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1,3-Dipolar Cycloaddition Chemistry for the Preparation of Novel Indolizinone-Based Compounds

Edwin M. Mmutlane, Joel M. Harris, and Albert Padwa*

Department of Chemistry, Emory University, Atlanta, Georgia 30322

chemap@emory.edu

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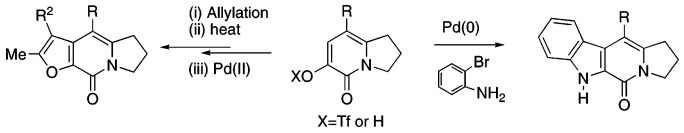

Starting from methyl 5-oxo-6-trifluoromethanesulfonyloxy-1,2,3,5-tetrahydroindolizine-8-carboxylate, obtained by a Rh(II)-catalyzed 1,3-dipolar cycloaddition reaction of 1-(2-benzenesulfonyl-2-diazoacetyl)pyrrolidin-2-one and methyl acrylate, several indolo- and furano-fused indolizinones were efficiently prepared. In the first case, a palladium-mediated C−N coupling of the triflate with a variety of substituted anilines provided the desired methyl 5-oxo-6-(arylamino)-1,2,3,5-tetrahydroindolizine-8-carboxylates in high yield. Methyl 6-(2-bromophenylamino)-5-oxo-1,2,3,5-tetrahydroindolizine-8-carboxylate as well as its decarboxylated analogue, 6-(2-bromophenylamino)-2,3-dihydro-1*H*-indolizin-5-one, were synthesized in excellent yield and were found to undergo an intramolecular Heck cyclization to give 1,2,3,6-tetrahydroindolizino[6,7-*b*]indol-5-ones. To prepare furano-fused indolizinones, methyl 6-hydroxy-5-oxo-1,2,3,5-tetrahydroindolizine-8-carboxylate was etherified with different allyl halides, and the resultant allyl ethers were subjected to a thermal Claisen rearrangement to give the corresponding methyl 7-allyl-6-hydroxy-5-oxo-1,2,3,4-tetrahydroindolizine-8-carboxylates. Cyclization under Wacker oxidation conditions afforded methyl 2-methyl-8-oxo-5,6,7,8-tetrahydro-1-oxa-7a-aza-*s*-indacene-4-carboxylates in near-quantitative yield.

Introduction

Indolizidine alkaloids are ubiquitous in nature and have been isolated from the entire spectrum of the animate world: monerans to higher plants and animals. The azabicyclic nucleus forms the main framework of what are commonly called "simple" indolizidine alkaloids. As can be gleaned from the select examples in Figure 1, these can be relatively simple structures such as ipalbidine **1** or polysubstituted and stereochemically challenging ones such as cyclizidine **4**.

Ipalbidine **1** was isolated from the crushed seeds of *Ipomoea alba*[1] as well as from purple moonflower, *Calonyction muricatum*.[2] The heteroatom-substituted slaframine **2**, bearing two additional stereogenic centers, is the neurotoxin derived from *Rhizoctonia leguminicola*,[3] a fungus that infects ruminant fodder, especially red clover, and causes profuse salivation, anorexia, diarrhea, and

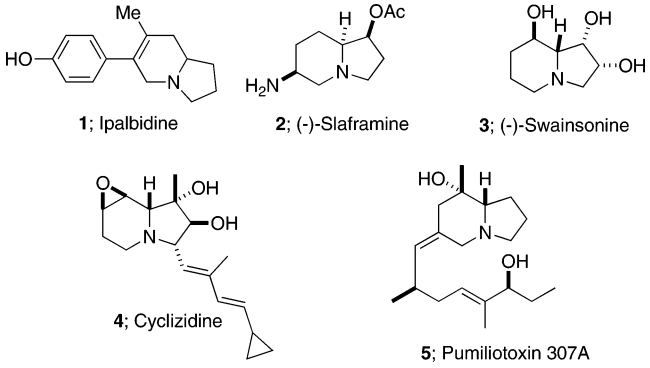

FIGURE 1. Some simple indolizidine alkaloids from natural sources.

even death among sheep, horses, and cattle.[4] The trihydroxylated swainsonine **3** was isolated from *Rhizoctonia leguminicola*[5] and has also been found in a variety of

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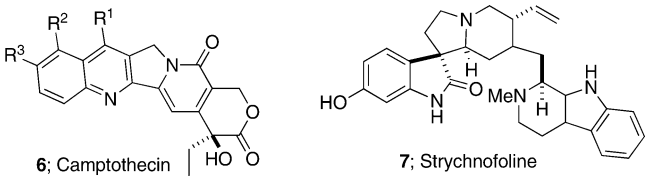

FIGURE 2. Some related indolizidine structures.

higher plants.[6] It is a potent toxin that inhibits mannosidase II, one of the enzymes required in N-linked glycoprotein processing, thereby inducing a condition similar to the genetic disease mannosidosis.[7] As a result, swainsonine is used clinically as an antimetastatic agent. Because of its ability to disrupt cellular recognition, it has been found to inhibit the association of *Trypanosoma cruzi*,[8] the causative agent of Chagas' disease. The unique, polyfunctionalized cyclizidine **4** was isolated from a soil bacterium, a *Streptomyces* species NCB 11649. This natural product shows nonselective immunostimulatory properties, and its secondary monoacetate has the same effect as some β-blocking drugs,[9] causing a reduction in beat frequency of cultured heart cells.[10] Last in the selection is pumiliotoxin 307A (**5**), an example of an indolizidine alkaloid obtained from kingdom animalia, and it, together with several other neurotoxins, was isolated from South American poison-dart frogs (Dendrobatidae).[11]

The indolizidine core or various unsaturated versions thereof are also embedded in a vast number of alkaloids that are not classified as indolizidine-based. An example is the antineoplastic agent camptothecin **6** (Figure 2), a monoterpenoid indole alkaloid first isolated from the Chinese tree *Camptotheca acuminata*.[12] Because of its antitumor activity, camptothecin received a great deal of attention from synthetic chemists, but eventually this scrutiny declined due to the severe side effects observed during clinical trials, associated with its low solubility in water.[13] It was only after Hsiang and co-workers elucidated the mechanism of action of camptothecin[14] that synthetic activity was reinvigorated.[15] Nowadays, several water-soluble derivatives of camptothecin, equally potent but with minimal side effects, are prescription drugs.[16] The alkaloid strychnofoline **7**, on the other hand, represents a fascinating combination of a spiroindolizidine−oxoindole core with a β-carboline (9*H*-pyrido[3,4-*b*]indole) pendant. The β-carboline is another ring combination that forms the core of numerous natural products, many of them biologically active. Isolated from the leaves of *Strychnos usambarensis*,[17] strychnofoline displays antimitotic activity against cultures of mouse melanoma and Ehrlich tumor cells.[18] The first total synthesis of this challenging molecule, as a racemate, has recently been reported.[19]

The potent biological activity of indolizidine and indolizidine-containing alkaloids, coupled with their challenging molecular architecture, continues to make them tantalizing and formidable targets for synthesis. Over the years, a vast array of methods, both general and target-specific, have been developed which are now conventional tools for the synthesis of indolizidine alkaloids. These synthetic approaches, together with the isolation, biosynthesis, and pharmacological activities of indolizidine alkaloids, are outlined in a series of comprehensive annual reviews.[20]

Our research group has previously demonstrated that the indolizidine ring system can be efficiently assembled in a few steps using the Rh(II)-catalyzed [3 + 2] dipolar cycloaddition of 1-(2-benzenesulfonyl-2-diazoacetyl)pyrrolidin-2-one (**8**) and an appropriately substituted dipolarophile **9** (Scheme 1).[21] The resultant pyridone **10** represents a very versatile synthon. As depicted in Scheme 2, hydrogenation of the pyridinone ring and subsequent functional group interconversions could provide access to a variety of "simple" indolizidine alkaloids and others containing the indolizidine core. The C-8 substituent (R = CO_2Me) allows for substitution/decarboxylation to give a hydrogen substituent or further oxidation under Baeyer−Villiger conditions (R = COMe). On the other hand, the C-6 hydroxyl substituent, protected as a triflate, allows for an assortment of cross-coupling possibilities: either Kumada,[22] Negishi,[23] Stille,[24]

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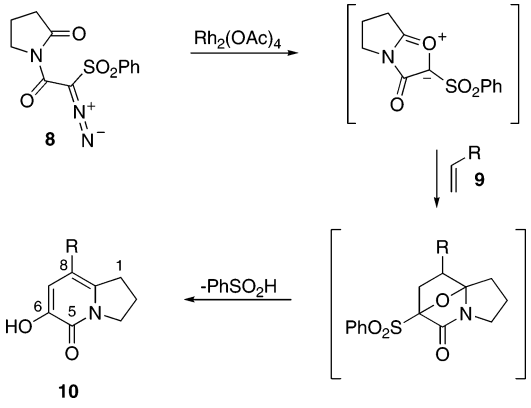
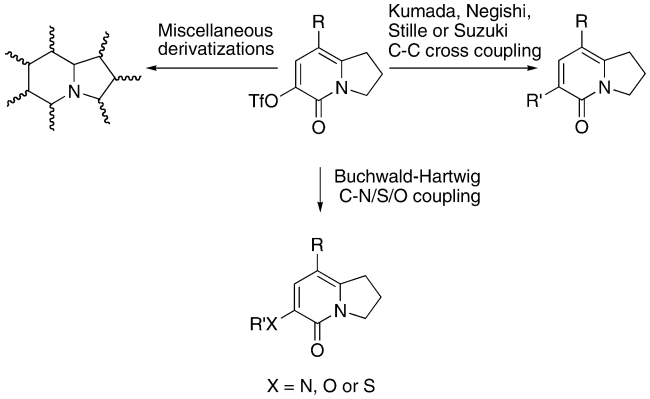
SCHEME 1. Rhodium(II)-Catalyzed [3 + 2]-Cycloaddition

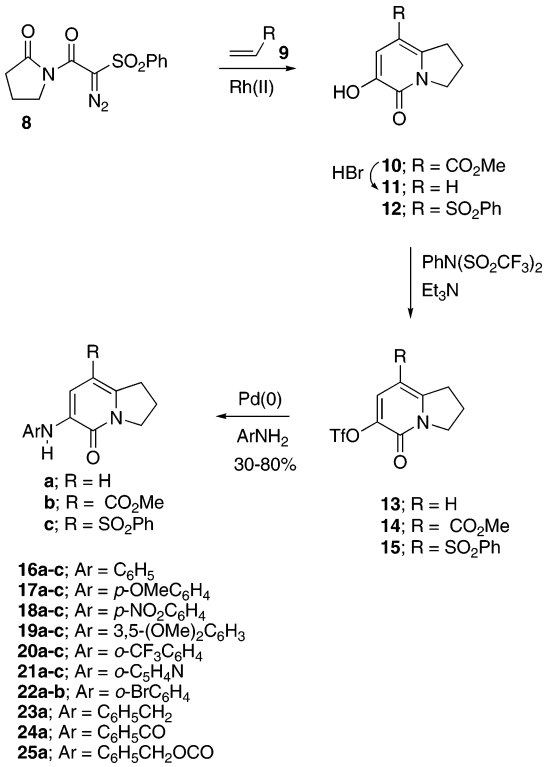


SCHEME 2. Use of Pyridone Triflate for Cross-Coupling Chemistry



or Suzuki−Miyaura[25] C−C couplings as well as Buchwald−Hartwig C−N/S/O coupling.[26] We have demonstrated some of these possibilities in the past through the syntheses of (±)-ipalbidine,[21] the angiotensin converting enzyme inhibitor (−)-A58365A,[27] (±) septicine,[28] and a variety of other novel indolizidine-based compounds. The use of **10** as a key intermediate in total synthesis has also been demonstrated recently by Greene and coworkers in a synthesis of the antiviral agent mappicine ketone, one of the alkaloids isolated together with camptothecin from the Indian plant *Nothapodytes foetida*.[29] We had previously reported our preliminary studies dealing with the conversion of **10**, via a triflate, to β-carbolinones.[30] The current paper aims at providing the full details of this endeavor and also reports on additional

SCHEME 3. Palladium(0)-Catalyzed Cross-Coupling



derivatives that we have since prepared owing to the versatility of compound **10**.

Results and Discussion

As depicted in Scheme 3, the Rh(II)-catalyzed 1,3-dipolar cycloaddition reaction of **8** with two different dipolarophiles **9** gave the requisite pyridones **10** and **12** (Scheme 3). Treatment of **10** (R = CO_2Me) with hot hydrobromic acid afforded the decarboxylated product **11**, which was then converted to the trifluoromethanesulfonate **13** by reaction with *N*-phenyltrifluoromethanesulfonimide.[31] Using this triflate, we explored C−N cross-coupling reactions which could allow access to novel heterocycles. In the first instance, we carried out the reaction with aniline and employed 0.1 molar equiv of 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (xantphos) as the ligand, 0.05 molar equiv of palladium(II) acetate, and 1.5 molar equiv of cesium carbonate as the base in toluene, under reflux for 6 h. Under these conditions, 6-phenylamino-2,3-dihydro-1*H*-indolizin-5-one (**16a**) (R = H) was obtained in 62% isolated yield. Using $Pd_2(dba)_3$ as the palladium source afforded a marginally improved 65% yield of product but at a much shorter reaction time of 1.5 h. The use of a microwave reactor further abridged the reaction time to a mere 20 min at 25 W. To further improve the yield, we tried a variety of different ligands [2,2′-bis(diphenylphosphino)-1,1′-binaphthalene [(±)-BINAP], (t-Bu)$_3$P, 1,1′-bis(diphenylphosphino)ferrocene (DPPF), 2-(dicyclohexylphosphino)biphenyl], but in all cases, the reaction resulted in much lower yields if it proceeded at all. Using a microwave reactor,

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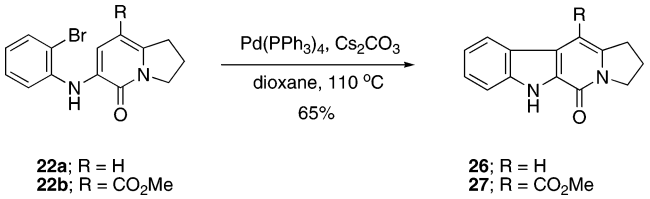
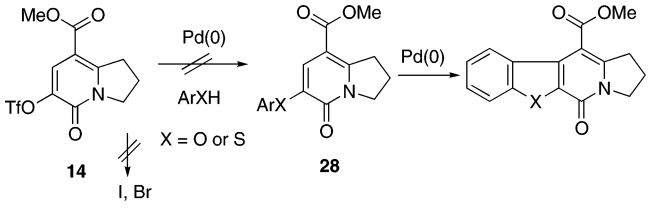
SCHEME 4. Intramolecular Heck Reaction



SCHEME 5. An Attempt To Cyclize Using Oxygen and Sulfur Nucleophiles

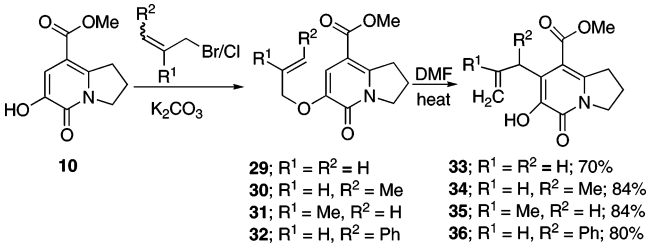


we employed a variety of substituted anilines, both electron-poor and electron-rich, and found that all of these aromatic amines underwent smooth coupling to give the requisite products **16**−**25** (R = H) in high yield.

Methyl 5-oxo-6-trifluoromethanesulfonyloxy-1,2,3,5-tetrahydroindolizine-8-carboxylate **14** as well as 8-benzenesulfonyl-5-oxo-1,2,3,5-tetrahydroindolizin-6-yl trifluoromethanesulfonate **15** were also found to readily undergo amination to afford the expected amination products (R = CO_2Me and R = SO_2Ph), although yields were varied in the case of **15**. We envisaged compounds **22a** (R = H) and **22b** (R = CO_2Me) as immediate precursors to the β-carbolinone unit found in many natural products (vide supra) and for that reason subjected them to an intramolecular Heck reaction[32] by treatment with a catalytic amount of [$Pd(PPh_3)_4$] and a slight excess of cesium carbonate in dioxane at 110 °C. This resulted in the formation of the desired β-carbolinones **26** and **27** in 65% yield, respectively (Scheme 4).

Emboldened by these positive results, we proceeded to investigate C−S and C−O coupling as outlined in Scheme 5, with the ultimate aim of producing furan and thiophene analogues of **27**. Diaryl thioethers have been previously prepared by the base-induced reaction of benzene thiols with appropriately substituted aryl triflates via an S_NAr mechanism.[33] We attempted to carry out a related coupling reaction with substrate **14** using Buchwald-Hartwig methodology. Unfortunately, all of our efforts to effect a C−O and C−S couplings and obtain compounds of general structure **28** have thus far been unsuccessful (Scheme 5). The reaction of **14** with several phenols and thiophenols employing various ligand/Pd and base combinations (biphenyl-2-yl-di-*tert*-butylphosphane,[34] DPPF,[35] (±)-BINAP,[36] and (*R*)-(*S*)-JOSIPHOS) led only to

SCHEME 6. Williamson Etherification/Claisen Rearrangement Sequence



the recovery of hydroxypyridone **10** and in some cases the starting material triflate **14**. With the oxygen substituent proving rather impervious to substitution, we attempted to use **10** as the oxygen donor and couple it with a variety of bromo- and iodoarenes. However, all of our attempts were unsuccessful and only resulted in the quantitative recovery of starting material. Still another attempt to circumvent the inertness of the substrate involved conversion of the triflate group of **14** to a bromide or iodide, which we thought could better permit oxidative insertion and subsequent coupling. In the simplest case, aryl triflates activated toward substitution with electron-withdrawing groups at the ortho and/or para position can be converted to the corresponding halide by reaction with tetrabutylammonium bromide[37] or sodium iodide[38] at elevated temperatures. However, all of our efforts to carry out a related reaction using substrate **14** and allowing it to react with sodium iodide were unsuccessful. Thus, we employed an indirect route which entailed conversion to the trimethylstannane under palladium catalysis, followed by displacement with elemental bromine.[39] Unfortunately, this attempt also failed to produce any of the desired bromide, and we decided instead to investigate several other transformations to which **14** could be subjected.

At this stage of our studies, we recognized that hydroxypyridone **10** allows for a classical Williamson etherification with allyl halides and the resulting ethers can then undergo a subsequent Claisen rearrangement. While Claisen rearrangements in the phenyl and naphthyl versions are commonly utilized in synthesis,[40] the pyridine and quinoline versions have rarely been reported.[29,41] Considering the paucity of such examples, we proceeded with the synthesis of the allyl ethers and subjected them to the Claisen rearrangement (Scheme 6). Reaction of **10** with allyl bromide in the presence of potassium carbonate in acetone under reflux for 18 h gave the requisite ether **29** in near-quantitative yield. Several related ethers were prepared analogously using the appropriate allylic chloride (crotyl, methallyl, and cinnamyl chloride) under Finkelstein conditions with sodium iodide.[42] The subsequent Claisen rearrangement was carried out in boiling DMF and required careful monitoring. We found that the best yields were obtained by

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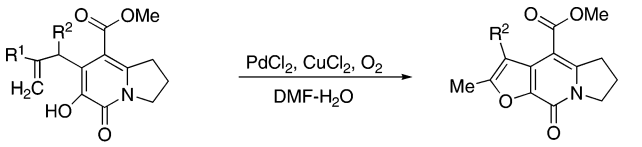
SCHEME 7. Wacker-Type Oxidation



33; $R^1 = R^2 = H$
34; $R^1 = H$, $R^2 = Me$
36; $R^1 = H$, $R^2 = Ph$

37; $R^2 = H$; 97%
38; $R^2 = Me$; 95%
39; $R^2 = Ph$; 80%

immersing the solution of the allyl ether in a minimal volume of DMF in an oil bath preheated to 160 °C. In this way, the requisite *C*-allyl products **33**−**36** were obtained in a matter of minutes in high yield.

The presence of the *C*-allyl substituent allows for functional group interconversions en route to different targets. For instance, rearrangement−internalization under transition metal[43] or *t*-BuOK catalysis,[44] followed by oxidative cleavage using ozone[45] or under Lemieux−Johnson conditions,[46] could provide a carbonyl substituent. Even more importantly, when in close proximity to a heteroatom, a *C*-allyl substituent offers an ideal opportunity for heterocycle ring construction under transition-metal catalysis.[47] In most cases, this has been achieved via an intramolecular Wacker oxidation[48] with the nucleophile being the proximal heteroatom in the substrate. Indeed, we found that when compounds **33**−**36** were treated with $PdCl_2$ and $CuCl_2$ as the co-oxidant in aqueous DMF under an oxygen atmosphere, the polysubstituted furans **37**−**39** were formed in near-quantitative yield (Scheme 7).

The reaction of alkenes with a catalytic amount of palladium is known to generate π-complexes, and the reaction of the latter with alcohols was reported as early as 1960.[49] In 1969, Lloyd and Luberoff investigated the acetalization of various alkenes with alcohols under Wacker oxidation conditions.[50] Intramolecular reactions were studied later on, and depending on the catalyst system used, cyclization can proceed by a 5-*exo-trig* process giving furans or via a 6-*endo-trig* cyclization to give chromenes. The intramolecular Wacker oxidation has since found wide application in heterocyclic chemistry, and a variety of structures including isochromenes, pyrans, and lactones have been prepared in this manner.[49] The synthesis of indoles has also been achieved in what has since become known as the Hegedus indole synthesis.[51] While the syntheses of indolizines annulated to thiophene, benzothiophene, benzene, and furan rings have been reported before,[52] our application of the intramolecular Wacker oxidation provides simple and rapid access to poly-substituted furans from a fully assembled indolizine core. Although a literature search revealed several instances in which a heteroarene-arene biaryl axis has been generated by means other than transition-metal-mediated biaryl coupling,[53] the formation of methyl 2-methyl-8-oxo-3-phenyl-5,6,7,8-tetrahydro-1-oxa-7a-aza-*s*-indacene-4-carboxylate **39** provides the only other example in which this has been accomplished from *o*-phenallylphenol.[54]

In conclusion, using the Buchwald−Hartwig C−N coupling regimen followed by an intramolecular Heck reaction, the β-carbolinone core structure present in a variety of alkaloids was efficiently prepared from 5-oxo-1,2,3,5-tetrahydroindolizine-6-trifluoromethanesulfonate precursors. Allylation of methyl 6-hydroxy-5-oxo-1,2,3,5-tetrahydroindolizine-8-carboxylate gave the corresponding ethers which subsequently underwent thermal Claisen rearrangement to afford the *C*-allyl products in high yields. Cyclization of the latter under Wacker oxidation conditions gave novel polysubstituted furans fused onto an indolizinone core.

Experimental Section

General Procedure for Pd-Catalyzed Couplings of Pyridone Triflates and Anilines/Amide/Carbamate. A flame-dried, 10 mL, round-bottom flask was charged with tris(dibenzylideneacetone)dipalladium(0) (0.005 mmol, 2.5 mol %), xantphos (0.02 mmol, 10 mol %), pyridone **11**, **14**, or **15** (0.18 mmol), and Cs_2CO_3 (0.27 mmol). The solid reactants were dissolved in 5 mL of dioxane, and the appropriate aniline derivative (0.27 mmol) was added to the flask. The flask was capped with a condensor and kept under an atmosphere of argon. The mixture was heated at 100 °C for 1−2 h or until the starting triflate had been completely consumed as judged by TLC. The solution was cooled to room temperature, diluted with ethyl acetate, filtered through a pad of Celite, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography on silica gel to give the corresponding 6-(*N*-arylamino)-2,3-dihydro-1*H*-indolizin-5-one.

6-Phenylamino-2,3-dihydro-1*H*-indolizin-5-one (16a). Recrystallization from hexane gave a cream-colored solid (65%): mp 166−168 °C; IR (thin film) 1645, 1596, 1560, 1497, 1235, and 1143 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.20 (m, 2H), 3.03 (t, 2H, $J = 7.2$ Hz), 4.20 (t, 2H, $J = 7.2$ Hz), 6.06 (d,

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1H, J = 7.2 Hz), 6.86 (brs, 1H), 6.95 (t, 1H, J = 7.8 Hz), 7.11 (d, 1H, J = 7.2 Hz), 7.15 (d, 2H, J = 7.8 Hz), and 7.29 (t, 2H, J = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.2, 30.7, 48.8, 100.9, 111.9, 118.7, 121.4, 129.2, 131.9, 137.4, 141.7, and 157.3; FAB HRMS calcd for $[(C_{14}H_{14}N_2O) + Li]^+$ 233.1266, found 233.1273.

6-(4-Methoxyphenylamino)-2,3-dihydro-1*H*-indolizin-5-one (17a). Recrystallization from hexane gave a tan solid (70%): mp 148−150 °C; IR (KBr) 1645, 1596, 1581, 1440, 1233, 1179, and 1030 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.18 (m, 2H), 3.00 (t, 2H, J = 7.2 Hz), 3.79 (s, 3H), 4.18 (t, 2H, J = 7.2 Hz), 6.02 (d, 1H, J = 7.8 Hz), 6.60 (brs, 1H), 6.84 (d, 1H, J = 7.8 Hz), 6.86 (d, 2H, J = 9.0 Hz), and 7.10 (d, 2H, J = 9.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.3, 30.6, 48.7, 55.5, 101.0, 110.0, 114.6, 122.2, 133.5, 134.7, 136.4, 155.1, and 156.9. Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.05; H, 6.29; N, 10.77.

6-(4-Nitrophenylamino)-2,3-dihydro-1*H*-indolizin-5-one (18a). Recrystallization from ethyl acetate gave a pale yellow solid (76%): mp 238−240 °C; IR (KBr) 1643, 1582, 1558, 1471, 1365, and 1111 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.24 (m, 2H), 3.09 (t, 2H, J = 7.2 Hz), 4.21 (t, 2H, J = 7.2 Hz), 6.18 (d, 1H, J = 7.2 Hz), 7.11 (d, 2H, J = 9.0 Hz), 7.32 (d, 1H, J = 7.2 Hz), 7.38 (brs, 1H), and 8.15 (d, 2H, J = 9.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.0, 31.1, 49.2, 100.6, 115.2, 118.0, 126.0, 128.8, 140.2, 141.4, 148.2, and 157.3. Anal. Calcd for $C_{14}H_{13}N_3O_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 61.62; H, 4.84; N, 15.22.

6-(3,5-Dimethoxyphenylamino)-2,3-dihydro-1*H*-indolizin-5-one (19a) was obtained as a pale yellow oil (70%): IR (thin film) 1646, 1600, 1519, 1441, 1194, and 1160 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.19 (m, 2H), 3.02 (t, 2H, J = 7.2 Hz), 3.76 (s, 6H), 4.17 (t, 2H, J = 7.2 Hz), 6.06 (d, 1H, J = 7.8 Hz), 6.08 (s, 1H), 6.31 (s, 2H), 6.85 (brs, 1H), and 7.15 (d, 1H, J = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.2, 30.7, 48.9, 55.2, 93.3, 96.8, 100.9, 113.2, 131.3, 137.7, 143.6, 157.1, and 161.4; FAB HRMS calcd for $[(C_{16}H_{18}N_2O_3) + L\ i]^+$ 293.1477, found 293.1478.

6-(2-Trifluoromethylphenylamino)-2,3-dihydro-1*H*-indolizin-5-one (20a) was obtained as a pale yellow oil (73%): IR (thin film) 1651, 1603, 1580, 1522, 1462, 1166, and 1041 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.21 (m, 2H), 3.04 (t, 2H, J = 7.2 Hz), 4.20 (t, 2H, J = 7.2 Hz), 6.07 (d, 1H, J = 7.2 Hz), 7.00 (t, 1H, J = 7.8 Hz), 7.07 (d, 1H, J = 7.2 Hz), 7.14 (brs, 1H), 7.43 (t, 1H, J = 7.8 Hz), 7.49 (d, 1H, J = 7.8 Hz), and 7.59 (d, 1H, J = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.2, 30.9, 48.9, 100.5, 114.2, 120.2, 120.9, 124.3 (q, 1C, J = 317.7 Hz), 127.0, 127.1, 131.1, 132.5, 139.1, 140.2, and 157.3; FAB HRMS calcd for $[(C_{15}H_{13}F_3N_2O)]^+$ 294.0980, found 294.0969.

6-(Pyridin-2-ylamino)-2,3-dihydro-1*H*-indolizin-5-one (21a). Recrystallization from hexane gave a white solid (88%): mp 208−210 °C; IR (KBr) 1644, 1601, 1571, 1481, 1422, 1368, and 1157 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.18 (m, 2H), 3.04 (t, 2H, J = 7.2 Hz), 4.18 (t, 2H, J = 7.2 Hz), 6.17 (d, 1H, J = 7.2 Hz), 6.77 (dd, 1H, J = 7.8 and 4.2 Hz), 6.74 (d, 1H, J = 7.8 Hz), 7.47 (ddd, 1H, J = 8.4, 7.8, and 1.8 Hz), 7.68 (brs, 1H), 8.23 (d, 1H, J = 4.2 Hz), and 8.52 (d, 1H, J = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.1, 30.8, 49.0, 101.5, 111.7, 114.8, 118.2, 129.2, 137.0, 138.6, 147.4, 155.2, and 156.9. Anal. Calcd for $C_{13}H_{13}N_3O$: C, 68.71; H, 5.77; N, 18.49. Found: C, 68.58; H, 5.82; N, 18.53.

6-(2-Bromophenylamino)-2,3-dihydro-1*H*-indolizin-5-one (22a). Recrystallization from hexane gave a white solid (80%): mp 125−127 °C; IR (KBr) 1649, 1586, 1519, 1440, 1365, 1275, 1181, and 1022 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.21 (m, 2H), 3.04 (t, 2H, J = 7.2 Hz), 4.21 (t, 2H, J = 7.2 Hz), 6.08 (d, 1H, J = 7.8 Hz), 6.79 (t, 1H, J = 7.8 Hz), 7.10 (d, 1H, J = 7.8 Hz), 7.18 (brs, 1H), 7.23 (t, 1H, J = 7.2 Hz), 7.37 (d, 1H, J = 7.8 Hz), and 7.56 (d, 1H, J = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.2, 30.9, 48.9, 100.6, 113.9, 114.5, 117.5, 121.9, 127.9, 130.9, 133.3, 138.8, 139.7, and 157.3. Anal. Calcd for $C_{14}H_{13}BrN_2O$: C, 55.10; H, 4.29; N, 9.18. Found: C, 55.05; H, 4.27; N, 8.98.

6-Benzylamino-2,3-dihydro-1*H*-indolizin-5-one (23a) was obtained as a pale yellow oil (65%): IR (thin film) 1646, 1590, 1485, 1453, 1379, and 1223 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.15 (m, 2H), 2.96 (t, 2H, J = 7.2 Hz), 4.14 (t, 2H, J = 7.2 Hz), 4.32 (s, 2H), 5.25 (brs, 1H), 5.98 (d, 1H, J = 7.2 Hz), 6.15 (d, 1H, J = 7.2 Hz), and 7.24−7.38 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.4, 30.5, 47.7, 48.5, 101.4, 108.5, 127.1, 127.2, 128.5, 135.0, 136.5, 138.8, and 156.8; FAB HRMS calcd for $[(C_{15}H_{16}N_2O) + Li]^+$ 247.1423, found 247.1412.

***N*-(5-Oxo-1,2,3,5-tetrahydroindolizin-6-yl)benzamide (24a).** Recrystallization from hexane gave a white solid (74%): mp 140−142 °C; IR (KBr) 1647, 1593, 1522, 1489, 1280, 1186, and 1031 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (m, 2H), 3.09 (t, 2H, J = 7.2 Hz), 4.20 (t, 2H, J = 7.2 Hz), 6.22 (d, 1H, J = 7.6 Hz), 7.50 (m, 3H), 7.92 (m, 2H), 8.55 (d, 1H, J = 7.6 Hz), and 9.08 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 31.1, 49.1, 101.4, 123.3, 126.8, 127.1, 128.7, 131.8, 134.4, 142.7, 156.7, and 165.6. Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.62; H, 5.31; N, 11.27.

Benzyl (5-oxo-1,2,3,5-tetrahydroindolizin-6-yl)-carbamate (25a) was obtained as a pale yellow oil (71%): IR (thin film) 1716, 1647, 1581, 1533, 1448, 1362, 1211, and 1065 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (m, 2H), 3.04 (t, 2H, J = 7.2 Hz), 4.15 (t, 2H, J = 7.2 Hz), 5.19 (s, 2H), 6.14 (d, 1H, J = 7.2 Hz), 7.32−7.41 (m, 5H), 7.75 (brs, 1H), and 8.02 (d, 1H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 31.1, 49.0, 66.9, 101.0, 121.1, 126.7, 128.1, 128.2, 128.5, 136.0, 141.7, 153.4, and 156.2; FAB HRMS calcd for $[(C_{16}H_{16}N_2O_3) + Li]^+$ 291.1232, found 291.1318.

Methyl 5-Oxo-6-phenylamino-1,2,3,5-tetrahydroindolizine-8-carboxylate (16b). Recrystallization from hexane gave a white solid (75%): mp 170−172 °C; IR (KBr) 1708, 1632, 1590, 1435, 1382, 1181, and 1098 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.23 (m, 2H), 3.48 (t, 2H, J = 7.2 Hz), 3.83 (s, 3H), 4.22 (t, 2H, J = 7.2 Hz), 6.82 (s, 1H), 7.00 (d, 1H, J = 7.2 Hz), 7.19 (d, 2H, J = 7.8 Hz), 7.33 (t, 2H, J = 8.4 Hz), and 7.62 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.3, 32.8, 49.3, 51.7, 105.6, 110.5, 119.1, 122.0, 129.4, 131.5, 141.1, 144.8, 157.6, and 165.8. Anal. Calcd for $C_{16}H_{16}N_2O_5$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.19; H, 5.70; N, 9.64.

Methyl 6-(4-methoxyphenylamino)-5-oxo-1,2,3,5-tetrahydroindolizine-8-carboxylate (17b) was obtained as a pale yellow oil (40%): IR (KBr) 1701, 1636, 1602, 1592, 1440, 1375, and 1098 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.22 (m, 2H), 3.45 (t, 2H, J = 7.2 Hz), 3.80 (s, 6H), 4.22 (t, 2H, J = 7.2 Hz), 6.57 (s, 1H), 6.90 (d, 2H, J = 9.0 Hz), 7.13 (d, 2H, J = 9.0 Hz), and 7.34 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.4, 32.7, 49.2, 51.7, 55.5, 105.8, 108.7, 114.7, 122.6, 134.0, 143.9, 155.5, and 165.9; FAB HRMS calcd for $[(C_{17}H_{18}N_2O_4) + Li]^+$ 321.1426, found 321.1425.

Methyl 6-(4-Nitrophenylamino)-5-oxo-1,2,3,5-tetrahydroindolizine-8-carboxylate (18b). Recrystallization from ethyl acetate gave a yellow solid (76%): mp 232−235 °C; IR (KBr) 1719, 1637, 1596, 1485, 1328, 1268, and 1110 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.27 (m, 2H), 3.53 (t, 2H, J = 7.2 Hz), 3.87 (s, 3H), 4.24 (t, 2H, J = 7.2 Hz), 7.17 (d, 2H, J = 9.0 Hz), 7.35 (s, 1H), 7.84 (s, 1H), and 8.17 (d, 2H, J = 9.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.1, 33.1, 49.6, 52.0, 105.3, 115.7, 116.4, 126.0, 128.5, 140.7, 147.5, 148.1, 157.6, and 165.2. Anal. Calcd for $C_{16}H_{15}N_3O_5$: C, 58.36; H, 4.59; N, 12.76. Found: C, 58.49; H, 4.63; N, 12.85.

Methyl 6-(3,5-dimethoxyphenylamino)-5-oxo-1,2,3,5-tetrahydroindolizine-8-carboxylate (19b) was obtained as a pale yellow oil (67%): IR (thin film) 1711, 1638, 1598, 1377, 1216, 1098, and 1068 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.24 (m, 2H), 3.49 (t, 2H, J = 7.2 Hz), 3.79 (s, 6H), 3.83 (s, 3H), 4.22 (t, 2H, J = 7.2 Hz), 6.13 (t, 1H, J = 1.8 Hz), 6.35 (d, 2H, J = 1.8 Hz), 6.79 (s, 1H), and 7.68 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.3, 32.8, 49.3, 51.8, 55.3, 94.2, 97.3, 105.6, 111.8,

131.1, 143.0, 145.1, 157.6, 161.5, and 165.8; FAB HRMS calcd for $[(C_{18}H_{20}N_2O_5) + Li]^+$ 351.1532, found 351.1530.

Methyl 5-oxo-6-(2-trifluoromethylphenylamino)-1,2,3,5-tetrahydroindoliz-ine-8-carboxylate (20b) was obtained as a pale yellow oil (73%): IR (thin film) 1711, 1642, 1585, 1526, 1439, 1274, 1094, and 1035 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.25 (m, 2H), 3.50 (t, 2H, J = 7.8 Hz), 3.82 (s, 3H), 4.24 (t, 2H, J = 7.8 Hz), 7.08 (dd, 1H, J = 8.4 and 6.6 Hz), 7.52 (m, 2H), 7.57 (s, 1H), and 7.63 (d, 1H, J = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.3, 33.0, 49.3, 51.8, 105.3, 112.4, 120.3, 121.8, 124.0 (q, 1C, J = 336 Hz), 127.1, 127.2, 131.0, 132.8, 139.5, 146.2, 157.7, and 165.7; FAB HRMS calcd for $[(C_{17}H_{15}N_2O_3F_3) + Li]^+$ 359.1195, found 359.1191.

Methyl 5-Oxo-6-(pyridin-2-ylamino)-1,2,3,5-tetrahydroindolizine-8-carboxylate (21b). Recrystallization from ethyl acetate gave a yellow solid (62%): mp 213-215 °C; IR (KBr) 1707, 1635, 1602, 1523, 1378, 1195, and 1095 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.24 (m, 2H), 3.51 (t, 2H, J = 7.8 Hz), 3.88 (s, 3H), 4.22 (t, 2H, J = 7.8 Hz), 6.78 (m, 2H), 7.52 (ddd,1H, J = 9.0 and 1.8 Hz), 7.59 (brs, 1H), 8.31 (d, 1H, J = 4.8 Hz), and 9.00 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.2, 29.7, 32.9, 49.4, 51.8, 106.0, 111.6, 115.3, 117.0, 128.7, 137.2, 146.1, 147.7, 154.8, 157.5, and 166.0. Anal. Calcd for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.07; H, 5.22; N, 14.81.

Methyl 6-(2-Bromophenylamino)-5-oxo-1,2,3,5-tetrahydroindolizine-8-carboxylate (22b). Recrystallization from hexane gave a white solid (80%): mp 134−136 °C; IR (KBr) 1709, 1639, 1522, 1413, 1269, and 1094 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.25 (m, 2H), 3.49 (t, 2H, J = 7.2 Hz), 3.84 (s, 3H), 4.24 (t, 2H, J = 7.2 Hz), 6.85 (ddd, 1H, J = 7.8, 7.2, and 1.8 Hz), 7.16 (brs, 1H), 7.30 (ddd, 1H, J = 7.8, 7.2, and 1.8 Hz), 7.44 (dd, 1H, J = 7.8 and 1.8 Hz), 7.58 (dd, 1H, J = 8.4 and 1.8 Hz), and 7.62 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.2, 32.9, 49.3, 51.8, 105.3, 112.2, 114.8, 118.1, 122.6, 128.2, 130.5, 133.3, 139.1, 146.0, 157.7, and 165.7. Anal. Calcd for $C_{16}H_{15}BrN_2O_3$: C, 52.91; H, 4.16; N, 7.71. Found: C, 52.71; H, 4.18; N, 7.54.

8-Benzenesulfonyl-6-phenylamino-2,3-dihydro-1*H*-indolizin-5-one (16c) was obtained as a pale yellow oil (50%): IR (thin film) 1638, 1589, 1520, 1446, 1150, and 1072 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.23 (m, 2H), 3.42 (t, 2H, J = 7.2 Hz), 4.17 (t, 2H, J = 7.2 Hz), 6.91 (brs, 1H), 7.06 (t, 1H, J = 7.8 Hz), 7.16 (d, 2H, J = 7.8 Hz), 7.36 (t, 2H, J = 7.8 Hz), 7.49 (s, 1H), 7.55 (m, 3H), and 7.87 (d, 2H, J = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.4, 31.5, 49.4, 107.3, 116.1, 119.4, 122.8, 126.9, 128.5, 129.3, 129.6, 132.5, 140.3, 141.1, 141.9, and 157.1; FAB HRMS calcd for $[(C_{20}H_{18}N_2SO_3) + Li]^+$ 373.1198, found 373.1194.

8-Benzenesulfonyl-6-(4-methoxyphenylamino)-2,3-dihydro-1*H*-indolizin-5-one (17c) was obtained as a pale yellow oil (65%): IR (thin film) 1636, 1599, 1306, 1151, and 1101 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.21 (m, 2H), 3.39 (t, 2H, J = 7.2 Hz), 3.83 (s, 3H), 4.16 (t, 2H, J = 7.2 Hz), 6.68 (s, 1H), 6.92 (d, 1H, J = 8.4 Hz), 7.11 (d, 2H, J = 8.4 Hz), 7.23 (s, 1H), 7.51 (m, 2H), 7.58 (m, 2H), and 7.84 (d, 2H, J = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5, 31.4, 49.3, 55.6, 105.7, 114.9, 116.3, 122.7, 126.9, 128.3, 129.2, 133.1, 134.1, 140.2, 142.0, 156.0, and 156.9; FAB HRMS calcd for $[(C_{21}H_{20}N_2SO_4) + Li]^+$ 403.1304, found 403.1302.

8-Benzenesulfonyl-6-(4-nitrophenylamino)-2,3-dihydro-1*H*-indolizin-5-one (18c) was obtained as a pale yellow oil (63%): IR (thin film) 1637, 1593, 1562, 1479, 1321, 1301, and 1112 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.27 (m, 2H), 3.47 (t, 2H, J = 7.2 Hz), 4.20 (t, 2H, J = 7.2 Hz), 7.17 (d, 2H, J = 9.0 Hz), 7.35 (brs, 1H), 7.57 (t, 2H, J = 7.8 Hz), 7.64 (t, 1H, J = 7.8 Hz), 7.90 (d, 2H, J = 7.8 Hz), and 8.23 (d, 2H, J = 9.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.2, 31.8, 49.7, 112.7, 116.0, 116.3, 126.1, 127.0, 129.5, 129.8, 133.5, 141.4, 141.6, 144.4, 146.6, and 157.0; FAB HRMS calcd for $[(C_{20}H_{17}N_3SO_5) + Li]^+$ 418.1049, found 418.1046.

8-Benzenesulfonyl-6-(3,5-dimethoxyphenylamino)-2,3-dihydro-1*H*-indolizin-5-one (19c) was obtained as a pale yellow oil (30%): IR (thin film) 1638, 1596, 1565, 1480, 1319, 1152, and 1069 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.23 (m, 2H), 3.44 (t, 2H, J = 7.2 Hz), 3.79 (s, 6H), 4.16 (t, 2H, J = 7.2 Hz), 6.17 (s, 1H), 6.32 (s, 2H), 6.86 (s, 1H), 7.52 (t, 2H, J = 7.2 Hz), 7.55 (s, 1H), 7.59 (t, 1H, J = 7.2 Hz), and 7.88 (d, 2H, J = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.4, 31.6, 49.4, 55.3, 95.1, 97.6, 108.7, 116.2, 126.9, 129.3, 132.2, 133.2, 141.3, 141.9, 142.1, 157.0, and 161.6; FAB HRMS calcd for $[(C_{22}H_{22}N_2SO_5) + Li]^+$ 433.1409, found 433.1411.

8-Benzenesulfonyl-6-(2-trifluoromethylphenylamino)-2,3-dihydro-1*H*-indolizin-5-one (20c) was obtained as a pale yellow oil (30%): IR (thin film) 1644, 1609, 1585, 1461, 1321, 1152, and 1036 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.24 (m, 2H), 3.41 (t, 2H, J = 7.2 Hz), 4.19 (t, 2H, J = 7.2 Hz), 7.16 (m, 2H), 7.42 (s, 1H), 7.53 (m, 4H), 7.60 (t, 1H, J = 7.8 Hz), 7.66 (d, 1H, J = 7.8 Hz), and 7.84 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.4, 31.6, 49.4, 108.9, 115.8, 120.9, 121.6, 122.8, 124.0 (q, 1C, J = 317.7 Hz), 126.9, 127.3, 129.4, 132.2, 133.0, 133.3, 138.7, 141.8, 142.6, and 157.0; FAB HRMS calcd for $[(C_{21}H_{17}N_2SO_3F_3) + Li]^+$ 441.1072, found 441.1070.

8-Benzenesulfonyl-6-(pyridin-2-ylamino)-2,3-dihydro-1*H*-indolizin-5-one (21c). Recrystallization from hexane gave a white solid: mp 218−220 °C; IR (KBr) 1642, 1591, 1520, 1475, 1317, and 1150 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.23 (m, 2H), 3.46 (t, 2H, J = 7.2 Hz), 4.21 (t, 2H, J = 7.2 Hz), 6.76 (d, 1H, J = 9.0 Hz), 6.81 (dd, 1H, J = 7.2 and 5.4 Hz), 7.52 (m, 3H), 7.58 (m, 1H), 7.63 (brs, 1H), 7.96 (d, 2H, J = 7.8 Hz), 8.33 (dd, 1H, J = 4.8 and 1.8 Hz), and 9.11 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.2, 31.7, 49.5, 111.7, 114.6, 115.8, 116.6, 127.1, 129.2, 129.7, 133.1, 137.2, 142.0, 142.3, 147.8, 154.4, and 156.9. Anal. Calcd for $C_{19}H_{17}N_3SO_3$: C, 62.11; H, 4.66; N, 11.44. Found: C, 62.37; H, 4.75; N, 11.30.

1,2,3,6-Tetrahydroindolizino[6,7-*b*]indol-5-one (26). A flame-dried, 20 mL, heavy-walled Pyrex tube was charged with $Pd(PPh_3)_4$ (0.03 g, 0.02 mmol, 10 mol %), pyridone **22a** (0.07 g, 0.23 mmol), and Cs_2CO_3 (0.11 g, 0.34 mmol). The solid reactants were dissolved in 4 mL of dioxane, and the tube was sealed with a Teflon screw cap. The reaction was heated at 110 °C for 24 h in an oil bath. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, filtered through a pad of Celite, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography on silica gel to give β-carbolinone **26** (0.03 g, 0.15 mmol) in 65% yield. Recrystallization from hexane gave a white solid: mp 170−172 °C; IR (KBr) 1661, 1594, 1566, 1301, and 1255 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.31 (m, 2H), 3.21 (t, 2H, J = 7.2 Hz), 4.35 (t, 2H, J = 7.2 Hz), 6.87 (s, 1H), 7.22 (t, 1H, J = 7.8 Hz), 7.45 (t, 1H, J = 7.2 Hz), 7.58 (d, 1H, J = 8.4 Hz), 7.92 (d, 1H, J = 7.8 Hz), and 10.09 (brs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.8, 31.1, 48.1, 95.7, 112.4, 119.8, 121.2, 122.2, 126.4 (2C), 126.8, 139.7, 140.2, and 159.5; FAB HRMS calcd for $[(C_{14}H_{12}N_2O) + Li]^+$ 231.1110, found 231.1109.

Methyl 5-Oxo-2,3,5,6-tetrahydro-1*H*-indolizino[6,7-*b*]-indole-11-carboxylate (27). A flame-dried, 20 mL, heavy-walled Pyrex tube was charged with $Pd(PPh_3)_4$ (0.06 g, 0.05 mmol, 10 mol %), pyridone **22b** (0.18 g, 0.5 mmol), and Cs_2CO_3 (0.24 g, 0.74 mmol). The solid reactants were dissolved in 5 mL of dioxane, and the tube was sealed with a Teflon screw cap. The reaction was heated at 110 °C for 24 h in an oil bath. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, filtered through a pad of Celite, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography on silica gel to give β-carbolinone **27** (0.09 g, 0.3 mmol) in 65% yield. Recrystallization from hexane gave a white solid: mp 250 °C; IR (KBr) 1707, 1655, 1555, 1383, 1307, and 1143 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.19 (m, 2H), 3.45 (t, 2H, J = 7.2 Hz), 3.94 (s, 3H), 4.18 (t, 2H, J = 7.2 Hz), 7.14 (ddd, 1H, J = 8.4 and 2.4 Hz), 7.40 (ddd, 1H, J = 8.4 and 2.4 Hz), 7.51 (d, 1H, J = 8.4 Hz), 8.35 (d, 1H, J = 8.4 Hz), and 12.18 (brs, 1H); ^{13}C NMR

(150 MHz, DMSO-d_6) δ 21.5, 32.2, 49.4, 52.1, 102.1, 112.0, 113.1, 119.0, 120.1, 121.2, 125.3, 126.7, 140.0, 147.3, 154.0, and 166.5; FAB HRMS Calcd for $[(C_{16}H_{14}N_2O_3) + Li]^+$ 289.1164, found 289.1151.

Methyl 6-Allyloxy-5-oxo-1,2,3,5-tetrahydroindolizidine-8-carboxylate (29). To a solution containing 0.5 g (2.4 mmol) of pyridone **10** in 50 mL of acetone were added 0.3 mL (3.6 mmol) of allyl bromide and 0.5 g (3.6 mmol) of potassium carbonate, and the resultant mixture was heated at reflux under nitrogen for 18 h. The mixture was allowed to cool to room temperature and filtered through Celite, and the filtrate was concentrated under reduced pressure. Purification of the resultant residue by silica gel column chromatography gave 0.57 g (96%) of **29** as a colorless oil: IR (NaCl film) 2951, 1709, 1655, 1611, and 1214 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.19 (quint, 2H, J = 7.5 Hz), 3.43 (t, 2H, J = 7.5 Hz), 3.81 (s, 3H), 4.15 (t, 2H, J = 7.4 Hz), 4.55 (d, 2H, J = 5.1 Hz), 5.26 (brd, 1H, J = 10.5 Hz), 5.38 (brd, 1H, J = 17.1 Hz), 5.95−6.08 (m, 1H), and 7.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 32.9, 49.1, 51.7, 69.8, 103.7, 115.1, 118.3, 132.3, 145.7, 148.6, 157.4, and 165.4; HRMS calcd for $C_{13}H_{16}NO_4$ $[M + H]^+$ 250.1079, found 250.1072.

Methyl 6-(But-2-enyloxy)-5-oxo-1,2,3,5-tetrahydroindolizidine-8-carboxylate (30). To a solution containing 0.5 g (2.4 mmol) of pyridone **10** in 50 mL of acetone were added 0.35 mL (3.6 mmol) of crotyl chloride, 0.5 g (3.6 mmol) of potassium carbonate, and 0.36 g (2.4 mmol) of sodium iodide, and the resultant mixture was heated at reflux under nitrogen for 18 h. The mixture was allowed to cool to room temperature and filtered through Celite, and the filtrate was concentrated under reduced pressure. Purification of the resultant residue by silica gel chromatography gave 0.57 g (90%) of **30** as a colorless oil: IR (NaCl film) 2949, 1709, 1658, 1612, and 1213 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69−1.73 (m, 3H), 2.14−2.22 (m, 2H), 3.43 (t, 2H, J = 7.8 Hz), 3.82 (s, 3H), 4.15 (t, 2H, J = 7.6 Hz), 4.46 (d, 1H, J = 6.0 Hz), 4.62 (d, 1H, J = 6.0 Hz), 5.64−5.75 (m, 1H), 5.78−5.85 (m, 1H), and 7.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 21.1, 32.9, 49.1, 51.7, 69.7, 103.7, 114.7, 125.2, 131.2, 145.9, 148.3, 157.5, and 165.5; HRMS calcd for $C_{14}H_{18}NO_4$ $[M + H]^+$ 264.1236, found 264.1228.

Methyl 6-(2-Methylallyloxy)-5-oxo-1,2,3,5-tetrahydroindolizidine-8-carboxylate (31). To a solution containing 0.5 g (2.4 mmol) of pyridone **10** in 50 mL of acetone was added 0.35 mL (3.6 mmol) of methallyl chloride, 0.5 g (3.6 mmol) of potassium carbonate, and 0.36 g (2.4 mmol) of sodium iodide, and the resultant mixture was heated at reflux under nitrogen for 18 h. The mixture was then allowed to cool to room temperature and filtered through Celite, and the filtrate was concentrated under reduced pressure. Purification of the resultant residue by silica gel column chromatography gave 0.62 g (98%) of **31** as a colorless oil: IR (NaCl film) 2950, 1710, 1657, 1612, and 1214 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78 (s, 3H), 2.18 (quint., 2H, J = 7.7 Hz), 3.42 (t, 2H, J = 7.6 Hz), 3.84 (s, 3H), 4.15 (t, 2H, J = 7.6 Hz), 4.46 (s, 2H), 4.96 (brs, 1H), 5.06 (brs, 1H), and 7.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 21.0, 32.9, 49.1, 51.7, 72.6, 103.7, 113.3, 115.3, 139.8, 145.8, 148.6, 157.4, and 165.4; HRMS calcd for $C_{14}H_{18}NO_4$ $[M + H]^+$ 264.1236, found 264.1228.

Methyl 5-Oxo-6-(3-phenylallyloxy)-1,2,3,5-tetrahydroindolizidine-8-carboxylate (32). To a solution containing 0.5 g (2.4 mmol) of pyridone **10** in 50 mL of acetone was added 0.36 mL (2.6 mmol) of cinnamyl chloride, 0.36 g (2.6 mmol) of potassium carbonate, and 0.36 g (2.4 mmol) of sodium iodide, and the resultant mixture was heated at reflux under nitrogen for 18 h. The mixture was then allowed to cool to room temperature and filtered through Celite, and the filtrate was concentrated under reduced pressure. Purification of the resultant residue by silica gel column chromatography gave 0.74 g (95%) of **32** as a colorless oil: IR (NaCl film) 3025, 2950, 1708, 1652, 1610, and 1214 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (quint., 2H, J = 7.2 Hz), 3.36 (t, 2H, J = 7.0 Hz), 3.80 (s, 3H), 4.10 (t, 2H, J = 7.6 Hz), 4.68 (d, 2H, J = 5.6 Hz), 6.37 (dt, 1H, J = 16.0 and 6.0 Hz), 6.65 (d, 1H, J = 16.0), 7.16−7.25 (m, 4H), and 7.32 (d, 2H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 32.8, 49.1, 51.7, 69.6, 103.9, 115.2, 123.2, 126.4, 127.8, 128.3, 133.6, 136.0, 145.5, 148.6, 157.5, and 165.4; HRMS calcd for $C_{19}H_{20}NO_4$ $[M + H]^+$ 326.1392, found 326.1383.

Methyl 7-Allyl-6-hydroxy-5-oxo-1,2,3,5-tetrahydroindolizine-8-carboxylate (33). A solution of 0.5 g of pyridone **29** in 2 mL of DMF was immersed in an oil bath that was preheated to 160 °C and was stirred under a nitrogen atmosphere. After heating for 1 h, the dark solution was cooled to room temperature and was purified by silica gel column chromatography followed by recrystallization from ethyl acetate−hexane to give 0.35 g (70%) of **33** as white crystals: mp 100−101 °C; IR (NaCl film) 3278, 2950, 1714, 1635, 1597, and 1271 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (quint., 2H, J = 7.6 Hz), 3.32 (t, 2H, J = 7.8 Hz), 3.62 (dt, 2H, J = 6.1 and 1.4 Hz), 3.82 (s, 3H), 4.19 (t, 2H, J = 7.6 Hz), 5.00−5.06 (m, 2H), 5.85−5.95 (m, 1H), and 6.68 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 30.7, 32.9, 49.2, 51.7, 108.0, 115.7, 126.7, 135.1, 141.9, 144.4, 156.7, and 166.5. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.76; H, 5.97, N, 5.60.

Methyl 6-Hydroxy-7-(1-methylallyl)-5-oxo-1,2,3,5-tetrahydroindolizidine-8-carboxylate (34). A solution of 0.5 g of pyridone **30** in 2 mL of DMF was immersed in an oil bath that was preheated to 160 °C and was stirred under a nitrogen atmosphere. After heating for 1 h, the dark solution was cooled to room temperature and was purified by silica gel chromatography followed by recrystallization from ethyl acetate−hexane to give 0.4 g (84%) of **34** as white needles: mp 89−90 °C; IR (NaCl film) 3247, 2971, 1716, 1638, 1596, and 1274 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (d, 3H, J = 7.2 Hz), 2.17 (quint, 2H, J = 7.5 Hz), 3.11−3.26 (m, 2H), 3.81 (s, 3H), 3.81−3.87 (m, 1H), 4.16 (t, 2H, J = 7.4 Hz), 5.00 (dt, 1H, J = 10.4 and 1.6 Hz), 5.04. (dt, 1H, J = 17.2 and 1.6 Hz), 6.18 (ddd, 1H, J = 17.2, 10.4 and 1.6 Hz), and 6.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 21.6, 32.0, 37.5, 49.1, 51.8, 108.9, 113.9, 130.6, 140.2, 141.8, 141.9, 156.9, and 167.2. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.99, H, 6.50; N, 5.32.

Methyl 6-Hydroxy-7-(2-methylallyl)-5-oxo-1,2,3,5-tetrahydroindolizidine-8-carboxylate (35). A solution of 0.5 g of pyridone **31** in 2 mL of DMF was immersed in an oil bath that was preheated to 160 °C and stirred under a nitrogen atmosphere. After heating for 1 h, the dark solution was cooled to room temperature and was purified by silica gel chromatography followed by recrystallization from ethyl acetate−hexane to give 0.42 g (84%) of **35** as a white solid: mp 124−125 °C; IR (NaCl film) 3259, 1713, 1640, 1599, and 1273 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.74 (s, 3H), 2.18 (quint, 2H, J = 7.6 Hz), 3.29 (t, 2H, J = 7.6 Hz), 3.58 (s, 2H), 3.77 (s, 3H), 4.19 (t, 2H, J = 7.4 Hz), 4.41 (brs, 1H), 4.69 (brs, 1H), and 7.02 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 23.0, 32.7, 33.8, 49.1, 51.6, 108.3, 110.1, 126.5, 142.2, 143.4, 143.9, 156.7, and 166.5. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.85; H, 6.56; N, 5.32.

Methyl 6-Hydroxy-5-oxo-7-(1-phenylallyl)-1,2,3,5-tetrahydroindolizidine-8-carboxylate (36). A solution of 0.2 g of pyridone **32** in 2 mL of DMF was immersed in an oil bath that was preheated to 160 °C and stirred under a nitrogen atmosphere. After heating for 1 h, the dark solution was cooled to room temperature and was purified by silica gel column chromatography followed by recrystallization from ethyl acetate−hexane to give 0.16 g (80%) of **36** as cream white crystals: mp 135−136 °C; IR (NaCl film) 3232, 2945, 1716, 1634, 1539, and 1270 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20−2.29 (m, 2H), 3.18−3.39 (m, 2H), 3.61 (s, 3H), 4.19−4.30 (m, 2H), 5.31−5.38 (m, 3H), 6.60 (ddd, 1H, J = 17.2, 10.0 and 8.6 Hz), 6.88 (brs, 1H), and 7.21−7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 32.3, 47.6, 49.2, 51.6, 108.6, 117.8, 126.0, 127.2, 128.0, 128.6, 137.1, 141.5, 142.3, 142.7, 156.9, and 166.8. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.26; H, 5.80; N, 4.25.

Methyl 2-Methyl-8-oxo-5,6,7,8-tetrahydro-1-oxa-7a-azaindacene-4-carboxylate (37). To a solution containing 0.3 g (1.2 mmol) of pyridone **33** in 6 mL of DMF at 25 °C was added a solution containing 0.21 g (1.2 mmol) of copper(II) chloride dihydrate in 4 mL of water followed by palladium(II) chloride (0.021 g, 0.11 mmol), and the reaction mixture was stirred at room temperature under an oxygen atmosphere for 12 h. The dark reaction mixture was poured into a separatory funnel containing 100 mL of water and was extracted with 100 mL of ethyl acetate. The organic layer was dried over $MgSO_4$ and filtered through Celite, and the filtrate was concentrated under reduced pressure. Purification of the resultant white solid by silica gel column chromatography gave 0.29 g (97%) of **37** as a white solid which was purified further by recrystallization from dichloromethane: mp 159−160 °C; IR (NaCl film) 1710, 1672, 1566, and 1235 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.23 (quint, 2H, $J = 7.7$ Hz), 2.44 (s, 3H), 3.52 (t, 2H, $J = 7.8$ Hz), 3.87 (s, 3H), 4.21 (t, 2H, $J = 7.4$ Hz), and 6.72 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 21.5, 33.3, 48.5, 51.5, 99.6, 105.4, 134.6, 140.5, 151.7, 152.8, 159.9, and 165.7. Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.34; H, 5.55; N, 5.44.

Methyl 2,3-Dimethyl-8-oxo-5,6,7,8-tetrahydro-1-oxa-7a-azaindacene-4-carboxylate (38). To a solution containing 0.32 g (1.2 mmol) of pyridone **34** in 6 mL of DMF, stirred at room temperature, was added a solution containing 0.21 g (1.2 mmol) of copper(II) chloride dihydrate in 4 mL of water followed by palladium(II) chloride (0.021 g, 0.11 mmol), and the reaction mixture was stirred at room temperature under an oxygen atmosphere for 12 h. The dark reaction mixture was poured into a separatory funnel containing 100 mL of water and was extracted with 100 mL of ethyl acetate. The organic layer was dried over $MgSO_4$ and filtered through Celite and the filtrate concentrated under reduced pressure. Purification of the resultant solid by silica gel column chromatography gave 0.3 g (95%) of **38** as a white solid: mp 128−129 °C; IR (NaCl film) 2980, 1708, 1669, 1556, and 1243 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.09 (s, 3H), 2.19 (quint, 2H, $J = 7.6$ Hz), 2.37 (s, 3H), 3.39 (t, 2H, $J = 7.8$ Hz), 3.85 (s, 3H), and 4.20 (t, 2H, $J = 7.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.0, 12.2, 21.7, 33.0, 48.4, 51.4, 101.4, 111.9, 133.2, 140.4, 150.0, 151.8, 156.4, and 165.9; HRMS calcd for $C_{14}H_{16}NO_4$ $[M + H]^+$ 262.1079, found 262.1074.

Methyl 2-Methyl-8-oxo-3-phenyl-5,6,7,8-tetrahydro-1-oxa-7a-azaindacene-4-carboxylate (39). To a solution containing 0.08 g (0.24 mmol) of **36** in 4 mL of DMF, stirred at room temperature, was added a solution containing 0.042 g (0.24 mmol) of copper(II) chloride dihydrate in 4 mL of water followed by palladium(II) chloride (4.2 mg, 0.024 mmol), and the reaction mixture was stirred at room temperature under an oxygen atmosphere for 12 h. The dark reaction mixture was poured into a separatory funnel containing 100 mL of water and was extracted with 100 mL of ethyl acetate. The organic layer was dried over $MgSO_4$ and filtered through Celite, and the filtrate was concentrated under reduced pressure. Purification of the resultant dark oil silica gel column chromatography gave 0.064 g (80%) of **39** as a colorless oil: IR (NaCl film) 2955, 1711, 1670, 1562, and 1219 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.26 (quint., 2H, $J = 7.6$ Hz), 2.40 (s, 3H), 2.93 (s, 3H) 3.42 (t, 2H, $J = 7.6$ Hz), 4.28 (t, 2H, $J = 7.2$ Hz), 7.19−7.21 (m, 2H), 7.33−7.36 (m, 1H), and 7.41−7.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8, 21.9, 32.3, 48.6, 50.6, 100.9, 119.0, 127.0, 127.1, 128.3, 128.7, 129.0, 134.0, 150.4, 157.2, and 165.7; HRMS calcd for $C_{19}H_{18}NO_4$ $[M + H]^+$ 324.1236, found 324.1230.

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Supporting Information Available: ^1H and ^{13}C NMR data of various key compounds lacking CH,N analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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