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Model Studies Directed toward the Alkaloid Mersicarpine Utilizing a Rh(II)-Catalyzed Insertion/Cycloaddition Sequence

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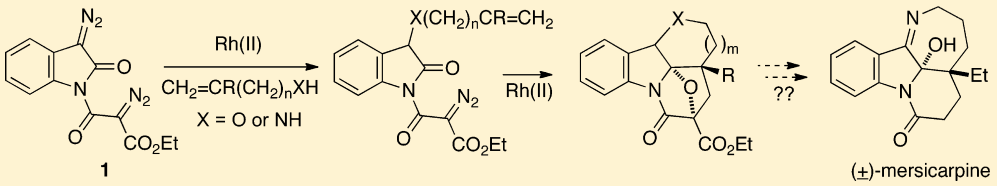
Supporting Information



ABSTRACT: Model studies dealing with the rhodium(II)-catalyzed carbenoid insertion/cyclization/cycloaddition cascade of several α-diazo dihydroindolinones have been carried out as an approach to the alkaloid mersicarpine. The cascade reaction of α-diazo dihydroindolinone **21** proceeded in high yield with excellent diastereoselectivity to give cycloadduct **22**, which possesses the required stereochemistry of the two adjacent quaternary carbon centers present in mersicarpine. The overall reaction enabled the rapid assemblage of a polycyclic ring system that contains three new stereocenters and three continuous quaternary carbons in a single operation in high yield with excellent diastereoselectivity. The 3-indolinone derivative **36** was eventually formed from cycloadduct **22** by an acid-induced hydrolysis of **22** to give **23**, which was subsequently converted in several steps to **36**. The synthesis of this compound constitutes a successful construction of the tricyclic core of mersicarpine. Reduction of the nitrile group of **36** followed by a subsequent reductive cyclization/ring-opening aromatization cascade, as was found to occur with the related compound **29**, will be employed for an eventual synthesis of demethylmersicarpine.

INTRODUCTION

Mersicarpine (**4**) is a structurally unique alkaloid that was isolated from the *Kopsia* species of plants by Kam and co-workers in 2004.[1] It contains a seven-membered cyclic imine and an intricately oxidized indole moiety centered in the tetracyclic ring system with two quarternary carbons (C_{20} and C_{21})[1] arranged adjacent to the imine moiety. The first total synthesis of mersicarpine was accomplished by Kerr and co-workers in 2008 using a Mn(III)-mediated malonic radical cyclization.[2] Somewhat later, a formal synthesis of mersicarpine was reported by Zard, who employed an intermolecular radical addition/cyclization cascade.[3] In addition to these two radical approaches, application of a Lewis acid-catalyzed allylic substitution of a tertiary alcohol for a formal synthesis of mersicarpine was demonstrated by Han and co-workers.[4] In 2010, Fukuyama and co-workers reported the first enantioselective synthesis of mersicarpine employing a combination of a Sonogashira coupling reaction with a gold(III)-catalyzed cyclization.[5] More recently, Tokuyama and co-workers applied a DIBAL-H-mediated reductive ring-expansion reaction in their enantioselective synthesis of mersicarpine, and this approach constitutes the most concise synthesis of this alkaloid to date.[6] Another interesting and rapid access to the core of mersicarpine was developed by Liang in 2013 and features an initial aldol reaction followed by a Beckmann rearrangement for the synthesis of a δ-lactam intermediate.[7] A subsequent intramolecular nucleophilic aromatic substitution (S_NAr) was then used for indoxyl formation, and this was followed by a final autoxidation reaction.

The synthetic plan that we have in mind for a mersicarpine synthesis highlights an entirely different approach to this alkaloid and involves a Rh(II)-catalyzed cascade reaction of bis(diazo) imide **1**.[8−10] Over a period of years, our research group has made extensive use of the rhodium(II)-catalyzed reaction of α-diazo carbonyl compounds as a method to generate various aza-containing carbonyl ylide dipoles such as isomünchnones.[11] A subsequent intramolecular dipolar cycloaddition was then employed to assemble the azapolycyclic framework of many different classes of alkaloids.[12] Should the reaction of bis(diazo) imide **1** with 4-methylenehexan-1-amine proceed in the manner that was encountered with several alkenyl substituted alcohols[10] (vide infra), compound **2** would be formed. Treatment of either **2** or an *N*-protected derivative with a Rh(II) catalyst was expected to give rise to cycloadduct **3** (Scheme 1). We believed that it would be possible to convert **3** to mersicarpine (**4**) following along the synthetic lines we had already worked out in our laboratory for an aspidophytine synthesis.[13] With this in mind, we set out to examine a number of related model systems to probe whether this sequence of reactions could be employed for an eventual synthesis of mersicarpine.

RESULTS AND DISCUSSION

Our initial set of model studies involved the use of alkenyl alcohols in order to establish the desired insertion/cyclo-

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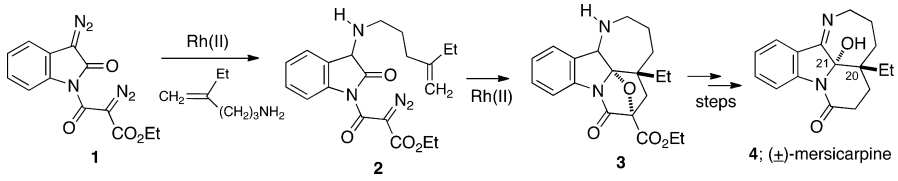
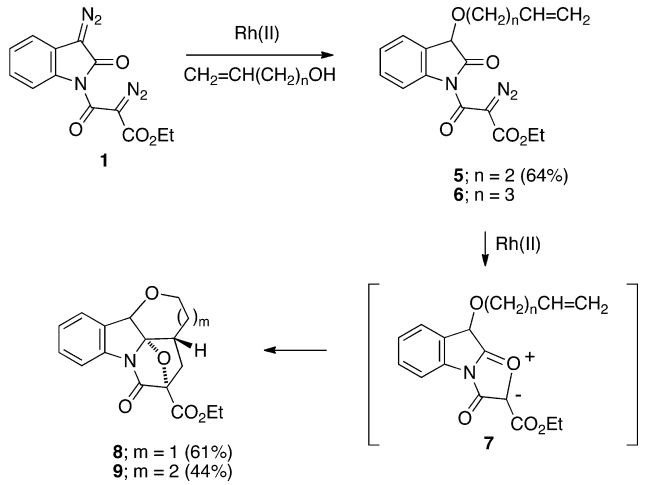
Scheme 1



addition cascade sequence. The reaction of **1** with but-3-en-1-ol in the presence of catalytic $Rh_2(OPiv)_4$ afforded the expected OH-insertion product **5** (n = 2) in 64% yield. When the same reaction was carried out in refluxing benzene, cycloadduct **8** was isolated in 61% yield, and its formation involves generation of the transient isomünchnone **7** from **5** followed by a subsequent intramolecular dipolar cycloaddition of this reactive 1,3-dipole (Scheme 2). We were pleased to note that the same sequence

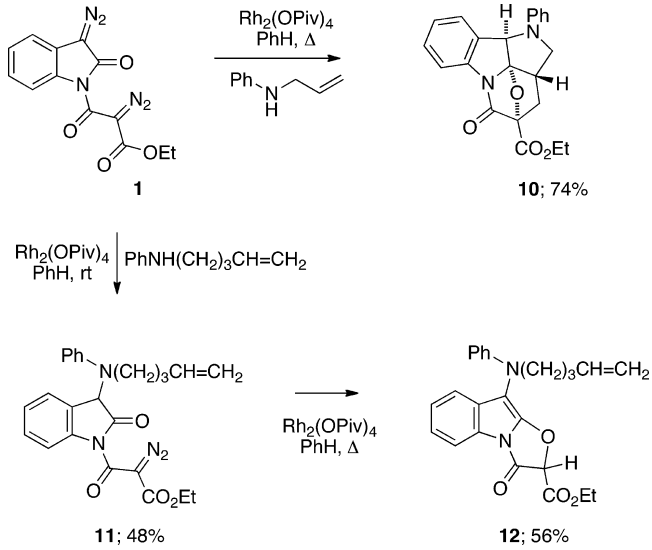
Scheme 2



of reactions occurred when bis(diazo) compound **1** was treated with pent-4-en-1-ol in refluxing benzene in the presence of the rhodium(II) catalyst. In this case, the seven-membered cycloadduct **9** was isolated in 44% yield, thereby establishing the feasibility of the desired cascade sequence that we hoped to use for an eventual synthesis of mersicarpine (**4**).

In order to further expand the scope of the Rh(II)-catalyzed insertion/cycloaddition cascade, an analogous sequence was carried out using *N*-allylaniline for the initial insertion reaction with bis(diazo) imide **1**. Since this particular Rh(II)-catalyzed reaction was carried out in refluxing benzene, the expected amine derived from insertion of the rhodium carbenoid into the NH bond was not detected. Instead, the initially formed insertion product simply underwent a very rapid cyclization/cycloaddition cascade to produce cycloadduct **10** in 74% isolated yield (Scheme 3). An analogous reaction was also carried out at room temperature using *N*-(pent-4-en-1-yl)aniline for the initial insertion with bis(diazo) imide **1**. Under these conditions, the amino-substituted diazo indolinone **11** was obtained in 48% yield. However, when **11** was heated at reflux in benzene in the presence of $Rh_2(OPiv)_4$, the only product (56%) that was isolated corresponded to oxazolo[3,2-*a*]indol-3(2*H*)-one **12**. All of our efforts to detect or isolate an intramolecular cycloadduct analogous to **9** or **10** failed, as there was no indication of its presence in the crude reaction mixture. Most likely a low rate of intramolecular cycloaddition due to

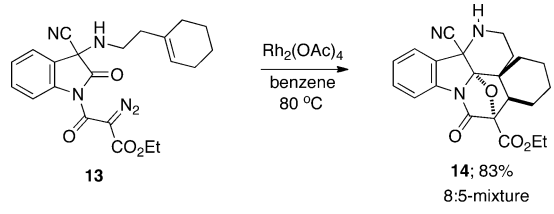
Scheme 3



unfavorable entropic factors in the transition state of the cycloaddition reaction results in a preferred proton exchange of the 1,3-dipole, giving rise to compound **12**. The difference in the Rh(II)-catalyzed behavior of ether **6**, which results in the formation of the seven-membered cycloadduct **9**, versus amine **11**, which affords **12**, is rather subtle and requires additional study in order to determine the reactivity disparity.

With the knowledge that the reaction of α-diazo amide **1** with *N*-allylaniline results in a facile Rh(II)-catalyzed cyclization/intramolecular dipolar cycloaddition cascade, we subsequently found that a 3-amino substituted α-diazo dihydroindolinone such as **13** also undergoes a related Rh(II)-catalyzed cyclization/cycloaddition cascade to furnish the azapolycyclic ring system **14** in 83% yield as a 8:5 mixture of diastereomeric cycloadducts (Scheme 4).[14] Although we did

Scheme 4



not probe the further chemistry of the resulting cycloadduct mixture, we assume that it should be possible to induce the loss of HCN and thereby generate the key imino group that is present in the alkaloid mersicarpine (**4**).

Since α-diazo-substituted dihydroindolinone **13** underwent such a smooth Rh(II)-catalyzed cycloaddition, we embarked on a further study of this type of reaction using α-amino nitrile **17**

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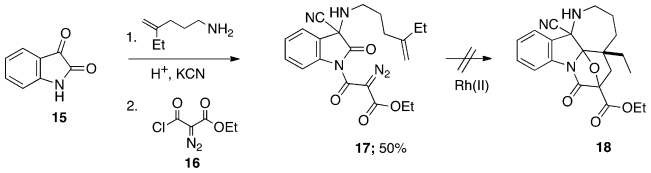
as the key substrate for the Rh(II)-catalyzed cascade with the hope of assembling all of the critical rings of mersicarpine in a one-pot procedure (Scheme 5). The preparation of **17** started

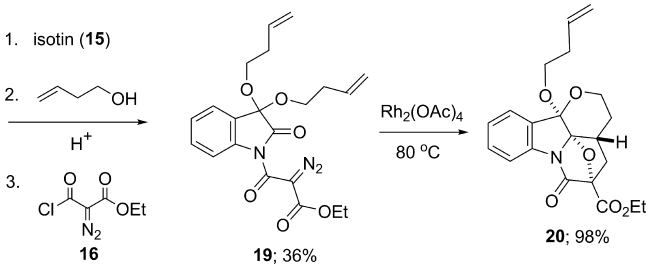
Scheme 5



with the generation of a transient imine formed by a reaction between isatin and the known 4-methylenehexan-1-amine.[15] Trapping of the initially formed imine with KCN followed by acylation with ethyl 2-diazomalonyl chloride (**16**)[16] delivered the desired α-diazo dihydroindolinone **17** in 50% yield. Unfortunately, the reaction of **17** with a variety of rhodium(II) catalysts did not produce the desired cycloaddition adduct **18**. Once again it would seem that formation of the seven-membered ring required for the dipolar cycloaddition reaction is entropically disfavored in the transition state and other competitive reactions occur instead.

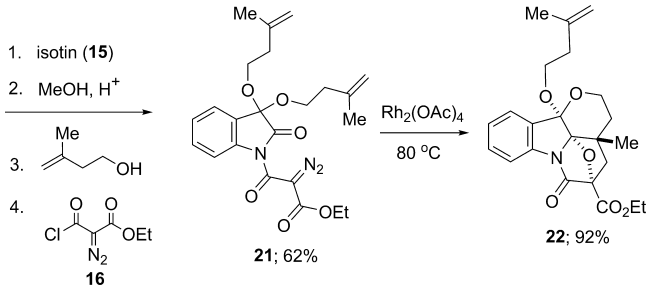
In order to promote the Rh(II)-catalyzed cyclization/cycloaddition cascade, α-diazo dihydroindolinone **19** containing a smaller alkenyl side chain was prepared with the expectation that the involvement of a six-membered-ring transition state for the intramolecular cycloaddition would be more likely to occur because of conformational factors. Our hope was that the resulting ketal functionality present in cycloadduct **20** would serve as a handle for the eventual introduction of the imino group that is necessary for a mersicarpine synthesis. Indeed, compound **19** was easily prepared by the reaction of isatin with but-3-en-1-ol followed by an acylation with **16**. Most satisfactorily, exposure of **19** to catalytic amounts of rhodium(II) acetate in benzene at 80 °C for 1 h afforded the desired cycloaddition product **20** in nearly quantitative yield as a single diastereomer (Scheme 6).

Scheme 6



One of the key synthetic challenges that must be solved for a synthesis of mersicarpine lies in the construction of the two adjacent quaternary carbon centers (C_{20} and C_{21}),[1] and whichever method is used should also proceed with high diastereoselectivity. In order to probe the feasibility of using the Rh(II)-catalyzed cascade sequence for a stereoselective synthesis of the C_{20} and C_{21} quaternary carbon centers of mersicarpine, α-diazo dihydroindolinone **21** was chosen as another model substrate (Scheme 7). Treatment of isatin with acid in MeOH provided the expected dimethyl ketal, which was then submitted to a ketal exchange using 3-methylbut-3-en-1-

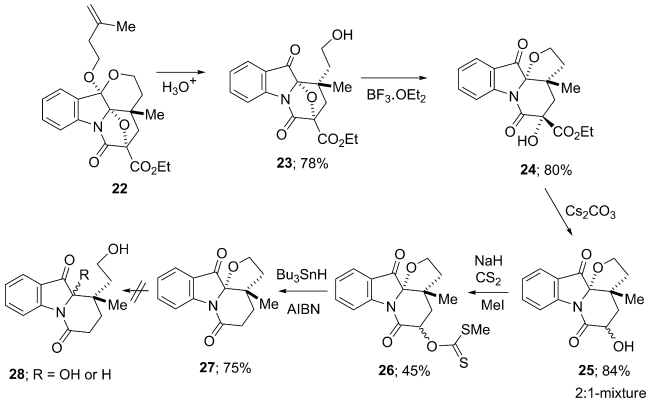
Scheme 7



ol; this was followed by acylation with **16** to deliver **21**, now containing a disubstituted alkenyl tethered side chain. We were please to find that when **21** was treated with the rhodium(II) acetate catalyst, the pentacyclic cycloadduct **22** was isolated in 92% yield (Scheme 7). Most importantly, cycloadduct **22** possesses the required stereochemistry of the two adjacent quaternary carbon centers present in mersicarpine. Notably, this particular cascade reaction enabled the rapid assemblage of a polycyclic ring system containing three new stereocenters and three continuous quaternary carbons in a single operation in high yield with excellent diastereoselectivity.

With cycloaddition product **22** in hand, we next examined its hydrolysis, which was found to furnish the primary alcohol **23** in 78% yield (Scheme 8). A Lewis acid-mediated oxabicyclic

Scheme 8



ring cleavage was then carried out using $BF_3{\cdot}Et_2O$ under refluxing conditions to afford α-hydroxy ester **24**. This reaction presumably involves an initial oxabicyclic ring opening to generate a transient iminium ion intermediate, which then reacts with the neighboring primary alcohol to give **24**. α-Hydroxy ester **24** was subsequently converted into the corresponding secondary alcohol **25** as a 2:1 mixture of inseparable diastereomers in 84% yield. This base-mediated reaction proceeds by an α-hydroxy ester rearrangement/hydrolysis cascade.[17,18] The mixture of diastereomeric alcohols **25** was easily converted to xanthate **26**, and this was followed by a facile Barton–McCombie deoxygenation[19] to produce tetracyclic 3-indolinone derivative **27**, which contains the tricyclic core of mersicarpine (Scheme 8). Most unfortunately, all of our efforts to induce opening of the tetrahydrofuran ring of **27** under either reductive or acidic conditions led to the complete decomposition of the starting material without a trace of the desired ring-opened alcohol **28**.

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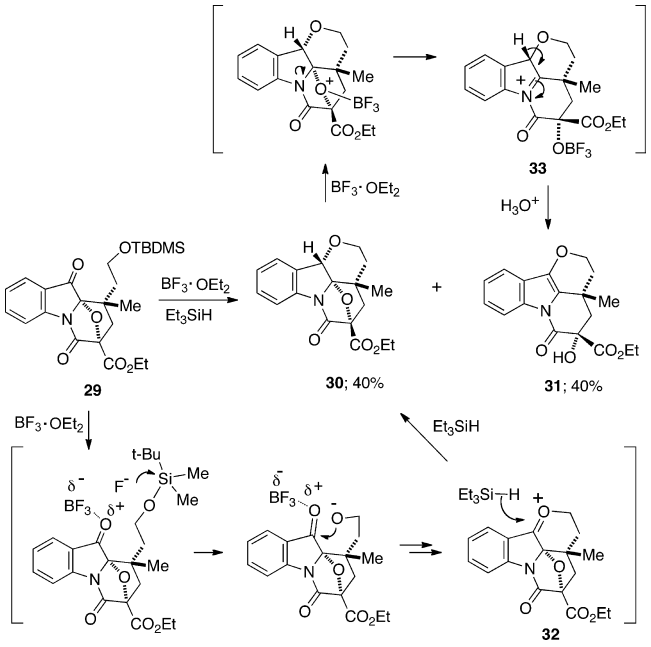
Intramolecular reductive cyclizations represent a powerful tool for the synthesis of heterocycles and natural products.[20] With this type of cyclization reaction in mind, we treated TBDMS-protected alcohol **29** derived from **23** with $BF_3{\cdot}Et_2O$/Et_3SiH at room temperature to produce a 1:1 mixture of products: in addition to the reductive cyclization product **30** (40%), indole **31** was also isolated in 40% yield (Scheme 9).

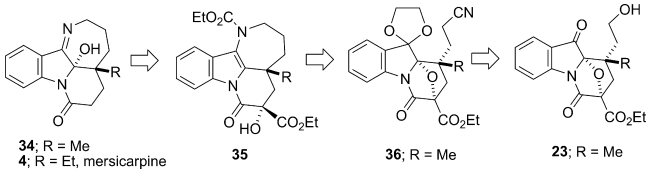
Scheme 9



We believe that tetrahydropyran derivative **30** arises by fluoride-mediated deprotection of TBDMS ether **29** followed by an intramolecular cyclization to eventually deliver the cyclic oxonium ion intermediate **32**, which is then reduced by Et_3SiH. The formation of indole **31** most likely occurs by a Lewis acid-mediated oxabicyclic ring cleavage of **30** to afford transient iminium intermediate **33**, which undergoes subsequent aromatization by loss of a proton.

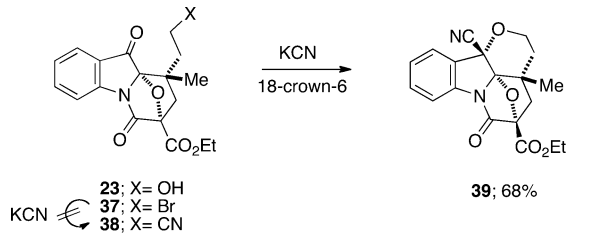
Inspired by the reductive cyclization/ring-opening aromatization cascade of **29**, we envisioned that a demethylated derivative of mersicarpine (i.e., **34**) could be obtained from α-hydroxy indolyl ester **35** and that this approach would serve as a model system for an eventual synthesis of mersicarpine. In principle, indole **35** could be prepared by the reduction of nitrile **36** to a primary amine followed by a similar sequence of reactions as outlined in Scheme 9. We expected that compound **36** would be quickly assembled from alcohol **23** by conversion of the OH group into a nitrile, and this would be followed by reduction of the cyano group and further transformation to give compound **35** (Scheme 10).

Scheme 10



Our attempted synthesis of nitrile **36** commenced by a standard bromination of alcohol **23** making use of the Appel reaction.[21] Unfortunately, exposure of the resulting bromide **37** to KCN did not provide the desired nitrile **38**. Instead, the unexpected cyclization product **39** was isolated in 68% yield (Scheme 11). The formation of **39** presumably proceeds by an

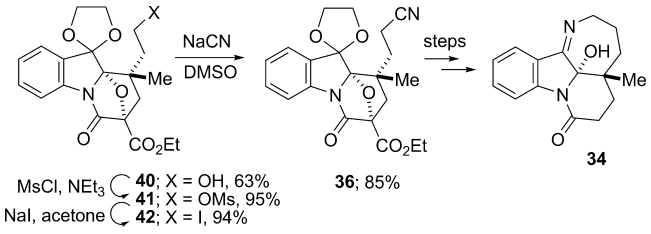
Scheme 11



initial nucleophilic addition of cyanide anion to the reactive carbonyl group of **37** to form an alkoxy anion that reacts further by an S_N2 displacement of the tethered alkyl bromide to furnish the tetrahydropyran ring present in structure **39**.

To inhibit this undesired reaction, alcohol **23** was first converted into the cyclic ketal **40** under acidic conditions in 63% yield (Scheme 12). Mesylation of **40** with MsCl and Et_3N

Scheme 12



followed by an S_N2 displacement reaction of the resulting mesylate **41** with NaI furnished iodide **42**. Subsequent cyanation of **42** using NaCN delivered **36** in 85% yield. With the key intermediate **36** in hand, our plan is to carry out a reduction of the nitrile group and then apply the reductive cyclization/ring-opening aromatization cascade (Scheme 9) toward an eventual synthesis of demethylmersicarpine **34**.

■ CONCLUSION

Model studies dealing with a rhodium(II)-catalyzed carbenoid cyclization/cycloaddition cascade of α-diazo dihydroindolinones have been carried out as an approach to the alkaloid mersicarpine. The model cascade sequence proceeds in high yield with excellent diastereoselectivity to afford intramolecular cycloadducts. The 3-indolinone derivative **36** was eventually formed from cycloadduct **22** by an acid-induced hydrolysis of **22** to give **23**, which was subsequently converted in several steps to **36**. The synthesis of this compound constitutes a successful construction of the tricyclic core of mersicarpine. Reduction of the nitrile group of **36** followed by a reductive cyclization/ring-opening aromatization cascade, as was found to occur with the related compound **29**, will be employed for an eventual synthesis of demethylmersicarpine.

■ EXPERIMENTAL SECTION

General Procedures. Melting points are uncorrected. Mass spectra were obtained at an ionizing voltage of 70 eV. Unless

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otherwise noted, reactions were performed in flame-dried glassware under an atmosphere of either dry nitrogen or argon. All solvents were distilled prior to use. Solutions were evaporated under reduced pressure with a rotary evaporator, and the residue was chromatographed on a silica gel column (0.04−0.062 mm) using an ethyl acetate/hexane mixture as the eluent unless specified otherwise. All solids were recrystallized from ethyl acetate/hexane for analytical data. Yields refer to isolated, spectroscopically pure compounds.

1-(Ethyl diazomalonyl)-3-diazoindolin-2-one (1). A sample of 3-diazoindolin-2-one[22] (1.2 g, 7.55 mmol) was dissolved in THF (38 mL), and the solution was cooled in an ice/water bath. A sample of NaH (604 mg, 60% dispersion in mineral oil, 15.1 mmol) was added in one portion, and the resulting suspension was allowed to stir for 10 min. Ethyl 2-diazomalonyl chloride (**16**)[16] (2.0 g, 11 mmol) was then added, and the mixture was allowed to stir for 30 min. The solution was concentrated under reduced pressure, and the combined extracts were washed with water followed by brine. The solution was dried over anhydrous magnesium sulfate, filtered, and concentrated to give an orange solid. The crude product was purified by crystallization to furnish 1.68 g (74% yield) of the title compound as orange crystals. Mp 117−118 °C; IR (film) 2983, 2140, 2105, 1713, 1663, 1605, and 1464 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, 3H, J = 7.2 Hz), 4.30 (q, 2H, J = 7.2 Hz), 7.17−7.25 (m, 3H), and 7.63−7.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 62.3, 62.8, 72.3, 114.7, 116.6, 118.1, 125.1, 126.4, 130.6, 160.0, 160.7, and 165.1; HRMS calcd for $[C_{13}H_9N_5O_4 + Na]^+$ 322.0547, found 322.0547.

3-(But-3-en-1-oxy)-1-(ethyl diazomalonyl)indolin-2-one (5). Bis(diazo) compound **1** (100 mg, 0.33 mmol), dichloromethane (6.7 mL), 3-buten-1-ol (86 μL, 1.0 mmol), and $Rh_2(OPiv)_4$ (1 mg, 0.002 mmol) were added sequentially to a 25 mL flask. The resulting orange solution was allowed to stir at rt under a nitrogen atmosphere for 30 min. The yellow solution was concentrated under reduced pressure, and the residue was purified by flash column chromatography to give 73 mg (64% yield) of the title compound **5** as a pale-yellow oil. IR (neat) 2980, 2139, 1766, 1724, 1659, 1609, 1480, and 1466 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, 3H, J = 7.1 Hz), 2.38−2.45 (m, 2H), 3.68 (dt, 1H, J = 8.9 and 6.6 Hz), 3.87 (dt, 1H, J = 8.9 and 6.6 Hz), 4.24−4.33 (m, 2H), 5.05−5.17 (m, 2H), 5.11 (s, 1H), 5.84 (ddt, 1H, J = 17.1, 10.3, and 6.7 Hz), 7.21 (t, 1H, J = 7.5 Hz), 7.37 (t, 1H, J = 8.0 Hz), 7.44 (d, 1H, J = 7.5 Hz), and 7.62 (d, 1H, J = 8.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.5, 34.4, 62.3, 68.8, 76.2, 114.5, 117.0, 124.8, 125.3, 125.5, 130.4, 134.9, 140.0, 160.2, 160.5, and 174.0; HRMS calcd for $[C_{17}H_{17}N_3O_5 + H]^+$ 344.1241, found 344.1248.

(3a*S*,3a^1*R*,5*R*)-Ethyl 6-Oxo-3,3a,4,5,6,11b-hexahydro-2*H*-3a^1,5-epoxybenzo[*b*]pyrano[4,3,2-*hi*]indolizine-5-carboxylate (8). Bis(diazo) compound **1** (30 mg, 0.1 mmol) was dissolved in benzene (2.0 mL), and homoallyl alcohol (8.6 μL, 0.10 mmol) followed by $Rh_2(OPiv)_4$ (0.3 mg) was added. The resulting orange solution was heated to reflux for 2 h, and the yellow solution was allowed to cool to rt and concentrated under reduced pressure. Purification by flash column chromatography gave 20 mg (61% yield) of the title compound **8** as a pale-yellow oil. IR ($CDCl_3$ film) 2980, 2871, 1733, 1607, 1467, 1479, and 1306 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, 1H, J = 7.1 Hz), 1.59−1.70 (m, 1H), 2.01 (dd, J = 12.8 and 4.0 Hz), 2.09−2.19 (m, 1H), 2.46−2.55 (m, 1H), 2.65 (dd, 1H, J = 12.8 and 8.1 Hz), 3.84−4.00 (m, 2H), 4.34−4.46 (m, 2H), 5.38 (s, 1H), 7.16 (t, 1H, J = 7.4 Hz), 7.36 (t, 1H, J = 7.5 Hz), 7.41 (d, 1H, J = 7.7 Hz), and 7.46 (d, 1H, J = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 27.1, 34.5, 36.2, 62.7, 62.8, 75.6, 90.8, 101.5, 114.1, 125.3, 127.0, 130.86, 130.93, 137.7, 165.0, and 165.2; HRMS calcd for $[C_{17}H_{17}NO_5 + H]^+$ 316.1180, found 316.1178.

(4a*S*,4a^1*R*,6*R*)-Ethyl 7-Oxo-2,3,4,4a,5,6,7,12*b*-octahydro-4a^1,6-epoxybenzo[*b*]oxepino-[4,3,2-*hi*]indolizine-6-carboxylate (9). Bis(diazo) compound **1** (75 mg, 0.25 mmol) was dissolved in benzene (5.0 mL), and 4-penten-1-ol (26 μL, 0.25 mmol) followed by $Rh_2(OPiv)_4$ (0.8 mg) was added. The resulting solution was heated to reflux for 3 h, and the solution was allowed to cool to rt and concentrated under reduced pressure. Purification by flash column chromatography gave 36 mg (44% yield) of the title compound **9** as a white solid. Mp 121−123 °C; IR (film) 2925, 1747, 1607, 1482, and 1466 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, 3H, J = 7.1 Hz), 1.75−1.92 (m, 5H), 2.74 (dd, 1H, J = 12.8 and 8.1 Hz), 2.77−2.83 (m, 1H), 3.68 (td, 1H, J = 12.0 and 1.7 Hz), 4.32−4.42 (m, 3H), 5.30 (s, 1H), 7.17 (td, 1H, J = 7.5 and 1.1 Hz), 7.34−7.37 (m, 1H), 7.41 (d, 1H, J = 7.9 Hz), and 7.45 (d, 1H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 31.5, 34.8, 35.9, 45.2, 62.6, 75.4, 83.6, 88.0, 108.5, 114.2, 125.2, 126.9, 130.5, 130.8, 139.8, 165.1, and 169.7; HRMS calcd for $[C_{18}H_{19}NO_5 + H]^+$ 330.1336, found 330.1334.

(2a*R*,2a^1*R*,4*R*,10b*S*)-Ethyl 5-Oxo-1-phenyl-2,2a,3,4,5,10b-hexahydro-1*H*-2a^1,4-epoxybenzo-[*b*]pyrrolo[4,3,2-*hi*]-indolizine-4-carboxylate (10). A catalytic amount (0.6 mg) of $Rh_2(OPiv)_4$, benzene (1.0 mL), and *N*-allylaniline (13 mg, 0.10 mmol) were added sequentially to a 10 mL flask with a side arm (which was stoppered with a septum) and equipped with a condenser. The resulting solution was heated at reflux, and a solution of bis(diazo) compound **1** (30 mg, 0.10 mmol) in benzene (1.0 mL) was added through the side arm over a 1 h period using a syringe pump. Stirring was continued at this temperature for an additional 3 h, and the solution was then concentrated under reduced pressure. Purification by flash column chromatography gave 28 mg (74% yield) of the title compound **10** as an off-white solid. Mp 196−198 °C; IR (film) 2982, 2845, 1728, 1602, 1502, and 1466 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.40 (t, 3H, J = 7.2 Hz), 2.36 (dd, 1H, J = 12.7 and 5.5 Hz), 2.61 (dd, 1H, J = 12.7 and 8.2 Hz), 2.80−2.86 (m, 1H), 3.09 (dd, 1H, J = 11.1 and 9.0 Hz), 3.97 (t, 1H, J = 8.1 Hz), 4.42 (q, 2H, J = 7.2 Hz), 6.85−6.92 (m, 3H), 7.15 (t, 1H, J = 7.6 Hz), 7.34 (t, 2H, J = 7.7 Hz), 7.34 (t, 1H, J = 7.8 Hz), and 7.63 (d, 1H, J = 7.7 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.4, 33.0, 46.2, 53.0, 60.2, 62.8, 96.2, 108.8, 113.1, 114.7, 118.7, 125.7, 127.9, 129.9, 130.4, 134.6, 135.3, 148.1, 161.8, and 164.5; HRMS calcd for $[C_{22}H_{20}N_2O_4 + H]^+$ 377.1496, found 377.1508.

Ethyl 2-Diazo-3-oxo-3-(2-oxo-3-(pent-4-en-1-yl(phenyl)-amino)indolin-1-yl)propanoate (11). $Rh_2(OAc)_4$ (3 mg, 0.007 mmol), benzene (2.8 mL), and *N*-(pent-4-en-1-yl)aniline (45 mg, 0.28 mmol) were added sequentially to a flask, and a solution of bis(diazo) compound **1** (75 mg, 0.28 mmol) in benzene (2.8 mL) at rt was added over 1 h using a syringe pump. Following the addition, the solution was concentrated under reduced pressure. Purification by flash column chromatography gave 59 mg (48% yield) of the title compound **11** as a pale-brown oil. IR (neat) 2934, 2139, 1701, 1652, 1601, 1581, 1505, and 1448 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, 3H, J = 7.2 Hz), 1.61−1.76 (m, 2H), 2.02 (q, 2H, J = 7.1 Hz), 3.11−3.34 (m, 2H), 4.27 (q, 2H, J = 7.2 Hz), 4.90−4.98 (m, 2H), 5.47 (s, 1H), 5.73 (ddt, 1H, J = 17.0, 10.3, and 6.6 Hz), 6.78−6.84 (m, 3H), 7.17 (t, 1H, J = 7.4 Hz), 7.20−7.25 (m, 2H), 7.31 (d, 1H, J = 7.4 Hz), 7.36 (t, 1H, J = 8.1 Hz), and 7.67 (d, 1H, J = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 27.3, 31.2, 49.4, 62.2, 64.7, 114.6, 115.3, 115.4, 119.1, 124.8, 125.2, 126.0, 129.5, 129.6, 138.0, 139.3, 147.9, 160.39, 160.41, and 174.4; HRMS calcd for $[C_{24}H_{24}N_4O_4 + H]^+$ 433.1870, found 433.1871.

Ethyl 3-Oxo-9-(pent-4-en-1-yl(phenyl)amino)-2,3-dihydrooxazolo[3,2-*a*]indole-2-carboxylate (12). Bis(diazo) compound **1** (30 mg, 0.10 mmol) was dissolved in benzene (2.0 mL), and *N*-(pent-4-en-1-yl)aniline (18 mg, 1.1 mmol) followed by $Rh_2(OPiv)_4$ (0.6 mg) was added. The resulting solution was heated to reflux, and after 5 h the solution was allowed to cool to rt and concentrated under reduced pressure. Purification by flash column chromatography gave 23 mg (56% yield) of the title compound **12** as a pale-yellow solid. Mp 109−111 °C; IR (neat) 2926, 1753, 1664, 1596, and 1498 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.36 (t, 3H, J = 7.1 Hz), 1.84 (pent, 2H, J = 7.5 Hz), 2.14 (q, 2H, J = 7.1 Hz), 3.69 (ABX_2, 2H, $\Delta\delta_{AB}$ = 0.03, J_{AB} = 14.5 Hz, J_{AX} = J_{BX} = 7.4 Hz), 4.37 (ABX_3, 2H, $\Delta\delta_{AB}$ = 0.02, J_{AB} = 10.7 Hz, J_{AX} = J_{BX} = 7.1 Hz), 4.96 (d, 1H, J = 10.2 Hz), 5.00 (d, 1H, J = 17.1 Hz), 5.58 (s, 1H), 5.82 (ddt, 1H, J = 17.1, 10.2, and 6.6 Hz), 6.75−6.81 (m, 3H), 7.11 (d, 2H, J = 7.6 Hz), 7.18−7.22 (m, 2H), 7.24 (t, 1H, J = 7.8 Hz), and 7.85 (d, 1H, J = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 27.3, 31.3, 51.0, 63.6, 84.8, 100.0, 113.7, 113.9, 115.3, 118.1, 119.7, 123.3, 124.7, 125.6, 129.4, 133.3, 138.2, 147.5, 149.3, 159.3, and 163.4; HRMS calcd for $[C_{24}H_{24}N_2O_4 + H]^+$ 405.1809, found 405.1804.

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Ethyl 3-(3-Cyano-3-((4-methylenehexyl)amino)-2-oxoindolin-1-yl)-2-diazo-3-oxopropanoate (17). To a 50 mL round-bottom flask charged with a solution of isatin (**15**) (1.65 g, 11.3 mmol) in ethanol (22.6 mL) were sequentially added 4-methylenehexan-1-amine[15] (1.40 g, 12.4 mmol) and two drops of glacial acetic acid. The mixture was stirred for 24 h at 25 °C. After removal of the solvent under reduced pressure, ether (20 mL) was added, and the yellow precipitate that formed was collected by filtration to furnish 1.90 g of (*Z*)-3-((4-methylenehexyl)imino)indolin-2-one, which was used without further purification. To a 10 mL round-bottom flask charged with a solution of the above imine (242 mg, 1.0 mmol) in methanol (5 mL) at 25 °C were sequentially added KCN (68 mg, 1.05 mmol) and HCl (1.25 M in methanol, 1.6 mL, 2.0 mmol). After 5 h of stirring, the mixture was quenched with aqueous NaOH (1 N, 2 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with water and brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to furnish 153 mg (50% yield) of 3-((4-methylenehexyl)amino)-2-oxoindoline-3-carbonitrile as a pale-yellow oil. IR (thin film) 2928, 1730, 1625, and 1480 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, 3H, J = 7.6 Hz), 1.65 (p, 2H, J = 7.6 Hz), 1.99 (q, 2H, J = 7.6 Hz), 2.08 (t, 2H, J = 7.6 Hz), 2.79−2.93 (m, 2H), 4.68 (s, 1H), 4.71 (s, 1H), 6.95 (d, 1H, J = 7.6 Hz), 7.16 (t, 1H, J = 7.6 Hz), 7.38 (t, 1H, J = 7.2 Hz), 7.47 (d, 1H, J = 8.0 Hz), and 7.78 (br s, 1H). This material was used in the next step without further purification.

To a 50 mL round-bottom flask charged with a solution of the above compound (128 mg, 0.47 mmol) in CH_2Cl_2 (10 mL) were sequentially added DMAP (115 mg, 0.94 mmol) and ethyl 2-diazomalonyl chloride (126 mg, 0.71 mmol). The mixture was stirred for 20 min at 25 °C. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to furnish 127 mg (82% yield) of the title compound **17** as a colorless oil. IR (thin film) 2964, 2144, 1766, 1728, 1668, and 1480 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, 3H, J = 7.6 Hz), 1.31 (t, 3H, J = 7.2 Hz), 1.65 (p, 2H, J = 7.6 Hz), 2.00 (q, 2H, J = 7.6 Hz), 2.08 (t, 2H, J = 7.6 Hz), 2.84−2.89 (m, 2H), 4.26−4.32 (m, 2H), 4.69 (s, 1H), 4.72 (s, 1H), 7.28 (t, 1H, J = 7.6 Hz), 7.46 (t, 1H, J = 7.6 Hz), 7.55 (d, 1H, J = 8.0 Hz), and 7.62 (d, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 14.5, 28.0, 28.7, 33.6, 44.0, 60.5, 62.4, 108.2, 114.7, 115.2, 124.0, 125.2, 125.9, 131.6, 139.3, 150.5, 159.8, 159.9, and 168.2; HRMS calcd for $[C_{21}H_{23}N_5O_4 + H]^+$ 410.1822, found 410.1824.

Ethyl 3-(3,3-Bis(but-3-en-1-yloxy)-2-oxoindolin-1-yl)-2-diazo-3-oxopropanoate (19). To a 10 mL round-bottom flask charged with a solution of isatin (147 mg, 1.0 mmol) in but-3-en-1-ol (2 mL, 23.4 mmol) was added anhydrous *p*-toluenesulfonic acid (PTSA) (35 mg, 0.2 mmol). The mixture was stirred for 20 h at 80 °C. After removal of the excess alcohol under reduced pressure, the resulting solution was filtered through a short plug of silica gel and concentrated under reduced pressure. The resulting residue containing 3,3-bis(but-3-en-1-yloxy)indolin-2-one was taken up in CH_2Cl_2 (6 mL), and DMAP (244 mg, 2.0 mmol) and ethyl 2-diazomalonyl chloride (265 mg, 1.5 mmol) were sequentially added. The mixture was stirred for 12 h at 25 °C. After removal of the solvent under reduced pressure at 20 °C, the residue was subjected to flash silica gel chromatography to furnish 149 mg (36% yield over two steps) of the title compound **19** as a colorless oil. IR (thin film) 2924, 2143, 1772, 1733, 1668, and 1465 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, 3H, J = 7.2 Hz), 2.36 (q, 4H, J = 6.8 Hz), 3.73−3.86 (m, 4H), 4.29 (q, 2H, J = 7.2 Hz), 5.04 (d, 2H, J = 9.6 Hz), 5.09 (dd, 2H, J = 17.2 and 1.6 Hz), 5.75−5.86 (m, 2H), 7.22 (t, 1H, J = 7.2 Hz), 7.41 (t, 1H, J = 8.0 Hz), 7.45 (d, 1H, J = 7.2 Hz), and 7.65 (d, 1H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 34.3, 62.3, 63.1, 96.8, 114.8, 117.0, 125.1, 131.1, 134.8, 139.3, 153.7, 159.9, 160.4, 169.7, and 177.2; HRMS calcd for $[C_{21}H_{23}N_3O_6 + Na]^+$ 436.1479, found 436.1480.

Ethyl 11b-(But-3-en-1-yloxy)-6-oxo-3,3a,4,5,6,11b-hexahydro-2*H*-3a^1,5-epoxybenzo[*b*]pyrano[4,3,2-*hi*]indolizine-5-carboxylate (20). To a 10 mL pressure tube charged with a solution containing the above diazo compound **19** (24 mg, 0.06 mmol) in benzene (2 mL) was added $Rh_2(OAc)_4$ (2.6 mg, 0.006 mmol). The mixture was heated at 80 °C for 1 h. After cooling to rt, the reaction mixture was concentrated under reduced pressure and subjected to flash silica gel chromatography to furnish 23 mg (98% yield) of the title compound **20** as a colorless oil. IR (thin film) 2947, 1732, 1607, and 1481 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, 3H, J = 7.2 Hz), 1.67−1.75 (m, 1H), 2.06 (dd, 1H, J = 12.8 and 7.6 Hz), 2.12−2.21 (m, 1H), 2.37−2.46 (m, 3H), 2.64 (dd, 1H, J = 12.8 and 8.0 Hz), 3.73−3.93 (m, 3H), 4.12−4.18 (m, 1H), 4.31−4.45 (m, 2H), 5.02−5.05 (m, 1H), 5.07−5.13 (m, 1H), 5.77−5.87 (m, 1H), 7.15 (td, 1H, J = 7.6 and 1.2 Hz), 7.40 (td, 1H, J = 7.6 and 1.2 Hz), 7.45 (d, 1H, J = 8.0 Hz), and 7.48 (d, 1H, J = 8.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3, 26.0, 34.3, 35.1, 36.7, 59.5, 62.6. 63.1, 90.4, 99.8, 99.9, 114.5, 117.1, 124.6, 125.8, 130.8, 131.5, 134.7, 136.3, 164.8, and 164.9; HRMS calcd for $[C_{21}H_{23}NO_6 + Na]^+$ 408.1417, found 408.1419.

Ethyl 3-(3,3-Bis(3-methylbut-3-en-1-yloxy)-2-oxoindolin-1-yl)-2-diazo-3-oxopropanoate (21). To a 250 mL round-bottom flask charged with a solution of 3,3-dimethoxyindolin-2-one (6.30 g, 32.6 mmol) in 3-methylbut-3-en-1-ol (66 mL, 652 mmol) was added anhydrous PTSA (561 mg, 3.26 mmol). The mixture was stirred for 24 h at 25 °C, filtered through a short plug of silica gel to remove PTSA, and concentrated under reduced pressure. The resulting residue containing 3,3-bis(3-methylbut-3-en-1-yloxy)indolin-2-one was taken up in CH_2Cl_2 (50 mL), and DMAP (9.54 g, 78.2 mmol) and ethyl 2-diazomalonyl chloride (8.63 g, 48.9 mmol) were sequentially added. The mixture was stirred for 12 h at 25 °C. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to furnish 8.91 g (62% yield over two steps) of the title compound **21** as a colorless oil. IR (thin film) 2969, 2139, 1772, 1704, and 1662 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.30 (t, 3H, J = 7.2 Hz), 1.73 (s, 6H), 2.31 (t, 4H, J = 7.2 Hz), 3.81−3.87 (m, 4H), 4.29 (q, 2H, J = 7.2 Hz), 4.72 (s, 2H), 4.77 (s, 2H), 7.22 (t, 1H, J = 7.8 Hz), 7.40 (t, 1H, J = 7.8 Hz), 7.45 (d, 1H, J = 7.8 Hz), and 7.65 (d, 1H, J = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.4, 22.9, 37.9, 62.2, 62.4, 112.1, 114.8, 125.0, 125.1, 125.3, 131.0, 139.3, 142.4, 159.9, 160.3, 169.8, and 173.2; HRMS calcd for $[C_{23}H_{27}N_3O_6 + H]^+$ 442.1972, found 442.1975.

Ethyl 3a-Methyl-11b-(3-methylbut-3-en-1-yloxy)-6-oxo-3,3a,4,5,6,11b-hexahydro-2*H*-3a^1,5-epoxybenzo[*b*]pyrano-[4,3,2-*hi*]indolizine-5-carboxylate (22). To a 350 mL pressure tube charged with a solution of the above diazo compound **21** (5.47 g, 12.4 mmol) in benzene (100 mL) was added $Rh_2(OAc)_4$ (273 mg, 0.62 mmol). The mixture was heated at 80 °C for 2 h. After cooling to rt, the reaction mixture was concentrated under reduced pressure and subjected to flash silica gel chromatography to furnish 4.71 g (92% yield) of the title compound **22** as a colorless oil. IR (thin film) 2939, 1735, 1607, and 1481 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.17 (s, 3H), 1.35 (t, 3H, J = 7.2 Hz), 1.74 (s, 3H), 2.01 (t, 2H, J = 7.2 Hz), 2.15 (d, 1H, J = 12.6 Hz), 2.31 (d, 1H, J = 13.2 Hz), 2.32−2.39 (m, 2H), 3.77 (td, 1H, J = 8.4 and 5.4 Hz), 3.86 (td, 1H, J = 9.0 and 6.6 Hz), 3.96 (dt, 1H, J = 11.4 and 8.4 Hz), 3.96 (dt, 1H, J = 12.0 and 6.6 Hz), 4.30−4.41 (m, 2H), 4.72 (s, 1H), 4.77 (s, 1H), 7.14 (t, 1H, J = 7.8 Hz), 7.40 (t, 1H, J = 7.8 Hz), 7.47 (d, 1H, J = 7.8 Hz), and 7.49 (d, 1H, J = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2, 23.1, 23.2, 31.6, 37.8, 41.5, 43.7, 58.4, 62.0, 62.6. 89.7, 99.3, 101.3, 112.0, 114.1, 124.5, 125.6, 131.4, 131.5, 136.9, 142.6, 164.4, and 164.9; HRMS calcd for $[C_{23}H_{27}NO_6 + H]^+$ 414.1911, found 414.1913.

Ethyl 9-(2-Hydroxyethyl)-9-methyl-6,10-dioxo-7,8,9,10-tetrahydro-6*H*-7,9a-epoxypyrido[1,2-*a*]indole-7-carboxylate (23). To a 350 mL pressure tube charged with a solution of cycloadduct **22** (3.0 g, 7.26 mmol) in acetone (150 mL) was added PTSA·H_2O (2.76 g, 14.52 mmol). The mixture was heated at 70 °C for 1 h. After cooling to rt, the reaction mixture was quenched with 100 mL of a saturated aqueous $NaHCO_3$ solution and extracted with ether. The combined organic layers were washed with water and brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to furnish 1.94 g (78% yield) of the title compound **23** as a white foam. IR (thin film) 3496, 2979, 1720, 1602, and 1467 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.35 (t, 3H, J = 7.2 Hz), 2.12 (t, 2H, J = 6.4 Hz), 2.20 (d, 1H, J = 13.2 Hz), 2.74 (d, 1H, J = 13.2 Hz), 3.89 (t, 2H, J = 6.8

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Hz), 4.37 (q, 2H, J = 7.2 Hz), 7.28 (t, 1H, J = 7.2 Hz), 7.69 (t, 1H, J = 8.0 Hz), 7.74 (d, 1H, J = 8.4 Hz), and 7.77 (d, 1H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 21.0, 38.5, 41.0, 47.9, 59.7, 62.8, 90.1, 98.5, 115.5, 125.4, 125.6, 131.3, 138.5, 148.5, 164.1, 165.8, and 189.7; HRMS calcd for $[C_{18}H_{19}NO_6 + H]^+$ 346.1285, found 346.1287.

Ethyl 5-Hydroxy-3a-methyl-6,12-dioxo-3,3a,4,5,6,12-hexahydro-2*H*-furo[2′,3′:2,3]pyrido[1,2-*a*]indole-5-carboxylate (24). To a 350 mL pressure tube charged with a solution of the above alcohol **23** (570 mg, 1.65 mmol) in CH_2Cl_2 (62 mL) was added $BF_3{\cdot}OEt_2$ (1.1 mL, 8.66 mmol). The mixture was heated at 60 °C for 18 h. After cooling to rt, the mixture was quenched with 50 mL of a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were washed with water and brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to furnish 455 mg (80% yield) of the title compound **24** as a colorless oil. IR (thin film) 3434, 2931, 1729, 1684, and 1603 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.30 (t, 3H, J = 7.2 Hz), 2.21 (ddd, 1H, J = 12.0, 7.8, and 4.2 Hz), 2.28 (d, 1H, J = 15.0 Hz), 2.48 (d, 1H, J = 14.4 Hz), 2.70 (dt, 1H, J = 12.0 and 8.4 Hz), 4.19 (td, 1H, J = 8.4 and 3.6 Hz), 4.29−4.34 (m, 4H), 7.27 (t, 1H, J = 7.8 Hz), 7.67 (t, 1H, J = 7.8 Hz), 7.74 (d, 1H, J = 7.8 Hz), and 8.40 (d, 1H, J = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.1, 22.1, 40.1, 40.4, 44.7, 63.2, 65.2. 76.1, 97.0, 118.1, 121.8, 124.8, 125.5, 137.7, 151.8, 166.7, 171.7, and 195.1; HRMS calcd for $[C_{18}H_{19}NO_6 + Na]^+$ 368.1104, found 368.1108.

5-Hydroxy-3a-methyl-3,3a,4,5-tetrahydro-2*H*-furo[2′,3′:2,3]-pyrido[1,2-*a*]indole-6,12-dione (25). To a 50 mL pressure tube charged with a solution of the above tertiary alcohol **24** (158 mg, 0.46 mmol) in CH_3CN (10 mL) were sequentially added Cs_2CO_3 (899 mg, 2.76 mmol) and distilled water (1 mL). The mixture was heated at 80 °C for 1 h. After cooling to rt, the mixture was quenched with 10 mL of a saturated aqueous NH_4Cl solution and extracted with ether. The combined organic layers were washed with water and brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to furnish 105 mg (84% yield) of the title compound **25** as a colorless oil consisting of a 2:1 mixture of inseparable diastereomers. IR (thin film) 3337, 2951, 2897, 1726, 1681, and 1602 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) major isomer δ 1.29 (s, 3H), 2.04−2.12 (m, 2H), 2.26 (t, 1H, J = 12.6 Hz), 2.82 (q, 1H, J = 10.2 Hz), 3.39 (br s, 1H), 4.12 (td, 1H, J = 10.2 and 2.4 Hz), 4.24 (q, 1H, J = 8.4 Hz), 4.37 (dd, 1H, J = 12.0 and 6.0 Hz), 7.26 (t, 1H, J = 7.2 Hz), 7.66 (t, 1H, J = 7.8 Hz), 7.73 (d, 1H, J = 7.8 Hz), and 8.37 (d, 1H, J = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) major isomer δ 18.2, 38.1, 40.0, 45.2, 64.6, 66.9. 97.0, 117.9, 122.3, 124.8, 125.4, 137.4, 151.6, 170.6, and 194.6; HRMS calcd for $[C_{15}H_{15}NO_4 + H]^+$ 274.1073, found 274.1072.

***S*-Methyl *O*-(3a-Methyl-6,12-dioxo-3,3a,4,5,6,12-hexahydro-2*H*-furo[2′,3′:2,3]pyrido[1,2-*a*]indol-5-yl) Carbonodithioate (26).** To a 10 mL round-bottom flask charged with a solution of the above alcohol mixture **25** (22 mg, 0.08 mmol) in THF (2 mL) was added NaH (60% dispersion in mineral oil, 16 mg, 0.4 mmol) at 0 °C. The solution was warmed to 25 °C and stirred at this temperature for 0.5 h. This was followed by the dropwise addition of CS_2 (24 μL, 0.4 mmol), and the solution was kept at 25 °C for 1 h. To this mixture was slowly added MeI (25 μL, 0.4 mmol). After 1 h of stirring, the mixture was quenched with 2 mL of a saturated aqueous NH_4Cl solution and warmed to rt. The solution was then extracted with ether, and the combined organic phases were washed with water and brine and dried over anhydrous $MgSO_4$. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to furnish 13 mg (45% yield) of the title compound **26** as a colorless oil. IR (thin film) 2938, 1750, 1604, and 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 3H), 2.07 (app t, 1H, J = 12.8 Hz), 2.24 (ddd, 1H, J = 12.4, 6.0, and 3.6 Hz), 2.43 (dd, 1H, J = 13.6 and 6.0 Hz), 2.66 (s, 3H), 2.77 (dt, 1H, J = 12.4 and 9.6 Hz), 4.31−4.35 (m, 2H), 6.54 (dd, 1H, J = 13.2 and 6.0 Hz), 7.24 (td, 1H, J = 7.6 and 0.8 Hz), 7.68 (td, 1H, J = 7.6 and 1.2 Hz), 7.72 (d, 1H, J = 7.2 Hz), and 8.40 (d, 1H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 23.4, 40.7, 41.5, 42.3, 66.6, 75.3, 96.7, 117.4, 121.5, 124.8, 125.1, 138.2, 151.6, 165.7, 195.8, and 216.0; HRMS calcd for $[C_{17}H_{17}NO_4S_2 + H]^+$ 364.0682, found 364.0679.

3a-Methyl-3,3a,4,5-tetrahydro-2*H*-furo[2′,3′:2,3]pyrido[1,2-*a*]indole-6,12-dione (27). To a 10 mL pressure tube charged with a solution of xanthate **26** (13 mg, 0.04 mmol) in benzene (2 mL) were sequentially added AIBN (4 mg, 0.02 mmol) and *n*-Bu_3SnH (53 μL, 0.2 mmol). The reaction mixture was heated at 80 °C for 4 h under argon. After the mixture was cooled to rt, the solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to furnish 8 mg (75% yield) of the title compound **27** as a colorless oil. IR (thin film) 2965, 1748, 1604, and 1480 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (s, 3H), 1.75−1.83 (m, 1H), 2.01−2.06 (m, 1H), 2.07−2.13 (m, 1H), 2.53 (dt, 1H, J = 16.4 and 4.8 Hz), 2.68−2.77 (m, 2H), 4.14 (app q, 1H, J = 8.4 Hz), 4.22 (td, 1H, J = 8.4 and 3.6 Hz), 7.21 (t, 1H, J = 7.6 Hz), 7.65 (t, 1H, J = 8.0 Hz), 7.70 (d, 1H, J = 7.6 Hz), and 8.41 (d, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 28.5, 32.0, 35.4, 41.7, 65.8. 76.1, 97.0, 118.1, 121.8, 124.8, 125.5, 137.7, 151.8, 166.7, 171.7, and 196.6; HRMS calcd for $[C_{15}H_{15}NO_3 + H]^+$ 258.1124, found 258.1127.

Ethyl 9-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-9-methyl-6,10-dioxo-7,8,9,10-tetrahydro-6*H*-7,9a-epoxypyrido[1,2-*a*]-indole-7-carboxylate (29). To a 10 mL round-bottom flask charged with a solution of alcohol **23** (50 mg, 0.15 mmol) in CH_2Cl_2 (3 mL) were sequentially added imidazole (21 mg, 0.3 mmol) and TBSCl (25 mg, 0.17 mmol). The mixture was stirred at 25 °C for 1.5 h. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to furnish 53 mg (77% yield) of the title compound **29** as a colorless oil. IR (thin film) 2981, 1722, 1610, and 1474 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.89 (s, 9H), 1.18 (s, 3H), 1.34 (t, 3H, J = 7.2 Hz), 2.09 (dt, 1H, J = 15.0 and 6.0 Hz), 2.12 (dt, 1H, J = 14.4 and 6.6 Hz), 2.15 (d, 1H, J = 13.2 Hz), 2.90 (d, 1H, J = 13.2 Hz), 3.85 (t, 2H, J = 6.0 Hz), 4.33−4.40 (m, 2H), 7.27 (t, 1H, J = 7.2 Hz), 7.69 (d, 1H, J = 8.0 Hz), 7.72 (t, 1H, J = 7.8 Hz), and 7.76 (d, 1H, J = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ −5.24, 14.3, 18.2, 20.5, 26.0, 38.0, 41.0, 48.1, 60.1, 62.7. 90.4, 98.6, 115.5, 125.4, 125.6, 126.5, 138.4, 148.6, 164.2, 166.1, and 189.8; HRMS calcd for $[C_{24}H_{33}NO_6Si + H]^+$ 460.2157, found 460.2158.

Ethyl 3a-Methyl-6-oxo-3,3a,4,5,6,11b-hexahydro-2*H*-3a^1,5-epoxybenzo[*b*]pyrano[4,3,2-*hi*]indolizine-5-carboxylate (30) and Ethyl 5-Hydroxy-3a-methyl-6-oxo-2,3,3a,4,5,6-hexahydrobenzo[*b*]pyrano[4,3,2-*hi*]indolizine-5-carboxylate (31). To a 10 mL round-bottom flask charged with a solution of the above TBDMS compound **29** (25 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) were sequentially added Et_3SiH (45 μL, 0.28 mmol) and $BF_3{\cdot}OEt_2$ (36 μL, 0.28 mmol) at 0 °C. The mixture was warmed to 25 °C and stirred at this temperature for 30 min. The reaction mixture was quenched with 2 mL of a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were washed with water and brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to furnish 7 mg (40% yield) of compound **30** and 7 mg (40% yield) of compound **31**.

Compound **30** was obtained as a colorless oil. IR (thin film) 2978, 2873, 1734, 1607, and 1479 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.36 (t, 3H, J = 7.2 Hz), 1.95−1.98 (m, 1H), 2.07 (ddd, 1H, J = 13.2, 9.6, and 4.8 Hz), 2.17 (d, 1H, J = 12.6 Hz), 2.27 (d, 1H, J = 13.2 Hz), 3.90−3.95 (m, 1H), 4.08−4.13 (m, 1H), 4.35−4.40 (m, 2H), 5.30 (s, 1H), 7.16 (t, 1H, J = 7.2 Hz), 7.37 (t, 1H, J = 7.2 Hz), 7.45 (d, 1H, J = 7.2 Hz), and 7.46 (d, 1H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 23.8, 32.6, 40.5, 43.7, 62.0, 62.7. 76.3, 90.0, 103.5, 113.8, 125.1, 127.0, 130.8, 131.2, 139.0, 165.2, and 165.4; HRMS calcd for $[C_{18}H_{19}NO_5 + H]^+$ 330.1336, found 330.1336.

The structure of the second fraction isolated from the column was assigned as **31**, which was obtained as a colorless oil. IR (thin film) 3430, 2923, 2852, 1732, 1686, and 1483 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.34 (t, 3H, J = 7.2 Hz), 1.37 (s, 3H), 1.84−1.92 (m, 2H), 2.03 (d, 1H, J = 13.2 Hz), 2.92 (d, 1H, J = 13.2 Hz), 4.28−4.36 (m, 2H), 4.34 (s, 1H), 4.42 (td, 1H, J = 12.0 and 3.6 Hz), 4.53 (ddd, 1H, J = 12.0, 4.2, and 1.8 Hz), 7.32 (t, 1H, J = 7.8 Hz), 7.37 (t, 1H, J = 7.2

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Hz), 7.49 (d, 1H, J = 7.8 Hz), and 8.36 (d, 1H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 26.2, 28.1, 37.0, 46.5, 62.9, 64.4, 76.3, 117.3, 117.5, 119.4, 124.0, 125.0, 125.7, 133.6, 137.2, 167.5, and 171.5; HRMS calcd for $[C_{18}H_{19}NO_5 + Na]^+$ 352.1153, found 352.1158.

Ethyl 9-(2-Bromoethyl)-9-methyl-6,10-dioxo-7,8,9,10-tetrahydro-6*H*-7,9a-epoxypyrido[1,2-*a*]indole-7-carboxylate (37). To a 50 mL round-bottom flask charged with a solution of alcohol **23** (100 mg, 0.29 mmol) in THF (4 mL) were sequentially added PPh_3 (304 mg, 1.16 mmol) and CBr_4 (385 mg, 1.16 mmol) at 0 °C. The mixture was stirred at 25 °C for 12 h. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to furnish 100 mg (85% yield) of the title compound **37** as a colorless oil. IR (thin film) 2964, 1718, 1606, and 1480 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.36 (t, 3H, J = 7.2 Hz), 2.24 (d, 1H, J = 12.8 Hz), 2.41−2.45 (m, 2H), 2.57 (d, 1H, J = 12.8 Hz), 3.41−3.48 (m, 1H), 3.61−3.67 (m, 1H), 4.38 (t, 2H, J = 7.2 Hz), 7.30 (t, 1H, J = 7.2 Hz), 7.68 (d, 1H, J = 8.4 Hz), 7.74 (t, 1H, J = 7.6 Hz), and 7.78 (d, 1H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 21.1, 28.5, 40.1, 40.6, 49.2, 63.0, 90.0, 98.2, 115.6, 125.6, 125.8, 126.3, 138.7, 148.6, 163.8, 165.8, and 189.3; HRMS calcd for $[C_{18}H_{18}NO_5Br + H]^+$ 408.0441, found 408.0444.

Ethyl 11b-Cyano-3a-methyl-6-oxo-3,3a,4,5,6,11b-hexahydro-2*H*-3a^1,5-epoxybenzo[*b*]pyrano[4,3,2-*hi*]indolizine-5-carboxylate (39). To a 10 mL round-bottom flask charged with a solution of the above bromide **37** (22 mg, 0.05 mmol) in CH_3CN (1 mL) were sequentially added 18-crown-6 (37 mg, 0.14 mmol) and KCN (4 mg, 0.06 mmol). The mixture was heated at 60 °C for 30 min and then cooled to rt. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to furnish 13 mg (68% yield) of the title compound **39** as a white solid. Mp 155−156 °C; IR (thin film) 2982, 2884, 1747, 1604, and 1477 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.35 (t, 3H, J = 7.2 Hz), 2.10−2.14 (m, 2H), 2.19 (d, 1H, J = 13.2 Hz), 2.38 (d, 1H, J = 12.6 Hz), 4.17 (dt, 1H, J = 11.4 and 9.0 Hz), 4.29 (ddd, 1H, J = 11.4, 8.4, and 3.6 Hz), 4.33−4.40 (m, 2H), 7.26 (td, 1H, J = 7.2 and 3.0 Hz), 7.48−7.51 (m, 2H), and 7.61 (d, 1H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 22.8, 31.0, 41.2, 43.1, 61.4, 62.9. 75.2, 90.0, 96.0, 102.0, 114.3, 125.9, 126.8, 128.8, 132.9, 138.7, 164.1, and 164.8; HRMS calcd for $[C_{19}H_{18}N_2O_5 + H]^+$ 355.1288, found 355.1289.

Ethyl 9-Methyl-9-(2-((methylsulfonyl)oxy)ethyl)-6-oxo-6,7,8,9-tetrahydrospiro[7,9a-epoxypyrido[1,2-*a*]indole-10,2′-[1,3]dioxolane]-7-carboxylate (41). To a 250 mL round-bottom flask charged with a solution of alcohol **23** (1.37 g, 4.0 mmol) in ethylene glycol (75 mL) was added anhydrous PTSA (688 mg, 4.0 mmol) at 25 °C. The mixture was stirred at 80 °C for 1 h. After cooling to rt, the reaction mixture was quenched with 75 mL of a saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with water and brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to furnish 974 mg (63% yield) of ethyl 9-(2-hydroxyethyl)-9-methyl-6-oxo-6,7,8,9-tetrahydrospiro[7,9a-epoxypyrido[1,2-*a*]indole-10,2′-[1,3]-dioxolane]-7-carboxylate (**40**) as a colorless oil. IR (thin film) 3485, 2970, 1731, 1604, and 1485 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.18 (s, 3H), 1.36 (t, 3H, J = 7.2 Hz), 2.01−2.06 (m, 2H), 2.18 (d, 1H, J = 13.2 Hz), 2.31 (d, 1H, J = 12.6 Hz), 3.75−3.82 (m, 3H), 3.91−3.94 (m, 1H), 4.00 (dt, 1H, J = 11.4 and 7.8 Hz), 4.21−4.25 (m, 1H), 4.32−4.41 (m, 2H), 7.15 (t, 1H, J = 7.8 Hz), 7.41 (t, 1H, J = 7.8 Hz), 7.48 (d, 1H, J = 8.4 Hz), and 7.50 (d, 1H, J = 8.4 Hz). This compound was used in the next step without further purification.

To a 250 mL round-bottom flask charged with a solution of the above alcohol **40** (529 mg, 1.36 mmol) in CH_2Cl_2 (50 mL) were sequentially added Et_3N (0.57 mL, 4.08 mmol) and MsCl (0.12 mL, 1.50 mmol) at 0 °C. The mixture was stirred for 1 h at 0 °C. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to furnish 603 mg (95% yield) of the title compound **41** as a colorless oil. IR (thin film) 2941, 1751, 1607, and 1481 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 3H), 1.35 (t, 3H, J = 6.8 Hz), 2.01−2.06 (m, 2H), 2.18 (d, 1H, J = 12.4 Hz), 2.31 (d, 1H, J = 12.8 Hz), 3.09 (s, 3H), 3.91 (ddd, 1H, J = 10.4, 5.6, and 2.8 Hz), 3.98−4.13 (m, 2H), 4.15−4.22 (m, 1H), 4.31−4.39 (m, 2H), 4.42 (dd, 1H, J = 6.0 and 2.8 Hz), 4.48 (ddd, 1H, J = 12.0, 5.6, and 2.8 Hz), 7.17 (t, 1H, J = 8.0 Hz), 7.42−7.46 (m, 2H), and 7.51 (d, 1H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 23.1, 31.6, 37.9, 41.4, 43.8, 58.7, 60.6. 62.5, 69.3, 89.6, 99.3, 100.9, 114.3, 124.7, 125.3, 130.8, 131.8, 136.8, 164.1, and 164.7; HRMS calcd for $[C_{21}H_{25}NO_9S]$ 467.1244, found 467.1246.

Ethyl 9-(2-Iodoethyl)-9-methyl-6-oxo-6,7,8,9-tetrahydrospiro[7,9a-epoxypyrido[1,2-*a*]indole-10,2′-[1,3]-dioxolane]-7-carboxylate (42). To a 150 mL pressure tube charged with a solution of mesylate **41** (785 mg, 1.68 mmol) in acetone (20 mL) was added NaI (277 mg, 1.85 mmol) at 25 °C. The mixture was heated at 80 °C for 24 h. After cooling to rt, the reaction mixture was quenched with 20 mL of a saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with water and brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to furnish 788 mg (94% yield) of the title compound **42** as a white solid. Mp 183−184 °C; IR (thin film) 2978, 1732, 1606, and 1481 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.16 (s, 3H), 1.36 (t, 3H, J = 7.2 Hz), 2.02−2.05 (m, 2H), 2.16 (d, 1H, J = 12.6 Hz), 2.32 (d, 1H, J = 12.6 Hz), 3.22−3.32 (m, 2H), 3.94−4.02 (m, 3H), 4.27−4.32 (m, 1H), 4.33−4.41 (m, 2H), 7.16 (t, 1H, J = 7.8 Hz), 7.42 (t, 1H, J = 7.8 Hz), 7.44 (d, 1H, J = 7.8 Hz), and 7.50 (d, 1H, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 2.1, 14.3, 23.1, 31.4, 41.4, 43.6, 58.8, 62.5, 64.2, 89.7, 99.3, 101.0, 114.1, 124.6, 125.3, 131.1, 131.6, 136.9, 164.2, and 164.7; HRMS calcd for $[C_{20}H_{22}NO_6I + H]^+$ 500.0564, found 500.0565.

Ethyl 9-(2-Cyanoethyl)-9-methyl-6-oxo-6,7,8,9-tetrahydrospiro[7,9a-epoxypyrido[1,2-*a*]indole-10,2′-[1,3]-dioxolane]-7-carboxylate (36). To a 100 mL round-bottom flask charged with a solution of iodide **42** (550 mg, 1.10 mmol) in DMSO (20 mL) was added NaCN (61 mg, 1.24 mmol) at 25 °C. The mixture was stirred at 25 °C for 20 h, quenched with 20 mL of distilled water, and extracted with ethyl acetate. The combined organic layers were washed with water and brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to furnish 374 mg (85% yield) of the title compound **36** a colorless oil. IR (thin film) 2979, 2899, 2158, 1751, 1607, and 1482 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.17 (s, 3H), 1.36 (t, 3H, J = 7.2 Hz), 2.03−2.08 (m, 2H), 2.17 (d, 1H, J = 12.6 Hz), 2.32 (d, 1H, J = 13.8 Hz), 2.63 (dt, 1H, J = 16.8 and 6.0 Hz), 2.71−2.77 (m, 1H), 3.83−3.86 (m, 1H), 3.98−4.04 (m, 2H), 4.29−4.40 (m, 3H), 7.16 (t, 1H, J = 7.2 Hz), 7.42−7.45 (m, 2H), and 7.51 (d, 1H, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 18.9, 22.9, 31.3, 41.4, 43.6, 58.4, 59.0, 62.6, 89.7, 99.6, 100.9, 114.2, 117.9, 124.7, 125.3, 130.5, 131.8, 137.0, 164.3, and 164.7; HRMS calcd for $[C_{21}H_{22}N_2O_6 + Na]^+$ 421.1370, found 421.1379.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR data of various key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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