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1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide Hydrochloride-Mediated Oxazole Rearrangement: Gaining Access to a Unique Marine Alkaloid Scaffold

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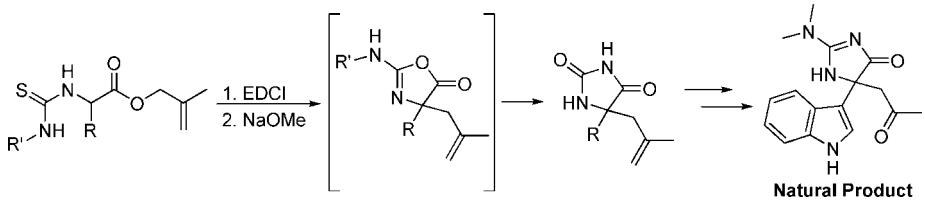

Reactions that create a quaternary stereocenter offer a wealth of synthetic utility and are often needed to provide access to the structural diversity of stereocenters found in natural products and biologically important molecules. We have developed a new 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI)-mediated oxazole rearrangement that affords quaternary 5,5-(aryl, allyl)-substituted hydantoins found in many biologically significant compounds. Furthermore, these quaternary hydantoins can be chemically manipulated to yield the corresponding quaternary imidazolones, which is a unique scaffold found in a compound from the tunicate *Dendrodoa grossularia*. Herein, we report the scope of this novel rearrangement and the proposed mechanism and showcase its utility through the total synthesis of a marine alkaloid from *D. grossularia* and two analogues.

Introduction

Quaternary hydantoins and imidazol-4-ones are synthetically intriguing and are contained in myriad compounds.[1−16] The quaternary hydantoin scaffold is found in herbicides, such as hydantocidin[14] (Figure 1), anticonvulsant drugs, such as 5,5-diphenylhydantoin[10] (Figure 1), and other pharmacologically significant compounds.[7,12] The imidazolone and quaternary imidazolone scaffold are found in a variety of natural products that also host interesting biological properties, such as leucettamine B, leucettamidine, hymenialdisine, and kottamides A−D, which exhibit anti-inflammatory activity.[1−3,5,6] Additional examples include some of the dispacamides, mauritiamine, and a few of the rhopaladins which display potent antihistamine, antifouling, and antibacterial activity, respectively.[4,13,15,16] Still there are others including calcaridine A,[9] polyandrocarpamines A and B,[8] and a unique indole marine alkaloid (**1**; Figure 1) from the tunicate *Dendrodoa grossularia*[11] whose biological activity has not yet been reported.

Prompted by the potent biological activity of the hymenialdisine analogue, indoloazepine[17,18] (Figure 1), we were interested in synthesizing indole alkaloid **1**. However, a synthetic route needed to be constructed to access the unique 5,5-

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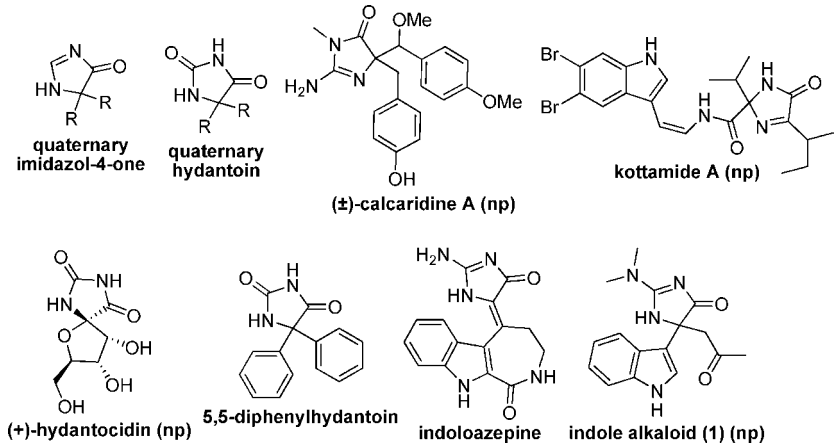
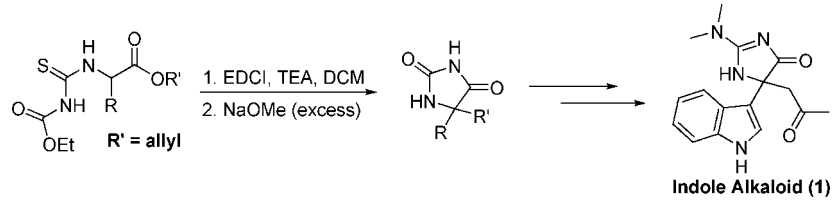


FIGURE 1. Compounds containing the imidazolone or hydantoin scaffold (np = natural product).

SCHEME 1. New Rearrangement Leading to the Synthesis of Indole Alkaloid (1)



(disubstituted)-imidazol-4-one scaffold found in the natural product. A 5,5-(aryl, allyl)-substituted hydantoin derived from an oxazole rearrangement, modeled after the rearrangement developed by Steglich and co-workers,[19] was thought to be a novel and ideal approach to access the indole alkaloid **1**. The hydantoin intermediate could serve as a building block to the imidazolone scaffold[20,21] and act as a synthetic handle with which we could replace the carbonyl in the 2-position of the hydantoin with potentially any amine, giving access to a number of analogues if desired. In addition, the allyl group would provide easy access to the keto functionality found in the indole alkaloid (**1**).

Overall, a novel rearrangement (Scheme 1) that gives access to a unique marine alkaloid scaffold was developed. The one-pot reaction converts a thiourea into a 5,5-(aryl, allyl)-oxazolone through a new twist on the oxazole rearrangement, which upon further treatment with sodium methoxide yields a 5,5-(aryl, allyl)-hydantoin. As a result, this hydantoin is able to offer a concise synthetic route to molecules such as indole alkaloid **1**. This article describes the scope and proposed mechanism of this novel rearrangement in addition to its utility in the synthesis of a natural product and analogues from the tunicate *D. grossularia*.

Results and Discussion

I. Scope of Rearrangement. Traditional reagents used for the activation of a thiourea toward attack by a nucleophile[22−26] were screened, and it was found that the success of the reaction was highly dependent on the reagent choice. Mercuric chloride did provide a reasonable yield of the quaternary hydantoin (49%), while Mukaiyama's reagent failed to produce any desired hydantoin. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) was the most effective at yielding the quaternary hydantoin in good yields (70%). Furthermore, the hazard of mercury waste removal and the ease of workup with EDCI solidified the reason to use EDCI as the reactant for the rest of the study. A more cost efficient carbodiimide, dicyclohexylcarbodiimide (DCC), was also attempted in the rearrangement but failed to provide any reasonable yields (<5%). Polymer-supported EDCI provided the desired product, although longer reaction times were necessary. A brief solvent screen revealed that dichloromethane (DCM) provided the best results (70%), while solvents such as acetonitrile, benzene, tetrahydrofuran, and dichloroethane all yielded poorer results (50%, 30%, 47%, and 12%, respectively).

The first structural aspect investigated in the rearrangement was the different groups compatible at the R position (Scheme 1). Each of the different thiourea starting materials was synthesized through standard amino acid chemistry (Scheme 2). The *N*-Boc protected amino acids **2a**−**f** (R = methyl, benzyl, phenyl, *p*OMe-phenyl, *p*F-phenyl, and napthyl) were esterified with the appropriate allylic alcohol using DCC to produce esters **3a**−**g**. Deprotection of the Boc group with a mixture of TFA and DCM (1:1) led to the TFA salt of the amino allylic esters **4a**−**g**. Upon treatment of the amine salts with ethyl isothiocyanatoformate under basic conditions, the desired thioureas **5a**−**g** were produced. The synthesis of thiourea **5h** (R = *N*-tosyl indole; Table 1) followed a modified synthetic pathway and was

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SCHEME 2. General Synthesis of Thioureas 5a−g; 10a,b

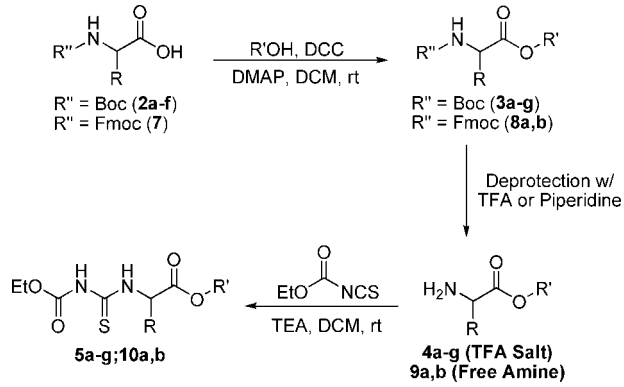
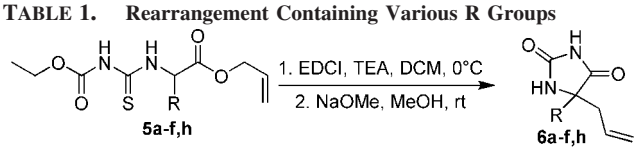


TABLE 1. Rearrangement Containing Various R Groups



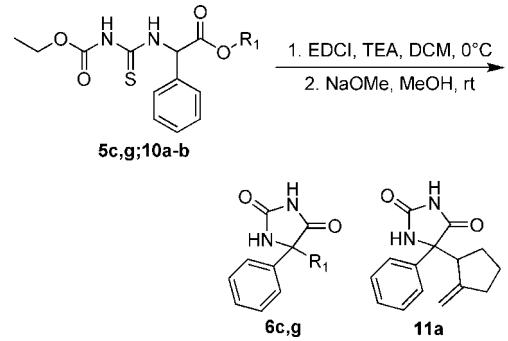
entry	R	yield (%)
5a	Me	0
5b	Bn	19
5c	Ph	70
5d	*p*-OmePh	67
5e	*p*-F-Ph	57
5f	napth	31
5h	*N*-tosyl indole	70

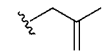
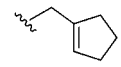
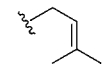
prepared following the procedures of Katz and co-workers (see Supporting Information).[27]

The results of the rearrangement with the various R groups are illustrated in Table 1. It is shown that an alkyl group such as a methyl provided no product, while a benzyl only performed slightly better by producing the quaternary hydantoin **6b** in low yields (19%). When R = aryl (**5c**−**5f**), the rearrangement occurred in good yields (Table 1) except for when R = napthyl, which could be attributed to the steric bulk of the napthyl group. The rearrangement was also successful in using a heterocycle in the R position with the *N*-tosyl indole thiourea **5h**, providing the corresponding hydantoin **6h** in good yields.

Different allyl groups compatible with the rearrangement were subsequently examined. The synthesis of the thiourea with a 1,1-disubstituted allylic moiety (**5g**) followed the synthetic route outlined in Scheme 2 (when R″ = Boc). However, when trisubstituted allylic thioureas were synthesized using the corresponding trisubstituted allylic alcohols, a different route was adopted. It was found that the higher substituted allylic esters would decompose to the corresponding carboxylic acids when treated with TFA during the deprotection of the Boc group.[28] As a result, the Fmoc protecting group was used for the synthesis of thioureas **10a**,**b** (Scheme 2). Using Fmoc protected phenyl glycine as the starting material, allylic esters **8a**,**b** were produced under the same conditions previously described using DCC and 4-(dimethylamino)pyridine (DMAP). Deprotection of the Fmoc group from the amine was completed using piperidine to afford the free amines **9a**,**b**. Upon treatment

TABLE 2. Rearrangement Containing Differently Substituted Allyl Groups



entry	R_1	Yield (%)
5c		70
5g		66
10a		66
10b		47

of the amines with ethyl isothiocyanatoformate, the corresponding thioureas **10a**,**b** were formed in moderate yields.

The rearrangement proceeded in good yields with all of the differently substituted allylic esters that were synthesized (Table 2). When the 1,1-disubstituted allyl group was used (entry **5g**) the rearrangement gave a similar yield of corresponding quaternary hydantoin as the allyl group (entry **5c**). With the success of this particular rearrangement, application of the new reaction could be used in the synthesis of the natural product (**1**). Entry **10a**, which contained a 1,1,2-trisubstitution pattern on the allylic group, was also as successful as the other entries. However, unlike the previous two quaternary hydantoins **6c** and **6g**, the product from the rearrangement (**11a**) contained two stereocenters allowing for the formation of diastereomers. It was observed by ^{1}H NMR and ^{13}C NMR that two inseparable diastereomers were formed from the reaction in about a 1:1.3 ratio. The last entry in Table 2 includes an allyl moiety containing a 1,2,2-trisubstitution pattern (**10b**). It is hypothesized that the lower yield resulting from this rearrangement could be attributed to the steric bulk of this particular trisubstituted allyl group. An electron withdrawing group (ethyl carbamate) on the thiourea was only used since it was previously found that electron withdrawing groups accelerate the reaction of a thiourea and desulfurizing reagent and increase the reactivity of the corresponding carbodiimide toward a nucleophile.[29]

II. Proposed Reaction Mechanism. The proposed mechanism is illustrated below in Scheme 3. The first step is thought to be the transformation of the starting thiourea to a carbodiimide intermediate (**12**). Although this intermediate has not been isolated or observed experimentally, it is presumed to be formed based on previous studies.[29] Several reports suggest that thioureas undergo a desulfurization with reagents such as EDCI, $HgCl_2$, Mukaiyama's

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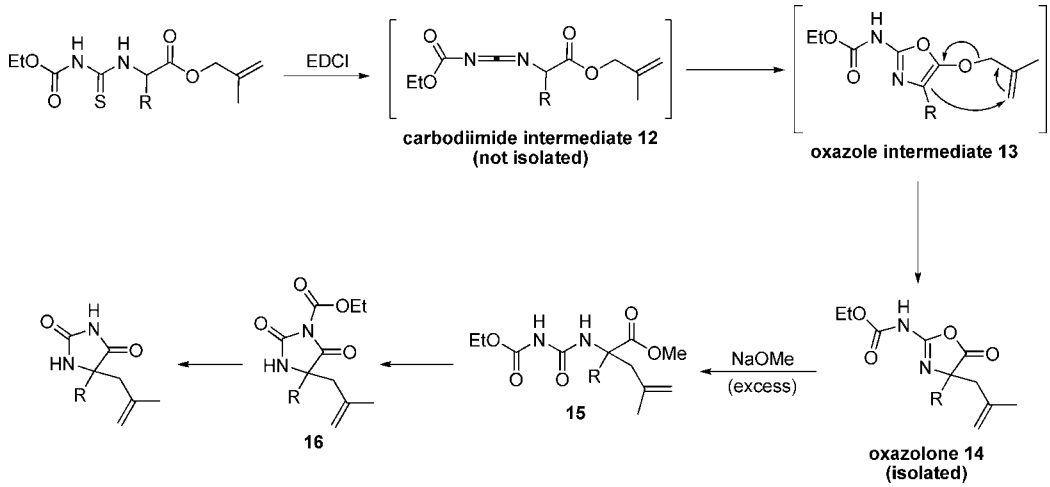
SCHEME 3. Proposed Reaction Mechanism of EDCI-Mediated Rearrangement



reagent, and others to afford a carbodiimide intermediate.[29−31] Subsequently, the transient carbodiimide could be attacked by an external nucleophile, such as an amine, to produce guanidines with various substitutions.[22−25,29,31−35] Furthermore, cyclizations to form different heterocycles have also been shown to occur through an attack of a nucleophile on a carbodiimide formed from the desulfurization of a thiourea. Batey and Evindar produced various iminohydantoins through a cyclization that occurred after a carbodiimide intermediate, formed using $HgCl_2$, was attacked by an internal amide.[36] Additionally, Drewry and Ghiron utilized a desulfurization of a thiourea with Mukaiyama's reagent to form 2-aminoimidazolinones.[30] It was suggested that when the thiourea was treated with Mukaiyama's reagent, a carbodiimide intermediate was formed and reacted with an external amine, resulting in a cyclization to yield an aminoimidazolinone.[30] These examples serve as supportive evidence to reasonably conclude that the initial step in the rearrangement involves the formation of a carbodiimide intermediate. The carbodiimide is believed to be very reactive, thus giving reason for a short lifespan and consequently being unobservable spectroscopically. As a consequence of the carbodiimide's high reactivity, the carbonyl of the ester is believed to be nucleophilic enough to attack the carbodiimide, in a similar fashion as the amide in the report by Batey and Evindar,[36] to cause a cyclization reaction affording an oxazole intermediate (**13**; Scheme 3).

After oxazole **13** undergoes a Claisen rearrangement, oxazolone intermediate **14** is formed (Scheme 3), which was isolated and characterized (when R = *N*-tosyl indole) using ^{1}H NMR, ^{13}C NMR, HRMS, and IR (see Supporting Information). It is proposed that, from oxazolone **14**, the mechanism of the novel rearrangement continues with the nucleophilic opening of the oxazolone by sodium methoxide to yield urea **15**. As a consequence of having excess sodium methoxide in the reaction mixture, urea **15** is deprotonated and cyclizes to form hydantoin **16**. Further modification of **16** by sodium methoxide yields the final quaternary hydantoin upon removal of the ethoxy carbonyl group (Scheme 3).

The step in which the quaternary stereocenter was formed illustrates an oxazole rearrangement first described by Steglich and co-workers, in which an allyl ester of an *N*-acyl amino acid is converted into an oxazolone using a variety of dehydrating reagents.[19,37] Steglich discusses an additional hetero-Cope rearrangement that occurs depending on the substitution of the allyl ester.[19,37] It is noteworthy to mention that this additional hetero-Cope rearrangement was not observed in our rearrangement.

Steglich's oxazole rearrangement is a useful tool to create a quaternary stereocenter and has been used to produce 4-fluoropyridines,[38] a variety of α-trifluoromethyl α-amino acids,[39−41] α-allenic α-amino acids,[42,43] α-benzyl γ-lactam derivatives,[44] α-benzyl δ-lactam derivatives,[44] α-benzylproline derivatives,[44] *C*-glycosyl α-amino acids,[45] and α-D-*C*-mannosyl-(*R*)-alanine.[46] Despite the many accounts to use this rearrangement to afford various substrates including precursors to **1**, the main disadvantage was the inability to remove the *N*-acyl group without using harsh basic or acidic conditions. This disadvantage was the driving force to create a new rearrangement in which the product could be more amenable toward synthesizing the natural product (**1**).

III. Application toward Syntheses of Indole Alkaloid 1 and Analogues. The EDCI-mediated oxazole rearrangement offers a unique and efficient way to create a quaternary heterocycle capable of being transformed into the scaffold needed for the synthesis of the indole alkaloid (**1**). The natural

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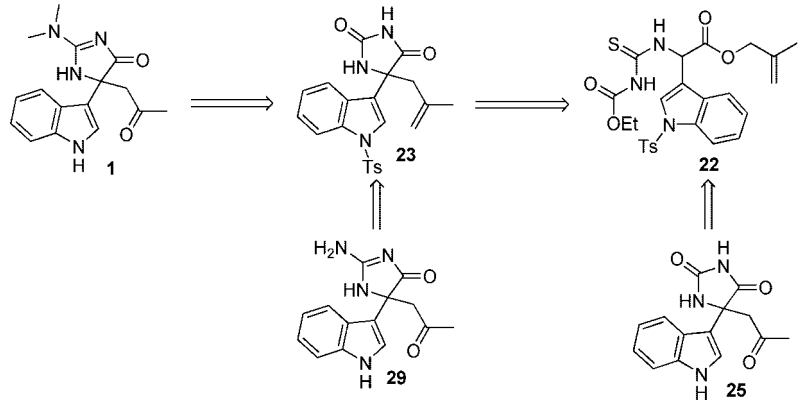
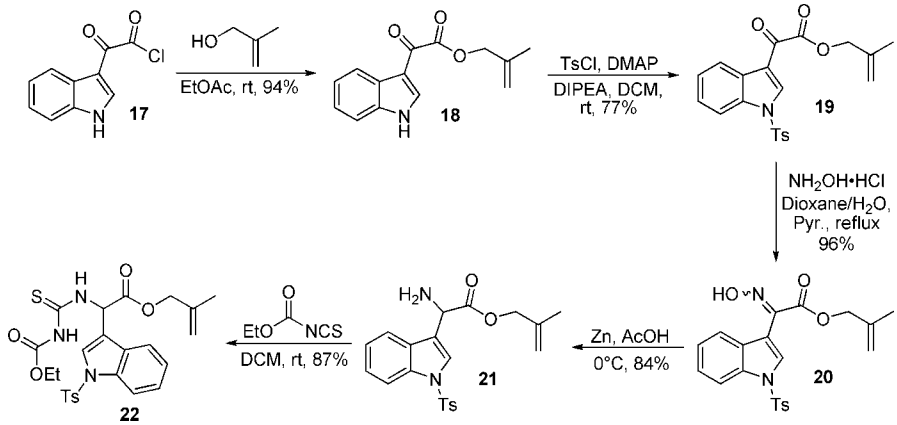
SCHEME 4. Retrosynthetic Strategy for the Synthesis of 1 and Analogues 25 and 29



SCHEME 5. Synthesis of Thiourea 22



product was isolated in 1998[11] and comes from the tunicate *D. grossularia,* which is a red marine organism that grows along the coasts of Brittany and in the Baltic and North Seas and contains small heterocyclic alkaloids with unique scaffolds.[47−52] Initial studies on the extracts of this tunicate unveiled definite cytotoxic activity toward the L1210 leukemia cell line. As a result, four indole alkaloids were isolated and tested, all with variable results.[52,53] As part of our laboratory's focus on the syntheses of pharmacologically significant scaffolds,[54] we recently reported the first total synthesis of the indole alkaloid (**1**).[55] Two additional analogues have since been synthesized and are reported herein.

Our retrosynthetic strategy for the total synthesis of indole alkaloid **1** and two analogues is illustrated in Scheme 4. It was envisioned that the imidazolone moiety of the indole alkaloid and analogue 2 (**29**) could be accessed from the hydantoin intermediate **23** utilizing classical chemical modifications.[20,21] After exploration of the new oxazole rearrangement, hydantoin **23** was thought to be formed from thiourea **22** using the protocol developed for the transformation. Analogue 1 (**25**) was also envisioned to be formed from thiourea **22** by slightly modifying the rearrangement to include a removal of the tosyl protecting group.

The synthetic route to thiourea **22** began with an esterification of the indole acid chloride **17**, which is the product of a known reaction between indole and oxalyl chloride[56,57] with 2-methyl-2-propen-1-ol to produce keto allyl ester **18** (Scheme 5). Subsequent protection of the indolic nitrogen with *p*-toluene sulfonyl chloride afforded keto ester **19**, which, when treated with hydroxylamine and pyridine in dioxane, produced oxime **20** in a 96% yield as a mixture of E and Z isomers. Reduction of the oxime using zinc and acetic acid led to amine **21**, which was treated with ethyl isothiocyanatoformate to yield thiourea **22**.

Subsequent treatment of thiourea **22** with EDCI followed by sodium methoxide yielded hydantoin **23** (Scheme 6) in a 71% yield, resulting from the oxazole rearrangement. The synthesis of indole alkaloid **1** was completed following the previously described pathway.[55] The versatility of the synthetic pathway developed for the natural product was illustrated in the synthesis of two analogues that required no major modification of the original synthetic route. Hypothetically, a number of analogues could be developed with the synthetic route as a result of the diversity allowed in the rearrangement and the variety of amines that could be used to create the final imidazolone.

The first analogue, hydantoin **25,** shown in Scheme 6, was synthesized using the same thiourea **22** used to produce the

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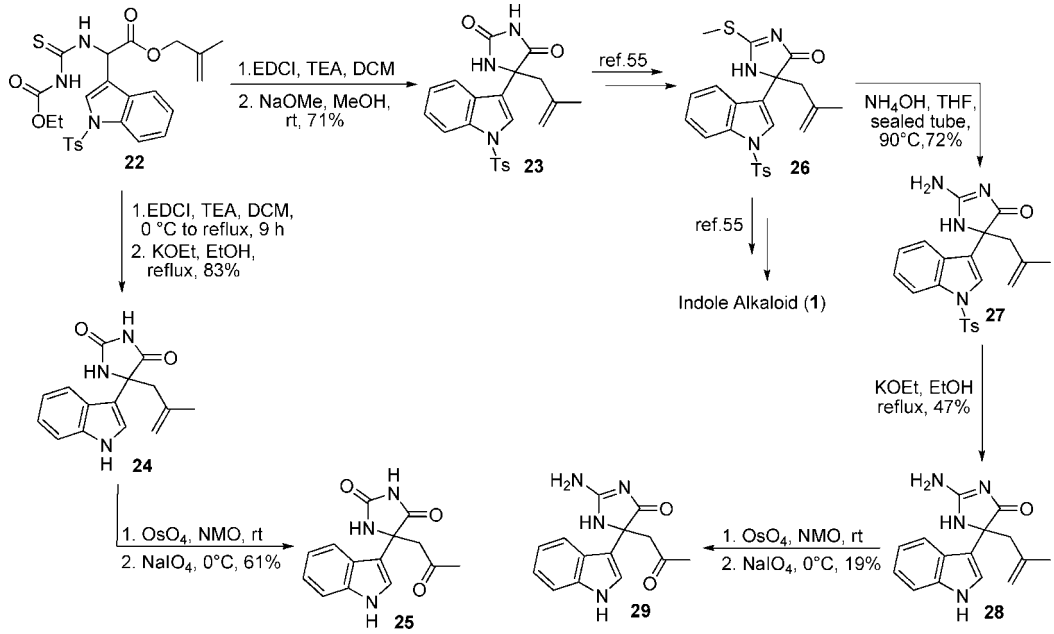
SCHEME 6. Synthesis of Indole Alkaloid 1 and Analogues 25 and 29



natural product. Instead of carefully monitoring the second step of the rearrangement to avoid removal of the tosyl protecting group, a mixture of potassium ethoxide and ethanol was used and refluxed overnight to yield hydantoin **24**. Using the same procedure as the natural product synthesis, the terminal olefin on hydantoin **24** was oxidized to the ketone in a 61% yield affording hydantoin **25** (analogue 1).

The second analogue also shown in Scheme 6, imidazolone **29,** took advantage of the synthetic handle that *S*-methylimidazolone **26** provided because of its reactivity and tendency to be substituted with a nucleophile. In this instance, the *S*-methyl group was replaced using ammonium hydroxide to give imidazolone **27** in a good yield. The deprotection method previously seen with the natural product synthesis was used to afford imidazolone **28**. Finally, the synthesis of analogue 2 (**29**) was completed after the terminal alkene of **28** was oxidized under previously determined conditions. Unfortunately, because of the difficult nature of isolating the product, only 19% of imidazolone **29** was recovered, although the overall conversion was higher.

In summary, we have developed a new EDCI-mediated oxazole rearrangement that yields a quaternary hydantoin as the final product. The rearrangement tolerates different aryl groups α to the ester of the thiourea and differently substituted allyl esters. The utility of the rearrangement allows us to gain access to a unique imidazolone scaffold found in nature, whose structure has only begun to be explored. Biological evaluation of the indole alkaloid (**1**) and analogues (**25** and **29**) is currently underway in our laboratory.

Experimental Section

Representative Example for the Preparation of *N*-Boc Protected Amino Esters (3a−g). To a flame-dried 100 mL round-bottom flask were added **2c** (1.5 g, 5.97 mmol) and anhydrous DCM (50 mL). Then allyl alcohol (0.82 mL, 11.95 mmol) and DMAP (73 mg, 0.597 mmol) were added, and the mixture was brought down to 0 °C. DCC (1.85 g, 8.96 mmol) was then added, and the mixture was allowed to warm to room temperature overnight while stirring under nitrogen. The white precipitate that formed was filtered off, and the DCM filtrate was washed with brine (1 × 20 mL), dried using anhydrous sodium sulfate, and concentrated. The crude residue was purified by column chromatography (silica gel, 20% EtOAc; 80% hexane) affording the product (**3c**) as a whitish solid. Yield (1.49 g, 86%). ^{1}H NMR (500 MHz), $CDCl_3$: δ 1.41 (s, 9H), 4.58−4.6 (m, 2H), 5.12−5.17 (m, 2H), 5.32 (d, J = 8 Hz, 1H), 5.56 (bs, 1H), 5.75−5.83 (m, 1H), 7.26−7.36 (m, 5H). ^{13}C NMR (125 MHz), $CDCl_3$: δ 28.2, 57.6, 65.9, 80.0, 118.3, 127, 128.3, 128.7, 131.3, 136.8, 154.7, 170.7. IR (NaCl): 3390 cm^{-1}, 1750 cm^{-1}, 1710 cm^{-1}. HRMS: $[M + H]^+$ = 292.1559, calcd for $C_{16}H_{22}NO_4$, 292.1549. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 66.78; H, 7.14; N, 4.78. Mp: 40−42 °C.

Representative Example for the Preparation of Amine−TFA (4a−g). To a 100 mL round-bottom flask were added **3c** (1.44 g, 4.95 mmol), DCM (2.5 mL), and TFA (2.5 mL). The resulting solution was stirred for 30 min. The excess TFA and DCM were removed, and $CHCl_3$ (3 × 15 mL) was added and subsequently taken off to remove any residual TFA. The product was precipitated out of the crude residue using ether/petroleum ether to afford the product (**4c**) as a white solid. Yield (1.48 g, 98%).^{1}H NMR (500 MHz), DMSO: δ 4.66 (m, 2H), 5.12−5.16 (m, 2H), 5.33 (s, 1H), 5.8 (m, 1H), 7.44−7.5 (m, 5H), 9.07 (bs, 3H). ^{13}C NMR (125 MHz), DMSO: δ 55.4, 66.0, 113.6, 115.9, 118.1, 118.3, 120.7, 128.1, 129.0, 129.5, 131.5, 132.6, 157.9, 158.2, 158.4, 158.7, 168.1. IR (KBr): 3150 (br) cm^{-1}, 1745 cm^{-1}, 1675 cm^{-1}. HRMS: $[M + H]^+$ = 192.1027, calcd for $C_{11}H_{14}NO_2$, 192.1025. Anal. Calcd for $C_{13}H_{14}F_3NO_4$: C, 51.15; H, 4.62; N, 4.59. Found: C, 50.95; H, 4.51; N, 4.45. Mp = 96−98 °C.

Representative Example for the Preparation of Thioureas (5a−g). To a flame-dried 100 mL round-bottom flask were added **4c** (1.48 g, 4.85 mmol) and anhydrous DCM (50 mL). Then the solution was brought down to 0 °C, and anhydrous tetraethylammonium (TEA; 0.74 mL, 5.33 mmol) was added followed by dropwise addition of ethoxycarbonyl isothiocyanate (0.66 mL, 5.82 mmol). The solution was allowed to warm to room temperature overnight while stirring under a nitrogen atmosphere. The solvent was removed, and ether (30 mL) was added to the crude residue and was washed with saturated sodium bicarbonate. The organics were dried using anhydrous sodium sulfate and concentrated. The crude residue was purified by column chromatography (silica gel, 30% EtOAc; 70% hexane) affording the product (**5c**) as a whitish solid. Yield (1.39 g, 89%). ^{1}H NMR (500 MHz), $CDCl_3$: δ 1.29 (t, J = 7 Hz, 3H), 4.23 (m, 2H), 4.64 (m, 2H), 5.14−5.22 (m, 2H),

5.81 (m, 1H), 5.98 (d, J = 7 Hz, 1H), 7.3−7.45 (m, 5H), 8.06 (s, 1H), 10.59 (d, J = 6 Hz, 1H). ^{13}C NMR (125 MHz), $CDCl_3$: δ 14.0, 61.8, 62.8, 66.2, 118.5, 127.5, 128.7, 128.9, 131.1, 135.0, 152.5, 169.3, 178.9. IR (KBr): 3290 cm^{-1}, 3225 cm^{-1}, 1750 cm^{-1}, 1720 cm^{-1}. HRMS: $[M + H]^+$ = 323.1070, calcd for $C_{15}H_{19}N_2O_4S$, 323.1066. Anal. Calcd for $C_{15}H_{18}N_2O_4S$: C, 55.88; H, 5.63; N, 8.69. Found: C, 55.46; H, 5.51; N, 8.68. Mp = 44−46 °C.

Representative Example for the Procedure of the Rearrangement Affording Hydantoins (6a−h, 11a,b). To a flame-dried 50 mL round-bottom flask were added **5c** (150 mg, 0.466 mmol) and anhydrous DCM (15 mL). Then anhydrous TEA (0.2 mL, 1.4 mmol) was added, and the mixture was cooled to 0 °C. EDCI (197 mg, 1.02 mmol) was then added, and the mixture was stirred at 0 °C under nitrogen for 1 h and then refluxed for 15 h. After the first step was completed (as indicated by TLC), the solution was cooled to 0 °C, and a solution of NaH (93 mg, 2.33 mmol) in MeOH (5 mL) was added dropwise. The cloudy mixture was stirred at 0 °C for 1 h and then at room temperature for 2 h. The mixture was acidified with 5% HCl, and then the solvents were removed. The aqueous mixture was extracted with EtOAc (3 × 30 mL), and then the organics were combined, dried using anhydrous sodium sulfate, and concentrated. The crude residue was purified by column chromatography (silica gel, 20% EtOAc; 80% DCM) affording the product (**6c**) as a whitish solid. Yield (70 mg, 70%). ^{1}H NMR (500 MHz), acetone: δ 2.78 (dd, J = 7, 14 Hz, 1H), 2.95 (dd, J = 7, 14 Hz, 1H), 5.13 (d, J = 10 Hz, 1H), 5.21 (d, J = 17 Hz, 1H), 5.73 (m, 1H), 7.33 (t, J = 8 Hz, 1H), 7.4 (t, J = 8 Hz, 2H), 7.64 (d, J = 8 Hz, 2H), 7.68 (s, 1H), 9.65 (s, 1H). ^{13}C NMR (125 MHz), acetone: δ 43.5, 68.6, 120.8, 126.3, 128.7, 129.3, 132.0, 139.7, 157.0, 175.9. IR (KBr): 3245 cm^{-1} (broad), 1774 cm^{-1}, 1724 cm^{-1}. HRMS: $[M + H]^+$ = 217.0979, calcd for $C_{12}H_{13}N_2O_2$, 217.0977. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.43; H, 5.49; N, 12.90. Mp = 172−174 °C.

Representative Example for the Preparation of Fmoc Protected Amino Esters (8a,b). To a flame-dried 100 mL round-bottom flask were added **7** (1.21 g, 3.24 mmol) and anhydrous DCM (50 mL). Then cyclopent-1-enylmethanol[58] (477 mg, 4.87 mmol) and DMAP (40 mg, 0.324 mmol) were added, and the mixture was brought down to 0 °C. DCC (1 g, 4.87 mmol) was then added, and the mixture was allowed to warm to room temperature overnight while stirring under nitrogen. The white precipitate that formed was filtered off, and the DCM filtrate was washed with brine (1 × 20 mL), dried using anhydrous sodium sulfate, and concentrated. The crude residue was purified by column chromatography (silica gel, 20% EtOAc; 80% hexane) affording the product (**8a**) as a whitish solid. Yield (997 mg, 68%). ^{1}H NMR (500 MHz), $CDCl_3$: δ 1.82 (p, J = 8 Hz, 2H), 2.13 (s, 2H), 2.27 (s, 2H), 4.2 (t, J = 7 Hz, 1H), 4.38 (m, 2H), 4.70 (m, 2H), 5.40 (d, J = 7 Hz, 1H), 5.52 (s, 1H), 5.89 (d, J = 7 Hz, 1H), 7.28−7.4 (m, 9H), 7.57 (d, J = 7 Hz, 2H), 7.74 (d, J = 8 Hz, 2H). ^{13}C NMR (125 MHz), $CDCl_3$: δ 23.1, 32.3, 32.5, 47.1, 58.0, 64.4, 67.1, 119.9, 125.0, 127.0, 127.1, 127.6, 128.5, 128.8, 129.1, 136.6, 138.1, 141.2, 143.7, 143.8, 155.3, 170.6. IR (NaCl): 3350 cm^{-1}, 1725 cm^{-1} (broad). HRMS: $[M + H]^+$ = 454.2020, calcd for $C_{29}H_{28}NO_4$, 454.2018. Anal. Calcd for $C_{29}H_{27}NO_4$: C, 76.80; H, 6.00; N, 3.09. Found: C, 76.97; H, 5.84; N, 3.12. Mp = 96−98 °C.

Representative Example for the Preparation of Amino Esters (9a,b). To a 100 mL round-bottom flask were added **8a** (947 mg, 2.09 mmol) and DCM (8 mL). The solution was brought down to 0 °C, and then piperidine (2 mL, 20.9 mmol) was added; the mixture was stirred under nitrogen for 1 h and then 1 h at room temperature. The solvent was then removed, and the crude residue was taken up in EtOAc (40 mL) and washed with saturated NH_4Cl (1 × 10 mL) and brine (1 × 10 mL). The organics were dried using anhydrous sodium sulfate and concentrated. The crude residue was purified by column chromatography (silica gel, 30% EtOAc; 70% hexane, then 90% DCM, 10% MeOH) affording the product (**9a**) as an oil. Yield (434 mg, 90%).^{1}H NMR (500 MHz), $CDCl_3$: δ 1.77−1.83 (m, 2H), 1.91 (s, 2H), 2.1−2.15 (m, 2H), 2.22−2.28 (m, 2H), 4.59 (s, 1H), 4.63 (m, 2H), 5.49 (m, 1H), 7.24−7.37 (m, 5H). ^{13}C NMR (125 MHz), $CDCl_3$: δ 23.4, 32.5, 32.9, 59.0, 64.1, 127.0, 128.1, 128.9, 138.8, 140.6, 174.0. IR (KBr): 3385 (br) cm^{-1}, 3321 cm^{-1}, 1733 cm^{-1}. HRMS: $[M + H]^+$ = 232.1341, calcd for $C_{14}H_{18}NO_2$, 232.1338. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.05; H, 7.30; N, 6.09.

Representative Example for the Preparation of Thioureas (10a,b). To a flame-dried 100 mL round-bottom flask were added **9a** (406 mg, 1.76 mmol) and anhydrous DCM (50 mL). Then the solution was brought down to 0 °C, and ethoxycarbonyl isothiocyanate (0.24 mL, 2.11 mmol) was added dropwise. The solution was allowed to warm to room temperature overnight while stirring under a nitrogen atmosphere. The solvent was removed, and ether (30 mL) was added to the crude residue and was washed with saturated sodium bicarbonate. The organics were dried using anhydrous sodium sulfate and concentrated. The crude residue was purified by column chromatography (silica gel, 20% EtOAc; 80% hexane), and the product was recrystallized with EtOAc/hexanes affording **10a** as a white solid. Yield (518 mg, 81%). ^{1}H NMR (500 MHz), $CDCl_3$: δ 1.29 (t, J = 7 Hz, 3H), 1.81 (m, 2H), 2.13 (m, 2H), 2.26 (m, 2H), 4.23 (m, 2H), 4.69 (s, 2H), 5.53 (s, 1H), 5.97 (d, J = 7 Hz, 1H), 7.3−7.42 (m, 5H), 8.08 (s, 1H), 10.62 (d, J = 6 Hz, 1H). ^{13}C NMR (125 MHz), $CDCl_3$: δ 14.1, 23.1, 32.3, 32.5, 61.8, 62.8, 64.5, 127.5, 128.7, 128.9, 129.1, 135.2, 138.1, 152.5, 169.4, 178.8. IR (KBr): 3289 cm^{-1}, 3226 cm^{-1}, 1743 cm^{-1}, 1724 cm^{-1}. HRMS: $[M + H]^+$ = 363.1387, calcd for $C_{18}H_{23}N_2O_4S$, 363.1379. Anal. Calcd for $C_{18}H_{22}N_2O_4S$: C, 59.65; H, 6.12; N, 7.73. Found: C, 59.36; H, 5.78; N, 7.69. Mp = 58−60 °C.

Preparation of 5-(1*H*-Indol-3-yl)-5-(2-methylallyl)imidazolidine-2,4-dione (24). To a flame-dried 250 mL round-bottom flask were added **22** (1 g, 1.89 mmol), anhydrous DCM (75 mL), and anhydrous TEA (0.78 mL, 5.67 mmol). The solution was cooled to 0 °C, and then EDCI (798 mg, 4.16 mmol) was added. The mixture was stirred at 0 °C for 1 h and then refluxed until disappearance of the starting material, as indicated on TLC. A solution of NaH (750 mg, 18.9 mmol) in MeOH (70 mL) was then added to the mixture and refluxed for 8 h. Since the detosylation was sluggish with NaOMe, the solvent was removed, and ethanol (120 mL) was added followed by KOEt (793 mg, 9.45 mmol) and the mixture refluxed overnight. The solvent was removed, and residue was acidified using 1% HCl and extracted using EtOAc (3 × 50 mL). The organics were dried using anhydrous sodium sulfate and concentrated. The crude residue was purified by column chromatography (silica gel, 20% acetone; 80% DCM) affording the product (**24**) as a white solid. Yield (426 mg, 83%). ^{1}H NMR (500 MHz), DMSO: δ 1.75 (s, 3H), 2.72 (d, J = 13 Hz, 1H), 3.01 (d, J = 13 Hz, 1H), 4.82 (s, 1H), 4.91 (s, 1H), 6.99 (t, J = 7 Hz, 1H), 7.09 (t, J = 7 Hz, 1H), 7.37 (m, 2H), 7.57 (d, J = 9 Hz, 1H), 8.38 (s, 1H), 10.7 (s, 1H), 11.1 (s, 1H). ^{13}C NMR (125 MHz), acetone-d_6: δ 23.9, 44.1, 65.9, 111.9, 114.7, 115.9, 119.5, 120.4, 121.9, 123.1, 125.2, 137.6, 140.3, 156.6, 175.8. IR (NaCl): 3300 cm^{-1}, 1790 cm^{-1}, 1720 cm^{-1}. HRMS: $[M + H]^+$ = 270.1255, calcd for $C_{15}H_{16}N_3O_2$, 270.1243. Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.38; H, 5.69; N, 15.11. Mp = 238−240 °C.

Preparation of 5-(1*H*-Indol-3-yl)-5-(2-oxopropyl)imidazolidine-2,4-dione (25). To a 25 mL round-bottom flask were added **24** (172 mg, 0.639 mmol), THF (8 mL), and water (1 mL). Then NMO (112 mg, 0.959 mmol) and OsO_4 (0.65 mL of a 0.098 M solution in THF, 0.0639 mmol) were added. The solution was stirred at room temperature for 2 h and then was cooled to 0 °C before a solution of $NaIO_4$ (410 mg, 1.917 mmol) in water (3 mL) was added and stirred at room temperature overnight. The solvents were removed, and EtOAc (10 mL) was added along with a saturated solution of K_2SO_3 (10 mL). This biphasic mixture was stirred for 10 min; then the organic layer was separated, and the aqueous layer was extracted with *n*-BuOH (3 × 10 mL). The EtOAc layer and

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n-BuOH layers were combined, dried using anhydrous sodium sulfate, and concentrated. The crude residue was purified by column chromatography (silica gel, 10% MeOH; 90% DCM) affording the product (**25**) as an off-white solid. Yield (107 mg, 61%). Product was recrystallized over 1 week with EtOAc. ^{1}H NMR (500 MHz), CD_3OD: δ 2.15 (s, 3H), 3.49 (d, J = 8 Hz, 1H), 3.59 (d, J = 8 Hz, 1H), 7.02 (t, J = 8 Hz, 1H), 7.11 (t, J = 8 Hz, 1H), 7.27 (s, 1H), 7.35 (d, J = 8 Hz, 1H), 7.69 (d, J = 8 Hz, 1H). ^{13}C NMR (125 MHz), CD_3OD: δ 30.5, 49.2, 64.1, 112.7, 113.9, 120.5, 120.6, 122.9, 123.9, 125.6, 138.8, 160.0, 179.0. IR (KBr): 3364 (br) cm^{-1}, 1774 cm^{-1}, 1711 cm^{-1}. HRMS: $[M + H]^+$ = 272.1055, calcd for $C_{14}H_{14}N_3O_3$, 272.1035. Anal. Calcd for $C_{14}H_{13}N_3O_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 61.10; H, 4.82; N, 15.38. Mp = 234−236 °C.

Preparation of 2-Amino-5-(2-methylallyl)-5-(1-tosyl-1*H*-indol-3-yl)-1*H*-imidazol-4(5*H*)-one (27). To a sealed tube were added **26** (850 mg, 1.876 mmol) in THF (5 mL) and NH_4OH (15 mL). The mixture was heated at 90 °C until the disappearance of the starting material, as indicated by TLC. The precipitate that formed was filtered, acidified with 5% HCl, extracted with *n*-BuOH (3 × 20 mL), dried using anhydrous sodium sulfate, and concentrated. The crude residue was purified by column chromatography (silica gel, 10% MeOH; 90% DCM) affording the product (**27**) as an off-white solid. Yield (575 mg, 72%). ^{1}H NMR (500 MHz), DMSO: δ 1.62 (s, 3H), 2.3 (s, 3H), 2.72 (d, J = 13 Hz, 1H), 2.81 (d, J = 13 Hz, 1H), 4.72 (s, 1H), 4.77 (s, 1H), 7.22 (t, J = 8 Hz, 1H), 7.32 (t, J = 8 Hz, 1H), 7.37 (d, J = 9 Hz, 2H), 7.64 (d, J = 8 Hz, 1H), 7.69 (s, 1H), 7.85 (d, J = 9 Hz, 2H), 7.90 (d, J = 8 Hz, 1H), 8.25 (s, 1H). ^{13}C NMR (125 MHz), DMSO: δ 20.9, 23.7, 43.1, 66.0, 113.0, 115.2, 121.5, 123.0, 123.3, 124.7, 126.7, 128.0, 130.2, 134.0, 134.5, 139.9, 145.5, 170.9, 187.5. IR (KBr): 3470 cm^{-1}, 3351 cm^{-1}, 3307 cm^{-1}, 3088 cm^{-1}, 1707 cm^{-1}, 1657 cm^{-1}. HRMS: $[M + H]^+$ = 423.1494, calcd for $C_{22}H_{23}N_4O_3S$, 423.1491. Anal. Calcd for $C_{22}H_{22}N_4O_3S$: C, 62.54; H, 5.25; N, 13.25. Found: C, 61.21; H, 5.17; N, 13.05. Mp = 273−275 °C.

Preparation of 2-Amino-5-(1*H*-indol-3-yl)-5-(2-methylallyl)-1*H*-imidazol-4(5*H*)-one (28). To a 100 mL round-bottom flask were added **27** (500 mg, 1.18 mmol) and EtOH (60 mL). Then KOEt (991 mg, 11.8 mmol) was added and the mixture refluxed for 24 h. The EtOH was taken off, and the pH of an aqueous mixture of the crude residue was adjusted to 8. The aqueous mixture was then extracted with *n*-BuOH (3 × 40 mL). The organics were combined, dried using anhydrous sodium sulfate, and concentrated. The crude residue was purified by column chromatography (silica gel, 20% MeOH; 90% DCM) affording the product (**28**) as an off-white solid. The product was recrystallized from EtOH. Yield (150 mg, 47%). ^{1}H NMR (500 MHz), DMSO: δ 1.67 (s, 3H), 2.75 (d, J = 14 Hz, 1H), 2.81 (d, J = 14 Hz, 1H), 4.75 (s, 1H), 4.78 (s, 1H), 6.92 (t, J = 7 Hz, 1H), 7.04 (t, J = 7 Hz, 1H), 7.26 (d, J = 2 Hz, 1H), 7.33 (d, J = 8 Hz, 1H), 7.48 (d, J = 8 Hz, 1H), 8.03 (s, 1H), 10.9 (s, 1H). ^{13}C NMR (125 MHz), DMSO: δ 23.9, 43.4, 66.3, 111.4, 114.7, 115.3, 118.3, 119.7, 120.9, 122.6, 124.8, 136.5, 140.7, 170.8, 189.1. IR (KBr): 3470 cm^{-1}, 3390 (br) cm^{-1}, 3200 (br) cm^{-1}, 1692 cm^{-1}, 1650 cm^{-1}. HRMS: $[M + H]^+$ = 269.1405, calcd for $C_{15}H_{17}N_4O$, 269.1402. Anal. Calcd for $C_{15}H_{16}N_4O$: C, 67.15; H, 6.01; N, 20.88. Found: C, 63.98; H, 5.89; N, 19.84. Mp = 264−266 °C.

Preparation of 2-Amino-5-(1*H*-indol-3-yl)-5-(2-oxopropyl)-1*H*-imidazol-4(5*H*)-one (29). To a 25 mL round-bottom flask were added (**28**) (99 mg, 0.366 mmol), DMF (7 mL), THF (1 mL), and water (1 mL). Then NMO (64 mg, 0.549 mmol) and OsO_4 (0.37 mL of a 0.098 M solution in THF, 0.0366 mmol) were added. The solution was stirred at room temperature for 3 h and then was cooled to 0 °C before a solution of $NaIO_4$ (235 mg, 1.098 mmol) in water (2 mL) was added and stirred at room temperature overnight. The solvents were removed, and EtOAc (10 mL) was added along with a saturated solution of K_2SO_3 (10 mL). This biphasic mixture was stirred for 10 min; then the organic layer was separated, and the aqueous layer was extracted with *n*-BuOH (6 × 10 mL). The EtOAc layer and *n*-BuOH layers were combined, dried using anhydrous sodium sulfate, and concentrated. The crude residue was purified by column chromatography (silica gel, 20% MeOH; 90% DCM) affording the product (**29**) as an off-white solid. The product was recrystallized from EtOH. Yield (19 mg, 19%). ^{1}H NMR (500 MHz), CD_3OD: δ 2.18 (s, 3H), 3.19 (d, J = 7 Hz, 1H), 3.64 (d, J = 7 Hz, 1H), 6.97 (t, J = 8 Hz, 1H), 7.08 (t, J = 8 Hz, 1H), 7.20 (s, 1H), 7.33 (d, J = 8 Hz, 1H), 7.51 (d, J = 8 Hz, 1H). ^{13}C NMR (125 MHz), CD_3OD: δ 30.9, 66.5, 112.5, 114.1, 120.28, 120.29, 122.7, 124.0, 125.9, 138.5, 171.7, 192.5, 207.7. IR (KBr): 3470 cm^{-1}, 3420 cm^{-1}, 3270 (br) cm^{-1}, 3176 (br) cm^{-1}, 1720 cm^{-1}, 1690 cm^{-1}, 1650 cm^{-1}. HRMS: $[M + H]^+$ = 271.1191, calcd for $C_{14}H_{15}N_4O_2$, 271.1195. Mp = 283−285 °C.

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Supporting Information Available: Experimental procedures and characterizations for all new compounds, copies of the ^{1}H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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