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An approach toward the alkaloid (±)-mersicarpine using a rhodium(II) carbenoid cyclization–cycloaddition cascade of an α-diazo dihydroindolinone

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Dedicated with admiration and fondness to Gilbert Stork on the occasion of his 90th anniversary

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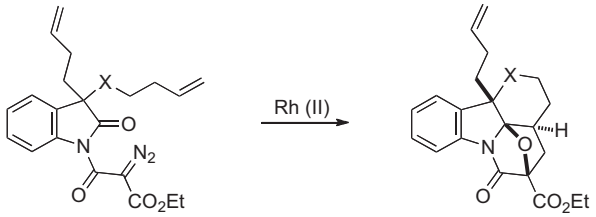
ABSTRACT

A tandem carbonyl ylide/1,3-dipolar cycloaddition cascade of α-diazo indole-2,3-dione with several different dipolarophiles was investigated. The intermolecular Rh(II)-catalyzed reaction occurs efficiently and affords dipolar cycloadducts in high yields. The analogous intramolecular reaction also takes place and gives an azapolycyclic product derived from trapping of the carbonyl ylide dipole with a tethered alkene. The power of the intramolecular cascade sequence is that it rapidly assembles polycyclic ring systems containing both multiple stereocenters and adjacent quaternary carbon centers in a single step in high yield. This cascade reaction was successfully utilized in a model study directed toward the total synthesis of mersicarpine.

1. Introduction

Developing novel strategies for the stereoselective synthesis of azapolycyclic ring systems is an ongoing quest for organic chemists.[1–7] Construction of complex nitrogen-containing heterocycles through tandem cascade chemistry[8–10] has been a fruitful area of investigation, and the synthesis of various natural products employing domino reactions has been carried out by numerous investigators.[11–14] A particularly interesting approach involves the rhodium(II)-catalyzed reaction of α-diazo carbonyl compounds to generate a carbonyl ylide dipole followed by 1,3-dipolar cycloaddition as a method to assemble the polycyclic framework of indole alkaloids.[15] This powerful cascade sequence has been successfully utilized for the construction of the *Aspidosperma*[16] and vinca alkaloids.[17] In a recent study from our laboratory using push-pull carbonyl ylide dipoles,[18] we found that α-diazo dihydroindolinones readily undergo a highly regio- and stereoselective cycloaddition cascade to furnish oxapolycyclic ring systems in high yield (Scheme 1). Interestingly, tethered alkenyl substituted ethers such as **1a** exhibited much higher reactivity than the corresponding carbocyclic system **1b**. This reactivity difference was attributed to conformational effects in the transition state for the cycloaddition reaction.[18]



1a; X = O
1b; X = CH_2

2a; X = O
2b; X = CH_2

Scheme 1.

In a further effort to explore the scope, generality, and synthetic applications of the rhodium(II) catalyzed carbenoid cyclization–cycloaddition cascade, we became interested in using this transformation as the key step in a total synthesis of the alkaloid mersicarpine. Mersicarpine (**3**) is a structurally unique natural product that was isolated from the *Kopsia* species of

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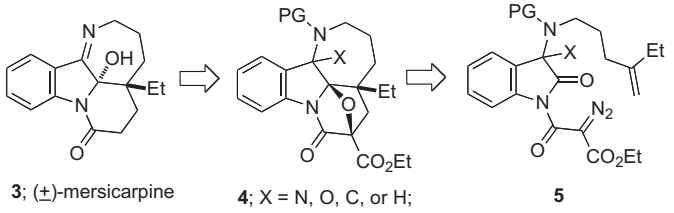
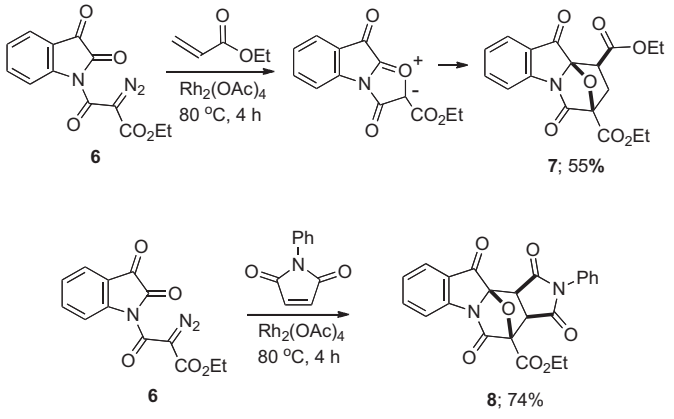
plants by Kam and co-workers in 2004.[19] It contains a seven-membered cyclic imine and an intricately oxidized indole moiety centered in the tetracyclic ring system. The first total synthesis of mersicarpine was accomplished by Kerr and co-workers via a Mn(III)-mediated malonic radical cyclization.[20] More recently, 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.[21] A formal synthesis of mersicarpine was also reported by Zard who used an intermolecular radical addition-cyclization cascade.[22] We envisioned that the core skeleton of mersicarpine could also come about by utilizing an intramolecular 1,3-dipolar cycloaddition of a carbonyl ylide dipole generated from the Rh(II)-catalyzed reaction of a masked α-diazo imino structure such as **5** (Scheme 2).



Scheme 2.

2. Results and discussion

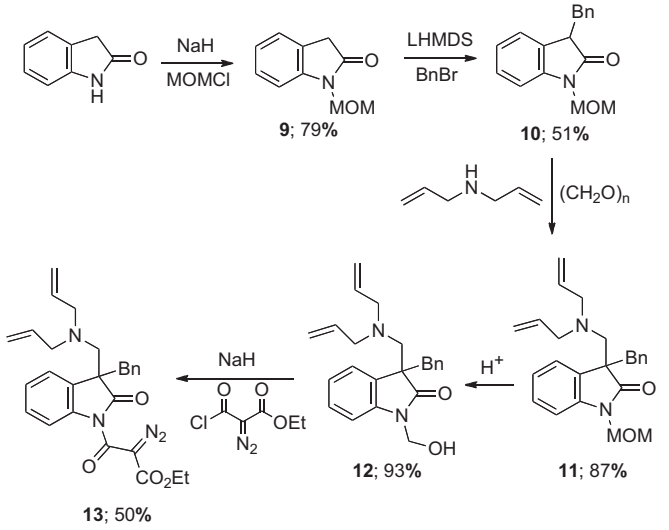
In order to establish the feasibility of this particular approach toward mersicarpine, we chose to explore the Rh(II) catalyzed cycloaddition reaction of the simpler α-diazo indole-2,3-dione **6** as a test substrate. Compound **6** was easily prepared by treating isatine with sodium hydride and ethyl 2-diazomalonyl chloride.[23] Heating **6** with ethyl acrylate in the presence of 5 mol% of $Rh_2(OAc)_4$ at 80 °C proceeded with complete regio- and diastereoselectivity and provided the cycloaddition product **7** in 55% yield (Scheme 3). In contrast to our previous study, which resulted in a mixture of four diastereomeric cycloadducts when α-diazo



Scheme 3.

dihydroindolinone was treated with methyl acrylate in the presence of a Rh(II) catalyst,[18] the high regioselectivity encountered in the cycloaddition of compound **6** with the acrylate ester can be rationalized by FMO theory.[24] The most favorable FMO interaction involves the HOMO of the carbonyl ylide dipole and the LUMO of the dipolarophile. The preferred *exo*-selectivity is associated with fewer nonbonded interactions in the transition state for the cycloaddition process. Thus, cycloadduct **7** is the preferred FMO product and is obtained as a single diastereomer from the cascade reaction. In a related manner, cycloadduct **8** was isolated in 74% yield as the *exo*-product when *N*-phenylmaleimide was used as dipolarophile.

The intramolecular dipolar cycloaddition of α-diazo dihydroindolinone **13** was next explored as a model system for an eventual approach toward mersicarpine. This compound was readily prepared from commercially available *NH*-oxindole (Scheme 4). MOM-protection of *NH*-oxindole followed by benzylation delivered the expected mono-substituted product **10**.[25] The Mannich reaction of **10** with diallylamine and paraformaldehyde delivered the aminomethylated oxindole **11**,[26] which underwent a subsequent demethylation under acidic conditions to give alcohol **12**. The required diazo functionality was then installed using ethyl 2-diazomalonyl chloride via a one-pot deprotection of the hydroxymethyl group followed by an acylation reaction to provide **13**.

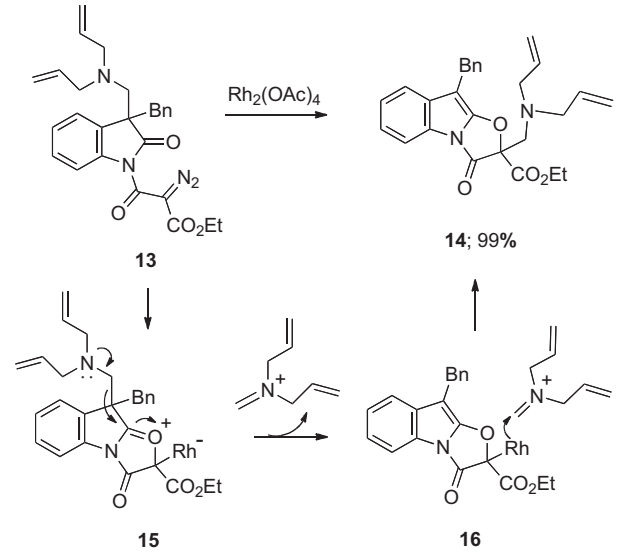


Scheme 4.

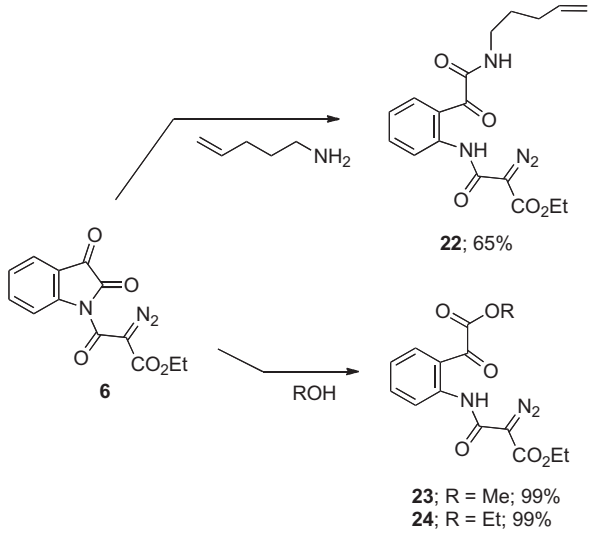
Exposure of **13** to the standard Rh(II) catalyzed cascade reaction conditions did not give the desired cycloaddition product but instead afforded the novel rearranged product **14** in quantitative yield. Compound **14** probably arises by carbonyl cyclization onto the initially formed rhodium carbenoid, followed by a retro-Mannich reaction of dipole **15** and a subsequent addition of the anionic center of **16** onto the resulting diallyliminum ion (Scheme 5).

In order to inhibit this side reaction, α-diazo dihydroindolinone **20** was prepared with the expectation that the presence of an acetyl group would diminish the electron density at the nitrogen atom and thereby retard the retro-Mannich reaction. The synthesis of **20** started with a selective mono-deallylation of oxindole **11** using $Pd(PPh_3)_4$[27] (Scheme 6). The resulting secondary amine **17** was then protected as the acetamide **18**. MOM-deprotection followed by acylation with ethyl 2-diazomalonyl chloride delivered **20** in good yield. Treatment of **20** with the rhodium acetate catalyst in benzene at 80 °C for 2 h now afforded the cycloaddition product **21** as a 2:1 mixture of inseparable diastereomers in 89% overall yield. Thus, this unique intramolecular cascade sequence rapidly assembled a pentacyclic ring system containing three new stereocenters and two adjacent quaternary centers in a single step and in high yield. Notably, the retro-Mannich/Mannich side reaction encountered with **13** was completely suppressed by the incorporation of an acetyl group on the nitrogen atom of allylacetamide **20**.

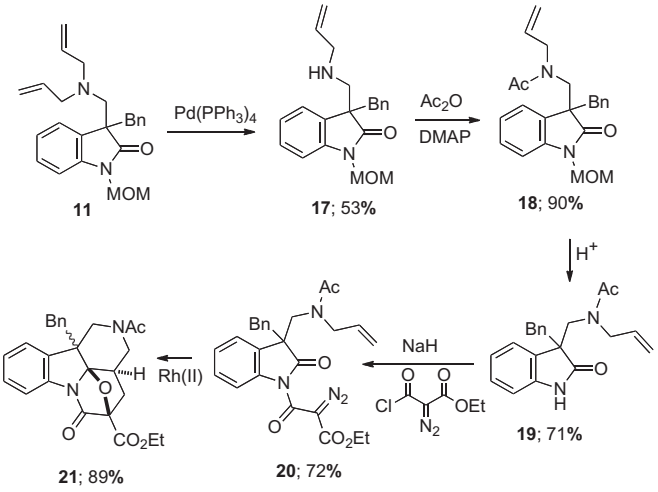
With the successful cycloaddition of 3-aminomethyl α-diazo dihydroindolinone **20** in hand, we embarked on a further



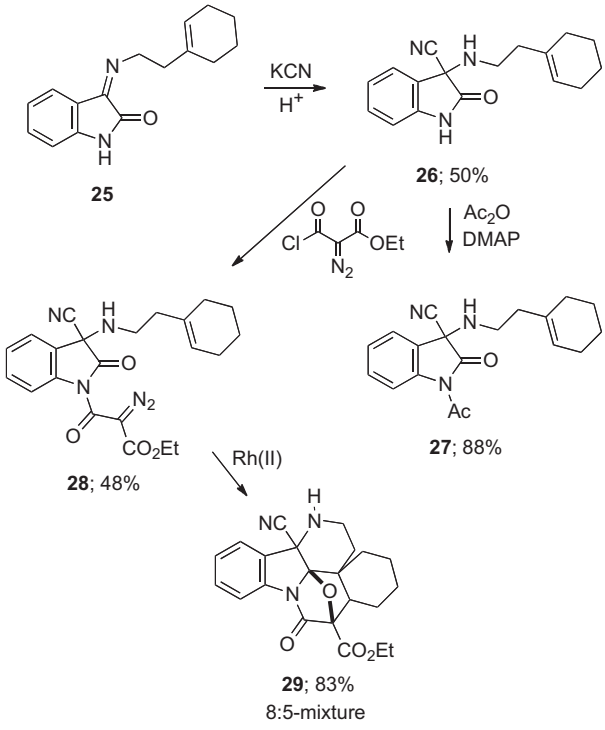
Scheme 5.



Scheme 7.



Scheme 6.



Scheme 8.

investigation to explore the intramolecular cycloaddition of several 3-imino substituted α-diazo dihydroindolinones. This study was initiated by an attempt to prepare an iminyl group in the 3-position of the oxindole ring by reacting 2-diazo-3-(2,3-dioxoindolin-1-yl)-3-oxopropanoate (**6**) with a primary amine. However, we found that the treatment of **6** with 4-pentenylamine only afforded the ring opened diazo amide **22** in 65% yield rather than the desired 3-pentenylimino-2-one. A similar ring opening reaction occurred when **6** was treated with methanol or ethanol producing esters **23** and **24**. These compounds are derived by attack of the alcohol at the more electron deficient carbonyl group corresponding to the 2-position of the indoline-2,3-dione system (Scheme 7).

The Strecker reaction has been one of the most important methods used for the synthesis of amino acids.[28,29] The α-amino nitrile product derived from the Strecker reaction of a ketimine and HCN is usually a robust compound and has been previously employed as a protected imine with a removable function handle.[30] In this spirit, we examined the reaction of imine **25** and KCN in presence of HCl in methanol. The resulting cyano amine product **26** was isolated in 50% yield (Scheme 8). Acetylation of **26** with acetic anhydride and DMAP proceeded smoothly to deliver the acetylated product **27**. Interestingly, the secondary amino group present in structure **27** was untouched in the acetylation reaction, probably due to steric hinderance around the adjacent quaternary carbon center. With this information on hand, the required diazo functionality was selectively introduced by allowing compound **26** to react with ethyl 2-diazomalonyl chloride, which afforded **28** as the exclusive product. Exposure of **28** to the standard Rh(II)-catalyzed conditions provided the polycyclic cycloaddition product **29** as an 8:5 mixture of two separable diastereomers in good yield.[31] Thus, this cascade reaction enabled us to quickly assemble a polycyclic ring system containing four new stereocenters and three continuous quaternary carbons in a single operation in high yield and we intend to use a related cycloaddition reaction for an eventual synthesis of mersicarpine.

3. Conclusion

In conclusion, an intramolecular tandem cyclization–cycloaddition reaction of an α-diazo dihydroindolinone has been employed for an efficient synthesis of a complex azapolycyclic ring system from an easily prepared substrate. 3-Amino α-diazo dihydroindolinone **28** was quickly assembled using the Strecker reaction in order to mask the sensitive imino functionality. The success of this model study provides an insightful hint for an eventual total synthesis of mersicarpine and related natural products. We are continuing to explore the scope, generality, and synthetic applications of the Rh(II)-catalyzed tandem cyclization–cycloaddition reaction of 3-amino α-diazo dihydroindolinones and will report additional findings at a later date.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on Varian Inova 600 MHz, 400 MHz spectrometers and VNMRS 400 MHz spectrometer in deuteriochloroform ($CDCl_3$) with the solvent residual peak ($CDCl_3$: ^{1}H=7.26 ppm, ^{13}C=77.23 ppm) as internal reference unless otherwise stated. Data are reported in the following order: chemical shifts are given (δ); multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), app (apparent); coupling constants, *J*, are reported (Hz). Infrared spectra were recorded on a Nicolet 510 FT-IT or ASI ReactIR 1000 spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, Georgia. Uncalibrated melting points were taken on a *Thomas-Hoover* melting point apparatus in open capillary tubes.

Analytical thin-layer chromatography (TLC) was performed on Merck silica gel glass plates with F-254 indicator. Visualization was accomplished by UV light, or with solutions of K_2CO_3/$KMnO_4$ in water, phosphomolybdic acid in ethanol, or *p*-anisaldehyde in ethanol. Solvents for reactions and chromatography were reagent grade and used as received. Solvents used as reaction media were purchased in >99% purity purged for several minutes with argon then dried and stored over 4 Å molecular sieves (water content below 10 ppm). All reactions requiring inert atmospheres were carried out under dry argon in oven-dried glassware. Bulb-to-bulb ('Kugelrohr') distillations were done on a Büchi GKR-50 Kugelrohr and boiling points (bp) correspond to uncorrected air bath temperatures. 'Brine' refers to a saturated aqueous solution of NaCl. Unless otherwise specified, solutions of NH_4Cl, $NaHCO_3$ refer to saturated solutions.

4.2. The Rh(II)-catalyzed dipolar cycloaddition

*4.2.1. Ethyl 2-diazo-3-(2,3-dioxoindolin-1-yl)-3-oxopropanoate (**6**).* To a 50 mL round-bottomed flask charged with a solution of isatin (0.26 g, 1.8 mmol) in THF (18 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 0.16 g, 4.0 mmol). After stirring for 30 min, ethyl 2-diazomalonyl chloride (0.71 g, 4.0 mmol) was added and the solution was stirred for 3 h at 23 °C. The mixture was then quenched with water and extracted with EtOAc. The combined organic layers were washed with water, brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to furnish 0.34 g (65%) of the title compound as a yellow oil. IR (thin film) 2964, 2148, 1733, 1606, and 1506 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.29 (t, 3H, *J*=7.2 Hz), 4.29 (q, 2H, *J*=7.2 Hz), 7.31 (t, 1H, *J*=7.2 Hz), 7.70 (t, 1H, *J*=7.8 Hz), 7.76 (app t, 2H, *J*=6.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.4, 62.5, 63.4, 115.9, 119.1, 125.7, 126.0, 139.0, 148.2, 156.2, 159.5, 159.9, and 180.1; HRMS calcd for [$C_{13}H_9N_3O_5-N_2+H^+$]: 260.0553; found: 260.0550.

*4.2.2. Diethyl 6,10-dioxo-7,8,9,10-tetrahydro-6H-7,9a-epoxypyrido[1,2-a]indole-7,9-dicarboxylate (**7**).* To a 10 mL pressure tube charged with a solution containing diazo **6** (28 mg, 0.1 mmol) in benzene (2 mL) were sequentially added $Rh_2(OAc)_4$ (2 mg, 0.005 mmol) and ethyl acrylate (15 mg, 0.15 mmol). The mixture was heated at reflux for 4 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and subjected to flash silica gel chromatography to furnish 20 mg (55%) of the title compound as a colorless oil; IR (thin film) 2964, 1735, 1605, and 1506 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.79 (t, 3H, *J*=7.2 Hz), 1.36 (t, 3H, *J*=7.2 Hz), 2.82 (dd, 1H, *J*=13.2 and 10.8 Hz), 2.97 (dd, 1H, *J*=13.2 and 4.8 Hz), 3.84 (dd, 1H, *J*=10.8 and 4.8 Hz), 3.86–3.90 (m, 1H), 4.01–4.06 (m, 1H), 4.39 (q, 2H, *J*=7.2 Hz), 7.31 (t, 1H, *J*=7.8 Hz), 7.62 (d, 1H, *J*=8.4 Hz), 7.71 (t, 1H, *J*=7.8 Hz), 7.84 (d, 1H, *J*=7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.5, 14.2, 31.5, 48.4, 61.9, 63.1, 91.2, 95.1, 115.7, 125.6, 125.8, 126.3, 138.1, 149.2, 163.5, 166.4, 167.9, and 188.0; HRMS calcd for [$C_{18}H_{17}NO_7$]$^+$: 359.0999; found: 359.0992.

*4.2.3. Ethyl 1,3,5,11-tetraoxo-2-phenyl-1,2,3,3a,4,5,11,11b-octahydro-4,11a-epoxypyrrolo[3′,4′:3,4]pyrido[1,2-a]indole-4-carboxylate (**8**).* To a 10 mL pressure tube charged with a solution containing diazo **6** (28 mg, 0.1 mmol) in benzene (2 mL) were sequentially added $Rh_2(OAc)_4$ (2 mg, 0.005 mmol) and 1-phenyl-1*H*-pyrrole-2,5-dione (35 mg, 0.2 mmol). The mixture was heated at reflux for 4 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and subjected to flash silica gel chromatography to furnish 32 mg (74%) of the title compound as a pale yellow oil; IR (thin film) 1769, 1724, 1604, and 1465 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, 3H, *J*=7.2 Hz), 4.32 and 4.36 (ABq, 2H, J_{AB}=13.2 Hz), 4.48 (q, 2H, *J*=7.2 Hz), 7.14–7.16 (m, 2H), 7.35 (t, 1H, *J*=7.6 Hz), 7.39–7.46 (m, 3H), 7.66 (d, 1H, *J*=8.0 Hz), 7.75 (t, 1H, *J*=8.0 Hz), 7.87 (d, 1H, *J*=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 49.1, 51.6, 64.0, 91.8, 94.7, 115.8, 125.6, 126.5, 126.6, 126.7, 129.5, 129.6, 131.0, 139.1, 148.6, 161.7, 163.1, 168.8, 169.3, and 185.7; HRMS calcd for [$C_{23}H_{16}N_2O_7+H^+$]: 433.1030; found: 433.1033.

*4.2.4. 1-(Methoxymethyl)indolin-2-one[25a] (**9**).* To a 50 mL round-bottomed flask charged with a solution of oxindole (0.53 g, 4.0 mmol) in THF (10 mL) and DMF (10 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 0.16 g, 4.0 mmol). After stirring for 30 min, MOMCl (0.40 mL, 5.2 mmol) was added and the solution was stirred for 24 h at 23 °C. The mixture was then quenched with ice water and extracted with EtOAc. The combined organic layers were washed with water, 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 0.56 g (79%) of the title compound as a pink solid: mp 71–72 °C (lit.[25a] 76–78 °C); IR (thin film) 2936, 1718, 1613, and 1486 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.35 (s, 3H), 3.61 (s, 2H), 5.13 (s, 2H), 7.02 (d, 1H, *J*=7.8 Hz), 7.07 (t, 1H, *J*=7.2 Hz), 7.26–7.29 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 36.1, 56.5, 71.4, 109.7, 123.1, 124.1, 124.6, 128.2, 143.6, and 175.8.

*4.2.5. 3-Benzyl-1-(methoxymethyl)indolin-2-one[25b] (**10**).* To a 50 mL round-bottomed flask charged with a solution of *N*-protected oxindole **9** (177 mg, 1.0 mmol) in THF (8 mL) and HMPA (1.7 mL) was added dropwise a solution of lithium bis(-trimethylsilyl)amide (1 M in THF, 1.2 mL, 1.2 mmol) at −78 °C under argon. The resulting solution was stirred at −78 °C for 1 h, and then BnBr (0.18 mL, 1.5 mmol) was added. After stirring for 2 h at −78 °C, the mixture was quenched with acetic acid (0.3 mL, 5% in THF). The reaction mixture was warmed to room temperature, and saturated aqueous $NaHCO_3$ was added followed by extraction with EtOAc. The combined organic layers were washed with water, 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 136 mg (51%) of the title compound as a pale yellow oil; IR (thin film) 2932, 1718, 1612, and 1487 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.03 (dd, 1H, J=13.2 and 8.4 Hz), 3.08 (s, 3H), 3.48 (dd, 1H, J=13.8 and 4.8 Hz), 3.82 (dd, 1H, J=8.4 and 4.2 Hz), 5.01 and 5.09 (ABq, 2H, J_{AB}=10.8 Hz), 6.89 (d, 1H, J=7.2 Hz), 6.93 (d, 1H, J=7.8 Hz), 6.98 (t, 1H, J=7.8 Hz), 7.11 (d, 2H, J=7.2 Hz), 7.17–7.23 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.8, 47.4, 56.0, 71.3, 109.5, 122.7, 124.7, 126.8, 127.9, 128.2, 128.4, 129.6, 137.5, 142.6, and 177.6.

*4.2.6. 3-Benzyl-3-((diallylamino)methyl)-1-(methoxymethyl)-indolin-2-one (**11**).* Following a literature procedure,[26] to a 50 mL round-bottomed flask charged with a solution of 3-benzyl oxindole **10** (267 mg, 1.0 mmol) in EtOAc (20 mL) were sequentially added paraformaldehyde (90 mg, 3.0 mmol) and diallylamine (291 mg, 3 mmol). The mixture was stirred for 72 h at 50 °C. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to furnish 326 mg (87%) of the title compound as a yellow wax-like solid; IR (thin film) 2930, 1714, 1640, and 1488 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.89 (s, 3H), 2.91–2.93 (m, 4H), 3.03–3.10 (m, 3H), 3.20 (d, 1H, J=13.8 Hz), 4.89 and 4.92 (ABq, 2H, J_{AB}=11.4 Hz), 4.97 (dd, 2H, J=17.4 and 1.8 Hz), 5.00 (dd, 2H, J=10.2 and 1.2 Hz), 5.49–5.55 (m, 2H), 6.81 (d, 1H, J=7.8 Hz), 6.84 (dd, 2H, J=7.2 and 1.2 Hz), 6.98–7.03 (m, 3H), 7.07 (td, 1H, J=7.2 and 0.6 Hz), 7.18 (td, 1H, J=7.8 and 1.2 Hz), 7.30 (d, 1H, J=7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.0, 55.6, 57.2, 57.8, 60.8, 71.1, 109.3, 117.1, 122.2, 126.4, 126.5, 127.7, 128.1, 130.1, 130.4, 135.5, 135.9, 143.0, and 179.3.

*4.2.7. 3-Benzyl-3-((diallylamino)methyl)-1-(hydroxymethyl)-indolin-2-one (**12**).* To a 50 mL round-bottomed flask charged with a solution of 3-aminomethyl oxindole **11** (180 mg, 0.48 mmol) in acetonitrile (18 mL) was added p-TsOH·H_2O (364 mg, 1.91 mmol). The mixture was stirred for 35 min at 85 °C. After cooling to room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed with water, 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 148 mg (93%) of the title compound as a pale yellow solid: mp 80–82 °C; IR (thin film) 3400, 2916, 1696, 1653, and 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.02 (br s, 1H), 2.94 (app t, 4H, J=6.0 Hz), 3.00 (d, 1H, J=12.8 Hz), 3.07–3.11 (m, 2H), 3.20 (d, 1H, J=14.0 Hz), 4.94–5.05 (m, 6H), 5.52–5.62 (m, 2H), 6.78–6.81 (m, 3H), 6.99–7.09 (m, 4H), 7.19 (t, 1H, J=8.0 Hz), 7.28 (d, 1H, J=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.6, 56.7, 57.9, 60.0, 63.6, 109.9, 117.2, 122.3, 124.6, 126.6, 127.7, 128.1, 130.1, 130.6, 135.6, 135.7, 142.5, and 179.4; HRMS calcd for [$C_{23}H_{26}N_2O_2$+H^+]: 363.20671; found: 363.2059.

*4.2.8. Ethyl 3-(3-benzyl-3-((diallylamino)methyl)-2-oxoindolin-1-yl)-2-diazo-3-oxopropanoate (**13**).* To a 50 mL round-bottomed flask charged with a solution of alcohol **12** (87 mg, 0.24 mmol) in THF (8 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 24 mg, 0.60 mmol). After stirring for 30 min, ethyl 2-diazomalonyl chloride (64 mg, 0.36 mmol) was added and the solution was stirred for 45 min at 23 °C. The mixture was then quenched with water and extracted with EtOAc. The combined organic layers were washed with water, brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to furnish 57 mg (50%) of the title compound as a colorless oil; IR (thin film) 2923, 2137, 1742, 1699, 1606, and 1496 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.33 (t, 3H, J=7.2 Hz), 2.87 (d, 4H, J=6.6 Hz), 3.04 (d, 1H, J=13.8 Hz), 3.09 and 3.12 (ABq, 2H, J_{AB}=13.8 Hz), 3.23 (d, 1H, J=13.2 Hz), 4.32 (q, 2H, J=7.2 Hz), 4.96 (dd, 2H, J=17.4 and 1.2 Hz), 5.01 (d, 2H, J=9.6 Hz), 5.52–5.59 (m, 2H), 6.84 (d, 2H, J=7.2 Hz), 7.05–7.09 (m, 3H), 7.15 (t, 1H, J=7.2 Hz), 7.21–7.24 (m, 2H), 7.47 (d, 1H, J=7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.5, 41.5, 57.4, 57.8, 61.3, 62.0, 114.6, 117.6, 124.3, 124.5, 127.0, 128.2, 128.4, 130.1, 130.3, 135.1, 135.3, 140.2, 158.6, 161.0, and 178.0; HRMS calcd for [$C_{27}H_{28}N_4O_4$+H^+]: 473.2183; found: 473.2182.

*4.2.9. Ethyl 9-benzyl-2-((diallylamino)methyl)-3-oxo-2,3-dihydrooxazolo[3,2-a]indole-2-carboxylate (**14**).* To a 10 mL pressure tube charged with a solution containing diazo **13** (10 mg, 0.021 mmol) in benzene (2 mL) was added $Rh_2(OAc)_4$ (0.9 mg, 0.002 mmol). The mixture was heated at reflux for 1.5 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and subjected to flash silica gel chromatography to furnish 10 mg (99%) of the title compound as a colorless oil; IR (thin film) 2923, 1769, 1668, and 1476 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.30 (t, 3H, J=7.2 Hz), 3.14 (dd, 2H, J=14.4 and 7.2 Hz), 3.21 (dd, 2H, J=14.4 and 6.6 Hz), 3.32 (d, 1H, J=15.0 Hz), 3.50 (d, 1H, J=15.0 Hz), 3.95 (s, 2H), 4.25–4.30 (m, 2H), 5.03–5.05 (m, 4H), 5.59–5.65 (m, 2H), 7.16–7.26 (m, 6H), 7.29 (d, 2H, J=7.8 Hz), 7.79 (d, 1H, J=7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2, 28.1, 55.3, 57.9, 63.1, 89.8, 96.8, 113.3, 117.9, 119.1, 122.3, 125.1, 125.8, 126.4, 128.6, 134.9, 135.8, 139.5, 152.0, 161.9, and 164.9; HRMS calcd for [$C_{27}H_{28}N_2O_4$+H^+]: 445.2121; found: 445.2120.

*4.2.10. 3-((Allylamino)methyl)-3-benzyl-1-(methoxymethyl)indolin-2-one (**17**).* To a 250 mL round-bottomed flask charged with 3-aminomethyl oxindole **11** (377 mg, 1.0 mmol), *N*,*N*′-dimethylbarbituric acid (468 mg, 3.0 mmol), and tetrakis(-triphenylphosphine)palladium(0) (23 mg, 0.02 mmol) was added degassed CH_2Cl_2 (50 mL). The mixture was stirred for 48 h at 23 °C. After removal of the solvent under reduced pressure, the residue was redissolved in ether and washed with 2.5 N NaOH aqueous solution. The organic layer was washed with water, brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting residue was subjected to flash silica gel chromatography to furnish 179 mg (53%) of the title compound as a colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 2.87 (s, 3H), 3.08–3.19 (m, 6H), 4.92 (s, 2H), 5.02 (dd, 1H, J=10.8 and 1.8 Hz), 5.07 (dd, 1H, J=17.4 and 1.2 Hz), 5.69–5.71 (m, 1H), 6.85 (app d, 3H, J=7.8 Hz), 7.00–7.04 (m, 3H), 7.10 (t, 1H, J=7.8 Hz), 7.22 (td, 1H, J=7.8 and 1.2 Hz), 7.25 (d, 1H, J=7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 41.1, 52.5, 55.2, 55.6, 56.0, 71.1, 109.5, 115.8, 122.6, 123.4, 126.6, 127.7, 128.4, 129.8, 130.0, 135.7, 136.8, 142.7, and 179.3.

*4.2.11. N-Allyl-N-((3-benzyl-1-(methoxymethyl)-2-oxoindolin-3-yl)methyl)acetamide (**18**).* To a 50 mL round-bottomed flask charged with a solution of 3-((allylamino)methyl) oxindole **17** (179 mg, 0.53 mmol) in CH_2Cl_2 (20 mL) were sequentially added DMAP (129 mg, 1.06 mmol) and Ac_2O (63 mg, 0.80 mmol). The mixture was stirred for 1.5 h at 23 °C. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to furnish 180 mg (90%) of the title compound as a white solid: mp 85–86 °C; IR (thin film) 2930, 1712, 1651, and 1611 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.88 (s, 3H), 2.77 (s, 3H), 3.14 and 3.18 (ABq, 2H, J_{AB}=13.2 Hz), 3.68–3.81 (m, 3H), 4.47 (d, 1H, J=13.8 Hz), 4.79 and 4.82 (ABq, 2H, J_{AB}=11.4 Hz), 4.95 (d, 1H, J=17.4 Hz), 5.11 (d, 1H, J=10.8 Hz), 5.56–5.62 (m, 1H), 6.74–6.77 (m, 3H), 6.95–7.03 (m, 3H), 7.11 (t, 1H, J=7.8 Hz), 7.18 (t, 1H, J=7.8 Hz), 7.52 (d, 1H, J=7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.3, 42.2, 49.8, 51.3, 55.7, 56.1, 71.4, 109.0, 116.5, 122.7, 125.3, 126.7, 127.6, 128.4, 129.9, 130.0, 132.4, 135.0, 142.2, 171.8, and 179.1.

*4.2.12. N-Allyl-N-((3-benzyl-2-oxoindolin-3-yl)methyl)acetamide (**19**).* To a 50 mL round-bottomed flask charged with a solution of MOM-protected oxindole **18** (136 mg, 0.36 mmol) in acetonitrile

(13.5 mL) was added *p*-TsOH·H_2O (274 mg, 1.44 mmol). The mixture was stirred for 35 min at 85 °C. After cooling to room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed with water, 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 85 mg (71%) of the title compound as a colorless oil; IR (thin film) 3061, 1709, 1635, and 1470 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) two rotamers δ 1.81 (s, 1.5H), 1.87 (s, 1.5H), 3.03–3.26 (m, 2H), 3.32 (br s, 1H), 3.66–3.78 (m, 2H), 4.20 (d, 0.5H, J=14.1 Hz), 4.46 (d, 0.5H, J=14.1 Hz), 4.77–5.14 (m, 2H), 5.33–5.44 (m, 0.5H), 5.55–5.65 (m, 0.5H), 6.60 (d, 0.5H, J=7.5 Hz), 6.66–6.74 (m, 1.5H), 6.79–6.89 (m, 1.5H), 6.97–7.14 (m, 2.5H), 7.18–7.23 (m, 1H), 7.22–7.24 (m, 1H), 7.35 (d, 0.5H, J=7.8 Hz), 7.42 (d, 0.5H, J=7.2 Hz), 7.70 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) two rotamers δ 21.4, 21.5, 42.3, 42.4, 49.5, 49.9, 51.0, 51.3, 56.1, 56.2, 109.3, 110.3, 116.4, 116.7, 122.3, 123.2, 125.1, 125.9, 126.5, 126.7, 127.6, 127.8, 128.3, 128.4, 128.8, 129.5, 130.1, 130.2, 132.2, 132.5, 134.9, 135.2, 140.8, 141.5, 172.0, 179.6, and 180.8; HRMS calcd for [$C_{21}H_{22}N_2O_2$+H^+]: 335.1754; found: 335.1749.

*4.2.13. Ethyl 3-(3-((N-allylacetamido)methyl)-3-benzyl-2-oxoindolin-1-yl)-2-diazo-3-oxopropanoate (**20**).* To a 50 mL round-bottomed flask charged with a solution of oxindole **19** (34 mg, 0.10 mmol) in THF (2 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 10 mg, 0.25 mmol). After stirring for 30 min, ethyl 2-diazomalonyl chloride (27 mg, 0.15 mmol) was added and the solution was stirred for 1.5 h at 23 °C. The mixture was then quenched with water and extracted with EtOAc. The combined organic layers were washed with water, brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to furnish 34 mg (72%) of the title compound as a colorless oil; IR (thin film) 2924, 2140, 1741, 1655, and 1480 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, 3H, J=7.2 Hz), 1.91 (s, 3H), 3.17 and 3.21 (ABq, 2H, J_{AB}=13.6 Hz), 3.71–3.74 (m, 2H), 3.84 (d, 1H, J=14.4 Hz), 4.26–4.33 (m, 3H), 4.99 (d, 1H, J=17.2 Hz), 5.13 (d, 1H, J=10.4 Hz), 5.58–5.65 (m, 1H), 6.74–6.76 (m, 2H), 7.02–7.11 (m, 3H), 7.18 (td, 1H, J=7.2 and 1.2 Hz), 7.22–7.24 (m, 1H), 7.39 (app t, 2H, J=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 21.4, 42.9, 50.0, 51.6, 56.3, 62.0, 114.3, 116.7, 124.6, 125.4, 127.2, 128.2, 128.7, 130.2, 132.4, 134.5, 139.6, 159.2, 160.6, 172.3, 177.9, and 180.0; HRMS calcd for [$C_{26}H_{26}N_4O_5$+H^+]: 475.1976; found: 475.1967.

*4.2.14. Ethyl 2-acetyl-11b-benzyl-6-oxo-1,2,3,3a,4,5,6,11b-octahydro-3a-1,5-epoxyindolo[3,2,1-ij][1,6]naphthyridine-5-carboxylate (**21**).* To a 10 mL pressure tube charged with a solution containing diazo **20** (14 mg, 0.03 mmol) in benzene (2 mL) was added $Rh_2(OAc)_4$ (0.7 mg, 0.0015 mmol). The mixture was heated at reflux for 2 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and subjected to flash silica gel chromatography to furnish 12 mg (89%) of the title compound as a colorless oil with dr=2:1; IR (thin film) 2928, 1752, 1733, 1652, and 1465 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) major isomer δ 1.41 (t, 3H, J=7.2 Hz), 2.04 (s, 3H), 2.29–2.36 (m, 1H), 2.56–2.66 (m, 2H), 3.09–3.16 (m, 3H), 3.74 (d, 1H, J=14.0 Hz), 3.83 (dd, 1H, J=12.4 and 5.2 Hz), 4.23 (d, 1H, J=14.0 Hz), 4.39–4.47 (m, 2H), 6.44 (d, 1H, J=7.2 Hz), 6.85 (d, 1H, J=6.8 Hz), 6.91 (td, 1H, J=8.0 and 0.8 Hz), 7.00–7.03 (m, 2H), 7.20–7.25 (m, 3H), 7.38 (dd, 1H, J=8.0 and 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 21.8, 32.5, 38.3, 40.6, 43.6, 47.6, 48.1, 62.8, 90.4, 103.7, 113.7, 124.4, 125.9, 127.0, 127.1, 128.1, 129.5, 134.6, 134.9, 135.0, 164.2, 164.8, and 170.1; HRMS calcd for [$C_{26}H_{26}N_2O_5$+H^+]: 447.1914; found: 447.1903.

*4.2.15. Ethyl 2-diazo-3-oxo-3-((2-(2-oxo-2-(pent-4-en-1-yl-amino)acetyl)phenyl)amino)propanoate (**22**).* To a 50 mL round-bottomed flask charged with a solution of pent-4-enoic acid (0.51 mL, 5.0 mmol) in CH_2Cl_2 (17 mL) at 0 °C was added Et_3N (0.70 mL, 5.0 mmol). The mixture was stirred for 10 min, and isobutyl chloroformate (0.72 mL, 5.5 mmol) was added dropwise. After stirring for 1 h at 0 °C, the reaction mixture was warmed to 23 °C and kept at this temperature for 30 min. The reaction mixture was then concentrated to 7 mL followed by the addition of ammonia (20.4 mL) at 0 °C. The mixture was stirred for 24 h at 23 °C, and then diluted with CH_2Cl_2 followed by extraction with EtOAc. The combined organic layers were washed with water, brine, and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the crude product was recrystallized from CH_2Cl_2/petroleum ether to furnish 297 mg (60%) of 4-pentenamide as a white solid: mp 105–106 °C (lit.[32] 104–106 °C); IR (thin film) 1668, 1404, and 904 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.33 (t, 2H, J=7.8 Hz), 2.41 (t, 2H, J=7.8 Hz), 5.03 (dd, 1H, J=10.2 and 1.2 Hz), 5.09 (dd, 1H, J=15.6 and 1.2 Hz), 5.48 (br s, 2H), 5.81–5.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.4, 35.0, 115.6, 137.0, and 175.5.

To a 50 mL round-bottomed flask charged with a solution of 4-pentenamide prepared as described above (297 mg, 3.0 mmol) in ether (10 mL) at 23 °C was added $LiAlH_4$ (1.0 M in ether, 6 mL, 6.0 mmol). After stirring for 24 h, the reaction mixture was cooled to 0 °C and quenched by water. The reaction mixture was filtered through Celite, washed with water, brine, and dried over $MgSO_4$. After removal of the solvent under reduced pressure at 20 °C, 4-pentenylamine (179 mg, 70%) was obtained as a colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 1.54 (quin, 2H, J=7.2 Hz), 2.09 (q, 2H, J=7.2 Hz), 2.70 (t, 2H, J=7.2 Hz), 4.97 (dd, 1H, J=11.4 and 1.2 Hz), 5.03 (dt, 1H, J=19.2 and 1.8 Hz), 5.78–5.85 (m, 1H).

To a 50 mL round-bottomed flask charged with a solution of diazo **6** (240 mg, 0.84 mmol) in CH_2Cl_2 (10 mL) at 23 °C was added the above amine (143 mg, 1.68 mmol). After stirring for 1 h, the solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to furnish 203 mg (65%) of the title compound as a pale yellow oil; IR (thin film) 2934, 2141, 1704, 1652, 1577, and 1521 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.37 (t, 3H, J=7.2 Hz), 1.71 (quin, 2H, J=7.2 Hz), 2.15 (q, 2H, J=7.2 Hz), 3.41 (t, 2H, J=7.2 Hz), 4.42 (q, 2H, J=7.2 Hz), 5.02 (d, 1H, J=11.4 Hz), 5.07 (dd, 1H, J=17.4 and 1.8 Hz), 5.78–5.85 (m, 1H). 7.06 (br s, 1H), 7.18 (t, 1H, J=7.8 Hz), 7.60 (t, 1H, J=8.4 Hz), 8.31 (d, 1H, J=7.8 Hz), 8.57 (d, 1H, J=7.8 Hz), 11.64 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 28.5, 31.2, 39.3, 62.2, 115.8, 121.2, 122.3, 123.2, 134.1, 135.7, 137.5, 140.5, 159.9, 162.3, 163.6, and 190.6; HRMS calcd for [$C_{18}H_{20}N_4O_5$+H^+]: 373.1506; found: 373.1499.

*4.2.16. Ethyl 2-diazo-3-((2-(2-methoxy-2-oxoacetyl)phenyl)-amino)-3-oxopropanoate (**23**).* To a 10 mL round-bottomed flask charged with diazo **6** (10 mg, 0.035 mmol) was added methanol (2 mL) at 23 °C. After stirring for 10 min, the solvent was removed under reduced pressure, and the title product (12 mg, 99%) was obtained as a pale yellow oil; IR (thin film) 2964, 2143, 1739, 1705, 1663, and 1558 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, 3H, J=7.2 Hz), 3.97 (s, 3H), 4.43 (q, 2H, J=7.2 Hz), 7.18 (t, 1H, J=8.0 Hz), 7.64 (t, 1H, J=7.2 Hz), 7.70 (dd, 1H, J=8.0 and 1.6 Hz), 8.77 (d, 1H, J=8.8 Hz), 11.97 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 53.0, 62.2, 119.2, 122.2, 123.2, 133.4, 136.5, 141.3, 160.6, 163.0, 164.2, and 188.9; HRMS calcd for [$C_{14}H_{13}N_3O_6$+H^+]: 320.0877; found: 320.0872.

*4.2.17. Ethyl 2-diazo-3-((2-(2-ethoxy-2-oxoacetyl)phenyl)-amino)-3-oxopropanoate (**24**).* To a 10 mL round-bottomed flask charged with diazo **6** (10 mg, 0.035 mmol) was added ethanol (2 mL) at 23 °C. After stirring for 10 min, the solvent was removed under reduced pressure, and the title product (12 mg, 99%) was obtained as a pale yellow oil; IR (thin film) 2990, 2137, 1733, 1698, 1651, and 1558 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.37 (t, 3H, J=7.2 Hz), 1.41

(t, 3H, J=7.2 Hz), 4.41–4.46 (m, 4H), 7.18 (t, 1H, J=7.8 Hz), 7.63 (t, 1H, J=8.4 Hz), 7.70 (dd, 1H, J=7.8 and 0.9 Hz), 8.77 (d, 1H, J=8.4 Hz), 11.99 (br s, 1H).

*4.2.18. (Z)-3-((2-(cyclohex-1-en-1-yl)ethyl)imino)indolin-2-one (**25**).* To a 50 mL round-bottomed flask charged with a solution of isatin (1.0 g, 6.8 mmol) in ethanol (13.6 mL) were sequentially added 2-(cyclohex-1-en-1-yl)ethanamine (0.95 mL, 6.8 mmol) and two drops of glacial acetic acid. The mixture was stirred for 4 h at 23 °C. The yellow precipitate was collected by filtration to furnish 1.26 g (73%) of the title compound as a yellow solid: mp 162–163 °C; IR (thin film) 2924, 1719, 1652, and 1614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.56–1.59 (m, 2H), 1.62–1.67 (m, 2H), 2.02–2.04 (m, 4H), 2.59 (t, 2H, J=8.0 Hz), 4.13 (t, 2H, J=8.0 Hz), 5.54 (s, 1H), 6.93 (d, 1H, J=7.6 Hz), 7.08 (t, 1H, J=7.6 Hz), 7.39 (t, 1H, J=8.0 Hz), 7.70 (d, 1H, J=7.6 Hz), 8.39 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 23.1, 25.4, 28.9, 38.9, 53.6, 112.2, 117.3, 122.7, 123.1, 127.1, 133.6, 136.6, 145.4, 155.0, and 166.1.

*4.2.19. 3-((2-(Cyclohex-1-en-1-yl)ethyl)amino)-2-oxoindoline-3-carbonitrile (**26**).* To a 10 mL round-bottomed flask charged with a solution of imine **25** (64 mg, 0.25 mmol) in methanol (5 mL) at 23 °C were sequentially added KCN (17 mg, 0.26 mmol) and HCl (1.25 M in methanol, 0.4 mL, 0.5 mmol). After stirring for 24 h, the reaction was quenched with aqueous NaOH (1 N, 2 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with water, 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 35 mg (50%) of the title compound as a pale yellow oil; IR (thin film) 3283, 2925, 1731, 1618, and 1472 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.56–1.62 (m, 4H), 1.91–2.16 (m, 6H), 2.84–2.94 (m, 2H), 5.50 (s, 1H), 6.98 (d, 1H, J=7.8 Hz), 7.14 (t, 1H, J=7.8 Hz), 7.37 (t, 1H, J=8.0 Hz), 7.45 (d, 1H, J=7.2 Hz), 9.09 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 22.9, 25.3, 28.0, 37.9, 41.9, 60.3, 111.5, 116.0, 123.9, 124.2, 125.0, 125.4, 131.4, 134.3, 140.8, and 171.8; HRMS calcd for $[C_{17}H_{19}N_3O+H^+]$: 282.1600; found: 282.1597.

*4.2.20. 1-Acetyl-3-((2-(cyclohex-1-en-1-yl)ethyl)amino)-2-oxoindoline-3-carbonitrile (**27**).* To a 10 mL round-bottomed flask charged with a solution of nitrile **26** (6 mg, 0.021 mmol) in CH_2Cl_2 (2 mL) were sequentially added DMAP (5 mg, 0.042 mmol) and Ac_2O (2.3 μL, 0.032 mmol). The mixture was stirred for 30 min at 23 °C. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to furnish 6 mg (88%) of the title compound as a yellow oil; IR (thin film) 2925, 1768, 1719, and 1465 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.61–1.63 (m, 4H), 1.91–2.15 (m, 6H), 2.70 (s, 3H), 2.76–2.90 (m, 2H), 5.49 (s, 1H), 7.32 (t, 1H, J=8.1 Hz), 7.46–7.52 (m, 2H), 8.28 (d, 1H, J=9.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 22.9, 25.4, 26.8, 28.0, 37.8, 41.8, 60.6, 115.5, 117.7, 123.6, 124.5, 124.8, 126.4, 131.8, 134.1, 140.2, 170.3 and 170.4; HRMS calcd for $[C_{19}H_{21}N_3O_2+H^+]$: 324.1706; found: 324.1703.

*4.2.21. Ethyl 3-(3-cyano-3-((2-(cyclohex-1-en-1-yl)ethyl)-amino)-2-oxoindolin-1-yl)-2-diazo-3-oxopropanoate (**28**).* To a 10 mL round-bottomed flask charged with a solution of nitrile **26** (25 mg, 0.09 mmol) in CH_2Cl_2 (4 mL) were sequentially added DMAP (22 mg, 0.18 mmol) and ethyl 2-diazomalonyl chloride (25 mg, 0.14 mmol). The mixture was stirred for 16 h at 23 °C. After removal of the solvent under reduced pressure at 20 °C, the residue was subjected to flash silica gel chromatography to furnish 18 mg (48%) of the title compound as a colorless oil; IR (thin film) 2924, 2854, 2141, 1768, 1728, 1668, and 1466 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, 3H, J=7.2 Hz), 1.54–1.65 (m, 4H), 1.91–2.16 (m, 6H), 2.84–2.89 (m, 2H), 4.23–4.34 (m, 2H), 5.49 (s, 1H), 7.29 (td, 1H, J=8.0 and 1.2 Hz), 7.46 (td, 1H, J=8.0 and 1.2 Hz), 7.54 (dd, 1H, J=7.6 and 0.8 Hz), 7.63 (d, 1H, J=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 22.5, 23.0, 25.4, 28.0, 38.0, 41.7, 60.6, 62.5, 114.8, 115.3, 124.1, 124.2, 125.2, 126.0, 131.6, 134.4, 139.4, 156.3, 159.9 and 168.4; HRMS calcd for $[C_{22}H_{23}N_5O_4+H^+]$: 422.1822; found: 422.1822.

*4.2.22. Ethyl 11b-cyano-6-oxo-2,3,4,4a,5,6,11b,12,13,14-decahydro-1H-5,7[1]-epoxybenzo[d]indolo[3,2,1ij][1,7]naphthyridine-5-carboxylate (**29**).* To a 10 mL pressure tube charged with a solution containing diazo **28** (8 mg, 0.02 mmol) in benzene (2 mL) was added $Rh_2(OAc)_4$ (0.9 mg, 0.002 mmol). The mixture was heated at reflux for 3 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and subjected to flash silica gel chromatography to furnish 6.5 mg (83%) of the title compound as a 8:5 diastereomeric mixture.

The major and less polar diastereomer is a colorless oil: IR (thin film) 3341, 2924, 1754, 1604, and 1480 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, 3H, J=7.2 Hz), 1.51–1.55 (m, 2H), 1.62–1.64 (m, 2H), 1.76–1.84 (m, 3H), 1.92 (br s, 1H), 2.02–2.06 (m, 2H), 2.14 (dd, 1H, J=12.0 and 6.6 Hz), 2.17 (ddd, 1H, J=13.2, 9.0, and 3.0 Hz), 3.20 (dd, 1H, J=19.8 and 10.2 Hz), 3.42 (t, 1H, J=10.8 Hz), 4.29–4.40 (m, 2H), 7.21 (td, 1H, J=7.8 and 1.2 Hz), 7.44 (td, 1H, J=7.8 and 1.2 Hz), 7.47 (d, 1H, J=8.4 Hz), 7.51 (d, 1H, J=7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3, 16.1, 18.9, 21.6, 24.9, 27.2, 37.7, 43.6, 49.1, 60.0, 62.6, 92.3, 103.5, 114.6, 115.9, 125.1, 125.6, 130.5, 131.8, 138.4, 164.5, and 165.8; HRMS calcd for $[C_{22}H_{23}N_3O_4+H^+]$: 394.1761; found: 394.1761.

The minor and more polar diastereomer is a colorless oil: IR (thin film) 3337, 2923, 1752, 1608, and 1480 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13–1.17 (m, 1H), 1.34 (t, 3H, J=7.2 Hz), 1.36–1.42 (m, 3H), 1.52–1.54 (m, 1H), 1.64–1.66 (m, 1H), 1.81–1.84 (m, 1H), 1.97–2.06 (m, 2H), 2.10–2.13 (m, 1H), 2.22 (dd, 1H, J=12.6 and 6.0 Hz), 4.09 (ddd, 1H, J=19.8, 9.0, and 6.6 Hz), 4.25 (dd, 1H, J=19.8 and 6.6 Hz), 4.31–4.40 (m, 2H), 7.23 (t, 1H, J=7.8 Hz), 7.48 (td, 1H, J=7.8 and 0.6 Hz), 7.59 (d, 1H, J=7.8 Hz), 7.78 (d, 1H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ14.3, 16.1, 18.9, 21.8, 22.4, 30.4, 39.9, 50.1, 50.9, 62.6, 93.1, 94.3, 103.4, 115.1, 123.2, 125.1, 127.3, 133.2, 145.5, 159.4, 165.0, and 169.8; HRMS calcd for $[C_{22}H_{23}N_3O_4+H^+]$: 394.1761; found: 394.1762.

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