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Direct 3-Acylation of Indolizines by Carboxylic Acids for the Practical Synthesis of Red Light-Releasable Caged Carboxylic Acids

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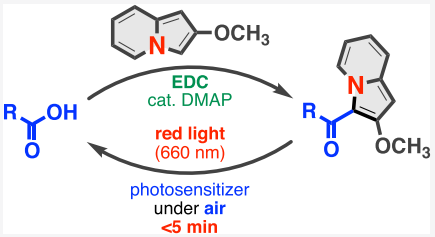
ABSTRACT: To enhance the practicality of photouncaging system using 3-acyl-2-methoxyindolizines, direct acylation of indolizines with carboxylic acids was developed using condensation reagents, generally used for peptide coupling. This method allowed for caging a broad range of carboxylic acids with indolizines. The method enabled a facile synthesis of water-soluble caged bioactive carboxylic acids having an intramolecular photosensitizer. The efficient release of carboxylic acids from the synthesized caged compounds upon red light irradiation was confirmed in neutral buffered solutions.

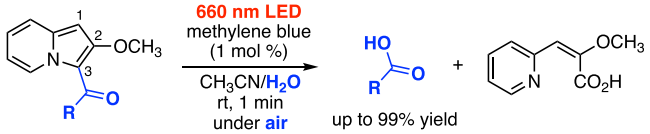


INTRODUCTION

Carboxylic acids are omnipresent in various bioactive molecules such as amino acids, lipids, natural products, and pharmaceuticals.[1] Generally, their bioactivities are triggered by the interaction of the carboxy group with the binding site of target molecules. The development of efficient protection/deprotection sequences for carboxylic acids is important for realizing the on-demand inactivation/activation of their biofunctions for practical use in prodrugs, drug delivery, and molecular biology tools. In particular, photoinduced uncaging systems have been often employed because they can release bioactive carboxylic acids at a desired position and at a specific time point simply upon activation by light irradiation.[2] For this purpose, compounds responsive to long-wavelength light are preferable for biological experiments, mainly due to the high tissue permeability of this type of light.[3] Although various ultraviolet- or visible light-responsive precursors have been developed, only a few precursors that efficiently release bioactive carboxylic acids upon irradiation of long-wavelength light have been reported so far.[4] In this context, we recently developed novel indolizine compounds that serve as light-activable precursors for the release of carboxylic acids.[5] Our study revealed that irradiation of 3-acyl-2-methoxyindolizines with a red light-emitting diode (LED; λ = 660 nm) in the presence of a catalytic amount of photosensitizer such as methylene blue triggered the photooxidation of the indolizine moiety,[6] resulting in the release of the corresponding carboxylic acid from the C3 position of the indolizine scaffold (Scheme 1).

Despite having several advantages compared with the related methods, such as the applicability of the long-wavelength light and a significantly high reaction rate, this system presents a drawback regarding the limited availability of 3-acyl-2-methoxyindolizines.[7] The acylation at the C3 position of indolizines is generally achieved by treatment with acyl chlorides.[8] However, the preparation of acyl chlorides from

Scheme 1. Photoinduced Release of a Carboxylic Acid from 3-Acyl-2-methoxyindolizine



the corresponding carboxylic acids generally requires strong acidic conditions,[9] which results in low functional group tolerance. To apply the indolizine-based photoreleasing system for bioactive carboxylic acids, which typically have complex structures with various functional groups, mild conditions are required for the acylation step. To establish a practical synthetic method for diverse 3-acyl-2-methoxyindolizines, we focused on direct acylation of 2-methoxyindolizine (**1**). Although direct electrophilic C-acylation using carboxylic acids as acyl donors has been described in the literature, such a transformation requires the use of a strong Lewis/Brønsted acid and/or high temperature (180−250 °C) to generate an acylium equivalent that is typically essential for C-acylation,[10] thereby limiting the scope of the employable carboxylic acids. The carbon at the 3 position of **1** is expected to exhibit significant nucleophilicity owing to the presence of the nitrogen atom and 2-methoxy group because C3-acylation using acyl chlorides does not require an activator such as a Lewis acid.[5] This unique reactivity inspired us to explore methods for the moderate electrophilic activation of carboxylic

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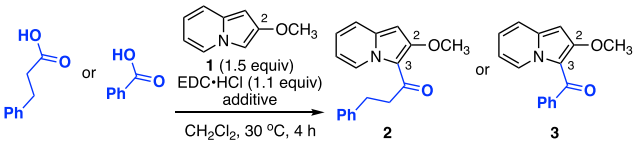
acids, such as their treatment with condensation reagents generally applied for N-acylation, to introduce an acyl group at the 3 position of **1** under neutral and mild conditions.

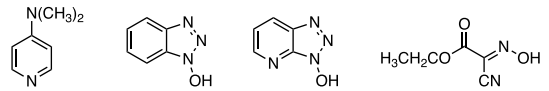
RESULTS AND DISCUSSION

Synthesis of 3-Acylindolizines. We selected 3-phenylpropanoic acid, as a model substrate to investigate the acylation of **1** using various condensation reagents, additives, and solvents (Table 1 and Table S1 for all of the screening

Table 1. C3-Acylation of 2-Methoxyindolizines (1) by Carboxylic Acids[a,b]



entry	additive (equiv)	**2** (%)[a]	**3** (%)[a]
1	DMAP (0.2), *i*-Pr$_2$NEt (1.5)	>95	>95
2	*i*-Pr$_2$NEt (1.5)	40	26
3	HOBt (0.2), *i*-Pr$_2$NEt (1.5)	67	>95
4	HOAt (0.2), *i*-Pr$_2$NEt (1.5)	88	92
5	oxyma (0.2), *i*-Pr$_2$NEt (1.5)	66	57
6	DMAP (0.2)	>95 (98)[b]	>95 (97)[b]



[a]^{1}H NMR yields. [b]Isolated yields in the parentheses.

results). We found that the combination of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl; 1.1 equiv) and a catalytic amount of 4-dimethylaminopyridine (DMAP; 0.2 equiv) in the presence of *N*,*N*-diisopropylethylamine (*i*-Pr$_2$NEt; 1.5 equiv) in dichloromethane (CH_2Cl_2) gave the desired product **2** in nearly quantitative yield (Table 1, entry 1). The addition of DMAP was critical for the effective transformation, although other nucleophilic organocatalysts, such as HOBt, HOAt, and oxyma, instead of DMAP, were also operational (entries 2−5). A similar trend was observed for the acylation using benzoic acid (**3**). Eventually, we found that the reaction proceeded in excellent yields under neutral conditions in the absence of *i*-Pr$_2$NEt (entry 6).

Next, we investigated the substrate scope of the acylation reaction (Scheme 2). Under the optimized conditions, the reactions proceeded efficiently with 4-substituted benzoic acids having various electron-withdrawing and -donating groups (Schemes 2, **4**−**10**); however, the substrates with electron-donating groups required longer reaction time (20 h) to afford the acylated products in high yields (**5** and **6**). In contrast, the reaction of 4-(hydroxymethyl)benzoic acid under the same conditions gave a poor yield of **11**. This was because indolizine **1** was less reactive for the acylation than the primary alcohol, and the formation of the corresponding ester was predominant, as demonstrated by a competition experiment (Figure S1). After reexamining the reaction conditions, acylated product **11** was obtained in 77% yield by employing 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM)[11] as a condensation reagent in methanol for 20 h (Table S2). *α*,*β*-Unsaturated carboxylic acids and isonicotinic acid containing a pyridinyl group participated in the reaction to afford the corresponding acylated products **12**−**14** in high yields. The C3-acylation using carboxylic acids having a relatively sterically hindering methyl group uneventfully gave the corresponding acylated products (**15** and **16**).

We also investigated the scope of indolizines for the C3-benzoylation. Indolizine having a sterically hindering methyl group at the 5 position was efficiently benzoylated to afford **17** in high yield. Similarly, indolizines bearing a substituent at other positions, such as 1-methyl and 6-progargyloxy derivatives, participated in the reaction to afford **18** and **19** in high yields, respectively. Notably, the terminal alkyne group remained intact when the 2-methoxy-6-(propargyloxy)-indolizine was used in the reaction affording **19**. Furthermore, 2-phenyl and 2-methylindolizines were successfully acylated by extending the reaction time and elevating the reaction temperature to afford **20** and **21** in moderate yields.

The excellent tolerance of the acylation to various functional groups prompted us to examine the acylation using functional carboxylic acids comprising various functionalities. We found that the reactions of various bioactive compounds and a polyethylene glycol (PEG) derivative containing a carboxylic acid proceeded uneventfully to give the corresponding indolizine adducts with *N*-Boc-phenylalanine (**22**), *N*-benzoylglycylglycine (**23**), cholic acid (**24**), indomethacin (**25**), and PEG (**26**) derivatives. For carboxylic acids that were insoluble in dichloromethane, *N*,*N*-dimethylformamide (DMF) was used as the solvent that provided the products with comparable efficiency (**23** and **24**). Particularly, the preparation of **22**, which could not be achieved by the conventional method via the formation of the acid chloride owing to the instability of the Boc group under acidic conditions, demonstrates the synthetic utility of our method (Figure S2). Furthermore, we confirmed that racemization at the *α* position of **22** did not occur during the acylation (>99% ee). Thus, this reaction was found to be convenient to introduce a variety of bioactive compounds having chiral centers into indolizines. To demonstrate the scalability, we performed the reaction using 2.0 mmol of indomethacin, which afforded 0.95 g of **25** (97% yield).

To gain insight into the mechanistic aspects of the reaction, we performed the following experiments. The treatment of **1** with EDC·HCl in the absence of a carboxylic acid afforded indolizine adduct **I** in almost quantitative yield (Scheme 3A). The subsequent addition of benzoic acid and DMAP to the solution containing **I** did not provide acylated product **3**, suggesting that EDC·HCl first reacts with the carboxylic acid to produce an activated ester, similar to conventional condensation reactions.[12] The ester could smoothly react with DMAP to afford urea **II** and acylpyridinium species **III**, which is a plausible intermediate for the acylation (Scheme 3B).[13]

The electrophilic addition of **III** to the 3 position of **1** with the concomitant regeneration of DMAP and deprotonation provides the acylated products, while urea **II** captures the liberated proton and keeps the reaction media neutral. The generation of the corresponding acylium cation, a well-known intermediate in the Friedel−Crafts C-acylation reaction, is not likely, as typical electron-rich arenes, such as 1,3,5-trimethoxybenzene, did not react under the optimized conditions.

Scope of Photoreactions. Next, we evaluated the reactivity of the synthesized 3-acylindolizines toward photooxidation. The reactions were conducted by irradiating a solution of the substrates in methanol-d_4, water-d_2, or an

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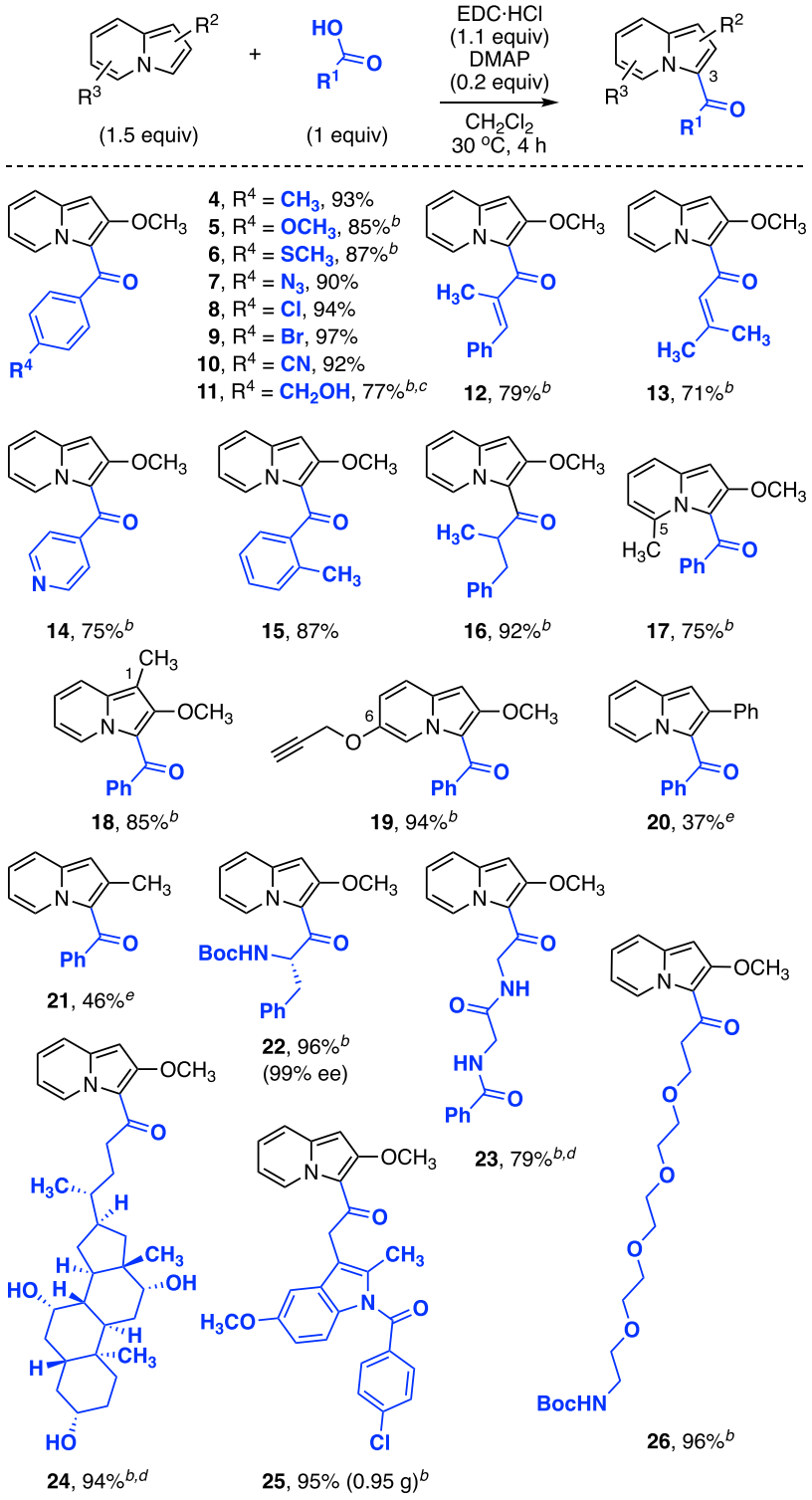
Scheme 2. Scope of the C3-Acylation of Indolizines[a]



[a]Isolated yields. [b]20 h. [c]In methanol with DMT-MM. [d]In DMF. [e]40 °C, 48 h.

aqueous acetonitrile solution (CH_3CN/H_2O = 4/1) in the presence of methylene blue (1 mol %) with a 660 nm red LED up to 1 min, which afforded the carboxylic acids in excellent yields (Scheme 4). Carboxylic acid **28** having a thioether group susceptible to oxidation[14] was also released in 85% yield after photoirradiation for 30 s. The release of 4-azidobenzoic acid (**29**), isonicotinic acid (**30**), and α,β-unsaturated carboxylic acid **31** proceeded in nearly quantitative yields without affecting the azido, pyridinyl, and alkene functionalities. Next, we prepared amine **33** from Boc-deprotection of **26** (Scheme 5). Efficient release of amine **32** from **33** was confirmed in neutral sodium phosphate water-d_2 buffer (pD 7.0) in the absence of any organic co-solvents (Scheme 4).

The release of 2-methyl-3-phenylpropionic acid (**34**), 2-methylbenzoic acid (**35**), and (*E*)-2-methyl-3-phenylacrylic acid (**36**) proceeded in nearly quantitative yields. The apparent

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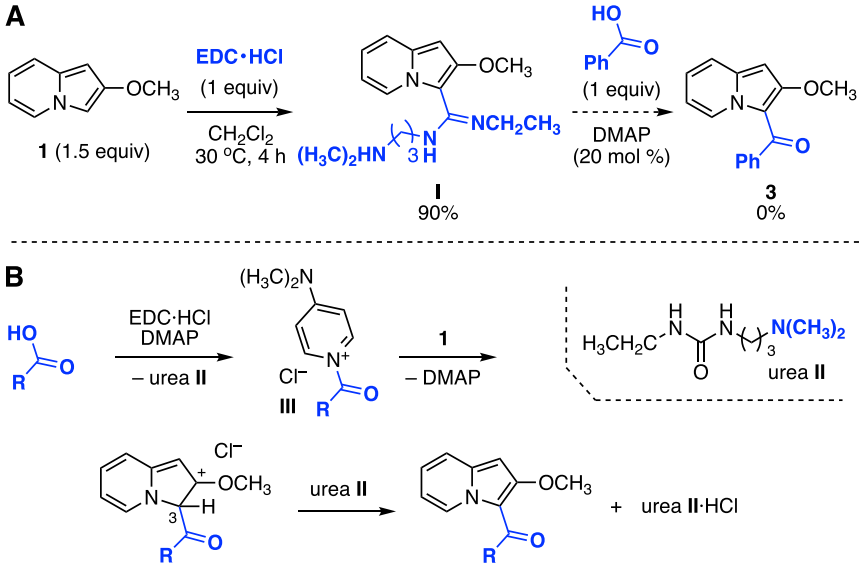
Scheme 3. (A) Control Experiments and (B) Plausible Mechanism of the C3-Acylation Reaction



rate constant for the release of 2-methylbenzoic acid from **15** (k_{obs} = 0.0720 s^{-1}) was relatively slower than that of benzoic acid (k_{obs} = 0.138 s^{-1}, released from **3**), but reached >95% yield within 1 min (Figures S3 and S4). In addition, the release of *N*-Boc-phenylalanine (**37**) took place without the loss of enantiopurity (>99% ee). The presence of substitutions at 1-, 6-, and sterically hindering 5 positions of indolizines did not affect the photoreaction efficiency (**17**−**19**). *N*-Benzoylglycylglycine (**38**), indomethacin (**39**), and cholic acid (**40**) were also released in excellent yields. Extension of the irradiation time to 2 min allowed to increase the substrate concentration and the reaction scale, as indomethacin (**39**) was successfully isolated in excellent yield. Because amino[15] and amide[16] groups are generally unstable to photooxidation, our method that can leave these functionalities intact is an effective system, demonstrating the broad applicability for releasing various molecules with a wide range of functional groups. Moreover, the release of carboxylic acid proceeded almost quantitatively even under hypoxic conditions (1% O_2), indicating the high photoreactivity of the present system (Figure S5).

There is still scope for the improvement of the indolizine system to realize biological applications. For instance, the indolizine core exhibits low water solubility, which compelled us to use an excess amount of organic solvents for the photoreactions in our previous research.[5] Moreover, the use of a photosensitizer is essential. A simultaneous addition of indolizines and the photosensitizer may decrease their concentrations in cells or at target tissues due to their diffusion, thereby reducing the efficiency of the photoreaction. To address these issues, we designed and synthesized acylindolizines having zinc protoporphyrin IX (ZnPPIX),[17] an intramolecular red light-absorbing dye, connected by water-soluble poly(ethylene glycol) (PEG) linkers. We selected two carboxylic acids as model compounds, i.e., pseudolaric acid B,[18] a bioactive natural product with potent microtubule-destabilizing activity,[19] and a tripeptide, Suc−Ala−Pro−Ala−*p*NA (Scheme 6).

Acylation of an indolizine bearing an alkyne moiety with these densely functionalized carboxylic acids proceeded efficiently using our newly developed acylation conditions, and the caged compounds **41** and **42** were obtained in high yields (Scheme 6A). Next, alkynes **41** and **42** were connected with ZnPPIX having two azido-PEG linkers (**43**) derived from PPIX, via copper-catalyzed Huisgen cyclization to afford **44** and **45**, respectively, in high yields (Scheme 6B). As expected, these acylindolizines dissolved well in pH 7.4 sodium phosphate buffer containing 5 v/v% dimethylsulfoxide (DMSO), and red light irradiation of the solutions for 5 min afforded pseudolaric acid B and Suc−Ala−Pro−Ala−*p*NA from **44** and **45** in 77 and 74% yields, respectively (Scheme 6C).

The releasing efficiencies of these compounds did not decrease significantly even in the presence of human serum albumin despite the high serum protein binding rate of ZnPPIX (K_d = 1 μM).[20] These results demonstrate that the all-in-one design, involving an indolizine core, a releasing carboxylic acid, and a photosensitizer, provides a platform for the use of the indolizine photouncaging system for biological applications.

■ CONCLUSIONS

In conclusion, we have developed a synthetic method for obtaining 3-acyl-2-methoxyindolizines from various carboxylic acids mediated by condensation reagents under neutral and mild conditions with wide functional group tolerance. This method enables the caging of a broad range of bioactive carboxylic compounds bearing various functional groups with indolizines. We have demonstrated the efficient photouncaging of the carboxylic acids from the corresponding 3-acyl-2-methoxyindolizines without any side reactions, such as oxidation of an amino and amide group or decomposition of an azido group. Moreover, we have designed and synthesized water-soluble photoreactive precursors conjugated with a photosensitizer through PEG linkers, which efficiently release bioactive carboxylic acids upon red LED irradiation in a neutral aqueous buffered solution in the presence of human serum albumin. Further studies including biological applications of this photouncaging system will be reported in due course.

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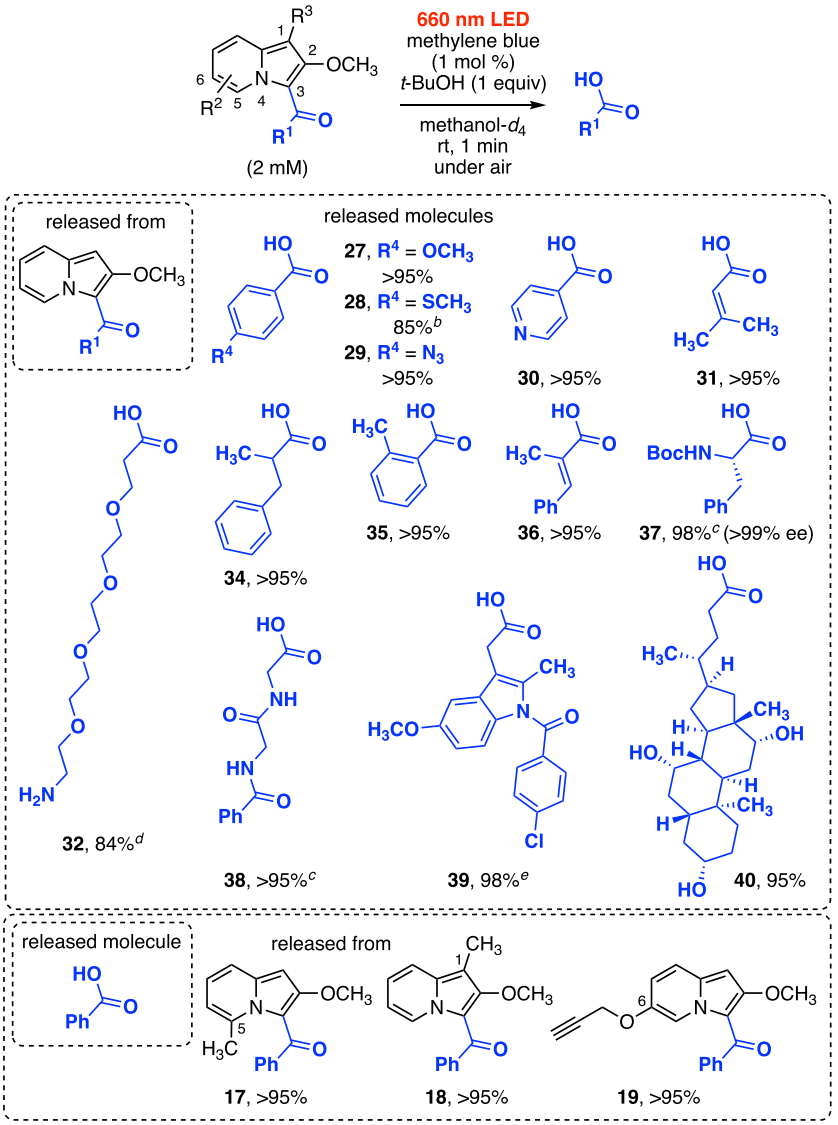
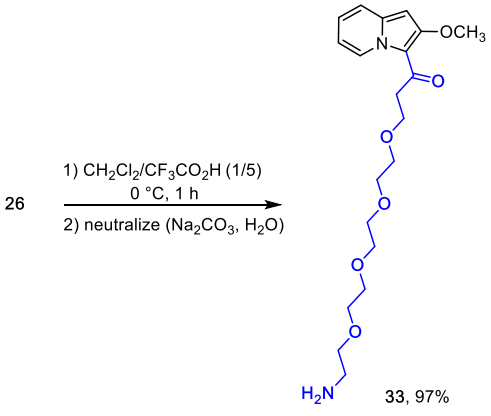
Scheme 4. Scope of the Photoreaction[a]



[a]^{1}H NMR yields, unless otherwise noted. [b]30 s irradiation. [c]In CH_3CN/H_2O (4/1), HPLC yields. [d]In sodium phosphate, D_2O (pD 7.0, 20 mM). [e]5 mM, 2 min irradiation, isolated yield.

Scheme 5. Synthesis of Amine 33



EXPERIMENTAL SECTION

General Information. All reactions for the synthesis of photoreactive substrates were performed under argon atmosphere and shading from light unless otherwise indicated. The definition for room temperature (rt) is 23−27 °C. An IKA RCT basic hot plate stirrer equipped with aluminum blocks was used for heating. Analytical thin-layer chromatography (TLC) was performed on precoated (0.25 mm) silica-gel plates (Merck, Merck Silica Gel 60 F254). Column chromatography was conducted on a YAMAZEN Automated Flash Chromatography System that consists of AI-580 and Parallel Frac FR-360 or a Biotage ISO-PSV Isolera Prime with a silica-gel-packed column (Universal Premium Silica Gel 30 μm or Biotage Sfär Silica HC D High Capacity Duo 20 μm). Freeze drying was conducted with an EYELA FDS-2000. Melting points (mp) were measured with an OptiMelt automated melting point apparatus (Stanford Research Systems, Inc.) and were uncorrected. ^{1}H NMR (400 MHz) and ^{13}C{^{1}H} NMR (100 MHz) spectra were obtained from measurements at room temperature on a JEOL ECS400 spectrometer. Chloroform-d_1 ($CDCl_3$) containing 0.05% tetramethylsilane (TMS) (99.8%D, Cambridge Isotope Laboratories, Inc.), methanol-d_4 (99.8%D, Merck, Inc.), and dimethylsulfoxide-d_6 (DMSO-d_6, 99.9%D, Cambridge Isotope Laboratories, Inc.) were used as a solvent for NMR measurements. Chemical shifts (δ) for ^{1}H NMR are given in parts per million (ppm) downfield from the signal of residual $CHCl_3$ (δ 7.26 ppm) and dimethylsulfoxide (δ 2.50 ppm)

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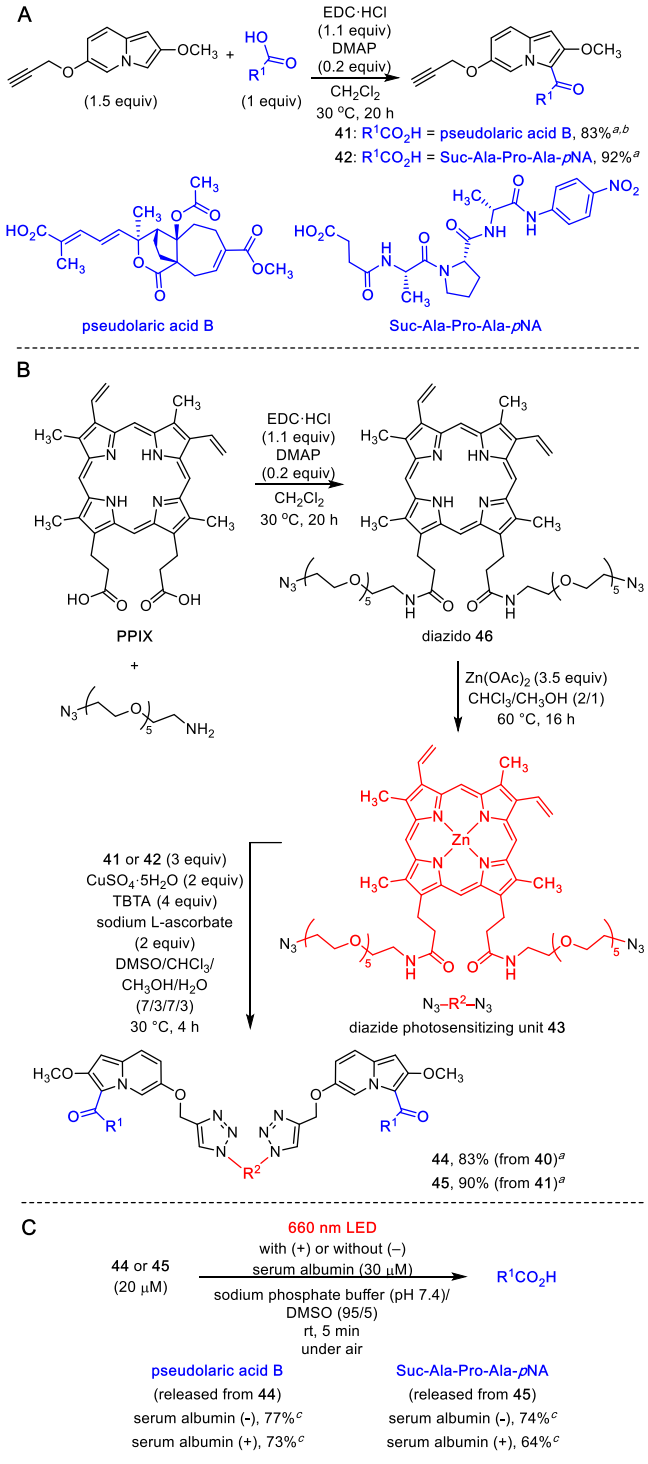
Scheme 6. (A) Synthesis of Pseudolaric Acid B and Suc−Ala−Pro−Ala−*p*NA-Caged Indolizines, (B) Connection to Photosensitizer, and (C) Evaluation of Photoreleasing Efficiency in Aqueous Buffered Solutions



[a]Isolated yields. [b]DMAP (1 equiv). [c]HPLC yields.

as internal standards with coupling constants (J) in hertz (Hz). Chemical shifts (δ) for $^{13}C\{^1H\}$ NMR are given in parts per million (ppm) downfield from the signal of residual $CDCl_3$ (δ 77.2 ppm) and dimethylsulfoxide-d_6 (δ 39.5 ppm) as internal standards. The abbreviations s, d, t, q, and m signify singlet, doublet, triplet, quartet, and multiplet, respectively. IR spectra were measured by attenuated total reflection method on a Shimadzu IRPrestige-21 spectrometer with the absorption band given in cm^{-1}. High performance liquid chromatography was performed on Shimadzu HPLC Systems that consists of LC-20AB (liquid chromatograph), DGU-20A3 (degasser), SPD-M20A (diode array detector), SIL-20A (autosampler), CTO-20AC (column oven), and CBM-20A (communication bus) or LC-20AR (liquid chromatograph), DGU-20A5R (degasser), SPD-M20A (diode array detector), FRC-40 (fraction collector), and CBM-20A (communications bus) units. Recycle gel permeation chromatography (GPC) was performed on a YMC LC-Forte/R multiple preparative HPLC system. High-resolution mass spectra (HRMS) were measured on a Thermo Fisher Scientific Exactive Plus Orbitrap mass spectrometer.

Synthesis of Substrates. 2-Methoxyindolizine (1),[5] 2-methoxy-6-(prop-2-yn-1-yloxy)indolizine,[5] 2-phenylindolizine,[21] 2-methylindolizine,[22] 1-(2-ethoxy-2-oxoethyl)-2-ethylpyridin-1-ium bromide,[23] and 1-(2-ethoxy-2-oxoethyl)-2,6-dimethylpyridin-1-ium bromide[23] were synthesized according to the literature.

2-Methoxy-5-methylindolizine. 1-(2-Ethoxy-2-oxoethyl)-2,6-dimethylpyridin-1-ium bromide (1.10 g, 4.01 mmol, 1 equiv), DMF (20 mL), and *i*-PrOH (20 mL) were added into a 100 mL round-bottom flask. The flask was filled with argon and set into an ice water bath. Cesium hydroxide monohydrate (1.34 g, 7.98 mmol, 2.0 equiv) was added to the solution in one portion. The resulting mixture was stirred at room temperature for 30 min. The flask was set into an ice water bath, and dimethyl sulfate (505 mg, 4.00 mmol, 1.0 equiv) was added dropwise to the mixture over 5 min. The mixture was further stirred at room temperature for 2 h. The mixture was then poured into a solution of *n*-hexane (120 mL) and ethyl acetate (EtOAc, 60 mL). The resulting mixture was washed with brine (120 mL × 3). The organic layer was dried with Na_2SO_4 and evaporated. The residue was purified by silica-gel column chromatography (*n*-hexane/EtOAc = 1/0 to 85/15) to afford the product. Yield: 389 mg (2.41 mmol, 60.1%). Red oil; TLC R_f = 0.47 (*n*-hexane/EtOAc = 6:1); ^1H NMR ($CDCl_3$): δ 7.18 (d, J = 8.8 Hz, 1H), 6.81 (d, J = 2.0 Hz, 1H), 6.69 (dd, J = 8.8, 6.8 Hz, 1H), 6.33 (d, J = 6.8 Hz, 1H), 6.15 (d, J = 1.6 Hz, 1H), 3.88 (s, 3H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 153.3, 132.6, 132.0, 117.9, 115.4, 108.8, 93.6, 86.5, 57.9, 19.0; IR (ZnSe, cm^{-1}) 710, 766, 1036, 1159, 1321, 1416, 1537, 1551, 2932; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{10}H_{12}NO^+$ 162.0913; found 162.0913.

2-Methoxy-1-methylindolizine. 1-(2-Ethoxy-2-oxoethyl)-2-ethylpyridin-1-ium bromide (1.92 g, 7.00 mmol, 1 equiv), DMF (35 mL), and *i*-PrOH (35 mL) were added into a 200 mL round-bottom flask. The flask was filled with argon and set into an ice water bath. Cesium hydroxide monohydrate (2.35 g, 14.0 mmol, 2.0 equiv) was added to the solution in one portion. The resulting mixture was stirred at room temperature for 30 min. The flask was set into an ice water bath, and dimethyl sulfate (883 mg, 7.00 mmol, 1.0 equiv) was added dropwise to the mixture over 5 min. The mixture was further stirred at room temperature for 2 h. The mixture was then poured into a solution of *n*-hexane (220 mL) and EtOAc (110 mL). The resulting mixture was washed with brine (300 mL × 3). The organic layer was dried with Na_2SO_4 and evaporated. The residue was purified by silica-gel column chromatography (*n*-hexane/EtOAc = 1/0 to 92/8) to afford the product. Yield: 244 mg (1.51 mmol, 21.6%); Pale yellow solid (mp 58.1−59.4 °C); TLC R_f = 0.56 (*n*-hexane/EtOAc = 4:1); ^1H NMR ($CDCl_3$): δ 7.76−7.74 (m, 1H), 7.15 (d, J = 8.8 Hz, 1H), 6.90 (s, 1H), 6.62−6.58 (m, 1H), 6.34−6.30 (m, 1H), 3.84 (s, 3H), 2.20 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 151.5, 129.1, 125.2, 116.3, 116.0, 108.4, 95.3, 94.6, 58.0, 6.8; IR (ZnSe, cm^{-1}) 733, 1016, 1067, 1211, 1294, 1350, 1535, 2909; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{10}H_{12}NO^+$ 162.0913; found 162.0912.

General Procedure for the Synthesis of 3-Acylindolizines (Schemes 2 and 6A). To a solution (CH_2Cl_2 or DMF, 2.0 mL) of carboxylic acid (0.400 mmol, 1 equiv), 2-methoxyindolizine (**1**, 88.3 mg, 0.600 mmol, 1.5 equiv), and DMAP (9.8 mg, 80 μmol, 20 mol %) in a 4 mL vial were added EDC·HCl (84.3 mg, 0.440 mmol, 1.1 equiv) and a magnetic stir bar. The vial was filled with argon, and the solution was stirred at 30 °C (or 40 °C) for the indicated time. The reaction mixture was poured into EtOAc (15 mL) and brine (15 mL)

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and extracted with EtOAc (15 mL × 3). The combined organic layer was dried with Na_2SO_4 and evaporated. The residue was purified by silica-gel column chromatography (*n*-hexane/EtOAc) to afford the product.

1-(2-Methoxyindolizin-3-yl)-3-phenylpropan-1-one (**2**). Prepared with 3-phenylpropionic (60.1 mg, 0.400 mmol) acid in CH_2Cl_2 at 30 °C for 4 h. Yield: 109 mg (0.390 mmol, 97.5%); Pale yellow solid (mp 94.0−96.0 °C); TLC R_f = 0.44 (*n*-hexane/EtOAc = 4:1); ^{1}H NMR ($CDCl_3$): δ 9.98 (d, J = 7.6 Hz, 1H), 7.35−7.28 (m, 5H), 7.23−7.17 (m, 1H), 7.15−7.10 (m, 1H), 6.81−6.77 (m, 1H), 6.01 (s, 1H), 3.97 (s, 3H), 3.25−3.21 (m, 2H), 3.07−3.03 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 187.9, 158.8, 142.4, 137.0, 128.8, 128.6, 128.4, 125.8, 124.8, 116.8, 112.6, 111.4, 85.1, 57.9, 42.7, 31.5; IR (ZnSe, cm^{-1}) 768, 1082, 1414, 1460, 1503, 1597, 2926; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{18}NO_2^+$ 280.1332; found 280.1332.

2-Methoxyindolizin-3-yl Phenyl Ketone (**3**). Prepared from benzoic acid (48.8 mg, 0.400 mmol) in CH_2Cl_2 at 30 °C for 4 h. Yield: 97.1 mg (0.386 mmol, 96.7%); Pale yellow solid (mp 60.0−61.0 °C); TLC R_f = 0.44 (*n*-hexane/EtOAc = 4:1); ^{1}H NMR ($CDCl_3$): δ 9.85 (d, J = 8.0 Hz, 1H), 7.69−7.66 (m, 2H), 7.49−7.36 (m, 4H), 7.19−7.15 (m, 1H), 6.86−6.82 (m, 1H), 6.01 (s, 1H), 3.70 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 183.9, 158.4, 141.3, 138.0, 130.4, 128.7, 127.6, 125.3, 117.0, 112.7, 111.6, 85.4, 57.6; IR (ZnSe, cm^{-1}) 696, 743, 1053, 1342, 1418, 1503, 1557; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{14}NO_2^+$ 252.1019; found 252.1019.

(2-Methoxyindolizin-3-yl)(p-tolyl)methanone (**4**). Prepared from 4-methylbenzoic acid (54.5 mg, 0.400 mmol) in CH_2Cl_2 at 30 °C for 4 h. Yield: 98.7 mg (0.372 mmol, 92.9%); Pale yellow solid (mp 127.3−128.6 °C); TLC R_f = 0.50 (*n*-hexane/EtOAc = 2:1); ^{1}H NMR ($CDCl_3$): δ 9.81 (d, J = 6.8 Hz, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.8 Hz, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.16−7.12 (m, 1H), 6.83−6.79 (m, 1H), 6.01 (s, 1H), 3.73 (s, 3H), 2.42 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 183.9, 158.1, 140.9, 138.4, 137.8, 129.1, 128.7, 128.3, 125.1, 117.1, 112.6, 111.7, 85.5, 57.7, 21.8; IR (ZnSe, cm^{-1}) 754, 768, 1063, 1310, 1339, 1418, 1441, 1503, 1557, 1585; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{16}NO_2^+$ 266.1176; found 266.1176.

(2-Methoxyindolizin-3-yl)(4-methoxyphenyl)methanone (**5**). Prepared from 4-methoxylbenzoic acid (60.9 mg, 0.400 mmol) in CH_2Cl_2 at 30 °C for 20 h. Yield: 95.9 mg (85.2%); Pale yellow solid (mp 150.0−151.0 °C); TLC R_f = 0.41 (*n*-hexane/EtOAc = 2:1); ^{1}H NMR ($CDCl_3$): δ 9.74 (d, J = 7.2 Hz, 1H), 7.73−7.70 (AA′BB′, 2H), 7.36 (d, J = 8.8 Hz, 1H), 7.15−7.10 (m, 1H), 6.93−6.91 (AA′BB′, 2H), 6.82−6.78 (m, 1H), 6.02 (s, 1H), 3.88 (s, 3H), 3.75 (s, 3H); $^{13}C\{1H\}$ NMR ($CDCl_3$): δ 183.2, 161.9, 157.8, 137.6, 133.7, 131.2, 128.6, 124.8, 117.1, 112.9, 112.5, 111.7, 85.4, 57.8, 55.5; IR (ZnSe, cm^{-1}) 762, 833, 1022, 1063, 1157, 1233, 1258, 1344, 1422, 1454, 1518, 1584; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{16}NO_3^+$ 282.1125; found 282.1124.

(2-Methoxyindolizin-3-yl)(4-(methylthio)phenyl)methanone (**6**). Prepared from 4-(methylthio)benzoic acid (60.9 mg, 0.400 mmol) in CH_2Cl_2 at 30 °C for 20 h. Yield: 103 mg (0.346 mmol, 86.6%); Pale yellow solid (mp 107.4−109.0 °C); TLC R_f = 0.56 (*n*-hexane/EtOAc = 2:1); ^{1}H NMR ($CDCl_3$): δ 9.79 (d, J = 7.6 Hz, 1H), 7.66−7.62 (AA′BB′, 2H), 7.37 (d, J = 8.8 Hz, 1H), 7.27−7.24 (m, 2H), 7.18−7.13 (m, 1H), 6.84−6.80 (m, 1H), 6.01 (s, 1H), 3.74 (s, 3H), 2.54 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 183.1, 158.1, 140.0, 137.9, 137.7, 129.6, 128.7, 125.3, 124.8, 117.1, 112.7, 111.6, 85.5, 57.8, 15.4; IR (ZnSe, cm^{-1}) 756, 824, 851, 895, 955, 1063, 1088, 1234, 1312, 1420, 1445, 1582; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{16}NO_2S^+$ 298.0896; found 298.0895.

(4-Azidophenyl)(2-methoxyindolizin-3-yl)methanone (**7**). Prepared from 4-azidobenzoic acid (65.3 mg, 0.400 mmol) in CH_2Cl_2 at 30 °C for 4 h. Yield: 105 mg (0.359 mmol, 89.7%); Brown solid (mp 120.2−121.8 °C); TLC R_f = 0.49 (*n*-hexane/EtOAc = 2:1); ^{1}H NMR ($CDCl_3$): δ 9.80 (d, J = 7.2 Hz, 1H), 7.72−7.69 (AA′BB′, 2H), 7.38 (d, J = 8.8 Hz, 1H), 7.20−7.15 (m, 1H), 7.08−7.05 (AA′BB′, 2H), 6.86−6.82 (m, 1H), 6.01 (s, 1H), 3.76 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 182.5, 158.2, 142.3, 138.1, 137.9, 130.9, 128.8, 125.5, 118.2, 117.2, 112.9, 111.6, 85.6, 57.8; IR (ZnSe, cm^{-1}) 752, 895, 955, 1063, 1285, 1419, 1445, 1452, 1499, 1514, 1585, 1603, 2033, 2118; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{13}N_4O_2^+$ 293.1033; found 293.1030.

(4-Chlorophenyl)(2-methoxyindolizin-3-yl)methanone (**8**). Prepared from 4-chlorobenzoic acid (62.6 mg, 0.400 mmol) in CH_2Cl_2 at 30 °C for 4 h. Yield: 107 mg (0.374 mmol, 93.7%); Pale yellow solid (mp 120.1−121.0 °C); TLC R_f = 0.52 (*n*-hexane/EtOAc = 2:1); ^{1}H NMR ($CDCl_3$): δ 9.83 (d, J = 6.4 Hz, 1H), 7.63−7.60 (AA′BB′, 2H), 7.39−7.36 (m, 3H), 7.21−7.17 (m, 1H), 6.87−6.83 (m, 1H), 6.00 (s, 1H), 3.72 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 182.4, 158.5, 139.7, 138.3, 136.5, 130.3, 128.8, 127.9, 125.7, 117.1, 113.0, 111.5, 85.6, 57.7; IR (ZnSe, cm^{-1}) 760, 826, 1069, 1344, 1416, 1445, 1502, 1585; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{13}ClNO_2^+$ 286.0629; found 286.0627.

(4-Bromophenyl)(2-methoxyindolizin-3-yl)methanone (**9**). Prepared from 4-bromobenzoic acid (80.4 mg, 0.400 mmol) in CH_2Cl_2 at 30 °C for 4 h. Yield: 128 mg (0.388 mmol, 96.9%); Pale yellow solid (mp 126.3−127.5 °C); TLC R_f = 0.52 (*n*-hexane/EtOAc = 2:1); ^{1}H NMR ($CDCl_3$): δ 9.83 (d, J = 6.8 Hz, 1H), 7.58−7.51 (m, 4H), 7.38 (d, J = 8.8 Hz, 1H), 7.21−7.17 (m, 1H), 6.87−6.83 (m, 1H), 6.00 (s, 1H), 3.72 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 182.4, 158.5, 140.2, 138.3, 130.8, 130.5, 128.8, 125.8, 124.9, 117.1, 113.0, 111.4, 85.6, 57.7; IR (ZnSe, cm^{-1}) 756, 823, 959, 1057, 1206, 1256, 1346, 1416, 1445, 1504, 1584; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{13}BrNO_2^+$ 330.0124; found 330.0121.

4-(2-Methoxyindolizine-3-carbonyl)benzonitrile (**10**). Prepared from 4-cyanobenzoic acid (58.9 mg, 0.400 mmol) in CH_2Cl_2 at 30 °C for 4 h. Yield: 102 mg (0.369 mmol, 92.2%); Pale yellow solid (mp 189.8−190.8 °C); TLC R_f = 0.39 (*n*-hexane/EtOAc = 2:1); ^{1}H NMR ($CDCl_3$): δ 9.88 (d, J = 7.2 Hz, 1H), 7.78−7.63 (m, 4H), 7.40 (d, J = 8.4 Hz, 1H), 7.25−7.23 (m, 1H), 6.92−6.88 (m, 1H), 5.99 (s, 1H), 3.69 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 181.2, 158.9, 145.6, 138.9, 131.6, 129.1, 129.0, 126.5, 119.0, 117.2, 113.4, 111.3, 85.8, 57.8; IR (ZnSe, cm^{-1}) 704, 760, 832, 959, 1059, 1231, 1252, 1342, 1418, 1445, 1504, 1580, 2224; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{13}N_2O_2^+$ 277.0972; found 277.0970.

(4-(Hydroxymethyl)phenyl)(2-methoxyindolizin-3-yl)methanone (**11**). To a solution (CH_3OH, 2.0 mL) of 4-(hydroxymethyl)benzoic acid (60.9 mg, 0.400 mmol, 1 equiv), 2-methoxyindolizine (**1**, 88.3 mg, 0.600 mmol, 1.5 equiv) in a 4 mL vial were added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (DMT-MM, 122 mg, 0.441 mmol, 1.1 equiv) and a magnetic stir bar. The vial was filled with argon, and the resulting solution was stirred at 30 °C for 20 h. The reaction mixture was poured into EtOAc (15 mL) and brine (15 mL) and extracted with EtOAc (15 mL × 3). The combined organic layer was dried with Na_2SO_4 and evaporated. The residue was purified by silica-gel column chromatography (*n*-hexane/EtOAc = 1/0 to 1/4) to afford the product. Yield: 86.1 mg (0.306 mmol, 76.5%); Pale yellow solid (mp 117.4−119.2 °C); TLC R_f = 0.44 (*n*-hexane/EtOAc = 1:2); ^{1}H NMR ($CDCl_3$): δ 9.84 (d, J = 8.0 Hz, 1H), 7.70−7.67 (m, 2H), 7.41−7.36 (m, 3H), 7.19−7.15 (m, 1H), 6.86−6.81 (m, 1H), 6.01 (s, 1H), 4.77 (s, 2H), 3.71 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 183.6, 158.4, 143.3, 140.7, 138.1, 129.2, 128.8, 126.0, 125.5, 117.1, 112.8, 111.7, 85.6, 65.4, 57.7; IR (ZnSe, cm^{-1}) 758, 953, 1053, 1231, 1346, 1416, 1505, 1545, 1578, 3383; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{16}NO_3^+$ 282.1125; found 282.1121.

(E)-1-(2-Methoxyindolizin-3-yl)-2-methyl-3-phenylprop-2-en-1-one (**12**). Prepared from (*E*)-2-methyl-3-phenyl-2-propenoic acid (64.9 mg, 0.400 mmol) in CH_2Cl_2 at 30 °C for 20 h. Yield: 92.5 mg (0.317 mmol, 79.3%); Colorless solid (mp 75.1−76.4 °C); TLC R_f = 0.57 (*n*-hexane/EtOAc = 2:1); ^{1}H NMR ($CDCl_3$): δ 9.75 (d, J = 7.6 Hz, 1H), 7.43−7.34 (m, 5H), 7.30−7.26 (m, 1H), 7.15−7.11 (m, 1H), 6.88 (d, J = 1.6 Hz, 1H), 6.82−6.78 (m, 1H), 6.01 (s, 1H), 3.87 (s, 3H), 2.21 (d, J = 1.2 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 187.2, 158.5, 138.6, 137.7, 137.5, 132.9, 129.4, 128.8, 128.4, 127.3, 125.0, 117.0, 112.6, 110.9, 85.5, 58.0, 15.3; IR (ZnSe, cm^{-1}) 768, 1024, 1063, 1252, 1412, 1452, 1555; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{18}NO_2^+$ 292.1332; found 292.1330.

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1-(2-Methoxyindolizin-3-yl)-3-methylbut-2-en-1-one (**13**). Prepared from 3-methylbut-2-enoic acid (40.0 mg, 0.400 mmol) in CH_2Cl_2 at 30 °C for 20 h. Yield: 65.1 mg (0.283 mmol, 71.1%); Colorless solid (mp 62.7−63.7 °C); TLC R_f = 0.43 (*n*-hexane/EtOAc = 4:1); ^{1}H NMR ($CDCl_3$): δ 10.08 (dd, J = 7.6, 0.8 Hz, 1H), 7.35−7.32 (m, 1H), 7.14−7.08 (m, 1H), 6.96−7.08 (m, 1H), 6.96−6.95 (m, 1H), 6.79−6.74 (m, 1H), 6.02 (s, 1H), 2.26 (d, J = 1.6 Hz, 3H), 1.98 (d, J = 0.8 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 180.5, 157.9, 151.2, 137.0, 128.8, 124.72, 124.65, 116.9, 112.7, 112.4, 85.4, 58.1, 28.2, 21.1; IR (ZnSe, cm^{-1}) 756, 1020, 1096, 1248, 1306, 1346, 1418, 1450, 1501, 1641, 2901, 2934s; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{14}H_{16}NO_2^+$ 230.1176; found 230.1172.

(2-Methoxyindolizin-3-yl)(pyridin-4-yl)methanone (**14**). Prepared from isonicotinic acid (75.3 mg, 0.400 mmol) in CH_2Cl_2 at 30 °C for 20 h. Yield: 75.3 mg (0.298 mmol, 74.7%); Colorless solid (mp 205.2−206.3 °C); TLC R_f = 0.55 (EtOAc); ^{1}H NMR ($CDCl_3$): δ 9.91 (d, J = 7.2 Hz, 1H), 8.70−8.68 (m, 2H), 7.46−7.44 (m, 2H), 7.40 (d, J = 9.2 Hz, 1H), 7.27−7.23 (m, 1H), 6.92−6.88 (m, 1H), 5.99 (s, 1H), 3.68 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 181.0, 159.2, 149.6, 148.8, 139.1, 129.1, 126.6, 122.4, 117.2, 113.4, 111.2, 85.8, 57.7; IR (ZnSe, cm^{-1}) 667, 760, 1053, 1233, 1344, 1422, 1462, 1504, 1539, 1564; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{15}H_{13}N_2O_2^+$ 253.0972; found 253.0969.

(2-Methoxyindolizin-3-yl)(o-tolyl)methanone (**15**). Prepared from 2-methylbenzoic acid (54.5 mg, 0.400 mmol) in CH_2Cl_2 at 30 °C for 4 h. Yield: 92.2 mg (0.348 mmol, 86.8%); Colorless solid (mp 117.1−118.9 °C); TLC R_f = 0.49 (*n*-hexane/EtOAc = 2:1); ^{1}H NMR ($CDCl_3$): δ 10.05 (d, J = 6.8 Hz, 1H), 7.38 (d, J = 8.8 Hz, 1H), 7.30−7.25 (m, 2H), 7.23−7.18 (m, 3H), 6.89−6.85 (m, 1H), 5.95 (s, 1H), 3.60 (s, 3H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 184.7, 159.3, 142.2, 138.3, 134.9, 130.0, 129.1, 128.6, 127.2, 125.8, 125.2, 117.0, 113.0, 112.1, 85.6, 57.9, 19.4; IR (ZnSe, cm^{-1}) 743, 770, 897, 959, 1059, 1196, 1250, 1344, 1416, 1445, 1504, 1568; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{17}H_{16}NO_2^+$ 266.1176; found 266.1174.

1-(2-Methoxyindolizin-3-yl)-2-methyl-3-phenylpropan-1-one (**16**). Prepared from 2-methyl-3-phenylpropanoic acid (65.7 mg, 0.400 mmol) in CH_2Cl_2 at 30 °C for 20 h. Yield: 108 mg (0.368 mmol, 92.0%); Colorless oil; TLC R_f = 0.60 (*n*-hexane/EtOAc = 4:1); ^{1}H NMR ($CDCl_3$): δ 10.02 (d, J = 7.6 Hz, 1H), 7.35−7.33 (m, 1H), 7.29−7.24 (m, 4H), 7.21−7.11 (m, 2H), 6.81−6.77 (m, 1H), 6.02 (s, 1H), 4.00 (s, 3H), 3.97−3.88 (m, 1H), 3.19 (dd, J = 13.6, 6.0 Hz, 1H), 2.62 (dd, J = 13.6, 8.8 Hz, 1H), 1.14 (d, J = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 192.4, 158.5, 141.2, 137.2, 129.4, 129.0, 128.3, 125.9, 125.0, 116.9, 112.7, 111.2, 85.4, 58.0, 43.6, 40.2, 16.7; IR (ZnSe, cm^{-1}) 698, 760, 970, 1074, 1248, 1368, 1418, 1503, 1597, 2932; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{19}H_{20}NO_2^+$ 294.1489; found 294.1487.

(2-Methoxy-5-methylindolizin-3-yl)(phenyl)methanone (**17**). Prepared from benzoic acid (48.8 mg, 0.400 mmol) and 2-methoxy-5-methylindolizine (96.7 mg, 0.600 mmol) in CH_2Cl_2 at 30 °C for 20 h. Yield: 79.5 mg, (0.300 mmol, 75.0%); Pale yellow solid (mp 108.1−109.2 °C); TLC R_f = 0.53 (*n*-hexane/EtOAc = 2:1); ^{1}H NMR ($CDCl_3$): δ 7.97−7.94 (m, 2H), 7.55−7.51 (m, 1H), 7.47−7.43 (m, 2H), 7.32 (d, J = 9.2 Hz, 1H), 7.15 (dd, J = 9.2, 6.8 Hz, 1H), 6.70 (d, J = 6.8 Hz, 1H), 6.09 (s, 1H), 3.69 (s, 3H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 182.5, 158.5, 140.4, 139.6, 139.3, 131.7, 130.5, 127.9, 124.7, 114.8, 114.4, 112.9, 85.4, 57.8, 23.3; IR (ZnSe, cm^{-1}) 710, 862, 1045, 1229, 1329, 1422, 1499, 1514, 1595, 2959; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{17}H_{16}NO_2^+$ 266.1176; found 266.1175.

(2-Methoxy-1-methylindolizin-3-yl)(phenyl)methanone (**18**). Prepared from benzoic acid (48.8 mg, 0.400 mmol) and 2-methoxy-1-methylindolizine (96.7 mg, 0.600 mmol) in CH_2Cl_2 at 30 °C for 20 h. Yield: 90.4 mg (0.341 mmol, 85.3%); Pale yellow solid (mp 111.9−113.2 °C); TLC R_f = 0.52 (*n*-hexane/EtOAc = 2:1); ^{1}H NMR ($CDCl_3$): δ 9.82 (d, J = 6.8 Hz, 1H), 7.74−7.71 (m, 2H), 7.52−7.39 (m, 4H), 7.19−7.15 (m, 1H), 6.88−6.84 (m, 1H), 3.33 (s, 3H), 2.23 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 184.1, 155.5, 141.0, 136.4, 130.7, 128.8, 128.7, 127.8, 124.3, 116.1, 113.3, 101.7, 62.4, 7.3; IR (ZnSe, cm^{-1}) 696, 750, 758, 867, 912, 1001, 1016, 1051, 1234, 1306, 1377, 1393, 1443, 1552, 1568, 1587, 2928; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{17}H_{16}NO_2^+$ 266.1176; found 266.1176.

(2-Methoxy-6-(prop-2-yn-1-yloxy)indolizin-3-yl)(phenyl)-methanone (**19**). Prepared from benzoic acid (24.4 mg, 0.200 mmol) and 2-methoxy-6-(prop-2-yn-1-yloxy)indolizine (60.4 mg, 0.300 mmol) in CH_2Cl_2 (1.0 mL) at 30 °C for 4 h. Yield: 57.6 mg (0.189 mmol, 94.4%); Pale yellow solid (mp 135.8−137.1 °C); TLC R_f = 0.47 (*n*-hexane/EtOAc = 2:1); ^{1}H NMR ($CDCl_3$): δ 9.80 (d, J = 2.4 Hz, 1H), 7.69−7.67 (m, 2H), 7.48−7.39 (m, 3H), 7.30 (d, J = 9.6 Hz, 1H), 7.04 (dd, J = 9.6, 2.0 Hz, 1H), 5.97 (s, 1H), 4.75 (d, J = 2.4 Hz, 2H), 3.68 (s, 3H), 2.60 (t, J = 2.4 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 184.1, 157.9, 147.6, 141.2, 134.6, 130.6, 128.9, 127.6, 120.0, 117.3, 113.7, 112.6, 85.4, 78.0, 76.5, 57.7, 57.4; IR (ZnSe, cm^{-1}) 654, 720, 810, 989, 1026, 1055, 1200, 1240, 1271, 1354, 1410, 1452, 1504, 1555; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{19}H_{16}NO_3^+$ 306.1125; found 306.1123.

Phenyl(2-phenylindolizin-3-yl)methanone (**20**). Prepared from benzoic acid (48.8 mg, 0.400 mmol) and 2-phenylindolizine (116 mg, 0.600 mmol) in CH_2Cl_2 at 40 °C for 48 h. Yield: 43.5 mg (0.146 mmol, 36.6%); Pale yellow solid (mp 135.1−136.6 °C); TLC R_f = 0.45 (*n*-hexane/EtOAc = 4:1); ^{1}H NMR ($CDCl_3$): δ 9.80 (dd, J = 7.2, 0.8, Hz, 1H), 7.57−7.54 (m, 1H), 7.43−7.40 (m, 2H), 7.20−7.12 (m, 2H), 7.10−7.06 (m, 2H), 7.03−6.99 (m, 5H), 6.92−6.88 (m, 1H), 6.59 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 186.9, 140.3, 139.9, 137.7, 136.1, 130.8, 130.3, 129.8, 128.4, 127.7, 127.5, 126.8, 124.3, 120.2, 118.5, 113.7, 104.3; IR (ZnSe, cm^{-1}) 692, 745, 752, 812, 883, 1015, 1136, 1341, 1404, 1570, 1585, 2853, 2922; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{21}H_{16}NO^+$ 298.1226; found 298.1224.

(2-Methylindolizin-3-yl)(phenyl)methanone (**21**). Prepared from benzoic acid (48.8 mg, 0.400 mmol) and 2-methylindolizine (78.7 mg, 0.600 mmol) in CH_2Cl_2 at 40 °C for 48 h. Yield: 43.0 mg (0.183 mmol, 45.7%); Pale yellow solid (mp 62.2−63.1 °C); TLC R_f = 0.50 (*n*-hexane/EtOAc = 4:1); ^{1}H NMR ($CDCl_3$): δ 9.74 (d, J = 6.8 Hz, 1H), 7.61−7.58 (m, 2H), 7.53−7.41 (m, 4H), 7.14−7.10 (m, 1H), 6.84−6.80 (m, 1H), 6.32 (s, 1H), 1.90 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 186.4, 142.3, 138.4, 135.7, 130.7, 128.8, 128.6, 128.3, 124.5, 121.7, 117.7, 113.1, 105.4, 15.8; IR (ZnSe, cm^{-1}) 704, 743, 841, 962, 1020, 1134, 1229, 1337, 1408, 1585, 3051; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{16}H_{14}NO^+$ 236.1070; found 236.1068.

tert-Butyl (S)-(1-(2-methoxyindolizin-3-yl)-1-oxo-3-phenylpropan-2-yl)carbamate (**22**). Prepared from (*tert*-butoxycarbonyl)-L-phenylalanine (106 mg, 0.400 mmol) in CH_2Cl_2 at 30 °C for 20 h. Yield: 152 mg (0.385 mmol, 96.4%, 99.2% ee); Colorless solid (mp 43.9−44.6 °C); TLC R_f = 0.60 (*n*-hexane/EtOAc = 2:1); ^{1}H NMR ($CDCl_3$): δ 9.87 (d, J = 7.2 Hz, 1H), 7.38 (d, J = 9.2 Hz, 1H), 7.24−7.14 (m, 6H), 6.83 (t, J = 7.2 Hz, 1H), 6.03 (s, 1H), 5.64−5.52 (m, 2H), 4.03 (s, 3H), 3.26−3.21 (m, 1H), 2.85−2.79 (m, 1H), 1.37 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 185.4, 158.9, 155.5, 138.3, 137.7, 129.8, 129.0, 128.2, 126.5, 125.8, 117.1, 113.0, 110.0, 85.6, 79.2, 58.3, 56.9, 40.6, 28.5; IR (ZnSe, cm^{-1}) 698, 764, 1020, 1076, 1167, 1248, 1420, 1504, 1593, 1705; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{23}H_{27}N_2O_4^+$ 395.1965; found 395.1962. Optical rotation $[\alpha]_D^{23}$ +7.6 (c 1.00, $CHCl_3$).

tert-Butyl (1-(2-methoxyindolizin-3-yl)-1-oxo-3-phenylpropan-2-yl)carbamate (rac-22). Prepared from a 1:1 mixture of (*tert*-butoxycarbonyl)-L-phenylalanine and (*tert*-butoxycarbonyl)-D-phenylalanine (53.1 mg, 0.200 mmol) in CH_2Cl_2 (1.0 mL) at 30 °C for 20 h. Yield: 76.1 mg (0.193 mmol, 96.4%); Colorless solid (110 °C, decomposed); TLC R_f = 0.60 (*n*-hexane/EtOAc = 2:1); ^{1}H NMR ($CDCl_3$): δ 9.87 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.23−7.14 (m, 6H), 6.82 (t, J = 6.8 Hz, 1H), 6.02 (s, 1H), 5.64−5.52 (m, 2H), 4.03 (s, 3H), 3.25−3.21 (m, 1H), 2.85−2.80 (m, 1H), 1.37 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 185.4, 158.9, 155.5, 138.3, 137.7, 129.8, 129.0, 128.2, 126.5, 125.8, 117.1, 113.0, 110.0, 85.6, 79.2, 58.3, 56.9, 40.6, 28.5; IR (ZnSe, cm^{-1}) 698, 1020, 1076, 1167, 1248, 1440, 1504, 1593, 1705; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{23}H_{27}N_2O_4^+$ 395.1965; found 395.1962.

N-(2-((2-(2-Methoxyindolizin-3-yl)-2-oxoethyl)amino)-2-oxoethyl)benzamide (**23**). Prepared from *N*-benzoylglycylglycine (94.5 mg, 0.400 mmol) in DMF at 30 °C for 20 h. Yield: 115 mg

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(0.315 mmol, 78.7%); Pale yellow solid (204 °C, decomposed); TLC R_f = 0.48 (EtOAc only); ^{1}H NMR (DMSO-d_6): δ 9.73 (d, J = 6.8 Hz, 1H), 8.83 (t, J = 6.0 Hz, 1H), 8.06 (t, J = 5.6 Hz, 1H),7.92−7.90 (m, 2H), 7.60−7.47 (m, 4H), 7.31−7.26 (m, 1H), 6.98−6.94 (m, 1H), 6.34 (s, 1H), 4.40 (d, J = 5.2 Hz, 2H), 3.99−3.98 (m, 5H); ^{13}C{^{1}H} NMR (DMSO-d_6): δ 181.6, 169.2, 166.5, 158.5, 137.0, 134.0, 131.3, 128.3, 127.3, 125.4, 117.4, 113.1, 109.1, 86.0, 58.4, 46.5, 42.7; IR (ZnSe, cm^{-1}) 675, 696, 764, 1076, 1231, 1312, 1416, 1470, 1537, 1578, 1641, 1690, 3312; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{20}H_{20}N_3O_4^+$ 366.1448; found 366.1444.

*(R)-1-(2-Methoxyindolizin-3-yl)-4-((3S,5R,7S,8S,9R,10S,12R,13S,-14R,16R)-3,7,12-trihydroxy-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-16-yl)pentan-1-one (**24**).* Prepared from cholic acid (163 mg, 0.399 mmol) in DMF at 30 °C for 20 h. Yield: 202 mg (0.376 mmol, 94.2%). White solid (mp 204.2−205.6 °C); TLC R_f = 0.44 (EtOAc); ^{1}H NMR ($CDCl_3$): δ 9.95 (d, J = 8.0 Hz, 1H), 7.34−7.31 (m, 1H), 7.13−7.09 (m, 1H), 6.78−6.75 (m, 1H), 6.01 (s, 1H), 4.01 (s, 1H), 3.98 (s, 3H), 3.84 (d, J = 2.4 Hz, 1H), 3.47−3.42 (m, 1H), 3.01−2.93 (m, 1H), 2.83−2.76 (m, 1H), 2.50 (s, 1H), 2.28−1.23 (m, 22H), 1.16−1.06 (m, 4H), 1.01−0.93 (m, 1H), 0.88 (s, 3H), 0.70 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 190.2, 158.7, 137.0, 128.8, 124.8, 116.8, 112.5, 111.6, 85.2, 73.3, 72.1, 68.6, 58.0, 47.6, 46.7, 42.0, 41.7, 39.83, 39.75, 38.3, 36.1, 35.5, 34.9, 34.8, 32.0, 30.7, 28.3, 27.7, 26.7, 23.4, 22.7, 17.9, 12.8; IR (ZnSe, cm^{-1}) 746, 1078, 1249, 1312, 1420, 1462, 1581, 2864, 2934, 3363; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{33}H_{48}NO_5^+$ 538.3527; found 538.3525. Optical rotation $[\alpha]_D^{23}$ +7.8 (c 1.00, $CHCl_3$).

*2-(1-(4-Chlorobenzoyl)-6-methoxy-2-methyl-1H-indol-3-yl)-1-(2-methoxyindolizin-3-yl)ethan-1-one (**25**).* To a solution (CH_2Cl_2, 10 mL) of indomethacin (716 mg, 2.00 mmol, 1 equiv), 2-methoxyindolizine (**1**, 442 mg, 3.00 mmol, 1.5 equiv), and DMAP (48.9 mg, 0.400 mmol, 20 mol %) in a 50 mL round-bottom flask were added EDC·HCl (422 mg, 2.20 mmol, 1.1 equiv) and a magnetic stir bar. The flask was filled with argon, and the solution was stirred at 30 °C for 20 h. The reaction mixture was poured into EtOAc (100 mL) and washed with brine (60 mL × 2). The organic layer was dried with Na_2SO_4 and evaporated. The residue was purified by silica-gel column chromatography (n-hexane/EtOAc = 1/0 to 1/1) to afford the product. Yield: 948 mg (1.95 mmol, 97.3%); Pale yellow solid (mp 151.0−151.9 °C); TLC R_f = 0.41 (n-hexane/EtOAc = 2:1); ^{1}H NMR ($CDCl_3$): δ 9.93 (d, J = 7.2 Hz, 1H), 7.71−7.68 (AA′BB′, 2H), 7.48−7.45 (AA′BB′, 2H), 7.38 (d, J = 8.8 Hz, 1H), 7.18−7.14 (m, 1H), 6.99 (d, J = 2.8 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 6.79−6.76 (m, 1H), 6.63 (dd, J = 9.2, 2.8 Hz, 1H), 6.10 (s, 1H), 4.32 (s, 2H), 4.09 (s, 3H), 3.78 (s, 3H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 184.8, 168.5, 158.9, 156.1, 139.0, 137.5, 136.1, 134.5, 132.0, 131.3, 131.1, 129.2, 129.0, 125.4, 117.0, 115.3, 115.1, 112.9, 111.3, 111.3, 102.0, 85.4, 58.2, 55.8, 35.7, 13.9; IR (ZnSe, cm^{-1}) 754, 851, 1015, 1067, 1080, 1223, 1310, 1352, 1418, 1454, 1599, 1672, 2926; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{28}H_{24}ClN_2O_4^+$ 487.1419; found 487.1417.

*tert-Butyl (15-(2-methoxyindolizin-3-yl)-15-oxo-3,6,9,12-tetraoxapentadecyl)carbamate (**26**).* Prepared from 2,2-dimethyl-4-oxo-3,8,11,14,17-pentaoxa-5-azaicosan-20-oic acid (146 mg, 0.400 mmol) in CH_2Cl_2 at 30 °C for 20 h. Yield: 189 mg (0.382 mmol, 95.6%); Colorless oil; TLC R_f = 0.44 (EtOAc only); ^{1}H NMR ($CDCl_3$): δ 9.93 (d, J = 7.2 Hz, 1H), 7.34 (d, J = 9.2 Hz, 1H), 7.15−7.11 (m, 1H), 6.80−6.76 (m, 1H), 6.01 (s, 1H), 5.08 (s, 1H), 3.98 (s, 3H), 3.93 (t, J = 6.8 Hz, 2H), 3.71−3.58 (m, 12H), 3.53 (t, J = 4.8 Hz, 2H), 3.33−3.29 (m, 2H), 3.26 (t, J = 6.8 Hz, 2H), 1.44 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 186.1, 159.0, 156.2, 137.2, 128.8, 125.1, 116.9, 112.7, 111.7, 85.2, 79.3, 70.74, 70.4, 67.5, 58.0, 40.9, 40.5, 28.6; IR (ZnSe, cm^{-1}) 762, 1020, 1686, 1248, 1422, 1503, 1599, 1709, 2868; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{25}H_{38}N_2NaO_8^+$ 517.2520; found 517.2520.

*Methyl (3S,4R,4aR,9aS)-4a-acetoxy-3-((1E,3E)-5-(2-methoxy-6-(prop-2-yn-1-yloxy)indolizin-3-yl)-4-methyl-5-oxopenta-1,3-dien-1-yl)-3-methyl-1-oxo-3,4,4a,5,6,9-hexahydro-1H-4,9a-ethanocyclohepta[c]pyran-7-carboxylate (**41**).* Prepared from pseudolaric acid B (32.4 mg, 74.9 μmol), 2-methoxy-6-(prop-2-yn-1-yloxy)indolizine (22.6 mg, 113 mmol), and DMAP (9.2 mg, 75 mmol) in CH_2Cl_2 at 30 °C for 20 h. Yield: 36.5 mg (61.9 μmol, 82.6%); Pale yellow solid (110 °C, decomposed); TLC R_f = 0.43 (n-hexane/EtOAc = 1:2); ^{1}H NMR ($CDCl_3$): δ 9.63 (d, J = 2.4 Hz, 1H), 7.30−7.28 (m, 1H), 7.24−7.21 (m, 1H), 7.01−6.98 (m, 1H), 6.62−6.55 (m, 1H), 6.45 (d, J = 12.4 Hz, 1H), 5.96 (s, 1H), 5.66 (d, J = 14.8 Hz, 1H), 4.71 (d, J = 2.8 Hz, 2H), 3.84 (s, 3H), 3.73 (s, 3H), 3.27 (d, J = 6.0 Hz, 1H), 3.11−3.06 (m, 1H), 2.93−2.88 (m, 1H), 2.80−2.74 (m, 1H), 2.64−2.59 (m, 2H), 2.19−2.11 (m, 4H), 2.08 (d, J = 0.8 Hz, 3H), 1.90−1.72 (m, 5H), 1.61 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 186.4, 173.3, 169.6, 168.3, 157.6, 147.4, 142.0, 140.0, 139.4, 134.6, 134.2, 131.7, 122.7, 119.6, 117.3, 113.6, 111.9, 90.4, 85.3, 84.1, 78.0, 76.5, 57.9, 57.4, 55.4, 52.2, 49.8, 33.5, 30.9, 28.8, 28.0, 24.4, 22.0, 20.4, 14.4; IR (ZnSe, cm^{-1}) 665, 748, 1028, 1206, 1236, 1449, 1504, 1552, 1730, 2949; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{35}H_{38}NO_9^+$ 616.2541; found 616.2539; Optical rotation $[\alpha]_D^{23}$ −6.1 (c 0.50, $CHCl_3$).

*(S)-1-((4-(2-Methoxy-6-(prop-2-yn-1-yloxy)indolizin-3-yl)-4-oxobutanoyl)-L-alanyl)-N-((S)-1-((4-nitrophenyl)amino)-1-oxopropan-2-yl)pyrrolidine-2-carboxamide (**42**).* Prepared from succinyl-L-alanyl-L-prolyl-L-alanine p-nitroanilide (Suc-Ala-Pro-Ala-pNA, 47.7 mg, 99.9 μmol) and 2-methoxy-6-(prop-2-yn-1-yloxy)indolizine (60.5 mg, 0.150 mmol) in CH_2Cl_2 (0.5 mmol) at 30 °C for 20 h. Yield: 60.5 mg (66.0 μmol, 91.7%); Pale yellow solid (115 °C, decomposed); TLC R_f = 0.56 ($CHCl_3$/CH_3OH = 8:1); ^{1}H NMR ($CDCl_3$): δ 9.75 (d, J = 2.4 Hz, 1H), 9.26 (s, 1H), 8.16−8.12 (m, 2H), 8.00−7.95 (m, 2H), 7.39 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 9.6 Hz, 1H), 7.06−7.03 (m, 1H), 6.82 (d, J = 4.0 Hz, 1H), 5.98 (s, 1H), 4.68 (d, J = 2.0 Hz, 2H), 4.53−4.45 (m, 3H), 3.95 (s, 3H), 3.90−3.84 (m, 1H), 3.77−3.71 (m, 1H), 3.40−3.32 (m, 1H), 3.21−3.11 (m, 1H), 2.77−2.60 (m, 2H), 2.58 (t, J = 2.4 Hz, 1H), 2.31−2.21 (m, 1H), 2.01−1.94 (m, 3H), 1.50 (d, J = 7.6 Hz, 3H), 1.29 (d, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 186.5, 174.1, 173.1, 171.7, 171.6, 158.9, 147.4, 144.8, 143.3, 134.2, 124.9, 124.7, 119.7, 119.4, 117.4, 114.3, 112.1, 85.4, 62.2, 58.1, 57.5, 51.7, 50.0, 47.6, 35.5, 30.1, 28.5, 25.9, 16.7, 16.5; IR (ZnSe, cm^{-1}) 629, 750, 1254, 1331, 1454, 1504, 1595; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{33}H_{37}N_6O_9^+$ 661.2617; found 661.2613; Optical rotation $[\alpha]_D^{23}$ +4.7 (c 0.40, $CHCl_3$).

Procedure for Synthesis of Amine 33 (Scheme 5). *1-Amino-15-(2-methoxyindolizin-3-yl)-3,6,9,12-tetraoxapentadecan-15-one (**33**).* To a solution of *tert*-butyl (15-(2-methoxyindolizin-3-yl)-15-oxo-3,6,9,12-tetraoxapentadecyl)carbamate (**26**, 98.0 mg, 0.200 mmol, 1 equiv) in CH_2Cl_2 (3.0 mL) was added trifluoroacetic acid (0.60 mL) and a magnetic stir bar on an ice water bath. The vial was filled with argon, and the resulting solution was stirred on an ice water bath for 1 h. The solution was evaporated, and the residue was dissolved in CH_2Cl_2 (15 mL) and washed with a Na_2CO_3 saturated aqueous solution (15 mL x 3). The organic layer was dried with Na_2SO_4 and evaporated to afford the product. Yield: 76.1 mg (0.193 mmol, 96.5%); Pale yellow oil; ^{1}H NMR ($CDCl_3$): δ 9.94 (d, J = 6.4 Hz, 1H), 7.36−7.34 (m, 1H), 7.16−7.12 (m, 1H), 6.81−6.77 (m, 1H), 6.02 (s, 1H), 3.99 (s, 3H), 3.93 (t, J = 6.8 Hz, 2H), 3.69−3.61 (m, 12H), 3.54 (t, J = 5.6 Hz, 2H), 3.26 (t, J = 6.8 Hz, 2H), 2.90 (t, J = 6.8 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 186.1, 159.1, 137.2, 128.8, 125.1, 116.9, 112.7, 111.7, 85.3, 73.1, 70.70, 70.66, 70.5, 70.4, 67.5, 58.0, 41.9, 40.9; IR (ZnSe, cm^{-1}) 764, 1020, 1084, 1248, 1308, 1422, 1462, 1503, 1597, 1694, 2864; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{20}H_{31}N_2O_6^+$ 395.2177; found 395.2177.

Procedures for Synthesis Indolizines Connected with an Intramolecular Photosensitizer (Scheme 6B). *Diazido **46**.* To a solution of PPIX (281 mg, 0.499 mmol, 1 equiv), 17-azido-3,6,9,12,15-pentaoxaheptadecan-1-amine (383 mg, 1.25 mmol, 2.5 equiv), and DMAP (61.1 mg, 0.500 mmol, 1.0 equiv) in DMF (10 mL) in a 20 mL vial were added EDC·HCl (211 mg, 1.10 mmol, 2.2 equiv) and a magnetic stir bar. The vial was filled with argon, and the solution was stirred at 30 °C for 20 h. The solution was poured into a mixture of CH_2Cl_2 (50 mL) and washed with saturated NH_4Cl aqueous solution (50 mL × 3). The organic layer was dried with Na_2SO_4 and evaporated. The residue was purified by silica-gel column

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chromatography ($CHCl_3/CH_3OH$) to afford the product. Yield: 386 mg (0.339 mmol, 67.8%). Purple oil; TLC R_f = 0.56 ($CHCl_3/CH_3OH$ = 8:1); ^1H NMR ($CDCl_3$): δ 9.99 (s, 1H), 9.95 (s, 2H), 9.81 (s, 1H), 8.25−8.16 (m, 2H), 7.03−6.95 (m, 2H), 6.37−6.31 (m, 2H), 6.20−6.16 (m, 2H), 4.35−4.32 (m, 4H), 3.63 (s, 6H), 3.55 (s, 3H), 3.53 (s, 3H), 3.35−3.26 (m, 20H), 3.19−3.09 (m, 12H), 3.05 (t, J = 7.6 Hz, 4H), 2.83−2.78 (m, 6H), 2.74 (t, J = 5.2 Hz, 2H), 2.23−2.10 (m, 8H), −4.33 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 173.1, 136.3, 130.4, 120.9, 97.7, 97.2, 97.1, 96.9, 70.48, 70.46, 70.41, 70.3, 70.1, 69.9, 69.84, 69.81, 69.5, 69.4, 69.31, 69.26, 69.2, 69.1, 50.6, 39.8, 39.2, 23.2, 12.9, 12.8, 11.8, 11.7; IR (ZnSe, cm^{-1}) 677, 737, 851, 1103, 1275, 1639, 2100, 2864, 3308; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{58}H_{82}N_{12}NaO_{12}^+$ 1161.6067; found 1161.6071.

Diazido Photosensitizing Unit ***43***. To a stirring solution of diazido **46** (114 mg, 0.100 mmol, 1 equiv) in $CHCl_3$ (10 mL) in a 20 mL vial was added a solution zinc(II) acetate (64.2 mg, 0.350 mmol, 3.5 equiv) in CH_3OH (5 mL) at 60 °C. The heating was continued for 16 h under argon atmosphere. After the reaction, the resulting solution was washed with brine (15 mL × 3). The organic layer was dried with Na_2SO_4 and evaporated. The residue was purified by silica-gel column chromatography ($CHCl_3/CH_3OH$ = 1/0 to 10/1) to afford the product. Yield: 118 mg (98.1 μmol, 98.2%). Purple oil; TLC R_f = 0.55 ($CHCl_3/CH_3OH$ = 8:1); ^1H NMR ($CDCl_3$): δ 9.46 (s, 2H), 9.22 (s, 1H), 9.17 (s, 1H), 8.21−8.06 (m, 2H), 6.77−6.72 (m, 2H), 6.33−6.24 (m, 2H), 6.18−6.12 (m, 2H), 4.21−4.13 (m, 4H), 3.54 (s, 3H), 3.50 (s, 3H), 3.43 (s, 3H), 3.35 (s, 3H), 3.18−2.98 (m, 24H), 2.86−2.77 (m, 12H), 2.69−2.61 (m, 4H), 2.54−2.50 (m, 4H), 2.17−2.05 (m, 8H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 173.2, 146.9, 146.7, 146.0, 145.5, 139.3, 139.1, 136.5, 136.4, 136.2, 136.0, 130.84, 130.77, 119.5, 97.7, 97.1, 96.8, 70.3, 70.2, 70.1, 69.8, 69.6, 69.5, 69.2, 69.0, 50.3, 39.8, 39.1, 23.1, 13.0, 12.9, 11.7, 11.6; IR (ZnSe, cm^{-1}) 708, 851, 934, 1103, 1553, 1638, 2100, 2864, 3289; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{58}H_{81}N_{12}O_{12}Zn^+$ 1201.5383; found 1201.5375.

Pseudolaric Acid B Caged ***44***. A solution of copper(II) sulfate pentahydrate (6.49 mg, 26.0 μmol, 2.0 equiv) in water (260 μL), a solution of TBTA (27.6 mg, 52.0 μmol, 4.0 equiv) in DMSO (900 μL), and a solution of sodium L-ascorbate (5.2 mg, 26 μmol, 2.0 equiv) in water (140 μL) were combined. The resulting solution was combined with solutions of alkyne **41** (39.6 mg, 59.9 μmol, 3.0 equiv) in CH_3OH (900 μL) and diazido **43** (15.6 mg, 13.0 μmol, 1 equiv) in $CHCl_3$ (0.4 mL) in a 4 mL vial. The resulting solution was stirred at 30 °C for 4 h under argon atmosphere. The solution was then diluted with EtOAc (15 mL), and the resulting mixture was washed with brine (10 mL × 3). The organic layer was dried with Na_2SO_4 and evaporated. The residue was purified by silica-gel column chromatography ($CHCl_3/CH_3OH$ = 1/0 to 9/1). The product was further purified by GPC (YMC-GPC T2000, 21.2 × 600 mm, $CHCl_3$) to afford the product. Yield: 26.1 mg (10.7 μmol, 82.7%). Purple solid (110 °C, decomposed); TLC R_f = 0.55 ($CHCl_3/CH_3OH$ = 8:1); ^1H NMR ($CDCl_3$): δ 10.17 (s, 1H), 10.05 (s, 1H), 10.02 (s, 1H), 9.96 (s, 1H), 9.14 (s, 1H), 8.38−8.30 (m, 2H), 7.23−7.21 (m, 1H), 7.13 (s, 1H), 7.11 (d, J = 2.4 Hz, 1H), 7.03 (d, J = 6.0 Hz, 1H), 6.64−6.52 (m, 4H), 6.33 (d, J = 16.8 Hz, 4H), 6.10 (d, J = 11.2 Hz, 2H), 5.85 (s, 2H), 5.66 (d, J = 14.8 Hz, 2H), 4.37−4.33 (m, 4H), 4.04 (d, J = 8.4 Hz, 3H), 3.81 (s, 5H), 3.73 (s, 8H), 3.70−3.69 (m, 8H), 3.65−3.57 (m, 3H), 3.54 (d, J = 5.2 Hz, 5H), 3.25−2.36 (m, 57H), 2.17−1.72 (m, 24H), 1.60 (s, 10H), 1.25 (s, 2H); IR (ZnSe, cm^{-1}) 642, 1231, 1416, 1447, 1516, 1714, 1730; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{128}H_{154}N_{14}NaO_{30}Zn^+$ 2454.0139; found 2454.0132; $^{13}C\{^1H\}$ NMR could not be characterized due to concentration-dependent self-aggregation of zinc porphyrin;[24] Optical rotation could not be characterized due to absorbance and emission of zinc porphyrin at 589 nm; HPLC R_t 24.5 min (COSMOSIL C_{18}-MS-II, 4.6 × 100 mm; H_2O/acetonitrile = 90/10 to 0/100, 30 min, 1.0 mL/min). Note that compound **44** is sensitive to daylight. The experiments were performed in the dark.

Succinyl-L-alanyl-L-prolyl-L-alanine p-nitroanilide Caged ***45***. A solution of copper(II) sulfate pentahydrate (9.99 mg, 40.0 μmol, 2.0 equiv) in water (400 μL), a solution of TBTA (42.5 mg, 80.1 μmol, 4.0 equiv) in DMSO (1.4 mL), and a solution of sodium L-ascorbate (7.94 mg, 40.0 μmol, 2.0 equiv) in water (200 μL) were combined. The resulting solution was combined with solutions alkyne **42** (39.6 mg, 59.9 μmol, 3.0 equiv) in CH_3OH (1.4 mL) and diazido **43** (24.1 mg, 20.1 μmol, 1 equiv) in $CHCl_3$ (0.6 mL) in a 4 mL vial. The resulting solution was stirred at 30 °C for 4 h under argon atmosphere. The solution was then passed through a 0.21 μm syringe filter and purified by HPLC (COSMOSIL C_{18}-MS-II, 10 × 250 mm; H_2O/acetonitrile, 95/5 to 5/95, 30 min, 5 mL/min). The eluent was freeze-dried to afford the product. Yield: 45.5 mg (18.0 μmol, 89.8%). Purple solid (121 °C, decomposed); TLC R_f = 0.55 ($CHCl_3/CH_3OH$ = 8:1); ^1H NMR ($CDCl_3$): δ 10.14 (s, 1H), 10.01 (s, 1H), 9.98 (s, 1H), 9.87 (s, 1H), 9.11 (s, 2H), 9.03 (s, 2H), 8.36−8.26 (m, 2H), 8.02 (d, J = 9.2 Hz, 4H), 7.81 (d, J = 9.2 Hz, 4H), 7.43−7.30 (m, 4H), 7.04−7.00 (m, 2H), 6.93 (d, J = 10.4 Hz, 2H), 6.88 (t, J = 6.0 Hz, 2H), 6.60−6.56 (m, 2H), 6.35−6.29 (m, 2H), 6.14−6.08 (m, 2H), 5.75 (d, J = 3.2 Hz, 2H), 4.33−4.18 (m, 10H), 3.96−3.88 (m, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.76−3.73 (m, 5H), 3.69 (s, 3H), 3.65 (s, 3H), 4.47−3.45 (m, 8H), 3.38−3.34 (s, 2H), 3.26−3.20 (m, 4H), 3.10−2.60 (m, 48H), 2.28−2.18 (m, 4H), 2.03−2.01 (m, 2H), 1.80−1.68 (m, 6H), 1.28 (s, 3H), 1.26 (s, 3H), 1.16 (s, 3H), 1.14 (s, 3H); HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{124}H_{152}N_{24}NaO_{30}Zn^+$ 2544.0290; found 2544.0281; $^{13}C\{^1H\}$ NMR could not be characterized due to concentration-dependent self-aggregation of zinc porphyrin;[24] Optical rotation could not be characterized due to absorbance and emission of zinc porphyrin at 589 nm; HPLC R_t 23.9 min (COSMOSIL C_{18}-MS-II, 4.6 × 100 mm; H_2O/acetonitrile = 90/10 to 0/100, 30 min, 1.0 mL/min). Note that compound **45** is sensitive to daylight. The experiments were performed in the dark.

Procedures for Photoreactions. The photoreaction setup and the method for determination of reaction yields using ^1H NMR and HPLC measurements are according to our previous report.[5] The photoreactions were performed in a 4 mL glass vial (GL Sciences) placed in PhotoRedOx Box (EvoluChem) equipped with a Kessil H160 Tuna Flora LED lamp (40 W, maximum irradiation of a red channel) as a light source without use of a filter, unless otherwise noted. The distance from the light source to the irradiation vessel was ca. 10 cm.

Procedure A. Photoinduced release of compounds **17**, **18**, **19**, **27**, **28**, **29**, **30**, **31**, **34**, **35**, **36**, and **40** was performed according to procedure A. To a solution of a substrate (2.0 mM) and *t*-BuOH (2.0 mM) in methanol-d_4 (700 μL) in a 4 mL vial were added a solution of methylene blue in methanol-d_4 (2.0 mM, 7.0 μL, 1.0 mol %) and a magnetic stir bar under air. The solution was vigorously stirred by a magnetic stirrer at room temperature and photoirradiated for 30−60 s. After the irradiation, the solution was transferred to an NMR tube, and ^1H NMR measurement was performed. The reaction yields (%) were determined by comparison of the integral values of the peaks corresponding to the carboxylic acids and that of *t*-BuOH as an internal standard.

Procedure B. Photoinduced release of compounds **32** was performed according to procedure B. To a solution of a substrate (2.0 mM), *t*-BuOH (2.0 mM), Na_2HPO_4/NaH_2PO_4 (20 mM) in D_2O (700 μL, pD 7.0) in a 4 mL vial were added a solution of methylene blue in D_2O (2.0 mM, 7.0 μL, 1.0 mol %) and a magnetic stir bar under air. The solution was vigorously stirred by a magnetic stirrer at room temperature and photoirradiated for 60 s. After the irradiation, the solution was transferred to an NMR tube, and ^1H NMR measurement was performed. The reaction yield (%) was determined by comparison of the integral values of the peaks corresponding to 1-amino-3,6,9,12-tetraoxapentadecan-15-oic acid and that of *t*-BuOH as an internal standard.

Procedure C. Photoinduced release of compounds **37** and **38** were performed according to procedure C. To a solution of a substrate in acetonitrile (2.5 mM, 400 μL) in a 4 mL vial were added ultrapure water (100 μL), an aqueous solution of methylene blue (1.0 mM, 10 μL, 1.0 mol %), and a magnetic stir bar under air. The solution was vigorously stirred by a magnetic stirrer at room temperature and photoirradiated for 60 s. After the photoirradiation, a solution of 1-naphthol in acetonitrile (4.0 mM, 250 μL) was added, and a portion of the resulting solution was subjected to HPLC analysis. The

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reaction yields (%) were determined by comparison of the peak area of the carboxylic acids and that of 1-naphthol as a standard. The peak areas of the products were calibrated against that of 1-naphthol (R^2>0.99). The conditions for HPLC analysis are as below: Column: L-column3 C18, 5 μm, 4.6 × 100 mm (Chemical Evaluation and Research Institution); Mobile phase: **A** = acetonitrile, **B** = aqueous H_3PO_4 (40 mM); Gradient method: **A**/**B** = 5/95 to 95/5 (0−30 min); Flow rate: 0.50 mL/min.

Procedure D. Photoinduced release of compounds **39** was performed according to procedure D. To an acetonitrile solution (32 mL) of **25** (97.4 mg, 0.200 mmol, 1 equiv) in a 100 mL round-bottom flask were added ultrapure water (7.0 mL), an aqueous solution of methylene blue (1.0 mL, 2.0 mM, 1.0 mol %), and a magnetic stir bar under air. The solution was vigorously stirred by a magnetic stirrer at room temperature and photoirradiated for 120 s. The distance from the light source to the flask was ca. 1 cm. After the photoirradiation, the solvent was evaporated, and the residue was dried under vacuum. The residue was purified by silica-gel column chromatography ($CHCl_3$/CH_3OH/HCO_2H = 99/0/1 to 80/19/1) to afford indomethacin (**39**) for 70.4 mg (0.197 mmol, 98.4%) yield. ^{1}H NMR ($CDCl_3$): δ 7.65 (AA′BB′, 2H), 7.47 (AA′BB′, 2H), 6.94 (d, *J* = 2.0 Hz, 1H), 6.85 (d, *J* = 9.2Hz, 1H), 6.67 (dd, *J* = 9.2, 2.0 Hz, 1H), 3.82 (s, 3H), 3.68 (s, 2H), 2.38 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 176.0, 168.5, 156.2, 139.6, 136.4, 134.0, 131.4, 131.0, 130.7, 129.3, 115.2, 112.1, 111.9, 101.4, 55.9, 30.1, 13.5. The spectral data was consistent with the literature.[25]

Procedure E. Photoreactions of compounds **44** and **45** were performed according to procedure C. To a pH 7.4 sodium phosphate-buffered solution (0.1 M, 475 μL) containing serum albumin (0−2.0 mg/mL) in a 4 mL vial was added a DMSO solution of a substrate (0.40 mM, 25 μL) and a magnetic stir bar under air. The solution was vigorously stirred by a magnetic stirrer at room temperature and photoirradiated for 300 s. After the photoirradiation, a solution of phenol in DMSO (4.0 mM, 5.0 μL) was added, and a portion of the resulting solution was subjected to HPLC analysis. The reaction yields (%) were determined by comparison of the peak area of the carboxylic acids and that of phenol as a standard. The peak areas of the carboxylic acids were calibrated against that of phenol (R^2>0.99). Photoirradiation of compound **44** (20 μM) produced pseudolaric acid B for 30.8 μM (77.1% yield) and 29.0 μM (72.6% yield) in the absence and presence of serum albumin (30 μM), respectively. Irradiation of compound **45** (20 μM) produced Suc-Ala-Pro-Ala-*p*NA for 29.2 μM (73.8% yield) and 25.6 μM (64.0% yield) in the absence and presence of serum albumin (30 μM), respectively. The conditions for HPLC analysis are as below: Column: COSMOSIL MS-II C18, 5 μm, 4.6 × 100 mm (Nacalai Tesque); Mobile phase: **A** = acetonitrile, **B** = aqueous H_3PO_4 (40 mM); Gradient method: **A**/**B** = 10/90 to 60/40 (0−30 min, for **44**), **A**/**B** = 10/90 to 90/10 (0−30 min, for **45**); Flow rate: 1.0 mL/min. Note that compounds **44** and **45** are sensitive to daylight. The experiments were performed in the dark.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01244.

Copies of ^{1}H and ^{13}C{^{1}H} NMR spectra and HPLC chromatogram (PDF)

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Notes

The authors declare no competing financial interest.

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