JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

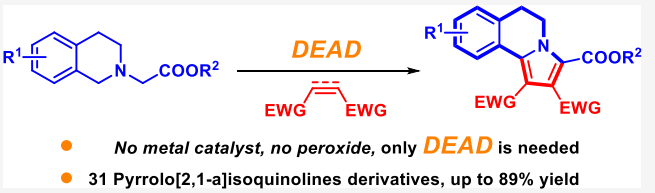
Diethyl Azodicarboxylate-Promoted Oxidative [3 + 2] Cycloaddition for the Synthesis of Pyrrolo[2,1-*a*]isoquinolines

Ya-Wen Xu, Jiankun Wang, Guangji Wang,* and Le Zhen*

Cite This: https://dx.doi.org/10.1021/acs.joc.0c01567 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A novel metal-free protocol for the effective and efficient construction of pyrrolo[2,1-*a*]isoquinolines via a diethyl azodicarboxylate (DEAD)-promoted oxidative [3 + 2] cycloaddition/aromatization tandem reaction is described. Instead of the reported two-component oxidation systems, DEAD, as the sole oxidant, could smoothly transfer the tertiary amines to azomethine ylides via oxidation-deprotonation tandem process. The reaction proceeded with a broad substrate scope, giving rise to products in moderate to good isolated yields.



INTRODUCTION

Lamellarins were first discovered by Faulkner and co-workers in 1985.[1] These marine natural alkaloids, bearing a pyrrolo[2,1-*a*]isoquinoline core, were proven to have a wide spectrum of pharmacological activities.[2,3] Some lamellarins exhibited potent antitumor activity including multidrug resistant cell lines by inhibition,[3a,d] for example, human topoisomerase I.[3e] Also, sulfated lamellarins such as lamellarin α-20-sulfate were expected to be selective human immunodeficiency virus integrase inhibitors at noncytotoxic concentrations.[3b,c] To better understand these attractive compounds and their biological activities, as early as 1997, a number of laboratories realized the total synthesis.[4,5] Furthermore, the construction of the pyrrolo[2,1-*a*]isoquinoline core has become a crucial issue, for which a variety of synthetic methods have been developed, including 1,3-dipolar cycloaddition,[4a,c,6] oxidative dimerization,[7] and double-barreled Heck cyclization,[8] providing a wealth of ideas for the synthesis of natural and non-natural lamellarins.

The 1,3-dipole cycloaddition reaction between azomethine ylides and dipolarophiles is currently a widely accepted approach to build the pyrrolo[2,1-*a*]isoquinoline core.[9−11] In this strategy, the ylide was generated by a deprotonation process of the corresponding iminium ion, which could originate from the direct oxidation of tertiary amines. Three two-component oxidation systems (Scheme 1) have been proposed for the formation of the fused-ring skeleton, including the metal catalyst/peroxide system,[9] the photocatalyst/O_2 system,[10] and the iodide/peroxide system.[11] Without a doubt, the exploration of a novel and efficient oxidation system has been the focus of research. Indeed, a mechanistically distinct method based on an external oxidant-free electrochemical protocol has been well established by Li and co-workers in 2019, making a breakthrough in the oxidation/[3 + 2] cycloaddition cascade.[12]

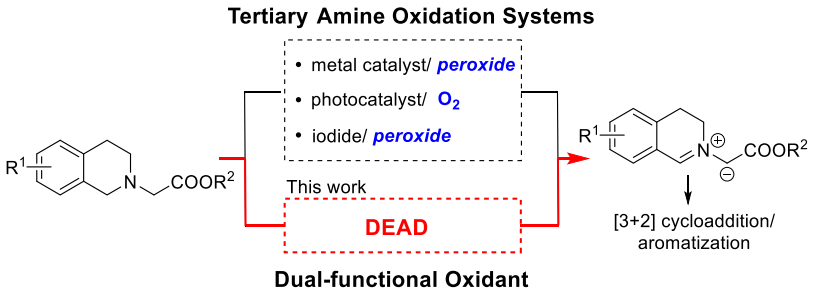
In the abovementioned three oxidation systems, the initial step always involves single-electron transfer to generate iminium ions, and the subsequent deprotonation process almost totally relies on the superstoichiometric peroxide anions, accumulating large amounts of hydrogen peroxide as a byproduct. In addition, complex catalytic system, high reaction temperature, and unsatisfactory yield are also potential factors that affect the practical application of the above methods. It is imminent to develop a simpler and more efficient synthetic technology. Therefore, we believe that choosing an appropriate dual-functional reagent with both oxidation and dehydrogenation functions may greatly simplify the reaction system.

Diethyl azodicarboxylate (DEAD) has long been employed as an essential electrophilic species in the Mitsunobu reaction.[13] For more than a decade, the oxidative abilities of DEAD for the transformation of tertiary amines to iminium ions have gradually come into view.[14,15] In 2008, Li and co-workers first revealed that DEAD could convert tertiary amines to corresponding enamines, which underwent the 1,3-dipolar addition with sulfonyl azide. Later, the same group expanded the application of DEAD in the alkynylation and hydration of tertiary amines. In 2016, the oxidative cross-dehydrogenative coupling promoted by DEAD was successfully achieved between *N*-phenyl tetrahydroisoquinoline and nucleophiles. Quite recently, our group explored two types of DEAD-promoted oxidative Ugi-type reactions of tertiary amines.[16,17] We have been committed to broadening the application range

Received: July 1, 2020

https://dx.doi.org/10.1021/acs.joc.0c01567
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 1. Oxidation Systems for the Generation of Azomethine Ylides

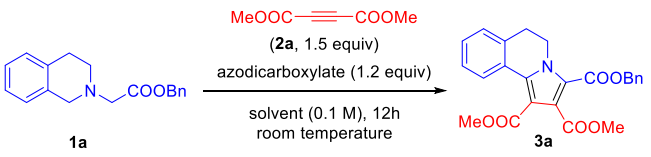


of DEAD-assisted oxidations, which prompted us to explore the [3 + 2] cycloaddition-based synthesis of pyrrolo[2,1-*a*]isoquinoline.

RESULTS AND DISCUSSION

We optimized the condition using benzyl 2-(3,4-dihydroisoquinolin-2-(1*H*)-yl) acetate **1a** and dimethyl but-2-ynedioate **2a** as model substrates, choosing 1.2 equiv of azodicarboxylate as the oxidant. All reactions were carried out at room temperature. The desired product **3a** was obtained in good yield (Table 1, entry 1) when using DEAD as the oxidant and

Table 1. Optimization of Reaction Conditions[a]



entry	azodicarboxylate	solvent	yield (%)[b]
1	DEAD	CH_3CN	80
2	DIAD	CH_3CN	55
3	DBAD	CH_3CN	13
4	DEAD	DCM	82
5	DEAD	DCE	89
6	DEAD	toluene	83
7	DEAD	THF	77
8	DEAD	1,4-dioxone	71
9	DEAD	DMF	64
10[c]	DEAD	DCE	87
11[d]	DEAD	DCE	74
12[e]	DEAD	DCE	53

[a]**1a** (0.3 mmol), **2a** (0.45 mmol), azodicarboxylate (0.36 mmol), and solvent (3.0 mL). DEAD and **2a** were added at the same time; reaction for 12 h at room temperature. [b]isolated yield. [c]azodicarboxylate (0.6 mmol). [d]**2a** (0.36 mmol). [e]**1a** was treated with DEAD for 2 h and treated with **2a** subsequently.

CH_3CN as the solvent, while with diisopropyl azodicarboxylate (DIAD) and di-*tert*-butyl azodicarboxylate (DBAD) in CH_3CN, **3a** was isolated only in 55 and 13% yields respectively (Table 1, entries 2−3). To our delight, the reaction proceeded smoothly under a better yield when nonpolar solvents such as dichloromethane (DCM), dichloroethane (DCE), or toluene were used (Table 1, entries 4−6). Unlike CH_3CN, other polar solvents such as tetrahydrofuran (THF), 1,4-dioxone, or dimethyl formamide (DMF) did not maintain the reactivity (Table 1, entries 7−9). With an excess amount of DEAD, only limited yield improvement was observed (Table 1, entries 10). The yield was slightly down as the equivalent of **2a** decreased, indicating that the equivalent was a key factor (Table 1, entries 11). In addition, the pretreatment of DEAD led to the decrease of yield (Table 1, entries 12). According to the above results, the sequential [3 + 2] cycloaddition/oxidative aromatization reaction of **1a** and **2a** (1.5 equiv), with DEAD (1.2 equiv) as the oxidant, was optimally carried out in DCE (0.1 M) at room temperature.

With these optimized reaction conditions in hand, we decided to explore the reaction scope, which is presented in Scheme 2. Dimethyl but-2-ynedioate (**2a**) and diethyl but-2-ynedioate (**2b**) were chosen as the dipolarophile. Substrate **1** with various ester groups (e.g., benzyl, methyl, ethyl, and *tert*-butyl) reacted smoothly with dipolarophile **2**, affording the corresponding products **3a**−**h** in 75−89% yield. The reaction appears quite general concerning the ester groups, and the steric hindrance effect of the ester group has little effect on the reaction. Moreover, the electron-donating group (e.g., methoxy) and the electron-withdrawing group (e.g., bromo) on the benzene ring of **1** were both well-tolerated, giving rise to **3i** and **3j** in good yield.

When another activated alkyne methyl propiolate **2c** was employed as the dipolarophile (Scheme 3), model substrate **1a** successfully provided the desired product **3k** in 71% yield. The reaction also gave comparable results when benzyl ester was replaced by the ethyl group. However, the substrate with dimethoxy on dihydroisoquinoline has poor reactivity to the [3 + 2] cycloaddition, and only a 29% yield of **3m** was obtained.

Next, we investigated other dipolarophiles such as 1,4-naphthoquinone and N-substituted maleimide (Scheme 4). We still examined the reactions involving **1** containing different ester groups. Similar to the above, the ester group has little effect on the reaction, and **1** can react well with 1,4-naphthoquinone in good yield. Structural variation in the ester groups of **1** can also be accomplished without obvious loss in the reaction efficiency. The electrical properties of the substituents also did not affect the reaction yield. In particular, the yield of the reaction involving the substrate containing the dimethoxy group reached 85%.

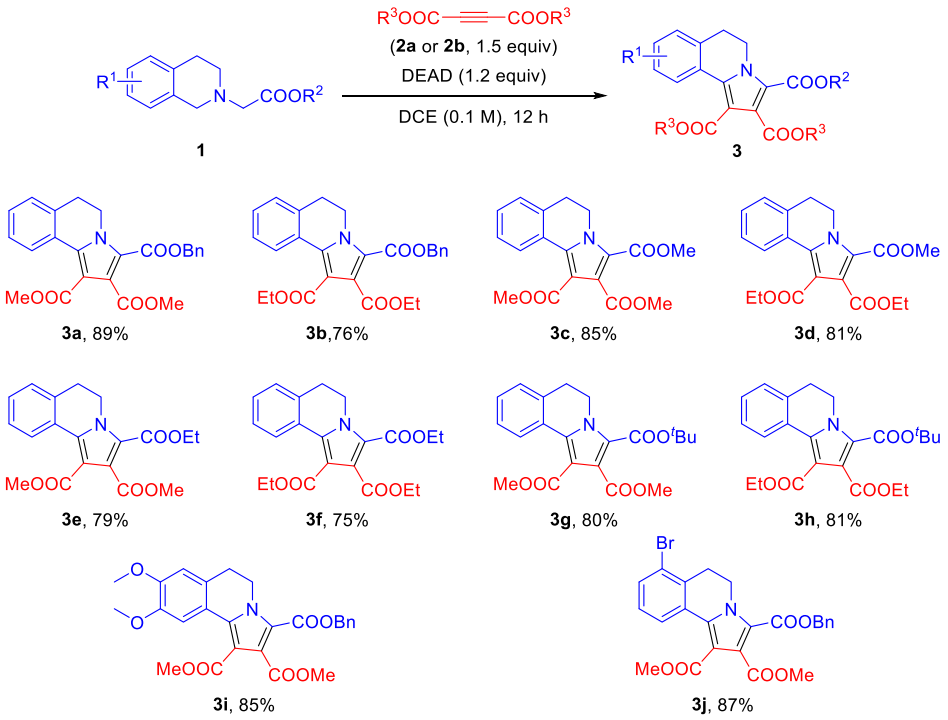
Similarly, **1** can also be reacted with N-substituted maleimide derivatives, getting the desired product in moderate to good yields. It is worth noting that *N*-bromosuccinimide (NBS) must be added to the reaction in which N-substituted maleimide participated.

Besides, **1a** and (*E*)-(2-nitrovinyl)benzene **2g** could also achieve the [3 + 2] cycloaddition reaction in 67% yield (Scheme 5).

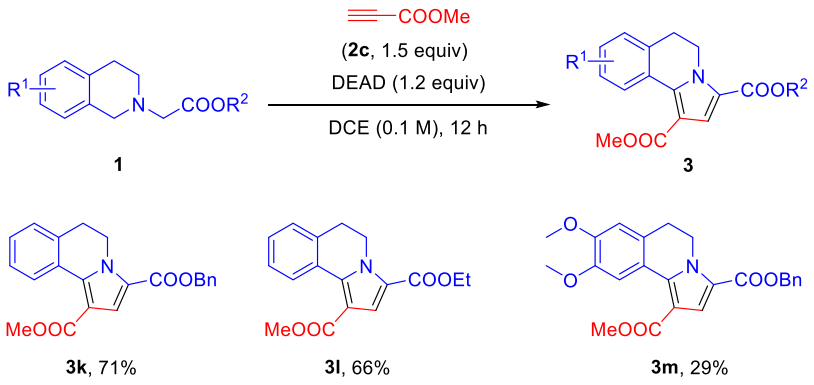
After carrying out a series of substrate expansions, we further investigated the practicality of the reaction. First, we completed the gram-scale preparation (up to **3g**) of product **3a**, which afforded the comparable yield and confirmed the convenience of the protocol in this study (Scheme 6).

https://dx.doi.org/10.1021/acs.joc.0c01567
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 2. Substrate Scope A



Scheme 3. Substrate Scope B



We also synthesized a series of pyrrolo[2,1-*a*]isoquinoline derivatives (Scheme 7). The benzyl ester of **3a** was removed from the Pd/C−H_2 system to obtain carboxylic acid **4**. The carboxyl group of **4** was selectively reduced, converting the carboxyl group to hydroxymethyl (Scheme 7, eq 1). On the other hand, after **4** was treated with trifluoroacetyl (TFA), decarboxylation occurs to generate **6**, which could further undergo hydrazinolysis and cyclization, giving rising to luminol analogue 7. The aromatization of products was also developed. **3a** was stable with the treatment of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), while **3i**, containing dimethoxy substitution, could smoothly undergo further aromatization. We have implemented a variety of derivation methods, and some of the derivatives, demonstrating potential for further applications in drug design, are now involved in the ongoing project in our group.

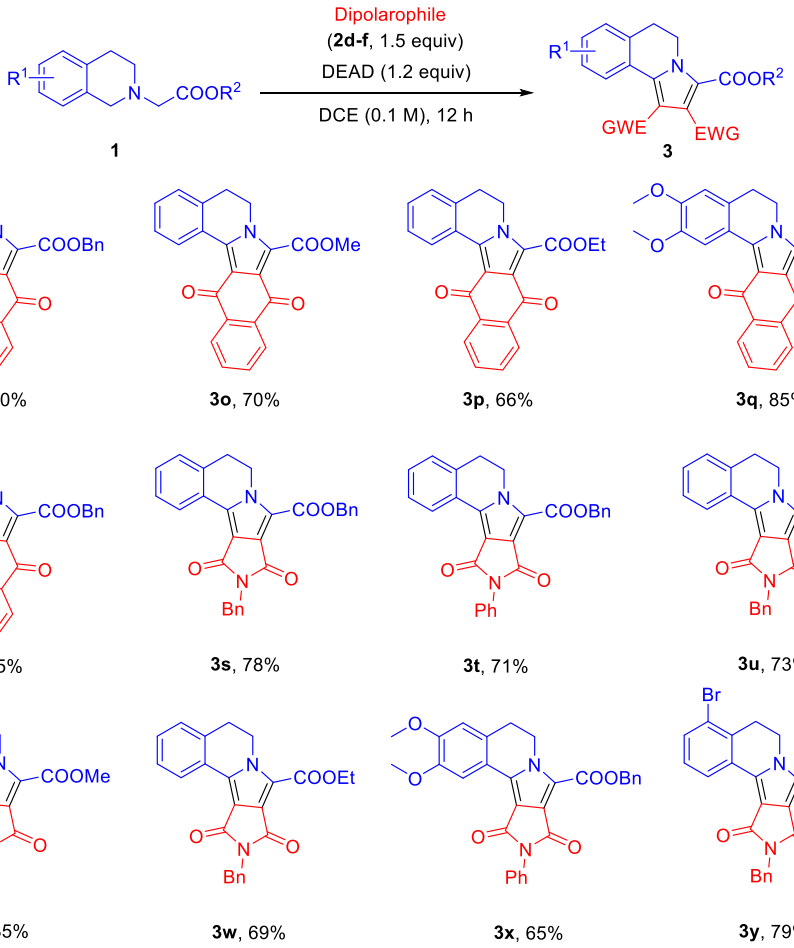
The plausible reaction pathway is illustrated in Scheme 8. The electrophilic DEAD and tertiary amine **1a** underwent nucleophilic addition, and the corresponding intermediate carried out intramolecular dehydrogenation, furnishing the iminium ion **A**. The formation of the key iminium ion **A** was accompanied by the production of the basic counter anion of DEAD (1*H*-DEAD anion). Subsequently, the anion could easily remove the α-H of the iminium ion **A**, affording the azomethine ylide **B**. The subsequent [3 + 2] cycloaddition occurred between ylide **B** and dimethyl but-2-ynedioate to form intermediate **C**, which is then aromatized to produce **3a**. Notably, DEAD served as both an oxidant and a base during this process.

CONCLUSIONS

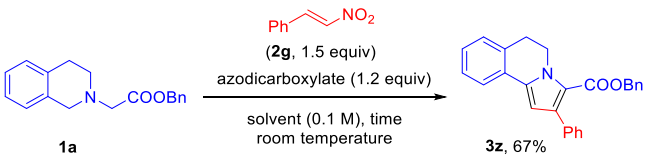
In conclusion, the novel metal-free methodology described above is a broadly reliable pathway for the synthesis of a range of pyrrolo[2,1-*a*]isoquinoline scaffolds. The substrate scope is large, and the isolated yields are desired under a simple oxidation system, suggesting that DEAD should be a promising oxidant for the practical synthesis of the complex natural product-like compounds via the oxidative [3 + 2] cycloaddition/aromatization tandem reactions. Moreover, DEAD is indeed a versatile oxidant of tertiary amines, which we are

https://dx.doi.org/10.1021/acs.joc.0c01567
J. Org. Chem. XXXX, XXX, XXX−XXX

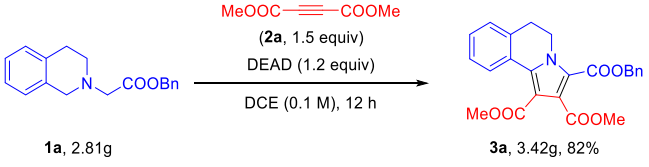
Scheme 4. Substrate Scope C



Scheme 5. Substrate Scope D



Scheme 6. Gram-Scale Preparation of 3a



exploring for application in the construction of complex molecules.

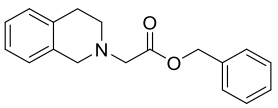
EXPERIMENTAL SECTION

General Methods. ^{1}H and ^{13}C NMR spectra were recorded on ACF*300Q and 500Q Bruker spectrometers. High-resolution mass spectra were recorded in a Q-TOF instrument equipped with an ESI source. Reactions were monitored by thin-layer chromatography (TLC) on silica gel 60 F254 plates. Column chromatography was carried out on silica gel (200−300 mesh). Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm); multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br s = broad singlet, and coupling constant (s) in Hz, integration). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm).

*General Procedure for Synthesis of Substrate **1**. Benzyl 2-(3,4-Dihydroisoquinolin-2(1H)-yl)acetate (**1a**).* A dried 250 mL round-bottom flask was equipped with a magnetic stir bar and charged with 1,2,3,4-tetrahydroisoquinoline (4 g, 30 mmol), Na_2CO_3 (6.3 g, 20 mmol), and THF (60 mL, 0.5 M). Then, methyl 2-bromoacetate (6.8 g, 40 mmol) was added, and the resulting mixture appeared as a pale yellow emulsion. The reaction was stirred at room temperature overnight. After 1,2,3,4-tetrahydroisoquinoline was completely consumed as indicated by TLC, ethyl acetate and water were added to the reaction. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. After the organic phase was filtered and concentrated, the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 20:1 to 2:1) to give **1a** (4.97 g, 59% yield).

The other substrates could be prepared with the abovementioned method.

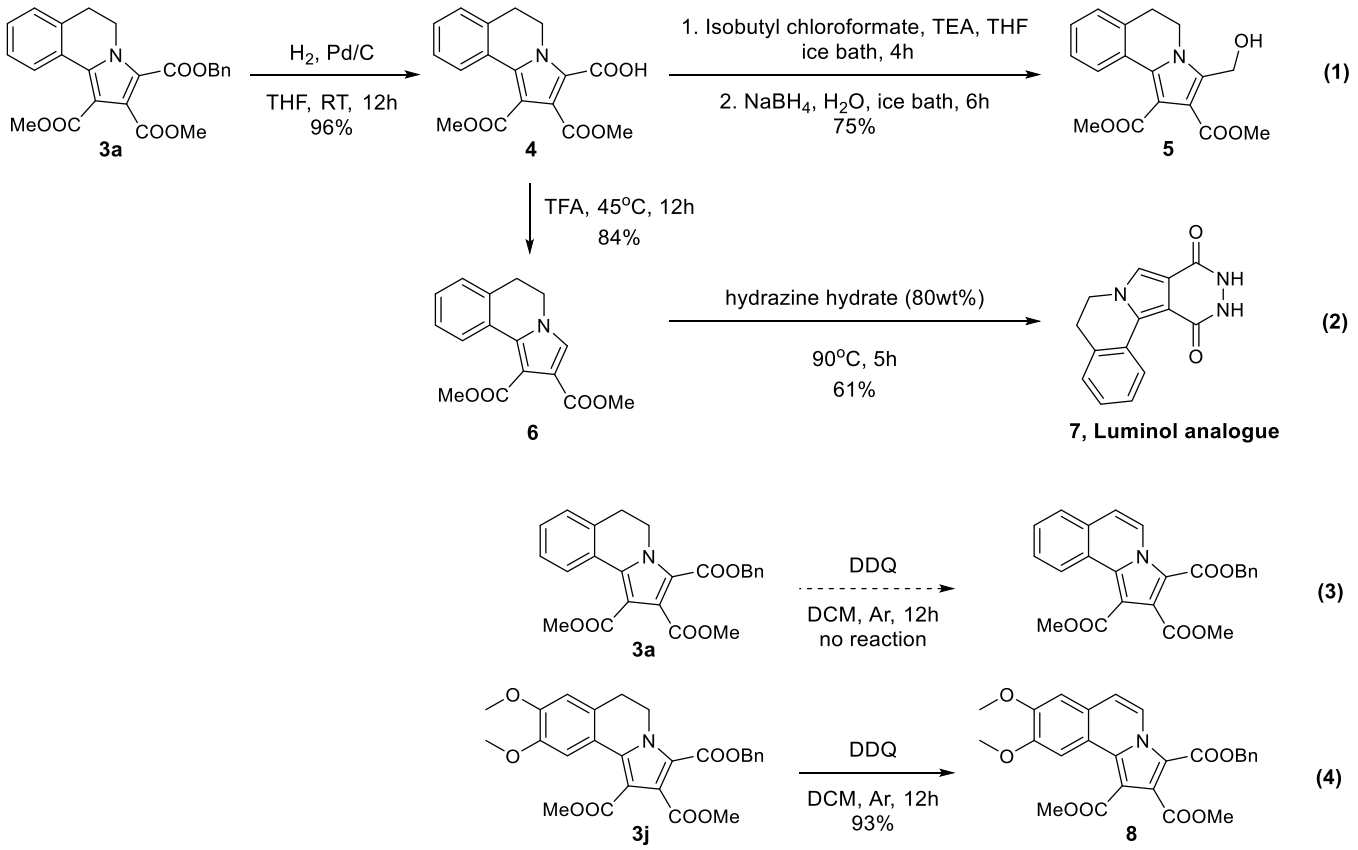
*Benzyl 2-(3,4-Dihydroisoquinolin-2(1H)-yl)acetate (**1a**).* Eluent: petroleum ether/ethyl acetate: 20/1 to 5/1. Colorless oil, 4.97 g, 59%



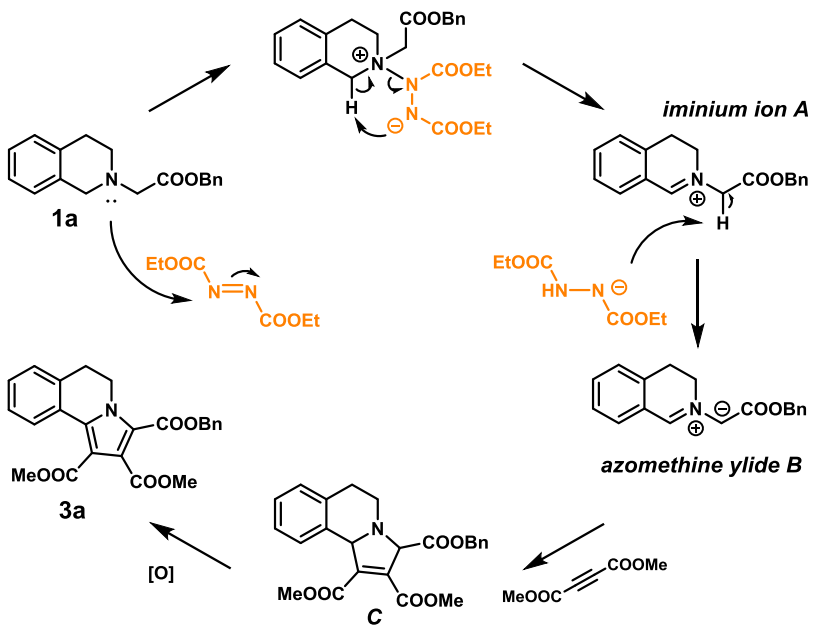
yield. ^{1}H NMR (300 MHz, chloroform-*d*): δ 7.46−7.27 (m, 5H), 7.17−7.07 (m, 3H), 7.04−6.95 (m, 1H), 5.21 (s, 2H), 3.81 (s, 2H), 3.48 (s, 2H), 3.02−2.84 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, chloroform-*d*): δ 169.6, 135.1, 133.6, 133.1, 128.0, 127.9, 127.6,

https://dx.doi.org/10.1021/acs.joc.0c01567
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 7. Further Experiments

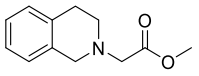


Scheme 8. Proposed Mechanism



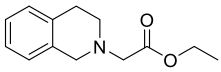
125.8, 125.5, 124.9, 65.7, 58.3, 54.6, 49.9, 28.2. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{20}NO_2$, 282.1489; found, 282.1493.

Methyl 2-(3,4-Dihydroisoquinolin-2(1H)-yl)acetate (**1b**). Eluent: petroleum ether/ethyl acetate: 20/1 to 5/1. Colorless oil, 330 mg, 54% yield. ^{1}H NMR (300 MHz, chloroform-d): δ 7.24−7.08 (m, 3H), 7.08−6.98 (m, 1H), 3.82 (s, 2H), 3.78 (s, 3H), 3.45 (s, 2H), 3.01−2.86 (m, 4H). ^{13}C{1H}NMR (75 MHz, chloroform-d): δ 170.9, 134.1, 133.7, 128.6, 126.4, 126.1, 125.6, 59.0, 55.3, 51.6, 50.7, 28.9. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{12}H_{16}NO_2$, 206.1176; found, 206.1180.



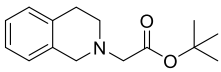
Ethyl 2-(3,4-Dihydroisoquinolin-2(1H)-yl)acetate (**1c**). Eluent: petroleum ether/ethyl acetate: 20/1 to 5/1. Light yellow oil, 513 mg, 78% yield. ^{1}H NMR (300 MHz, chloroform-d): δ 7.45−6.64 (m,

https://dx.doi.org/10.1021/acs.joc.0c01567
J. Org. Chem. XXXX, XXX, XXX−XXX



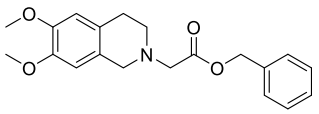
4H), 4.25 (q, J = 7.1 Hz, 2H), 3.84 (s, 2H), 3.45 (s, 2H), 2.94 (dt, J = 9.2, 4.7 Hz, 4H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 170.3, 134.2, 133.8, 128.7, 126.4, 126.2, 125.6, 60.6, 59.0, 55.2, 50.6, 28.8. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{13}H_{18}NO_2$, 220.1332; found, 220.1330.

*tert-Butyl 2-(3,4-Dihydroisoquinolin-2(1H)-yl)acetate (**1d**).* Eluent: petroleum ether/ethyl acetate: 20/1 to 5/1. Light yellow oil, 555



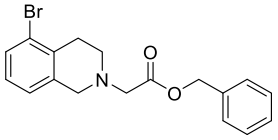
mg, 75% yield. ^{1}H NMR (300 MHz, chloroform-d): δ 7.20−6.92 (m, 4H), 3.83 (s, 2H), 3.34 (s, 2H), 2.94 (h, J = 5.1 Hz, 4H), 1.52 (s, 9H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 169.7, 134.5, 133.9, 128.6, 126.4, 126.0, 125.5, 81.0, 59.7, 55.2, 50.5, 29.0, 28.2. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{15}H_{22}NO_2$, 248.1645; found, 248.1652.

*Benzyl 2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-acetate (**1e**).* Eluent: petroleum ether/ethyl acetate: 20/1 to 2/1.



Colorless oil, 808 mg, 79% yield. ^{1}H NMR (300 MHz, chloroform-d): δ 7.41 (d, J = 2.7 Hz, 5H), 6.62 (s, 1H), 6.52 (s, 1H), 5.23 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.76 (s, 2H), 3.50 (s, 2H), 2.95−2.71 (m, 4H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 170.3, 147.6, 147.3, 135.7, 128.6, 128.3, 126.0, 125.7, 111.5, 109.4, 66.4, 58.8, 55.9, 55.9, 54.8, 50.7, 28.4. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{20}H_{24}NO_4$, 342.1700; found, 342.1702.

*Benzyl 2-(5-Bromo-3,4-dihydroisoquinolin-2(1H)-yl)acetate (**1f**).* Eluent: petroleum ether/ethyl acetate: 20/1 to 5/1. White semi-solid,

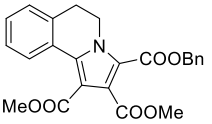


940 mg, 87% yield. ^{1}H NMR (300 MHz, chloroform-d): δ 7.40 (d, J = 4.0 Hz, 6H), 7.09−6.82 (m, 2H), 5.23 (s, 2H), 3.83 (s, 2H), 3.50 (s, 2H), 3.11−2.63 (m, 4H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 170.0, 136.6, 135.6, 133.6, 130.3, 128.6, 128.4, 127.0, 125.6, 66.5, 58.5, 55.2, 50.6, 29.9. HRMS(ESI)m/z: [M + H]$^+$ calcd for $C_{18}H_{19}NO_2Br$, 360.0594; found, 360.0599.

*General Procedure for the Synthesis of **3a−z**. Method **A**.* Substrate **1** (0.3 mmol), dipolarophiles (0.45 mmol), and DCE (3.0 mL) were added to a 10 mL flask. DEAD (58 μL, 63 mg, 0.36 mmol, 1.2 equiv) was then added, and the resulting mixture was stirred at room temperature for 12 h. Then, the solvent was directly extracted with ethyl acetate (3 × 5 mL), and the combined organic layer was washed with brine and dried over Na_2SO_4. After the organic phase was removed under reduced pressure, the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 500:1−20:1) to give products **3a−q**, **3z**. Some products could be further purified by trituration with diethyl ether or *tert*-butyl ether.

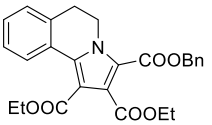
Method B. After the abovementioned reaction was stirred for 12 h, NBS (0.3 mmol) was added and the resulting mixture was stirred for another 2 h. Then, the solvent was directly extracted with ethyl acetate (3 × 5 mL), and the combined organic layer was washed with brine and dried over Na_2SO_4. After the organic phase was removed under reduced pressure, the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 100:1 to 2:1) to give products **3r−3y**. Some products could be further purified by trituration with diethyl ether or *tert*-butyl ether.

*Spectral Data of Products. 3-Benzyl 1,2-Dimethyl 5,6-Dihydropyrrolo[2,1-a]isoquinoline-1,2,3-tricarboxylate (**3a**).* Elu-



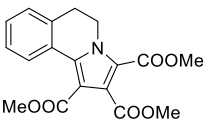
ent: petroleum ether/ethyl acetate: 50/1 to 2/1. White solid, 112 mg, 89%. mp 127−129 °C; ^{1}H NMR (300 MHz, chloroform-d): δ 8.19−8.12 (m, 1H), 7.75−6.97 (m, 9H), 5.27 (s, 2H), 4.56 (t, J = 6.5 Hz, 2H), 3.81 (s, 3H), 3.55 (s, 3H), 3.01 (t, J = 6.5 Hz, 2H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 165.9, 163.3, 159.1, 136.5, 134.7, 133.8, 128.9, 128.1, 128.0, 127.9, 126.9, 126.5, 125.9, 66.6, 51.7, 51.3, 42.2, 28.9. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{24}H_{22}NO_6$, 420.1442; found, 420.1439.

*3-Benzyl 1,2-Diethyl 5,6-Dihydropyrrolo[2,1-a]isoquinoline-1,2,3-tricarboxylate (**3b**).* Eluent: petroleum ether/ethyl acetate:



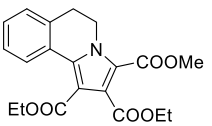
50/1 to 2/1. White solid, 102 mg, 76%. mp 111−112 °C; ^{1}H NMR (300 MHz, chloroform-d): δ 8.29−8.13 (m, 1H), 7.49−7.21 (m, 8H), 5.30 (s, 2H), 4.67−4.47 (m, 2H), 4.32 (q, J = 7.1 Hz, 2H), 4.03 (q, J = 7.2 Hz, 2H), 3.02 (t, J = 6.6 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H), 1.18 (t, J = 7.2 Hz, 3H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 165.9, 163.3, 159.6, 137.0, 135.3, 134.2, 129.2, 128.54, 128.49, 128.47, 128.4, 127.2, 126.9, 126.4, 66.9, 61.4, 60.7, 42.6, 29.3, 14.0, 13.8. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{26}H_{26}NO_6$, 448.1755; found, 448.1760.

*Trimethyl 5,6-Dihydropyrrolo[2,1-a]isoquinoline-1,2,3-tricarboxylate (**3c**).* Eluent: petroleum ether/ethyl acetate: 50/1 to 2/1. White



solid, 88 mg, 85%. mp 123−125 °C; ^{1}H NMR (300 MHz, chloroform-d): δ 8.28−7.91 (m, 1H), 7.45−7.19 (m, 3H), 4.57 (t, J = 6.5 Hz, 2H), 3.96 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 3.05 (t, J = 6.5 Hz, 2H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 169.1, 166.4, 162.8, 139.3, 136.8, 131.9, 130.9, 130.0, 129.6, 129.0, 121.6, 113.2, 55.2, 54.6, 54.4, 45.3, 31.9. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{18}H_{18}NO_6$, 344.1129, found 344.1133.

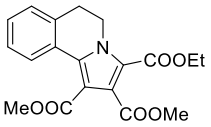
*1,2-Diethyl 3-Methyl 5,6-Dihydropyrrolo[2,1-a]isoquinoline-1,2,3-tricarboxylate (**3d**).* Eluent: petroleum ether/ethyl acetate:



50/1 to 2/1. White solid, 91 mg, 81%. mp 92−94 °C; ^{1}H NMR (300 MHz, chloroform-d): δ 8.27−8.17 (m, 1H), 7.42−7.22 (m, 3H), 4.56 (t, J = 6.5 Hz, 2H), 4.48−4.25 (m, 4H), 3.88 (s, 3H), 3.03 (t, J = 6.5 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H), 1.36 (t, J = 7.1 Hz, 3H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 168.5, 166.0, 162.9, 139.3, 136.8, 131.8, 131.0, 129.9, 129.7, 129.5, 129.0, 121.4, 119.5, 64.0, 63.3, 54.4, 45.2, 31.9, 16.8, 16.6. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{20}H_{22}NO_6$, 372.1442; found, 372.1451.

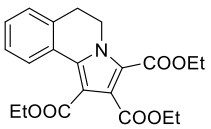
*3-Ethyl 1,2-Dimethyl 5,6-Dihydropyrrolo[2,1-a]isoquinoline-1,2,3-tricarboxylate (**3e**).* Eluent: petroleum ether/ethyl acetate: 50/1 to 2/1. White solid, 85 mg, 79%. mp 114−116 °C; ^{1}H NMR (300 MHz, chloroform-d): δ 8.25−8.10 (m, 1H), 7.43−7.16 (m, 3H), 4.56 (t, J = 6.5 Hz, 2H), 4.33 (q, J = 7.1 Hz, 2H), 3.94 (s, 3H), 3.85 (s, 3H), 3.02 (t, J = 6.5 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 169.1, 166.4, 162.4, 139.3, 136.8,

https://dx.doi.org/10.1021/acs.joc.0c01567
J. Org. Chem. XXXX, XXX, XXX−XXX



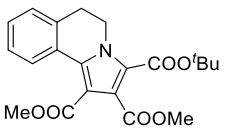
131.9, 130.9, 129.9, 129.6, 129.0, 121.7, 113.1, 63.6, 55.0, 54.4, 45.2, 31.9, 16.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{20}NO_6$, 358.1285; found, 358.1291.

*Triethyl 5,6-Dihydropyrrolo[2,1-a]isoquinoline-1,2,3-tricarboxylate (**3f**).* Eluent: petroleum ether/ethyl acetate: 50/1 to 2/1.



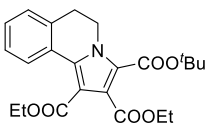
Colorless oil, 87 mg, 75%; ^{1}H NMR (300 MHz, chloroform-d): δ 8.26−8.15 (m, 1H), 7.38−7.22 (m, 3H), 4.70−4.52 (m, 2H), 4.47−4.27 (m, 6H), 3.02 (t, J = 6.6 Hz, 2H), 1.54−1.27 (m, 9H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 166.0, 163.4, 159.8, 136.6, 134.2, 129.2, 128.4, 127.2, 126.9, 126.4, 119.0, 110.8, 61.4, 60.9, 60.7, 42.6, 29.3, 14.1, 14.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{21}H_{24}NO_6$, 386.1598; found, 386.1606.

*3-(tert-Butyl) 1,2-Dimethyl 5,6-Dihydropyrrolo[2,1-a]isoquinoline-1,2,3-tricarboxylate (**3g**).* Eluent: petroleum ether/



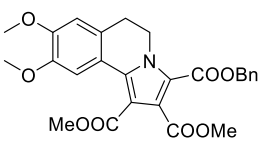
ethyl acetate: 50/1 to 2/1. White solid, 92 mg, 80%. mp 115−117 °C; ^{1}H NMR (300 MHz, chloroform-d): δ 8.21−8.12 (m, 1H), 7.40−7.24 (m, 3H), 4.55 (t, J = 6.5 Hz, 2H), 3.95 (s, 3H), 3.86 (s, 3H), 3.03 (t, J = 6.5 Hz, 2H), 1.59 (s, 9H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 166.5, 163.9, 159.1, 136.2, 134.2, 129.1, 128.2, 127.3, 126.9, 126.5, 126.0, 120.3, 110.3, 82.5, 52.3, 51.7, 42.5, 29.4, 28.1. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{21}H_{24}NO_6$, 386.1598; found, 386.1604.

*3-(tert-Butyl) 1,2-Diethyl 5,6-Dihydropyrrolo[2,1-a]isoquinoline-1,2,3-tricarboxylate (**3h**).* Eluent: petroleum ether/ethyl acetate: 50/



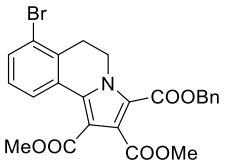
1 to 2/1. White solid, 100 mg, 81%. mp 129−131 °C; ^{1}H NMR (300 MHz, chloroform-d): δ 8.52−7.49 (m, 1H), 7.48−6.78 (m, 3H), 4.54 (t, J = 6.5 Hz, 2H), 4.45−4.37 (m, 2H), 4.37−4.30 (m, 2H), 3.02 (t, J = 6.5 Hz, 2H), 1.59 (s, 9H), 1.44 (t, J = 7.2 Hz, 3H), 1.36 (t, J = 7.1 Hz, 3H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 166.0, 163.6, 159.2, 136.1, 134.2, 129.0, 128.3, 127.2, 126.8, 126.6, 126.1, 120.3, 82.4, 61.3, 60.6, 42.5, 29.4, 28.1, 14.1, 14.0. HRMS (ESI) m/z: $[M + H]^+$ calcd, for $C_{23}H_{28}NO_6$, 414.1911; found, 414.1919.

*3-Benzyl 1,2-Dimethyl 8,9-Dimethoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-1,2,3-tricarboxylate (**3i**).* Eluent: petroleum ether/ethyl



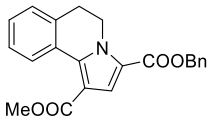
acetate: 50/1 to 2/1. White solid, 120 mg, 85%. mp 102−104 °C; ^{1}H NMR (300 MHz, chloroform-d): δ 8.04 (s, 1H), 7.49−7.31 (m, 5H), 6.76 (s, 1H), 5.28 (s, 2H), 4.58 (t, 2H), 3.94 (s, 6H), 3.81 (s, 3H), 3.56 (s, 3H), 2.96 (t, J = 6.6 Hz, 2H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 166.6, 163.8, 159.6, 149.9, 147.6, 137.6, 135.2, 128.8, 128.4, 127.6, 127.5, 124.4, 123.5, 119.0, 118.1, 112.2, 110.3, 67.0, 56.1, 56.0, 52.2, 51.7, 42.7. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{26}H_{26}NO_8$, 480.1653; found, 480.1655.

*3-Benzyl 1,2-Dimethyl 7-Bromo-5,6-dihydropyrrolo[2,1-a]isoquinoline-1,2,3-tricarboxylate (**3j**).* Eluent: petroleum ether/



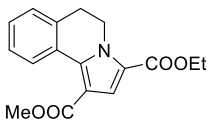
ethyl acetate: 50/1 to 2/1. White solid, 129 mg, 87%. mp 143−144 °C; ^{1}H NMR (300 MHz, chloroform-d): δ 8.10 (d, J = 7.9 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.47−7.29 (m, 5H), 7.19 (t, J = 8.0 Hz, 1H), 5.28 (s, 2H), 4.56 (t, J = 6.6 Hz, 2H), 3.79 (s, 3H), 3.55 (s, 3H), 3.17 (t, J = 6.6 Hz, 2H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 166.1, 163.6, 159.4, 135.8, 135.0, 133.9, 133.2, 128.6, 128.5, 128.0, 127.5, 127.2, 123.1, 118.7, 67.2, 52.2, 51.8, 42.1, 29.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{21}NO_6Br$, 498.0547; found, 498.0555.

*3-Benzyl 1-Methyl 5,6-Dihydropyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate (**3k**).* Eluent: petroleum ether/ethyl acetate: 50/1 to



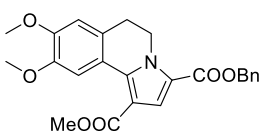
2/1. Colorless oil, 77 mg, 71%; ^{1}H NMR (300 MHz, chloroform-d): δ 8.53−8.44 (m, 1H), 7.82−6.80 (m, 10H), 5.35 (d, J = 2.1 Hz, 2H), 4.65 (t, J = 6.6 Hz, 2H), 3.89 (s, 3H), 3.05 (t, J = 6.6 Hz, 2H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 164.8, 160.6, 138.1, 136.1, 134.0, 129.0, 128.6, 128.5, 128.2, 127.3, 127.0, 121.7, 120.8, 112.1, 66.0, 51.4, 42.4, 29.4. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{20}NO_4$, 362.1387; found, 362.1393.

*3-Ethyl 1-Methyl 5,6-Dihydropyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate (**3l**).* Eluent: petroleum ether/ethyl acetate: 50/1 to 2/



1. White solid, 59 mg, 66%. mp 90−92 °C; ^{1}H NMR (300 MHz, chloroform-d): δ 8.49−8.28 (m, 1H), 7.52 (s, 1H), 7.43−7.20 (m, 3H), 4.62 (t, J = 6.6 Hz, 2H), 4.34 (q, J = 7.1 Hz, 2H), 3.88 (s, 3H), 3.04 (t, J = 6.6 Hz, 3H), 1.40 (t, J = 7.1 Hz, 4H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 164.9, 160.9, 137.8, 134.0, 128.8, 128.4, 127.2, 126.9, 121.3, 111.9, 60.3, 51.3, 42.3, 29.4, 14.3. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{18}NO_4$, 300.1230; found, 300.1237.

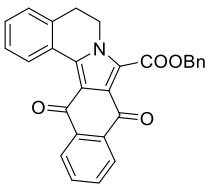
*3-Benzyl 1-Methyl 8,9-Dimethoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate (**3m**).* Eluent: petroleum ether/ethyl



acetate: 50/1 to 2/1. Yellow solid, 37 mg, 29%. mp 128−130 °C; ^{1}H NMR (300 MHz, chloroform-d): δ 8.39 (s, 1H), 7.53−7.35 (m, 5H), 6.78 (s, 1H), 5.34 (s, 2H), 4.64 (t, J = 6.7 Hz, 2H), 4.01 (s, 3H), 3.96 (s, 3H), 3.88 (s, 3H), 3.00 (t, J = 6.7 Hz, 2H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 164.9, 160.6, 149.5, 147.6, 138.5, 136.1, 128.6, 128.2, 128.1, 127.2, 120.3, 119.8, 112.3, 111.1, 110.3, 65.9, 56.1, 55.9, 51.4, 42.5, 28.9. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{24}NO_6$, 422.1598; found, 422.1604.

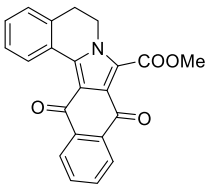
*Benzyl 9,14-Dioxo-5,6,9,14-tetrahydrobenzo[5,6]isoindolo[1,2-a]isoquinoline-8-carboxylate (**3n**).* Eluent: petroleum ether/ethyl acetate: 50/1 to 2/1. Yellow solid, 78 mg, 60%. mp 174−179 °C; ^{1}H NMR (300 MHz, chloroform-d): δ 9.46−8.76 (m, 1H), 8.46−8.17 (m, 2H), 7.80−7.64 (m, 2H), 7.60 (d, J = 7.1 Hz, 2H), 7.53−7.35 (m,

https://dx.doi.org/10.1021/acs.joc.0c01567
J. Org. Chem. XXXX, XXX, XXX−XXX



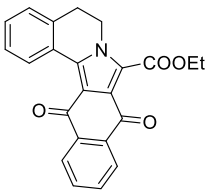
5H), 7.28 (s, 1H), 5.55 (s, 2H), 4.28 (t, J = 6.5 Hz, 2H), 3.09 (t, J = 6.5 Hz, 2H). ^{13}C{1H} NMR (75 MHz, chloroform-d) :δ 179.2, 179.0, 160.8, 135.3, 135.2, 134.6, 134.3, 133.2, 132.8, 132.5, 129.6, 128.4, 128.22, 128.17, 128.1, 127.0, 126.9, 126.8, 126.2, 125.9, 125.0, 123.2, 117.1, 67.8, 42.8, 28.6. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{28}H_{20}NO_4$, 434.1387; found, 434.1392.

*Methyl 9,14-Dioxo-5,6,9,14-tetrahydrobenzo[5,6]isoindolo[1,2-a]isoquinoline-8-carboxylate (**3o**).* Eluent: petroleum ether/ethyl



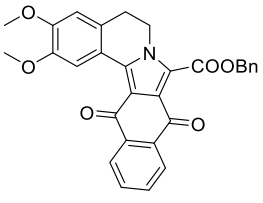
acetate: 50/1 to 2/1. Yellow solid, 75 mg, 70%. mp 190−193 °C; ^{1}H NMR (300 MHz, chloroform-d): δ9.07 (d, J = 7.7 Hz, 1H), 8.52−8.33 (m, 1H), 8.33−8.22 (m, 1H), 7.91−7.69 (m, 2H), 7.66−7.38 (m, 2H), 7.37−7.25 (m, 1H), 4.37 (t, J = 6.5 Hz, 2H), 4.14 (s, 3H), 3.18 (t, J = 6.5 Hz, 2H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 179.6, 179.5, 161.9, 135.8, 135.7, 134.7, 133.6, 133.3, 133.0, 130.1, 128.9, 127.42, 127.37, 127.2, 126.6, 126.3, 117.6, 53.0, 43.2, 29.1. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{22}H_{16}NO_4$, 358.1074; found, 358.1077.

*Ethyl 9,14-Dioxo-5,6,9,14-tetrahydrobenzo[5,6]isoindolo[1,2-a]-isoquinoline-8-carboxylate (**3p**).* Eluent: petroleum ether/ethyl



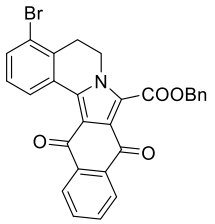
acetate: 50/1 to 2/1. Light brown solid, 74 mg, 66%. mp 134−136 °C; ^{1}H NMR (300 MHz, chloroform-d): δ 9.05 (d, J = 7.8 Hz, 1H), 8.38−8.29 (m, 1H), 8.25 (d, J = 7.4 Hz, 1H), 7.82−7.68 (m, 2H), 7.68−7.35 (m, 2H), 7.31 (d, J = 6.7 Hz, 1H), 4.58 (q, J = 7.1 Hz, 2H), 4.33 (t, J = 6.5 Hz, 2H), 3.15 (t, J = 6.6 Hz, 2H), 1.54 (t, J = 7.1 Hz, 3H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 182.3, 182.1, 164.0, 138.3, 137.4, 136.2, 135.9, 135.5, 132.7, 131.5, 130.1, 130.0, 129.8, 129.2, 129.0, 65.1, 45.8, 31.8, 16.6. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{23}H_{18}NO_4$, 372.1230; found, 372.1234.

*Benzyl 2,3-Dimethoxy-9,14-dioxo-5,6,9,14-tetrahydrobenzo-[5,6]isoindolo[1,2-a]isoquinoline-8-carboxylate (**3q**).* Eluent: petro-



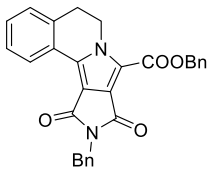
leum ether/ethyl acetate: 50/1 to 2/1. Brown solid, 126 mg, 85%. mp 106−109 °C; ^{1}H NMR (300 MHz, chloroform-d): δ 8.94 (s, 1H), 8.36−8.27 (m, 1H), 8.25−8.19 (m, 1H), 7.78−7.33 (m, 7H), 6.74 (s, 1H), 5.52 (s, 2H), 4.23 (t, J = 6.6 Hz, 2H), 4.11 (s, 3H), 3.95 (s, 3H), 3.03 (t, J = 6.6 Hz, 2H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 179.6, 179.5, 161.4, 150.3, 147.7, 136.4, 135.8, 135.1, 134.7, 133.1, 132.7, 128.7, 128.6, 128.5, 127.3, 126.9, 126.5, 125.3, 123.4, 119.1, 116.5, 112.5, 110.3, 68.2, 56.3, 55.9, 43.3, 28.5. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{30}H_{24}NO_6$, 494.1598; found, 494.1600.

*Benzyl 4-Bromo-9,14-dioxo-5,6,9,14-tetrahydrobenzo[5,6]-isoindolo[1,2-a]isoquinoline-8-carboxylate (**3r**).* Eluent: petroleum



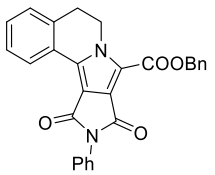
ether/ethyl acetate: 50/1 to 2/1. Yellow solid, 99 mg, 65%. mp 155−157 °C; ^{1}H NMR (300 MHz, chloroform-d): δ 9.20−8.79 (m, 1H), 8.39−8.09 (m, 2H), 7.81−7.49 (m, 5H), 7.49−7.20 (m, 4H), 5.93−5.09 (m, 2H), 4.25 (dd, J = 13.2, 6.7 Hz, 2H), 3.23 (dq, J = 13.6, 6.7 Hz, 2H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 179.6, 179.3, 161.0, 144.0, 135.5, 135.0, 134.61, 134.55, 133.9, 133.4, 133.3, 133.1, 128.69, 128.65, 128.60, 128.4, 128.2, 128.1, 127.2, 126.7, 125.4, 123.9, 123.1, 117.9, 68.4, 42.7, 28.8. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{28}H_{19}NO_4Br$, 512.0492; found, 512.0495.

*Benzyl 10-Benzyl-9,11-dioxo-5,9,10,11-tetrahydro-6H-pyrrolo-[3′,4′:3,4]pyrrolo[2,1a]isoquinoline-8-carboxylate (**3s**).* Eluent: pe-



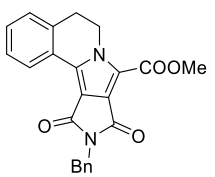
troleum ether/ethyl acetate: 50/1 to 2/1. Light yellow solid, 108 mg, 78%. mp 173−175 °C; ^{1}H NMR (300 MHz, chloroform-d): δ 8.59−8.50 (m, 1H), 7.62 (s, 2H), 7.54−7.08 (m, 11H), 5.47 (s, 2H), 4.84 (s, 2H), 4.72 (t, J = 6.9 Hz 2H), 3.13 (t, J = 6.9 Hz, 2H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 163.7, 162.1, 159.4, 137.1, 135.6, 133.2, 132.3, 130.2, 128.5, 128.4, 128.2, 127.91, 127.89, 127.6, 127.5, 126.0, 125.5, 117.9, 116.7, 66.9, 43.4, 41.9. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{29}H_{23}N_2O_4$, 463.1652; found, 463.1655.

*Benzyl 9,11-Dioxo-10-phenyl-5,9,10,11-tetrahydro-6H-pyrrolo-[3′,4′:3,4]pyrrolo[2,1a]isoquinoline-8-carboxylate (**3t**).* Eluent: pe-



troleum ether/ethyl acetate: 50/1 to 2/1. Light yellow solid, 95 mg, 71%. mp 217−218 °C; ^{1}H NMR (300 MHz, Chloroform-d): δ 8.63 (d, J = 6.9 Hz, 1H), 7.99−7.18 (m, 13H), 5.49 (s, 2H), 4.80 (t, J = 7.0 Hz, 2H), 3.20 (t, J = 7.0 Hz, 2H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 163.1, 161.4, 159.5, 135.5, 133.7, 132.7, 132.4, 130.4, 128.9, 128.6, 128.4, 128.3, 128.0, 127.8, 127.6, 127.2, 125.5, 67.0, 43.5, 28.3. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{28}H_{21}N_2O_4$, 449.1496; found, 449.1500.

*Methyl 10-Benzyl-9,11-dioxo-5,9,10,11-tetrahydro-6H-pyrrolo-[3′,4′:3,4]pyrrolo[2,1a]isoquinoline-8-carboxylate (**3u**).* Eluent: pe-

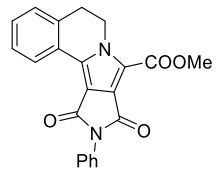


troleum ether/ethyl acetate: 50/1 to 2/1. Light yellow solid, 84 mg, 73%. mp 226−227 °C; ^{1}H NMR (300 MHz, chloroform-d): δ 8.81−

https://dx.doi.org/10.1021/acs.joc.0c01567
J. Org. Chem. XXXX, XXX, XXX−XXX

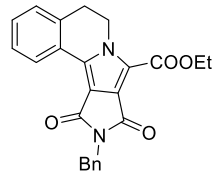
8.31 (m, 1H), 7.83−6.72 (m, 8H), 4.82 (s, 2H), 4.74 (t, J = 6.9 Hz, 2H), 4.01 (s, 3H), 3.16 (t, J = 6.9 Hz, 2H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 163.7, 162.4, 160.1, 137.1, 132.3, 130.2, 128.6, 127.92, 127.86, 127.6, 127.52, 125.49, 117.8, 116.5, 52.3, 43.3, 41.9, 28.3. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{23}H_{19}N_2O_4$, 387.1339; found, 387.1346.

*Methyl 9,11-Dioxo-10-phenyl-5,9,10,11-tetrahydro-6H-pyrrolo-[3′,4′:3,4]pyrrolo[2,1a]isoquinoline-8-carboxylate (**3v**).* Eluent: pe-



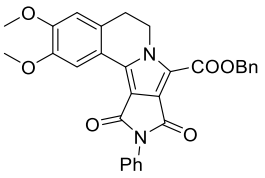
troleum ether/ethyl acetate: 50/1 to 2/1. Brown solid, 95 mg, 85%. mp 233−234 °C; ^{1}H NMR (300 MHz, chloroform-d): δ 8.68−8.52 (m, 1H), 7.71−7.36 (m, 7H), 7.35−7.19 (m, 1H), 4.80 (t, J = 6.9 Hz, 2H), 4.02 (s, 3H), 3.21 (t, J = 6.9 Hz, 2H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 162.9, 161.5, 160.0, 133.6, 132.6, 132.4, 130.3, 128.8, 128.0, 127.7, 127.6, 127.0, 125.5, 125.3, 118.1, 116.3, 52.3, 43.4, 28.3. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{22}H_{17}N_2O_4$, 373.1183; found, 373.1181.

*Ethyl 10-Benzyl-9,11-dioxo-5,9,10,11-tetrahydro-6H-pyrrolo-[3′,4′:3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (**3w**).* Eluent:



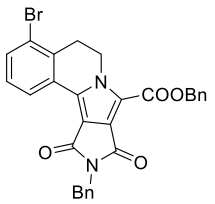
petroleum ether/ethyl acetate: 50/1 to 2/1. White solid, 83 mg, 69%. mp 195−196 °C; ^{1}H NMR (300 MHz, chloroform-d): δ 8.80−8.39 (m, 1H), 7.77−6.76 (m, 8H), 4.83 (s, 2H), 4.74 (t, J = 6.9 Hz, 2H), 4.46 (q, J = 7.1 Hz, 2H), 3.16 (t, J = 6.9 Hz, 2H), 1.51 (t, J = 7.1 Hz, 3H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ163.8, 162.2, 159.6, 137.1, 133.0, 132.3, 130.1, 128.5, 128.4, 127.9, 127.8, 127.6, 127.4, 125.7, 125.6, 118.3, 116.5, 61.5, 43.3, 41.8, 28.3, 14.2. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{24}H_{21}N_2O_4$, 401.1496; found, 401.1501.

*Benzyl 2,3-Dimethoxy-9,11-dioxo-10-phenyl-5,9,10,11-tetrahydro-6H-pyrrolo[3′,4′:3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (**3x**).* Eluent: petroleum ether/ethyl acetate: 50/1 to 2/1. Yellow solid,



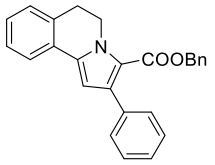
100 mg, 65%. mp 190−192 °C; ^{1}H NMR (300 MHz, chloroform-d): δ 8.29 (s, 1H), 7.89−7.00 (m, 10H), 6.77 (s, 1H), 5.47 (s, 2H), 4.76 (t, J = 6.9 Hz, 2H), 4.01 (s, 3H), 3.96 (s, 3H), 3.12 (t, J = 7.0 Hz, 2H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 163.5, 161.5, 159.4, 150.8, 148.7, 135.6, 134.3, 132.7, 129.0, 128.5, 128.3, 128.2, 127.9, 127.3, 125.6, 125.4, 118.1, 117.9, 110.6, 110.3, 66.9, 56.2, 56.0, 43.6, 27.9. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{30}H_{25}N_2O_6$, 509.1707; found, 509.1711.

*Benzyl 10-Benzyl-4-bromo-9,11-dioxo-5,9,10,11-tetrahydro-6H-pyrrolo[3′,4′:3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (**3y**).* Eluent: petroleum ether/ethyl acetate: 50/1 to 2/1. White solid, 128 mg, 79%. mp 187−188 °C; ^{1}H NMR (300 MHz, chloroform-d): δ 8.59−8.52 (m, 1H), 7.95−7.49 (m, 3H), 7.55−7.01 (m, 9H), 5.46 (s, 2H), 4.82 (s, 2H), 4.72 (t, J = 7.0 Hz, 2H), 3.26 (t, J = 7.0 Hz, 2H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 163.6, 161.9, 159.3, 137.0, 135.5, 134.0, 132.0, 129.1, 128.5, 128.4, 128.3, 127.5, 127.4, 127.1,



126.2, 123.6, 118.0, 117.2, 67.0, 42.9, 41.9, 28.3. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{29}H_{22}N_2O_4Br$, 541.0757; found, 541.0762.

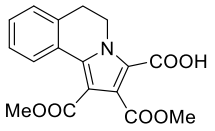
*Benzyl 2-Phenyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (**3z**).* Eluent: petroleum ether/ethyl acetate: 100/1 to 5/1.



Colorless oil, 74 mg, 67%. ^{1}H NMR (300 MHz, chloroform-d): δ 7.61 (d, J = 7.2 Hz, 1H), 7.48−7.40 (m, 2H), 7.38−7.23 (m, 9H), 7.12−7.00 (m, 2H), 6.62 (s, 1H), 5.19 (s, 2H), 4.70 (t, J = 6.7 Hz, 2H), 3.15 (t, J = 6.8 Hz, 2H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 161.0, 136.3, 135.3, 134.5, 134.3, 131.4, 129.1, 127.7, 127.5, 127.5, 127.3, 127.2, 127.0, 126.7, 126.1, 123.1, 117.9, 106.6, 106.6, 65.0, 42.2, 28.5. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{26}H_{22}NO_2$, 380.1645; found, 380.1642.

*Synthesis of Compound **4**.* A two-necked, 50 mL round-bottom flask was charged with **3a** (419 mg, 1 mmol) and 10% Pd−C (41.9 mg, 10 wt % of the substrate). Then, the reaction was stirred at room temperature under a hydrogen atmosphere (balloon) for 12 h. Finally, the mixture was removed by filtration with Celite, and the filtrate was concentrated under reduced pressure to give the crude product, which was further purified by trituration with diethyl ether to give compound **4**.

*1,2-bis(Methoxycarbonyl)-5,6-dihydropyrrolo[2,1-a]-isoquinoline-3-carboxylic acid (**4**).* Eluent: dichloromethane/men-

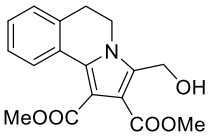


thol: 50/1 to 20/1. White solid, 316 mg, 96%. mp 181−182 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.36 (br s, 1H), 8.01−7.91 (m, 1H), 7.43−7.29 (m, 3H), 4.60−3.93 (m, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 3.04 (t, J = 6.5 Hz, 2H). ^{13}C{1H} NMR (75 MHz, DMSO-d_6): δ 165.3, 163.5, 160.5, 134.4, 128.9, 127.5, 127.1, 126.5, 125.9, 125.0, 120.4, 109.8, 52.0, 51.6, 42.3, 28.3. HRMS (ESI) m/z: [M − H]$^+$ calcd for $C_{17}H_{14}NO_6$, 328.0827; found, 328.0831.

*Synthesis of Compound **5**.* To a solution of **4** (66 mg, 0.2 mmol) and triethylamine (28 μL, 0.2 mmol) in THF (3 mL) at 0 °C was added a solution of isobutyl chloroformate (26 μL, 0.2 mmol) in THF (1 mL) dropwise. The mixture was stirred in an ice bath for 4 h and filtered directly into a stirred solution of sodium borohydride (16 mg, 0.4 mmol) in water (1 mL) at 0 °C. After stirring for 6 h, the mixture was acidified with 1 N HCl and poured into a mixture of ethyl acetate (20 mL) and water (20 mL). The aqueous phase was separated and extracted with ethyl acetate (2 × 10 mL), and the combined organic extracts were washed with brine and dried over anhydrous $NaSO_4$. After removal of the solvent, the residue was further purified by trituration with diethyl ether to give compound **5**.

*Dimethyl 3-(Hydroxymethyl)-5,6-dihydropyrrolo[2,1-a]-isoquinoline-1,2-dicarboxylate (**5**).* Eluent: petroleum ether/ethyl acetate: 5/1 to 1/1. White solid, 70 mg, 75%. mp 144−145 °C; ^{1}H NMR (300 MHz, chloroform-d): δ 7.72−7.61 (m, 1H), 7.34−7.21 (m, 3H), 4.85 (s, 2H), 4.13 (t, J = 6.5 Hz, 2H), 3.93 (s, 3H), 3.86 (s, 3H), 3.07 (t, J = 6.5 Hz,2H). ^{13}C{1H} NMR (75 MHz, chloroform-d): δ 167.1, 164.6, 136.3, 131.6, 127.9, 127.3, 127.2, 127.0, 126.7,

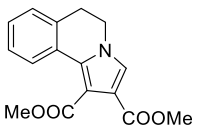
https://dx.doi.org/10.1021/acs.joc.0c01567
J. Org. Chem. XXXX, XXX, XXX−XXX



124.0, 112.7, 112.3, 53.5, 51.8, 51.2, 40.8, 28.6. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{17}NO_5Na$, 338.0999; found, 338.1007.

Synthesis of Compound ***6***. A 15 mL round-bottom flask was charged with compound **4** (66 mg, 0.2 mmol) and TFA (2 mL) and stirred at 45 °C for 12 h in oil bath. The reaction was monitored by TLC until **4** was consumed completely. After TFA was removed under reduced pressure, the crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 100:1 to 20:1) to give desired compound **6**.

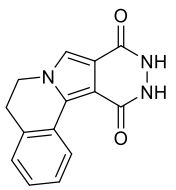
*Dimethyl 5,6-Dihydropyrrolo[2,1-a]isoquinoline-1,2-dicarboxylate (**6**)*. Eluent: petroleum ether/ethyl acetate: 30/1 to 5/1. White



solid, 48 mg, 84%. mp 114−116 °C; ^{1}H NMR (300 MHz, chloroform-*d*): δ 7.65 (d, J = 7.5 Hz, 1H), 7.38−7.05 (m, 4H), 4.06 (t, J = 6.5 Hz, 2H), 3.94 (s, 3H), 3.81 (s, 3H), 3.05 (t, J = 6.5 Hz, 2H). ^{13}C{1H} NMR (75 MHz, chloroform-*d*): δ 167.6, 163.9, 132.0, 129.1, 128.1, 127.63, 127.58, 125.50, 125.47, 124.5, 114.7, 113.2, 52.5, 51.4, 44.7, 29.4. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{15}NO_4Na$, 308.0893; found, 308.0899.

Synthesis of Compound ***7***. In a 10 mL sealed glass vial, **6** (28.5 mg, 0.1 mmol) and hydrazine hydrate (80 wt %,1 mL) were added. The mixture was stirred at 90 °C for 1 h in oil bath. Then, the redundant hydrazine hydrate was removed under reduced pressure to get the crude product, which was purified by trituration with diethyl ether and isopropyl alcohol, giving the desired compound **7**.

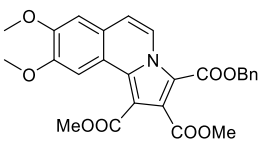
*5,6,10,11-Tetrahydropyridazino[4′,5′:3,4]pyrrolo[2,1-a]isoquinoline-9,12-dione (**7**)*. Eluent: dichloromethane/menthol: 50/



1 to 10/1. White solid, 35 mg, 61%. mp over 300 °C; ^{1}HNMR (300 MHz, DMSO-d_6): δ 10.71 (s, 2H), 9.02 (d, J = 7.7 Hz, 1H), 7.54 (s, 1H), 7.37−7.14 (m, 3H), 4.27 (t, J = 6.8 Hz, 2H), 3.07 (t, J = 6.7 Hz, 2H). ^{13}C{1H} NMR (75 MHz, DMSO-d_6): δ 157.1, 152.9, 133.1, 129.1, 128.4, 128.1, 128.0, 127.9, 127.3, 119.0, 115.8, 112.1, 45.4, 29.0. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{14}H_{10}N_3O_2$, 252.0779; found, 252.0771.

Synthesis of Compound ***8***. A suspension of **3j** (144 mg, 0.3 mmol) and DDQ (84 mg, 0.375 mmol) in anhydrous DCM (3 mL) was stirred under argon at room temperature for 12 h. After **3j** was consumed completely, 2 M NaOH solution (2 mL) was added. The resulting mixture was extracted by DCM (3 × 5 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. After the organic phase was removed under reduced pressure, the crude product was further purified by flash chromatography (petroleum ether/ethyl acetate, 20:1 to 5:1) to give desired compound **8**.

*3-Benzyl 1,2-Dimethyl 8,9-Dimethoxypyrrolo[2,1-a]isoquinoline-1,2,3-tricarboxylate (**8**)*. Eluent: petroleum ether/ethyl acetate: 50/1



to 5/1. White solid, 45 mg, 93%. mp 179−180 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.18 (d, J = 7.5 Hz, 1H), 8.95 (s, 1H), 7.57−7.26 (m, 7H), 5.32 (s, 2H), 3.92 (s, 3H), 3.89 (s, 3H), 3.80 (s, 3H), 3.54 (s, 3H). ^{13}C{1H} NMR (75 MHz, DMSO-d_6): δ 167.5, 163.9, 131.9, 129.1, 128.0, 127.58, 127.58, 127.4, 125.4, 124.5, 114.7, 113.2, 52.4, 51.3, 44.7, 29.4. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{24}NO_8$, 478.1496; found, 478.1501.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01567.

^{1}H and ^{13}C NMR spectra for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Guangji Wang − *Key Laboratory of Drug Metabolism and Pharmacokinetics, China Pharmaceutical University, Nanjing 210009, Jiangsu, China*; orcid.org/0000-0002-8297-1921; Email: guangjiwang@hotmail.com

Le Zhen − *Key Laboratory of Drug Metabolism and Pharmacokinetics, China Pharmaceutical University, Nanjing 210009, Jiangsu, China*; orcid.org/0000-0002-1854-0764; Email: i_m_zhenle@163.com

Authors

Ya-Wen Xu − *Key Laboratory of Drug Metabolism and Pharmacokinetics, China Pharmaceutical University, Nanjing 210009, Jiangsu, China*

Jiankun Wang − *Key Laboratory of Drug Metabolism and Pharmacokinetics, China Pharmaceutical University, Nanjing 210009, Jiangsu, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c01567

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This project was supported by the National Natural Science Foundation of China (grant nos. 81973186 and 81903707) and the National Major Scientific and Technological Special Project for "Significant New Drugs Development" (2019ZX09301-151).

■ REFERENCES

(1) Andersen, R. J.; Faulkner, D. J.; He, C. H.; Van Duyne, G. D.; Clardy, J. Metabolites of the marine prosobranch mollusk Lamellaria sp. *J. Am. Chem. Soc.* **1985**, *107*, 5492−5495.

(2) For previous reviews on lamellarins and related alkaloids, see: (a) Bailly, C. Lamellarins, From A to Z: A Family of Anticancer Marine Pyrrole Alkaloids. *Curr. Med. Chem.: Anti-Cancer Agents* **2004**, *4*, 363−378. (b) Handy, S. T.; Zhang, Y. Approaches to the Synthesis of the Lamellarins and Related Natural Products. A Review. *Org. Prep. Proced. Int.* **2005**, *37*, 411−445. (c) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. Lamellarins and Related Pyrrole-Derived Alkaloids From Marine Organisms. *Chem. Rev.* **2008**, *108*, 264−287. (d) Pla, D.; Albericio, F.; Álvarez, M. Recent Advances in Lamellarin Alkaloids: Isolation, Synthesis and Activity. *Anti-Cancer Agents Med. Chem.* **2008**, *8*, 746−760. (e) Pla, D.; Albericio, F.; Álvarez, M. Progress on Lamellarins. *MedChemComm* **2011**, *2*, 689−697. (f) Fukuda, T.; Ishibashi, F.; Iwao, M. Synthesis and Biological Activity of Lamellarin Alkaloids: an Overview. *Heterocycles* **2011**, *83*, 491−529. (g) *Outstanding Marine Molecules: Chemistry, Biology, Analysis*; La Barre, S.,

https://dx.doi.org/10.1021/acs.joc.0c01567
J. Org. Chem. XXXX, XXX, XXX−XXX

Kornprobst, J.-M., Eds.; Wiley-VCH: Weinheim, 2014; pp 377−386. (h) Bailly, C. Anticancer Properties of Lamellarins. *Mar. Drugs* **2015**, *13*, 1105−1123.

(3) (a) Quesada, A.; García Grávalos, M.; Fernández Puentes, J. Polyaromatic Alkaloids From Marine Invertebrates as Cytotoxic Compounds and Inhibitors of Multidrug Resistance Caused by P-glycoprotein. *Br. J. Cancer* **1996**, *74*, 677−682. (b) Reddy, M. V. R.; Rao, M. R.; Rhodes, D.; Hansen, M. S. T.; Rubins, K.; Bushman, F. D.; Venkateswarlu, Y.; Faulkner, D. J. Lamellarin Alpha 20-sulfate, an Inhibitor of HIV-1 Integrase Active Against HIV-1 Virus in Cell Culture. *J. Med. Chem.* **1999**, *42*, 1901−1907. (c) Aubry, A.; Pan, X.-S.; Fisher, L. M.; Jarlier, V.; Cambau, E. Mycobacterium Tuberculosis DNA Gyrase: Interaction With Quinolones and Correlation With Antimycobacterial Drug Activity. *Antimicrob. Agents Chemother.* **2004**, *48*, 1281−1288. (d) Reddy, S. M.; Srinivasulu, M.; Satyanarayana, N.; Kondapi, A. K.; Venkateswarlu, Y. New Potent Cytotoxic Lamellarin Alkaloids from Indian Ascidian Didemnum Obscurum. *Tetrahedron* **2005**, *61*, 9242−9247. (e) Marco, E.; Laine, W.; Tardy, C.; Lansiaux, A.; Iwao, M.; Ishibashi, F.; Bailly, C.; Gago, F. Molecular Determinants of Topoisomerase I Poisoning by Lamellarins: Comparison With Camptothecin and Structure-Activity Relationships. *J. Med. Chem.* **2005**, *48*, 3796−3807.

(4) For the first total syntheses of fused lamellarins achieved in 1997, see: (a) Heim, A.; Terpin, A.; Steglich, W. Biomimetic Synthesis of Lamellarin G. Trimethyl Ether. *Angew. Chem., Int. Ed.* **1997**, *36*, 155−156. (b) Ishibashi, F.; Miyazaki, Y.; Iwao, M. Total Synthesis of Lamellarin D and H. The First Synthesis of Lamellarin-Class Marine Alkaloids. *Tetrahedron* **1997**, *53*, 5951−5962. (c) Banwell, M.; Hockless, D.; Hockless, D. Convergent Total Synthesis of Lamellarin K. *Chem. Commun.* **1997**, *33*, 2259−2260.

(5) For the syntheses of lamellarins achieved in the recent three years, see: (a) Lade, D. M.; Pawar, A. B.; Mainkar, P. S.; Chandrasekhar, S. Total Synthesis of Lamellarin D Trimethyl Ether, Lamellarin D, and Lamellarin H. *J. Org. Chem.* **2017**, *82*, 4998−5004. (b) Zheng, K.-L.; You, M.-Q.; Shu, W.-M.; Wu, Y.-D.; Wu, A.-X. Acid-Mediated Intermolecular [3+2] Cycloaddition Toward Pyrrolo-[2,1-a]isoquinolines: Total Synthesis of the Lamellarin Core and Lamellarin G Trimethyl Ether. *Org. Lett.* **2017**, *19*, 2262−2265. (c) Manjappa, K. B.; Lin, J.-M.; Yang, D.-Y. Construction of Pentacyclic Lamellarin Skeleton via Grob Reaction: Application to Total Synthesis of Lamellarins H and D. *J. Org. Chem.* **2017**, *82*, 7648−7656. (d) Colligs, V.; Hansen, S. P.; Imbri, D.; Seo, E.-J.; Kadioglu, O.; Efferth, T.; Opatz, T. Synthesis and Biological Evaluation of a D-ring-contracted Analogue of Lamellarin D. *Bioorg. Med. Chem.* **2017**, *25*, 6137−6148. (e) Colligs, V. C.; Dialer, C.; Opatz, T. Synthesis of Lamellarin G Trimethyl Ether by von Miller-Plochl-Type Cyclocondensation. *Eur. J. Org. Chem.* **2018**, *2018*, 4064−4070. (f) Mandrekar, K. S.; Kadam, H. K.; Tilve, S. G. Domino Bischler-Napieralski - Michael Reaction and Oxidation - New Route to Coumarin-Pyrrole-Isoquinoline Fused Pentacycles. *Eur. J. Org. Chem.* **2018**, *2018*, 6665−6670. (g) Vyasamudri, S.; Yang, D.-Y. Application of differential reactivity towards synthesis of lamellarin and 8-oxoprotoberberine derivatives: Study of photochemical properties of aryl-substituted benzofuran-8-oxoprotoberberines. *Tetrahedron* **2018**, *74*, 1092−1100. (h) Alves Esteves, C. H.; Koyioni, M.; Christensen, K. E.; Smith, P. D.; Donohoe, T. J. OBO-Protected Pyruvates as Reagents for the Synthesis of Functionalized Heteroaromatic Compounds. *Org. Lett.* **2018**, *20*, 4048−4051. (i) Shirley, H. J.; Koyioni, M.; Muncan, F.; Donohoe, T. J. Synthesis of Lamellarin Alkaloids Using Orthoester-Masked α-keto Acids. *Chem. Sci.* **2019**, *10*, 4334−4338.

(6) (a) Ruchirawat, S.; Mutarapat, T. An Efficient Synthesis of Lamellarin Alkaloids: Synthesis of Lamellarin G Trimethyl Ether. *Tetrahedron Lett.* **2001**, *42*, 1205−1208. (b) Cironi, P.; Manzanares, I.; Albericio, F.; Álvarez, M. Solid-phase Total Synthesis of the Pentacyclic System Lamellarins U and L. *Org. Lett.* **2003**, *5*, 2959−2962. (c) Ploypradith, P.; Petchmanee, T.; Sahakitpichan, P.; Litvinas, N. D.; Ruchirawat, S. Total Synthesis of Natural and Unnatural Lamellarins with Saturated and Unsaturated D-rings. *J. Org. Chem.* **2006**, *71*, 9440−9448.

(7) Shen, Y.-M.; Grampp, G.; Leesakul, N.; Hu, H.-W.; Xu, J.-H. Synthesis and Emitting Properties of the Blue-light Fluorophores Indolizino[3,4,5-ab]isoindole Derivatives. *Eur. J. Org. Chem.* **2007**, *2007*, 3718−3726.

(8) (a) Banwell, M. G.; Hockless, D. C. R.; Flynn, B. L.; Longmore, R. W.; Rae, D. Assessment of Double-barrelled Heck Cyclizations As a Means for Construction of the 14-phenyl-8,9-dihydro-6h-[1]-benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6- one Core Associated with Certain Members of the Lamellarin Class of Marine Natural Product. *Aust. J. Chem.* **1999**, *52*, 755−765. (b) Nyerges, M.; Tóth, J.; Nedves, A.; Dancsó, A.; Blaskó, G.; Tőke, L. Synthesis of Pyrrolo[2,1-a]isoquinolines by a Tandem 1,5-Electrocyclisation-oxidation Process. *Synthesis* **2007**, *2007*, 1003−1014. (c) Chen, L.; Xu, M.-H. A New Approach to Pyrrolocoumarin Derivatives by Palladium-Catalyzed Reactions: Expedient Construction of Polycyclic Lamellarin Scaffold. *Adv. Synth. Catal.* **2009**, *351*, 2005−2012.

(9) (a) Yu, C.; Zhang, Y.; Zhang, S.; Li, H.; Wang, W. Cu(ii) Catalyzed Oxidation-[3+2] Cycloaddition-aromatization Cascade: Efficient Synthesis of Pyrrolo [2, 1-a] Isoquinolines. *Chem. Commun.* **2011**, *47*, 1036−1038. (b) Feng, C.; Su, J.-H.; Yan, Y.; Guo, F.; Wang, Z. Cobalt-catalyzed Oxidative [3+2] Cycloaddition Reactions: an Efficient Synthesis of Pyrrolo- and Imidazo-[2,1-a]isoquinolinest. *Org. Biomol. Chem.* **2013**, *11*, 6691−6694. (c) Wang, H.-T.; Lu, C.-D. Synthesis of 3,4-dihydropyrrolo[2,1-a]isoquinolines Based on [3+2] Cycloaddition Initiated by Rh-2(cap)(4)-catalyzed Oxidation. *Tetrahedron Lett.* **2013**, *54*, 3015−3018.

(10) (a) Zou, Y.-Q.; Lu, L.-Q.; Fu, L.; Chang, N.-J.; Rong, J.; Chen, J.-R.; Xiao, W.-J. Visible-Light-Induced Oxidation/[3+2] Cycloaddition/Oxidative Aromatization Sequence: A Photocatalytic Strategy To Construct Pyrrolo[2,1-a]isoquinolines. *Angew. Chem., Int. Ed.* **2011**, *50*, 7171−7175. (b) Rueping, M.; Leonori, D.; Poisson, T. Visible Light Mediated Azomethine Ylide Formation−Photoredox catalyzed [3+2] Cycloadditions. *Chem. Commun.* **2011**, *47*, 9615−9617. (c) Huang, L.; Zhao, J. C-60-bodipy Dyad Triplet Photosensitizers As Organic Photocatalysts for Photocatalytic Tandem Oxidation/[3+2] Cycloaddition Reactions to Prepare Pyrrolo[2,1-a]isoquinoline. *Chem. Commun.* **2013**, *49*, 3751−3753. (d) Vila, C.; Lau, J.; Rueping, M. Visible-light Photoredox Catalyzed Synthesis of Pyrroloisoquinolines via Organocatalytic Oxidation/[3+2] Cycloaddition/oxidative Aromatization Reaction Cascade with Rose Bengal. *Beilstein J. Org. Chem.* **2014**, *10*, 1233−1238. (e) Fujiya, A.; Tanaka, M.; Yamaguchi, E.; Tada, N.; Itoh, A. Sequential Photooxidative [3 + 2] Cycloaddition/Oxidative Aromatization Reactions for the Synthesis of Pyrrolo[2,1-a]isoquinolines Using Molecular Oxygen as the Terminal Oxidant. *J. Org. Chem.* **2016**, *81*, 7262−7270.

(11) (a) Huang, H.-M.; Huang, F.; Li, Y.-J.; Jia, J.-H.; Ye, Q.; Han, L.; Gao, J.-R. A General, Simple and Green Access to Pyrrolo[2,1-a]isoquinolines Using KI/TBHP Catalytic System. *RSC Adv.* **2014**, *4*, 27250−27258. (b) Huang, H.-M.; Li, Y.-J.; Ye, Q.; Yu, W.-B.; Han, L.; Jia, J.-H.; Gao, J.-R. Iodine-Catalyzed 1,3-Dipolar Cycloaddition/Oxidation/Aromatization Cascade with Hydrogen Peroxide as the Terminal Oxidant: General Route to Pyrrolo[2,1-a]isoquinolines. *J. Org. Chem.* **2014**, *79*, 1084−1092. (c) Nekkanti, S.; Kumar, N. P.; Sharma, P.; Kamal, A.; Nachtigall, F. M.; Forero-Doria, O.; Santos, L. S.; Shankaraiah, N. TBAI/TBHP-Catalyzed [3+2] Cycloaddition/Oxidation/Aromatization Cascade and Online ESI-MS Mechanistic Studies: Synthesis of Pyrrolo[2,1-a]isoquinolines and Indolizino[8,7-b]indoles. *RSC Adv.* **2016**, *6*, 2671−2677.

(12) Wang, Q.; Yuan, T.; Liu, Q.; Xu, Y.; Xie, G.; Lv, X.; Ding, S.; Wang, X.; Li, C. External Oxidant-free Oxidation/[3+2] Cycloaddition/aromatization Cascade: Electrochemical Synthesis of Polycyclic N-heterocycles. *Chem. Commun.* **2019**, *55*, 8398−8401.

(13) Selected reviews on application of azodicarboxylates: (a) Nair, V.; Biju, A. T.; Mathew, S. C.; Babu, B. P. Carbon-nitrogen Bond-forming Reactions of Diakyl Azodicarboxylate: a Promsing Synthetic Strategy. *Chem.—Asian J.* **2008**, *3*, 810−820. (b) Zhirov, A. M.; Aksenov, A. V. Azodicarboxylates: Synthesis and Functionalization of

https://dx.doi.org/10.1021/acs.joc.0c01567
J. Org. Chem. XXXX, XXX, XXX−XXX

Organic Compounds. *Russ. Chem. Rev.* **2014**, *83*, 502. (c) Yang, Z.; Wang, B.; Xu, X.; Wang, H.; Li, X. Dimerization Coupling Reaction of Terminal Alkyne Promoted by CuI/DEAD. *Chin. J. Org. Chem.* **2015**, *35*, 207−211.

(14) Azodicarboxylate-mediated oxidation: (a) Yoneda, F.; Suzuki, K.; Nitta, Y. A New Hydrogen-Abstracting Reaction with Diethyl Azodicarboxylate. *J. Am. Chem. Soc.* **1966**, *88*, 2328. (b) Axen, R.; Chaykovsky, M.; Witkop, B. The Selective Oxidation of Sulfur-Containing Amino Acids by Diethyl Azodicarboxylate. *J. Org. Chem.* **1967**, *32*, 4117. (c) Kato, K.; Mitsunobu, O. Oxidation of Mercaptans with Diethyl Azodicarboxylate and Trivalent Phosphorus Compounds. *J. Org. Chem.* **1970**, *35*, 4227−4229. (d) Markó, I. E.; Giles, P. R.; Tsukazaki, M.; Brown, S. M.; Urch, C. J. Copper-Catalyzed Oxidation of Alcohols to Aldehydes and Ketones: An Efficient, Aerobic Alternative. *Science* **1996**, *274*, 2044−2046. (e) Markó, I. E.; Tsukazaki, M.; Giles, P. R.; Brown, S. M.; Urch, C. J. Anaerobic Copper-Catalyzed Oxidation of Alcohols to Aldehydes and Ketones. *Angew. Chem., Int. Ed.* **1997**, *36*, 2208−2210. (f) Cao, H. T.; Grée, R. DEAD-(cat)$ZnBr_2$ an Efficient System for the Oxidation of Alcohols to Carbonyl Compounds. *Tetrahedron Lett.* **2009**, *50*, 1493−1494. (g) Iranpoor, N.; Firouzabadi, H.; Khalili, D.; Shahin, R. A New Application for Diethyl Azodicarboxylate: Efficient and Regioselective Thiocyanation of Aromatics Amines. *Tetrahedron Lett.* **2010**, *51*, 3508−3510. (h) Hayashi, M.; Shibuya, M.; Iwabuchi, Y. Oxidation of Alcohols to Carbonyl Compounds with Diisopropyl Azodicarboxylate Catalyzed by Nitroxyl Radicals. *J. Org. Chem.* **2012**, *77*, 3005−3009.

(15) DEAD-promoted oxidation of tertiary amines: (a) Vincent, G.; Chen, Y.; Lane, J. W.; Williams, R. M. Formation of the C3-C4 Unsaturated Framework of Cribrostatin 4 via DEAD-Mediated Oxidation of an Allylic Tertiary Amine. *Heterocycles* **2007**, *72*, 385−389. (b) Xu, X.; Li, X.; Ma, L.; Ye, N.; Weng, B. An Unexpected Diethyl Azodicarboxylate-Promoted Dehydrogenation of Tertiary-amine and Tandem Reaction with Sulfonyl Azide. *J. Am. Chem. Soc.* **2008**, *130*, 14048−14049. (c) Xu, X.; Li, X. Copper/Diethyl Azodicarboxylate Mmediated Regioselective Alkynylation of Unactivated Aliphatic Tertiary Methylamine with Terminal Alkyne. *Org. Lett.* **2009**, *11*, 1027−1029. (d) Xu, X.; Du, P.; Cheng, D.; Wang, H.; Li, X. Highly Stereoselective Synthesis of cis-β-Enaminones Mediated by Diethyl Azodicarboxylate. *Chem. Commun.* **2012**, *48*, 1811−1813. (e) Singh, K.; Singh, P.; Kaur, A.; Singh, P. C-1 Alkynylation of N-Methyltetrahydroisoquinolines through CDC: A Direct Access to Phenethylisoquinoline Alkaloids. *Synlett* **2012**, *23*, 760−764. (f) Huang, W.; Ni, C.; Zhao, Y.; Hu, J. DIAD-Mediated Metal-Free Cross Dehydrogenative Coupling Between Tertiary Amines and α-Fluorinated Sulfones. *New J. Chem.* **2013**, *37*, 1684−1687. (g) Suga, T.; Iizuka, S.; Akiyama, T. Versatile and Highly Efficient Oxidative C(sp3)−H Bond Functionalization of Tetrahydroisoquinoline Promoted by Bifunctional Diethyl Azodicarboxylate (DEAD): Scope and Mechanistic Insights. *Org. Chem. Front.* **2016**, *3*, 1259−1264.

(16) Wang, J.; Sun, Y.; Wang, G.; Zhen, L. DEAD-promoted Oxidative Ugi-type Reaction Including an Unprecedented Ugi Amidation Assisted by Dicarboxylic Acids. *Eur. J. Org. Chem.* **2017**, *2017*, 6338−6348.

(17) Wang, J.; Sun, Y.; Jiang, M.-H.; Hu, T.-Y.; Zhao, Y.-J.; Li, X.; Wang, G.; Hao, K.; Zhen, L. Iminium Ion and N-hydroxyimide as the Surrogate Components in DEAD-promoted Oxidative Ugi Variant. *J. Org. Chem.* **2018**, *83*, 13121−13131.

https://dx.doi.org/10.1021/acs.joc.0c01567
J. Org. Chem. XXXX, XXX, XXX−XXX