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A Cascade Approach for the Synthesis of 5-(Indol-3-yl)hydantoin: An Application to the Total Synthesis of (±)-Oxoaplysinopsin B

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Cite This: J. Org. Chem. 2021, 86, 3730–3740 Read Online

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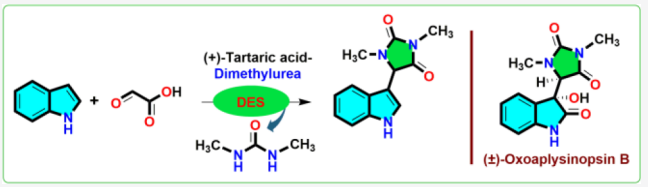
ABSTRACT: A cascade approach to the synthesis of 5-(indol-3-yl)hydantoin framework has been developed by the reaction of indole with glyoxylic acid/pyruvic acid under a deep eutectic solution, (+)-tartaric acid-dimethylurea. *N*,*N*′-Dimethylurea from a deep eutectic solution functions as a reactant as well as a solvent mixture. Isolation of the intermediate, 5-hydroxyhydantoin, and its reaction with indole provides the mechanistic evidence for this reaction. This method was successfully applied in the first total synthesis of an alkaloid, (±)-oxoaplysinopsin B, with an overall yield of 48%.



INTRODUCTION

Indole is a distinctive heterocycle that is widely present in many biologically potent molecules, pharmaceuticals, alkaloids, and functional materials.[1] Functionalization of the indole core with different motifs could tune biological functions, medicinal potency, and material characteristics[1] and, hence, attracts synthetic chemists for devising new methods to install diverse carbocyclic and heterocyclic frameworks on it. New approaches for the coupling of indole with novel entities are always of high value. Great effort has been reported for the substitution/functionalization of indole, mostly by metal-mediated transformations.[2−5] Nevertheless, an elegant approach for direct functionalization of indole with a biologically significant drug scaffold, hydantoin,[6,7] is not explored so far. The synthesis of hydantoin-substituted indole has been established by conventional methods, which involved the conversion of functionalities attached on indole into respective indolyl hydantoins by the Bucherer−Bergs method,[8a,b] Biltz method,[8c] and Read method.[8d] A few other routes were reported by Shi,[9a] Tepe,[9c] and Nakamura.[9e] In 2008, the Shi group described a Cu(I)-catalyzed cascade amination-cyclization of aryl acetic acid esters to synthesize 5-(hetero)-arylhydantoin derivatives and a 5-(indol-3-yl)hydantoin derivative as one of the examples with a modest yield.[9a] Gong et al. demonstrated an asymmetric version of Shi's method using a Lewis base/copper(I) cooperative catalysis strategy.[9b] In 2008, Tepe and co-workers developed a method to synthesize a 5-(indol-3-yl)hydantoin derivative by oxazole rearrangement of 2-methylallyl-2-(3-(ethoxycarbonyl)-thioureido)-2-(1-tosyl-1*H*-indol-3-yl)acetate and further hydrolysis.[9c] Nakamura et al. demonstrated the synthesis of a substrate of indolylhydantoin as an application of the aza-Friedel−Crafts reaction product obtained by their developed method. This strategy involves initial synthesis of (*R*)-2-benzhydryl-4-(1*H*-indol-3-yl)-4-phenyl-1,2,5-thiadiazolidin-3-one-1,1-dioxide followed by its reduction into an α-indolyl-α-aryl amino acid derivative. The amino acid derivative was further treated with phosgene to produce a 5-aryl-5-(indol-3-yl)hydantoin derivative. These strategies relied on the conversion of functionalities attached to indoles into the hydantoin moiety and not direct functionalization of the indole.

Hence, there is a need to develop a new method to synthesize hydantoin-substituted indoles from an unfunctionalized and unprotected indole in a short and cost-effective synthetic route. In this concern, we report a cascade approach for the synthesis of 5-(indol-3-yl)-1,3-substituted hydantoins from indole and glyoxylic acid/pyruvic acid using (+)-tartaric acid-*N*,*N*′-dimethylurea (DMU) as a deep eutectic solution (DES). DMU is involved in the reaction as a reactant in addition to function as DES. Immediate access to 5-hydroxyhydantoin through a quick reaction between DMU and glyoxylic acid has been uncovered during this study. Further, we exhibit a utility of the method in the first total synthesis of (±)-oxoaplysinopsin B with a good overall yield.

RESULT AND DISCUSSION

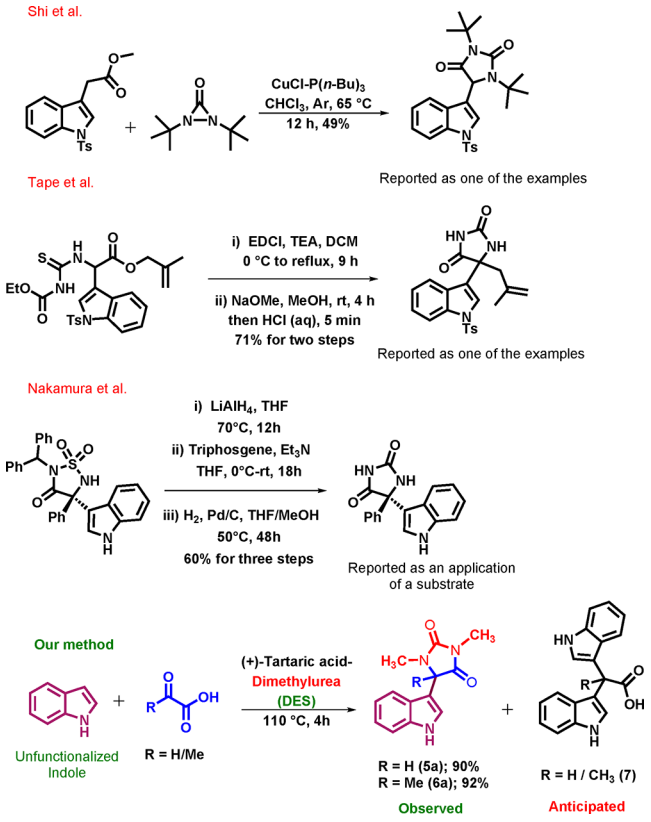
We found a serendipitous formation of 5-(indol-3-yl)-1,3,5-trimethylhydantoin when attempted to synthesize 2,2-di(1*H*-indol-3-yl)propanoic acid **7** with (+)-tartaric acid-*N*,*N*′-dimethylurea as DES. Deep eutectic solution/melt,[10] consisting of components from a sustainable and natural source,

Received: October 14, 2020
Published: February 18, 2021

https://dx.doi.org/10.1021/acs.joc.0c02435
J. Org. Chem. 2021, 86, 3730−3740

nontoxic, and nonvolatile, acts as a green alternative to organic solvents to carry out organic transformations. In general, the reaction between aldehyde/ketone and indole in a deep eutectic solution produces a corresponding bisindole product.[11] In contrast to the formation of the expected bisindole product, 2,2-di(1*H*-indol-3-yl)propanoic acid, **6a** was produced exclusively in a 48% of yield over 8 h (Scheme 1).

Scheme 1. Previous Reports and Present Approach for the Synthesis of 5-Indolylhydantoin



Unexpectedly, DMU participated as a reactant in addition to function as DES. Further, the accessibility of the reaction was examined with glyoxylic acid monohydrate instead of pyruvic acid. Fortunately, it proceeded well and furnished 5-(indol-3-yl)-1,3-dimethylhydantoin (**5a**).

To the best of our knowledge, there is no literature report involving a direct approach for the synthesis of **5a** or **6a** from indole, glyoxylic acid/pyruvic acid, and dimethylurea. The formerly discussed methods by Shi, Tepe and, Nakamura are the routes reported for the synthesis of the core similar to **5a**, which involved functional group conversions, not direct functionalization of indole. Hence, we envisioned to develop a method for the direct functionalization of indoles with hydantoin and extend its application in the total synthesis of (±)-oxoaplysinopsin B.

Indole and glyoxylic acid monohydrate were used as substrates to study the optimization reaction to produce 5-indolylhydantoin **5a**. We began initial optimization for the synthesis of **5a** by varying the amounts of equivalents of glyoxylic acid to improve the yield. While using equimolar quantities of indole and glyoxylic acid, the yield of **5a** was found to be 53%, and the indole was left unreacted even after 24 h. Excess equivalents of glyoxylic acid (2 equiv) favored the formation of **5a** and enhanced the yield to 68% in 8 h. While using 3 and 4 equiv of glyoxylic acid, the yield of **5a** was increased to 68% and 90%, respectively when reaction time was shortened to 4 h, and the temperature was raised to 110 °C (Figure 1).

With the optimized conditions identified, the scope of this method was investigated with various substituted indoles. A little influence of inductive factors of the electron-donating group on the reaction was observed. Most of the substituted indoles reacted well with glyoxylic acid and pyruvic acid in DES to furnish analogues of **5a** and **6a**, respectively, in 78−93% yields (Scheme 2). In the case of the indole substituted with electron-withdrawing functionality (−NO_2 and −CN) at the C-5 position, the corresponding product formation was not observed and resulted in inseparable mixtures. It is a fact that the electron-withdrawing substituents decrease the electron density at the third position of the indole, which renders the usual reactivity, and the same was observed in our reaction.

Further, the synthesis of **5a** using a 50% aqueous solution of glyoxylic acid (less expensive compared to glyoxylic acid monohydrate) was demonstrated, which gave a 90% yield. This approach was amenable in a gram-scale synthesis as well with a minute change in yield. Compounds **5a** and **6a** were obtained in 86% and 88% yields, respectively, in a 10 mmol scale reaction, which implies the scalability and industrial applicability of this method.

To check the reactivity of other substituted ureas other than dimethyl urea, the reaction was examined with urea, diphenylurea, dicyclohexylurea, and monomethylurea under optimized conditions. In the case of diphenylurea/dicyclohexylurea, it did not form deep eutectic solution with (+)-tartaric acid at any higher temperatures. Further, the pyruvic acid/glyoxylic acid monohydrate and indole were added to the solid mixture of diphenylurea/dicyclohexylurea and (+)-tartaric acid at 110 °C; however, the reaction was not successful and did not give the desired hydantoin. Then, the reaction between diphenylurea/dicyclohexylurea, pyruvic acid, and indole was checked using other solvents, instead of a deep eutectic mixture, such as water, methanol, acetic acid, water−methanol mixture, and water−acetic acid mixture. However, these conditions did not produce the corresponding hydantoin, whereas urea formed a deep eutectic solution with (+)-tartaric acid but did not produce the respective hydantoin when pyruvic acid and indole were added; instead, it produced 2,2-bis(1-*H*-indolyl) propanoic acid. Monomethyl urea has formed a deep eutectic solution with (+)-tartaric acid, and the further addition of pyruvic acid and indole produced respective hydantoin (**6l**). When we replaced the glyoxylic acid monohydrate with phenylglyoxylic acid/phenylpyruvic acid under optimized reaction conditions, the reaction proceeded well with the corresponding hydantoin (**6k** and **6m**) in a good yield (Scheme 2).

Next, the possible reaction mechanism was investigated. The expected intermediate was the 5-hydroxy-1,3-dimethylhydantoin **8a**, as it was found in the reaction mixture in the absence of indole under the optimized condition. Initially, the focus was on the reaction between the glyoxylic acid and dimethylurea to produce 5-hydroxy-1,3-dimethylhydantoin and study its reaction with indole using (+)-tartaric acid-dimethylurea deep eutectic conditions. The reaction was examined with 10 mol % of an acid catalyst (*p*-TSA, acetic acid, trichloro/trifluoroacetic acid) in chloroform as a solvent

https://dx.doi.org/10.1021/acs.joc.0c02435
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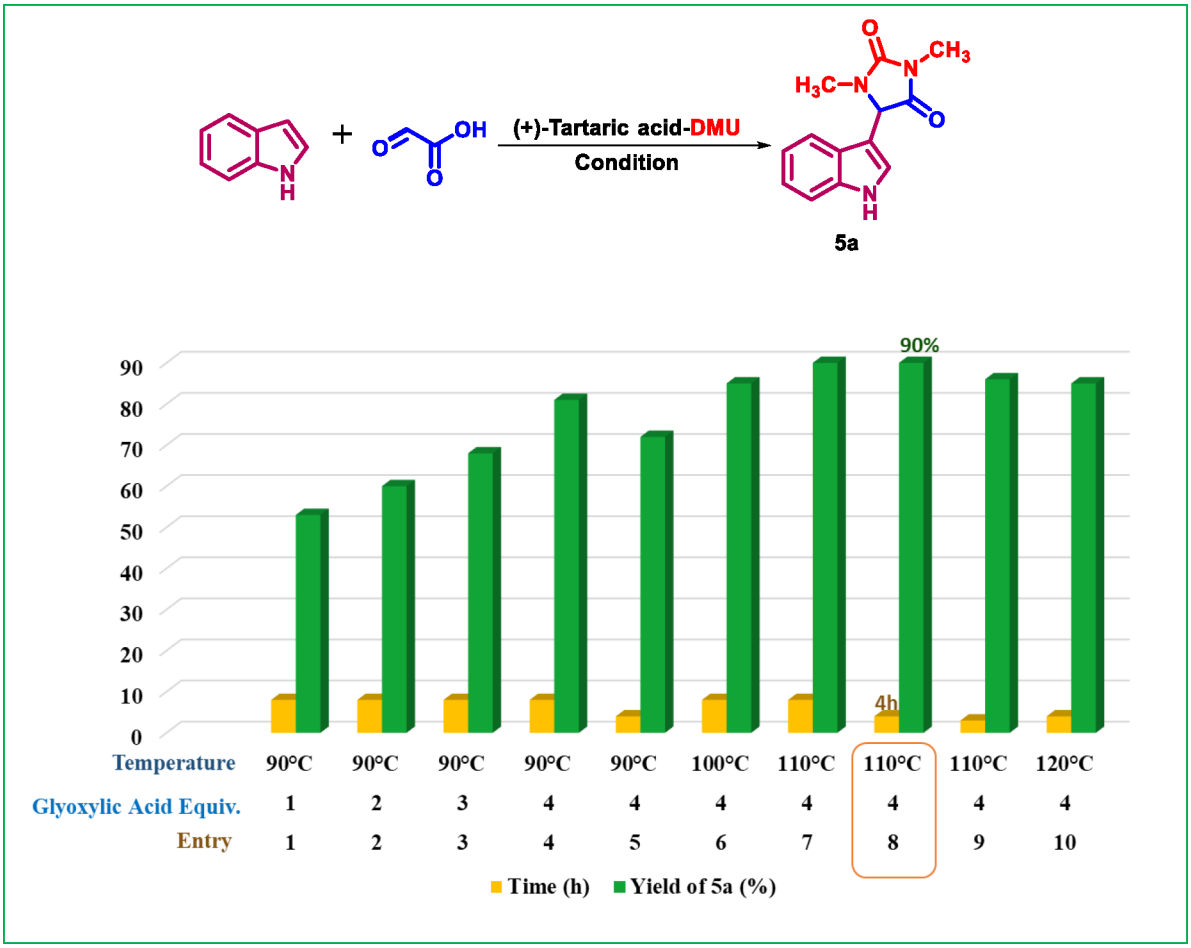

Figure 1. Optimization for the synthesis of **5a**.

along with (+)-tartaric acid-dimethylurea deep eutectic conditions (Figure 2).

All conditions furnished the product in good to excellent yields (85−95%). Further, the same reaction was performed without using any catalyst in neat conditions and, to our surprise, resulted in 5-hydroxy-1,3-dimethylhydantoin **8a** quantitatively. A careful observation of the reaction time revealed a very fast reaction profile between glyoxylic acid and dimethylurea. It was found that under neat conditions **8a** was efficiently produced within a minute in a quantitative yield. To the best of our knowledge, there is no report for such a direct and rapid approach for the synthesis of 5-hydroxy-1,3-dimethylhydantoin **8a** at an ambient temperature. The product **8a** was converted to its acyl and benzoyl ester for further confirmation of its structure. The structure of benzoyl ester **8b** was unambiguously confirmed by SC-XRD analysis (Scheme 4). Pyruvic acid was also reacted with DMU and produced respective 5-hydroxy-1,3,5-trimethylhydantoin (**8d**) within 15 min in a 91% yield.

To gain insight into the mechanism, further, we studied the reaction between the 5-hydroxyhydantoin **8a** and indole in the deep eutectic solution at 110 °C, which produced hydantoin **5a** (Scheme 3).

This supports that the reaction proceeds through the formation of 5-hydroxy-1,3-dimethylhydantoin as a reaction intermediate. The proposed mechanism (Scheme 4) involves the initial formation of an oxonium intermediate **A**, and nucleophilic attack with dimethylurea produces **B**. The intramolecular amidation−cyclization of **B** leads to 5-hydroxy-1,3-dimethylhydantoin **8a**. Intermediate **8a** under the acidic condition undergoes protonation, dehydration, and then reacts with indole to produce intermediate **D**, which, upon fast aromatization, produces product **5a**.

Further, we applied this approach to the first total synthesis of the natural product (±)-oxoaplysinopsin B. (±)-Oxoaplysinopsin B (**9**) is an indole alkaloid that possesses an intriguing oxindole−imidazolinone (hydantoin) hybrid skeleton. It was isolated very recently (2019) as a racemic pair of enantiomers from Xisha Islands sponge *Fascaplysinopsis reticulata* along with oxoaplysinopsin A, oxoaplysinopsins C−G, and other natural products.[12] (±)-Oxoaplysinopsin B (**9**) showed stronger activity than the positive controls in tyrosine phosphatase 1B (PTP1B) inhibition (IC_{50} = 20.8 μM). There is no literature report to date on its synthesis.

Our approach is depicted in Figure 3. The 3-hydroxyoxindole skeleton of **9** can be derived from **5a** by oxidation of an indole moiety. Compound **5a** could be obtained by the present method developed, directly from glyoxylic acid, dimethylurea, and indole under (+)-tartaric acid-dimethylurea deep eutectic conditions.

When compound **5a** was ready in hand, we envisioned oxidation of the C-2 position of indole to carbonyl and introduction of hydroxyl functionality at the C-3 position to reach **9**. In general, the C-2 and C-3 positions of the indole are electron-rich and are prone to easy oxidation. The oxidation of the indole, the ring of **5a**, was attempted with different

https://dx.doi.org/10.1021/acs.joc.0c02435
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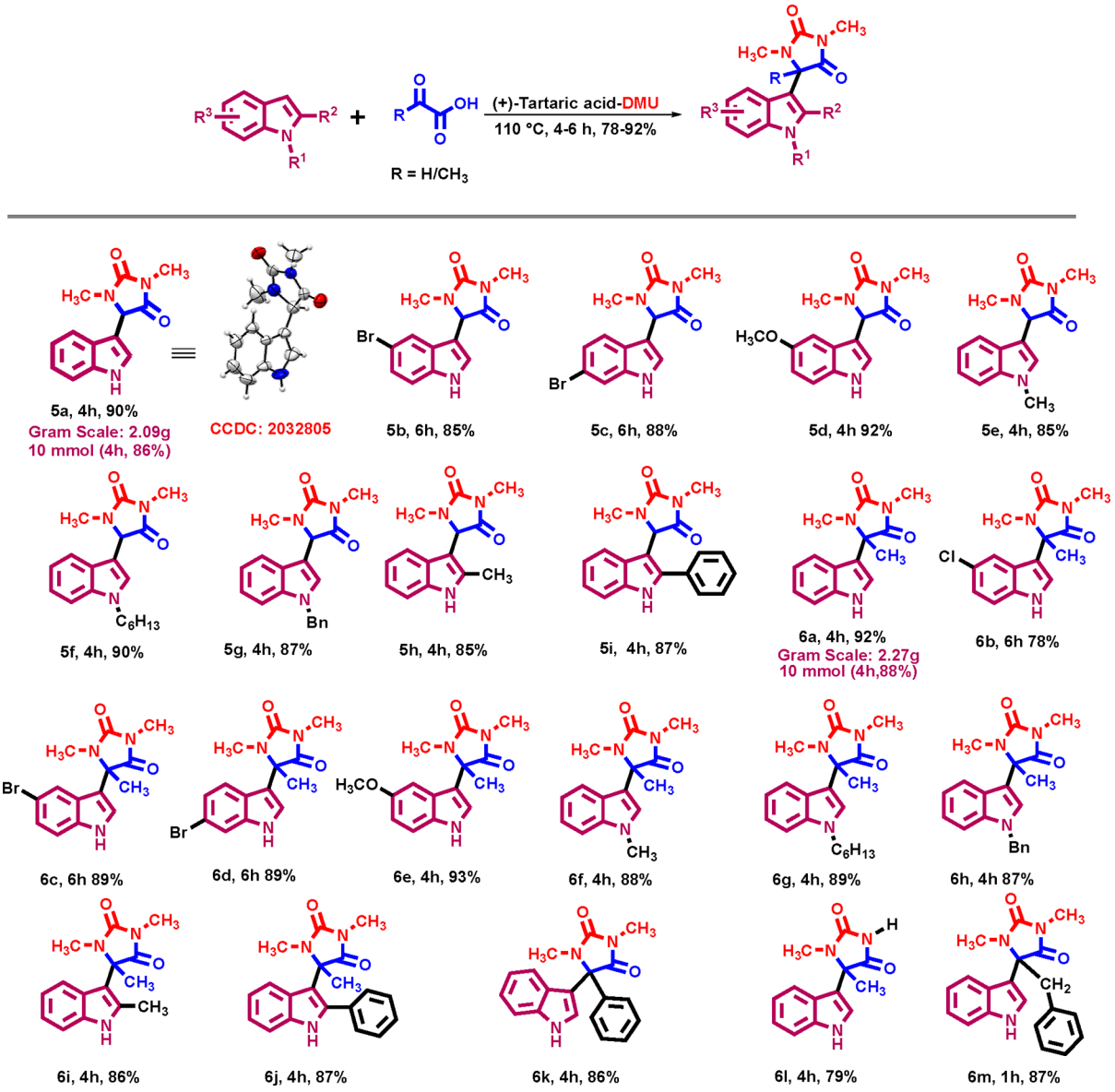
Scheme 2. Synthesis of 5a, 6a, and Their Analogues



conditions such as $CeCl_3$–IBX,[13] DMDO,[14,15] and PCC[16] to produce **9** directly from **5a**. However, these methods failed to furnish **9** (Scheme 5).

Hence, an alternative approach has been designed (Figure 3 and Scheme 6). The revised strategy involves the conversion of **5a** into a 3-halo-oxindole derivative followed by substitution of halogen with hydroxy to obtain **9**.

We investigated the conversion of the indole moiety of **5a** into a 3-halo-oxindole derivative by the initial treatment with NBS or NCS followed by the hydroxylation reaction under basic conditions.[17] After, indolylhydantoin **5a** was entirely consumed (TLC) on a reaction with NBS or NCS; then, the crude product was treated with a base ($NaHCO_3$, Na_2CO_3, K_2CO_3, KOH, NaOH, Cs_2CO_3, and Ag_2O) to produce **9**. The combination NCS and Ag_2O was only found to produce (±)-oxoaplysinopsin B (8%) and its 5-chloro analogue **10** (30%) through a series of optimization. Next, the dechloro-hydrogenation of **10** with Pd–C/H_2[18] in methanol furnished **9** quantitatively in 30 min. To increase the overall yield, the yield of **10** had to be enhanced. Hence, **5a** was treated with higher equivalents of NCS to improve the yield of **10**. The investigation of the reaction revealed that, while using four equivalents of NCS, **10** was produced in 54% yield over 40 min. Further dechloro-hydrogenation was carried out as earlier method, which produced the (±)-oxoaplysinopsin B in 48% overall yield starting from indole. The spectral data of synthesized (±)-oxoaplysinopsin B (**9**) matched with that of the isolated compound. The specific rotation of the synthesized (±)-oxoaplysinopsin B was determined as zero, which indicates the presence of a racemic mixture. The structures of (±)-oxoaplysinopsin B (**9**)[19] and 5-chloro analogue **10** were unambiguously confirmed by SC-XRD analysis.

CONCLUSION

In summary, we have developed an operationally simple route to synthesize indole substituted with hydantoin in a high yield for the first time. The mechanistic investigation showed that 5-hydroxy-1,3-dimethylhydantoin was identified as a reaction intermediate. Further, this method was utilized in the first total

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J. Org. Chem. 2021, 86, 3730–3740

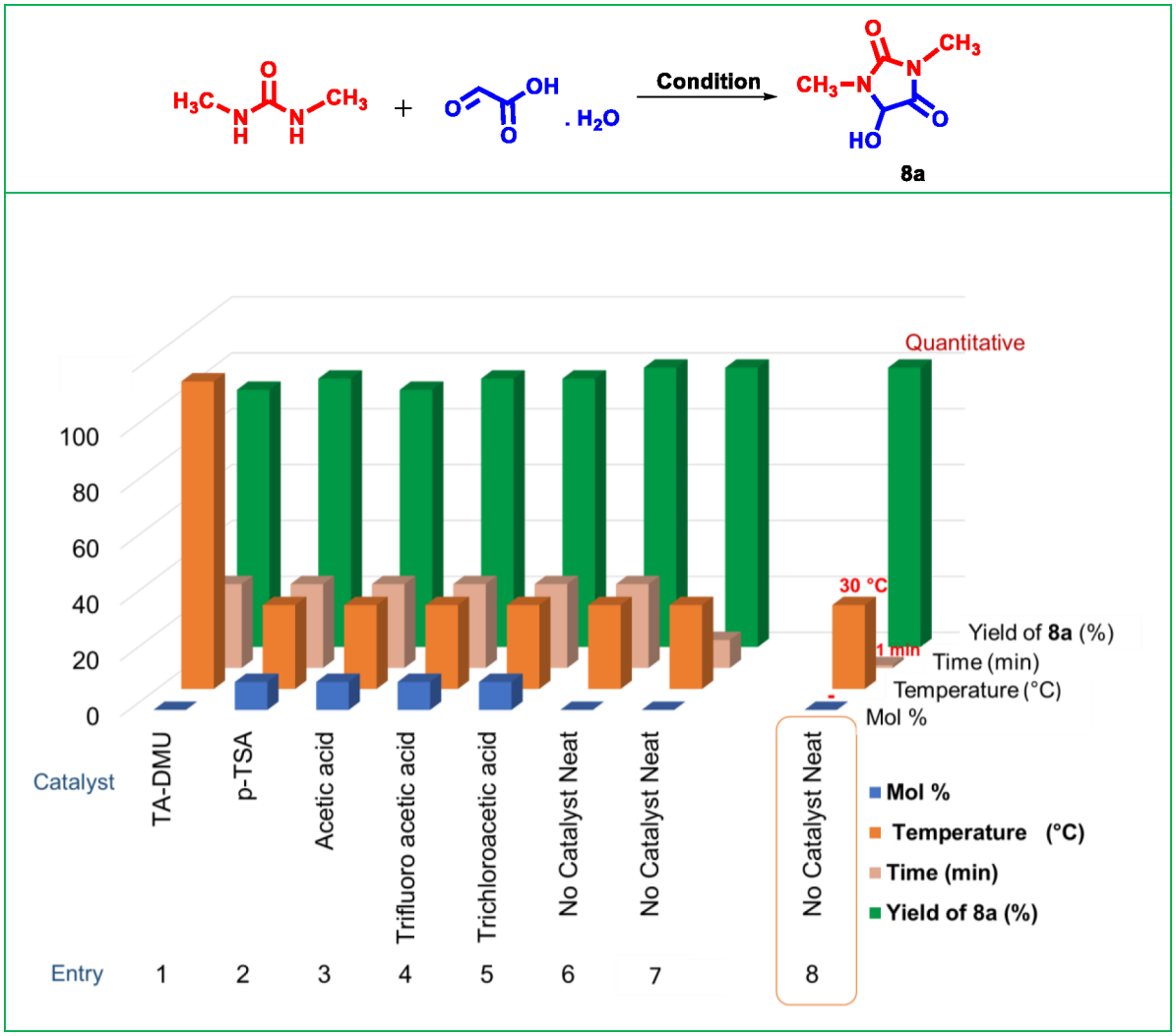
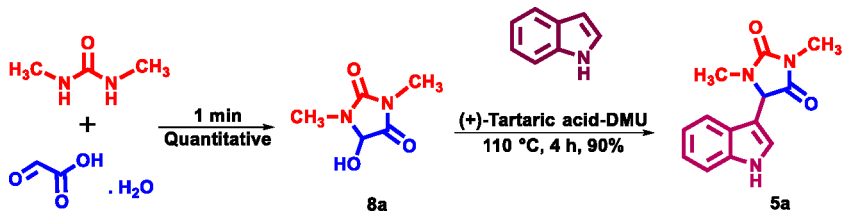


Figure 2. Optimization for the synthesis of **8a**.

Scheme 3. Synthesis of 5a from 5-Hydroxyhydantoin and Indole



synthesis of (±)-oxoaplysinopsin B with a 48% overall yield from a commercially available indole.

EXPERIMENTAL SECTION

Material and Methods. IR measurements were performed in FT-IR 500. NMR was recorded on a 500/400 MHz (proton) or 125/100 MHz (carbon) Bruker spectrometer. Chemical shift values are assigned relative to NMR solvent residual peaks, and the splitting pattern was presented as s, singlet; br s, broad singlet; d, doublet; t, triplet; dt, doublet of triplet; td, triplet of doublet; m, multiplet. HRMS was obtained from TOF and quadrupole mass analyzer types. The crystal data collection was obtained from D8 Quest or Rigaku. Melting points were recorded in open tubes and uncorrected. Purification of all synthesized compounds was carried out in 100−200 mesh silica gel columns. All solvents and chemicals purchased were used as such unless otherwise mentioned.

General Experimental Procedure for the Synthesis of 5a and 6a. A mixture of (+)-tartaric acid (120 mg) and *N,N*-dimethylurea (280 mg) was heated in an RB flask at 110 °C on an oil bath for 5 min to get a clear eutectic mixture. To this mixture was added glyoxylic acid monohydrate (92 mg, 1 mmol, 4 equiv), and the mixture was stirred for two minutes; then indole (29 mg, 0.25 mmol, 1 equiv) was added. After complete consumption of indole, the reaction mixture was quenched while hot by the slow addition of water and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain the brown mass. Pure product **5a** was isolated by column chromatography using a 40% ethyl acetate−hexane mixture in a 90% (55 mg) yield. Using the same procedure analogues of **5a** were synthesized. The same procedure was repeated with pyruvic acid (88 mg, 1 mmol, 4 equiv) instead of glyoxylic acid monohydrate to synthesize **6a** and its analogues. For the synthesis of

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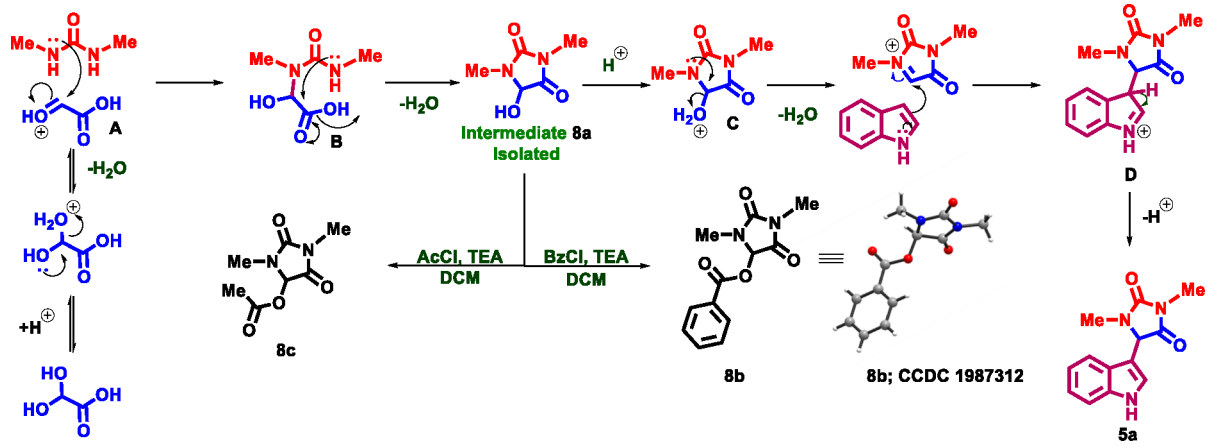
Scheme 4. Proposed Mechanism for the Formation of 5a



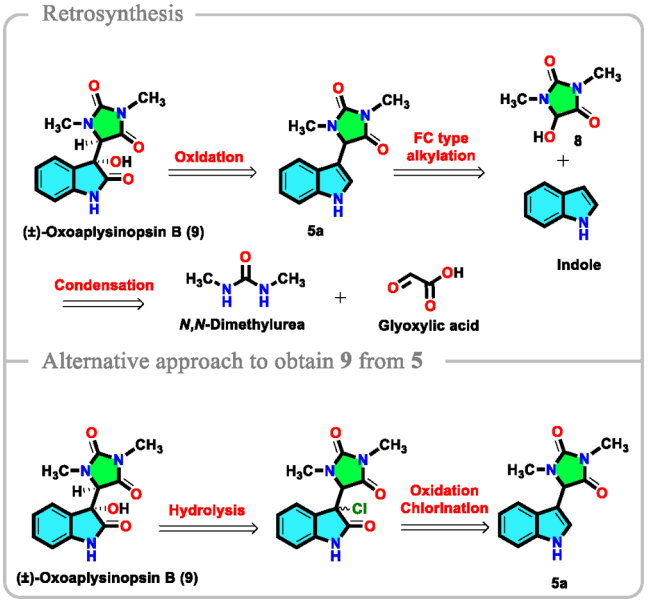
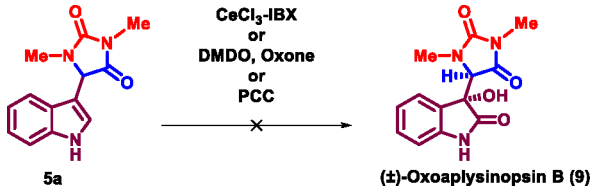


Figure 3. Retrosynthesis of (±)-oxoaplysinopsin B.

Scheme 5. Unsuccessful Attempts for the Synthesis of 9 Directly from 5a



6k phenylglyoxylic acid (134 mg, 1 mmol, 4 equiv) was used in place of glyoxylic acid monohydrate under optimized conditions. In the case of **6l**, the monomethylurea (280 mg) was used instead of *N,N*-dimethylurea under the optimized conditions. The product **6m** was synthesized using phenylpyruvic acid (136 mg, 1 mmol, 4 equiv) in the place of glyoxylic acid monohydrate under optimized conditions.

For the gram-scale synthesis of **5a** and **6a**, a mixture of (+)-tartaric acid (4.80 g) and *N,N*-dimethylurea (11.2 g) was heated in an RB flask at 110 °C on an oil bath for 10 min to get a clear eutectic mixture. To this mixture was added glyoxylic acid monohydrate (3.68 g, 40 mmol, 4 equiv), and the mixture was stirred for two minutes; then indole (1.17 g, 10 mmol, 1 equiv) was added. The same workup procedure as earlier was followed, and the product was isolated in an 86% (2.09 g) yield. In the case of using 50% solution of a glyoxylic acid aqueous solution, a wide-neck, open-mouth RB flask was utilized, and 8 mL of 50% solution was added in the place of glyoxylic acid monohydrate over 10 min. The mixture was stirred for an additional 20 min before the indole was added.

For the gram-scale synthesis of **6a**, pyruvic acid (2.8 mL, 40 mmol, 4 equiv) was used instead of glyoxylic acid monohydrate to produce **6a** in an 88% (2.27g) yield.

Synthesis of 5a from 8a under a Deep Eutectic Solution. A mixture of (+)-tartaric acid (90 mg) and *N,N*-dimethylurea (210 mg) was heated in an RB flask at 110 °C on an oil bath for 5 min to get a clear eutectic solution. To this were added **8a** (144 mg, 1 mmol) and indole (29 mg, 0.25 mmol, 1 equiv), and the mixture was stirred for 4 h. After completion of the reaction, the reaction mixture was quenched while hot by the slow addition of water and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain the brown mass. The pure product was isolated by column chromatography using a 40% ethyl acetate/hexane mixture in a 90% (55 mg) yield.

*5-(1H-Indol-3-yl)-1,3-dimethylimidazolidine-2,4-dione (**5a**):* 55 mg; 90% yield; off white solid; mp 172−174 °C; R_f = 0.24 (70% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 3285, 2974, 1754, 1691, 1454; ^1H NMR (400 MHz, DMSO-d_6) δ 11.30 (br s, 1H), 7.54 (d, J = 2.5 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.15−7.10 (m, 1H), 6.99 (t, J = 7.8 Hz, 1H), 5.31 (s, 2H), 2.99 (s, 3H), 2.67 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 172.6, 156.5, 137.1, 127.4, 125.5, 122.1, 119.9, 118.3, 112.5, 106.6, 59.7, 27.8, 25.1; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{13}H_{13}N_3O_2Na$ 266.0905, found 266.0907.

*5-(5-Bromo-1H-indol-3-yl)-1,3-dimethylimidazolidine-2,4-dione (**5b**):* 68 mg; 85% yield; off white solid; mp >200 °C; R_f = 0.27 (70% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 3360, 3120, 2914, 1752, 1697, 1448, 595; ^1H NMR (500 MHz, DMSO-d_6) δ 11.52 (br s, 1H), 7.58 (d, J = 2.6 Hz,1H), 7.41 (d, J = 8.7 Hz, 1H), 7.34 (d, J = 1.8 Hz, 1H), 7.25 (dd, J = 8.6 Hz, J = 1.9 Hz, 1H), 5.36 (s, 1H), 2.98 (s, 3H), 2.70 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 177.1, 161.3, 140.6, 133.3, 132.3, 129.5, 125.3, 199.3, 117.2, 111.4, 64.0, 32.7, 29.9; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{13}H_{12}BrN_3O_2Na$ 344.0011, found 344.0012.

*5-(6-Bromo-1H-indol-3-yl)-1,3-dimethylimidazolidine-2,4-dione (**5c**):* 70 mg; 88% yield; off white solid; mp 182−184 °C; R_f = 0.33 (70% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 3278, 3123, 2928, 1750, 1689, 1451, 585; ^1H NMR (500 MHz, DMSO-d_6) δ 11.43 (s, 1H), 7.62 (d, J = 1.6 Hz, 1H), 7.57 (d, J = 2.6 Hz, 1H), 7.16−7.11 (m, 2H), 5.33 (s, 1H), 2.98 (s, 3H), 2.68 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 172.3, 156.5, 138.0, 128.3, 124.6, 122.9, 120.1, 115.1, 114.9, 107.1, 59.4, 27.9, 25.1; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{13}H_{12}BrN_3O_2Na$ 344.0011, found 344.0014.

*5-(5-Methoxy-1H-indol-3-yl)-1,3-dimethylimidazolidine-2,4-dione (**5d**):* 63 mg; 92% yield; off white solid; mp 192−194 °C; R_f =

https://dx.doi.org/10.1021/acs.joc.0c02435
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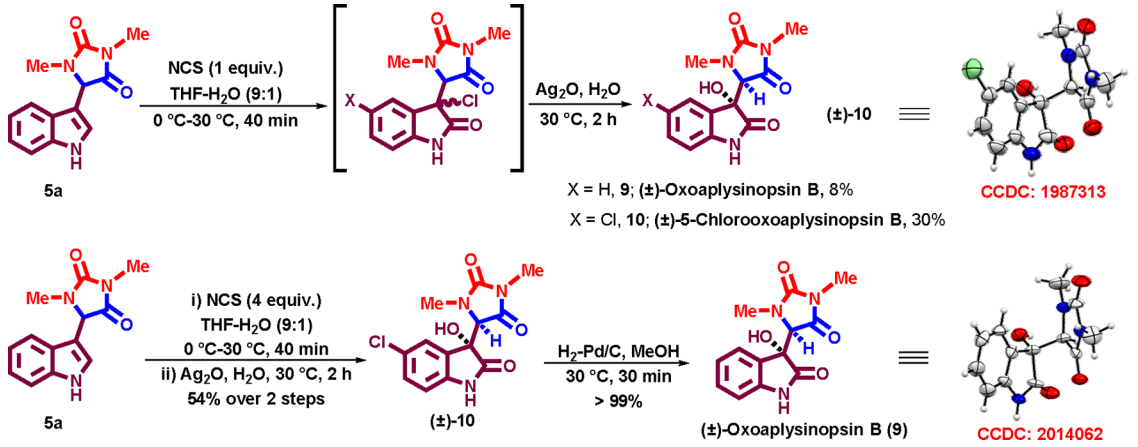
Scheme 6. Alternative Approach to the Total Synthesis of (±)-Oxoaplysinopsin B



0.33 (70% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 3314, 3140, 2932, 1748, 1693, 1439, 1058; ^1H NMR (500 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.58 (d, J = 1.8, 1H), 7.37 (d, J = 2.7 Hz, 1H), 7.21 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H), 7.05 (d, J = 2.36 Hz, 1H), 5.39 (s, 1H), 4.13 (s, 3H), 3.51 (s, 3H), 3.19 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 172.6, 156.5, 154.6, 131.9, 126.1, 125.4, 112.7, 112.7, 106.0, 100.2, 60.0, 55.8, 27.7, 25.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{15}N_3O_3H$ 274.1192, found 274.1192.

1,3-Dimethyl-5-(1-methyl-1H-indol-3-yl)imidazolidine-2,4-dione ***(5e)****:* 57 mg; 85% yield; off white solid; mp 172−174 °C; R_f = 0.26 (50% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 3248, 2928, 1758, 1692, 1459; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.24 (m, 3H), 7.16 (s, 1H), 7.15−7.11 (dd, J = 7.5 Hz, J = 0.5 Hz, 1H), 5.08 (s, 1H), 3.79 (s, 3H), 3.15 (s, 3H), 2.86 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 172.1, 156.6, 137.5, 129.5, 125.6, 122.6, 120.3, 118.6, 109.9, 105.4, 59.9, 33.0, 27.8, 25.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{15}N_3O_2H$ 258.1243, found 258.1238.

5-(1-Hexyl-1H-indol-3-yl)-1,3-dimethylimidazolidine-2,4-dione ***(5f)****:* 74 mg; 90% yield; off white solid; mp 62−64 °C; R_f = 0.60 (50% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 3276, 2914, 1755, 1692, 1418; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 8.3 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.24 (t, J = 8.1 Hz, 1H), 7.18 (s, 1H),7.10 (t, J = 7.9 Hz, 1H), 5.09 (s, 1H), 4.09 (t, J = 7.0 Hz, 2H), 3.15 (s, 3H), 2.86 (s, 3H), 1.87−1.82 (m, 2H), 1.35−1.29 (m, 6H), 0.88 (t, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 172.1, 156.5, 136.8, 128.4, 125.7, 122.3, 120.2, 118.6, 110.0, 105.2, 59.9, 46.6, 31.3, 30.0, 27.7, 26.6, 25.1, 22.5, 13.9; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{25}N_3O_2H$ 328.2025, found 328.2027.

5-(1-Benzyl-1H-indol-3-yl)-1,3-dimethylimidazolidine-2,4-dione ***(5g)****:* 73 mg; 87% yield; off white solid; mp 168−170 °C; R_f = 0.43 (50% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 3251, 2915, 1751, 1985, 1428; ^1H NMR (500 MHz, DMSO-d_6) δ 7.34−7.30 (m, 5H), 7.23−7.21 (m, 2H), 7.15−7.11 (m, 3H), 5.31 (s, 2H), 5.09 (s, 1H), 3.16 (s, 3H), 2.87 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 171.9, 156.5, 137.1, 136.6, 128.9, 128.8, 127.9, 126.9, 125.8, 122.7, 120.5, 118.7, 110.3, 106.1, 59.8, 50.2, 27.7, 25.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{19}N_3O_2H$ 334.1556, found 334.1557.

1,3-Dimethyl-5-(2-methyl-1H-indol-3-yl)imidazolidine-2,4-dione ***(5h)****:* 55 mg; 85% yield; colorless solid; mp 158−160 °C; R_f = 0.46 (70% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 3312, 2911, 1752, 1688, 1438; ^1H NMR (500 MHz, $CDCl_3$) δ 8.66 (br s, 1H), 7.23 (d, J = 8.1 Hz, 1H), 7.13−7.03 (m, 3H), 5.05 (s, 1H), 3.21 (s, 3H), 2.76 (s, 3H), 2.01 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 172.8, 156.4, 135.4, 121.8, 121.8, 120.3, 120.3, 117.2, 110.9, 101.7, 58.9, 27.5, 25.1, 11.0; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{15}N_3O_2H$ 258.1243, found 258.1243.

1,3-Dimethyl-5-(2-phenyl-1H-indol-3-yl)imidazolidine-2,4-dione ***(5i)****:* 70 mg; 87% yield; colorless solid; mp 186−188 °C; R_f = 0.64 (50% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 3245, 2923, 1766, 1691, 1459; ^1H NMR (500 MHz, $CDCl_3$) δ 10.10 (s, 1H), 7.68−7.32 (m, 6H), 7.12−7.01 (m, 3H), 5.22 (s, 1H), 3.10 (s, 3H), 2.66 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 172.8, 156.5, 140.2, 136.2, 131.5, 129.1, 128.8, 128.7, 125.9, 122.6, 120.6, 118.1, 111.8, 102.5, 59.3, 27.6, 25.0; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{17}N_3O_2H$ 320.1399, found 320.1399.

5-(1H-Indol-3-yl)-1,3,5-trimethylimidazolidine-2,4-dione ***(6a)****:* 59 mg; 92% yield; off white solid; mp >200 °C; R_f = 0.47 (70% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 3261, 3133, 1760, 1699, 1438; ^1H NMR (500 MHz, DMSO-d_6) δ 11.34 (s, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.13−7.09 (m, 1H), 7.01−6.96 (m, 2H), 3.01 (s, 3H), 2.60 (s, 3H), 1.78 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 175.5, 155.7, 137.2, 126.6, 124.7, 122.0, 120.1, 118.1, 112.6, 110.8, 63.7, 25.2, 25.1, 20.8; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{15}N_3O_2H$ 258.1243, found 258.1242.

5-(5-Chloro-7,7a-dihydro-1H-indol-3-yl)-1,3,5-trimethylimidazolidine-2,4-dione ***(6b)****:* 57 mg; 78% yield; off white solid; mp 168−170 °C; R_f = 0.48 (70% EtOAc/hexane); IR (Neat):ν_{max}(cm^{-1}) 3298, 2932, 1758, 1691, 1482, 636; ^1H NMR (500 MHz, $CDCl_3$) δ 9.05 (brs, 1H), 7.22 (d, J = 8.6 Hz, 1H), 7.12−7.08 (m, 2H), 6.90 (s, 1H), 3.20 (s, 3H), 2.75 (s, 3H), 1.79 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 176.0, 155.5, 135.1, 126.3, 126.0, 125.2, 123.0, 117.9, 112.9, 110.7, 63.5, 25.2, 25.1, 21.0; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{14}ClN_3O_2H$ 292.0853, found 292.0853.

5-(5-Bromo-1H-indol-3-yl)-1,3,5-trimethylimidazolidine-2,4-dione ***(6c)****:* 75 mg; 89% yield; off white solid; mp 158−160 °C; R_f = 0.38 (70% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 3308, 2978, 1761, 1701, 1694, 1452, 605; ^1H NMR (500 MHz, $CDCl_3$) δ 9.03 (br s, 1H), 7.25−7.24 (m, 2H), 7.18−7.16 (m, 1H), 6.89 (s,1H), 3.20 (s, 3H), 2.75 (s, 3H), 1.79 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 175.9, 155.5, 135.4, 125.9, 125.8, 125.7, 121.0, 113.9, 113.3, 110.8, 63.5, 25.2, 25.2, 21.0; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{14}BrN_3O_2H$ 336.0348, found 336.0348.

5-(6-Bromo-1H-indol-3-yl)-1,3,5-trimethylimidazolidine-2,4-dione ***(6d)****:* 75 mg; 89% yield; off white solid; mp 152−154 °C; R_f = 0.47 (70% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 3310, 2937, 1763, 1691, 1450, 552; ^1H NMR (500 MHz $CDCl_3$) δ 8.57 (br s, 1H), 7.50 (s, 1H), 7.19 (dd, J = 8.6 Hz, J = 0.9 Hz, 1H), 7.07−7.02 (m, 2H), 3.16 (s, 3H), 2.78 (s, 3H), 1.83 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 175.7, 155.7, 137.6, 125.1, 124.1, 123.2, 119.7, 116.4, 114.8, 111.8, 63.6, 25.2, 25.15, 20.9; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{14}BrN_3O_2H$ 336.0348, found 336.0342.

5-(5-Methoxy-1H-indol-3-yl)-1,3,5-trimethylimidazolidine-2,4-dione ***(6e)****:* 67 mg; 93% yield; off white solid; mp 168−170 °C; R_f = 0.44 (70% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 3320, 2928, 1759, 1695, 1451, 1031; ^1H NMR (500 MHz, $CDCl_3$) δ 8.76 (br s, 1H), 7.22 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 2.6 Hz, 1H), 6.84 (dd, J = 8.8 Hz, J = 2.2 Hz, 1H), 6.56 (d, J = 2.0 Hz, 1H), 3.77 (s, 3H), 3.18 (s, 3H), 2.75 (s, 3H), 1.79 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 175.9, 155.8, 154.6, 131.8, 125.2, 124.8, 112.7, 112.5, 110.9, 100.3,

https://dx.doi.org/10.1021/acs.joc.0c02435
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63.8, 55.7, 25.1, 25.0, 20.7; HRMS(ESI): $[M + H]^+$ calcd for $C_{15}H_{17}N_3O_3H$ 288.1348, found 288.1350.

*1,3,5-Trimethyl-5-(1-methyl-1H-indol-3-yl)imidazolidine-2,4-dione (**6f**):* 60 mg; 88% yield; off white solid; mp 176−178 °C; R_f = 0.34 (50% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 3278, 2925, 1754, 1689, 1442; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, J = 8.3 Hz, 1H), 7.23 (dt, J = 7.0 Hz, J = 1.0 Hz, 1H), 7.16 (d, J = 8.1 Hz, 1H), 7.13 (s, 1H), 7.09 (dt, J = 7.0 Hz, J = 0.9 Hz, 1H), 3.78 (s, 3H), 3.15 (s, 3H), 2.78 (s, 3H), 1.84 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 175.4, 155.9, 137.5, 128.8, 124.9, 122.3, 120.4, 118.8, 110.0, 109.7, 63.7, 33.0, 25.1, 25.0, 20.9; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{15}H_{17}N_3O_2Na$ 294.1218, found 294.1219.

*5-(1-Hexyl-1H-indol-3-yl)-1,3,5-trimethylimidazolidine-2,4-dione (**6g**):* 76 mg; 89% yield; off white solid; mp 182−184 °C; R_f = 0.70 (50% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 3281, 2947, 1755, 1678, 1439; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, J = 8.4 Hz, 1H), 7.22−7.15 (m, 3H), 7.07 (t, J = 7.6 Hz, 1H), 4.08 (q, J = 7.1 Hz, 2H), 3.16 (s, 3H), 2.77 (s, 3H), 1.86−1.82 (m, 5H), 1.35−1.30 (m, 6H), 0.88 (t, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 175.4, 155.9, 136.8, 127.7, 125.0, 122.1, 120.2, 118.9, 110.0, 109.9, 63.7, 46.7, 31.3, 30.0, 26.6, 25.1, 25.0, 22.5, 21.0, 13.9; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{27}N_3O_2H$ 342.2182, found 342.2184.

*5-(1-Benzyl-1H-indol-3-yl)-1,3,5-trimethylimidazolidine-2,4-dione (**6h**):* 76 mg; 87% yield; off white solid; mp 188−190 °C; R_f = 0.53 (50% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 3269, 2917, 1759, 1694, 1461; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.28 (m, 4H), 7.21−7.17 (m, 3H), 7.13−7.08 (m, 3H), 5.30 (s, 2H), 3.16 (s, 3H), 2.79 (s, 3H), 1.84 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 175.3, 156.0, 237.2, 136.8, 128.9, 128.3, 127.9, 126.8, 125.3, 122.6, 120.7, 119.0, 110.9, 110.3, 63.8, 50.3, 25.2, 25.1, 21.0; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{21}H_{21}N_3O_2H$ 348.1712, found 348.1710.

*1,3,5-Trimethyl-5-(2-methyl-1H-indol-3-yl)imidazolidine-2,4-dione (**6i**):* 58 mg; 86% yield; off white solid; mp 174−176 °C; R_f = 0.61 (70% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 3273, 2919, 1758, 1681, 1454; ^1H NMR (500 MHz, $CDCl_3$) δ 8.48 (br s, 1H), 7.25−7.19 (m, 2H), 7.10 (t, J = 7.4 Hz, 1H), 7.03 (t, J = 7.2 Hz, 1H), 3.17 (s, 3H), 2.76 (s, 3H), 2.19 (s, 3H), 1.95 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 176.3, 155.5, 134.9, 134.4, 127.0, 121.5, 120.5, 118.4, 110.7, 105.2, 65.2, 25.2, 24.9, 22.8, 14.0; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{15}H_{17}N_3O_2Na$ 294.1218, found 294.1211.

*1,3,5-Trimethyl-5-(2-phenyl-1H-indol-3-yl)imidazolidine-2,4-dione (**6j**):* 73 mg; 87% yield; colorless solid; mp 186−188 °C; R_f = 0.67 (50% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 3277, 2926, 1755, 1684, 1459; ^1H NMR (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.49−7.40 (m, 6H), 7.34 (d, J = 8.1 Hz, 1H), 7.21 (dd, J = 7.1 Hz, J = 0.9 Hz, 1H), 7.14 (t, J = 7.3 Hz, 1H), 2.91 (s, 3H), 2.76 (s, 3H), 1.66 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 175.7, 155.4, 138.4, 135.3, 133.2, 130.2, 129.1, 128.2, 126.7, 122.5, 120.9, 119.6, 111.1, 107.6, 64.9, 25.2, 24.7, 23.0; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{19}N_3O_2H$ 334.1556, found 334.1556

*5-(1H-Indol-3-yl)-1,3-dimethyl-5-phenylimidazolidine-2,4-dione (**6k**):* 69 mg; 86% yield; colorless solid; mp 196−198 °C; R_f = 0.34 (50% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 3393, 3304, 1761, 1698, 1450; ^1H NMR (500 MHz, DMSO-d_6) δ 11.43 (s, 1H), 7.46−7.37 (m, 6H), 7.21 (d, J = 2.5 Hz, 1H), 7.11 (t, J = 8.5 Hz, 1H), 6.92 (t, J = 8.0 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 3.02 (s, 3H), 2.70 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 173.7, 156.0, 137.2, 136.7, 129.1, 129.0, 127.8, 127.1, 125.5, 122.1, 119.9, 119.7, 112.6, 110.5, 70.6, 27.0, 25.4; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{17}N_3O_2H$ 320.1399, found 320.1392.

*5-(1H-Indol-3-yl)-1,5-dimethylimidazolidine-2,4-dione (**6l**):* 48 mg; 79% yield; colorless solid; mp 164−166 °C; R_f = 0.29 (50% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 3272, 2962, 1749, 1696, 1439; ^1H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 8.72 (s, 1H), 7.41−7.38 (m, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.10 (t, J = 7.2 Hz, 1H), 6.99 (t, J = 6.8 Hz, 1H), 2.93 (s, 3H), 1.76 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 176.5, 156.4, 137.2, 125.0, 124.3. 121.8, 119.5, 119.4, 114.0, 112.3, 60.5, 24.6, 24.4; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{13}N_3O_2H$ 244.1086, found 244.1073

*5-Benzyl-5-(1H-indol-3-yl)-1,3-dimethylimidazolidine-2,4-dione (**6m**):* 73 mg; 87% yield; colorless solid; mp 162−164 °C; R_f = 0.48 (50% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 3302, 2922, 1762, 1694, 1455. ^1H NMR (500 MHz, $CDCl_3$); δ 8.54 (s, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.36−7.37 (d, J = 2.7 Hz, 1H), 7.30−7.34 (m, 3H), 7.22−7.26 (m, 1H), 7.18−7.20 (m, 2H), 7.14−7.16 (d, J = 7.7 Hz, 1H), 7.11 (m 1H), 3.81−3.40 (m, 2H), 2.87 (s, 3H), 2.81 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): 174.1, 156.2, 136.6, 133.4, 129.7, 128.5, 127.7, 124.6, 124.2, 123.0, 121.0, 118.7, 111.7, 111.4, 68.4, 38.9, 26.0, 24.6; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{20}H_{19}N_3O_2Na$ 356.1375 Found 356.1372.

Synthesis of 2,2-Bis(1*H*-indol-3-yl)propanoic Acid. The procedure similar to the synthesis of **5a** was followed with urea (280 mg) instead of *N*,*N*-Dimethylurea. Once the DES formed by (+)-tartaric acid (120 mg) and urea (280 mg) at 110 °C, the pyruvic acid (88 mg 1 mmol, 4 equiv) and indole (29 mg, 0.25 mmol, 1 equiv) were added in a 15 min interval. After complete consumption of indole, the reaction mixture was quenched while in hot by the slow addition of water and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain the brown mass. Pure product **7** was isolated by column chromatography using an 80% ethyl acetate−hexane mixture in 82% (31 mg) yield.

*2,2-Bis(1H-indol-3-yl)propanoic Acid (**7**):* 31 mg; 82% yield; pink solid; mp 90−92 °C (reported mp = 90 °C);[20] R_f = 0.37 (only EtOAc); IR (neat) ν_{max} (cm^{-1}) 3224, 2939, 2826, 1711; ^1H NMR (500 MHz, DMSO-d_6) δ 12.29 (s, 1H), 10.89 (s, 2H), 7.34−7.32 (m, 4H), 7.05−7.00 (m, 4H), 6.83 (t, J = 7 Hz, 2H), 1.99 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 176.7, 137.2, 126.4, 123.6, 121.2, 121.0, 118.6, 118.4, 111.9, 46.0, 26.5; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{18}H_{14}N_2O_2Na$ 313.0953, found 313.0939.

Synthesis of Intermediate 8a. *N*,*N*-Dimethylurea (88 mg, 1 mmol, 1 equiv) and glyoxylic acid monohydrate (92 mg, 1 mmol, 1 equiv) were stirred in an RB flask for a minute. Then the reaction mixture was diluted with ethyl acetate (15 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to obtain **8a** in a quantitative yield (143 mg): colorless liquid; R_f = 0.31 (70% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 3391, 2945, 1774, 1695, 1474; ^1H NMR (500 MHz, DMSO-d_6) δ 6.92 (d, J = 8.5 Hz, 1H), 5.02 (d, J = 8.5 Hz, 1H), 2.84 (s, 3H), 3.80 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 171.7, 155.8, 79.9, 26.8, 24.6; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_5H_8N_2O_3Na$ 167.0433, found 167.0433

Synthesis of Benzoyl Ester 8b and Acyl Ester 8c. To a solution of 5-hydroxyhydantoin **8a** (72 mg, 0.5 mmol, 1 equiv) in DCM were added benzoyl chloride (70 mg = 58 μL, 0.55 mmol, 1.1 equiv) followed by triethylamine (79 mg = 0.1 mL, 0.75 mmol, 1.5 equiv) at 0 °C, and the mixture was stirred for 15 min. Then the reaction mixture was quenched with water (15 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure, and pure product was isolated by column chromatography using a 35% ethyl acetate−hexane mixture to obtain **8b** in 80% yield. The same reaction procedure was repeated with acetyl chloride instead of benzoyl chloride to obtain **8c** in 97% yield (181 mg).

*1,3-Dimethyl-2,5-dioxoimidazolidin-4-yl benzoate (**8b**):* 198 mg, 80% yield; colorless solid; mp 128−130 °C; R_f = 0.64 (30% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 2944, 2551, 1786, 1712, 1709, 1681, 1450; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J = 8.5 Hz, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 8.0 Hz, 2H), 6.34 (s, 1H), 3.10 (s, 3H), 3.02 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 167.5, 165.5, 156.1, 134.1, 130.2, 128.6, 128.1, 78.5, 27.9, 25.1; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{12}H_{12}N_2O_4Na$ 271.0695, found 271.0695.

*1,3-Dimethyl-2,5-dioxoimidazolidin-4-yl acetate (**8c**):* 181 mg; 97% yield; colorless liquid; R_f = 0.28 (30% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 2948, 1789, 1756, 1715, 1460; ^1H NMR (500 MHz, DMSO-d_6) δ 6.08 (s, 1H), 2.88 (s, 3H), 2.83 (s, 3H), 2.14 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 170.3, 168.2, 156.4, 79.3, 28.2, 25.0, 20.8; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_7H_{10}N_2O_4Na$ 209.0538, found 209.0536.

https://dx.doi.org/10.1021/acs.joc.0c02435
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Synthesis of 5-(Indol-3-yl)-1,3,5-trimethylhydantoin (8d). The procedure for the synthesis of intermediate **8a** was followed with pyruvic acid (134 mg, 1 mmol, 1 equiv) instead of glyoxylic acid monohydrate. The reaction was completed in 15 min.

*5-Hydroxy-1,3,5-trimethylhydantoin (**8d**):*[27] 148 mg; 91% yield; colorless liquid; R_f = 0.28 (50% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 3343, 2920, 2849, 1771, 1698 ^1H NMR (500 MHz, DMSO-d_6) δ 6.61 (s, 1H), 2.87 (s, 3H), 2.77 (s, 3H), 1.39 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 173.9, 155.1, 84.0, 24.6, 23.8, 21.0.

*Synthesis of (±)-(R)-5-((R)-5-Chloro-3-hydroxy-2-oxoindolin-3-yl)-1,3-dimethylimidazo-lidine-2,4-dione (±)-(**10**).* To a solution of **5a** (61 mg, 0.25 mmol, 1 equiv) in a 5 mL mixture of THF/H_2O (9:1) was added NCS (134 mg, 1 mmol, 4 equiv) at 0 °C, and the reaction temperature was raised to 30 °C and stirred for 40 min. Then the reaction mixture was quenched by the addition of water (10 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain a crude yellow mass. The crude mass (without further purification) was stirred with Ag_2O (29 mg, 0.13 mmol, 0.5 equiv) in water (1 mL); after 2 h, an additional amount of water (2 mL) was added and extracted with ethyl acetate (3 × 15 mL). The combined organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain brown mass. The product was isolated in a 54% (37 mg) yield by column chromatography using a 50% ethyl acetate−hexane mixture: pale yellow solid; mp 172−174 °C; R_f = 0.20 (70% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 3265, 2919, 1771, 1705, 1620, 1446, 672; ^1H NMR (500 MHz, DMSO-d_6+$CDCl_3$) δ 10.60 (br s, 1H), 7.31 (dd, J = 7.3 Hz, J = 1.3 Hz, 1H), 7.05 (d, J = 2.2 Hz, 1H), 6.82−6.80 (m, 2H), 4.41 (s, 1H), 3.13 (s, 3H), 2.55 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6+$CDCl_3$) δ 175.5, 169.0, 157.8, 142.0, 130.4, 129.4, 125.8, 124.5, 111.9, 76.8, 66.5, 32.0, 24.8; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{13}H_{12}ClN_3O_4Na$ 332.0414, found 332.0409; $[\alpha]_D^{25}$ +0.00 (c 0.5 in methanol).

*Synthesis of (±)-(R)-5-((R)-3-Hydroxy-2-oxoindolin-3-yl)-1,3-dimethylimidazolidine-2,4-dione; (±)-Oxoaplysinopsin B (**9**).* Thirty mg of **10** was dissolved in 1 mL of methanol. Palladium (10%) on charcoal (25 mg) was added to it, and the reaction mixture was stirred for 30 min under a hydrogen atmosphere (balloon). Then, the reaction mixture was diluted with ethyl acetate (10 mL) and filtered through a Celite bed, and the Celite bed was washed with ethyl acetate (10 mL); the combined filtrate (from filtration + from the Celite bed wash) was evaporated to obtain **9** in a quantitative yield (26 mg). The product was used for characterization without further purification: pale yellow solid; mp 182−184 °C; R_f = 0.20 (70% EtOAc/hexane); IR (neat) ν_{max} (cm^{-1}) 3511, 3475, 3313, 3153, 1759, 1692, 1617, 1468; ^1H NMR (500 MHz, DMSO-d_6 δ 10.43 (br s, 1H), 7.22 (dt, J = 7.7, J = 1.2 Hz, 1H), 7.08 (d, J = 7.2 Hz, 1H), 6.90 (dd, J = 7.5 Hz, J = 0.9 Hz, 1H), 6.78 (d, J = 7.8 Hz, 1H), 6.62 (s, 1H), 4.40 (s, 1H), 3.14 (s, 3H), 2.50 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 175.3, 168.6, 157.1, 142.6, 130.0, 126.9, 124.1, 121.5, 109.9, 76.3, 66.1, 31.3, 24.2; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{13}H_{13}N_3O_4Na$ 298.0804, found 298.0802; $[\alpha]_D^{25}$ +0.00 (c 0.5 in methanol)

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02435.

Experimental procedures; spectral data; crystallographic data of **5a**, **8b**, **9**, and **10**; ^1H, ^{13}C, and HRMS spectra (PDF)

FAIR data, including the primary NMR FID files, for compounds **5a−5i**, **6a−6l**, **8a−8d**, **9**, and **10** (ZIP)

Accession Codes

CCDC 1987312−1987313, 2014062, and 2032805 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors greatly acknowledge SERB, India, for financial support (EEQ/2017/000422). P.P.S.K. thanks CSIR for SRF, and M.D.A.S. thanks UGC for a fellowship.

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