.10 (m, 5 H), 6.23 (d, 1 H, $J$ = 2.4 Hz), 6.85 (d, 1 H, $J$ = 2.2 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 14.0 ($CH_3$), 22.4 ($CH_2$), 29.7 ($CH_2$), 35.5 ($CH_3$), 47.8 ($CH_2$), 48.7 ($CH_2$), 100.5 (CH), 118.6, 123.0, 130.4 (CH), 131.5, 139.1, 154.1; MS (EI, 70 eV) $m/z$ 187 (20), 188 (29), 229 (18), 230 (77), 244 (73), 259 (100) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{15}H_{21}N_3O$ 259.1685, found 259.1690.

**1-Methyl-4-(pyrrolidin-1-yl)-5,6,7,9-tetrahydropyrrolo[2,3-*f*]indolizin-9-one (14c).** Compound **14c** was prepared from **8c** by the method described for **14a**. The reaction was purified by flash column chromatography (EtOAc, $R_f$ = 0.2) to give **14c** (white amorphous solid, 81.4 mg, 34%): mp 101−104 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.92−1.95 (m, 4 H), 2.08−2.15 (m, 2 H), 3.06 (t, 2 H, $J$ = 7.6 Hz), 3.14−3.17 (m, 4 H), 4.09 (t, 2 H, $J$ = 7.3 Hz), 4.12 (s, 3 H), 6.21 (d, 1 H, $J$ = 2.6 Hz), 6.89 (d, 1 H, $J$ = 2.6 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 22.4 ($CH_2$), 25.6 ($CH_2$), 29.2 ($CH_2$), 29.6 ($CH_2$), 35.6 ($CH_3$), 47.6 ($CH_2$), 51.4 ($CH_2$), 100.0 (CH), 120.0, 123.1, 130.5 (CH), 130.8, 136.3, 153.9; MS (EI, 70 eV) $m/z$ 256 (23), 257 (100) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{15}H_{19}N_3O$ 257.1528, found 257.1536.

**1-Methyl-4-(morpholin-1-yl)-5,6,7,9-tetrahydropyrrolo[2,3-*f*]indolizin-9-one (14d).** Compound **14d** was prepared from **8d** by the method described for **14a**. The reaction was purified by flash column chromatography (EtOAc, $R_f$ = 0.25) to give **14d** (brown amorphous solid, 0.1466 g, 62%): mp 148−151 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.10−2.17 (m, 2 H), 3.07−3.12 (m, 6 H), 3.78 (t, 4 H, $J$ = 4.4 Hz), 4.01 (t, 2 H, $J$ = 7.0 Hz), 4.13 (s, 3 H), 6.35 (d, 1 H, $J$ = 2.8 Hz), 6.91 (d, 1 H, $J$ = 2.8 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 22.4 ($CH_2$), 29.2 ($CH_2$), 35.5 ($CH_3$), 47.6 ($CH_2$), 51.5 ($CH_2$), 68.0 ($CH_2$), 100.3 (CH), 122.0, 122.9, 130.7 (CH), 131.2, 136.2, 154.0; MS (EI, 70 eV) $m/z$ 108 (13), 214 (15), 215 (36), 273 (100) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{15}H_{19}N_3O_2$ 273.1477, found 273.1480.

**4-Dimethylamino-5,6,7,9-tetrahydropyrrolo[2,3-*f*]indolizin-9-one (15a).** To a solution of **9a** (0.47 g, 2.0 mmol) in THF (20 mL) was added $POCl_3$ (0.55 mL, 6.0 mmol, 3.0 equiv) at 0 °C. After the addition was completed, the mixture was stirred at reflux temperature for 3 h. The solution was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was partitioned between $CHCl_3$ and $H_2O$. The aqueous layer was separated and then neutralized with saturated aqueous $Na_2CO_3$ solution. The aqueous solution was extracted with $CHCl_3$, and the organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (Hex/EtOAc = 2:8 to EtOAc) to give **15a** (yellow amorphous solid, 0.1521 g, 0.7 mmol, 35%, $R_f$ = 0.25 (EtOAc)): mp 219−220 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 2.05−2.11 (m, 2 H), 2.72 (s, 6 H), 3.04 (t, 2 H, $J$ = 6.0 Hz), 3.97 (t, 2 H, $J$ = 5.7 Hz), 6.39 (t, 1 H, $J$ = 1.6 Hz), 7.21 (t, 1 H, $J$ = 2.0 Hz), 11.85 (bs, 1 H, NH); $^{13}$C NMR (DMSO-$d_6$, 125 MHz) $\delta$ 22.1 ($CH_2$), 28.7 ($CH_2$), 43.9 ($CH_3$), 47.3 ($CH_2$), 101.5 (CH), 122.5, 123.5, 126.0 (CH), 129.1, 135.0, 152.4; MS (EI, 70 eV) $m/z$ 202 (100), 217 (78) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{12}H_{15}N_3O$ 217.1215, found 217.1219.

**4-Diethylamino-5,6,7,9-tetrahydropyrrolo[2,3-*f*]indolizin-9-one (15b).** Compound **15b** was prepared from **9b** by the method described for **15a**. The reaction was purified by flash column chromatography (Hex/EtOAc = 2:8 then EtOAc) to give **15b** (yellow amorphous solid, 0.12 g, 21%, $R_f$ = 0.18 (EtOAc)): mp 158−159 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.77−0.86 (m, 6 H), 2.05−2.11 (m, 2 H), 2.97−3.06 (m, 6 H), 3.23−3.38 (m, 2 H), 3.48−3.53 (m, 2 H), 3.85−3.97 (m, 6 H), 4.16 (t, 2 H, $J$ = 7.2 Hz), 6.29 (s, 1 H), 7.17 (s, 1 H), 11.90 (bs, 1 H, NH); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 14.0 ($CH_3$), 22.6 ($CH_2$), 29.6 ($CH_2$), 29.7 ($CH_2$), 48.2 ($CH_2$), 48.9 ($CH_2$), 101.9 (CH), 119.8, 124.1, 126.6 (CH), 130.8, 138.7, 153.5; MS (EI, 70 eV) $m/z$ 173 (34), 174 (24), 216 (58), 230 (90), 245 (100) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{14}H_{19}N_3O$ 245.1528, found 245.1530.

**4-(Pyrrolidin-1-yl)-5,6,7,9-tetrahydropyrrolo[2,3-*f*]indolizin-9-one (15c).** Compound **15c** was prepared from **9c** by the method described for **15a**. The reaction was purified by flash column chromatography ($CH_2Cl_2$/MeOH = 97:3) to give **15c** (amorphous solid, 0.21 g, 44%, $R_f$ = 0.25 (EtOAc)): mp 225−226 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$ 1.90 (bs, 4 H), 2.04−2.10 (m, 2 H), 3.02 (t, 2 H, $J$ = 6.0 Hz), 3.34 (s, 4 H), 3.98 (t, 2 H, $J$ = 5.6 Hz), 6.29 (s, 1 H), 7.21 (s, 1 H), 11.88 (bs, 1 H, NH); $^{13}$C NMR (DMSO-$d_6$, 125 MHz) $\delta$ 22.6 ($CH_2$), 25.6 ($CH_2$), 29.3 ($CH_2$), 47.9 ($CH_2$), 51.7 ($CH_2$), 101.7 (CH), 119.5, 124.1, 126.5 (CH), 129.3, 136.2, 152.9; MS (EI, 70 eV) $m/z$ 70 (93), 94 (100), 120 (34), 205 (35), 243 (44) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{14}H_{17}N_3O$ 243.1372, found 243.1371.

**4-(Morpholin-1-yl)-5,6,7,9-tetrahydropyrrolo[2,3-*f*]-indolizin-9-one (15d).** Compound **15d** was prepared from **9d** by the method described for **15a**. The reaction was purified by flash column chromatography ($CH_2Cl_2$/MeOH = 99:1 to 98:2) to give **15d** (amorphous solid, 0.10 g, 13%, $R_f$ = 0.1 ($CH_2Cl_2$/MeOH = 98/2)): mp 198−199 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 2.05−2.12 (m, 2 H), 3.00 (s, 4 H), 3.08 (t, 2 H, $J$ = 7.6 Hz), 3.69 (s, 4 H), 3.98 (t, 2 H, $J$ = 7.0 Hz), 6.40 (s, 1 H), 7.22 (s, 1 H), 11.89 (bs, 1 H, NH); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 22.6 ($CH_2$), 29.2 ($CH_2$), 47.9 ($CH_2$), 51.8 ($CH_2$), 67.7 ($CH_2$), 102.0, 121.7, 123.9, 126.7, 129.8, 136.0, 152.9; MS (EI, 70 eV) $m/z$ 173 (14), 177 (10), 200 (15), 201 (47), 259 (100) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{14}H_{17}N_3O_2$ 259.1321, found 259.1322.

**1-Methyl-4a-hydroxy-4,4a,5,6,7,9-hexahydropyrolo[2,3-*f*]-indolizine-4,9-dione (16).** *Method A.* To a solution of **8e** (0.2340 g, 1.0 mmol) in acetonitrile (20 mL) at 0 °C was added phosphorus oxychloride (0.28 mL, 3.05 mmol, 3 equiv) and *N*-methylmorpholine (0.22 mL, 1.92 mmol, 2 equiv). After the addition was completed, the reaction mixture was heated at 65 °C for 16 h under argon. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. The residue was dissolved in chloroform (10 mL), washed with saturated aqueous $Na_2CO_3$ solution, saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (Hex/EtOAc = 5:5, $R_f$ = 0.1) to give **16** (amorphous solid, 0.1299 g, 0.59 mmol, 59%). The product was recrystallized from toluene to give an analytical sample of **16**: mp 136−137 °C (white solid, toluene).

*Method B.* To a solution of **29** (188 mg, 1.0 mmol) in acetone (1 mL) was added *N*-methylmorpholine *N*-oxide (NMO, 234.3 mg, 2.0 mmol, 2 equiv) and $OsO_4$ (25.4 mg, 0.10 mmol, 0.1 equiv). The reaction mixture was stirred at room temperature for 3 h. The reaction mixiture was quenched with saturated aqueous $Na_2SO_3$ solution at 0 °C for 10 min. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc (50 mL), washed with $H_2O$, saturated aqueous $Na_2CO_3$ solution, saturated aqueous NaCl solution, and then dried over anhydrous $Na_2SO_4$. The solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography to give **16** (amorphous solid, 127.7 mg, 0.58 mmol, 58%).

*Method C.*[13] To a solution of **29** (150 mg, 0.80 mmol) in $CH_2Cl_2$ (1 mL) was added *m*-chloroperbenzoic acid (*m*CPBA, 300 mg, 1.72 mmol, 2.2 equiv) at 0 °C. After the addition was completed, the reaction temperature was raised to room temperature, and the reaction mixture was stirred for 2 h. The mixiture was quenched with saturated aqueous $Na_2SO_3$ solution at 0 °C for 10 min. The residue was extracted with EtOAc, and the organic layer was washed with $H_2O$, saturated aqueous NaCl solution, dried over anhydrous $Na_2SO_4$ and then concentrated under reduced pressure. The residue was purified by flash column chromatography to give **16** (amorphous solid, 109.8 mg, 0.50 mmol, 63%): $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 1.88−1.98 (m, 2 H), 2.02−2.12 (m, 2 H), 3.57−3.58 (m, 2 H), 3.94 (s, 3 H), 6.46 (d, 1 H, $J$ = 2.6 Hz), 6.61 (s, 1 H), 7.15 (d, 1 H, $J$ = 2.6 Hz); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 20.1 ($CH_2$), 34.9 ($CH_2$), 36.0 ($CH_3$), 44.7 ($CH_2$), 91.4, 105.8 (CH), 122.7, 130.2, 130.9 (CH), 156.5, 188.7; MS


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(EI, 20 eV) $m/z$ 108 (100), 202 (27), 220 (50) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{11}H_{12}N_2O_3$ 220.0848, found 220.0849. Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.96; H, 5.50; N, 12.51.

**1-Methyl-4a-allyl-4,4a,5,6,7,9-hexahydropyrrolo[2,3-*f*]indolizine-4,9-dione (18).** To a solution of **8f** (0.7727 g, 2.95 mmol) in acetonitrile (60 mL) at 0 °C was added phosphorus oxychloride (0.81 mL, 8.85 mmol, 3 equiv) and *N*-methylmorpholine (0.67 mL, 5.86 mmol, 2 equiv). After the addition was completed, the reaction mixture was heated at 65 °C for 21 h under argon. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. The residue was dissolved in chloroform (50 mL), washed with saturated aqueous $Na_2CO_3$ solution, saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (Hex/EtOAc = 5:5 to EtOAc) to give products **18** (amorphous solid, 0.1096 g, 0.45 mmol, 15%, $R_f$ = 0.5 (EtOAc)) and **16** (amorphous solid, 0.0213 g, 0.10 mmol, 3%, $R_f$ = 0.3 (EtOAc). **18**: $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 1.95−2.03 (m, 3 H), 2.14−2.17 (m, 1 H), 2.45 (ddd, 1 H, $J$ = 5.8, 10.9, and 16.7 Hz), 3.49−3.55 (m, 1 H), 3.85−3.90 (m, 1 H), 3.97 (s, 3 H), 4.92 (t, 2 H, $J$ = 9.3 Hz), 5.41−5.50 (m, 1 H), 6.44 (d, 1 H, $J$ = 2.9 Hz), 6.69 (d, 1 H, $J$ = 2.9 Hz); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 20.5 ($CH_2$), 32.8 ($CH_2$), 35.9 ($CH_3$), 43.5 ($CH_2$), 44.1 ($CH_2$), 75.2, 105.1 (CH), 119.2, 124.1, 129.6 (CH), 131.2, 131.4 (CH), 156.8, 192.8; MS (EI, 20 eV) $m/z$ 108 (15), 136 (92), 202 (77), 204 (100), 244 (35) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{14}H_{16}N_2O_2$ 244.1212, found 244.1212.

**4a-Hydroxy-4,4a,5,6,7,9-hexahydropyrrolo[2,3-*f*]indolizine-4,9-dione[13] (17).** To a solution of **9e** (0.2210 g, 1.00 mmol) in THF (10 mL) was added $POCl_3$ (0.28 mL, 3.0 mmol, 3.0 equiv) at 0 °C. After the addition was completed, the reaction mixture was heated at reflux temperature for 16 h. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. The residue was dissolved in $CHCl_3$/EtOH (15 mL/15 mL), and then $Na_2CO_3$ (3.18 g, 30 mmol, 30 equiv) was added. The mixture was stirred for 2.5 h. After filtration, the solvent was evaporated and the residue was purified by flash column chromatography ($CH_2Cl_2$/MeOH = 99:1 to 98:2) to give the **17** (amorphous solid, 49.4 mg, 24%, $R_f$ = 0.28 (EtOAc)): mp 188−189 °C;[13] $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 1.88−1.96 (m, 2 H), 2.06−2.12 (m, 2 H), 3.57−3.61 (m, 2 H), 6.49 (t, 1 H, $J$ = 2.4 Hz), 6.62 (s, 1 H, OH), 7.10 (t, 1 H, $J$ = 2.6 Hz), 12.60 (bs, 1 H, NH); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 20.2 ($CH_2$), 34.8 ($CH_2$), 44.5 ($CH_2$), 91.8, 106.7 (CH), 121.7, 125.3 (CH), 132.7, 156.0, 188.9; MS (EI, 70 eV) $m/z$ 93 (74), 94 (100), 206 (29) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{10}H_{10}N_2O_3$ 206.0691, found 206.0694.

**4a-Allyl-4,4a,5,6,7,9-hexahydropyrrolo[2,3-*f*]indolizine-4,9-dione (19).** To a solution of **9f** (5.40 g, 21.84 mmol) in THF (218 mL) was added $POCl_3$ (6.01 mL, 65.5 mmol, 3.0 equiv) at 0 °C. After the addition was completed, the reaction mixture was heated at reflux temperature for 14 h. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. The residue was dissolved in $CH_2Cl_2$. The solution was washed with saturated aqueous $Na_2CO_3$ solution, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (Hex/$CHCl_3$ = 1:9 then $CHCl_3$/MeOH = 99:1) to give the products **19** (amorphous solid, 0.34 g, 1.48 mmol, 7%, $R_f$ = 0.45 (EtOAc)) and **17** (amorphous solid, 0.95 g, 4.61 mmol, 21%, $R_f$ = 0.28 (EtOAc)). **19**: mp 138−139 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.08−2.15 (m, 3 H), 2.22−2.28 (m, 1 H), 2.48−2.53 (m, 1 H), 2.59−2.64 (m, 1 H), 3.61−3.66 (m, 1 H), 3.99−4.06 (m, 1 H), 4.96−5.03 (m, 2 H), 5.47−5.57 (m, 1 H), 6.59 (s, 1 H), 7.02 (s, 1 H), 11.92 (bs, 1 H, NH); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 20.5 ($CH_2$), 32.8 ($CH_2$), 43.5 ($CH_2$), 44.1 ($CH_2$), 75.7, 106.2 (CH), 119.4 ($CH_2$), 123.4, 125.1 (CH), 131.2 (CH), 133.0, 156.9, 192.8; MS (ESI) $m/z$ 188 (34), 229 (100) (M − 1); HRMS (ESI, TOF) calcd for $C_{13}H_{13}N_2O_2$ 229.0977 (M − 1), found 229.0978.

***N*-[(1-Methylpyrrol-2-yl)carbonyl]-*N*-benzylglycine methyl ester (24).** A mixture of *N*-methylpyrrole-2-carboxylic acid (**23**) (1.0572 g, 8.45 mmol, 1.2 equiv), EDC (1.6291 g, 8.50 mmol, 1.2 equiv) and HOBt (1.1482 g, 8.50 mmol, 1.2 equiv) in dichloromethane (50 mL) was stirred for 10 min at room temperature under argon. *N*-Benzylglycine methyl ester[29] (*N*-Bn-Gly-OMe, 1.2852 g, 7.17 mmol) and triethylamine (3.0 mL, 21.34 mmol, 3 equiv) were added to the solution, and the reaction mixture was stirred at room temperature for 18 h. The solution was concentrated under reduced pressure. The residue was dissolved in chloroform (30 mL), washed with $H_2O$ and saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by flash column chromatography (Hex/EtOAc = 9:1 then EtOAc) to give **24** (brown amorphous solid, 1.7011 g, 5.94 mmol, 83%, $R_f$ = 0.1 (Hex/EtOAc = 9:1)): mp 91−94 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.72 (s, 3 H), 3.82 (s, 3 H), 4.12 (bs, 2 H), 4.89 (bs, 1 H), 6.00 (t, 2 H, $J$ = 2.8 Hz), 6.36−6.37 (m, 1 H), 6.71 (s, 1 H), 7.25−7.31 (m, 3 H), 7.35−7.39 (m, 2 H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 36.0, 47.2, 52.1, 54.4, 107.0, 112.6, 124.3, 126.7, 127.6, 128.9, 136.7, 165.1, 169.9; MS (EI, 70 eV) $m/z$ 91 (22), 108 (100), 178 (48), 286 (10) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{16}H_{18}N_2O_3$ 286.1317, found 286.1322.

**3-[[(1-Methylpyrrol-2-yl)carbonyl]-*N*-benzyl-amino]ethanic acid (25).** To a solution of *N*-[(1-methylpyrrol-2-yl)carbonyl]-*N*-benzylglycine methyl ester (**24**) (1.4493 g, 5.06 mmol) in methanol (30 mL) was added 15% aqueous NaOH solution (30 mL). The reaction mixture was heated at reflux temperature for 3 h. The mixture was concentrated under reduced pressure. The residue was partitioned between water and chloroform. The pH of the aqueous layer was adjusted to 2 with 4 N aqueous HCl solution. The aqueous solution was then extracted with chloroform (30 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give **25**, which was used for the subsequent reaction without further purification (brown oil, 1.3753 g, 5.05 mmol, quantitatively, $R_f$ = 0.5 (Hex/EtOAc = 5:5)): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.81 (s, 3 H), 4.14 (s, 2 H), 4.90 (bs, 2 H), 6.01 (t, 2 H, $J$ = 2.8 Hz), 6.40 (t, 2 H, $J$ = 1.0 Hz), 6.72 (s, 1 H), 7.26−7.40 (m, 5 H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 36.1, 47.9, 54.2, 107.2, 113.2, 123.9, 127.0, 127.5, 127.7, 129.0, 136.3, 165.6, 173.4; MS (EI, 70 eV) $m/z$ 81 (54), 91 (31), 108 (100), 109 (29), 272 (57) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{15}H_{16}N_2O_3$ 272.1161, found 272.1163.

***N*-[(1-Methylpyrrol-2-yl)carbonyl]-*N*-benzylglycine dimethylamide (26).** A mixture of *N*-[(1-methylpyrrol-2-yl)carbonyl]-*N*-benzylglycine (**25**) (1.0106 g, 3.71 mmol), EDC (1.4180 g, 7.40 mmol, 2 equiv) and HOBt (1.0000 g, 7.40 mmol, 2 equiv) in $CH_2Cl_2$ (30 mL) was stirred for 10 min at room temperature under argon. Dimethylammonium chloride (0.4532 g, 5.55 mmol, 1.5 equiv) and triethylamine (2.1 mL, 14.80 mmol, 4 equiv) were added to the solution. The reaction mixture was stirred for an additional 19 h at ambient temperature under argon and then concentrated under reduced pressure. The residue was dissolved in chloroform (30 mL), washed with $H_2O$ and saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by flash column chromatography (Hex/EtOAc = 3:7, $R_f$ = 0.1) to give **26** (brown amorphous solid, 1.0744 g, 3.59 mmol, 97%): mp 92−95 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.90 (bs, 3 H), 2.95 (s, 3 H), 3.80 (s, 3 H), 4.16 (s, 2 H), 4.91 (bs, 2 H), 5.96 (bs, 1 H), 6.32 (bs, 1 H), 6.67 (bs, 1 H), 7.27−7.29 (m, 3 H), 7.34−7.37 (m, 2 H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 35.6 ($CH_3$), 35.8 ($CH_3$), 36.1 ($CH_3$), 46.1 ($CH_2$), 54.0 ($CH_2$), 106.7 (CH), 111.8 (CH), 124.7, 126.4 (CH), 126.7 (CH), 127.3 (CH), 127.5 (CH), 128.7 (CH), 137.1, 165.2, 167.5; MS (EI, 70 eV) $m/z$ 91 (34), 108 (100), 191 (95), 213 (71), 299 (4) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{17}H_{21}N_3O_2$ 299.1634, found 299.1626.

**6-Benzyl-1-methyl-4,5,6,7-tetrahydropyrrolo[2,3-*c*]pyridine-4,5,7-trione (28).** To a solution of *N*-[(1-methylpyrrol-2-yl)-carbonyl]-*N*-benzylglycine dimethylamide (**26**) (0.2995 g, 1.0 mmol) in acetonitrile (20 mL) at 0 °C was added phosphorus oxychloride (0.28 mL, 3.05 mmol, 3 equiv) and *N*-methylmorpholine (0.23 mL, 2.01 mmol, 2 equiv). After the addition was completed, the reaction mixture was heated at 65 °C for 21 h. The solution was cooled to room temperature and then concentrated under reduced pressure. The residue was dissolved in chloroform (20 mL), washed with saturated

aqueous $Na_2CO_3$ solution, saturated NaCl solution, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The first attempt to purify the resulting residue by flash column chromatography (Hex/EtOAc = 3:7, $R_f$ = 0.3) gave a part of the crude product **27**, which was characterized only by $^1$H NMR. 6-Benzyl-4-dimethylamino-1-methylpyrrolo[2,3-*c*]pyridin-7-one (**27**): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.70 (s, 6 H), 4.16 (s, 3 H), 5.16−5.16 (m, 2 H), 6.29 (s, 1 H), 6.34 (d, 1 H, $J$ = 2.9 Hz), 6.96 (d, 1 H, $J$ = 2.8 Hz), 7.22−7.31 (m, 5 H). Further purification by flash column chromatography (Hex/EtOAc = 3:7, $R_f$ = 0.5) afforded **28** (white amorphous solid, 0.1207 g, 0.45 mmol, 45%). The solid was recrystallized with toluene to give the analytical sample of **28** (white solid, 0.0982 g, 0.35 mmol, 37%). 6-Benzyl-1-methyl-4,5,6,7-tetrahydropyrrolo[2,3-*c*]pyridine-4,5,7-trione (**28**): mp 151−154 °C (toluene); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 4.04 (s, 3 H), 5.11 (s, 2 H), 6.71 (d, 1 H, $J$ = 2.0 Hz), 6.92 (d, 1 H, $J$ = 1.8 Hz), 7.23−7.31 (m, 3 H), 7.43−7.45 (m, 2 H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 36.7 ($CH_3$), 43.4 ($CH_2$), 108.2 (CH), 124.9, 127.4, 127.8 (CH), 128.5 (CH), 129.1 (CH), 132.1 (CH), 136.3, 157.1, 158.8, 169.7; MS (EI, 70 eV) $m/z$ 107 (70), 108 (15), 177 (14), 240 (11), 268 (100) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{15}H_{12}N_2O_3$ 268.0848, found 268.0851.

***N*-[(1-Methylpyrrol-2-yl)carbonyl]prolinol (5c).** *Method A.* To a solution of *N*-[(1-methylpyrrol-2-yl)carbonyl]proline methyl ester (**5b**, 0.24 g, 1.02 mmol) in THF/EtOH (1/2 mL) was added LiCl (0.0861 g, 2.03 mmol, 2 equiv) and $NaBH_4$ (0.0768 g, 2.03 mmol, 2 equiv) at 0 °C. The reaction mixture was stirred for 8 h at room temperature then the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (20 mL), washed with $H_2O$, saturated aqueous NaCl solution, dried over anhydrous $Na_2SO_4$, and then concentrated under reduced pressure. The residue was purified by flash column chromatography (Hex/EtOAc = 6:4, $R_f$ = 0.3) to give **5c** (oil, 0.19 g, 0.92 mmol, 90%).

*Method B.* A mixture of 1-methyl-2-trichloroacetylpyrrole (0.23 g, 1.0 mmol), prolinol (151.6 mg, 1.50 mmol) and $Na_2CO_3$ (0.32 g, 3 mmol) in $CH_3CN$ (10 mL) was heated at reflux temperature for 4 h. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (20 mL), washed with $H_2O$, saturated aqueous NaCl solution, and then dried over anhydrous $Na_2SO_4$. The solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (Hex/EtOAc = 6:4, $R_f$ = 0.3) to give **5c** (oil, 0.19 g, 0.92 mmol, 92%): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.58−1.67 (m, 1 H), 1.73−1.96 (m, 2 H), 2.08−2.16 (m, 1 H), 3.60−3.72 (m, 2 H), 3.84 (s, 3 H), 3.90−3.95 (m, 1 H), 4.41 (dd, 1 H, $J$ = 2.7 and 7.5 Hz), 4.96 (bs, 1 H, OH), 6.09 (dd, 1 H, $J$ = 2.7 and 3.7 Hz), 6.54 (dd, 1 H, $J$ = 1.5 and 3.9 Hz), 6.70 (d, 1 H, $J$ = 1.8 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 25.1 ($CH_2$), 28.3 ($CH_2$), 36.6 (CH), 50.9 ($CH_2$), 61.5 (CH), 67.6 (CH), 106.9 (CH), 114.3 (CH), 125.6, 127.2 (CH), 164.4; MS (FAB) $m/z$ 84 (36), 108 (100), 209 (53) (M + 1); HRMS (FAB, magnetic sector) calcd for $C_{11}H_{17}N_2O_2$ 209.1290 (M + 1), found 209.1300.

**1-Methyl-5,6,7,9-tetrahydropyrrolo[2,3-*f*]indolizin-9-one (29).** A mixture of **5c** (0.1000 g, 0.48 mmol) and IBX[18] (0.4032 g, 1.44 mmol) in EtOAc (5 mL) was heated at reflux temperature for 3 h. After cooling to room temperature, the reaction mixture was filtered through Celite, and the solid was quickly washed with EtOAc. The combined filtrate was concentrated under reduced pressure to give the crude product of *N*-[(1-methylpyrrol-2-yl)carbonyl]-2-formylpyrrolidine (**5d**), which was used for subsequent reaction without further purification. To the solution of the crude **5d** (0.48 mmol, obtained from the oxidation of **5c** without purification) in $CH_2Cl_2$ (5 mL) was slowly added methanesulfonic acid (69.2 mg, 0.72 mmol, 1.5 equiv) at 0 °C. After the addition was completed, the reaction temperature was raised to room temperature, and the reaction mixture was stirred for 1.5 h under argon. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc (25 mL), washed with $H_2O$, saturated aqueous $Na_2CO_3$ solution, saturated aqueous NaCl solution, and then dried over anhydrous $Na_2SO_4$. The solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (Hex/EtOAc = 5:5, $R_f$ = 0.3) to give **29** (amorphous solid, 61.4 mg, 0.33 mmol, 68%). The solid was recrystallized with Hex/EtOAc to give the analytical sample of **29**: mp 89−91 °C (Hex/EtOAc); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.11−2.20 (m, 2 H), 3.02 (t, 2 H, $J$ = 7.6 Hz), 4.10 (t, 2 H, 7.2 Hz), 4.15 (s, 3 H), 6.15 (d, 1 H, $J$ = 2.4 Hz), 6.32 (s, 1 H), 6.92 (d, 1 H, $J$ = 2.4 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 22.7 ($CH_2$), 30.8 ($CH_2$), 35.6 ($CH_3$), 47.3 ($CH_2$), 96.1 (CH), 101.0 (CH), 121.2, 131.3, 132.7, 140.2, 155.0; MS (EI, 70 eV) $m/z$ 187 (100), 188 (68) ($M^+$); HRMS (EI, magnetic sector) calcd for $C_{11}H_{12}ON_2$ 188.0950, found 188.0944. Anal. Calcd for $C_{11}H_{12}ON_2$: C, 70.19; H, 6.43; N, 14.88. Found: C, 69.98; H, 6.36; N, 14.86.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

$^1$H and $^{13}$C NMR spectra of all the synthesized compounds and X-ray structural data (CIF) of compound **28**. 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 interest.

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## ■ DEDICATION

Dedicated to Professor Hung-wen (Ben) Liu on the occasion of his 60th birthday.

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