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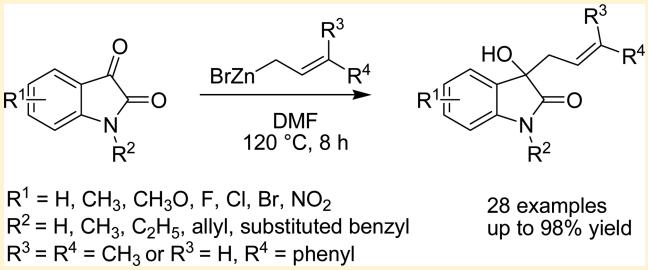
Zinc-Mediated C-3 α-Prenylation of Isatins with Prenyl Bromide: Access to 3-Prenyl-3-hydroxy-2-oxindoles and Its Application

Li-Ming Zhao,* Ai-Li Zhang, Jie-Huan Zhang, Hua-Shuai Gao, and Wei Zhou

School of Chemistry and Chemical Engineering and Jiangsu Key Laboratory of Green Synthetic Chemistry for Functional Materials, Jiangsu Normal University, Xuzhou 221116, Jiangsu, China

Supporting Information

ABSTRACT: A convenient and highly α-regioselective strategy for the synthesis of 3-prenyl-3-hydroxy-2-oxindoles has been developed starting from isatins and prenylzinc with good to excellent yields. This protocol provides a straightforward and practical way to introduce an α-prenyl moiety into the C-3 position of isatins. The advantages of this reaction are use of the cheap and readily available reagents, operational simplicity, and wide substrate scope. Furthermore, this transformation was applied to the synthesis of several oxindole-containing natural products, which further demonstrated the synthetic utility of this methodology.



INTRODUCTION

3-Substituted 3-hydroxy-2-oxindoles have attracted increasing interest because of their potential biological activities and their role as key precursors in the synthesis of bioactive molecules and natural products.[1] Among those oxindole derivatives, 3-allyl-3-hydroxy-2-oxindoles are some of the most versatile building blocks for accessing various alkaloids and molecules that are biologically important.[2] Accordingly, over the decades, many methods for the synthesis of this class of compounds via the reactions of isatins with allyl metal reagents such as indiums,[3a,b] stannanes,[3c,g] and silanes[3d−f] as nucleophilic allyl sources have been reported. However, in contrast to the well-established allylation of isatins, the analogous prenylation of isatins for the generation of 3-prenyl-3-hydroxy-2-oxindoles has rarely been explored because of the challenging issue of regioselectivity. Generally, α-regioselective prenylation of isatins is difficult to achieve when using α-substituted allyl metal reagents such as prenylmetal.[3a,b,d] Consequently, these oxindole derivatives are often assembled in a stepwise fashion by the initial preparation of a 3-substituted 2-oxindole intermediate, which is then further elaborated to the target (Scheme 1a).[4a] In 2014, Viswanathan and co-workers reported a potentially rate-accelerated "anionic-oxy-Cope" rearrangement for prenylating the C-4 position of oxindoles. Coincidentally, they observed an internal prenyl migratory event leading to C-3 normal prenylated derivatives (Scheme 1b).[4b] Considering the importance of the prenyl moiety, which represents an important natural product substructure[5] and plays a significant role in the metabolism of living organisms,[6] it is conceivable that the development of a simple and general method for the synthesis of 3-prenyl-3-hydroxy-2-oxindoles via a one-step procedure featuring facile operation and readily available starting materials will be highly desirable.

In the recent past, our research group was interested in the development of methodologies toward simple and efficient regioselective prenylation using prenylzinc as the allyl metal reagent for the synthesis of various α-prenylated compounds[7] and their applications.[8] As a logical extension of our previous work and to explore the use of prenylzinc in the preparation of structurally interesting compounds that may otherwise be inaccessible, we report herein a powerful zinc-mediated prenylation reaction that allows direct access to 3-prenyl-3-hydroxy-2-oxindoles from simple and commercially available stating materials (Scheme 1c). This method has several significant advantages. First, it provides a straightforward route to these structurally interesting molecules in a single step, which represents high synthetic efficiency. Second, the reaction shows a broader substrate scope, tolerating different types of substituted isatins. Third, isatins, prenyl bromide, and zinc as well as *N*,*N*-dimethylformamide (DMF) are all cheap and readily available chemicals, which allows great efficiency and convenience for the construction of the corresponding compound library. Fourth, a Bn-protecting group at the N-1 position is necessary for oxindoles in Scheme 1a. For the synthetic method reported in this paper, a Bn-protecting group (or any group) is unnecessary. This is a practical advantage as it is well-known that removal of such a protecting group (especially late in a multistep synthetic effort) may prove to be a challenge in reality and that many oxindole-containing natural products do not carry a protecting group at N-1.[9]

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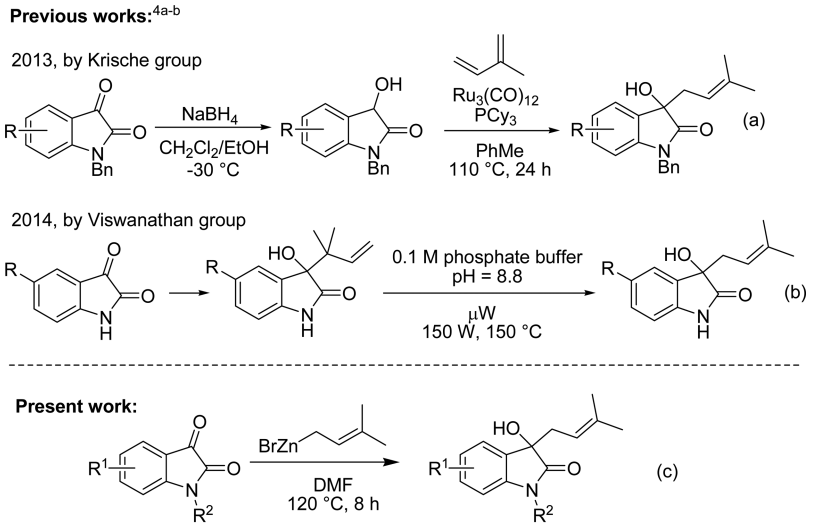
Scheme 1. Methods for the Preparation of 3-Prenyl-3-hydroxy-2-oxindoles

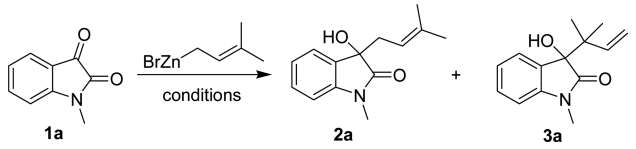


one-step preparation of 3-prenyl-3-hydroxy-2-oxindoles using cheap and readily available reagents with a broader substrate scope

RESULTS AND DISCUSSION

Exposure of 1-methyl isatin **1a** as a model substrate to the previously reported reaction conditions[7a] that involve heating the reaction mixture to 120 °C in hexamethylphosphoramide (HMPA) resulted in the formation of desired product **2a** in excellent yield (Table 1, entry 1). Under the previous conditions, a high yield of **2a** was attained, but the carcinogenic solvent HMPA was employed. The use of hazardous and toxic solvents in chemical laboratories is considered a very important problem for the health and safety of chemists. Furthermore, the solvent is the major source of waste in a chemical reaction; therefore, the replacement of toxic solvents with greener alternatives is a crucial point in designing environmentally improved methods toward functionalized molecules. Thus, other polar aprotic solvents, including 1,3-dimethyl-2-imidazolidinone (DMI) (entry 2), tetramethylurea (TMU) (entry 3), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)pyrimidinone (DMPU) (entry 4), and DMF (entry 5), were evaluated, and DMI and DMF were proven to be optimal, affording **2a** in 93 and 92% yields, respectively. Compared with DMI, which is relatively expensive and can be difficult to process because of its high boiling point (222 °C), DMF is obviously economically and operationally attractive. Consequently, DMF was chosen as the optimal solvent for the reaction. We also noticed that a temperature of 120 °C was necessary to achieve the highly α-regioselective result. When the reaction temperature was decreased from 120 to 110 °C, the yield of desired product **2a** was reduced to 69% and was accompanied by 15% γ-adduct **3a** (entry 6). When the temperature was decreased to 80 °C, the γ-isomer was almost exclusively formed (entry 7). An attempt to conduct the reaction for a shorter reaction time gave a decreased yield of **2a** as well as a trace amount of **3a** (entry 8). Therefore, we decided to perform the subsequent reactions of isatins and prenylzinc at 120 °C in DMF for 8 h.

Table 1. Optimization of the Reaction Conditions[a]



entry	solvent	T (°C)	t (h)	**2a** (%)[b]	**3a** (%)[b]
1	HMPA	120	8	95	0
2	DMI	120	8	93	0
3	TMU	120	8	52	0
4	DMPU	120	8	67	0
5	DMF	120	8	92	0
6	DMF	110	8	69	15
7	THF/DMF	80	8	trace	80
8	DMF	120	6	84	trace

[a]Reactions were performed with **1a** (0.5 mmol), prenyl bromide (1.0 mmol), and zinc (1.5 mmol). [b]Isolated yield.

With the optimal conditions in hand, the reaction scope was examined by using various isatins (Table 2). Initial investigation of the scope of the reaction was focused on varying the substituents on the phenyl ring of isatins. Pleasingly, the reaction tolerated well all the *N*-methylisatin derivatives with an electron-donating or electron-withdrawing group, giving the corresponding α-prenylated products in good to excellent yields (entries 1−5). For instance, *N*-methylisatin substrates with a methyl (**1b**) and a methoxy group (**1c**) at the C-5 position led to corresponding products **2b** and **2c** in 85 and 90% yields, respectively (entries 1 and 2, respectively). Similarly, 5-bromo-*N*-methylisatin worked equally well (entry 3). More importantly, the conditions showed noteworthy tolerance to the nitro group, albeit with a decreased yield (entry 4). In addition, we assessed the influence of a bromo group at the C-4 position of *N*-methylisatin. Despite the possible steric interaction, the reaction of **1f** proceeded smoothly to afford **2f** in 75% yield (entry 5). Further exploration of different *N*-protective groups reveals that various groups such as ethyl, allyl, and benzyl were appropriate for the reaction. For example, when the *N*-methyl protective group at the isatin framework (**1a**) was changed into *N*-ethyl (**1g**), *N*-allyl (**1i**), and *N*-benzyl (**1m**) groups, the corresponding isatins were smoothly converted into 3-prenyl-3-hydroxy-2-oxindoles **2g**, **2i**, and **2m** in 81, 90, and 85% yields, respectively (entries 6, 8, and 12, respectively). Moreover, almost all isatins with *N*-ethyl groups (**1g** and **1h**), *N*-allyl groups (**1i**−**l**), and *N*-benzyl groups (**1m**−**o**) gave the desired

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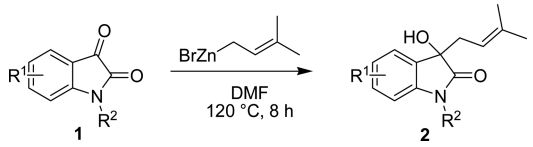
Table 2. Formation of 3-Prenyl-3-hydroxy-2-oxindoles from Various Isatins 1 under the Zinc-Mediated Prenylation Conditions



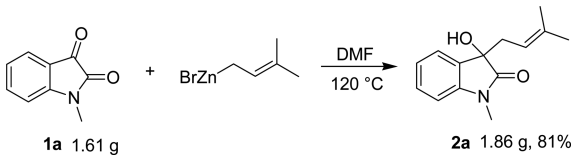
entry	1	R^1, R^2	2	yield (%)[a]	α/γ[b]
1	**1b**	5-CH_3, CH_3	**2b**	85	>95:5
2	**1c**	5-OCH_3, CH_3	**2c**	90	>95:5
3	**1d**	5-Br, CH_3	**2d**	84	>95:5
4	**1e**	5-NO_2, CH_3	**2e**	60	>95:5
5	**1f**	4-Br, CH_3	**2f**	75	>95:5
6	**1g**	H, C_2H_5	**2g**	81	>95:5
7	**1h**	5-CH_3, C_2H_5	**2h**	92	>95:5
8	**1i**	H, allyl	**2i**	90	>95:5
9	**1j**	5-CH_3, allyl	**2j**	91	>95:5
10	**1k**	5-OCH_3, allyl	**2k**	85	>95:5
11	**1l**	5-Br, allyl	**2l**	98	>95:5
12	**1m**	H, 4-$FC_6H_4CH_2$	**2m**	85	>95:5
13	**1n**	H, 4-$BrC_6H_4CH_2$	**2n**	89	>95:5
14	**1o**	H, 4-$NO_2C_6H_4CH_2$	**2o**	53	>95:5
15	**1p**	H, H	**2p**	83	>95:5
16	**1q**	5-CH_3, H	**2q**	80	>95:5
17	**1r**	5-OCH_3, H	**2r**	71	>95:5
18	**1s**	5-F, H	**2s**	62	>95:5
19	**1t**	5-Br, H	**2t**	73	>95:5
20	**1u**	5-NO_2, H	**2u**	55	>95:5
21	**1v**	4-Cl, H	**2v**	72	>95:5
22	**1w**	4-Br, H	**2w**	82	>95:5

[a]Isolated yield. [b]Determined by NMR.

products in excellent yields (entries 6−14, respectively), with the exception of adducts **2o** containing a nitro group (entry 14) for which the isolated yields were somewhat lower but still acceptable. It is noteworthy that the *N*-unprotected isatins **1p−w** were also suitable reaction partners for this regioselective prenylation and afforded corresponding α-products **2p−w** in good yields (entries 15−22, respectively). This is particularly advantageous because the introduction and removal of protective groups impose extra labor on the synthesis of target compounds. These results show that the reaction is quite general and the variation of the protective group on the N atom or substituents on the phenyl ring of isatins have no significant influence on the reaction efficiency. This methodology thus provides a practical and efficient means of realizing the rapid introduction of an α-prenyl moiety at the C-3 position of isatins. All the products were identified via NMR and HRMS. The structure of **2p** was further confirmed by X-ray crystallography (CCDC 1483838, see the Supporting Information).

To demonstrate the practicality of this protocol, a gram-scale synthesis of **2a** was performed under the standard conditions. As shown in Scheme 2, when 1.61 g of **1a** was utilized, 1.86 g of product **2a** was obtained in 81% yield without a significant loss of efficiency [small scale, 92% (entry 5 in Table 1)]. Thus, this simple, one-step protocol could be extended as a practical and efficient method for preparing various potentially bioactive 3-prenyl-3-hydroxy-2-oxindoles. The straightforward one-step process constitutes an important practical feature of this method.

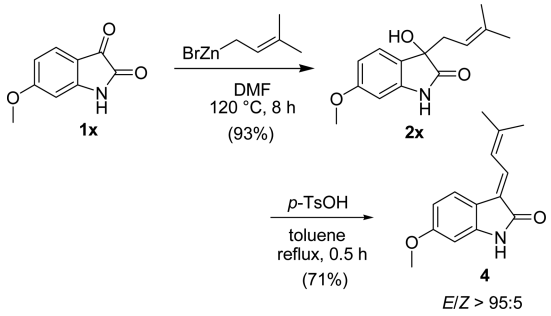
Scheme 2. Gram-Scale α-Prenylation of Isatin 1a



The synthesis of natural products constitutes one of the most demanding tests of the viability of a new synthetic methodology. Therefore, a synthesis of soulieotine **4** was undertaken to further test the viability of our zinc-mediated prenylation procedure as an entry into some natural products.

Soulieotine **4** is an alkaloid isolated from the rhizomes of *Souliea vaginata*, a plant widely distributed in China and used as an anti-inflammatory analgesic.[9d] Taylor and co-workers described the first synthesis of **4** by starting from 2-bromo-5-methoxybenzenamine via a four-step procedure in an overall yield of 22%.[10] More recently, Curti and co-workers have synthesized soulieotine through a condensation of 6-methoxyoxindole with 3-methyl-2-butenal in 50% yield.[11] In contrast, using our novel method, soulieotine **4** can be obtained via **2x**, prepared from commercially available 6-methoxyisatin **1x**, in two steps with an overall yield of 66% (Scheme 3). More importantly, our procedure is highly stereoselective for the production of almost exclusively *E* geometry (soulieotine). This is particularly advantageous because preparing certain natural products with specific geometry is not always an easy task. For example, Taylor's procedure resulted in the formation of a mixture of soulieotine (*E* geometry) and its *Z* isomer in a 2:1 ratio, although they could be separated by chromatography.[10] Curti's procedure yielded a 3:1 (*E*:*Z*) mixture of soulienotine.[11] This result thus highlights the usefulness of our procedure for synthesis of oxindole-containing natural products.

Scheme 3. Synthesis of Soulieotine via the Zinc-Mediated Prenylation of 6-Methoxyisatin



Encouraged by the efficiency and high stereoselectivity observed in the synthesis of soulieotine, we sought to examine the effects of this chemistry with respect to other oxindole-containing natural products. (*E*)-3-(3-Methyl-2-butenylidene)-2-indolinone **5** was isolated from the rhizomes of *Cimicifuga fetida*, a traditional Chinese medicine named "Shengma".[12] It has in the past been synthesized through Wittig reaction of isatin with γ,γ-dimethylallylphosphonium bromide via a short route.[13] Unfortunately, the practical use of this route is limited by low yield (12%) and low stereoselectivity (2:1 *E*:*Z*) in the Wittig reaction. In our laboratory, zinc-mediated prenylation of isatin **1p** followed by dehydration of **2p** provided a 54% overall yield of (*E*)-3-(3-methyl-2-butenylidene)-2-indolinone **5** (Scheme 4). No stereoisomer was found in the reaction product, thus demonstrating the stereospecific character of the process.

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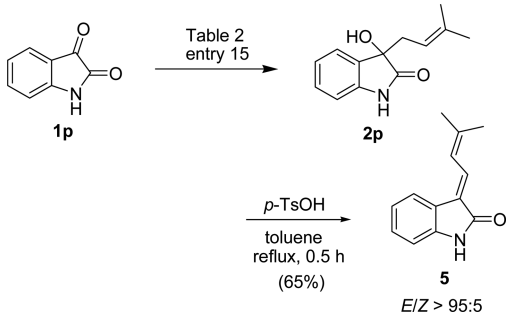
Scheme 4. Synthesis of (*E*)-3-(3-Methyl-2-butenylidene)-2-indolinone

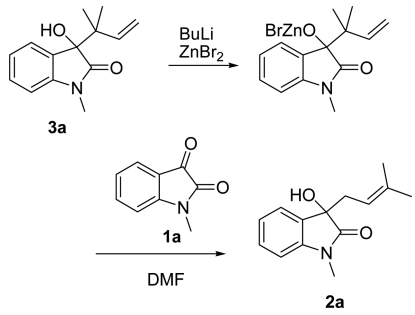


On the basis of the experimental results and previous reports,[4b,7a] two plausible pathways for this one-step method to generate 3-prenyl-3-hydroxy-2-oxindoles were proposed as shown in Scheme 5. Both pathway I and patheway II are initiated by the nucleophilic attack of the γ-carbon of prenylzinc at the 3-carbonyl of isatin to yield zinc alcoholate **A** via a six-membered cyclic transition state (TS) analogous to that reported previously.[14] Then, in path I, DMF acts as a Lewis base interacting with the zinc atom of initially formed zinc alcoholate **A**,[15] and the resulting intermediate further coordinates the isatin, which results in the formation of **B**. Subsequently, a metallo[3,5]-sigmatropic shift at an elevated temperature via a eight-membered TS occurs to generate **C**. Finally, elimination of the parent isatin from **C** could produce intermediate **D**, which could convert to target product **2** after workup. Alternatively, at high temperatures, the thermolysis of zinc alcoholate **A** could also occur leading to the homolytic cleavage of the C-3 reverse prenyl σ bond to afford the prenyl radical intermediate and a carbon radical as shown in intermediate **E**. Subsequent recombination of these two radicals and final workup would furnish α-adduct **2** (pathway II).

To gain mechanistic insight, **1p** was treated with hydroquinone or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) under the standard conditions. It was observed that the addition of the radical-trapping reagents did not inhibit the reaction and **2p** was obtained in a 85 or 81% yield, respectively. These results indicate that the radical process might not be involved in the regioselective prenylation (pathway II) (see the Supporting Information).

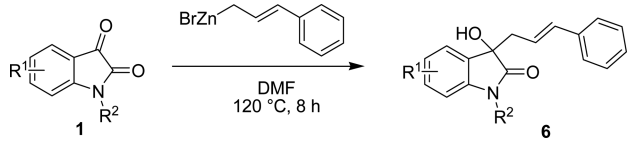
For verification of pathway I, an experiment involving the reaction of zinc alcoholate **A** with *N*-methylisatin **1a** was performed. 3-γ-Prenyl-3-hydroxy-2-oxindoles **3a** was first transformed to its zinc alkoxide in the presence of BuLi and zinc bromide. Then, the zinc alkoxide was treated with *N*-methylisatin **1a** in DMF in 120 °C, and after 7 h, α-product **2a** was obtained in 85% yield (Scheme 6). On the basis of the observations mentioned above, we consider that it is possible that the reaction proceeded via the former mechanism.

Scheme 6. Reaction of Zinc Alcoholate and *N*-Methylisatin



Because of the success described above, other 3-substituted allylmetal reagents, such as cinnamylzinc bromide, were also investigated in the reaction with isatins. As clearly shown in Table 3, it was also found that cinnamyl bromide worked well for various isatins bearing different substituents on the phenyl ring of isatins, including electron-donating (methyl, entries 1 and 3) and electron-withdrawing (bromo, entries 2 and 4) groups as well as different *N*-protective groups such as methyl

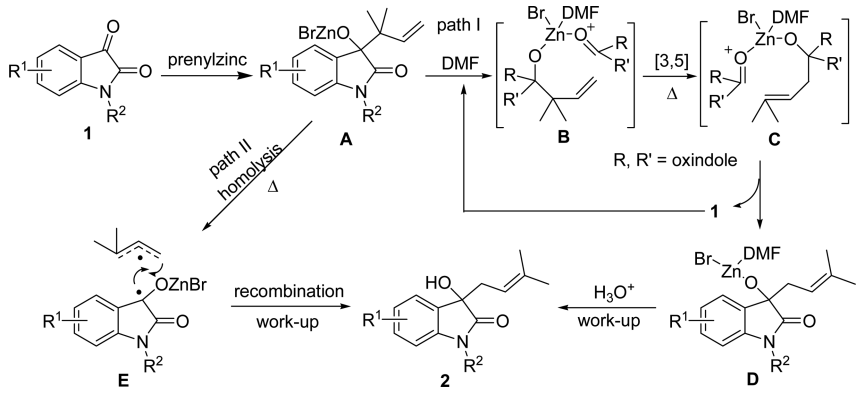
Table 3. α-Selective Allylation of Isatins 1 Using Cinnamyl Bromide as the Allylation Reagent



entry	1	R^1, R^2	6	yield (%)[a]	α/γ[b]
1	**1b**	5-CH_3, CH_3	**6b**	80	>95:5
2	**1d**	5-Br, CH_3	**6d**	72	>95:5
3	**1h**	5-CH_3, C_2H_5	**6h**	77	>95:5
4	**1l**	5-Br, allyl	**6l**	75	>95:5
5	**1n**	H, 4-$BrC_6H_4CH_2$	**6n**	84	>95:5

[a]Isolated yield. [b]Determined by NMR.

Scheme 5. Two Potential Mechanistic Pathways



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(entries 1 and 2), ethyl (entry 3), allyl (entry 4), and benzyl (entry 5) groups under the standard reaction conditions to afford the corresponding α-products in good yields.

CONCLUSIONS

In conclusion, we show that 3-prenyl-3-hydroxy-2-oxindoles can be directly prepared from isatins and prenyl bromide by means of a convenient and efficient procedure based on a zinc-mediated highly α-regioselective prenylation. A wide range of isatins were tolerated in this method, and all the α-prenylated products could be obtained in good to excellent yields. Because of the easy accessibility and low cost of the reactants and reagents and the simple manipulations of the reaction, this method is very practical and is economically and environmentally advantageous. Furthermore, the utility of this reaction has been demonstrated via the syntheses of some natural products, and this procedure provides an efficient and stereoselective route to those natural products. Thus, the reaction, obviously, offers significant advantages over the previous protocols for the synthesis of 3-prenyl-3-hydroxy-2-oxindoles and some related natural products. Moreover, the importance of these compounds would render this protocol attractive for both synthetic and medicinal chemistry.

EXPERIMENTAL SECTION

General Methods. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz in $CDCl_3$ or DMSO-d_6 with chemical shifts (δ) given in parts per million relative to TMS as an internal standard. Multiplicities are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublets; etc. Coupling constants (J) are given in hertz. High-resolution mass spectra (HRMS) were recorded using atmospheric-pressure chemical ionization (APCI) or electrospray ionization (ESI) and time-of-flight (TOF) mass analysis.

General Procedure for the Synthesis of 2 and 6. Allyl bromide (1.0 mmol) was added to a suspension of activated zinc powder (1.5 mmol) in dry THF (10 mL); the reaction mixture was stirred for 1 h at room temperature (reflux for 1 h with cinnamyl bromide). The solution was filtered through a Schlenk filter and kept under N_2 for the following reaction. A solution of isatins **1** (0.5 mmol) in dry THF (3 mL) was added to the solution of allylzinc bromide prepared as described above. Then DMF (1.5 mL) was added to the reaction mixture, followed by removal of initial reaction solvent (THF). The mixture was heated to 120 °C under N_2 for 8 h. Analysis of the final reaction mixtures by ^{1}H NMR showed that no γ-products were observed. After the mixture had cooled to room temperature, the residue was purified by flash column chromatography (3/1 petroleum ether/ethyl acetate) to afford α-products **2** and **6**.

3-Hydroxy-1-methyl-3-(3-methylbut-2-enyl)indolin-2-one (2a). White solid (106 mg, 92% yield): mp 101−103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.28 (m, 2H), 7.13−7.04 (m, 1H), 6.82 (d, J = 7.8 Hz, 1H), 5.03 (t, J = 7.6 Hz, 1H), 3.18 (s, 3H), 3.00 (s, 1H), 2.63 (d, J = 7.7 Hz, 2H), 1.65 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 143.4, 137.4, 130.2, 129.6, 124.1, 123.1, 115.9, 108.4, 76.3, 37.5, 26.3, 26.1, 18.1; HRMS (APCI) calcd for $C_{14}H_{18}NO_2$ $[M + H]^+$ m/z 232.1338, found m/z 232.1341.

3-Hydroxy-1,5-dimethyl-3-(3-methylbut-2-enyl)indolin-2-one (2b). White solid (105 mg, 85% yield): mp 142−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 1H), 7.11−7.09 (m, 1H), 6.70 (d, J = 7.9 Hz, 1H), 5.08−4.93 (m, 1H), 3.17 (s, 1H), 3.15 (s, 3H), 2.68−2.55 (m, 2H), 2.34 (s, 3H), 1.65 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 141.0, 137.2, 132.6, 130.3, 129.7, 124.9, 116.0, 108.1, 76.4, 37.5, 26.3, 26.1, 21.2, 18.1; HRMS (APCI) calcd for $C_{15}H_{20}NO_2$ $[M + H]^+$ m/z 246.1494, found m/z 246.1524.

3-Hydroxy-5-methoxy-1-methyl-3-(3-methylbut-2-enyl)-indolin-2-one (2c). Pale yellow solid (117 mg, 90% yield): mp 148−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 2.6 Hz, 1H), 6.84 (dd, J = 8.5, 2.6 Hz, 1H), 6.72 (d, J = 8.5 Hz, 1H), 5.04−5.01 (m, 1H), 3.80 (s, 3H), 3.15−3.13 (m, 4H), 2.62 (d, J = 7.6 Hz, 2H), 1.66 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 156.4, 137.3, 136.8, 131.5, 116.0, 114.2, 111.3, 108.8, 76.7, 56.0, 37.5, 26.4, 26.1, 18.2; HRMS (APCI) calcd for $C_{15}H_{20}NO_3$ $[M + H]^+$ m/z 262.1443, found m/z 262.1441.

5-Bromo-3-hydroxy-1-methyl-3-(3-methylbut-2-enyl)-indolin-2-one (2d). White solid (130 mg, 84% yield): mp 155−157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.39 (m, 2H), 6.70 (d, J = 8.2 Hz, 1H), 5.05−5.00 (m, 1H), 3.16 (s, 3H), 2.82 (s, 1H), 2.60 (d, J = 7.7 Hz, 2H), 1.68 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 142.5, 138.2, 132.5, 132.2, 127.5, 115.8, 115.3, 109.9, 76.2, 37.5, 26.4, 26.1, 18.2; HRMS (APCI) calcd for $C_{14}H_{17}BrNO_2$ $[M + H]^+$ m/z 310.0443, found m/z 310.0460.

3-Hydroxy-1-methyl-3-(3-methylbut-2-enyl)-5-nitroindolin-2-one (2e). Yellow solid (83 mg, 60% yield): mp 154−156 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (dd, J = 8.7, 2.4 Hz, 1H), 8.09 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 8.7 Hz, 1H), 4.77−4.76 (m, 1H), 3.13 (s, 3H), 2.69−2.47 (m, 2H), 1.49 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.2, 149.7, 143.0, 136.0, 132.7, 126.7, 119.5, 116.6, 109.1, 75.4, 36.6, 26.7, 26.0, 18.2; negative ion HRMS (ESI) calcd for $C_{14}H_{15}N_2O_4$ $[M - H]^-$ m/z 275.1032, found m/z 275.1018.

4-Bromo-3-hydroxy-1-methyl-3-(3-methylbut-2-enyl)-indolin-2-one (2f). Pale yellow solid (116 mg, 75% yield): mp 136−138 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.22−7.07 (m, 2H), 6.91 (dd, J = 7.6, 0.9 Hz, 1H), 4.40−4.36 (m, 1H), 3.00 (s, 3H), 2.95 (dd, J = 13.6, 7.5 Hz, 1H), 2.52 (dd, J = 13.6, 7.5 Hz, 1H), 1.40 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 177.1, 146.0, 135.6, 131.3, 128.9, 126.6, 118.9, 116.5, 108.1, 77.6, 34.2, 26.3, 26.0, 18.3; negative ion HRMS (ESI) calcd for $C_{14}H_{15}BrNO_2$ $[M - H]^-$ m/z 308.0286, found m/z 308.0309.

1-Ethyl-3-hydroxy-3-(3-methylbut-2-enyl)indolin-2-one (2g). White solid (99 mg, 81% yield): mp 110−113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, J = 7.3, 0.8 Hz, 1H), 7.36−7.23 (m, 1H), 7.09−7.05 (m, 1H), 6.82 (d, J = 7.8 Hz, 1H), 4.93−4.89 (m, 1H), 3.87−3.78 (m, 1H), 3.65−3.56 (m, 1H), 3.19 (s, 1H), 2.79−2.53 (m, 2H), 1.60 (s, 3H), 1.52 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 142.5, 137.0, 130.5, 129.5, 124.2, 122.86, 116.0, 108.4, 76.4, 37.7, 34.7, 26.0, 18.1, 12.7; HRMS (APCI) calcd for $C_{15}H_{20}NO_2$ $[M + H]^+$ m/z 246.1494, found m/z 246.1505.

1-Ethyl-3-hydroxy-5-methyl-3-(3-methylbut-2-enyl)indolin-2-one (2h). Pale yellow solid (119 mg, 92% yield): mp 150−153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 1.1 Hz, 1H), 7.10−7.08 (m, 1H), 6.71 (d, J = 7.9 Hz, 1H), 4.91−4.89 (m, 1H), 3.84−3.75 (m, 1H), 3.62−3.53 (m, 1H), 3.29−3.26 (m, 1H), 2.72−2.58 (m, 2H), 2.34 (s, 3H), 1.60 (s, 3H), 1.53 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 140.1, 136.9, 132.4, 130.5, 129.7, 125.0, 116.1, 108.2, 76.5, 37.7, 34.7, 26.0, 21.2, 18.1, 12.70; HRMS (APCI) calcd for $C_{16}H_{22}NO_2$ $[M + H]^+$ m/z 260.1651, found m/z 260.1658.

1-Allyl-3-hydroxy-3-(3-methylbut-2-enyl)indolin-2-one (2i). White solid (116 mg, 90% yield): mp 117−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8.1 Hz, 1H), 7.30−7.26 (m, 1H), 7.10−7.06 (m, 1H), 6.79 (d, J = 7.8 Hz, 1H), 5.89−5.67 (m, 1H), 5.24−5.12 (m, 2H), 4.94−4.90 (m, 1H), 4.50−4.45 (m, 1H), 4.14−4.08 (m, 1H), 3.20 (s, 1H), 2.75−2.64 (m, 2H), 1.60 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 142.7, 137.3, 131.2, 130.2, 129.5, 124.1, 123.0, 117.3, 116.0, 109.3, 76.5, 42.3, 37.7, 26.0, 18.1; HRMS (APCI) calcd for $C_{16}H_{20}NO_2$ $[M + H]^+$ m/z 258.1494, found m/z 258.1513.

1-Allyl-3-hydroxy-5-methyl-3-(3-methylbut-2-enyl)indolin-2-one (2j). Pale yellow solid (123 mg, 91% yield): mp 112−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 1.1 Hz, 1H), 7.08−7.05 (m, 1H), 6.67 (d, J = 7.9 Hz, 1H), 5.83−5.73 (m, 1H), 5.23−5.11 (m, 2H), 4.91−4.87 (m, 1H), 4.52−4.36 (m, 1H), 4.13−4.02 (m, 1H), 3.38 (s, 1H), 2.76−2.61 (m, 2H), 2.33 (s, 3H), 1.60 (s, 3H), 1.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 140.3, 137.1, 132.6, 131.3, 130.18, 129.7, 124.9, 117.2, 116.1, 109.0, 76.6, 42.3, 37.7, 26.0,

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21.2, 18.1; HRMS (APCI) calcd for $C_{17}H_{22}NO_2$ $[M + H]^+$ m/z 272.1651, found m/z 272.1677.

1-Allyl-3-hydroxy-5-methoxy-3-(3-methylbut-2-enyl)-indolin-2-one (2k). Pale yellow solid (122 mg, 85% yield): mp 109−111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, J = 2.6 Hz, 1H), 6.80 (dd, J = 8.5, 2.6 Hz, 1H), 6.70 (d, J = 8.5 Hz, 1H), 5.83−5.74 (m, 1H), 5.26−5.10 (m, 2H), 4.94−4.90 (m, 1H), 4.48−4.42 (m, 1H), 4.15−4.01 (m, 1H), 3.80 (s, 3H), 3.15 (s, 1H), 2.79−2.57 (m, 2H), 1.62 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 156.3, 137.3, 136.0, 131.4, 131.4, 117.3, 116.0, 114.3, 111.1, 109.8, 76.8, 56.0, 42.4, 37.8, 26.1, 18.14; HRMS (APCI) calcd for $C_{17}H_{22}NO_3$ $[M + H]^+$ m/z 288.1600, found m/z 288.1619.

1-Allyl-5-bromo-3-hydroxy-3-(3-methylbut-2-enyl)indolin-2-one (2l). Pale yellow solid (164 mg, 98% yield): mp 93−94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 2.0 Hz, 1H), 7.40 (dd, J = 8.3, 2.0 Hz, 1H), 6.67 (d, J = 8.3 Hz, 1H), 5.82−5.72 (m, 1H), 5.22−5.14 (m, 2H), 4.92−4.89 (m, 1H), 4.49−4.43 (m, 1H), 4.12−4.06 (m, 1H), 3.19 (s, 1H), 2.74−2.61 (m, 2H), 1.62 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 141.7, 138.0, 132.4, 132.2, 130.8, 127.5, 117.6, 115.8, 115.4, 110.8, 76.4, 42.4, 37.7, 26.1, 18.1; HRMS (APCI) calcd for $C_{16}H_{19}BrNO_2$ $[M + H]^+$ m/z 336.0599, found m/z 336.0583.

1-(4-Fluorobenzyl)-3-hydroxy-3-(3-methylbut-2-enyl)-indolin-2-one (2m). Pale yellow solid (138 mg, 85% yield): mp 146−148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.39 (m, 1H), 7.26−7.17 (m, 3H), 7.09−7.05 (m, 1H), 7.0−6.96 (m, 2H), 6.65 (d, J = 7.8 Hz, 1H), 5.07 (d, J = 15.7 Hz, 1H), 4.89−4.85 (m, 1H), 4.59 (d, J = 15.7 Hz, 1H), 3.31 (s, 1H), 2.83−2.68 (m, 2H), 1.60 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 162.3 (J = 244.6 Hz), 142.5, 137.4, 131.5, 131.4, 130.1, 129.6, 129.0, 128.9, 124.2, 123.3, 116.0 (J = 3.0 Hz), 115.7, 109.3, 76.5, 43.2, 37.7, 26.1, 18.2; HRMS (APCI) calcd for $C_{20}H_{21}FNO_2$ $[M + H]^+$ m/z 326.1556, found m/z 326.1562.

1-(4-Bromobenzyl)-3-hydroxy-3-(3-methylbut-2-enyl)-indolin-2-one (2n). Pale yellow solid (171 mg, 89% yield): mp 186−188 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.40 (m, 3H), 7.22−7.18 (m, 1H), 7.13 (d, J = 8.4 Hz, 2H), 7.09−7.06 (m, 1H), 6.62 (d, J = 7.8 Hz, 1H), 5.06 (d, J = 15.9 Hz, 1H), 4.90−4.86 (m, 1H), 4.57 (d, J = 15.9 Hz, 1H), 2.99 (s, 1H), 2.82−2.68 (m, 2H), 1.62 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 142.4, 137.6, 134.8, 132.1, 132.1, 130.0, 129.7, 129.0, 129.0, 124.2, 123.3, 121.7, 115.9, 109.3, 76.5, 43.3, 37.7, 26.1, 18.2; HRMS (APCI) calcd for $C_{20}H_{21}BrNO_2$ $[M + H]^+$ m/z 386.0756, found m/z 386.0742.

3-Hydroxy-3-(3-methylbut-2-enyl)-1-(4-nitrobenzyl)indolin-2-one (2o). Pale yellow solid (93 mg, 53% yield): mp 136−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19−8.15 (m, 2H), 7.62−7.34 (m, 3H), 7.26−7.20 (m, 1H), 7.13−7.08 (m, 1H), 6.58 (d, J = 7.8 Hz, 1H), 5.20 (d, J = 16.5 Hz, 1H), 4.91−4.87 (m, 1H), 4.73 (d, J = 16.5 Hz, 1H), 3.17 (s, 1H), 2.87−2.69 (m, 2H), 1.64 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 147.6, 143.2, 142.1, 137.8, 130.0, 129.8, 127.9, 127.9, 124.5, 124.2, 124.2, 123.7, 115.8, 109.0, 76.5, 43.3, 37.7, 26.2, 18.2; HRMS (APCI) calcd for $C_{20}H_{21}N_2O_4$ $[M + H]^+$ m/z 353.1501, found m/z 353.1477.

3-Hydroxy-3-(3-methylbut-2-enyl)indolin-2-one (2p). Pale yellow solid (90 mg, 83% yield): mp 144−146 °C. This compound has been previously reported, and ^{1}H and ^{13}C NMR spectral data match those published previously:[4b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.37 (d, J = 7.4 Hz, 1H), 7.28−7.23 (m, 1H), 7.06 (td, J = 7.6, 0.9 Hz, 1H), 6.86 (d, J = 7.7 Hz, 1H), 5.06−5.02 (m, 1H), 3.13 (s, 1H), 2.65 (d, J = 7.6 Hz, 2H), 1.65 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.4, 140.4, 137.6, 130.7, 129.7, 124.5, 123.1, 115.7, 110.3, 76.7, 37.4, 26.1, 18.1; HRMS (APCI) calcd for $C_{13}H_{16}NO_2$ $[M + H]^+$ m/z 218.1181, found m/z 218.1178.

3-Hydroxy-5-methyl-3-(3-methylbut-2-enyl)indolin-2-one (2q). Pale yellow solid (92 mg, 80% yield): mp 194−196 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.18 (s, 1H), 7.05 (d, J = 7.8 Hz, 1H), 6.74 (d, J = 7.9 Hz, 1H), 5.03 (t, J = 7.2 Hz, 1H), 2.93 (s, 1H), 2.76−2.50 (m, 2H), 2.33 (s, 3H), 1.66 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.5, 139.7, 134.5, 132.4, 130.6, 129.4, 125.1, 117.8, 109.5, 76.1, 37.0, 26.1, 21.2, 18.3; HRMS (APCI) calcd for $C_{14}H_{18}NO_2$ $[M + H]^+$ m/z 232.1338, found m/z 232.1333.

3-Hydroxy-5-methoxy-3-(3-methylbut-2-enyl)indolin-2-one (2r). Pale yellow solid (87 mg, 71% yield): mp 142−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 6.97 (s, 1H), 6.77 (d, J = 1.9 Hz, 2H), 5.03−5.0 (m, 1H), 3.78 (s, 3H), 3.66 (s, 1H), 2.64 (d, J = 8.6 Hz, 2H), 1.64 (s, 3H), 1.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.8, 156.2, 137.3, 133.7, 132.0, 115.8, 114.6, 111.1, 110.9, 77.5, 55.9, 37.4, 26.1, 18.1; HRMS (APCI) calcd for $C_{14}H_{18}NO_3$ $[M + H]^+$ m/z 248.1287, found m/z 248.1291.

5-Fluoro-3-hydroxy-3-(3-methylbut-2-enyl)indolin-2-one (2s). Pale yellow solid (72 mg, 62% yield): mp 188−190 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 7.02 (dd, J = 8.2, 2.7 Hz, 1H), 6.95−6.90 (m, 1H), 6.67 (dd, J = 8.4, 4.3 Hz, 1H), 4.70−4.64 (m, 1H), 2.42−2.34 (m, 2H), 1.44 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.47, 158.4 (J = 235.4 Hz), 138.3, 135.0, 134.2 (J = 7.4 Hz), 117.3, 115.4 (J = 23.1 Hz), 112.2 (J = 24.1 Hz), 110.5 (J = 7.8 Hz), 76.3, 36.8, 26.1, 18.2; negative ion HRMS (ESI) calcd for $C_{13}H_{13}FNO_2$ $[M - H]^-$ m/z 234.0930, found m/z 234.0936.

5-Bromo-3-hydroxy-3-(3-methylbut-2-enyl)indolin-2-one (2t). Pale yellow solid (107 mg, 73% yield): mp 214−216 °C. This compound has been previously reported, and ^{13}C NMR spectral data match those published previously;[4b] the proton signals were not quite superimposed with those of the previously reported compound because a different solvent was used in the NMR measurement: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 7.41−7.21 (m, 2H), 6.67 (d, J = 8.1 Hz, 1H), 4.71−4.67 (m, 1H), 2.43−2.36 (m, 2H), 1.54 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.0, 141.4, 135.2, 134.8, 131.9, 127.4, 117.2, 113.6, 111.8, 76.2, 36.8, 26.1, 18.3; HRMS (APCI) calcd for $C_{13}H_{15}BrNO_2$ $[M + H]^+$ m/z 296.0286, found m/z 296.0316.

3-Hydroxy-3-(3-methylbut-2-enyl)-5-nitroindolin-2-one (2u). Pale yellow solid (72 mg, 55% yield): mp 231−233 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.87 (s, 1H), 8.11 (dd, J = 8.6, 2.4 Hz, 1H), 8.03 (d, J = 2.4 Hz, 1H), 6.92 (d, J = 8.6 Hz, 1H), 4.75−4.72 (m, 1H), 2.57−2.44 (m, 2H), 1.47 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 179.8, 148.7, 142.5, 135.9, 133.3, 126.7, 120.0, 116.8, 110.1, 75.8, 36.6, 26.1, 18.2; HRMS (APCI) calcd for $C_{13}H_{15}N_2O_4$ $[M + H]^+$ m/z 263.1032, found m/z 263.1058.

4-Chloro-3-hydroxy-3-(3-methylbut-2-enyl)indolin-2-one (2v). Pale yellow solid (90 mg, 72% yield): mp 211−213 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (s, 1H), 7.12 (t, J = 8.0 Hz, 1H), 6.85 (dd, J = 8.2, 0.8 Hz, 1H), 6.66 (dd, J = 7.7, 0.8 Hz, 1H), 4.45 (s, 1H), 2.85 (dd, J = 13.5, 7.4 Hz, 1H), 2.51 (dd, J = 13.5, 7.7 Hz, 1H), 1.40 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.6, 144.4, 135.4, 131.1, 130.8, 127.9, 122.8, 116.9, 108.8, 77.2, 34.4, 26.1, 18.2; negative ion HRMS (ESI) calcd for $C_{13}H_{13}ClNO_2$ $[M - H]^-$ m/z 250.0635, found m/z 250.0650.

4-Bromo-3-hydroxy-3-(3-methylbut-2-enyl)indolin-2-one (2w). White solid (121 mg, 82% yield): mp 208−210 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.18 (dd, J = 8.2, 0.9 Hz, 1H), 7.11 (t, J = 7.9 Hz, 1H), 6.80 (dd, J = 7.6, 0.9 Hz, 1H), 4.84−4.80 (m, 1H), 3.10−2.97 (m, 2H), 2.91 (dd, J = 13.6, 8.5 Hz, 1H), 1.60 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.7, 144.6, 135.3, 131.3, 129.5, 125.9, 119.2, 116.9, 109.3, 77.8, 34.2, 26.1, 18.3; HRMS (APCI) calcd for $C_{13}H_{15}BrNO_2$ $[M + H]^+$ m/z 296.0286, found m/z 296.0303.

3-Cinnamyl-3-hydroxy-1,5-dimethylindolin-2-one (6b). Yellow oil (117 mg, 80% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.18 (m, 6H), 7.13 (d, J = 7.9 Hz, 1H), 6.71 (d, J = 7.9 Hz, 1H), 6.46 (d, J = 15.9 Hz, 1H), 6.20−5.93 (m, 1H), 3.15 (s, 3H), 3.03−2.76 (m, 2H), 2.77−2.68 (m, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 141.0, 137.2, 135.3, 132.9, 130.1, 129.8, 128.6, 128.6, 127.6, 126.4, 126.4, 125.0, 122.1, 108.4, 76.3, 42.4, 26.4, 21.3; HRMS (APCI) calcd for $C_{19}H_{20}NO_2$ $[M + H]^+$ m/z 294.1494, found m/z 294.1480.

5-Bromo-3-cinnamyl-3-hydroxy-1-methylindolin-2-one (6d). Yellow oil (129 mg, 72% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 1.9 Hz, 1H), 7.43 (dd, J = 8.3, 2.0 Hz, 1H), 7.27−7.12 (m, 5H), 6.66 (d, J = 8.3 Hz, 1H), 6.41 (d, J = 15.8 Hz, 1H), 6.12−5.78 (m, 1H), 4.12 (s, 1H), 3.09 (s, 3H), 2.89−2.84 (m, 1H), 2.80−2.66 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 177.7, 142.2, 136.9, 135.6, 132.5, 132.1, 132.0, 128.6, 127.6, 127.5, 126.4, 121.3, 116.0,

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110.1, 76.5, 42.1, 26.4; HRMS (APCI) calcd for $C_{18}H_{17}BrNO_2$ $[M + H]^+$ m/z 358.0443, found m/z 358.0458.

3-Cinnamyl-1-ethyl-3-hydroxy-5-methylindolin-2-one (6h). White solid (119 mg, 77% yield): mp 137−139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.22 (m, 5H), 7.19 (d, J = 8.6 Hz, 1H), 7.11 (d, J = 8.8 Hz, 1H), 6.72 (d, J = 7.9 Hz, 1H), 6.43 (d, J = 15.8 Hz, 1H), 6.04−5.82 (m, 1H), 3.81−3.72 (m, 1H), 3.64−3.55 (m, 1H), 3.04 (dd, J = 15.3, 6.0 Hz, 1H), 2.94−2.69 (m, 2H), 2.35 (s, 3H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 140.0, 137.2, 135.2, 132.7, 130.0, 130.0, 128.6, 128.6, 127.5, 126.4, 126.4, 125.2, 122.1, 108.5, 76.5, 42.5, 34.8, 21.2, 12.8; HRMS (APCI) calcd for $C_{20}H_{22}NO_2$ $[M + H]^+$ m/z 308.1651, found m/z 308.1671.

1-Allyl-5-bromo-3-cinnamyl-3-hydroxyindolin-2-one (6l). White solid (143 mg, 75% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 1.8 Hz, 1H), 7.41 (dd, J = 8.3, 2.0 Hz, 1H), 7.28−7.17 (m, 5H), 6.67 (d, J = 8.3 Hz, 1H), 6.44 (d, J = 15.8 Hz, 1H), 6.04−5.81 (m, 1H), 5.72−5.62 (m, 1H), 5.08 (dd, J = 18.8, 13.9 Hz, 2H), 4.42−4.36 (m, 1H), 4.10 (dd, J = 16.9, 4.8 Hz, 1H), 3.40 (s, 1H), 2.92−2.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 141.6, 136.8, 135.9, 132.6, 131.8, 130.7 128.6, 128.6, 127.8, 127.6, 126.4, 126.4, 121.1, 118.1, 116.0, 111.1, 76.5, 42.5, 42.5' HRMS (APCI) calcd for $C_{20}H_{19}BrNO_2$ $[M + H]^+$ m/z 384.0599, found m/z 384.0569.

1-(4-Bromobenzyl)-3-cinnamyl-3-hydroxyindolin-2-one (6n). White solid (182 mg, 84% yield): mp 179−181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 7.2 Hz, 1H), 7.27−7.22 (m, 4H), 7.24−7.13 (m, 3H), 7.11 (t, J = 7.5 Hz, 1H), 7.05−6.99 (m, 3H), 6.61 (d, J = 7.8 Hz, 1H), 6.45 (d, J = 15.8 Hz, 1H), 5.94−5.71 (m, 1H), 5.09 (d, J = 15.9 Hz, 1H), 4.47 (d, J = 15.9 Hz, 1H), 3.36 (s, 1H), 3.07−2.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 142.4, 136.8, 135.6, 134.3, 132.0, 132.0, 130.0, 129.6, 128.9, 128.9, 128.7, 128.7, 127.9, 126.5, 126.5, 124.3, 123.6, 121.6, 121.6, 109.5, 76.6, 43.5, 42.5; HRMS (APCI) calcd for $C_{24}H_{21}BrNO_2$ $[M + H]^+$ m/z 434.0756, found m/z 434.0733.

Synthesis of Soulieotine 4. Compound **2x** (100 mg, 0.4 mmol) was dissolved in toluene (5.0 mL). Then *p*-toluenesulfonic acid (0.2 equiv) was added. The mixture was heated to reflux for 0.5 h. After the mixture had been cooled to room temperature, the solvent was evaporated under vacuum. The residue was purified by flash column chromatography (3/1 petroleum ether/ethyl acetate) to afford **4** (66 mg, 71% yield) as a yellow solid. The product was identified as a *E* geometry by a typical trans coupling constant of 12.6 Hz for the double bond: mp 201−203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (br s, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.45 (d, J = 12.6 Hz, 1H), 6.73 (ddd, J = 12.6, 2.4, 1.2 Hz, 1H), 6.55 (dd, J = 8.5, 2.4 Hz, 1H), 6.45 (d, J = 2.3 Hz, 1H), 3.83 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 160.4, 150.7, 142.0, 130.2, 124.8, 122.9, 121.5, 116.5, 107.2, 96.8, 55.7, 27.6, 19.1; HRMS (ESI) calcd for $C_{14}H_{16}NO_2$ $[M + H]^+$ m/z 230.1175, found m/z 230.1134. All spectral data are consistent with that previously reported.[9d,10]

Synthesis of (*E*)-3-(3-Methyl-2-butenylidene)-2-indolinone 5. (*E*)-3-(3-Methyl-2-butenylidene)-2-indolinone **5** was prepared according to the procedure for the synthesis of soulieotine **4** from commercially available isatin **1p** as the starting material to afford **5** as a yellow solid. The product was identified as a *E* geometry by a typical trans coupling constant of 12.8 Hz for the double bond: mp 196−198 °C. (lit.[13] mp 200−203 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (br s, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.60 (d, J = 12.8 Hz, 1H), 7.19 (dt, J = 7.7, 1.0 Hz, 1H), 7.03 (dt, J = 7.6, 1.0 Hz, 1H), 6.87 (d, J = 7.6 Hz, 1H), 6.78 (ddd, J = 12.8, 2.4, 1.2 Hz, 1H), 2.07 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 152.4, 140.5, 132.9, 128.4, 123.8, 123.4, 123.1, 122.1, 121.6, 109.9, 27.7, 19.2; HRMS (ESI) calcd for $C_{13}H_{14}NO$ $[M + H]^+$ m/z 200.1070, found m/z 200.1036.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00836.

Copies of ^{1}H and ^{13}C NMR spectra for all prepared products and the X-ray crystal structure of **2p** (PDF)

Crystal data of **2p** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: lmzhao@jsnu.edu.cn.

Notes

The authors declare no competing financial interest.

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