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Synthesis of 2-Vinylindole-3-Acetic Acid Derivatives via Cyanide-Catalyzed Imino-Stetter Reaction

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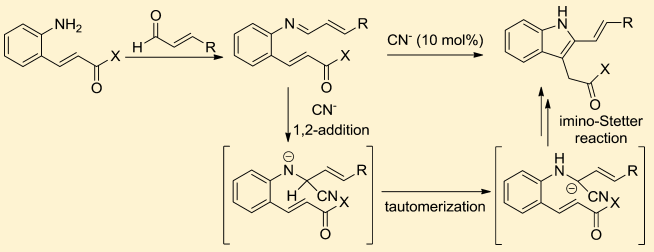
Supporting Information

ABSTRACT: A new method for the synthesis of 2-vinylindole-3-acetic acid derivatives from aldimines, which are derived from 2-aminocinnamic acid derivatives and α,β-unsaturated aldehydes, via a cyanide-catalyzed imino-Stetter reaction is described. Various types of 2-aminocinnamic acid derivatives and α,β-unsaturated aldehydes could be used in this protocol, and the desired 2-vinyl substituted indole-3-acetic acid derivatives were obtained in high yields. This cyanide-catalyzed imino-Stetter reaction was further extended to the preparation of indole-3-acetic acid derivatives bearing a carboxylic acid functionality at the 2-position, using aldimines obtained from glyoxylates and 2-aminocinnamic acid derivatives.



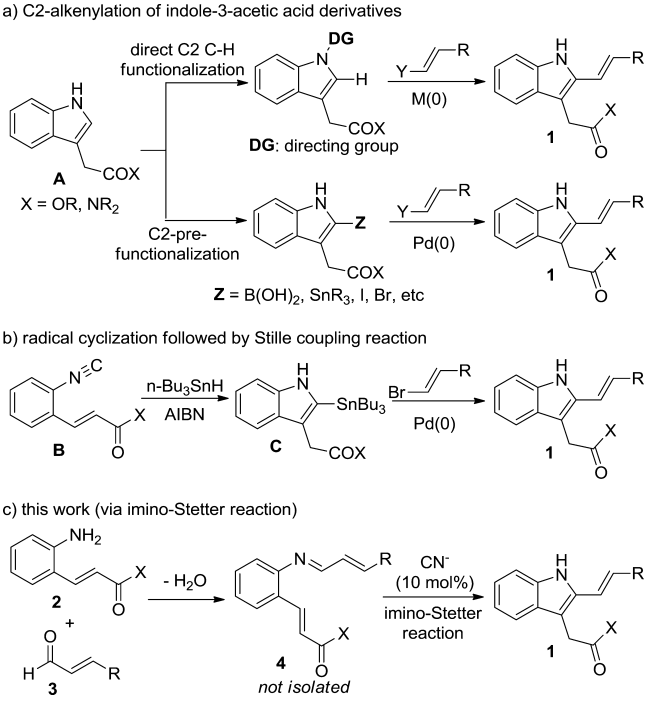
INTRODUCTION

The indole motif is found in a wide range of biologically active natural products, such as alkaloids and peptides, and is an important scaffold in the pharmaceutical industry. Hence, the development of new methods to access specific indole scaffolds has received significant attention from the synthetic and pharmaceutical communities.[1] Among the numerous indole derivatives developed, 2-vinylindole-3-acetic acid derivatives **1** are particularly important because they are the key building blocks in the synthesis of several natural products[2−5] such as flinderoles A−C[2] and chartellines A−C.[3] Therefore, the synthesis of indole derivatives **1** bearing various vinyl moieties at the 2-position is an important research topic, and several versatile synthetic routes to **1** have been developed.[6−9]

One of the conventional methods for the synthesis of 2-vinylindole-3-acetic acid derivatives **1** involves the C-2 alkenylation of indole-3-acetic acid derivatives **A** via either direct C−H alkenylation bearing a suitable directing group on the nitrogen atom[6] or a cross-coupling reaction of 2-prefunctionalized indole-3-acetic acid with an appropriate vinyl counterpart[7] (Scheme 1a). Moreover, the Fukuyama group developed an excellent method for the synthesis of these important compounds via the radical cyclization of isonitriles **B** derived from 2-aminocinnamic acid derivatives, followed by the Stille coupling of the resulting 2-stannylindoles **C** with alkynyl bromides (Scheme 1b).[8,9] Despite the progress in the synthesis of 2-vinylindole-3-acetic acid derivatives **1**, we strongly envisioned the need for the development of a new high-efficiency protocol for the synthesis of these important compounds.

Herein, we describe the development of a new method for the synthesis of 2-vinylindole-3-acetic acid derivatives **1** from aldimines **4**, which in turn were obtained from 2-aminocinnamic acid derivatives **2** and α,β-unsaturated aldehydes **3** via the cyanide-catalyzed imino-Stetter reaction (Scheme 1c). Various 2-aminocinnamic acid derivatives **2** and α,β-unsaturated aldehydes **3** were applicable to this protocol, and the desired indole products **1** were obtained in excellent yields.

Scheme 1. Synthetic Routes to 2-Vinylindole-3-Acetic Acid Derivatives 1



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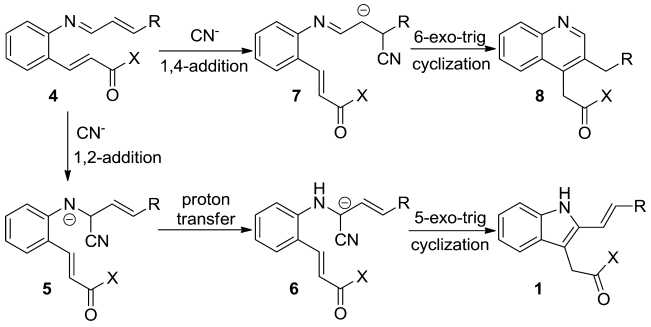
Furthermore, this protocol was extended to nonvinyl conjugate aldehydes such as glyoxylates, affording the desired indoles.

RESULTS AND DISCUSSION

Very recently, we developed a new protocol to access 2-arylindole-3-acetic acid derivatives from aldimines, which were obtained from 2-aminocinnamic acid derivatives and aromatic aldehydes, in the presence of a catalytic amount of cyanide via a cyanide-catalyzed imino-Stetter reaction.[10,11] Based on this result, we hypothesized that if a similar reaction mechanism was possible for aldimines **4**, which were derived from 2-aminocinnamic acid derivatives **2** and α,β-unsaturated aldehydes **3**, then indole-3-acetic acid derivatives **1** bearing a vinyl moiety at the 2-position could be synthesized from **4** in the presence of a catalytic amount of cyanide.

However, we expected a few challenges in the initial stages of the investigation (Scheme 2). The first and major concern was

Scheme 2. Expected Challenges in the Synthesis of 2-Vinylindole-3-Acetic Acid Derivatives 1 from Aldimines 4 with Cyanide

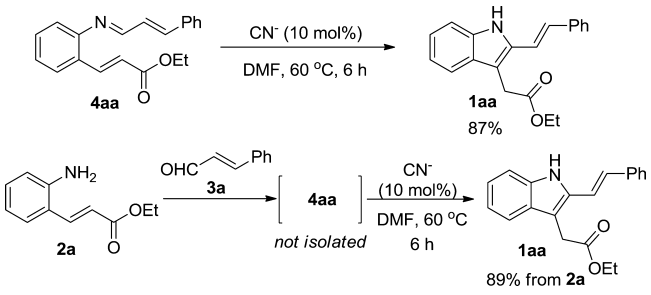


the regioselectivity in the addition of cyanide to aldimines **4** (1,2- vs 1,4-addition). If cyanide undergoes 1,2-addition to **4**, the resulting cyanide adducts **5** might undergo proton transfer to generate anions **6**, which are the corresponding umpolung of aldimines **4**. Subsequent imino-Stetter reaction via 5-*exo-trig* cyclization would afford the expected 2-vinylindole-3-acetic acid derivatives **1**. On the other hand, 1,4-adducts **7** of cyanide to **4** could yield quinoline compounds **8** via 6-*exo-trig* cyclization. Another concern was the efficiency of the tautomerization of 1,2-adducts **5** to generate anionic intermediates **6**.

Regarding the regioselectivity, we expected that 1,2-addition of cyanide to **4** would be the major pathway leading to **5**, since HCN addition of the aldimines of α,β-unsaturated aldehydes with an aniline derivative, i.e., the Strecker reaction of α,β-unsaturated aldehydes, generally provided 1,2-adducts rather than 1,4-adducts.[12] In addition, the efficiency of tautomerization of cyanide adducts **5** might depend on the relative stability between 1,2-adducts **5** and anionic **6**. Because the pK_a values of benzylic and allylic protons are similar,[13] we could anticipate that the stability of carbanions **6** generated from **5** via proton transfer might be similar to that in the case of the cyanide adducts of aldimines obtained from 2-aminocinnamic acid derivatives **2** and aromatic aldehydes. Thus, we expected that umpolung **6** could be generated from cyanide adducts **5** via tautomerization.

With these considerations in mind, we tested our working hypothesis in the synthesis of 2-vinylindole-3-acetic acid derivatives using aldimine **4aa**, which was derived from ethyl 2-aminocinnamate **2a** and cinnamaldehyde **3a**, as a model compound with a catalytic amount of cyanide (Scheme 3). When **4aa** was subjected to the previous optimal conditions[10]

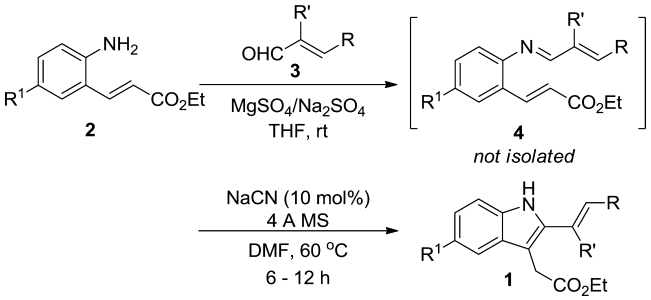
Scheme 3. Initial Trials for the Synthesis of 2-Vinylindole-3-Acetic Acid Derivative 4aa



used for the synthesis of 2-arylindole-3-acetic acid derivatives, to our delight, the desired indole **1aa** was obtained in 87% yield. Furthermore, the treatment of **4aa**, which generated in situ by the condensation of **2a** with **3a** without further purification, with a catalytic amount of cyanide provided **1aa** without any loss of efficiency. Since **1aa** was obtained in a sufficiently high yield and with high reproducibility, we decided to use these conditions as the optimal reaction conditions for the synthesis of 2-vinylindole-3-acetic acid derivatives without any further optimization.

Under these conditions, the generality of α,β-unsaturated aldehydes **3** was first investigated using ethyl 2-aminocinnamate **2a** (Table 1). Various cinnamaldehyde derivatives participated in the reaction to afford the corresponding indoles **1** in high yields, regardless of the electronic and steric nature of the aryl group (entries 1−5). Furthermore, an α,β-unsaturated aldehyde bearing a heteroaromatic group was applied to this protocol,

Table 1. Substrate Scope of α,β-Unsaturated Aldehydes



entry	indole **1**	R^1	R′	R	yield (%)
1	**1aa**	H	H	Ph	89
2	**1ab**	H	H	4-ClC_6H_4	93
3	**1ac**	H	H	4-BrC_6H_4	88
4	**1ad**	H	H	4-$MeOC_6H_4$	90
5	**1ae**	H	H	2-$MeOC_6H_4$	94
6	**1af**	H	H	2-furyl	88
7	**1ag**	H	H	H	34
8	**1ah**	H	H	Me	62
9	**1ai**	H	H	Et	49
10	**1aj**	H	Me	Ph	96
11[a]	**1ba**	Br	H	Ph	95
12[a,b]	**1ca**	OMe	H	Ph	20

[a]Methyl ester of 2-aminocinnamic acid was used. [b]Reaction was performed at 100 °C for 24 h.

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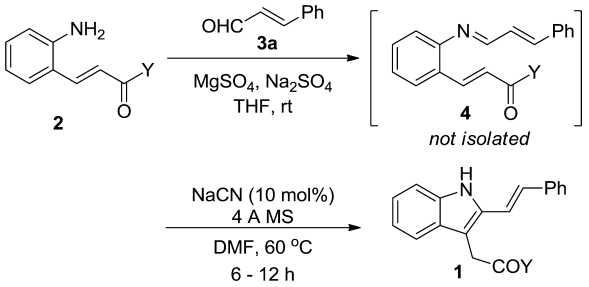
and the desired product **1af** was obtained without any decrease in catalytic efficiency (entry 6). However, when the aldimines obtained from α,β-unsaturated aldehydes bearing an alkyl group at the β-position were subjected to the optimized conditions, the desired indoles **1** were obtained in only moderate yields, and hydrolysis of the aldimines competed with the indolization, leading to ethyl 2-aminocinnamate **2a** (entries 7−9).[14] An α,β-disubstituted α,β-unsaturated aldehyde was applicable to in this protocol, providing the desired indole **1aj** in an excellent yield (entry 10). Finally, the effect of substituents at the 2-aminocinnamate moiety on this transformation was investigated. The electronic nature of the substituent on the aryl group in 2-aminocinnamates **2** had a dramatic effect on this reaction (entries 1, 11, and 12). The reactions of 2-aminocinnamate derivatives bearing electron-neutral and withdrawing groups provided the corresponding indoles in excellent yields (entries 1 and 11). On the other hand, the presence of an electron-donating substituent led to low yield of the indole product **1ca** even at an elevated temperature (entry 12).

The substrate scope of 2-aminocinnamic acid derivatives **2** was further explored in this transformation with cinnamaldehyde **3a** (Table 2). First, the effect of the size of an alkyl group

Table 2. Substrate Scope of 2-Aminocinnamic Acid Derivatives



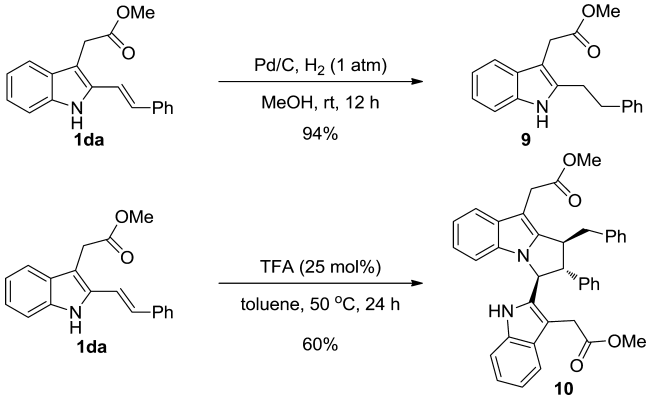
entry	indole **1**	Y	yield (%)
1	**1da**	OMe	98
2	**1aa**	OEt	89
3	**1ea**	O*i*-Pr	98
4	**1fa**	O*t*-Bu	85
5	**1ga**	$N(Et)_2$	88
6	**1ha**	$N(CH_2)_5$	74
7	**1ia**	N(Bn)Boc	88

in the ester moiety of 2-aminocinnamate was examined. The size of the alkyl group in the ester moiety had little influence on this transformation, and the desired indoles **1** were obtained in excellent yields, regardless of the structure of the ester moiety (entries 1−4). Furthermore, several 2-aminocinnamides bearing different *N*-alkyl groups could be applied to this protocol, and the substituents on the nitrogen atom in the amide had negligible effect on the outcome of this reaction (entries 5−7).[15]

To test the practicality of this protocol, this reaction was performed on a 20 mmol scale (Scheme 4). We found that this transformation could be performed without any decrease in efficiency.

With these results in hand, we further investigated the utility of this protocol (Scheme 5). Since many indole monoterpene

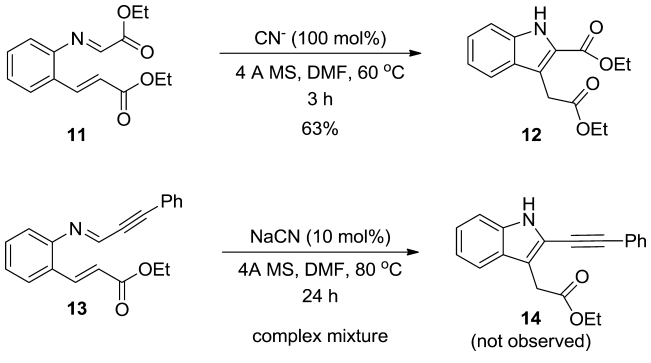
Scheme 5. Further Transformations of Indole 1da



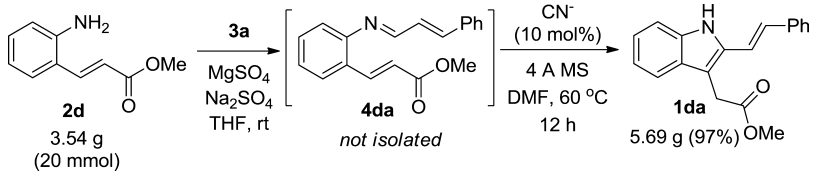
alkaloids possess the structural scaffold of an indole-3-acetic acid derivative bearing an alkyl group at the 2-position,[16] we first attempted to develop a synthetic route to 2-alkylindole-3-acetic acid derivatives[17] from 2-vinylindole-3-acetic acid derivatives. When **1da** was subjected to palladium-catalyzed hydrogenation conditions, 2-alkylindole-3-acetic acid derivative **9** was obtained in a quantitative yield. In addition, we attempted to establish the diastereoselective construction of a pyrroloindole framework from the resulting vinylindoles **1** via a Brønsted acid-catalyzed [3 + 2]-cyclodimerization.[18] Upon the treatment of **1da** with a catalytic amount of trifluoroacetic acid (TFA), dimerization occurred to afford compound **10** in 60% yield.

Next, the possibility of extending this protocol to other nonvinyl conjugate aldehydes such as glyoxylates and propargyl aldehydes was examined (Scheme 6). The structural motif

Scheme 6. Extension to Other Conjugated Aldehydes



Scheme 4. 20 mmol Scale Reaction



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present in the conjugate aldehydes strongly affected the efficiency of this transformation. The reaction of aldimine **11** derived from ethyl glyoxylate with **2a** provided the expected indole **12** in 63% yield, even under unoptimized conditions.[19] However, this protocol could not be extended to aldimines derived from propargyl aldehydes. Disappointingly, when aldimine **13** was subjected to this protocol,[20] the desired product **14** was not formed; instead, a complex mixture was obtained.

CONCLUSIONS

In conclusion, a new method for the synthesis of 2-vinyl substituted indole-3-acetic acid derivatives from aldimines, which were prepared using 2-aminocinnamic acid derivatives and α,β-unsaturated aldehydes, was developed via a cyanide-catalyzed imino-Stetter reaction. Various α,β-unsaturated aldehydes and 2-aminocinnamic acid derivatives were applicable to this protocol, and the desired 2-vinylindole-3-acetic acid derivatives were obtained in excellent yields. The synthetic utility of our method was demonstrated by converting the resulting indoles into various other compounds. This cyanide-catalyzed imino-Stetter reaction was further extended to the synthesis of indole-3-acetic acid derivatives bearing a carboxylic acid functionality at the 2-position, using aldimines obtained from glyoxylates and 2-aminocinnamic acid derivatives. Further studies on the application of the current method to the total synthesis of indole monoterpene alkaloids and the extension of cyanide-catalyzed imino-Stetter reaction to other N-containing heterocyclic compounds are underway in our laboratory.

EXPERIMENTAL SECTION

General. All reactions were carried out in oven-dried glassware under an argon atmosphere, unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin-layer chromatography (TLC) using precoated silica gel glass plates (0.25 mm) with F254 indicator. Visualization was accomplished by UV light (254 nm), with a combination of potassium permanganate and/or phosphomolybdic acid solution as an indicator. Flash column chromatography was performed using silica gel 60 (230−400 mesh). Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted. Commercial grade reagents and solvents were used without further purification. 2-Aminocinnamic acid derivatives **2** were prepared from 2-nitrocinnamic acid by the literature procedure.[10] 2-Nitrocinnamic acid and all α,β-unsaturated aldehydes were purchased from commercial suppliers and used without further purification unless otherwise noted. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400/500 and 100/125 MHz spectrometers, respectively. Tetramethylsilane (δ: 0.0 ppm) and a residual NMR solvent (either $CDCl_3$ (δc: 77.16 ppm) or DMSO (δ_C: 39.52 ppm) were used as internal standards for ^{1}H NMR and ^{13}C NMR spectra, respectively. The proton spectra are reported as follows: δ (position of proton, multiplicity, coupling constant J, number of protons). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), h (septet), m (multiplet) and br (broad). High-resolution mass spectra (HRMS) were recorded on a quadrupole time-of-flight mass spectrometer (QTOF-MS) in electrospray ionization (ESI) mode as ionization method.

General Procedure for the Synthesis of 2-Vinylindole-3-acetic acid Derivatives (Tables 1 and 2). To a 50 mL round-bottom flask were added (*E*)-2-aminocinnamic acid derivative **2** (1.0 mmol), Na_2SO_4 (330 mg), and $MgSO_4$ (330 mg), and the reaction mixture was dissolved in THF (10 mL). To the above solution was added an α,β-unsaturated aldehyde **3** (1.0 mmol). The mixture was stirred at room temperature and monitored by ^{1}H NMR analysis of the crude mixture. After the complete consumption of the starting materials, the reaction mixture was concentrated in vacuo to furnish the crude product of aldimine **4**. Without further purification, 4 Å molecular sieves and sodium cyanide (0.10 mmol, 0.1 equiv) were added to a solution of **4** in DMF (10 mL) at room temperature. The mixture was stirred at 60 °C under an argon atmosphere until TLC analysis indicated the complete consumption of **4**. Upon the complete consumption of **4**, the reaction mixture was cooled to room temperature and filtered to remove the molecular sieves. The filtrate was concentrated in vacuo to provide the crude indole **1**. The crude mixture was purified by column chromatography on silica to provide the desired indole **1**.

*(E)-Ethyl 2-(2-Styryl-1H-indol-3-yl)acetate (**1aa**).* Purification by column chromatography on silica (ethyl acetate/hexanes = 1:5) yielded a yellow solid (244 mg, 89%). R_f = 0.3 (ethyl acetate/hexanes = 1:4); mp 100−102 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.23 (br, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.51 (d, J = 7.8 Hz, 2H), 7.37 (t, J = 7.4 Hz, 2H), 7.29 (t, J = 8.6 Hz, 2H), 7.25 (d, J = 16.4 Hz, 1H), 7.17−7.21 (m, 1H), 7.11 (t, J = 7.4 Hz, 1H), 6.87 (d, J = 16.4 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.85 (s, 2H), 1.24 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 171.9, 137.1, 136.6, 133.9, 129.0, 129.0(2C), 128.0, 127.6, 126.6(2C), 123.5, 120.2, 119.2, 116.9, 110.9, 109.1, 61.2, 30.8, 14.5. HRMS (ESI) calcd for $C_{20}H_{19}NNaO_2$ 328.1308, found 328.1309.

*(E)-Ethyl 2-(2-(4-Chlorostyryl)-1H-indol-3-yl)acetate (**1ab**).* Purification by column chromatography on silica (ethyl acetate/hexanes = 1:5) yielded a yellow solid (316 mg, 93%). R_f = 0.3 (ethyl acetate/hexanes = 1:5); mp 144−145 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.23 (br, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.40−7.43 (m, 2H), 7.28−7.34 (m, 3H), 7.17−7.23 (m, 2H), 7.11 (t, J = 7.0 Hz, 1H), 6.80 (d, J = 16.4 Hz, 1H), 4.15 (q, J = 7.0 Hz, 2H), 3.85 (s, 2H), 1.24 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 172.0, 136.7, 135.6, 133.6, 133.4, 129.1(2C), 129.0, 127.7(2C), 126.1, 123.7, 120.3, 119.2, 117.4, 110.9, 109.3, 61.3, 30.8, 14.5. HRMS (ESI) calcd for $C_{20}H_{18}ClNNaO_2$ 362.0918, found 362.0919.

*(E)-Ethyl 2-(2-(4-Bromostyryl)-1H-indol-3-yl)acetate (**1ac**).* Purification by column chromatography on silica (ethyl acetate/hexanes = 1:5) yielded a yellow solid (338 mg, 88%). R_f = 0.5 (ethyl acetate/hexanes = 1:3); mp 146−148 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.22 (br, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.48 (d, J = 8.6 Hz, 2H), 7.35 (d, J = 8.6 Hz, 2H), 7.29 (d, J = 7.8 Hz, 1H), 7.11 (t, J = 7.1 Hz, 2H), 7.09−7.14 (m, 1H), 6.78 (d, J = 16.4 Hz, 1H), 4.15 (q, J = 7.0 Hz, 2H), 3.86 (s, 2H), 1.24 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 172.1, 136.7, 136.1, 133.7, 132.0(2C), 128.9, 128.0(2C), 126.2, 123.7, 121.5, 120.3, 119.2, 117.4, 110.9, 109.3, 61.4, 30.8, 14.5. HRMS (ESI) calcd for $C_{20}H_{18}BrNNaO_2$ 406.0413, found 406.0415.

*(E)-Ethyl 2-(2-(4-Methoxystyryl)-1H-indol-3-yl)acetate (**1ad**).* Purification by column chromatography on silica (ethyl acetate/hexanes = 1:5) yielded a yellow solid (302 mg, 90%). R_f = 0.3 (ethyl acetate/hexanes = 1:5); mp 104−105 °C. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 11.21 (br, 1H), 7.53 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 7.8 Hz, 1H), 7.29, (d, J = 7.8 Hz, 1H), 7.21 (d, J = 16.4 Hz, 1H), 7.05−7.15, (m, 2H), 6.96 (m, 3H), 4.04 (q, J = 7.0 Hz, 2H), 3.89 (s, 2H), 3.77 (s, 3H), 1.15 (t, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 171.9, 159.7, 136.4, 134.2, 129.9, 129.2, 127.9(2C), 127.2, 123.2, 120.2, 119.1, 114.9, 114.5(2C), 110.7, 108.4, 61.1, 55.6, 30.8, 14.5. HRMS (ESI) calcd for $C_{21}H_{21}NNaO_3$ 358.1414, found 358.1413.

*(E)-Ethyl 2-(2-(2-Methoxystyryl)-1H-indol-3-yl)acetate (**1ae**).* Purification by column chromatography on silica (ethyl acetate/hexanes = 1:3) yielded a yellow solid (315 mg, 94%). R_f = 0.3 (ethyl acetate/hexanes = 1:3); mp 108−110 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.48 (br, 1H), 7.54 (dd, J = 12.7, 7.6 Hz, 2H), 7.15−7.25 (m, 3H), 7.01−7.12 (m, 3H), 6.91 (t, J = 7.4 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 4.10 (q, J = 6.7 Hz, 2H), 3.80 (s, 2H), 3.77 (s, 3H), 1.16 (t, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 172.2, 157.0, 136.7, 134.7, 129.1, 126.4, 126.1, 123.3, 122.1, 121.2, 120.1, 119.2, 117.2, 111.3, 111. 0, 108.6, 61.3, 55.7, 30.9, 14.5. HRMS (ESI) calcd for $C_{21}H_{21}NNaO_3$ 358.1414, found 358.1415.

*(E)-Ethyl 2-(2-(2-(Furan-2-yl)vinyl)-1H-indol-3-yl)acetate (**1af**).* Purification by column chromatography on silica (ethyl acetate/

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hexanes = 1:5) afforded a yellow solid (260 mg, 88%). R_f = 0.4 (ethyl acetate/hexanes = 1:3); mp 145−146 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.14 (br, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.41 (s, 1H), 7.27 (d, J = 7.0 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 7.07−7.15 (m, 2H), 6.65 (d, J = 16.4 Hz, 1H), 6.41−6.45 (m, 1H), 6.35 (d, J = 3.1 Hz, 1H), 4.15 (q, J = 7.0 Hz, 2H), 3.84 (s, 2H), 1.24 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 171.7, 153.0, 142.6, 136.6, 133.6, 129.1, 123.6, 120.3, 119.3, 115.3, 115.3, 112.0, 110.7, 109.4, 109.1, 61.1, 30.7, 14.4. HRMS (ESI) calcd for $C_{18}H_{17}NNaO_3$ 318.1101, found 318.1101.

*Ethyl 2-(2-Vinyl-1H-indol-3-yl)acetate (**1ag**).* Purification by column chromatography on silica (ethyl acetate/hexanes = 1:5) yielded yellow liquid (78 mg, 34%). R_f = 0.5 (ethyl acetate/hexanes = 1:3). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.15 (br, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.19 (t, J = 7.2 Hz, 1H), 7.10 (t, J = 7. 0 Hz, 1H), 6.88 (dd, J = 17.8, 11.2 Hz, 1H), 5.53 (d, J = 18. 0 Hz, 1H), 5.32 (d, J = 11.0 Hz, 1H), 4.13 (q, J = 7.2 Hz, 2H), 3.78 (s, 2H), 1.23 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 171.9, 136.2, 133.7, 128.8, 125.5, 123.4, 120.1, 119.4, 112.7, 110.9, 108.3, 61.1, 30.6, 14.4. HRMS (ESI) calcd for $C_{14}H_{15}NNaO_2$ 252.0995, found 252.0996.

*(E)-Ethyl 2-(2-(Prop-1-en-1-yl)-1H-indol-3-yl)acetate (**1ah**).* Purification by column chromatography on silica (ethyl acetate/hexanes = 1:8) yielded a yellow solid (151 mg, 62%). R_f = 0.5 (ethyl acetate/hexanes = 1:5); mp 81−86 °C. Existed as an inseparable mixture of (*E*)- and (*Z*)-isomers (*E*/*Z* = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.23 (br, 1H), 7.53 (d, J = 7.4 Hz, 1H), 7.03−7.14 (m, 3H), 6.43 (d, J = 15.7 Hz, 1H), 5.83−5.93 (m, 1H), 4.11 (q, J = 7.0 Hz, 2H), 3.73 (s, 2H), 1.80 (d, J = 6.7 Hz, 3H), 1.20 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 172.4, 136.2, 134.2, 129.0, 125.6, 122.6, 122.6, 120.0, 119.9, 118.9, 110.9, 105.9, 61.2, 30.7, 19.0, 14.5. HRMS (ESI) calcd for $C_{15}H_{17}NNaO_2$ 266.1151, found 266.1150.

*(E)-Ethyl 2-(2-(but-1-en-1-yl)-1H-indol-3-yl)acetate (**1ai**).* Purification by column chromatography on silica (ethyl acetate/hexanes = 1:6) yielded a yellow solid (127 mg, 49%). R_f = 0.6 (ethyl acetate/hexanes = 1:3); mp 77−78 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.04 (br, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.28 (d, J = 7.4 Hz, 1H), 7.15 (t, J = 7.4 Hz, 1H), 7.08 (t, J = 7.4 Hz, 1H), 6.54 (d, J = 16.0 Hz, 1H), 6.08 (dt, J = 15.9, 6.5 Hz, 1H), 4.13 (q, J = 7.0 Hz, 2H), 3.75 (s, 2H), 2.25−2.34 (m, 2H), 1.23 (t, J = 7.0 Hz, 3H), 1.12 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 172.5, 136.3, 134.2, 132.5, 129.0, 122.7, 119.9, 118.9, 117.9, 110.9, 106.2, 61.2, 30.8, 26.6, 14.5, 13.9. HRMS (ESI) calcd for $C_{16}H_{19}NNaO_2$ 280.1313, found 280.1307.

*(E)-Ethyl 2-(2-(1-Phenylprop-1-en-2-yl)-1H-indol-3-yl)acetate (**1aj**).* Purification by column chromatography on silica (ethyl acetate/hexanes = 1:3) yielded brown liquid (306 mg, 96%). R_f = 0.3 (ethyl acetate/hexanes = 1:3). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.05 (br, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 4.7 Hz, 3H), 7.33 (d, J = 7.8 Hz, 1H), 7.26−7.31 (m, 1H), 7.11−7.22 (m, 3H), 6.97 (s, 1H), 4.16 (q, J = 7.3 Hz, 2H), 3.89 (s, 2H), 2.33 (s, 3H), 1.25 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 172.5, 139.5, 137.6, 135.5, 131.4, 129.5, 129.2, 128.6, 128.6, 127.2, 122.7, 120.1, 119.3, 111.0, 105.8, 61.1, 31.8, 18.3, 14.5. HRMS (ESI) calcd for $C_{21}H_{21}NNaO_2$ 342.1464, found 342.1463.

*(E)-Methyl 2-(5-Bromo-2-styryl-1H-indol-3-yl)acetate (**1ba**).* Purification by column chromatography on silica (ethyl acetate/hexanes = 1:5) yielded a yellow solid (352 mg, 95%). R_f = 0.3 (ethyl acetate/hexanes = 1:5); mp 149−150 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.29 (br, 1H), 7.69 (s, 1H), 7.49 (d, J = 7.4 Hz, 2H), 7.37 (t, J = 7.6 Hz, 2H), 7.30 (d, J = 7.4 Hz, 1H), 7.24−7.27 (m, 1H), 7.13−7.19 (m, 2H), 6.88 (d, J = 16.4 Hz, 1H), 3.81 (s, 2H), 3.71 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 172.0, 136.7, 135.1, 135.1, 130.7, 129.0 (2C), 128.7, 128.3, 126.7(2C), 126.3, 121.6, 116.3, 113.5, 112.2, 108.2, 52.5, 30.3. HRMS (ESI) calcd for $C_{19}H_{16}BrNNaO_2$ 392.0257, found 392.0260.

*(E)-Methyl 2-(5-Methoxy-2-styryl-1H-indol-3-yl)acetate (**1ca**).* Purification by column chromatography on silica (ethyl acetate/hexanes = 1:5) yielded a brown solid (64 mg, 20%). R_f = 0.4 (ethyl acetate/hexanes = 1:3); mp 142−144 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.12 (br, 1H), 7.52 (d, J = 7.4 Hz, 2H), 7.38 (t, J = 7.4 Hz, 2H), 7.29 (d, J = 7.4 Hz, 1H), 7.23 (d, J = 1.6 Hz, 1H), 7.20 (d, J = 5.5 Hz, 1H), 7.02−7.05 (m, 1H), 6.84−6.90 (m, 2H), 3.87 (s, 3H), 3.84 (s, 2H), 3.69 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 172.1, 154.4, 136.9, 134.4, 131.5, 129.2, 128.8, 127.8, 127.2, 126.4, 116.6, 113.5, 111.4, 108.5, 100.7, 55.9, 52.1, 30.4. HRMS (ESI) calcd for $C_{20}H_{19}NNaO_3$ 344.1257, found 344.1259.

*(E)-Methyl 2-(2-Styryl-1H-indol-3-yl)acetate (**1da**).* Purification by column chromatography on silica (ethyl acetate/hexanes = 1:6) yielded a yellow solid (285 mg, 98%). R_f = 0.6 (ethyl acetate/hexanes = 1:3); mp 104−105 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.27 (br, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.47 (d, J = 7.4 Hz, 2 H), 7.35 (t, J = 7.4 Hz, 2H), 7.22−7.28 (m, 2H), 7.15−7.21 (m, 2H), 7.10 (t, J = 7.4 Hz, 1H), 6.82 (d, J = 16.4 Hz, 1H), 3.85 (s, 2H), 3.68 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 172.4, 137.1, 136.6, 133.9, 129.0(2C), 128.1, 127.7, 126.6(2C), 123.6, 120.3, 119.2, 116.8, 110.9, 108.9, 52.4, 30.5. HRMS (ESI) calcd for $C_{19}H_{17}NNaO_2$ 314.1151, found 314.1152.

*(E)-Isopropyl 2-(2-Styryl-1H-indol-3-yl)acetate (**1ea**).* Purification by column chromatography on silica (ethyl acetate/hexanes = 1:6) yielded a yellow solid (313 mg, 98%), R_f = 0.6 (ethyl acetate/hexanes = 1:3); mp 96−98 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.23 (br, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.51 (d, J = 7.4 Hz, 2H), 7.37 (t, J = 7.6 Hz, 2H), 7.30 (t, J = 8.6 Hz, 2H), 7.25 (d, J = 16.4 Hz, 1H), 7.20 (t, J = 7.4 Hz, 1H), 7.11 (t, J = 7.4 Hz, 1H), 6.87 (d, J = 16.4 Hz, 1H), 4.96−5.06 (m, 1H), 3.82 (s, 2H), 1.21 (d, J = 6.3 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 171.6, 137.2, 136.6, 133.9, 129.0, 129.0(2C), 127.9, 127.5, 126.6(2C), 123.4, 120.1, 119.2, 117.0, 110.9, 109.1, 68.7, 31.2, 22.1(2C). HRMS (ESI) calcd for $C_{21}H_{21}NNaO_2$ 342.1464, found 342.1468.

*(E)-tert-Butyl 2-(2-Styryl-1H-indol-3-yl)acetate (**1fa**).* Purification by column chromatography on silica (ethyl acetate/hexanes = 1:5) yielded a brown solid (284 mg, 85%). R_f = 0.3 (ethyl acetate/hexanes = 1:5); mp 124−125 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.20 (br, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.52 (d, J = 7.4 Hz, 2H), 7.37 (t, J = 7.6 Hz, 2H), 7.27−7.33 (m, 2H), 7.17−7.24 (m, 2H), 7.11 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 16.4 Hz, 1H), 3.77 (s, 2H), 1.42 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 171.1, 137.2, 136.6, 133.7, 129.1, 129.0(2C), 127.9, 127.2, 126.6(2C), 123.4, 120.1, 119.4, 117.1, 110.7, 109.8, 81.1, 32.2, 28.3(3C). HRMS (ESI) calcd for $C_{22}H_{23}NNaO_2$ 356.1621, found 356.1621.

*(E)-N,N-Diethyl-2-(2-styryl-1H-indol-3-yl)acetamide (**1ga**).* Purification by column chromatography on silica (ethyl acetate/hexanes = 1:3) yielded a yellow solid (293 mg, 88%). R_f = 0.3 (ethyl acetate/hexanes = 1:3); mp 151−152 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.49 (br, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.47 (d, J = 7.4 Hz, 2H), 7.34 (t, J = 7.4 Hz, 2H), 7.21−7.30 (m, 3H), 7.15 (t, J = 7.4 Hz, 1H), 7.07 (t, J = 7.1 Hz, 1H), 6.83 (d, J = 16.4 Hz, 1H), 3.91 (s, 2H), 3.39 (q, J = 7.0 Hz, 2H), 3.32 (q, J = 7.0 Hz, 2H), 1.09 (t, J = 7.0 Hz, 3H), 1.02 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 170.8, 137.3, 136.8, 133.7, 128.9, 128.8, 127.8, 127.3, 126.6, 123.3, 120.0, 119.0, 117.1, 110.9, 109.8, 42.6, 40.8, 31.4, 14.3, 13.3. HRMS (ESI) calcd for $C_{22}H_{24}N_2NaO$ 355.1781, found 355.1782.

*(E)-1-(Piperidin-1-yl)-2-(2-styryl-1H-indol-3-yl)ethanone (**1ha**).* The spectroscopic data were in good agreement with the literature.[11] Purification by column chromatography on silica (ethyl acetate/hexanes = 1:3) yielded a yellow solid (255 mg, 74%). R_f = 0.2 (ethyl acetate/hexanes = 1:3). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.27 (br, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.51 (d, J = 7.4 Hz, 2H), 7.28−7.40 (m, 5H), 7.20 (t, J = 7.4 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 3.94 (s, 2H), 3.55−3.61 (m, 2H), 3.34−3.41 (m, 2H), 1.41−1.54 (m, 4H), 1.18−1.25 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 169.8, 137.2, 136.7, 133.4, 129.0(2C), 128.6, 127.9, 127.3, 126.6(2C), 123.4, 120.1, 119.2, 117.1, 110.8, 109.9, 47.5, 43.4, 31.5, 26.2, 25.8, 24.6. HRMS (ESI) calcd for $C_{23}H_{24}N_2NaO$ 367.1781, found 367.1780.

*(E)-N-Benzyl-N-(tert-butyoxycarbonyl)-2-(2-styryl-1H-indol-3-yl)-acetamide (**1ia**).* Purification by column chromatography on silica (ethyl acetate/hexanes = 1:5) yielded a brown solid (411 mg, 88%). R_f = 0.3 (ethyl acetate/hexanes = 1:5); mp 144−145 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.21 (br, 1H) 7.45−7.51 (m, 3H) 7.34 (t, J = 7.4 Hz, 2H) 7.20−7.29 (m, 8H) 7.16 (t, J = 7.6 Hz, 1H) 7.05 (t, J =

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7.5 Hz, 1H) 6.80 (d, J = 16.3 Hz, 1H) 4.88 (s, 2H) 4.53 (s, 2H) 1.39 (d, J = 1.4 Hz, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 174.3, 153.4, 138.2, 137.1, 136.5, 133.9, 129.2, 128.7, 128.3, 127.7, 127.6, 127.1, 126.8, 126.4, 123.2, 119.9, 119.4, 117.4, 110.5, 110.2, 83.4, 47.9, 33.7, 27.9. HRMS (ESI) calcd for $C_{30}H_{30}N_2NaO_3$ 489.2149, found 489.2147.

*Ethyl 3-(2-Ethoxy-2-oxoethyl)-1H-indole-2-carboxylate (**12**).* The spectroscopic data were in good agreement with the literature.[19] Purification by column chromatography on silica (ethyl acetate/hexanes = 1:5) yielded a yellow solid (173 mg, 63%). R_f = 0.5 (ethyl acetate/hexanes = 1:3). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.85 (br, 1H), 7.66 (d, J = 8.2 Hz, 1H), 7.37−7.42 (m, 1H), 7.33 (t, J = 7.4 Hz, 1H), 7.17 (t, J = 7.4 Hz, 1H), 4.41 (q, J = 7.0 Hz, 2H), 4.13−4.20 (m, 4H), 1.41 (t, J = 7.0 Hz, 3H), 1.25 (t, J = 7.0 Hz, 3H). HRMS (ESI) calcd for $C_{15}H_{17}NNaO_4$ 298.1050, found 298.1048.

*Methyl 2-(2-Phenethyl-1H-indol-3-yl)acetate (**9**).* Purification by column chromatography on silica (ethyl acetate/hexanes = 1:6) yielded yellow liquid (276 mg, 94%). R_f = 0.6 (ethyl acetate/hexanes = 1:3). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.73 (br, 1H), 7.51−7.56 (m, 1H), 7.07−7.28 (m, 8H), 3.63 (s, 3H), 3.60 (s, 2H), 2.98−3.03 (m, 2H), 2.89−2.94 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 172.8, 141.3, 136.4, 135.4, 128.8, (2C) 128.7, (2C) 128.5, 126.6, 121.7, 119.8, 118.6, 110.7, 104.8, 52.2, 36.2, 30.4, 28.5. HRMS (ESI) calcd for $C_{19}H_{19}NNaO_2$ 316.1308, found 316.1310.

*Compound (**10**).* Purification by column chromatography on silica (ethyl acetate/hexanes = 1:5) yielded a yellow solid (175 mg, 60%). R_f = 0.5 (ethyl acetate/hexanes = 1:3); mp 208−210 °C. ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 7.62 (d, J = 8.1 Hz, 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.26−7.29 (m, 2H), 7.18−7.24 (m, 3H), 7.07−7.16 (m, 9H), 6.91−6.95 (m, 1H), 6.69 (d, J = 8.1 Hz, 1H), 5.53 (d, J = 7.3 Hz, 1H), 4.03−4.07 (m, 1H), 3.74−3.84 (m, 3H), 3.73 (s, 3H), 3.47 (s, 3H), 3.38−3.43 (m, 2H), 3.20 (d, J = 15.9 Hz, 1H), 3.13 (dd, J = 14.1, 5.9 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, ppm) δ 172.3, 171.5, 144.2, 140.8, 138.3, 135.7, 133.3, 133.3, 132.8, 130.0, 128.9, 128.6, 128.0, 127.8, 127.4, 126.9, 122.5, 121.4, 120.2, 119.9, 118.9, 118.7, 111.2, 110.5, 106.7, 99.8, 61.3, 60.9, 52.0, 51.8, 46.5, 38.1, 30.4, 29.6. HRMS (ESI) calcd for $C_{38}H_{34}N2NaO_4$ 605.2411, found 605.2413.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01621.

^1H NMR and $^{13}C\{^1H\}$ NMR spectra for compounds **1**, **9**, **10**, **12** (PDF)

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Notes

The authors declare no competing financial interest.

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(15) The poor solubility of compound **1ha** decreased its yield compared to other indoles. The piperidine moiety in the amide in **1ha** significantly decreased the solubility, leading to loss of yield during the separation of **1ha**.

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