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Polycyclic Indolines by an Acid-Mediated Intramolecular Dearomative Strategy: Reversing Indole Reactivity in the Pictet–Spengler-Type Reaction

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Abstract. Indoline-fused polycycles were synthesized through a TFA-promoted intramolecular dearomative cyclization of indole-tethered pyrroles. Mechanistically, the strategic carbon-carbon bond formation is hypothesized to proceed via a Pictet–Spengler-type reaction wherein a reversal of conventional indole reactivity of tryptamine derivatives occurs. The synthetic versatility of this operationally simple, atom-economic approach is demonstrated in the preparation of the pyrido[1,2-*a*:3,4-*b'*]diindole core of natural product homofascaplysin C.

Keywords: Indoline; Indolium; Dearomatization; Pictet–Spengler; Metal-free

Polycyclic indolines constitute important structural motifs found in many indole alkaloids such as kopsanone, malagashanine, aspidophylline A, dasyrachine, vindolinine/vindoline, minfiensine, vincorine, picratidine, and strychnine. Due to their diverse architectures, properties, and pharmaceutical activities, polycyclic indoline structures have inspired synthetic chemists to develop novel synthetic methodologies.[1]

Among the reported strategies, dearomatization of indoles[2] represents an attractive, robust, and atom-economic strategy towards these fascinating polycyclic skeletons. Over the past 15 years, various indoles with a pendant alkene/(hetero)arene functionality linked to either nitrogen or carbon as possible substrates have been the focus of intramolecular dearomative cyclization reactions. In 2003, Harrowven et al. disclosed one example of radical spirocyclization of a 2-iodoaryl-containing 3-substituted indole to synthesize spiroindoline.[3] In 2010, Chen et al. discovered a highly efficient, direct, and diastereoselective intramolecular ene reaction of indoles via a Lewis acid-catalyzed enamine–imine isomerization.[4] Recently, Jia and co-workers reported an elegant enantioselective arylative dearomatization of indoles via a Pd-catalyzed intramolecular reductive Heck reactions.[5] Almost at the same time, the Lautens research group developed diastereoselective indole dearomative bisfunctionalizations with cyanide and organoboron reagents via a domino arylation/Suzuki[6a] or arylation/cyanation[6b] sequence. More recently, Vincent's group reported the synthesis of 3,3-spiroindolines via $FeCl_3$-mediated cyclization of aryl- or alkene-containing 3-substituted N-Ac indoles.[7] Despite these achievements, dearomative coupling reactions still have limited applications owing to the intrinsic drawbacks of transition metal catalysts such as cost, toxicity, sensitivity to oxygen and moisture, need for non-commercial ligands, use of additives/cocatalysts. Besides, the removal of trace metal impurities due to the extended use of precious metal promoters remains problematic. Undoubtedly, complementary protocols for the selective installation of new carbon-carbon bonds under metal-free conditions[8] to satisfy the classical metal-catalyzed dearomative cyclizations are of primary importance. Herein, we disclose the successful development of an efficient Brønsted acid-promoted dearomative cyclization for the synthesis of polycyclic C2,C3-fused indoline compounds.[9]

While the nucleophilic Friedel–Crafts-type reactivity of indoles has been widely exploited in organic synthesis (enamine-type reactivity), the electrophilic iminium type reactivity of the corresponding intermediates (**II**) is encountered less frequently.[10] For the intramolecular in-situ trapping of the incipient C2 electrophile in the resulting indolium, a built-in (hetero)nucleophile such as an amino or hydroxy group is involved (Figure 1).

However, the use of aryl/heteroaryl nucleophiles[11] to access polycyclic indoline frameworks using this iminium-trapping approach still remains a challenging task and is therefore highly desirable.

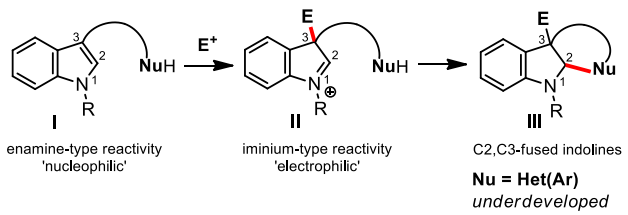
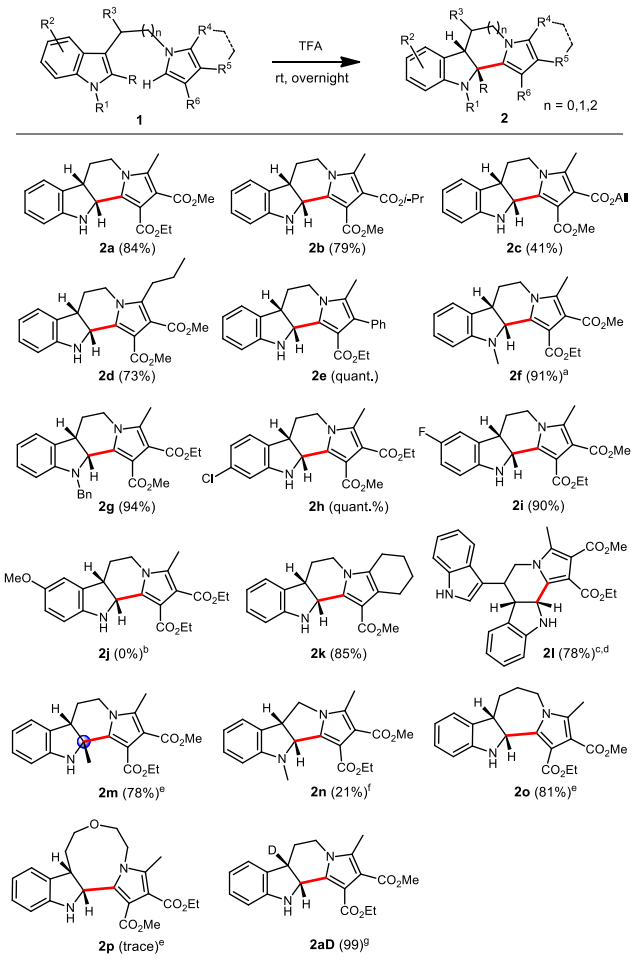


Figure 1. Intramolecular iminium-type reactivity of indoles.

This less exploited reactivity profile of indoles combined with our continuing interest in synthesizing new tryptamine-derived architectures[12] offered a starting point to identify suitable reaction conditions to allow for protonative dearomatizations of indole-tethered pyrroles.

Only one literature precedent utilizing the electrophilic iminium species formed in-situ after C3 protonation of the indole core of tryptamine derivatives has been reported, and this example occurred between two indole subunits.[13] As a result, two different 2,2'-diindole derivatives were obtained irrespective of which indole portion was protonated, with a preference for indolium ion formation arising from the protonation of the more basic C3-unsubstituted indole double bond. Thus, the utility of this reaction would be greatly enhanced if it could be applied to other indole-based tethered biheterocycles such as the indole-pyrrole[14] system.

Using this literature example as a guide, indole-pyrrole **1a** was subjected to neat TFA at room temperature. To our delight, the reaction proceeded in 84% yield with exclusive formation of tetrahydro-5*H*-indolizino[8,7-*b*]indole (**2a**). The propensity to form indoline can be attributed to the preferential protonation of the indole core to produce indolium, which undergoes an intramolecular cross-Mannich reaction by the CH bond of the pyrrole. A variety of indole-based C3,N-linked biheterocycles of general structure **1**[15] were prepared and screened as potential substrates for the present acid-promoted intramolecular dearomative cross-coupling reaction. As shown in Scheme 1, differently substituted indole-pyrroles bearing an electron-neutral (4-H) or electron-deficient (5-F, 6-Cl) indole framework reacted smoothly to afford fused tetracyclic compounds in excellent yields. Under identical acidic conditions, the presence of an electron rich (5-OMe) group delivered the oxidative coupling product **2j'**[16,17] in 40% yield without any appreciable formation of dearomatization cross-coupling product **2j**. Also, alkyl, aryl, and ester substituents on the pyrrole portion were also tolerated in this transformation to afford the desired fused tetraheterocycles. Notably, protection of the indole nitrogen was unnecessary. Despite the propensity of indolium species to form 2,2'-dimers,[18] no intermolecular acid-catalyzed homodimerizations of C3-substituted indoles **1** were formed in our cases. Most importantly, the reaction worked well to furnish product **2l** when branched tryptamine-derived indole-pyrrole **1l** was employed. It is worth noting that the desymmetrization of bisindole moieties[19] occurs to give an intriguing hexacyclic architecture. The substrate bearing a methyl group at the C2-position of the indole ring afforded polycyclic indoline **2m** with a newly formed azaquaternary center in 78% yield. Dehomologation of the chain of substrate **1a** resulted in a decreased yield of the five-membered ring product **2n**. Also, the intramolecular dearomative cross-coupling reaction proceeded successfully to deliver the seven-membered ring product **2o** when the C3-carbon chain was extended. Unfortunately, when the indole-pyrrole **1p** was subjected to cyclization only trace amounts of the embedded nine-membered fused ring system **2p** was observed. In addition, compound **2aD** was recovered in almost quantitative yield (99%) when CF_3COOD was used. It is important to note that the current reaction proceeded in a highly diastereoselective manner, and only one diastereoisomer was obtained for the examples.[20]

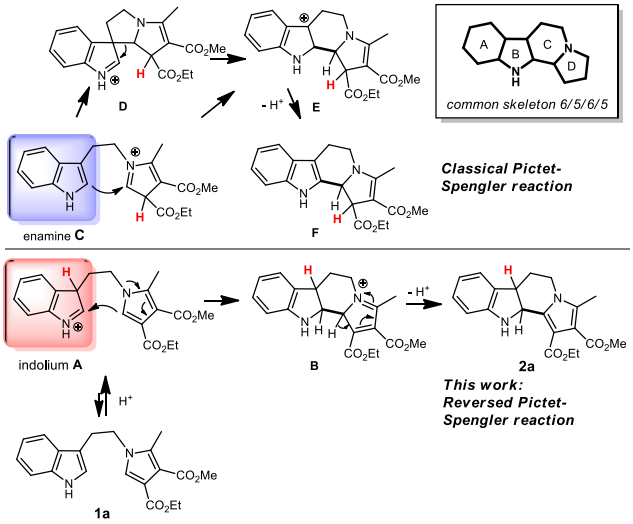


Scheme 1. Scope of the Reaction.[a] [a]Standard reaction conditions: **1** (0.2 mmol), TFA (1 mL), rt, overnight, unless otherwise noted. [b]Only the oxidized cross-coupling

product **2j'** was isolated (40%), see ref. [16]. [c]**1** (0.2 mmol), TFA (4 equiv), DCM (1 mL), 55 °C. [d]dr: 9:1 (see the Supporting Information for details). [e]90 °C. [f]60 °C, 10 h. [g]CF_3COOD was used.

Importantly, the use of free (NH) indoles as substrates in this protocol could provide the opportunity for various further chemical manipulations such as N-glycosylation[21] and N-arylation,[22] which are important in pharmaceutical (i.e., antitumor antibiotics) and material systems (i.e., sensitizers for dye-sensitized solar cells).

Based on these findings, a plausible mechanism was proposed using indole-pyrrole **1a** as an example (Scheme 2).

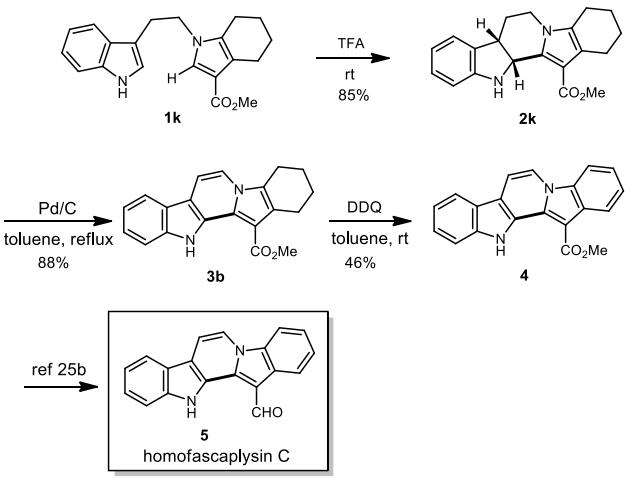


Scheme 2. Proposed mechanism: enamine versus iminium type reactivity of indole in Pictet-Spengler reactions.

In the presence of TFA, substrate **1a** proceeds via the initial formation of indolium ion **A**, which upon attack of the pyrrole nucleophile generates intermediate **B**. Finally, a proton elimination on **B** driven by aromatization furnishes the product **2a**. Evidence for indolium formation was given by the formation of **2aD**, which is deuterated exclusively at the C3 position of the indole ring. Thus, an alternative pathway involving C-3 protonation of the pyrrole moiety of **1a** (intermediate **C**) and subsequent intramolecular attack by the indole C-2 to give dearomatized intermediate **F** via intermediate **E** is excluded.[23]

It should be pointed out that this acid-promoted intramolecular Friedel–Crafts cyclization can be recognized as a Pictet–Spengler-type reaction in which dearomatization of the indole ring occurs. Distinct from classical Pictet–Spengler[24] reaction derived from tryptamine derivatives, the rare and straightforward addition of heteroarenes (pyrroles) to an indolium ion such as **A** was developed. This means that between two different heteroaryl units such as pyrrole and indole, the iminium intermediate is selectively formed by protonation of the indole instead of the pyrrole nucleus (**A** vs **C**), in contrast to what has been hypothesized by Yan and coworkers.[23] Thus, the construction of the six-membered ring (C-ring) of **II** from indole-pyrrole biheterocyclic system (A,B,D-ring) was realized by a reversed (non classical) Pictet-Spengler reaction. Since the vast majority of natural products featuring the indolizino[8,7-*b*]indole (A/B/C/D) moiety presents an aromatized cycle B (**F**), the possibility of chemoselectively synthetize their rarely represented D aromatized congeners (**2**) is very attractive. Besides, the scope of the reaction was not limited to tryptamine-based biheterocycles, so that the construction of hitherto unknown structures (five- and seven-membered C ring) was feasible. Also, substitution at C2 of the indole ring was tolerated in the process.

Given our success with the cyclization of substrates **2**, we decided to apply the present approach to the synthesis of natural product homofascaplysin C.[13,25] Accordingly, the intramolecular dearomative coupling of **1k** in TFA gave the corresponding product **2k** in 85% yield. Our next endeavor was to obtain pyrido[1,2-*a*:3,4-*b*]-diindole core **4** from substrate **2k**, thereby providing a concise synthesis of this characteristic fused pentacyclic framework. Upon treatment with Pd/C in refluxing toluene, a partial oxidation of **2k** was achieved,[26] affording compound **3b** in 88% yield. A further oxidation with DDQ in toluene at room temperature resulted in the formation of the fully aromatized diindole **4** (46% yield), which is the direct precursor of the target molecule **5** (Scheme 3)[25b].



Scheme 3. Approach to the synthesis of homofascaplysin C.

In conclusion, we have developed an efficient TFA-promoted dearomative cyclization of indole-tethered pyrroles that gives rapid access to a variety of challenging indoline-fused polycycles including pyrido[1,2-*a*:3,4-*b*]-diindole core of homofascaplysin C alkaloid. The reaction described here, which is

realized via indolium chemistry, represents a significant advance in the field of C-C dearomative cross-coupling reactions.

Experimental Section

General methods. Chromatographic purification of compounds was carried out on silica gel (60–200 μm). TLC analysis was performed on pre-loaded (0.25 mm) glass supported silica gel plates (Kieselgel 60); compounds were visualized by exposure to UV light and by dipping the plates in 1% $Ce(SO_4)\cdot 4H_2O$, 2.5% $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ in 10% sulphuric acid followed by heating on a hot plate. All ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using [D_6]DMSO or CD_3Cl_3 on K_2CO_3 as solvent. Chemical shift (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent and are sorted in ascending order within each group. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, td = triplet of doublet, q = quartet, quint = quintet, sex = sextet, sept = septet, m = multiplet and br = broad signal. All coupling constants (*J* value) are given in Hertz [Hz]. FT-IR spectra were obtained as Nujol mulls or neat. ESI-MS spectra were taken on a Waters Micromass ZQ instrument. Melting points were determined in open capillary tubes and are uncorrected. Elemental analyses were within ± 0.4 of the theoretical values (C, H, N).

General procedure for the TFA-promoted Intramolecular Cross Coupling Reaction (2). Bi-heterocycle compound (**1**) (0.2 mmol) was dissolved in TFA (1 mL), afterwards the solution was stirred at room temperature for the indicate time (TLC check). The crude mixture was then purified by column chromatography on silica gel to afford product (**2**).

1-Ethyl 2-methyl 3-methyl-6,6a,11,11a-tetrahydro-5*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (2a). Indoline-Pyrrole **2a** was isolated by column chromatography (ethyl acetate/cyclohexane 25:75) in 84% yield (59.5 mg); White solid; mp: 114–116 °C; ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.34 (t, *J* = 7.0 Hz, 3H), 2.08−2.26 (m, 2H), 2.32 (s, 3H), 3.49−3.55 (m, 1H), 3.66−3.72 (m, 1H), 3.82 (s, 3H), 3.83−3.89 (m, 1H), 4.24−4.35 (m, 2H), 5.03 (d, *J* = 8.4 Hz, 1H), 6.65 (d, *J* = 7.6 Hz, 1H), 6.75 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 7.07 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 10.4, 14.3, 25.5, 38.4, 40.7, 51.4, 55.0, 60.2, 109.9, 112.2, 113.2, 118.7, 123.6, 128.2, 130.0, 132.2, 135.1, 150.1 165.1, 166.2; IR (nujol): υ_{max} = 3390, 1719, 1676 cm^{-1}; MS (EI) m/z (%) = 355 $[M + H]^+$; anal. calcd. for $C_{20}H_{22}N_2O_4$ (354.40): C 67.78, H 6.26, N 7.90; found: C 67.84, H 6.19, N 8.01.

2-Isopropyl 1-methyl 3-methyl-6,6a,11,11a-tetrahydro-5*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (2b). Indoline-Pyrrole **2b** was isolated by column chromatography (ethyl acetate/cyclohexane 15:85) in 79% yield (58.2 mg); White solid; mp: 98–100 °C; ^1H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.23 (t, *J* = 6.4 Hz, 6H), 2.05 (q, *J* = 6.4 Hz, 2H), 2.25 (s, 3H), 3.52 (q, *J* = 6.4 Hz, 1H), 3.73 (s, 3H), 3.73−3.77 (m, 2H), 4.94 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 5.03 (sept, *J* = 6.4 Hz, 1H), 5.62 (d, *J* = 1.6 Hz, 1H), 6.60−6.64 (m, 2H), 6.96 (t, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 10.3, 22.0, 22.1, 25.7, 38.0, 40.6, 51.5, 54.6, 67.2, 109.5, 111.2, 113.4, 118.0, 124.1, 128.1, 130.4, 132.1, 135.3, 151.0, 164.9, 165.1; IR (nujol): υ_{max} = 3373, 1701, 1683 cm^{-1}; MS (ESI) *m/z* = 391 $[M + Na]^+$, 369 $[M + H]^+$; anal. calcd. for $C_{21}H_{24}N_2O_4$ (368.43): C 68.46, H 6.57, N 7.60; found: C 68.33, H 6.49, N 7.52.

2-Allyl 1-methyl 3-methyl-6,6a,11,11a-tetrahydro-5*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (2c). Fused Indoline **2c** was isolated by column chromatography (ethyl acetate/cyclohexane 2:98) in 41% yield (30.1 mg); White solid; mp: 117–119 °C; ^1H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 2.05 (q, *J* = 6.0 Hz, 2H), 2.27 (s, 3H), 3.52 (q, *J* = 7.0 Hz, 1H), 3.71 (s, 3H), 3.75−3.81 (m, 2H), 4.64−4.67 (m, 2H), 4.95 (dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz, 1H), 5.22−5.25 (m, 1H), 5.31−5.37 (m, 1H), 4.64 (d, *J* = 1.6 Hz, 1H), 5.92−6.02 (m, 1H), 6.60−6.64 (m, 2H), 6.96 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 10.4, 25.7, 38.0, 40.2, 40.6, 51.6, 54.5, 64.9, 109.5, 111.5, 112.6, 118.1, 118.2, 124.1, 128.1, 130.5, 132.8, 133.3, 135.4, 151.0, 165.0; IR (nujol): υ_{max} = 3359, 1716, 1690 cm^{-1} MS (ESI) *m/z* = 389 $[M + Na]^+$, 367 $[M + H]^+$; anal. calcd. for $C_{21}H_{22}N_2O_4$ (366.41): C 68.84, H 6.05, N 7.65; found: C 68.96, H 6.13, N 7.68.

Dimethyl 3-propyl-6,6a,11,11a-tetrahydro-5*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (2d). Fused Indoline **2d** was isolated by column chromatography (ethyl acetate/cyclohexane 15:85) in 73% yield (53.8 mg); White solid; mp: 114–116 °C; ^1H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 0.85 (t, *J* = 7.4 Hz, 3H), 1.44 (sex, *J* = 7.4 Hz, 2H), 1.97−2.09 (m, 2H), 2.62−2.70 (m, 2H), 3.57−3.62 (m, 1H), 3.71 (s, 3H), 3.74 (s, 3H), 3.78−3.86 (m, 2H), 5.08 (d, *J* = 8.8 Hz, 1H), 6.53 (br, 1H), 6.73−6.76 (m, 2H), 7.03 (t, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 13.9, 22.7, 26.0, 26.4, 38.1, 40.7, 51.7, 51.8, 54.5, 110.8, 111.8, 113.3, 124.3, 128.3, 131.6, 134.2, 136.3, 158.5, 158.8, 164.8, 165.9; IR (nujol): υ_{max} =3383, 1729, 1703 cm^{-1}; MS (ESI) *m/z* = 391 $[M + Na]^+$, 369 $[M + H]^+$; anal. calcd. for $C_{21}H_{24}N_2O_4$ (368.43): C 68.46, H 6.57, N 7.60; found: C 68.33, H 6.52, N 7.69.

Ethyl 3-methyl-2-phenyl-6,6a,11,11a-tetrahydro-5*H*-indolizino[8,7-*b*]indole-1-carboxylate (2e). Fused Indoline **2e** was isolated by column chromatography (ethyl acetate/cyclohexane 15:85) in 100% yield (74.4 mg); White solid; mp: 115–117 °C; ^1H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 0.98 (t, *J* = 7.2 Hz, 3H), 2.03 (s, 3H), 2.08−2.15 (m, 2H), 3.59 (q, *J* = 7.0 Hz, 1H), 3.82 (t, *J* = 5.6 Hz, 2H), 3.97−4.06 (m, 2H), 5.18 (d, *J* = 8.0 Hz, 1H), 6.32 (br, 1H), 6.74−6.79 (m, 2H), 7.04 (t, *J* = 7.4 Hz, 1H), 7.16−7.18 (m, 2H), 7.24−7.27 (m, 2H), 7.31−7.35 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.9, 13.7, 25.9, 38.5, 40.9, 55.8, 59.6, 111.7, 111.8, 118.0, 119.5, 122.1, 122.2, 123.3, 124.0, 126.1, 127.3, 128.5, 130.5, 130.6, 135.8, 166.0; IR (nujol): υ_{max} = 3395, 1671 cm^{-1}; MS (ESI) *m/z* = 395 $[M + Na]^+$, 373 $[M + H]^+$; anal. calcd. for $C_{24}H_{24}N_2O_2$ (372.46): C 77.39, H 6.49, N 7.52; found: C 77.51, H 6.41, N 7.39.

1-Ethyl 2-methyl 3,11-dimethyl-6,6a,11,11a-tetrahydro-5*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (2f). Fused Indoline **2f** was isolated by column chromatography (ethyl acetate/cyclohexane 10:90) in 91% yield (67.1 mg); White solid; mp: 114–116 °C; ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.34 (t, *J* = 7.2 Hz, 3H), 1.95−2.10 (m, 2H), 2.39 (s, 3H), 2.67 (s, 3H), 3.60−3.70 (m, 2H), 3.83 (s, 3H), 3.85−3.92 (m, 1H), 4.26−4.36 (m, 2H), 5.04 (d, *J* = 9.3 Hz, 1H), 6.44 (d, *J* = 7.4 Hz, 1H), 6.74 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 7.10−7.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 10.4, 14.3, 31.5, 33.0, 38.2, 39.9, 51.3, 59.7, 60.3, 107.1, 111.9, 114.4, 118.2, 124.2, 128.4, 130.7, 131.5, 133.9, 152.8, 165.0, 166.0; IR (nujol): υ_{max} = 1705, 1697 cm^{-1}; MS (ESI) *m/z* = 391 $[M + Na]^+$, 369 $[M + H]^+$; anal. calcd. for $C_{21}H_{24}N_2O_4$ (368.43): C 68.46, H 6.57, N 7.60; found: C 68.59, H 6.48, N 7.53.

2-Ethyl 1-methyl 11-benzyl-3-methyl-6,6a,11,11a-tetrahydro-5*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (2g). Fused Indoline **2g** was isolated by column chromatography (ethyl acetate/cyclohexane 15:85) in 94% yield (83.6 mg); Whitish oil; ^1H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 1.21 (t, *J* = 7.0 Hz, 3H), 1.93−2.05 (m, 2H), 2.34 (s, 3H), 3.41−3.48 (m, 1H), 3.50 (s, 3H), 3.82–3.85 (m, 1H), 4.03 (d, *J* = 16.8 Hz, 1H), 4.06−4.11 (m, 1H), 4.14 (q, *J* = 7.0 Hz, 2H), 4.45 (d, *J* = 16.8 Hz, 1H), 5.33 (d *J* = 9.6 Hz, 1H), 6.18 (d, *J* = 8.0 Hz, 1H), 6.62 (dt,

J_1 = 7.4 Hz, J_2 = 0.8 Hz, 1H), 6.93 (dt, J_1 = 7.4 Hz, J_2 = 0.8 Hz, 1H), 7.02 (d, J = 6.8 Hz, 2H), 7.16 (t, J = 6.8 Hz, 2H), 7.23 (t, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 10.4, 14.5, 31.9, 38.0, 40.6, 48.4, 51.5, 57.7, 59.9, 106.5, 111.6, 114.4, 118.0, 124.9, 126.9, 127.0, 128.4, 128.7, 130.4, 131.4, 134.6, 139.1, 151.7, 164.8, 165.2; IR (nujol): υ_{max} = 1729, 1693 cm^{-1}; MS (ESI) *m/z* = 467 [M + Na]$^+$, 445 [M + H]$^+$; anal. calcd. for $C_{27}H_{28}N_2O_4$ (444.52): C 72.95, H 6.35, N 6.30; found: C 73.04, H 6.24, N 6.21.

2-Ethyl 1-methyl 9-chloro-3-methyl-6,6a,11,11a-tetrahydro-5*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (2h). Fused Indoline **2h** was isolated by column chromatography (ethyl acetate/cyclohexane 15:85) in 100% yield (77.7 mg); White solid; mp: 105−107 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.33 (t, J = 7.2 Hz, 3H), 2.06−2.22 (m, 2H), 2.32 (s, 3H), 3.46−3.51 (m, 1H), 3.65−3.72 (m, 1H), 3.81−3.88 (m, 1H), 3.82 (s, 3H), 4.24−4.35 (m, 2H), 5.03 (d, J = 8.4 Hz, 1H), 6.59 (d, J = 1.6 Hz, 1H), 6.68 (dd, J_1 = 7.8 Hz, J_2 = 1.6 Hz, 1H), 7.01 (dd, J_1 = 7.8 Hz, J_2 = 0.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 10.4, 14.3, 25.5, 37.8, 40.5, 51.4, 55.3, 60.3, 109.7, 111.8, 113.5, 118.2, 124.2, 128.3, 132.2, 133.8, 134.8, 151.5, 165.6, 165.7; IR (nujol): υ_{max} = 3359, 1716, 1690 cm^{-1}; MS (ESI) *m/z* = 411 [M + Na]$^+$, 389 [M + H]$^+$; anal. calcd. for $C_{20}H_{21}ClN_2O_4$ (388.84): C 61.78, H 5.44, N 7.20; found: C 61.89, H 5.36, N 7.25.

2-Ethyl 1-methyl 8-fluoro-3-methyl-6,6a,11,11a-tetrahydro-5*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (2i). Fused Indoline **2i** was isolated by column chromatography (ethyl acetate/cyclohexane 15:85) in 90% yield (67.0 mg); White solid; mp: 130–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.33 (t, J = 7.2 Hz, 3H), 2.06−2.24 (m, 2H), 2.32 (s, 3H), 3.47−3.52 (m, 1H), 3.65−3.72 (m, 1H), 3.81 (s, 3H), 3.84−3.89 (m, 1H), 4.21−4.36 (m, 2H), 4.64 (br, 1H), 5.04 (d, J = 8.4 Hz, 1H), 6.57 (dd, J_1 = 8.8 Hz, J_2 = 4.4 Hz, 1H), 6.76 (dt, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 6.86 (dd, J_1 = 8.2 Hz, J_2 = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 10.3, 14.2, 25.3, 38.6, 40.6, 51.4, 55.5, 60.2, 110.2 ($^3J_{CF}$ = 7.8 Hz), 110.1 ($^2J_{CF}$ = 23.7 Hz), 112.2, 113.3, 114.3 ($^2J_{CF}$ = 23.1 Hz), 131.6 ($^3J_{CF}$ = 7.4 Hz), 132.2, 134.7, 146.0, 156.9 ($^1J_{CF}$ = 234 Hz), 165.1, 166.2; IR (nujol): υ_{max} = 3378, 1721, 1685 cm^{-1}; MS (ESI) *m/z* = 373 [M + H]$^+$; anal. calcd. for $C_{20}H_{21}FN_2O_4$ (372.39): C 64.51, H 5.68, N 7.52; found: C 64.38, H 5.61, N 7.45.

Diethyl 8-methoxy-3-methyl-6,11-dihydro-5*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (2j'). Fused Indole **2j'** was isolated by column chromatography (ethyl acetate/cyclohexane 20:80) in 40% yield (31.7 mg); White solid, mp: 135−137 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.26 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 2.38 (s, 3H), 3.10 (t, J = 7.2 Hz, 2H), 3.78 (s, 3H), 4.11 (t, J = 7.2 Hz, 2H), 4.21 (q, J = 7.2 Hz, 2H), 4.27 (q, J = 7.2 Hz, 2H), 6.77 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 7.04 (d, J_1 = 2.4 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 10.5 (s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 10.9, 14.4, 14.6, 20.1, 42.2, 55.7, 60.3, 60.7, 100.1, 107.9, 108.7, 113.3, 113.4, 113.7, 126.1, 126.4, 128.3, 131.8, 134.8, 154.2, 165.3, 165.7; IR (nujol): υ_{max} = 3348, 1708, 1678 cm^{-1}; MS (ESI) *m/z* = 419 [M + Na]$^+$, 397 [M + H]$^+$;anal. calcd. for $C_{22}H_{24}N_2O_4$ (396.44): C 66.65, H 6.10, N 7.07; found: C 66.77, H 6.17, N 6.99.

Methyl 2,3,4,6,7,7a,12,12a-octahydro-1*H*-pyrido[1,2-a:3,4-*b'*]diindole-13-carboxylate (2k). Fused Indoline **2k** was isolated by column chromatography on neutral alumina (ethyl acetate/cyclohexane 30:70) in 85% yield (54.9 mg); White solid; mp: 113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.70−1.82 (m, 4H), 2.06−2.20 (m, 2H), 2.40−2.51 (m, 2H), 2.63−2.76 (m, 2H), 3.45−3.51 (m, 1H), 3.61−3.68 (m, 1H), 3.82−3.87 (m, 1H), 3.83 (s, 3H), 5.16 (d, J = 8.0 Hz, 1H), 5.34 (br, 1H), 6.65 (d, J = 7.4 Hz, 1H), 6.74 (dt, J_1 = 7.4 Hz, J_2 = 1.0 Hz, 1H), 7.07 (dt, J_1 = 7.4 Hz, J_2 = 1.0 Hz, 1H), 7.15 (d, J = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 21.3, 22.7, 23.2, 23.4, 25.8, 38.8, 40.2, 50.6, 55.2, 109.7, 109.8, 118.4, 119.1, 123.6, 127.4, 128.0, 130.8, 134.6, 150.5, 166.7; IR (nujol): υ_{max} = 3378, 1688 cm^{-1}; MS (EI) *m/z* (%) = 323 [M + H]$^+$; anal. calcd. for $C_{20}H_{22}N_2O_2$ (322.40): C 74.51, H 6.88, N 8.69; found: C 74.60, H 6.99, N 8.57.

1-Ethyl 2-methyl 6-(1*H*-indol-3-yl)-3-methyl-6,6a,11,11a-tetrahydro-5*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (2l). Fused Indoline **2l** was isolated as an inseparable mixture of diastereomers in a 9:1 ratio by column chromatography (ethyl acetate/cyclohexane 25:75) in 78% yield (73.4 mg); White solid; The stereochemistry of the major diastereoisomer was tentatively assigned by comparison of its ^{1}H NMR spectral data with that of similar structures;[4] major diastereomer; White solid; mp 185−187 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.26 (t, J = 7.2 Hz, 3H), 2.23 (s, 3H), 3.49−3.55 (m, 1H), 3.72 (s, 3H), 3.90 (t, J = 8.4 Hz, 1 H), 4.04−4.06 (m, 2H), 4.17−4.28 (m, 2H), 5.10 (d, J = 8.0 Hz, 1H), 5.67 (br, 1H), 6.31−6.37 (m, 2H), 6.68 (d, J = 8.0 Hz, 1H), 6.88−6.97 (m, 2H), 7.06−7.12 (m, 2H), 7.38 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 10.99 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 10.4, 14.5, 33.9, 43.3, 46.8, 51.6, 55.3, 60.1, 109.5, 111.6, 112.1, 113.1, 113.3, 117.7, 118.9, 119.3, 121.5, 123.9, 125.3, 126.8, 128.0, 130.3, 132.3, 134.9, 136.7, 150.9, 164.6, 166.0; IR (nujol): υ_{max} = 3410, 3371, 1717, 1688 cm^{-1}; MS (EI) *m/z* (%) = 492 [M + Na]$^+$, 470 [M + H]$^+$; anal. calcd. for $C_{28}H_{27}N_3O_4$ (469.53): C 71.62, H 5.80, N 8.95; found: C 71.71, H 5.87, N 9.06.

1-Ethyl 2-methyl 3,11a-dimethyl-6,6a,11,11a-tetrahydro-5*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (2m). Fused Indoline **2m** was isolated by column chromatography (ethyl acetate/cyclohexane 2:8) in 78% yield (57.5 mg); Whitish oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ =1.24 (t, J = 7.2 Hz, 3H), 1.53 (s, 3H), 2.13−2.18 (m, 1H), 2.20 (s, 3H), 2.32−2.39 (m, 1H), 3.25 (t, J = 4.8 Hz, 1H), 3.57−3.63 (m, 1H), 3.67 (s, 3H), 3.84−3.90 (m, 1H), 4.19−4.25 (m, 2H), 6.05 (s, 1H), 6.57 (d, J = 7.6 Hz, 1H), 6.62 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 6.93 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 10.4, 14.4, 22.5, 26.8, 26.9, 46.6, 51.6, 60.7, 62.9, 109.3, 110.7, 113.2, 118.2, 123.7, 128.2, 128.6, 131.6, 139.1, 150.3, 165.7, 166.6; IR (nujol): υ_{max} = 3343, 1733, 1686 cm^{-1}; MS (EI) *m/z* (%) = 369 [M + H]$^+$; anal. calcd. for $C_{21}H_{24}N_2O_4$ (368.43): C 68.46, H 6.57, N 7.60; found: C 68.32, H 6.65, N 7.54.

3-Ethyl 2-methyl 1,4-dimethyl-3b,4,8b,9-tetrahydropyrrolizino[1,2-*b*]indole-2,3-dicarboxylate (2n). Fused Indoline **2n** was isolated by column chromatography (ethyl acetate/cyclohexane 15:85) in 21% yield (15.1 mg); White solid, mp: 199–201 °C (with decomposition); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.89 (t, J = 7.6 Hz, 3H), 2.43 (s, 3H), 3.00 (s, 3H), 3.78−3.83 (m, 1H), 3.95 (s, 3H), 3.98−4.00 (m, 1H), 4.29−4.34 (m, 1H), 4.50 (q, J = 7.6 Hz, 2H), 5.34 (d, J = 8.4 Hz, 1H), 6.50 (d, J = 7.6 Hz, 1H), 6.71 (t, J = 7.6 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.3, 29.6, 35.2, 48.7, 51.7, 52.6, 69.0, 77.1, 107.8, 110.9, 111.3, 117.8, 123.7, 128.0, 129.1, 134.6, 144.9, 152.9, 164.1, 169.6; IR (nujol): υ_{max} = 1719, 1626 cm^{-1}; MS (EI) *m/z* (%) = 377 [M + Na]$^+$, 355 [M + H]$^+$; anal. calcd. for $C_{20}H_{22}N_2O_4$ (354.40): C 67.78, H 6.26, N 7.90; found: C 67.89, H 6.18, N 7.94.

1-Ethyl 2-methyl 3-methyl-5,6,7,7a,12,12a-hexahydropyrrolo[1',2':1,2]azepino[3,4-*b*]indole-1,2-dicarboxylate (2o). Fused Indoline **2o** was isolated by column chromatography (ethyl acetate/cyclohexane 50:50) in 81% yield (59.7 mg); White solid; mp 142−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.99 (t, J = 7.2 Hz, 3H), 1.80 (t, J = 12.8 Hz, 1H), 2.05−2.31 (m, 3H), 2.46 (s, 3H), 3.57−3.67 (m, 2H), 3.68−3.75 (m, 1H), 3.73 (s, 3H), 3.86 (d, J = 10.0 Hz, 1H), 4.06 (dd, J_1 = 12.4 Hz, J_2 = 4.4 Hz, 1H), 4.19 (d, J = 10.0 Hz, 1H), 5.38 (br, 1H), 6.98−7.03 (m, 2H), 7.08 (d, J = 8.0 Hz, 1H), 7.20 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 10.7, 13.8, 20.0, 34.2, 43.2, 47.1, 51.0, 58.8, 60.5, 111.3, 114.3,

114.5, 123.9, 124.3, 128.6, 132.5, 133.8, 137.7, 143.7, 165.0, 166.3; IR (nujol): υ_{max} = 3343, 1705, 1677 cm^{-1}; MS (EI) *m/z* (%) = 391 $[M + Na]^+$, 369 $[M + H]^+$; anal. calcd. for $C_{21}H_{24}N_2O_4$ (368.43): C 68.46, H 6.57, N 7.60; found: C 68.59, H 6.59, N 7.49.

1-Ethyl 2-methyl 6a-deutero-3-methyl-6,6a,11,11a-tetrahydro-5*H*-indolizino[8,7-*b*]indole-1,2-dicarboxylate (2aD). Indoline-Pyrrole **2aD** was isolated by column chromatography on neutral alumina (ethyl acetate/cyclohexane 20:80) in 99% yield (70.4 mg); Whitish oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.25 (t, *J* = 7.2 Hz, 3H), 1.98−2.04 (m, 1H), 2.07−2.14 (m, 1H), 2.23 (s, 3H), 3.55−3.63 (m, 1H), 3.73 (s, 3H), 3.74−3.80 (m, 1H), 4.13−4.28 (m, 2H), 4.91 (s, 1H), 5.19 (br, 1H), 6.55 (d, *J* = 7.6 Hz, 1H), 6.65 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 6.98 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 10.4, 14.3, 25.4, 38.0 (1 C, t, $^1J_{CD}$ = 20.4 Hz), 40.7, 51.4, 54.9, 60.2, 109.7, 112.1, 113.2, 118.5, 123.6, 128.2, 129.9, 132.2, 135.2, 150.3, 165.1, 166.3; IR (nujol): υ_{max} = 3390, 1714, 1706 cm^{-1}; MS (EI) *m/z* (%) = 356 $[M + H]^+$; anal. calcd. for $C_{20}H_{21}DN_2O_4$ (355.41): C 67.59, H 6.52, N 7.88; found: C 67.45, H 6.59, N 7.96.

Procedure for Oxidation of 2k to 3b. A mixture of compound **2k** (0.15 mmol), Pd/C (10%, 2 mg) and toluene (2 mL) was refluxed for 1.5 hours (TLC check). After removal of the solvent, the crude mixture was purified by column chromatography on neutral alumina to afford product **3b**.

Methyl 2,3,4,12-tetrahydro-1*H*-pyrido[1,2-*a*:3,4-*b'*]diindole-13-carboxylate (3b). Fused Indole **3b** was isolated by column chromatography (ethyl acetate/cyclohexane 10:90) in 88% yield (42.1 mg); White solid; mp: 172–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.86−2.02 (m, 4H), 2.75 (t, *J* = 6.0 Hz, 2H), 2.98 (t, *J* = 6.0 Hz, 2H), 3.96 (s, 3H), 7.25−7.29 (m, 1H), 7.39−7.43 (m, 2H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 11.62 (s, 1H); ^{13}C NMR (100 MHz, , $CDCl_3$, 25 °C): δ = 21.7, 22.5, 23.4, 24.1, 51.0, 100.5, 106.3, 111.7, 113.4, 114.8, 119.3, 119.6, 122.7, 123.4, 123.9, 124.6, 127.1, 129.4, 137.4, 167.9; IR (nujol): υ_{max} = 3302, 1670 cm^{-1}; MS (EI) *m/z* (%) = 224 $[M + H]^+$; anal. calcd. for $C_{20}H_{18}N_2O_2$ (318.31): C 75.45, H 5.70, N 8.80; found: C 75.37, H 5.61, N 8.94.

Procedure for Oxidation of 3b to 4. DDQ (0.33 mmol) was added portionwise to a solution of compound **3b** (0.15 mmol) in toluene (2 mL) and the mixture was stirred for 2 hours (TLC check). The crude mixture was purified by column chromatography on neutral alumina to afford product **4**.

Methyl 12*H*-pyrido[1,2-*a*:3,4-*b'*]diindole-13-carboxylate (4): Fused Indole **4** was isolated by column chromatography (ethyl acetate/cyclohexane 5:95) in 46% yield (21.7 mg), Yellow solid, mp: 163–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.10 (s, 3H), 7.31 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 7.38 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 7.46−7.52 (m, 3H), 7.65 (td, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 8.02 (td, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H), 8.21 (d, *J* = 7.2 Hz, 1H), 8.31 (d, *J* = 8.0 Hz, 1H), 12.08 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 51.3, 94.7, 106.1, 110.3, 112.2, 116.6, 116.9, 119.9, 120.2, 121.5, 122.0, 122.3, 124.8, 125.8, 127.6, 128.4, 131.7, 133.3, 138.0, 167.9; IR (nujol): υ_{max} = 3382, 1729 cm^{-1}; MS (EI) *m/z* (%) = 315 $[M + H]^+$; anal. calcd. for $C_{20}H_{14}N_2O_2$ (314.34): C 76.42, H 4.49, N 8.91; found: C 76.29, H 4.54, N 8.789.

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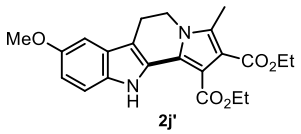

2j'

Analogous compound **2a'** was also obtained by oxidation of **2a** with Pd/C (see the Supporting Information for details).

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[26] Disappointingly, when the reaction was conducted in AcOEt as solvent (see ref. 13), the selective C2,C3 dehydrogenation was not observed.

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