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Isocyanide-Based Multicomponent Bicyclization with Substituted Allenoate and Isatin: Synthesis of Unusual Spirooxindole Containing [5.5]-Fused Heterocycle

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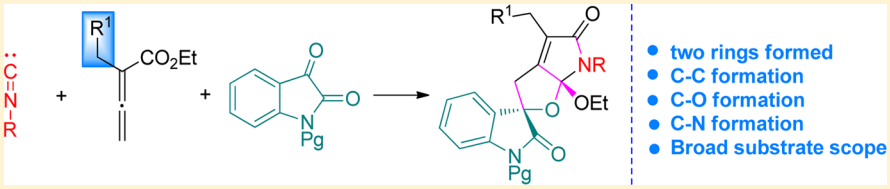
Supporting Information

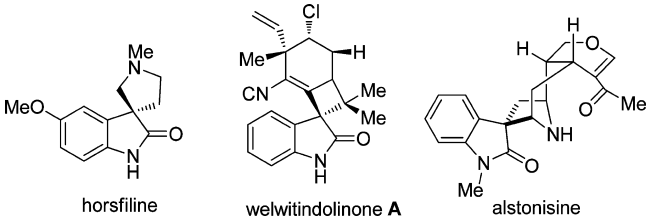


ABSTRACT: A three-component bicyclization reaction of isocyanide, substituted allenoate, and isatin has been disclosed. This protocol is proposed to proceed through Michael addition, double cyclization, and [1,5]-hydride shift sequence, thus leading to the formation of two new rings and five new chemical bonds, including C−C, C−O, and C−N bonds.

INTRODUCTION

Because of their significant biological activities and molecular complexity, spirocyclic oxindoles have become highly valuable synthetic frameworks in organic synthesis (Scheme 1).[1] For instance, compounds containing 3,3′-pyrrolidinylspirooxindole core structure are often found to show a series of biological activities.[2] Other natural products including welwitindolinone **A** have also enjoyed much attention from organic chemists due to their unique structural characters.[3] As such, the past decades have witnessed much progress in the efficient and selective construction of these spirocyclic oxindole skeletons.[4] Up to now, the organocatalyzed reactions in an enantioselective manner have been well documented, thus dramatically facilitating the investigation on biological evaluation.[5] Additionally, metal-catalyzed domino processes also provided a quick access to approach spirooxindole derivatives in an efficient manner.[6] On the other hand, isatin has the potential to be easily prepared and used both as electrophile and as nucleophile, which makes them irreplaceable building blocks in organic synthesis.[7] Isatin-based methyleneindolinone,[8] ketemine,[9] and other derivatives[10] have been widely applied in the preparation of such challenging spirocyclic frameworks. Despite these significant advances, the development of new methods to construct these core structures using isatin as starting materials remains desirable.

Scheme 1. Natural Products Possessing Spirooxindole as Core Structure



In the past decades, the development of new methods and strategies that provide high synthetic efficiency and excellent atom economy continues to be a significant goal of synthetic chemistry. In this regard, isocyanide-based multicomponent reactions (IMCRs) are found to be good candidates to achieve this goal due to their inherent features including atom- and step-economy, and convergence.[11,12] Moreover, IMCRs allowed the rapid and efficient construction of heterocycles and drug like molecules with increased complexity and diversity, which made them powerful tools in organic synthesis.[13] Of note are the isocyanide-based multicomponent bicyclization reactions,[14,15] which have drawn considerable attention from the synthetic community due to multiple bonds-forming events and high synthetic efficiency. As a consequence, a variety of new transformations using this strategy have been developed.

In the past years, we became particularly interested in the development of isocyanide-based multicomponent reactions and other novel transformations.[16] In particular, we reported the first multicomponent reaction involving isocyanide and allenoate, thus offering a new opportunity for the synthesis of spirooxindole-containing butenolide (Scheme 2).[17] This strategy was subsequently proven to be particularly effective

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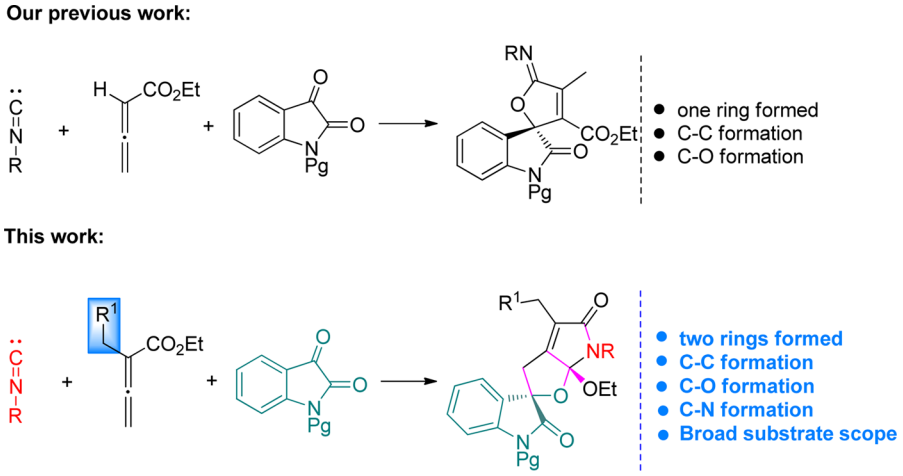
Scheme 2. Multicomponent Bicyclization To Approach Spirooxindole with Increased Molecular Complexity Using Substituted Allenoate

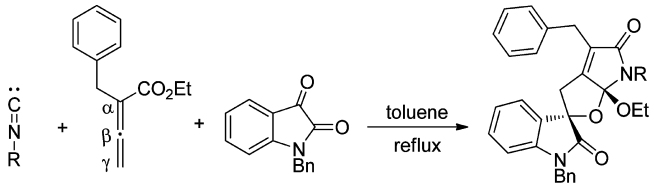


for the construction of five-membered carbocycles and heterocycles by simply changing the electron-deficient components.[18] Taking the mechanism and reactivity mode into consideration, this strategy shares many similarities with phosphine-catalyzed cycloaddition involving allenoate.[19] As a continuation, herein we wish to report that the three-component reaction with isocyanide, substituted allenoate, and isatin gives quick access to synthesize structurally complex spirooxindole (Scheme 2).

RESULTS AND DISCUSSION

Initially, *tert*-butyl isocyanide **1a**, substituted allenoate **2a**, and isatin **3a** were selected as model substrates. Treatment of this mixture in toluene under reflux essentially afforded a polycyclic cycloadduct **4a** in 80% yield (Table 1, entry 1). Encouraged by this experimental result, reaction parameters including the solvent and the temperature were briefly screened to acquire the optimal reaction conditions. Of the solvents examined, CH_3CN (33%) and DMSO (27%) gave rise to decreased yields, whereas the employment of THF and DCM only led to a trace amount of product **4a**. The experimental outcome also revealed that the temperature had a significant impact on the reaction performance. No reaction occurred when the present reaction was conducted at room temperature in toluene. The yield of product **4a** decreased dramatically (35%) when the reaction was performed at 80 °C.

Table 1. Multicomponent Reaction of Isocyanide 1, Allenoate 2a, and Isatin 3a



1 **2a** **3a** **4**

entry	R	product	yield (%)[b]
1	*tert*-butyl	**4a**	80
2	*i*-propyl	**4b**	62
3	1,1,3,3-tetramethylbutyl	**4c**	74
4	cyclohexyl	**4d**	86
5	*n*-butyl	**4e**	67
6	*n*-pentyl	**4f**	68
7	2,6-dimethylphenyl	**4g**	77
8	2,4,6-trimethylphenyl	**4h**	69

[a]Reaction conditions: 1.0 mmol of isocyanide **1**, 1.0 mmol of allenoate **2a**, 1.0 mmol of isatin **3a** in 5 mL of toluene, reflux. [b]Isolated yields of one isomer after silica gel chromatography.

Having established the optimal conditions, various aliphatic and aromatic isocyanides were subsequently used to undergo the standard conditions. As shown in Table 1, several substituents including the *tert*-butyl, *i*-propyl, and 1,1,3,3-tetramethylbutyl groups were well tolerated, which indicated that the present reaction was not sensitive to sterical hindrance caused by isocyanide (Table 1, entries 1−3). In addition, linear isocyanides were also found to be good reaction partners (Table 1, entries 5, 6). Although aromatic isocyanides were usually believed to be less reactive, the employment of 2,6-dimethylphenyl and 2,4,6-trimethylphenyl isocyanides gave the corresponding products **4g** and **4h** in satisfactory yields (Table 1, entries 7, 8). It was also worthy to note that all new compounds **4** were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS spectra, and only one stereoisomer was formed. Furthermore, the structure of compound **4d** was unambiguously confirmed by single-crystal X-ray analysis.[20]

After a broad isocyanide scope had been established, we sought to briefly examine the possibility of substituted allenoate **2**. As shown in Table 2, a variety of allenoates **2** bearing different substituents on the aromatic ring were screened under the standard reaction conditions. To our delight, most of the substituents were compatible to present cycloaddition with good performance. Notably, the presence of electron-rich groups on the aromatic ring of substrate **2** seemed to significantly increase the reaction yields (Table 2, entries 6, 7).

To further explore the versatility of present reaction, a series of substituted isatins **3** were then employed to react with *tert*-butyl isocyanide **1a** and allenoate **2**. Reactions with substituted isatins **3** having electron-withdrawing and -donating groups on the aromatic rings were subsequently conducted, and the representative results were summarized in Scheme 3. Pleasingly, all reactions proceeded smoothly to give the corresponding cycloadducts **6a**−**6d**. To test the sterical influence on the present reaction, reactions with isatins **3** containing substituents at position 4 were also carried out to produce compounds **6e**

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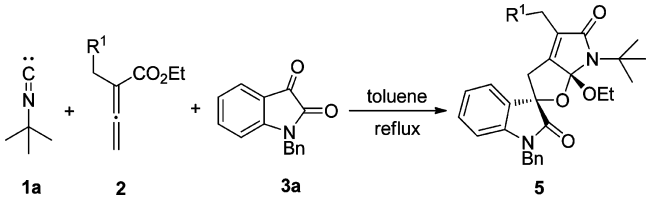
Table 2. Multicomponent Reaction of *tert*-Butyl Isocyanide 1a, Allenoate 2, and Isatin 3a



entry	R^1	product	yield (%)[b]
1	4-ClC_6H_4	**5a**	67
2	3-ClC_6H_4	**5b**	61
3	2-ClC_6H_4	**5c**	64
4	3-BrC_6H_4	**5d**	60
5	2-BrC_6H_4	**5e**	59
6	4-MeC_6H_4	**5f**	82
7	2-MeC_6H_4	**5g**	85

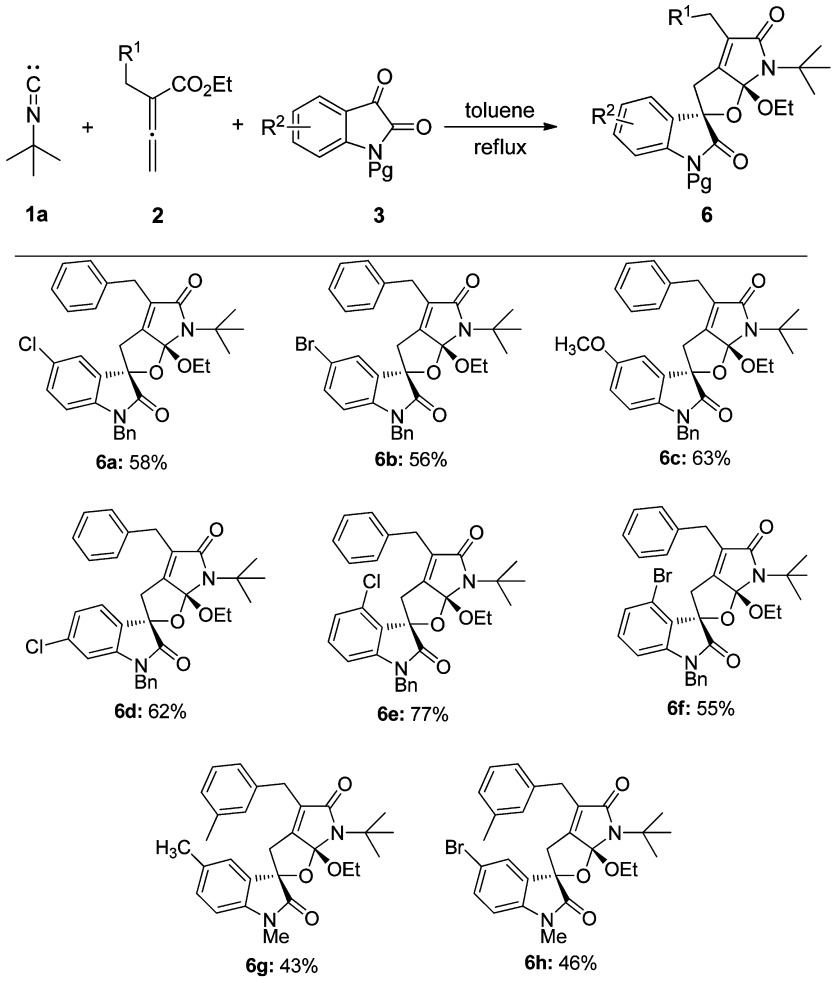
[a]Reaction conditions: 1.0 mmol of *tert*-butyl isocyanide **1a**, 1.0 mmol of substituted allenoate **2**, 1.0 mmol of isatin **3a** in 5 mL of toluene, reflux. [b]Isolated yields of one isomer after silica gel chromatography.

and **6f**. Finally, changing the nitrogen protecting group of isatin from Bn group to Me group was also conducted. In such case, the Me protecting group was well tolerated to yield **6g** and **6h** with slightly decreased yields.

On the basis of these above-mentioned experimental outcomes, a reasonable possibility is outlined to explain the present multicomponent bicyclization (Scheme 4). Initially, the blending of substrates **1** and **2** gives rise to a reactive zwitterionic intermediate, which exists as a resonance-stabilized form **A**↔**B**. Subsequently, the nucleophilic attack of allylic carbanion **B** toward isatin **3** followed by intramolecular cyclization essentially leads to the formation of intermediate **D**. The sequential [1,5]-hydride shift[21] then takes place to afford **G** via intermediate **F**. Finally, ethoxy group elimination occurs to yield a reactive *N*-acyl iminum cation intermediate **H**,[22] which undergoes nucleophilic addition to yield the product **4**.

To gain further insight into the aforementioned three-component cycloaddition reaction, several controlled experiments were conducted. As shown in Scheme 5, the ethoxy group in compounds **4b** and **4h** was easily replaced by a methoxy group when the reaction was conducted in the presence of acidic conditions using methanol as solvents. According to our analysis, this transformation may proceed through protonation, elimination of ethanol, and nucleophilic addition to generate the products **7a** and **7b**. The experimental results could also explain the formation of *N*-acyl iminium cation intermediate, thus lending support to our proposed mechanism.

Scheme 3. Multicomponent Reaction of *tert*-Butyl Isocyanide 1a, Allenoate 2, and Isatin 3



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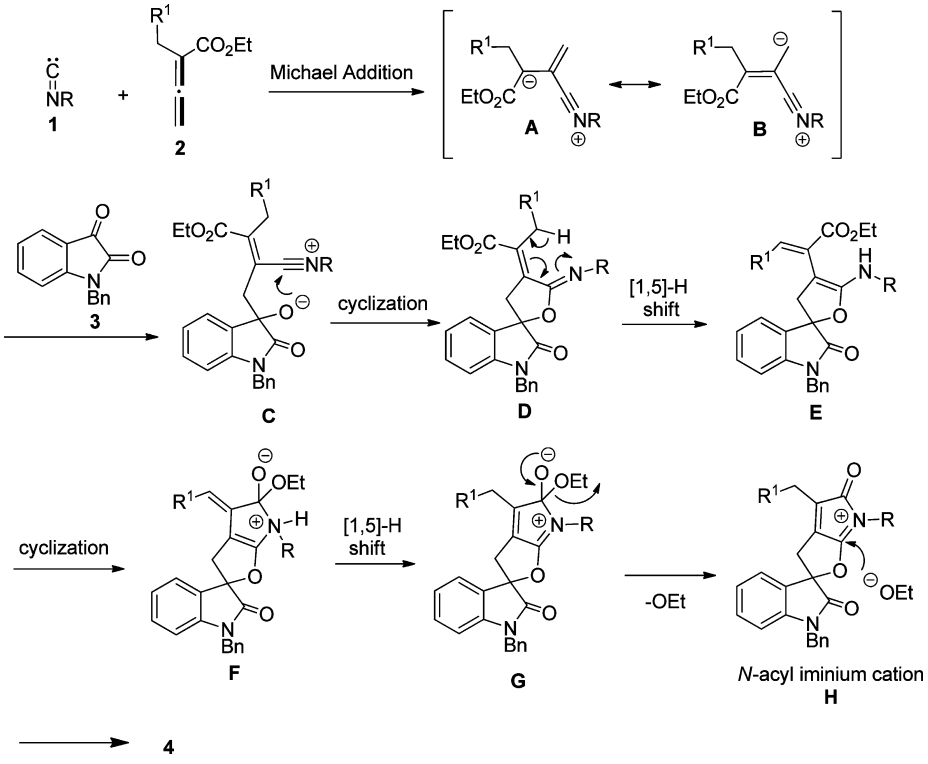
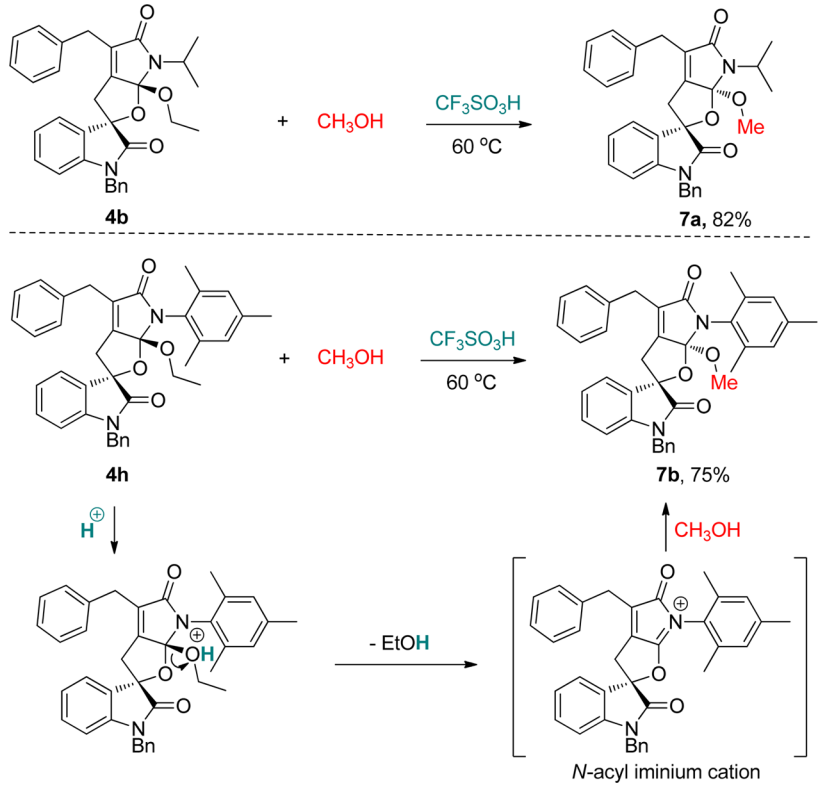
Scheme 4. Proposed Mechanism



Scheme 5. Controlled Experiments



On the basis of the above-mentioned experimental results and our previous works, we can see that two kinds of reaction pathways exist in the three-component reaction of isocyanide, allenoate, and isatin (Scheme 6). The initial steps of two paths both involve the generation of resonance-stabilized zwitterion **A**↔**B**. As shown in Scheme 6, path a represents a more simple transformation in which resonance form **A** attacks the reactive carbonyl group of isatin **3** to furnish a new five-membered ring. In contrast, the installation of a substitutent at the α-position of allenoate **2** brings great change to the reaction outcome. In

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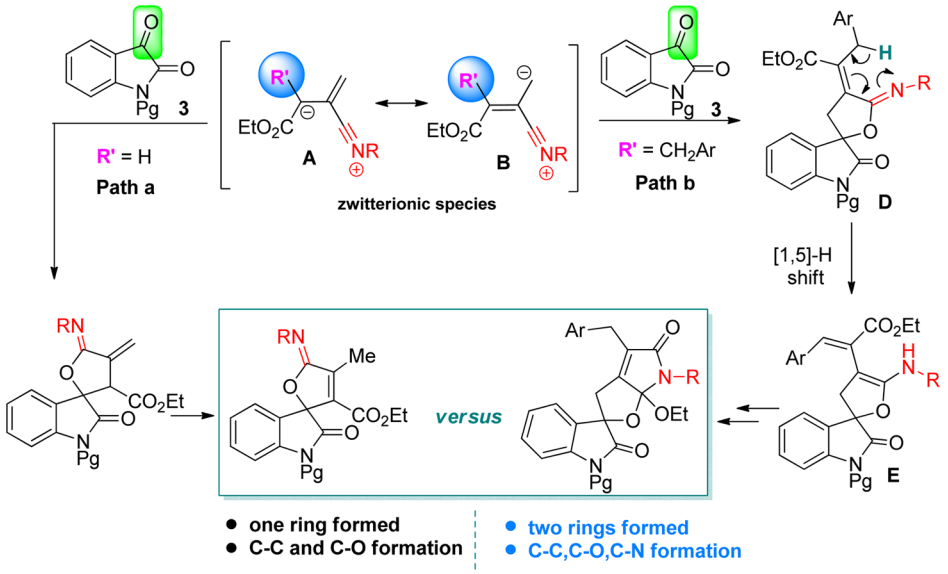
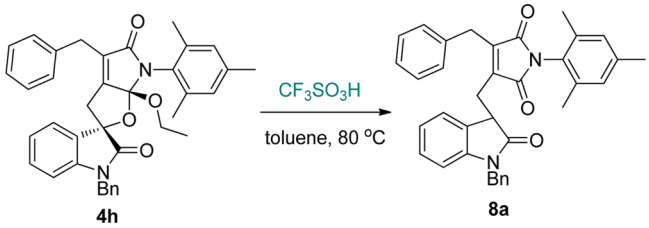
Scheme 6. Comparison of Reactivity Behavior between α-Substituted Allenoate and Unsubstituted Allenoate



such case, allylic anion **B** has the priority to react with isatin **3** to afford intermediate **D**. In the following step, we can see that the presence of H atom at the α-position of allenoate **2** enables the occurrence of a subsequent [1,5]-H shift, which is quite significant for the whole transformation. As compared to the traditional method, the present strategy allowed the construction of two rings in one step, and thus greatly increased the synthetic efficiency.

Furthermore, the reaction with compound **4h** under acidic conditions in toluene other than alcohol resulted in different conversion. As shown in Scheme 7, unexpected ring-opening of

Scheme 7. Ring-Opening Experiments under Acidic Conditions

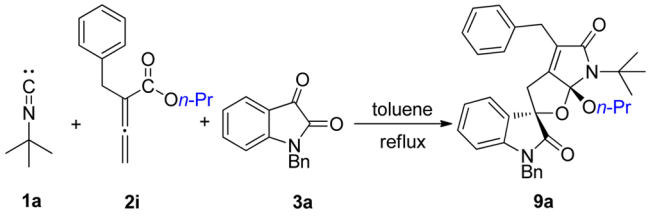


4h led to the formation of compound **8a**. This interesting result also indicated that the present reaction had potential to experience versatile transformations.

The reaction with *n*-propyl allenoate **2i** other than ethyl allenoate was also conducted under standard conditions (Scheme 8). In this case, the bicyclization reaction proceeded smoothly to give rise the corresponding product **9a**, thereby expanding the scope of the present reaction.

In conclusion, we have described the multicomponent bicyclization of isocyanide, substituted allenoate, and isatin, thus proving a quick access to structurally complex spirooxindoles. This protocol is proposed to proceed through Michael addition, double cyclization, double [1,5]-hydride shift, and nucleophilic addition. The reactive *N*-acyl iminium cation was believed to be the key intermediate of the whole transformation. The present strategy also features excellent atom economy, wide substrate scope, easy experimental setup,

Scheme 8. Expanded Experiments



as well as mild conditions. Furthermore, the unusual product spirooxindole derivatives may also be interested to biological evaluation. Given these advantages, the present reaction has potential to be applied in organic syntheis.

EXPERIMENTAL SECTION

General Information. The NMR spectra were recorded on a 500 MHz spectrometer (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) with $CDCl_3$ as the solvent and TMS as the internal reference. ^{1}H NMR spectral data were reported as follows: chemical shift (δ, ppm), multiplicity, integration, and coupling constant (Hz). ^{13}C NMR spectral data were reported in terms of the chemical shift. The following abbreviations were used to indicate multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. IR spectra were recorded on a FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on a FTMS instrument in ESI mode and reported as *m*/*z*. Melting points were obtained on a digital melting point apparatus without correction. Unless otherwise stated, all reagents were commercially purchased and used without further purification.

General Procedure for the Formation of Products 4–6. Isocyanide **1** (1.0 mmol) was added to a solution of allenoate **2** (1.0 mmol) and isatin **3** (1.0 mmol) in 5 mL of toluene. The stirred mixture was heated under reflux for several hours, and the progress was monitored using TLC detection. After completion of the present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel [silica, 200–300; eluant, petroleum ether/ethyl acetate = 8:1] to afford the desired products **4–6**.

(2S,6aR)-1′,4-Dibenzyl-6-(tert-butyl)-6a-ethoxy-6,6a-dihydrospiro[furo[2,3-b]pyrrole-2,3′-indoline]-2′,5(3H)-dione ***(4a).*** 417 mg, 80% yield; white solid: mp 147–148 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.32–7.12 (m, 11H), 6.83 (t, J = 7.5 Hz, 1H), 6.64 (d, J = 7.5 Hz, 1H), 6.61–6.59 (m, 1H), 4.87 (d, J = 15.5

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Hz, 1H), 4.80 (d, J = 16.0 Hz, 1H), 3.71 (dd, J = 16.0, 1.5 Hz, 1H), 3.66 (dd, J = 16.0, 1.5 Hz, 1H), 3.59−3.48 (m, 2H), 3.15−3.12 (m, 1H), 2.31 (d, J = 14.0 Hz, 1H), 1.50 (s, 9H), 1.31 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 173.8, 170.7, 148.4, 141.7, 137.6, 135.3, 132.3, 130.1, 129.9, 129.0, 128.8, 128.7, 127.8, 127.4, 127.3, 126.7, 123.3, 122.9, 117.4, 109.4, 86.7, 59.9, 55.3, 44.1, 33.9, 30.8, 28.2, 15.4. HRMS (ESI): calcd for $C_{33}H_{34}N_2NaO_4$ $[M + Na]^+$, 545.2416; found, 545.2411.

(2S,6aR)-1′,4-Dibenzyl-6a-ethoxy-6-isopropyl-6,6a-dihydrospiro-[furo[2,3-b]pyrrole-2,3′-indoline]-2′,5(3H)-dione (**4b**). 314 mg, 62% yield; white solid: mp 152−153 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.32−7.19 (m, 10H), 7.13 (dt, J = 8.0, 1.0 Hz, 1H), 6.82 (t, J = 8.0 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 6.58 (d, J = 7.5 Hz, 1H), 4.87 (d, J = 16.0 Hz, 1H), 4.80 (d, J = 15.5 Hz, 1H), 4.05−4.02 (m, 1H), 3.72−3.71 (m, 2H), 3.61−3.58 (m, 1H), 3.50−3.47 (m, 1H), 3.20−3.16 (m, 1H), 2.38 (d, J = 14.0 Hz, 1H), 1.38−1.30 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 173.8, 169.8, 148.3, 141.7, 137.4, 135.3, 132.7, 130.1, 129.7, 129.1, 128.8, 127.8, 127.5, 126.8, 123.4, 122.9, 116.5, 109.4, 86.8, 44.6, 44.1, 33.6, 30.9, 21.1, 20.4, 15.4. HRMS (ESI): calcd for $C_{32}H_{33}N_2O_4$ $[M + H]^+$, 509.2440; found, 509.2448.

(2S,6aR)-1′,4-Dibenzyl-6a-ethoxy-6-(2,4,4-trimethylpentan-2-yl)-6,6a-dihydrospiro[furo[2,3-b]pyrrole-2,3′-indoline]-2′,5(3H)-dione (**4c**). 427 mg, 74% yield; white solid: mp 154−155 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.33−7.20 (m, 10H), 7.13 (dt, J = 7.5, 1.0 Hz, 1H), 6.78 (t, J = 8.0 Hz, 1H), 6.64 (d, J = 7.5 Hz, 1H), 6.53 (d, J = 7.5 Hz, 1H), 4.93 (d, J = 15.5 Hz, 1H), 4.76 (d, J = 15.5 Hz, 1H), 3.76 (dd, J = 16.5, 1.5 Hz, 1H), 3.66 (dd, J = 16.5, 1.5 Hz, 1H), 3.59−3.48 (m, 2H), 3.13 (d, J = 14.5 Hz, 1H), 2.72 (d, J = 14.5 Hz, 1H), 2.41 (d, J = 14.5 Hz, 1H), 1.61 (s, 3H), 1.52 (s, 3H), 1.37 (d, J = 14.5 Hz, 1H), 1.33 (t, J = 7.0 Hz, 3H), 0.89 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 173.7, 170.4, 148.9, 141.7, 139.9, 135.3, 131.9, 131.5, 130.3, 130.2, 129.9, 129.8, 128.9, 127.8, 127.7, 127.4, 123.5, 122.8, 122.7, 117.4, 109.5, 86.7, 59.9, 55.4, 44.1, 33.6, 30.3, 28.2, 15.4. HRMS (ESI): calcd for $C_{37}H_{43}N_2O_4$ $[M + H]^+$, 579.3223; found, 579.3228.

(2S,6aR)-1′,4-Dibenzyl-6-cyclohexyl-6a-ethoxy-6,6a-dihydrospiro[furo[2,3-b]pyrrole-2,3′-indoline]-2′,5(3H)-dione (**4d**). 471 mg, 86% yield; white solid: mp 161−162 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.32−7.20 (m, 10H), 7.13 (t, J = 8.0 Hz, 1H), 6.81 (t, J = 7.5 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 6.56 (d, J = 7.0 Hz, 1H), 4.86 (d, J = 15.5 Hz, 1H), 4.80 (d, J = 15.5 Hz, 1H), 3.72 (s, 2H), 3.69−3.64 (m, 1H), 3.56−3.46 (m, 2H), 3.18 (d, J = 14.0 Hz, 1H), 2.40 (d, J = 14.0 Hz, 1H), 2.03−1.89 (m, 2H), 1.81−1.72 (m, 3H), 1.59−1.57 (m, 1H), 1.32 (t, J = 7.0 Hz, 3H), 1.26−1.17 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 173.8, 169.6, 148.1, 141.7, 137.5, 135.3, 132.5, 130.1, 129.7, 129.1, 128.8, 127.8, 127.5, 126.7, 123.4, 122.9, 116.5, 109.8, 86.9, 59.9, 52.7, 44.1, 33.6, 30.9, 30.9, 30.5, 26.2, 26.1, 25.4, 15.4. HRMS (ESI): calcd for $C_{35}H_{36}N_2NaO_4$ $[M + Na]^+$, 571.2573; found, 571.2577.

(2S,6aR)-1′,4-Dibenzyl-6-butyl-6a-ethoxy-6,6a-dihydrospiro[furo-[2,3-b]pyrrole-2,3′-indoline]-2′,5(3H)-dione (**4e**). 349 mg, 67% yield, white solid: mp 163−164 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.32−7.20 (m, 10H), 7.14 (dt, J = 7.5, 1.0 Hz, 1H), 6.83−6.80 (m, 1H), 6.64 (d, J = 8.0 Hz, 1H), 6.56 (d, J = 7.0 Hz, 1H), 4.86 (d, J = 15.5 Hz, 1H), 4.80 (d, J = 15.5 Hz, 1H), 3.75 (d, J = 2.0 Hz, 2H), 3.62−3.59 (m, 1H), 3.48−3.45 (m, 1H), 3.35−3.32 (m, 1H), 3.24−3.20 (m, 1H), 3.11−3.08 (m, 1H), 2.42 (d, J = 14.0 Hz, 1H), 1.58−1.54 (m, 2H), 1.32 (t, J = 7.0 Hz, 3H), 1.28−1.24 (m, 2H), 0.83 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 173.8, 170.7, 148.4, 141.773, 137.4, 135.3, 132.4, 130.1, 129.6, 129.0, 128.9, 128.8, 127.8, 127.5, 126.8, 123.3, 123.0, 116.0, 109.4, 86.8, 59.8, 44.1, 38.9, 33.4, 31.1, 30.9, 20.1, 15.3, 13.7. HRMS (ESI): calcd for $C_{33}H_{34}N_2NaO_4$ $[M + Na]^+$, 545.2416; found, 545.2411.

(2S,6aR)-1′,4-Dibenzyl-6a-ethoxy-6-pentyl-6,6a-dihydrospiro-[furo[2,3-b]pyrrole-2,3′-indoline]-2′,5(3H)-dione (**4f**). 364 mg, 68% yield; white solid: mp 155−157 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.28−7.20 (m, 10H), 7.13 (dt, J = 8.0, 1.0 Hz, 1H), 6.81 (dt, J = 7.5, 0.5 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 6.56 (dd, J = 7.5, 1.0 Hz, 1H), 4.86 (d, J = 15.5 Hz, 1H), 4.80 (d, J = 15.5 Hz, 1H), 3.75 (d, J = 1.5 Hz, 2H), 3.63−3.57 (m, 1H), 3.49−3.43 (m, 1H), 3.36−3.30 (m, 1H), 3.24−3.20 (m, 1H), 3.13−3.07 (m, 1H), 2.43 (d, J = 14.0 Hz, 1H), 1.59−1.56 (m, 2H), 1.32 (t, J = 7.0 Hz, 3H), 1.23−1.19 (m, 4H), 0.75 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 170.8, 170.7, 148.4, 141.7, 137.4, 135.3, 132.4, 130.2, 129.6, 129.0, 128.9, 128.8, 127.8, 127.4, 126.8, 123.3, 123.1, 116.0, 109.4, 86.8, 59.8, 44.1, 39.1, 33.3, 30.9, 29.1, 25.6, 22.2, 15.2, 13.9. HRMS (ESI): calcd for $C_{34}H_{36}N_2NaO_4$ $[M + Na]^+$, 559.2573; found, 559.2576.

(2S,6aR)-1′,4-Dibenzyl-6-(2,6-dimethylphenyl)-6a-ethoxy-6,6a-dihydrospiro[furo[2,3-b]pyrrole-2,3′-indoline]-2′,5(3H)-dione (**4g**). 438 mg, 77% yield; white solid: mp 183−185 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.34−7.13 (m, 13H), 7.04−7.03 (m, 1H), 6.86−6.83 (m, 1H), 6.74 (dd, J = 7.5, 0.5 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 4.86 (d, J = 16.5 Hz, 1H), 4.76 (d, J = 16.5 Hz, 1H), 4.00−3.95 (m, 1H), 3.88−3.80 (m, 2H), 3.38−3.35 (m, 1H), 3.17−3.14 (m, 1H), 2.48 (d, J = 14.0 Hz, 1H), 2.35 (s, 3H), 2.13 (s, 3H), 1.11 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 173.8, 170.4, 150.6, 141.6, 138.9, 138.5, 137.3, 135.3, 133.7, 130.7, 130.2, 129.3, 129.3, 128.9, 128.9, 128.6, 128.5, 128.5, 127.9, 127.3, 126.8, 123.4, 123.2, 115.7, 109.4, 86.7, 60.8, 44.1, 33.5, 31.1, 19.6, 18.9, 14.9. HRMS (ESI): calcd for $C_{37}H_{35}N_2O_4$ $[M + H]^+$, 571.2597; found, 571.2591.

(2S,6aR)-1′,4-Dibenzyl-6a-ethoxy-6-mesityl-6,6a-dihydrospiro-[furo[2,3-b]pyrrole-2,3′-indoline]-2′,5(3H)-dione (**4h**). 416 mg, 69% yield; white solid: mp 188−190 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.37−7.27 (m, 10H), 7.20 (t, J = 8.0 Hz, 1H), 6.97 (s, 1H), 6.88 (t, J = 7.5 Hz, 2H), 6.76 (d, J = 7.5 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 4.92 (d, J = 15.5 Hz, 1H), 4.81 (d, J = 15.5 Hz, 1H), 4.04−4.01 (m, 1H), 3.87 (d, J = 14.0 Hz, 1H), 3.84 (d, J = 14.0 Hz, 1H), 3.39 (d, J = 13.5 Hz, 1H), 3.25−3.22 (m, 1H), 2.49 (d, J = 13.7 Hz, 1H), 2.35 (s, 3H), 2.31 (s, 3H), 2.21 (s, 3H), 1.16 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 173.9, 170.5, 150.5, 141.6, 138.5, 138.2, 138.0, 137.4, 135.3, 131.0, 130.8, 130.2, 129.3, 129.3, 129.3, 128.9, 128.8, 127.9, 127.3, 126.8, 123.3, 123.2, 115.6, 109.4, 86.7, 60.7, 44.0, 33.5, 31.1, 21.1, 19.5, 18.8, 18.2, 15.0. HRMS (ESI): calcd for $C_{38}H_{36}N_2NaO_4$ $[M + Na]^+$, 607.2573; found, 607.2600.

(2S,6aR)-1′-Benzyl-6-(tert-butyl)-4-(4-chlorobenzyl)-6a-ethoxy-6,6a-dihydrospiro[furo[2,3-b]pyrrole-2,3′-indoline]-2′,5(3H)-dione (**5a**). 372 mg, 67% yield, white solid: mp 174−175 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.33−7.14 (m, 10H), 6.83 (dt, J = 7.5, 0.5 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.49 (dd, J = 7.5, 0.5 Hz, 1H), 4.89 (d, J = 15.5 Hz, 1H), 4.81 (d, J = 15.5 Hz, 1H), 3.66 (d, J = 1.5 Hz, 2H), 3.60−3.49 (m, 2H), 3.23−3.20 (m, 1H), 2.43 (d, J = 14.0 Hz, 1H), 1.49 (s, 9H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 173.7, 170.5, 148.6, 141.7, 136.2, 135.3, 132.6, 131.8, 130.4, 130.2, 129.8, 128.96, 128.94, 128.87, 127.83, 127.5, 123.3, 122.7, 117.4, 109.5, 86.7, 59.9, 55.3, 44.1, 33.6, 30.1, 28.5, 28.2, 15.3. HRMS (ESI): calcd for $C_{33}H_{34}ClN_2O_4$ $[M + H]^+$, 557.2207; found, 557.2209.

(2S,6aR)-1′-Benzyl-6-(tert-butyl)-4-(3-chlorobenzyl)-6a-ethoxy-6,6a-dihydrospiro[furo[2,3-b]pyrrole-2,3′-indoline]-2′,5(3H)-dione (**5b**). 345 mg, 61% yield, white solid: mp 176−178 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.28−7.13 (m, 10H), 6.86 (t, J = 8.0 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.62 (d, J = 7.5 Hz, 1H), 4.88 (d, J = 15.5 Hz, 1H), 4.82 (d, J = 15.5 Hz, 1H), 3.69 (dd, J = 16.0, 1.0 Hz, 1H), 3.65 (dd, J = 16.0, 1.0 Hz, 1H), 3.62−3.47 (m, 2H), 3.22 (dd, J = 16.5, 1.5 Hz, 1H), 2.41 (d, J = 14.0 Hz, 1H), 1.50 (s, 9H), 1.32 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 173.7, 170.4, 148.9, 141.7, 139.6, 135.3, 134.5, 131.5, 130.2, 130.0, 129.8, 129.0, 128.9, 127.8, 127.5, 127.2, 126.9, 123.4, 122.7, 117.4, 109.5, 86.7, 59.9, 55.4, 44.1, 33.6, 30.3, 28.5, 18.2, 15.4. HRMS (ESI): calcd for $C_{33}H_{33}ClN_2NaO_4$ $[M + Na]^+$, 579.2027; found, 579.2021.

(2S,6aR)-1′-Benzyl-6-(tert-butyl)-4-(2-chlorobenzyl)-6a-ethoxy-6,6a-dihydrospiro[furo[2,3-b]pyrrole-2,3′-indoline]-2′,5(3H)-dione (**5c**). 355 mg, 64% yield; white solid: mp 175−177 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.38−7.14 (m, 10H), 6.90 (t, J = 7.5 Hz, 1H), 6.80 (dd, J = 7.5, 1.0 Hz, 1H), 6.65 (d, J = 8.0 Hz, 1H), 4.86 (d, J = 15.5 Hz, 1H), 4.82 (d, J = 15.5 Hz, 1H), 3.89 (dd, J = 16.0, 2.0 Hz, 1H), 3.78 (dd, J = 16.0, 2.0 Hz, 1H), 3.58−3.46 (m, 2H), 3.13 (d, J = 14.0 Hz, 1H), 2.26 (d, J = 14.0 Hz, 1H), 1.50 (s, 9H) 1.30 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 173.8, 170.5, 148.8, 141.7, 135.3, 135.3, 134.0, 131.5, 130.3, 130.2, 130.0, 129.7, 128.8, 128.4, 127.8, 127.5, 127.2, 123.3, 122.9, 117.4, 109.4, 86.7, 59.9,

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55.3, 44.1, 33.4, 28.8, 28.2, 15.4. HRMS (ESI): calcd for $C_{33}H_{33}ClN_2NaO_4$ $[M + Na]^+$, 579.2027; found, 579.2021.

(2S,6aR)-1′-Benzyl-4-(3-bromobenzyl)-6-(tert-butyl)-6a-ethoxy-6,6a-dihydrospiro[furo[2,3-b]pyrrole-2,3′-indoline]-2′,5(3H)-dione ***(5d)***. 360 mg, 60% yield, white solid: mp 208−210 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.38−7.26 (m, 7H), 7.20−7.10 (m, 3H), 6.87 (dt, J = 7.5, 1.0 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.20 (d, J = 7.5 Hz, 1H), 4.88 (d, J = 15.5 Hz, 1H), 4.82 (d, J = 15.5 Hz, 1H), 3.66−3.49 (m, 4H), 3.22 (dd, J = 14.0 Hz, 1H), 2.41 (d, J = 14.0 Hz, 1H), 1.50 (m, 9H), 1.32 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 173.8, 170.8, 148.2, 141.7, 136.2, 135.4, 134.5, 132.5, 130.0, 129.9, 129.5, 128.9, 128.8, 127.8, 127.5, 123.3, 122.9, 117.4, 109.4, 86.7, 59.9, 55.2, 44.1, 33.4, 30.4, 21.1, 15.4. HRMS (ESI): calcd for $C_{33}H_{34}BrN_2O_4$ $[M + H]^+$, 601.1702; found, 601.1701.

(2S,6aR)-1′-Benzyl-4-(2-bromobenzyl)-6-(tert-butyl)-6a-ethoxy-6,6a-dihydrospiro[furo[2,3-b]pyrrole-2,3′-indoline]-2′,5(3H)-dione ***(5e)***. 328 mg, 59% yield; white solid: mp 196−197 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.52 (dd, J = 8.0, 1.0 Hz, 1H), 7.39 (dd, J = 8.0, 1.5 Hz, 1H), 7.33−7.28 (m, 5H), 7.23−7.17 (m, 2H), 7.10−7.07 (m, 1H), 6.96−6.93 (m, 1H), 6.86 (dd, J = 7.5, 1.0 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 4.88 (d, J = 15.5 Hz, 1H), 4.84 (d, J = 15.5 Hz, 1H), 3.96−3.80 (m, 2H), 3.64−3.58 (m, 1H), 3.53−3.47 (m, 1H), 3.15 (d, J = 14.0 Hz, 1H), 2.24 (d, J = 14.0 Hz, 1H), 1.53 (s, 9H), 1.33 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 173.7, 170.5, 148.9, 141.7, 137.0, 135.3, 133.0, 131.5, 130.2, 130.2, 130.0, 128.8, 128.6, 127.8, 127.5, 124.5, 123.3, 122.9, 117.4, 109.4, 86.7, 59.9, 55.3, 44.1, 33.6, 31.6, 28.2, 15.4. HRMS (ESI): calcd for $C_{33}H_{33}BrN_2NaO_4$ $[M + Na]^+$, 623.1521; found, 623.1519.

(2S,6aR)-1′-Benzyl-6-(tert-butyl)-6a-ethoxy-4-(4-methylbenzyl)-6,6a-dihydrospiro[furo[2,3-b]pyrrole-2,3′-indoline]-2′,5(3H)-dione ***(5f)***. 439 mg, 82% yield, white solid: mp 155−157 °C. ^{1}H NMR (500 M Hz, $CDCl_3$): δ (ppm) = 7.31−7.26 (m, 5H), 7.16−7.11 (m, 3H), 7.04 (d, J = 8.0 Hz, 2H), 6.82 (t, J = 7.5 Hz, 1H), 6.65 (d, J = 8.0 Hz, 1H), 6.59 (d, J = 7.5 Hz, 2H), 4.88 (d, J = 15.5 Hz, 1H), 4.81 (d, J = 15.5 Hz, 1H), 3.70−3.49 (m, 4H), 3.15 (d, J = 14.0 Hz, 1H), 2.37 (d, J = 14.0 Hz, 1H), 2.29 (s, 3H), 1.51 (s, 9H), 1.32 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 173.8, 170.8, 148.2, 141.7, 136.2, 135.3, 134.5, 132.5, 130.0, 129.9, 129.5, 128.9, 128.8, 127.8, 127.5, 123.3, 122.9, 117.2, 109.4, 86.7, 59.9, 55.2, 44.1, 33.4, 30.4, 28.2, 21.1, 15.4. HRMS (ESI): calcd for $C_{34}H_{37}N_2O_4$ $[M + H]^+$, 537.2753; found, 537.2758.

(2S,6aR)-1′-Benzyl-6-(tert-butyl)-6a-ethoxy-4-(2-methylbenzyl)-6,6a-dihydrospiro[furo[2,3-b]pyrrole-2,3′-indoline]-2′,5(3H)-dione ***(5g)***. 472 mg, 85% yield, white solid: mp 153−154 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.33−7.27 (m, 5H), 7.17−7.11 (m, 3H), 7.04 (d, J = 8.0 Hz, 2H), 6.82 (dd, J = 7.5, 0.5 Hz, 1H), 6.65 (d, J = 8.0 Hz, 1H), 6.60 (d, J = 7.0 Hz, 1H), 4.88 (d, J = 16.0 Hz, 1H), 4.81 (d, J = 16.0 Hz, 1H), 3.67−3.50 (m, 4H), 3.18−3.14 (m, 1H), 2.38 (d, J = 14.0 Hz, 1H), 2.29 (s, 3H), 1.51 (s, 9H), 1.32 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 170.7, 170.4, 148.9, 141.7, 139.9, 135.3, 131.9, 131.5, 130.3, 130.2, 129.9, 129.8, 128.9, 127.8, 127.7, 127.4, 123.5, 122.8, 122.7, 117.4, 109.5, 86.7, 59.9, 55.4, 44.1, 33.6, 30.3, 28.2, 15.4. HRMS (ESI): calcd for $C_{34}H_{37}N_2O_4$ $[M + H]^+$, 537.2753; found, 537.2760.

(2S,6aR)-1′,4-Dibenzyl-6-(tert-butyl)-5′-chloro-6a-ethoxy-6,6a-dihydrospiro[furo[2,3-b]pyrrole-2,3′-indoline]-2′,5(3H)-dione ***(6a)***. 332 mg, 58% yield, white solid: mp 183−184 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.32−7.11 (m, 10H), 7.12 (dd, J = 8.0, 2.0 Hz, 1H), 6.68 (d, J = 2.0 Hz, 1H), 6.55 (d, J = 8.5 Hz, 1H), 4.82−4.81 (m, 2H), 3.71 (d, J = 2.0 Hz, 2H), 3.56−3.47 (m, 2H), 3.08 (dd, J = 14.0, 2.0 Hz, 1H), 2.17 (d, J = 14.0 Hz, 1H), 1.51 (s, 9H), 1.31 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 173.5, 170.6, 147.9, 140.2, 137.2, 134.8, 132.5, 131.5, 130.9, 129.0, 128.97, 128.93, 128.89, 128.85, 128.6, 127.9, 127.8, 127.5, 127.4, 126.9, 123.4, 117.5, 110.5, 86.6, 59.9, 55.3, 44.2, 33.1, 30.9, 29.9, 15.4. HRMS (ESI): calcd for $C_{33}H_{34}ClN_2O_4$ $[M + H]^+$, 557.2207; found, 557.2201.

(2S,6aR)-1′,4-Dibenzyl-5′-bromo-6-(tert-butyl)-6a-ethoxy-6,6a-dihydrospiro[furo[2,3-b]pyrrole-2,3′-indoline]-2′,5(3H)-dione ***(6b)***. 336 mg, 56% yield, white solid: mp 198−199 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.31−7.21 (m, 11H), 6.88 (d, J = 2.0 Hz, 1H), 6.53 (d, J = 8.0 Hz, 1H), 4.83 (s, 2H), 3.74 (s, 2H), 3.58−3.47 (m, 2H), 3.08−3.05 (m, 1H), 2.14 (d, J = 14.0 Hz, 1H), 1.54 (s, 9H), 1.34 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 173.3, 170.6, 147.9, 140.7, 137.1, 134.8, 133.0, 132.6, 131.8, 129.0, 128.9, 128.9, 127.9, 127.3, 126.9, 126.2, 117.5, 115.8, 110.0, 86.5, 59.9, 55.3, 44.2, 33.0, 30.9, 15.3. HRMS (ESI): calcd for $C_{33}H_{33}BrN_2NaO_4$ $[M + Na]^+$, 623.1521; found, 623.1527.

(2S,6aR)-1′,4-Dibenzyl-6-(tert-butyl)-6a-ethoxy-5′-methoxy-6,6a-dihydrospiro[furo[2,3-b]pyrrole-2,3′-indoline]-2′,5(3H)-dione ***(6c)***. 347 mg, 63% yield, white solid: mp 172−174 °C. ^{1}H NMR (500 M Hz, $CDCl_3$): δ (ppm) = 7.27−7.18 (m, 10H), 6.68 (dd, J = 8.5, 2.5 Hz, 1H), 6.55 (d, J = 8.5 Hz, 1H), 6.42 (d, J = 3.0 Hz, 1H), 4.85 (d, J = 15.5 Hz, 1H), 4.79 (d, J = 15.5 Hz, 1H), 3.78 (dd, J = 16.5, 2.0 Hz, 1H), 3.65 (s, 3H), 3.62−3.59 (m, 2H), 3.52−3.49 (m, 1H), 3.15−3.11 (m, 1H), 2.26 (d, J = 14.5 Hz, 1H), 1.50 (s, 9H), 1.30 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 173.6, 170.6, 156.4, 148.4, 137.4, 135.4, 134.9, 132.6, 131.2, 129.0, 128.8, 127.8, 127.4, 126.7, 117.5, 114.3, 110.3, 109.9, 86.9, 59.9, 55.7, 55.3, 44.2, 33.7, 31.0, 28.2, 15.4. HRMS (ESI): calcd for $C_{34}H_{36}N_2NaO_5$ $[M + Na]^+$, 575.2522; found, 575.2527.

(2S,6aR)-1′,4-Dibenzyl-6-(tert-butyl)-6′-chloro-6a-ethoxy-6,6a-dihydrospiro[furo[2,3-b]pyrrole-2,3′-indoline]-2′,5(3H)-dione ***(6d)***. 342 mg, 62% yield; white solid: mp 189−190 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.28−7.18 (m, 10H), 7.12 (dd, J = 8.5, 2.0 Hz, 1H), 6.68 (d, J = 2.0 Hz, 1H), 6.54 (d, J = 8.0 Hz, 1H), 4.82−4.80 (m, 2H), 3.71 (d, J = 2.0 Hz, 2H), 3.54−3.47 (m, 2H), 3.09−3.06 (m, 1H), 2.17 (d, J = 14.5 Hz, 1H), 1.51 (s, 9H), 1.31 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 173.4, 170.6, 147.9, 140.2, 137.2, 134.8, 132.5, 131.5, 130.1, 128.9, 128.9, 128.9, 128.8, 128.6, 127.9, 127.5, 127.4, 126.9, 123.4, 117.5, 110.4, 86.6, 59.9, 55.3, 44.2, 33.1, 30.9, 29.9, 28.2, 15.4. HRMS (ESI): calcd for $C_{33}H_{34}ClN_2O_4$ $[M + H]^+$, 557.2207; found, 557.2213.

(2S,6aR)-1′,4-Dibenzyl-6-(tert-butyl)-4′-chloro-6a-ethoxy-6,6a-dihydrospiro[furo[2,3-b]pyrrole-2,3′-indoline]-2′,5(3H)-dione ***(6e)***. 428 mg, 77% yield, white solid: mp 188−189 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.28−7.19 (m, 10H), 7.12 (dd, J = 8.0, 2.0 Hz, 1H), 6.68 (d, J = 2.0 Hz, 1H), 6.54 (d, J = 8.5 Hz, 1H), 4.82−4.81 (m, 2H), 3.71 (d, J = 1.5 Hz, 2H), 3.56−3.47 (m, 2H), 3.09−3.06 (m, 1H), 2.16 (d, J = 14.0 Hz, 1H), 1.51 (s, 9H), 1.31 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 173.4, 170.6, 147.9, 140.2, 137.2, 134.6, 132.5, 131.5, 130.1, 128.97, 128.93, 128.8, 127.9, 127.4, 126.9, 123.4, 117.5, 110.5, 85.5, 59.9, 55.3, 44.2, 33.0, 30.9, 28.2, 15.3. HRMS (ESI): calcd for $C_{33}H_{33}ClN_2NaO_4$ $[M + Na]^+$, 579.2027; found, 579.2029.

(2S,6aR)-1′,4-Dibenzyl-4′-bromo-6-(tert-butyl)-6a-ethoxy-6,6a-dihydrospiro[furo[2,3-b]pyrrole-2,3′-indoline]-2′,5(3H)-dione ***(6f)***. 330 mg, 55% yield; white solid: mp 193−195 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.33−7.12 (m, 11H), 7.02 (t, J = 8.0 Hz, 1H), 6.57 (d, J = 7.5 Hz, 1H), 4.95 (d, J = 15.5 Hz, 1H), 4.60 (d, J = 15.5 Hz, 1H), 3.78 (dd, J = 17.5, 1.5 Hz, 1H), 3.66 (dd, J = 17.5, 1.0 Hz, 1H), 3.47−3.38 (m, 2H), 3. 33 (d, J = 14.0 Hz, 1H), 1.94 (d, J = 14.0 Hz, 1H), 1.54 (s, 9H), 1.23 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 174.1, 170.6, 145.1, 144.9, 137.9, 135.1, 134.8, 131.6, 129.5, 128.9, 128.5, 127.9, 127.9, 127.1, 126.4, 124.6, 120.7, 117.7, 108.2, 86.8, 59.3, 54.9, 43.6, 31.7, 29.0, 28.2, 15.2. HRMS (ESI): calcd for $C_{33}H_{34}BrN_2O_4$ $[M + H]^+$, 601.1702; found, 601.1696.

(2S,6aR)-6-(tert-Butyl)-6a-ethoxy-1′,5′-dimethyl-4-(3-methylbenzyl)-6,6a-dihydrospiro[furo[2,3-b]pyrrole-2,3′-indoline]-2′,5(3H)-dione ***(6g)***. 204 mg, 43% yield, white solid: mp 123−125 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.15−7.09 (m, 2H), 7.04−6.99 (m, 3H), 6.66 (d, J = 8.0 Hz, 1H), 6.55 (t, J = 0.5 Hz, 1H), 3.68 (s, 2H), 3.61−3.48 (m, 2H), 3.14 (s, 3H), 3.04−3.00 (m, 1H), 2.25 (s, 3H), 2.22 (s, 3H), 2.14 (d, J = 14.5 Hz, 1H), 1.50 (s, 9H), 1.32 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 173.6, 170.7, 148.674, 140.3, 138.3, 137.3, 132.8, 132.1, 130.4, 129.9, 129.8, 128.5, 127.7, 126.1, 123.7, 117.3, 108.1, 86.9, 59.6, 55.1, 32.9, 30.9, 28.2, 26.4, 21.3, 21.1, 15.3. HRMS (ESI): calcd for $C_{29}H_{34}N_2NaO_4$ $[M + Na]^+$, 497.2416; found, 497.2420.

(2S,6aR)-5′-Bromo-6-(tert-butyl)-6a-ethoxy-1′-methyl-4-(3-methylbenzyl)-6,6a-dihydrospiro[furo[2,3-b]pyrrole-2,3′-indoline]-2′,5(3H)-dione ***(6h)***. 247 mg, 46% yield, white solid: mp 147−149 °C.

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^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.21−7.15 (m, 3H), 7.10 (s, 1H), 7.07 (d, J = 7.5 Hz, 1H), 7.01 (d, J = 7.0 Hz, 1H), 6.72 (dd, J = 7.5, 1.5 Hz, 1H), 3.76 (dd, J = 17.0, 1.5 Hz, 1H), 3.59 (dd, J = 17.0, 1.5 Hz, 1H), 3.45−3.36 (m, 3H), 3.12 (s, 3H), 2.31 (s, 3H), 2.10 (d, J = 14.0, 1H), 1.59 (s, 9H), 1.24 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 174.0, 170.6, 146.1, 145.4, 138.0, 134.7, 131.8, 130.2, 128.3, 127.9, 126.3, 124.7, 120.7, 117.6, 107.3, 86.9, 59.3, 54.9, 31.2, 29.1, 28.2, 26.2, 22.4, 15.2. HRMS (ESI): calcd for $C_{28}H_{31}BrN_2NaO_4$ $[M + Na]^+$, 561.1365; found, 561.1362.

General Procedure for the Formation of Product 7. Trifluoromethylsulfonyl acid (0.3 equiv) was added to a solution of compound **4** (0.3 mmol) in a 3 mL solution of alcohol. The stirred mixture was heated to 60 °C, and the progress was carefully monitored using TLC detection. After completion of the present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel [silica, 200−300; eluant, petroleum ether/ethyl acetate = 8:1] to afford the desired product **7**.

*(2S,6aS)-1′,4-Dibenzyl-6-isopropyl-6a-methoxy-6,6a-dihydrospiro[furo[2,3-b]pyrrole-2,3′-indoline]-2′,5(3H)-dione (**7a**).* 122 mg, 82% yield; white solid: mp 153−155 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.31−7.27 (m, 9H), 7.23−7.20 (m, 3H), 7.03 (t, J = 7.5 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 4.91 (d, J = 16.0 Hz, 1H), 4.87 (d, J = 15.5 Hz, 1H), 4.22−4.16 (m, 1H), 3.87 (d, J = 14.5 Hz, 1H), 3.82 (d, J = 14.5 Hz, 1H), 3.03 (d, J = 2.5 Hz, 2H), 3.01 (s, 3H), 1.27 (d, J = 7.0 Hz, 3H), 1.23 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 175.0, 171.3, 142.8, 137.4, 135.5, 134.7, 130.2, 128.95, 128.92, 127.8, 127.3, 126.6, 125.7, 124.9, 122.9, 109.6, 82.2, 53.2, 43.9, 42.9, 30.9, 29.7, 20.2. HRMS (ESI): calcd for $C_{31}H_{31}N_2O_4$ $[M + H]^+$, 495.2284; found, 495.2280.

*(2S,6aS)-1′,4-Dibenzyl-6-mesityl-6a-methoxy-6,6a-dihydrospiro-[furo[2,3-b]pyrrole-2,3′-indoline]-2′,5(3H)-dione (**7b**).* 128 mg, 75% yield; white solid: mp 182−183 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.37−7.21 (m, 12H), 7.06 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 8.5 Hz, 2H), 6.73 (d, J = 8.0 Hz, 1H), 4.97 (d, J = 16.0 Hz, 1H), 4.86 (d, J = 16.0 Hz, 1H), 4.01 (d, J = 14.5 Hz, 1H), 3.92 (d, J = 14.5 Hz, 1H), 3.25 (d, J = 13.5 Hz, 1H), 3.20 (d, J = 13.5 Hz, 1H), 3.06 (s, 3H), 2.28 (s, 3H), 1.95 (s, 3H), 1.77 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 174.9, 170.4, 143.5, 143.0, 138.9, 137.4, 136.8, 136.4, 135.4, 135.0, 130.3, 129.1, 128.9, 128.8, 128.7, 127.9, 127.2, 126.6, 125.5, 125.4, 123.1, 109.5, 82.1, 53.1, 44.0, 31.0, 29.6, 21.1, 17.8, 17.6. HRMS (ESI): calcd for $C_{37}H_{35}N_2O_4$ $[M + H]^+$, 571.2597; found, 571.2591.

General Procedure for the Formation of Product 8. Trifluoromethylsulfonyl acid (0.3 equiv) was added to a solution of compound **4** (0.3 mmol) in a 3 mL solution of toluene. The stirred mixture was heated to 80 °C, and the progress was carefully monitored using TLC detection. After completion of the present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel [silica, 200−300; eluant, petroleum ether/ethyl acetate = 8:1] to afford the desired product **8**.

*3-Benzyl-4-((1-benzyl-2-oxoindolin-3-yl)methyl)-1-mesityl-1H-pyrrole-2,5-dione (**8a**).* 102 mg, 63% yield; yellow solid: mp 162−164 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.41 (d, J = 7.0 Hz, 1H), 7.34−7.22 (m, 9H), 7.15 (d, J = 7.0 Hz, 2H), 7.07 (t, J = 7.5 Hz, 1H), 6.96 (s, 1H), 6.94 (s, 1H), 6.74 (d, J = 8.0 Hz, 1H), 4.94 (d, J = 15.5 Hz, 1H), 4.77 (d, J = 15.5 Hz, 1H), 4.47 (s, 1H), 3.77 (s, 2H), 3.17 (d, J = 14.0 Hz, 1H), 3.14 (d, J = 14.0 Hz, 1H), 2.31 (s, 3H), 2.09 (s, 3H), 1.92 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 174.9, 170.4, 170.2, 143.5, 143.0, 138.9, 137.4, 136.8, 136.4, 135.4, 135.0, 130.3, 129.1, 128.9, 128.8, 128.7, 127.9, 127.2, 126.6, 125.5, 125.4, 123.1, 109.5, 82.1, 53.1, 44.0, 31.0, 29.6, 21.1, 17.8, 17.6. HRMS (ESI): calcd for $C_{36}H_{33}N_2O_3$ $[M + H]^+$, 541.2491; found, 541.2498.

General Procedure for the Formation of Product 9. Isocyanide **1** (1.0 mmol) was added to a solution of allenoate **2** (1.0 mmol) and isatin **3** (1.0 mmol) in 5 mL of toluene. The stirred mixture was heated under reflux for several hours, and the progress was monitored using TLC detection. After completion of the present reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel [silica, 200−300; eluant, petroleum ether/ethyl acetate = 8:1] to afford the desired product **9**.

*(2S,6aR)-1′,4-Dibenzyl-6-(tert-butyl)-6a-propoxy-6,6a-dihydrospiro[furo[2,3-b]pyrrole-2,3′-indoline]-2′,5(3H)-dione (**9a**).* 364 mg, 68% yield; white solid: mp 147−148 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.33−7.23 (m, 10H), 7.14 (t, J = 7.5 Hz, 1H), 6.82 (t, J = 7.5 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 6.59 (d, J = 7.5 Hz, 1H), 4.88 (d, J = 16.0 Hz, 1H), 4.81 (d, J = 16.0 Hz, 1H), 3.72 (d, J = 16.0 Hz, 1H), 3.67 (d, J = 16.0 Hz, 1H), 3.45−3.39 (m, 2H), 3.14 (d, J = 14.0 Hz, 1H), 2.32 (d, J = 14.0 Hz, 1H), 1.72−1.66 (m, 2H), 1.50 (s, 9H), 1.02 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 173.8, 170.7, 148.4, 141.7, 137.6, 135.3, 132.3, 130.0, 129.9, 129.5, 129.0, 128.8, 128.8, 128.5, 127.8, 127.4, 127.3, 126.7, 123.3, 122.9, 117.5, 109.4, 86.6. HRMS (ESI): calcd for $C_{34}H_{36}N_2NaO_4$ $[M + Na]^+$, 559.2573; found, 559.2574.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01711.

Copies of ^{1}H NMR and ^{13}C NMR spectra of all compounds (PDF)

X-ray crystallographic data for compound **4d** (CIF)

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Notes

The authors declare no competing financial interest.

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