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Synthesis of 9*H*-Pyrrolo[1,2-*a*]indole and 3*H*-Pyrrolizine Derivatives via a Phosphine-Catalyzed Umpolung Addition/Intramolecular Wittig Reaction

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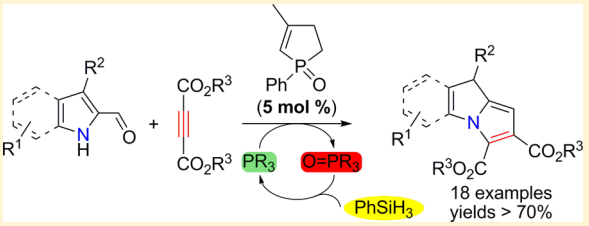
Supporting Information

ABSTRACT: The first umpolung addition/intramolecular Wittig reaction, catalytic in phosphine, is described. The in situ phosphine oxide reduction was accomplished by the use of silane and a catalytic amount of *bis*(4-nitrophenyl)phosphate. This catalytic protocol is applicable to the synthesis of a wide range of functionalized 9*H*-pyrrolo[1,2-*a*]indoles and pyrrolizines (18 examples, 70−98% yields).



Tricyclic indole derivatives are found in many natural products and pharmaceuticals. Some of them have attracted much attention due to their potent biological activities.[1] For example, the pyrrolo[1,2-*a*]indole scaffold is present in numerous bioactive compounds (**I**-**III** in Figure 1).[2]

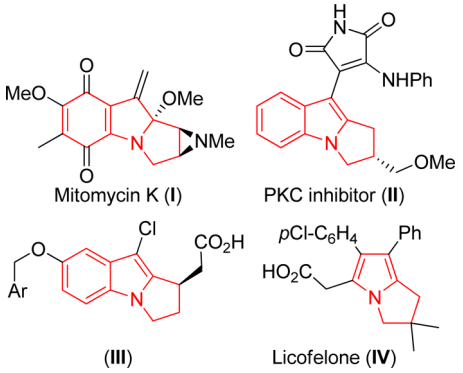


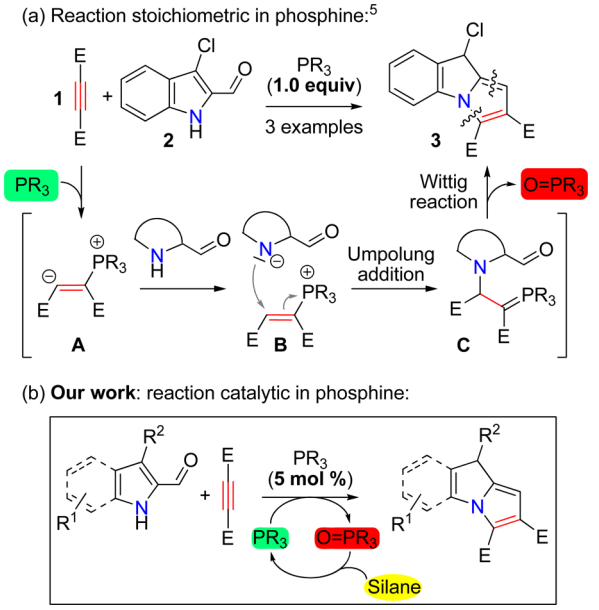
Figure 1. Some natural products and/or bioactives pyrrolo[1,2-*a*]indole and pyrrolizine derivatives.

As representative molecules, we can mention the mitomycin K (**I**), an effective antitumor agent[2c] and compound (**II**), which is a protein kinase C inhibitor, selective for isozyme β.[2d−f] Recently, compound (**III**) proved to be a sphingosine-1 phosphate ($S1P_1$) antagonist.[2g,h] On the other hand, pyrrolizine backbones, such as in licofelone (**IV**), showed diverse pharmacological activities.[2i]

Although several strategies for the synthesis of the pyrrolo-[1,2-*a*]indole scaffold have been explored, this structure still instigates the curiosity of the scientific community.[3]

A known strategy for the synthesis of 9*H*-pyrrolo[1,2-*a*]indole derivatives[4] was developed by Yavari and Esmaeili,[5] using a stoichiometric amount of triphenylphosphine, dialkylacetylenedicarboxylate **1** (DAAD)[6] and indole-2-carboxaldehyde **2** (Scheme 1a). According to the accepted mechanism, the phosphine adds to **1** and the zwitterionic species **A** is formed. The latter is subsequently protonated by the indolic proton of **2**, to give the corresponding vinylphosphonium salt **B**. Umpolung addition[7] of the conjugate base of the indole to **B** furnish a phosphorus ylide **C**, which undergoes an intramolecular Wittig reaction. Subsequent migration of the double bonds furnishes **3**.

Scheme 1. Phosphine-Catalyzed Synthesis of 9*H*-Pyrrolo[1,2-*a*]indole Derivatives (E = CO_2R)



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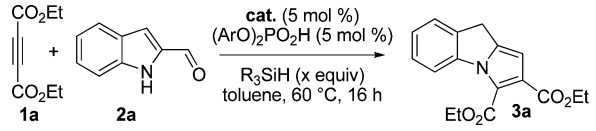
While this procedure proves to be very efficient in terms of yield, at least 1 equiv of triphenylphosphine oxide is formed during the reaction. Considering the new standards in organic chemistry, where catalytic processes are now being promoted,[8] we propose in this work to use a substoichiometric amount of phosphine, by recycling in situ the phosphine oxide formed during the reaction, by mean of a reducing agent (Scheme 1b).

This strategy aiming at reducing waste via an in situ reduction of phosphine oxide has already been successfully implemented in the Wittig,[9] aza-Wittig,[10] Staudinger,[11] Appel[12] and others reactions.[13] Thus, O'Brien et al. described the first Wittig reaction, catalytic in phosphine, thanks to the use of stoichiometric amounts of both Ph_2SiH_2 and a base.[9a] In 2015, Werner developed a catalytic base-free Wittig reaction between maleate and diverse aldehydes.[9f] On the basis of these studies and thanks to prior experiences in our group, concerning the catalytic cyclization reactions of Huisgen zwitterion with α-ketoesters,[14] we envisioned to develop the first sequential umpolung addition/intramolecular Wittig reaction, catalytic in phosphine.

We started our studies by using triphenylphosphine as catalyst (5 mol %), phenylsilane as reducing agent, and a catalytic amount of *bis*(4-nitrophenyl)phosphate (Table 1, entry 1).

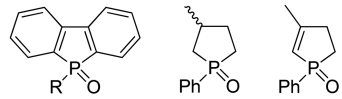
Previous results of our group and others have already proved the efficiency of this reductive system combining a silane with a Brønsted acid to reduce in situ the phosphine oxide formed during the reaction process.[9b,13b,14,15] Unfortunately, both PPh_3 and P*n*-Bu_3 gave disappointing results (entries 1 and 2). Cyclic phosphines **4**–**6** and **7**–**8**, based on dibenzophosphole or phosphole backbones, have proved to possess all the required properties suitable for this reaction. They afforded product **3a** in moderate to good yields (entries 3–7, 60–99% yields). The phosphine must be nucleophilic enough to form the zwitterionic species **A** (Scheme 1a), as well as an active phosphorus ylide for the final Wittig reaction. Furthermore, the phosphine oxide should be easily reduced without using harsh conditions, i.e., strong reducing agents and/or high reaction temperature. The cyclic phosphines **4**–**6** with a P-phenyl, P-*n*-butyl and P-cyclohexyl substituent, as well as the phospholane **7** and the phospholene **8** positively fulfill these requirements. A 60 °C reaction temperature was necessary to obtain a decent yield (entry 8, 17% conversion at 40 °C). Toluene was the best solvent for this reaction among the others solvent tested (dichloroethane, THF, dioxane). The presence of a Brønsted acid is also fundamental, mainly for the in situ reduction of the phosphine oxide (entry 9, <5% conversion). The reaction rate was not improved by the use of different organosilanes (Ph_2SiH_2 and $Me(EtO)_2SiH$, entries 10 and 11, <12% conversion). However, the quantity of reducing agent could be decreased up to 1.0 equiv without erosion of the yield (entries 12 and 13). Finally, the catalytic amount of phosphine **8** could be decreased to 2 mol % (entry 14), but the yield dropped to 30%, after a reaction time of 16 h. The optimized protocol for this reaction was the use of phosphine **8** (5 mol %), with a stoichiometric amount of **1a**, **2a** and phenylsilane, in the presence of a phosphate (5 mol %), at 60 °C in toluene. The practicability of this base-free protocol was further demonstrated by a 1 mmol-scale synthesis of **3a**. The desired product was obtained easily by a simple extraction, followed by a quick filtration through a short pad of silica gel (291 mg, 97% yield). Indubitably, this very easy purification process could present a major advantage of our method, compared to the phosphine-promoted reaction, which suffers from the not always straightforward removal of stoichiometric amount of phosphine oxide.

Table 1. Optimization of the Catalytic Reaction between Acetylenedicarboxylate 1a and 1*H*-Indole-2-carbaldehyde 2a[e]



entry	cat.	R_3SiH (x equiv)	yield **3a** (%)[a]
1	PPh_3	$PhSiH_3$ (1.4)	5
2	PBu_3	$PhSiH_3$ (1.4)	<5
3	**4**	$PhSiH_3$ (1.4)	91
4	**5**	$PhSiH_3$ (1.4)	74
5	**6**	$PhSiH_3$ (1.4)	60
6	**7**	$PhSiH_3$ (1.4)	94
7	**8**	$PhSiH_3$ (1.4)	99
8[b]	**8**	$PhSiH_3$ (1.4)	17
9[c]	**8**	$PhSiH_3$ (1.4)	<5
10	**8**	Ph_2SiH_2 (1.4)	12
11	**8**	$Me(EtO)_2SiH$ (1.4)	<5
12	**8**	$PhSiH_3$ (1.0)	99 (97)
13	**8**	$PhSiH_3$ (0.7)	81
14[d]	**8**	$PhSiH_3$ (1.0)	30

cat. =



4 R = Ph
5 R = *n*-Bu
6 R = Cy

7 **8**

[a]Yields determined by ^1H NMR with trimethoxybenzene as internal standard (yield of isolated compound). [b]Reaction temperature: 40 °C. [c]Reaction conditions of entry 7, without $(4\text{-}NO_2\text{–}C_6H_4O)_2PO_2H$. [d]2 mol % of catalyst **8** and $(ArO)_2PO_2H$ were used. [e]Reaction conditions: **1a** (1 equiv, 0.15 mmol), **2a** (1 equiv), silane (*x* equiv), catalyst (5 mol %), $(4\text{-}NO_2\text{–}C_6H_4O)_2PO_2H$ (5 mol %) and solvent (10 mL/mmol **1a**) at 60 °C for 16 h.

Using this catalytic protocol, it was possible to realize a wide range of umpolung addition/intramolecular Wittig reactions, using electron-rich and electron-poor indole derivatives (Scheme 2).

Three different alkyl acetylenedicarboxylates **1a-c** reacted smoothly with 1*H*-indole-2-carbaldehyde **2a**, to furnish the corresponding products **3a**–**c** in 95–98% yields. Substrates possessing electron-donating groups, such as 5-methyl-,

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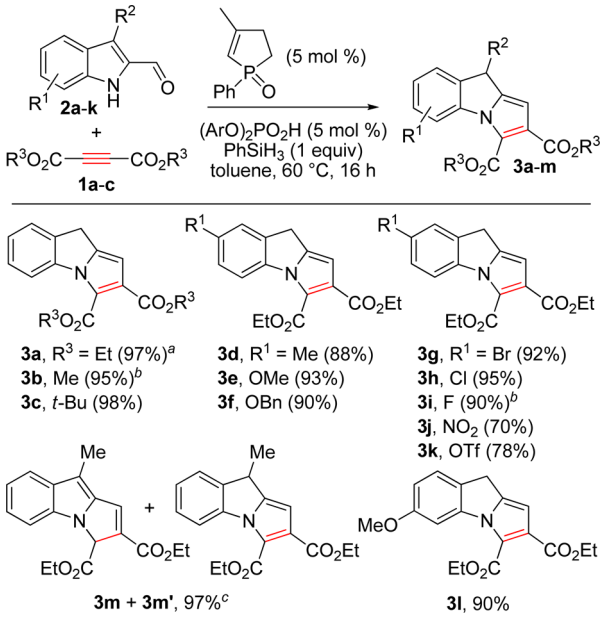
Scheme 2. Scope of the Catalytic Cyclization Reaction[a,b,c]



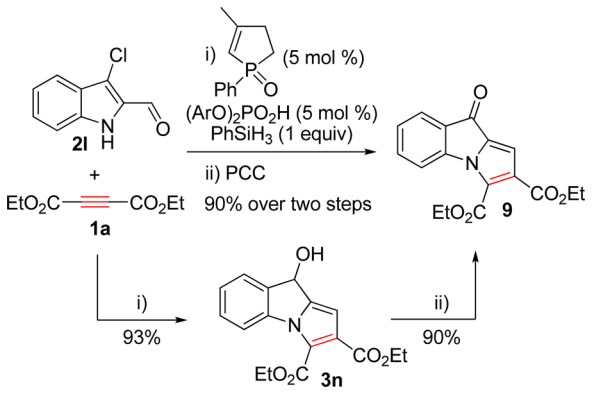
[a]Yields of isolated compounds. [b]Further 24 h of refluxing in toluene was needed to obtain one isomer. [c]Products **3m** and **3m′** were obtained as a mixture of two isomers, with an 85/15 *ratio*. After refluxing in toluene for 24 h, the *ratio* changed to 30/70.

methoxy- and benzyloxy-indoles exhibit good reactivities (**3d–f**, 88–93% yield). Substrates substituted with electron-whithdrawing groups such as halogens (Br, Cl, F), nitro and trifluoromethanesulfonate groups were all tolerated (products **3g–k**, 70–95% yields). 6-methoxy- and 3-methyl-indole derivatives underwent the tandem reaction to give **3l** (R^2 = H) and **3m** (R^2 = Me) in 90% and 97% yield, respectively. In the latter case, the migration of the double bond after the Wittig reaction was not total, and an 85/15 mixture of the two isomers was obtained.

Using the same reaction conditions, and starting with 3-chloro-1*H*-indole-2-carbaldehyde **2l**, we isolated the corresponding hydroxylated compound **3n**[5a] in 93% yield, resulting from hydrolysis of the chlorinated intermediate (Scheme 3).

Traces of water in toluene and filtration over silica gel of the crude mixture may be responsible for this hydrolysis. Subsequent oxidation of **3n** into 9*H*-pyrrolo[1,2-*a*]indol-9-one (fluorazone) derivative **9** was accomplished in 90% yield, using

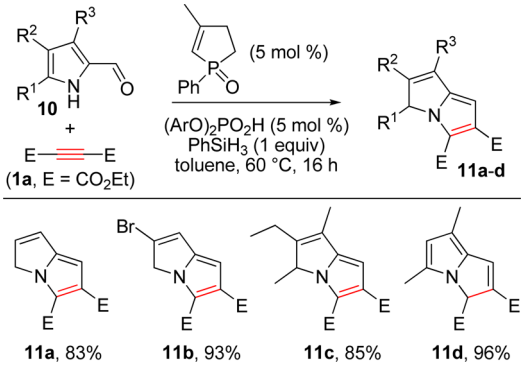
Scheme 3. Synthesis of 9-Oxo-pyrrolo[1,2-*a*]indole Derivative



pyridinium chlorochromate (PCC). The whole procedure (cyclization/hydrolysis/oxidation) could be achieved sequentially in one pot, with 90% overall yield. This protocol compares favorably with the reactions already developed for the synthesis of this skeleton of interest.[16]

Subsequently, the scope of the catalytic one-pot sequential umpolung addition/Wittig reaction could be readily expanded to the synthesis of 3*H*-pyrrolizine-dicarboxylate derivatives[17] (Scheme 4).

Scheme 4. Synthesis of Dimethyl 3*H*-pyrrolizine-dicarboxylate Derivatives



Using the optimized catalytic protocol, it was possible to obtain in a single pot directly the corresponding diethyl 3*H*-pyrrolizine-dicarboxylate products **11a–d**. The described catalytic system displayed good tolerance to bromine and alkyl groups in different positions of the pyrrolizine backbone (83–96% isolated yields).

Concerning the reduction of the phosphine oxide to trivalent phosphine, we can propose that the *bis*(4-nitrophenyl)-phosphate could react with phenylsilane to form a bifunctional silyl phosphate intermediate. This intermediate could act as a *bifunctional catalyst*, and activates simultaneously both the triphenylsilane and the phosphine oxide, allowing the smooth reduction of the phosphine oxide.[15a] Indeed, the phosphate proved to be necessary for the phosphine oxide reduction (see entries 7 and 9, Table 1, same reaction conditions with or without $(4\text{-}NO_2\text{–}C_6H_4O)_2PO_2H$). Additional studies will be required to have a better understanding of this mechanism.

In conclusion, we have developed a new catalytic sequential umpolung addition/intramolecular Wittig reaction. Thanks to the chemoselective in situ reduction of phosphine oxide, only 5 mol % of phosphine catalyst proved to be necessary for the synthesis of 9*H*-pyrrolo[1,2-*a*]indole and 3*H*-pyrrolizine derivatives. This protocol affords an important complement to the already described synthesis of these polycyclic nitrogen-containing heterocycles.

EXPERIMENTAL SECTION

General Information. All nonaqueous reactions were run under a positive pressure of argon, by using standard techniques for manipulating air-sensitive compounds. Toluene was distilled over CaH_2 under an argon atmosphere. Tetrahydrofuran was distilled over sodium/benzophenone under an argon atmosphere. Dry diethyl ether (>99.5% extra dry) was of commercial quality and was used without further purification. All other reagents and solvents were of commercial quality and used without further purification. Analytical thin-layer chromatography (TLC) was performed on plates precoated with silica gel layers. The developed chromatogram was visualized by UV

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absorbance and/or vanillin stain. Purification of compounds were performed with an automated chromatography system using prepacked silica columns. Nuclear magnetic resonance spectra (^{1}H, ^{13}C, ^{19}F) were recorded at 500 or 300 MHz spectrometers. Chemical shifts are reported in parts per million relative to an internal standard of residual chloroform (δ = 7.19 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR). IR spectra were recorded using an IR spectrometer (diamond plate) and are reported in reciprocal centimeters (cm^{-1}). High-resolution mass spectrometry (HRMS) was performed using electrospray ionization (ESI) and time-of-flight (TOF) analyzer, in positive-ion or negative-ion detection mode.

*Representative Procedure for the Synthesis of Indole Carbaldehydes **2** and **10**.* Indole carbaldehydes [**2a** (R^1 = R^2 = H), **2e** (R^1 = 5-Br, R^2 = H), **2f** (R^1 = 5-Cl, R^2 = H), **2h** (R^1 = 5-NO_2, R^2 = H)],[18a] **2b** (R^1 = 5-Me, R^2 = H),[18b] **2c** (R^1 = 5-OMe, R^2 = H),[18c] **2d** (R^1 = 5-OBn, R^2 = H),[18d] **2g** (R^1 = 5-F, R^2 = H),[18e] **2j** (R^1 = 6-OMe, R^2 = H),[18f] **2l**[18g] and 4-bromo-1*H*-pyrrole-2-carbaldehyde **10b** (R^1 = R^3 = H, R_2 = Br)[18h] were prepared according to literature procedures.

*Synthesis of 2-Formyl-1H-indol-5-yl trifluoromethanesulfonate (**2i**).* Ethyl 5-hydroxy-1*H*-indole-2-carboxylate (150 mg, 0.73 mmol) was dissolved in CH_2Cl_2 (7 mL), *N*-phenyl-*bis*(trifluoromethanesulfonimide) (0.8 mmol, 287 mg) was added, and the reaction mixture was cooled to 0 °C. Later on, NEt_3 (0.8 mmol, 113 μL) was added dropwise at 0 °C and a clear yellow solution was formed. After stirring for 1 h at 0 °C, the mixture was warmed to room temperature and stirred overnight until the reaction was finished (as monitored by TLC). Then, the solvent was evaporated and the crude mixture was used for the next step without further purification. A solution of $LiAlH_4$ (1.46 mmol, 55 mg) in distillated THF was cooled to 0 °C. The crude mixture was dissolved in THF and added dropwise then stirred for 2 h at 0 °C. The reaction was then quenched by dropwise addition of 2 M NaOH solution, then filtrated over Celite with THF as eluent. Later on, activated MnO_2 (7.3 mmol, 640 mg) was added over the THF solution and stirred at 40 °C overnight. After filtration over Celite, the crude product was purified over silica gel column chromatography with ethyl acetate (1 to 3)/heptane (9 to 7) as eluents to recover the product in 50% yield (107 mg) over two steps as a white precipitate, mp 135−137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.83 (1H, s), 9.07 (1H, bs), 7.62 (1H, d, J = 2.3 Hz), 7.44 (1H, d, J = 9.0 Hz), 7.28−7.20 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.3 (*C*H), 144.2 (*C*), 137.6 (*C*), 136.6 (*C*), 127.2 (*C*), 120.7 (*C*H), 116.7 (*C*), 115.7 (*C*H), 114.7 (*C*H), 114.1 (*C*H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.7; IR ν_{max} = 3302, 1660, 1526, 1414, 1225, 1210, 1136, 749 cm^{-1}; LRMS (ESI) cacld. for $C_{10}H_7F_3NO_4S$ [M + H]$^+$ 294.0, found 294.0.

*Representative Procedure for the Reaction of Indole Carbaldehyde Derivatives **2** with Acetylene Dicarboxylate **1**, to Form Products **3**.* In a Schlenk tube, indole carbaldehyde **2** (0.15 mmol, 1 equiv), phospholene (5 mol %) *bis*(4-nitrophenyl)phosphate (5 mol %), and freshly distillated degazed toluene (0.15 M) were added. Then, the acetylene dicarboxylate **1** (0.15 mmol, 1 equiv) and phenylsilane (1 equiv) were added using microsyringes. The reaction mixture was then heated at 60 °C for 16 h and the crude reaction mixture was concentrated and purified by flash chromatography using silica gel prepacked column and EtOAc/heptanes as eluent (0 to 20% of EtOAc over 25 min, 18 mL/min). **Note:** Some indole carbaldehydes were not soluble in toluene, thus some THF (0.1 mL) was added to enhance their solubility (compounds **3j**, **3k**). Some products were obtained in two resonance structures, so further 24 h of refluxing in toluene was needed to obtain one isomer (compounds **3b, 3i**).

*Diethyl 9H-pyrrolo[1,2-a]indole-2,3-dicarboxylate (**3a**).* (43 mg, 97% yield). Yellow oil; R_f 0.36 (20% EtOAc/heptanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (1H, d, J = 7.9 Hz), 7.33 (1H, d, J = 7.5 Hz), 7.28−7.21 (1H, m), 7.11 (1H, td, J = 7.5, 1.1 Hz), 6.42 (1H, t, J = 1.3 Hz), 4.36 (2H, q, J = 7.1 Hz), 4.24 (2H, q, J = 7.1 Hz), 3.75 (2H, s), 1.34 (3H, t, J = 7.1 Hz), 1.28 (3H, t, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7 (*C*O), 161.6 (*C*O), 140.6 (*C*), 138.6 (*C*), 135.0 (*C*), 127.8 (*C*H), 125.6 (*C*H), 125.0 (*C*H), 124.6 (*C*), 119.1 (*C*), 114.5 (*C*H), 104.3 (*C*H), 61.5 (CH_2), 60.6 (CH_2), 28.9 (CH_2), 14.3 (CH_3), 14.1 (CH_3); IR ν_{max} = 2983, 1706, 1480, 1273, 1211, 1186, 1054, 1029, 752 cm^{-1}; HRMS (ESI) cacld. for $C_{17}H_{18}NO_4$ [M + H]$^+$ 300.1236, found 300.1246.

The reaction was also started at 1 mmol scale: the product **3a** was isolated in 97% yield (291 mg). (Check ^{1}H NMR spectra after simple extraction and filtration. The product was isolated almost in pure form without purification by column chromatography.)

*Dimethyl 9H-pyrrolo[1,2-a]indole-2,3-dicarboxylate (**3b**).* (39 mg, 95% yield). Yellow solid; mp 94−96 °C; R_f 0.25 (20% EtOAc/heptanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (1H, d, J = 8.3 Hz), 7.35 (1H, d, J = 7.5 Hz), 7.27 (1H, t, J = 7.9 Hz), 7.17−7.10 (1H, m), 6.45 (1H, bs), 3.91 (3H, s), 3.79 (5H, bs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9 (*C*O), 162.0 (*C*O), 140.5 (*C*), 138.8 (*C*), 135.0 (*C*), 127.9 (*C*H), 125.6 (*C*H), 125.1 (*C*H), 124.2 (*C*), 118.8 (*C*), 114.5 (*C*H), 104.6 (*C*H), 52.4 (CH_3), 51.8 (CH_3), 29.0 (CH_2); IR ν_{max} = 2952, 1709, 1480, 1442, 1277, 1215, 1166, 1057, 752 cm^{-1}; HRMS (ESI) cacld. for $C_{15}H_{14}NO_4$ [M + H]$^+$ 272.0923, found 272.0916.

*Di-tert-butyl 9H-pyrrolo[1,2-a]indole-2,3-dicarboxylate (**3c**).* (52 mg, 98% yield). Yellow solid; mp 98−100 °C; R_f 0.55 (20% EtOAc/heptanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (1H, d, J = 7.5 Hz), 7.32 (1H, d, J = 7.5 Hz), 7.28−7.21 (1H, m), 7.14−7.07 (1H, m), 6.33 (1H, bs), 3.75 (2H, s), 1.57 (9H, s), 1.51 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5 (*C*O), 160.8 (*C*O), 140.9 (*C*), 137.6 (*C*), 135.0 (*C*), 127.7 (*C*H), 125.8 (*C*), 125.5 (*C*H), 124.7 (*C*H), 120.1 (*C*), 114.5 (*C*H), 104.2 (*C*H), 82.3 (*C*), 80.4 (*C*), 28.8 (CH_2), 28.3 (CH_3), 28.1 (CH_3); IR ν_{max} = 2978, 1706, 1478, 1366, 1288, 1227, 1154, 1054, 751 cm^{-1}; HRMS (ESI) cacld. for $C_{21}H_{26}NO_4$ [M + H]$^+$ 356.1862, found 356.1870.

*Diethyl 7-methyl-9H-pyrrolo[1,2-a]indole-2,3-dicarboxylate (**3d**).* (41 mg, 88% yield). Yellow solid; mp 69−71 °C; R_f 0.39 (20% EtOAc/heptanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (1H, d, J = 8.3 Hz), 7.14 (1H, bs), 7.04 (1H, dd, J = 8.3, 0.9 Hz), 6.45−6.37 (1H, m), 4.36 (2H, q, J = 7.1 Hz), 4.24 (2H, q, J = 7.1 Hz), 3.73 (2H, s), 2.30 (3H, s), 1.33 (3H, t, J = 7.6 Hz), 1.28 (3H, t, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8 (*C*O), 161.6 (*C*O), 138.7 (*C*), 138.4 (*C*), 135.1 (*C*), 134.9 (*C*), 128.3 (*C*H), 126.3 (*C*H), 124.2 (*C*), 118.8 (*C*), 114.2 (*C*H), 104.3 (*C*H), 61.4 (CH_2), 60.6 (CH_2), 28.9 (CH_2), 21.1 (CH_3), 14.3 (CH_3), 14.1 (CH_3); IR ν_{max} = 2981, 1705, 1486, 1272, 1198, 1178, 1119, 1054, 1027, 815, 771 cm−1; HRMS (ESI) cacld. for $C_{18}H_{20}NO_4$ [M + H]$^+$ 314.1392, found 314.1390.

*Diethyl 7-methoxy-9H-pyrrolo[1,2-a]indole-2,3-dicarboxylate (**3e**).* (46 mg, 93% yield). Yellow solid; mp 58−60 °C; R_f 0.22 (20% EtOAc/heptanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (1H, d, J = 9.0 Hz), 6.90 (1H, bs), 6.76 (1H, dd, J = 9.0, 2.4 Hz), 6.45−6.40 (1H, m), 4.34 (2H, q, J = 7.5 Hz), 4.24 (2H, q, J = 7.2 Hz), 3.75 (5H, s), 1.35−1.25 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8 (*C*O), 161.5 (*C*O), 157.4 (*C*), 138.5 (*C*), 136.7 (*C*), 134.5 (*C*), 124.0 (*C*), 118.6 (*C*), 115.2 (*C*H), 112.5 (*C*H), 111.8 (*C*H), 104.5 (*C*H), 61.3 (CH_2), 60.6 (CH_2), 55.7 (CH_3), 29.2 (CH_2), 14.3 (CH_3), 14.1 (CH_3); IR ν_{max} = 2980, 1701, 1481, 1427, 1275, 1197, 1115, 1054, 1034, 759 cm^{-1}; HRMS (ESI) cacld. for $C_{18}H_{20}NO_5$ [M + H]$^+$ 330.1341, found 330.1324.

*Diethyl 7-(benzyloxy)-9H-pyrrolo[1,2-a]indole-2,3-dicarboxylate (**3f**).* (55 mg, 90% yield). Yellow oil; R_f 0.24 (20% EtOAc/heptanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (1H, d, J = 9.0 Hz), 7.39−7.20 (5H, m), 6.95 (1H, bs), 6.84 (1H, dd, J = 9.0, 3.0 Hz), 6.40 (1H, s), 4.99 (2H, s), 4.34 (2H, q, J = 7.1 Hz), 4.22 (2H, q, J = 7.1 Hz), 3.72 (2H, s), 1.35−1.20 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8 (*C*O), 161.5 (*C*O), 156.6 (*C*), 138.5 (*C*), 136.8 (*C*), 136.7 (*C*), 134.7 (*C*), 128.6 (*C*H), 128.1 (*C*H), 127.4 (*C*H), 124.1 (*C*), 118.6 (*C*), 115.2 (*C*H), 113.6 (*C*H), 112.8 (*C*H), 104.5 (*C*H), 70.5 (CH_2), 61.3 (CH_2), 60.6 (CH_2), 29.2 (CH_2), 14.3 (CH_3), 14.1 (CH_3); IR ν_{max} = 2982, 1703, 1482, 1286, 1276, 1200, 1177, 1055, 1027, 769 cm−1; HRMS (ESI) cacld. for $C_{24}H_{24}NO_5$ [M + H]$^+$ 406.1654, found 406.1663.

*Diethyl 7-bromo-9H-pyrrolo[1,2-a]indole-2,3-dicarboxylate (**3g**).* (52 mg, 92% yield). Yellow solid; mp 101−104 °C; R_f 0.32 (20% EtOAc/heptanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (1H, d, J = 8.5 Hz), 7.50−7.46 (1H, m), 7.39 (1H, dd, J = 8.5, 2.1 Hz), 6.44−6.41 (1H, m), 4.35 (2H, q, J = 7.1 Hz), 4.25 (2H, q, J = 7.1 Hz), 3.79 (2H, s), 1.33 (3H, t, J = 7.1 Hz), 1.29 (3H, t, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6 (*C*O), 161.2 (*C*O), 139.8 (*C*), 138.6 (*C*), 137.1 (*C*), 130.8 (*C*H), 128.7 (*C*H), 125.4 (*C*), 119.0 (*C*), 118.2 (*C*), 116.2 (*C*H),

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104.6 (CH), 61.5 (CH_2), 60.8 (CH_2), 28.9 (CH_2), 14.3 (CH_3), 14.1 (CH_3); IR ν_{max} = 2980, 1706, 1479, 1467, 1270, 1212, 1181, 1113, 1053, 751 cm^{-1}; HRMS (ESI) cacld. for $C_{17}H_{17}BrNO_4$ $[M + H]^+$ 378.0341, found 378.0312.

*Diethyl 7-chloro-9H-pyrrolo[1,2-a]indole-2,3-dicarboxylate (**3h**).* (48 mg, 95% yield). White solid; mp 126−128 °C; R_f 0.32 (20% EtOAc/heptanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (1H, d, J = 8.7 Hz), 7.32−7.29 (1H, m), 7.22 (1H, dd, J = 8.7, 2.3 Hz), 6.43−6.40 (1H, m), 4.35 (2 H, q, J = 7.1 Hz), 4.25 (2H, q, J = 7.1 Hz), 3.77 (2H, s), 1.33 (3H, t, J = 7.1 Hz), 1.29 (3H, t, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6 (CO), 161.3 (CO), 139.3 (C), 138.7 (C), 136.7 (C), 130.6 (C), 127.9 (CH), 125.8 (CH), 125.3 (C), 118.8 (C), 115.7 (CH), 104.6 (CH), 61.5 (CH_2), 60.8 (CH_2), 28.9 (CH_2), 14.3 (CH_3), 14.1 (CH_3); IR ν_{max} = 2984, 1726, 1698, 1486, 1468, 1272, 1218, 1185, 1163, 814, 756 $cm^{-1;}$ HRMS (ESI) cacld. for $C_{17}H_{17}ClNO_4$ $[M + H]^+$ 334.0846, found 334.0831.

*Diethyl 7-fluoro-9H-pyrrolo[1,2-a]indole-2,3-dicarboxylate (**3i**).* (43 mg, 90% yield). Yellow solid; mp 76−78 °C; R_f 0.27 (20% EtOAc/heptanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (1H, dd, J = 9.0, 4.5 Hz), 7.13−7.02 (1H, m), 6.96 (1H, td, J = 8.9, 2.6 Hz), 6.43 (1H, t, J = 1.3 Hz), 4.35 (2H, q, J = 7.1 Hz), 4.25 (2H, q, J = 7.1 Hz), 3.79 (2H, s), 1.33 (3H, t, J = 7.1 Hz), 1.29 (3H, t, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7 (CO), 162.00 (C), 161.4 (CO), 158.7 (C) 138.8 (C), 137.0 (C, d, $^2J_{C-F}$ = 8.8 Hz), 124.9 (C), 118.7 (C), 115.7 (CH, d, $^3J_{C-F}$ = 8.8 Hz), 114.3 (CH, d, $^2J_{C-F}$ = 21.2 Hz), 113.1 (CH, d, $^2J_{C-F}$ = 24.1 Hz), 104.6 (CH), 61.5 (CH_2), 60.7 (CH_2), 29.2 (CH_2), 14.3 (CH_3), 14.1 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ −117.4; IR ν_{max} = 2985, 1729, 1701, 1487, 1475, 1273, 1210, 1198, 1164, 848, 762 cm^{-1}; HRMS (ESI) cacld. for $C_{17}H_{17}FNO_4$ $[M + H]^+$ 318.1142, found 318.1136.

*Diethyl 7-nitro-9H-pyrrolo[1,2-a]indole-2,3-dicarboxylate (**3j**).* (36 mg, 70% yield). White solid; mp 144−146 °C; R_f 0.22 (20% EtOAc/heptanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25−8.20 (3H, m), 6.49 (1H, t, J = 1.5 Hz), 4.37 (2H, q, J = 7.1 Hz), 4.27 (2H, q, J = 7.1 Hz), 3.92 (2H, t, J = 1.1 Hz), 1.33 (3H, t, J = 7.1 Hz), 1.29 (3H, t, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4 (CO), 160.9 (CO), 145.4 (C), 144.9 (C), 139.9 (C), 136.2 (C), 127.2 (C), 124.7 (CH), 121.1 (CH), 119.3 (C), 114.9 (CH), 105.3 (CH), 61.8 (CH_2), 61.1 (CH_2), 29.0 (CH_2), 14.3 (CH_3), 14.1 (CH_3); IR ν_{max} = 2985, 1706, 1523, 1479, 1341, 1281, 1213, 1189, 1174, 748 $cm^{-1;}$ HRMS (ESI) cacld. for $C_{17}H_{17}N_2O_6$ $[M + H]^+$ 345.1087, found 345.1081.

*Diethyl 7-(((trifluoromethyl)sulfonyl)oxy)-9H-pyrrolo[1,2-a]-indole-2,3-dicarboxylate (**3k**).* (52 mg, 78% yield). Colorless oil; R_f 0.36 (20% EtOAc/heptanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (1H, d, J = 9.0 Hz), 7.32−7.25 (1H, m), 7.22−7.12 (1H, m), 6.49−6.36 (1H, m), 4.35 (2H, q, J = 7.1 Hz), 4.25 (2H, q, J = 7.1 Hz), 3.86 (2H, s), 1.33 (3H, t, J = 7.1 Hz), 1.29 (3H, t, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5 (CO) 161.1 (CO) 146.4 (C) 140.4(C) 139.0 (C) 137.3 (C) 126.0 (C) 121.0 (CH) 120.8 (C) 119.0 (CH) 116.6 (C) 116.0 (CH) 104.9 (CH) 61.6 (CH_2) 60.9 (CH_2) 29.2 (CH_2) 14.3 (CH_3) 14.1 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.6; IR ν_{max} = 2986, 1705, 1477, 1423, 1276, 1249, 1207, 1189, 1140, 1101, 933, 842, 771 cm^{-1}; HRMS (ESI) cacld. for $C_{18}H_{17}NO_7F_3S$ $[M + H]^+$ 448.0678, found 448.0687.

*Diethyl 6-methoxy-9H-pyrrolo[1,2-a]indole-2,3-dicarboxylate (**3l**).* (44 mg, 90% yield). Yellow solid; mp 88−90 °C; R_f 0.30 (20% EtOAc/heptanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (1H, d, J = 2.3 Hz), 7.23−7.12 (1H, m), 6.65 (1H, dd, J = 8.3, 2.6 Hz), 6.41−6.38 (1H, m), 4.35 (2H, q, J = 7.1 Hz), 4.24 (2H, q, J = 7.1 Hz), 3.77 (3H, s), 3.69 (2H, s), 1.33 (3H, t, J = 7.1 Hz), 1.28 (3H, t, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8 (CO), 161.5 (CO), 159.7 (C), 141.6 (C), 140.0 (C), 126.6 (C), 125.7 (CH), 124.7 (C), 118.9 (C), 110.6 (CH), 104.3 (CH), 101.3 (CH), 61.5 (CH_2), 60.6 (CH_2), 55.7 (CH_3), 28.3 (CH_2), 14.3 (CH_3), 14.1 (CH_3); IR ν_{max} = 2982, 1704, 1626, 1489, 1287, 1274, 1209, 1184, 1150, 1107, 1030, 858, 771 cm^{-1}; HRMS (ESI) cacld. for $C_{18}H_{20}NO_5$ $[M + H]^+$ 330.1341, found 330.1335.

Products **3m** and **3m′** were obtained as a mixture of two isomers, with an 85/15 ratio. After refluxing of 24 h in toluene, the ratio changed to 30/70 without going to 100% pure product **3m′**, even after heating for 72 h.

*Diethyl 9-methyl-3H-pyrrolo[1,2-a]indole-2,3-dicarboxylate (**3m**).* (45 mg, 97% total yield). Yellow solid; mp 65−67 °C; R_f 0.35 (20% EtOAc/heptanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (1H, d, J = 1.7 Hz), 7.54−7.49 (1H, m), 7.29−7.24 (1H, m), 7.21−7.14 (1H, m), 7.07−7.00 (1H, m), 5.44 (1H, m), 4.31−4.07 (4H, m), 2.33 (3H, d, J = 1.7 Hz), 1.29 (3H, t, J = 7.1 Hz), 1.20 (3H, t, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5 (CO), 162.6 (CO), 141.0 (C), 134.8 (C), 133.4 (C), 132.8 (C), 132.2 (CH), 123.9 (CH), 120.7 (CH), 119.6 (C), 109.5 (CH), 108.4 (C), 63.1 (CH), 62.2 (CH_2), 60.9 (CH_2), 14.3 (CH_3), 14.1 (CH_3), 9.2 (CH_3).

*Diethyl 9-methyl-9H-pyrrolo[1,2-a]indole-2,3-dicarboxylate (**3m′**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (1 H, d, J = 7.9 Hz), 7.31 (1 H, dd, J = 7.9, 1.1 Hz), 7.28−7.22 (1H, m), 7.17−7.13 (1H, m), 6.45−6.39 (1H, m), 4.37 (2H, q, J = 7.1 Hz), 4.25 (2H, q, J = 7.1 Hz), 3.93 (1H, q, J = 7.1 Hz), 1.44 (3H, d, J = 7.1 Hz), 1.37−1.27 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7 (CO) 161.6 (CO), 144.7 (C), 140.8 (C), 139.8 (C), 128.2 (C), 127.9 (CH), 125.2 (CH), 124.4 (CH), 118.8 (C), 114.5 (CH), 103.6 (CH), 61.5 (CH_2), 60.8 (CH_2), 35.2 (CH), 18.6 (CH_3), 14.3 (CH_3), 14.1 (CH_3); IR (mixture) ν_{max} = 2983, 2923, 1743, 1706, 1569, 1479, 1453, 1376, 1326, 1266, 1209, 1182, 1170, 1093, 1022, 756, 741 cm^{-1}; HRMS (ESI) cacld. for $C_{18}H_{20}NO_4$ $[M + H]^+$ 314.1392, found 314.1375.

*Diethyl 9-hydroxy-9H-pyrrolo[1,2-a]indole-2,3-dicarboxylate (**3n**).* The product was prepared by following the general procedure. However, the presence of trace of water in the solvent, or during the workup and filtration over silica gel, resulted in the substitution of chloride atom by a OH group, to obtain the product **3n**. (44 mg, 93% yield). Red solid; mp 83−85 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76−7.81 (1H, d, J = 8 Hz), 7.47−7.52 (1H, m), 7.29−7.38 (1H, td, J = 7.6, 1.9 Hz), 7.16−7.23 (td, J = 7.6, 1.1 Hz), 6.68 (1H, d, J = 1.1 Hz), 5.77 (1H, s), 4.37 (2H, q, J = 7.2 Hz), 4.23 (2H, q, J = 7.2 Hz), 1.33 (3H, t, J = 7.2 Hz), 1.27 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8 (CO), 161.2 (CO), 139.2 (C), 138.1 (C), 136.3 (C), 130.4 (CH), 126.6 (CH), 126.1 (CH), 124.4 (C), 121.1 (C), 114.5 (CH), 108.0 (CH), 61.9 (CH_2), 60.8 (CH_2), 14.3 (CH_3), 14.0 (CH_3); IR ν_{max} = 2982, 1710, 1470, 1432, 1287, 1273, 1210, 1182, 1150, 1104, 1035, 751 cm^{-1}; HRMS (ESI) cacld. for $C_{17}H_{18}NO_5$ $[M + H]^+$ 316.1185, found 316.1169.

*Diethyl 9-oxo-9H-pyrrolo[1,2-a]indole-2,3-dicarboxylate (**9**).* In a Schlenk tube, 3-chloro indole carbaldehyde **2n** (27 mg, 0.15 mmol, 1 equiv), phospholene **8** (5 mol %) *bis*(4-nitrophenyl)phosphate (5 mol %), and toluene (0.15 M) were added. Then, the acetylene dicarboxylate **1a** (0.15 mmol, 1 equiv) and phenylsilane (1 equiv) were added using microsyringes. The reaction mixture was then heated at 80 °C for 16 h. Later on, toluene was removed under vacuum and the crude mixture was dissolved in CH_2Cl_2. PCC (65 mg, 0.3 mml) was added in one portion and the reaction was stirred overnight at room temperature. After removing of solvent under rotary vapor, purification over silica gel column chromatography afforded **9** (47 mg, 90% yield) Yellow solid; mp 111−113 °C; R_f 0.32 (20% EtOAc/heptanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (1H, dt, J = 7.6, 0.9 Hz), 7.52−7.48 (1H, m), 7.46−7.40 (1H, m), 7.22−7.15 (1H, m), 7.03 (1H, s), 4.43 (2H, q, J = 7.1 Hz), 4.24 (2H, q, J = 7.1 Hz), 1.37 (3H, t, J = 7.1 Hz), 1.28 (3H, t, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.4 (CO), 162.6 (CO), 160.8 (CO), 143.5 (C), 135.3 (CH), 131.5 (C), 129.5 (C), 127.1 (CH), 126.7 (C), 124.8 (CH), 124.1 (C), 114.2 (CH), 113.3 (CH), 62.8 (CH_2), 61.0 (CH_2), 14.2 (CH_3), 14.0 (CH_3); IR ν_{max} = 2984, 1706, 1614, 1543, 1458, 1273, 1204, 1187, 1155, 1089, 1054, 907, 751 cm^{-1}; HRMS (ESI) cacld. for $C_{17}H_{16}NO_5$ $[M + H]^+$ 314.1028, found 314.1040.

*Diethyl 3H-pyrrolizine-5,6-dicarboxylate (**11a**).* (31 mg, 83% yield). Yellow solid; mp 48−50 °C; R_f 0.39 (20% EtOAc/heptanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.56 (1H, dt, J = 6.0, 2.1 Hz), 6.46 (1H, dt, J = 6.0, 1. Nine Hz), 6.35 (1H, s), 4.68−4.64 (2H, m), 4.34−4.21 (4H, m), 1.33−1.26 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7 (CO), 160.4 (CO), 143.5 (C), 132.4 (CH), 124.6 (C), 122.3 (CH), 120.3 (C), 101.9 (CH), 60.6 (CH_2), 55.3 (CH_2), 14.33 (CH_3), 14.30 (CH_3); IR ν_{max} = 2982, 1725, 1688, 1487, 1442, 1286, 1250, 1210, 1151, 1077, 1054, 766 cm^{-1}; HRMS (ESI) cacld. for $C_{13}H_{16}NO_4$ $[M + H]^+$ 250.1079, found 250.1066.

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*Diethyl 2-bromo-3H-pyrrolizine-5,6-dicarboxylate (**11b**).* (46 mg, 93% yield). Brown-yellow solid; mp 58−61 °C; R_f 0.37 (20% EtOAc/heptanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71−6.63 (1H, m), 6.32 (1H, s), 4.76−4.67 (2H, m), 4.36−4.18 (4H, m), 1.36−1.24 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4 (*C*O), 160.0 (*C*O), 142.0 (*C*), 124.0 (*C*), 123.2 (*C*H), 121.5 (*C*), 120.6 (*C*), 102.3 (*C*H), 60.9 (CH_2), 60.8 (CH_2), 59.3 (CH_2), 14.33 (CH_3), 14.27 (CH_3); IR ν_{max} = 2981, 1728, 1686, 1487, 1440, 1289, 1245, 1195, 1143, 1062, 1028, 856, 757 cm^{-1}; HRMS (ESI) cacld. for $C_{13}H_{15}BrNO_4$ $[M + H]^+$ 328.0184, found 328.0187.

*Diethyl 2-ethyl-1,3-dimethyl-3H-pyrrolizine-5,6-dicarboxylate (**11c**).* (39 mg, 85% yield). Dark-yellow oil; R_f 0.62 (20% EtOAc/heptanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.12 (1H, s), 4.84 (1H, dq, J = 6.9, 1.5 Hz), 4.29−4.19 (4H, m), 2.45−2.35 (1H, m), 2.20−2.10 (1H, m), 1.86 (3H, t, J = 1.3 Hz), 1.37 (3H, d, J = 6.9 Hz), 1.30−1.20 (6H, m), 1.02 (3H, t, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2 (*C*O), 160.6 (*C*O), 147.5 (*C*), 146.1 (*C*), 124.6 (*C*), 122.4 (*C*), 119.8 (*C*), 99.1 (*C*H), 62.4 (*C*H), 60.5 (CH_2), 60.4 (CH_2), 19.0 (CH_2), 18.1 (CH_3), 14.3 (CH_3), 14.2 (CH_3), 13.6 (CH_3), 19.5 (CH_3); IR ν_{max} = 2978, 2937, 1727, 1693, 1489, 1268, 1238, 1224, 1187, 1136, 1056, 1027, 766 cm^{-1}; HRMS (ESI) cacld. for $C_{17}H_{24}NO_4$ $[M + H]^+$ 306.1705, found 306.1678.

*Diethyl 5,7-dimethyl-3H-pyrrolizine-2,3-dicarboxylate (**11d**).* (40 mg, 96% yield). Dark-yellow oil; R_f 0.43 (20% EtOAc/heptanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (1H, d, J = 1.9 Hz), 5.80 (1H, s), 5.14 (1H, q, J = 1.5 Hz), 4.22−4.07 (4H, m), 2.08 (3H, s), 2.05 (3H, d, J = 1.5 Hz), 1.25−1.12 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7 (*C*O), 163.0 (*C*O), 134.9 (*C*), 133.0 (*C*H), 131.0 (*C*), 126.7 (*C*), 117.0 (*C*), 114.0 (*C*H), 63.0 (*C*H), 62.0 (CH_2), 60.2 (CH_2), 14.3 (CH_3), 14.1 (CH_3), 12.1 (CH_3), 11.4 (CH_3); IR ν_{max} = 2981, 1743, 1557, 1505, 1368, 1326, 1247, 1184, 1136, 1073, 1028, 848, 764 cm^{-1}; HRMS (ESI) cacld. for $C_{15}H_{20}NO_4$ $[M + H]^+$ 278.1392, found 278.1380.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00473.

Copies of ^{1}H NMR and ^{13}C NMR spectra of the products. (PDF)

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Notes

The authors declare no competing financial interest.

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