Syntheses of New Multisubstituted 1-Acylxyindole Compounds

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Abstract: The syntheses of novel 1-acetylxyindole compounds 1 and the investigations on reaction pathways are presented. Nitro ketoester substrate 2, obtained in a two-step synthetic process, underwent reduction, intramolecular addition, nucleophilic 1,5-addition, and acylation to afford 1-acetylxyindoles 1 in one pot. Based on the systematic studies, we established the optimized reaction conditions for 1 focusing on the final acylation step of the intermediate 1-hydroxyindole 8. With the optimized conditions, we succeeded in synthesizing 21 examples of new 1-acetylxyindole derivatives 1 in modest yields (Y = 24 – 35%). Among the 1-acetylxyindole compounds, 1-acetylxyindole compounds 1x were generally unstable, and their yields were relatively lower than the other 1-acetylxyindoles. We expect that a bulkier alkyl or aromatic group on R2 could stabilize the 1-acetylxyindole compounds. Significantly, one-pot reactions of a four-step sequence successfully generated compounds 1 that are all new and might be difficult to be synthesized otherwise.

Keywords: 1-hydroxyindole; 1-acetylxyindole; tin(II) chloride; conjugate nitrone; 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)

1. Introduction

The indole structure is an important component of many biologically active natural and synthetic compounds. Indeed, 1-acetylxyindole compounds are one of the N(1)-substituted indole derivatives containing an acyloxy group (-OCOR) instead of hydrogen on N(1) position (Figure 1). Among 1-acetylxyindole compounds, 1-benzoylxyindole was first reported by Acheson et al. in 1970 [1], and 1-acetylxyindole was then reported in 1974 [2]. Further, 1-hydroxyindole, 1-alkoxyindole, and 1-acetylxyindole derivatives have attracted attention by the emergence of several potent 1-hydroxyindole derivatives [3-5] and 1-methoxyindole derivatives [6,7] in natural products. Furthermore, these unique structures demonstrated potential as indole substitutes and indole precursors associated with metabolic transformations [8-10].

![Figure 1](https://creativ commons.org/licenses/by/4.0/)
due to the instability of 1-hydroxyindole compounds [10,18], studies on synthetic methods and their derivatization have not been extensively explored. Somei et al. developed a synthetic method for structurally concise 1-hydroxyindoles by oxidation of 2,3-dihydroindoles with a catalytic amount of sodium tungstate (Na$_2$WO$_4$) [19,20]. Other groups employed Zn/NH$_4$Cl [2], tin chloride (SnCl$_2$) [21–23], or Pd/triethylammonium formate (TEAF) [24] for reductive cyclization to produce 1-hydroxyindole moiety, and 1-Alkoxyindole compounds were also synthesized by alkylation of 1-hydroxyindoles [25] or intramolecular cyclization of methoxime structure [26]. Although a few simple 1-acyloxyindole derivatives were synthesized by alkylation of 1-hydroxyindoles [17,27–30], the generated 1-acyloxyindoles were unstable and easily hydrolyzed to afford 1-hydroxyindoles [31]. Consequently, these compounds suffer from chemical instabilities and difficult manipulation.

In this study, we aimed to create novel derivatives of multisubstituted 1-acyloxyindoles (Figure 2) with improved chemical stability and meaningful biological activity. With the nitro ketoester substrate obtained in a two-step sequence, we devised a convenient one-pot synthetic method of consecutive four-step sequence to afford the desired 1-acyloxyindole compounds 1. In addition, we expect that the compounds could serve as useful prodrugs for valuable medicinal agents or pharmacokinetic structural components for drug delivery.

![Figure 2. Structure of multisubstituted 1-acyloxyindoles 1.](image)

**Figure 2. Structure of multisubstituted 1-acyloxyindoles 1.**

**2. Results and Discussion**

**2.1. Synthesis of Conjugate Ketoester 2**

At first, we prepared the substrate 2 [25,32–34] in two-step reactions using 2-chloro-6-nitrotoluene as a starting material. For this purpose, we applied our previous procedures [32] with minor modifications. As shown in Scheme 1, 2-chloro-6-nitrotoluene 3 was reacted with dimethyloxalate in the presence of excess sodium hydride to afford 4 [32] in an excellent yield (Y = 96%). Subsequently, 4 was reacted with dimethylmethylenemimminium chloride to add a methylene group at α-carbon in 4, affording conjugate ketoester 2 [32] in a good yield (Y = 85%). The result of synthesis of 2 was slightly improved compared to the previous results [32].

![Scheme 1. Synthesis of conjugate ketoester 2.](image)

**Scheme 1. Synthesis of conjugate ketoester 2.**

**2.2. Optimization for Formation of 1-Acyloxyindoles 1**

The reactions to generate 1-acyloxyindoles 1 consist of two main parts: formation of 1-hydroxyindole intermediates 8 and formation of 1-acyloxyindoles 1 by acylation of 8. Although we previously established the reaction conditions for 1-hydroxyindoles 8 [32], re-optimization for synthesis of 1-acyloxyindoles 1 is required because the whole process, including the acylation step, needs to be carried out in one pot. With substrate 2,
we first attempted to perform systematic studies on the reaction conditions suitable for formation of 1-acyloxyindole 1. As indicated in Scheme 2, the substrate 2 was reduced to generate hydroxylamine 5, cyclized to provide hydroxyindoline 6, and dehydrated to produce conjugate nitrone 7. Then, nucleophilic 1,5-addition of alcohol to 7 produced the intermediate 1-hydroxyindole 8, and, finally, acylation of 8 afforded 1-acyloxyindole 1.

![Scheme 2](image)

**Scheme 2.** Proposed scheme for synthesis of multisubstituted 1-acyloxyindoles 1.

In particular, as a base for the acylation reaction, we tested several reagents, such as K₂CO₃, triethylamine (TEA), N,N-diisopropylethylamine (DIEA), 4-dimethylaminopyridine (DMAP), and 1,8-diazabicyclo [5.4.0]undece-7-ene (DBU). Among them, DBU provided the best results (data not shown), which are consistent with our previous reports [25]. Thus, we chose DBU for our purpose. Optimization of the reaction conditions was performed by varying the amount of SnCl₂·2H₂O, DBU, alcohol (R¹OH), and acylating agent (R²COX). SnCl₂·2H₂O, an appropriate reducing agent for aromatic nitro group [35], was applied to convert 2 to 7 (2 → 5 → 6 → 7). We used benzyl alcohol (BnOH) as a template nucleophile and pivaloyl chloride as a template acylating agent in dimethoxyethane (DME) to produce 1dy (Table 1). Considering our previous procedure for synthesis of 1-alkoxyindoles [25], we applied the range of reagents as such: SnCl₂·2H₂O 2.5–3.7 eq and DBU 10.6–15.7 eq for synthesis of 1. Here, we used an increased amount of DBU due to expected extra consumption by carboxylic acids that could be generated by partial hydrolysis of the acylating agents. At lower or higher amounts than 3.3 eq for SnCl₂·2H₂O and 14.0 eq for DBU, the product 1dy was obtained in relatively poor yields (entries 1, 2, and 7, Table 1). We also compared the yields of 1-hydroxyindole intermediate 8d by varying the amount of SnCl₂·2H₂O and found that the isolated yield of 1-hydroxyindole 8d with 3.3 eq of SnCl₂·2H₂O was better (Y = 48%) than 3.7 eq (Y = 33%) and 2.5 eq (Y = 32%)
in the case of 2.0 eq of BnOH. The orders of yields for intermediate 1-hydroxyindole 8d and 1-pivaloyloxyindole 1dy were generally correlated. The amount of SnCl2·2H2O might be an important factor for construction of 1-acyloxyindole as well as 1-hydroxyindole intermediate by triggering the reduction of nitro group in 2. We further tested the amount of BnOH (1.5–3.0 eq) and pivaloyl chloride (1.5–3.0 eq). When using BnOH less than 1.5 eq, the product 1dy was obtained in poor yields (entries 3 and 4). More than 2.0 eq of BnOH and pivaloyl chloride did not seem to improve the yield (entry 6). Taken together, we chose the optimized condition for 1dy (entry 5): 1.0 eq of 2, 3.3 eq of SnCl2·2H2O, 2.0 eq of BnOH at 40 °C, and then 14.0 eq of DBU and 2.0 eq of pivaloyl chloride at room temperature, which was applied to all other reactions unless otherwise noted.

Table 1. Optimization of the reaction conditions for 1dy.

| Entry | SnCl2·2H2O (eq) | BnOH (eq) | DBU (eq) | Pivaloyl Chloride (eq) | Yield (%) |
|-------|-----------------|-----------|----------|----------------------|-----------|
| 1     | 2.5             | 2.0       | 10.6     | 2.0                  | 21        |
| 2     | 2.9             | 2.0       | 12.3     | 2.0                  | 27        |
| 3     | 3.3             | 1.5       | 14.0     | 1.5                  | 25        |
| 4     | 3.3             | 1.5       | 14.0     | 3.0                  | 26        |
| 5     | 3.3             | 2.0       | 14.0     | 2.0                  | 35        |
| 6     | 3.3             | 3.0       | 14.0     | 3.0                  | 35        |
| 7     | 3.7             | 2.0       | 15.7     | 2.0                  | 22        |

*a All reactions were run in 0.056 mmol scale of conjugate ketoester 2 [1.0 eq, [c] = 0.3 M] for formation of 8d in DME at 40 °C; [c] = 0.1 M at 25 °C for formation of 1dy.

2.3. Synthesis of New Derivatives of 1-Acloyxyindole 1

Under the optimized condition (entry 5, Table 1), we synthesized new 1-acloyxyindole derivatives by employing various nucleophiles and several acylating reagents (acetic anhydride and acyl chlorides) (Scheme 3). First, SnCl2·2H2O and 4Å molecular sieves were stirred in DME for 30 min at room temperature. We added alcohol and substrate 2, and then the reaction mixture was stirred at 40 °C for 1.5–3 h. After confirming that the starting material 2 was converted to 1-hydroxyindole 8 by checking TLC, we slowly added 14.0 eq of DBU with vigorous stirring. The reaction mixture was stirred for 30 min at room temperature and then acetic anhydride or acyl chloride was added in an ice bath. We kept stirring the reaction mixture at room temperature for 1.5–4 h, leading to formation of targeted 1-acloyxyindoles 1.

As acylating agents of 1-hydroxyindole intermediate 8, acetic anhydride, pivaloyl chloride, benzoyl chloride, butanoyl chloride, hexanoyl chloride, and hydrocinnamoyl chloride were employed (Table 2). For acetylation reactions, we used acetic anhydride instead of acetyl chloride due to the high reactivity and instability of acetyl chloride. For example, both acetic anhydride and acetyl chloride provided 1dx in similar yields (Y = ~30%), so we chose acetic anhydride. The yields for acetylation were generally lower than those for pivaloylation and benzoylation. For example, among 1dx, 1dy, and 1dz (entries 13–15), the yield of 1-acetoxyindole 1dx was lower than those for 1dy and 1dz with bulkier alkyl and aromatic group, respectively. Moreover, the yield of 1dw with phenethyl group (entry 12) was higher than that of 1dx. We expected that low yields of 1-acetoxyindoles might be due to the instability of the compounds and that a bulkier alkyl or aromatic group on R2 could stabilize the 1-acetoxyindole compounds. Interestingly, when
we analyzed the spectroscopic features of these compounds, we found some consistence. For example, we found that the $\delta$ values ($^{13}$C NMR) of carbonyl carbons of N-OC(O)CH$_3$ in 1-acetoxyindoles 1x were ~168.5, which means an upfield shift (~2) compared with those of carbonyl carbons in corresponding esters (R-OC(O)CH$_3$). In addition, the $\lambda_{\text{max}}$ values in UV–Vis were in the range of 229–236 nm. We also performed some of the reactions for 1du, 1dx, and 1dz in a larger scale (1.1 mmol of 2) and confirmed robust reproducibility of the established optimized conditions. Consequently, we successfully synthesized 21 new 1-acyloxyindole compounds 1 in modest yields ($Y = 24$–$35\%$).

Scheme 3. Synthesis of various 1-acyloxyindoles 1.

Table 2. Synthesis of derivatives of 1-acyloxyindole 1$^a$.

| Entry | ROH   | RCOX         | Product          | Yield (%) |
|-------|-------|--------------|------------------|-----------|
| 1     | MeOH  | acetic anhydride | 1a                | 28        |
| 2     | MeOH  | pivaloyl chloride | 1c               | 35        |
| 3     | MeOH  | benzoyl chloride | 1c               | 33        |
| 4     | n-BuOH| acetic anhydride | 1b               | 25        |
Table 2. Cont.

| Entry | ROH     | RCOX              | Product                                                        | Yield (%) |
|-------|---------|-------------------|                                                               |-----------|
| 5     | n-BuOH  | pivaloyl chloride | ![Image](1by.png)                                              | 28        |
| 6     | n-BuOH  | benzoyl chloride  | ![Image](bz.png)                                              | 32        |
| 7     | n-HexOH | acetic anhydride  | ![Image](cx.png)                                              | 27        |
| 8     | n-HexOH | pivaloyl chloride | ![Image](cy.png)                                              | 29        |
| 9     | n-HexOH | benzoyl chloride  | ![Image](cz.png)                                              | 30        |
| 10    | BnOH    | butanoyl chloride | ![Image](du.png)                                              | 26        |
| 11    | BnOH    | hexanoyl chloride | ![Image](dv.png)                                              | 30        |
| 12    | BnOH    | hydrocinnamoyl chloride | ![Image](dw.png)                                          | 32        |
| 13    | BnOH    | acetic anhydride  | ![Image](dx.png)                                              | 30        |
| 14    | BnOH    | pivaloyl chloride | ![Image](dy.png)                                              | 33        |
| 15    | BnOH    | benzoyl chloride  | ![Image](dz.png)                                              | 33        |
Furthermore, some degree of decomposition of 1-acyloxyindoles (1du, 1dv, and 1dx) with linear alkyl groups (R² = n – Pr, n – Pen, and Me) on a TLC plate was observed. Partial degradation was observed for 1-acetoxyindole 1dx within 30 min, and for 1-butanoyloxyindole 1du and 1-hexanoyloxyindole 1dv, within 2 h. However, 1-pivaloyloxyindole 1dy and 1-benzoyloxyindole 1dz were not easily decomposed on TLC. Consequently, we found that these 1-acyloxyindole compounds seem to exhibit significantly different stabilities depending on the R² in the acyl group (R²CO). Furthermore, these observations prompted us to test the stability of these compounds under hydrolysis conditions. We found that 1-butanoyloxyindole 1du and 1-acetoxyindole 1dx were easily hydrolyzed to provide 1-hydroxyindole under mildly basic conditions (data not shown). It is expected that this instability is due to the labile ester bond of NO-C(O)R². This bond seems easily cleavable in even weakly acidic or basic conditions, resulting in 1-hydroxyindole and carboxylic acids (Scheme 4). We believed that this labile ester bond might provide us with an interesting possibility of its application in a prodrug strategy, which aims to explore drug delivery by lowering the polarity of the compounds by acylation of 1-hydroxyindole. Thus, further application studies on stability are in progress.

2.4. Mechanistic Investigations on Reaction Pathways

We investigated the reaction mechanisms and pathways based on the observed products, as shown in Scheme 5. We suggest that three pathways, A₁, A₂, and B, are involved in the reaction mechanism, which derives some support from our previous work [34]. The nitro group of conjugate ketoester derivative 2 was reduced to afford hydroxylamine compound 5 (or conformer 5'). The pathways A₁ and A₂ proceeded through conformer 5, and pathway B through conformer 5'. The intramolecular addition of N-H of two conformers, 5
and 5', provided two different indoline derivatives, 6 and 10, respectively. Following dehydration of 6, it was possible to generate conjugate nitrone 7. Nucleophilic 1,5-addition of alcohol (R¹OH) produced 1-hydroxyindole 8 (Path A₁); subsequent acylation of the hydroxy group with R²COX provided 1-acyloxyindole 1. However, instead of alcohol, H₂O as a nucleophile could be added to conjugate nitrone 7 to produce dihydroxy species 9 (Path A₂). Dihydroxy compound 9 could be acylated with R²COX to provide diacylated compound 12. In the process of synthesizing 1dy, dipivaloylated compound 12 (R² = t-Bu) was obtained and identified by mass analysis (446 [M + Na⁺]). On the other hand, conformer 5' produced enolic compound 10 through intramolecular conjugate addition (aza-Michael addition) (Path B). Then, subsequent oxidative aromatization provided 1-hydroxyindole 11 [34]. Although we expected that acylation of 11 could produce 13, the acylated product 13 was difficult to be isolated and even identified. In most of the reactions in Table 2, we believed that substrate 2 proceeded through not only Path A₁ but also Path A₂ and Path B, which might explain the low yields of the products 1.

**Scheme 4.** Decomposition of 1-acyloxyindole under weakly acidic and basic conditions.

**Scheme 5.** Proposed pathways for 1, 12, and 13.
3. Experimental

3.1. General

Reagents were obtained from Sigma-Aldrich (Darmstad, Germany), Thermo Fisher (Waltham, MA, USA), and TCI (Tokyo, Japan). They were of commercial quality and used without further purification unless otherwise stated. Reactions were periodically monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (20 × 20 cm; Merck F254) (Darmstad, Germany) and visualized by UV light. Purifications were performed by preparative TLC (PTLC) and column chromatography. PTLC separations were carried out on the same silica gel plates. Column chromatography was performed using Merck silica gels (230–400 mesh) (Zvornik, Bosnia and Herzegovina). Melting points (uncorrected) were determined in Deckgläser microscope cover glasses (Lauda-Königshofen, Germany) using a Thermo Scientific 00590Q apparatus (Dubuque, Iowa, USA). 1H (300 MHz) and 13C (75 MHz) NMR spectra were obtained by a Bruker DRX 300 spectrometer (Zürich, Switzerland), and chemical shifts (δ) are expressed with respect to tetramethylsilane (TMS). NMR spectra are presented in the Supplementary Materials. Mass spectra were obtained in EI or ESI ionization modes (Agilent, Santa Clara, CA, USA). High resolution mass spectra were obtained using JEOL apparatus (Tokyo, Japan) at the Korea Basic Science Institute, Republic of Korea. HPLC analyses were performed using the following Waters Associate Units: 515 A pump, 515 B pump, dual λ absorbance 2487 detector, and COSMOSIL 5C18-AR-II Packed Column (4.6 × 250 mm) (Worcester, MA, USA). The products were analyzed using a linear gradient: from 70% A (aqueous) and 30% B (acetonitrile) for 3 min (isocratic) to 10% A and 90% B over 30 min at a flow rate of 1 mL/min with eluent monitoring at 254 nm. HPLC solvents were filtered (aqueous solution with PALL FP-450, 0.45 μm, 47 mm; acetonitrile with PALL TF-450, 0.45 μm, 47 mm) and degassed before use.

3.2. Substrate Synthesis

Methyl 3-(2′-Chloro-6′-Nitrophenyl)-2-Oxopropanoate (4) [32]

2-Chloro-6-nitrotoluene (3, 1.17 g, 6.8 mmol, 1.0 eq) and dimethyl oxalate (4.02 g, 34.0 mmol, 5.0 eq) were dissolved in anhydrous DMF (8.2 mL). To a stirred mixture of NaH (60% in mineral oil, 1.09 g, 27.2 mmol, 4.0 eq) in anhydrous DMF (4.1 mL) at 0 °C was added dropwise a solution of dimethyl oxalate and 2-chloro-6-nitrotoluene. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 4.5 h. The reaction mixture was quenched with saturated NH4Cl (15 mL) at 0 °C, extracted with methylene chloride (2 × 50 mL), and washed with H2O (2 × 50 mL). The organic layer was dried over MgSO4 and concentrated. The residue was purified by column chromatography (1:4 → 1:2 EtOAc/hexanes) to obtain compound 4 (1.68 g, 96%) as a pale-yellow solid. Spectral data are in accordance with literature information [32].

Methyl 3-(2′-chloro-6′-nitrophenyl)-2-oxobut-3-enoate (2) [32]

Ketoester (4, 1.53 g, 5.95 mmol, 1.0 eq) was dissolved in anhydrous THF (50 mL). To a stirred mixture of NaH (60% in mineral oil, 262 mg, 6.54 mmol, 1.1 eq) in anhydrous THF (100 mL) at 0 °C was added dropwise a solution of ketoester. After stirring for 1 h at 0 °C, N,N-dimethylmethylenedioimin chloride (1.85 g, 17.84 mmol, 3.0 eq) was added and the reaction mixture was stirred for 1 h at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for additional 5 h. The reaction mixture was quenched with saturated NH4Cl (10 mL) at 0 °C, extracted with EtOAc (2 × 250 mL), and washed with H2O (2 × 250 mL). The organic layer was dried over MgSO4 and concentrated. The residue was purified by column chromatography (1:4 → 1:2 EtOAc/hexanes) to obtain compound 2 (1.36 g, 85%) as a pale-yellow solid. Spectral data are in accordance with literature information [32].
3.3. General Procedure for Synthesis of 1-Acyloxyindoles 1

SnCl₂·2H₂O and 4Å molecular sieves stirred in DME for 30 min at room temperature. To a stirred mixture was added alcohol and conjugate ketoster 2. The resulting mixture was stirred for 1.5–3 h at 40 °C. After confirming that the starting material was disappeared by using TLC, DME and DBU were added and stirred strongly for 30 min at room temperature. The acetic anhydride or acyl chloride was added in ice bath and kept stirring at room temperature for 1.5–4 h until reaction ends. The reaction mixture was diluted with CH₂Cl₂ and washed with diluted water, saturated aqueous ammonium chloride, sodium bicarbonate, and brine. The organic layer was dried over MgSO₄ and concentrated. The residue was purified by preparative TLC (PTLC) and column chromatography to provide 1-acyloxyindoles 1.

Methyl 4-chloro-1-acetoxy-3-[(methoxy)methyl]-1H-indole-2-carboxylate (1ax)

Use of SnCl₂·2H₂O (82.8 mg, 0.37 mmol, 3.3 eq), methanol (9 µL, 0.22 mmol, 2.0 eq), and 2 (30 mg, 0.11 mmol, 1.0 eq) for 1.5 h at 40 °C, then use of DBU (233 µL, 1.56 mmol, 14.0 eq) and acetic anhydride (32 µL, 0.22 mmol, 2.0 eq) for 4 h in general procedure afforded the title compound 1ax (9.6 mg, 28%) as a yellow solid. Mp 104–106 °C; Rf 0.35 (1:2 EtOAc/hexanes); HPLC tR 12.1 min; UV–Vis (CH₂Cl₂) λmax 231, 232, 296 nm; ¹H NMR (300 MHz, CDCl₃) δ 7.30–7.14 (m, 3H, Ar), 5.12 (s, 2H, C(3)CH₂O), 3.95 (s, 3H, CO₂CH₃), 3.46 (s, 3H, CH₂OCH₃), 2.43 (s, 3H, OC(O)CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 164.6 (NOC(O)), 160.2 (C(3)CH₃), 137.0, 128.9, 127.0, 125.7, 123.6, 120.3, 118.3, 107.8 (Ar), 63.5 (C₂H₅OCH₃), 58.1 (C(3)CH₂O), 52.4 (CO₂CH₃), 18.2 (OC(O)CH₃); MS m/z 311 [M]+; HRMS (+ESI) calcd for C₁₄H₁₄CINO₃ [M]+ 311.0561, found 311.0559.

Methyl 4-chloro-1-pivaloyloxy-3-[(methoxy)methyl]-1H-indole-2-carboxylate (1ay)

Use of SnCl₂·2H₂O (82.8 mg, 0.37 mmol, 3.3 eq), methanol (9 µL, 0.22 mmol, 2.0 eq), and 2 (30 mg, 0.11 mmol, 1.0 eq) for 1.5 h at 40 °C, then use of DBU (233 µL, 1.56 mmol, 14.0 eq) and pivaloyl chloride (28 µL, 0.22 mmol, 2.0 eq) for 2 h in general procedure afforded the title compound 1ay (14.1 mg, 35%) as a pale-yellow solid. Mp 88–89 °C; Rf 0.28 (1:2 EtOAc/hexanes); HPLC tR 12.7 min; UV–Vis (CH₂Cl₂) λmax 235, 296 nm; ¹H NMR (300 MHz, CDCl₃) δ 7.28–7.18 (m, 3H, Ar), 7.06 (dd, J = 7.8, 0.9 Hz, 1H, Ar), 5.13 (s, 2H, C(3)CH₃), 3.92 (s, 3H, CO₂CH₃), 3.44 (s, 3H, CH₂OCH₃), 1.47 (s, 9H, C(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃) δ 175.7 (NOC(O)), 160.4 (CO₂CH₃), 136.9, 128.9, 127.1, 125.0, 123.7, 120.1, 118.2, 108.0 (Ar), 63.5 (C₂H₅OCH₃), 58.1 (C(3)CH₂O), 52.4 (CO₂CH₃), 18.2 (OC(O)CH₃); MS m/z 353 [M]+; HRMS (+ESI) calcd for C₁₇H₂₅CINO₃ [M]+ 353.1030, found 353.1028.

Methyl 4-chloro-1-benzoyloxy-3-[(methoxy)methyl]-1H-indole-2-carboxylate (1az)

Use of SnCl₂·2H₂O (82.8 mg, 0.37 mmol, 3.3 eq), methanol (9 µL, 0.22 mmol, 2.0 eq), and 2 (30 mg, 0.11 mmol, 1.0 eq) for 1.5 h at 40 °C, then use of DBU (233 µL, 1.56 mmol, 14.0 eq) and benzoyl chloride (26 µL, 0.22 mmol, 2.0 eq) for 2 h in general procedure afforded the title compound 1az (13.5 mg, 33%) as a pale-yellow solid. Mp 112–114 °C; Rf 0.39 (1:2 EtOAc/hexanes); HPLC tR 37.1 min; UV–Vis (CH₂Cl₂·2H₂O) λmax 236, 296 nm; ¹H NMR (300 MHz, CDCl₃) δ 8.22 (d, J = 7.6 Hz, 2H, Ar), 7.72 (t, J = 7.4 Hz, 1H, Ar), 7.57 (t, J = 7.7 Hz, 2H, Ar), 7.29–7.19 (m, 3H, Ar), 5.18 (s, 2H, C(3)CH₂O), 3.83 (s, 3H, CO₂CH₃), 3.48 (s, 3H, CH₂OCH₃); ¹³C NMR (75 MHz, CDCl₃) δ 164.6 (NOC(O)), 160.3 (CO₂CH₃), 137.4, 134.9, 130.6, 129.2, 128.9, 127.2, 126.4, 125.5, 123.8, 120.4, 118.8, 108.3 (Ar), 63.5 (C₂H₅OCH₃), 58.1 (C(3)CH₂O), 52.4 (CO₂CH₃); MS m/z 373 [M]+; HRMS (+ESI) calcd for C₁₉H₁₂CINO₃ [M]+ 373.0717, found 373.0718.

Methyl 4-chloro-1-acetoxy-3-[(n-butoxy)methyl]-1H-indole-2-carboxylate (1bx)

Use of SnCl₂·2H₂O (82.8 mg, 0.37 mmol, 3.3 eq), n-butanol (21 µL, 0.22 mmol, 2.0 eq), and 2 (30 mg, 0.11 mmol, 1.0 eq) for 1.5 h at 40 °C, then use of DBU (233 µL, 1.56 mmol, 14.0 eq) and acetic anhydride (32 µL, 0.22 mmol, 2.0 eq) for 2 h in general procedure afforded the title compound 1bx (9.7 mg, 25%) as a pale-yellow solid. Mp 48–50 °C;
Methyl 4-chloro-1-pivaloyloxy-3-[(n-butyloxy)methyl]-1H-indole-2-carboxylate (1by)

Use of SnCl₂·2H₂O (82.8 mg, 0.37 mmol, 3.3 eq), n-butanol (21 μL, 0.22 mmol, 2.0 eq), and 2 (30 mg, 0.11 mmol, 1.0 eq) for 1.5 h at 40 °C, then use of DBU (233 μL, 1.56 mmol, 14.0 eq) and pivaloyl chloride (28 μL, 0.22 mmol, 2.0 eq) for 2 h in general procedure afforded the title compound 1by (12.0 mg, 28%) as a pale-yellow solid. Mp 66–68 °C; Rf 0.53 (1:4 EtOAc/hexanes); HPLC τg 33.3 min; UV–Vis (CH₃CN–H₂O) λmax 211, 230, 296 nm; ¹H NMR (300 MHz, CDCl₃) δ 7.27–7.17 (m, 2H, Ar), 7.04 (d, J = 7.8 Hz, 1H, Ar), 5.13 (s, 2H, C(3)CH₂O), 3.91 (s, 3H, CO₂CH₃), 3.58 (t, J = 6.5 Hz, 2H, OCH₂CH₂), 2.68–1.32 (m, 4H, OCH₂CH₂), 1.47 (s, 9H, C(CH₃)₃), 0.89 (t, J = 7.3 Hz, 3H, O(CH₂)₂CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 175.7 (NOCC(O)), 160.3 (CO₂CH₃), 137.2, 129.0, 126.9, 125.7, 123.5, 120.4, 118.8, 107.8 (Ar), 70.3 (OCH₂CH₂), 61.9 (C(3)CH₂O), 52.3 (CO₂CH₃), 38.8 (C(CH₃)₃), 32.1 (OCH₂CH₂), 27.4 (C(CH₃)₂), 19.6 (O(CH₂)₂CH₃), 14.1 (O(CH₂)₃CH₃); MS m/z 395 [M⁺]; HRMS (+ESI) calcd for C₂₂H₂₀ClN₂O₃ [M⁺] 395.1500, found 395.1500.

Methyl 4-chloro-1-benzyloxy-3-[(n-butyloxy)methyl]-1H-indole-2-carboxylate (1bz)

Use of SnCl₂·2H₂O (82.8 mg, 0.37 mmol, 3.3 eq), n-butanol (21 μL, 0.22 mmol, 2.0 eq), and 2 (30 mg, 0.11 mmol, 1.0 eq) for 1.5 h at 40 °C, then use of DBU (233 μL, 1.56 mmol, 14.0 eq) and benzyloxy chloride (26 μL, 0.22 mmol, 2.0 eq) for 2 h in general procedure afforded the title compound 1bz (14.4 mg, 32%) as a pale-yellow solid. Mp 56–58 °C; Rf 0.38 (1:4 EtOAc/hexanes); HPLC τg 32.6 min; UV–Vis (CH₃CN–H₂O) λmax 229, 296 nm; ¹H NMR (300 MHz, CDCl₃) δ 8.22 (d, J = 7.3 Hz, 2H, Ar), 7.72 (t, J = 7.5 Hz, 1H, Ar), 7.57 (t, J = 7.8 Hz, 2H, Ar), 7.29–7.18 (m, 3H, Ar), 5.17 (s, 2H, C(3)CH₂O), 3.83 (s, 3H, CO₂CH₃), 3.62 (t, J = 6.5 Hz, 2H, OCH₂CH₂), 1.63 (quintet, J = 6.5 Hz, 2H, OCH₂CH₂), 1.41 (sextet, J = 7.2 Hz, 2H, O(CH₂)₂CH₃), 0.91 (t, J = 7.3 Hz, 3H, O(CH₂)₂CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 164.6 (NOCC(O)), 160.3 (CO₂CH₃), 137.5, 134.9, 130.6, 129.2, 129.0, 127.1, 126.3, 125.5, 123.7, 120.5, 119.2, 108.4 (Ar), 70.4 (OCH₂CH₂), 61.9 (C(3)CH₂O), 52.3 (CO₂CH₃), 32.1 (OCH₂CH₂), 19.6 (O(CH₂)₂CH₃), 14.1 (O(CH₂)₃CH₃); MS m/z 415 [M⁺]; HRMS (+ESI) calcd for C₂₂H₂₁ClN₂O₄ [M⁺] 415.1187, found 415.1185.

Methyl 4-chloro-1-acetoxy-3-[(n-hexyloxy)methyl]-1H-indole-2-carboxylate (1cx)

Use of SnCl₂·2H₂O (82.8 mg, 0.37 mmol, 3.3 eq), n-hexanol (44 μL, 0.22 mmol, 2.0 eq), and 2 (30 mg, 0.11 mmol, 1.0 eq) for 2 h at 40 °C, then use of DBU (233 μL, 1.56 mmol, 14.0 eq) and acetic anhydride (32 μL, 0.22 mmol, 2.0 eq) for 2 h in general procedure afforded the title compound 1cx (11.3 mg, 27%) as a pale-yellow solid. Mp 51–53 °C; Rf 0.26 (1:4 EtOAc/hexanes); HPLC τg 31.4 min; UV–Vis (CH₃CN–H₂O) λmax 235, 296 nm; ¹H NMR (300 MHz, CDCl₃) δ 7.29–7.19 (m, 2H, Ar), 7.14 (dd, J = 7.1, 0.9 Hz, 1H, Ar), 5.12 (s, 2H, C(3)CH₂O), 3.94 (s, 3H, CO₂CH₃), 3.58 (t, J = 6.6 Hz, 2H, OCH₂CH₂), 2.42 (s, 3H, OC(O)CH₃), 1.62 (quintet, J = 6.8 Hz, 2H, OCH₂CH₂), 1.40–1.25 (m, 6H, O(CH₂)₂CH₂), 0.86 (t, J = 6.5 Hz, 3H, O(CH₂)₂CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 168.5 (NOCC(O)), 160.4 (CO₂CH₃), 137.1, 129.0, 127.0, 125.0, 123.6, 120.3, 118.6, 108.0 (Ar), 70.7 (OCH₂CH₂), 62.0 (C(3)CH₂O), 52.4 (CO₂CH₃), 31.9 (OCH₂CH₂), 30.0 (O(CH₂)₂CH₃), 26.1 (O(CH₂)₃CH₂), 22.8 (O(CH₂)₄CH₂), 18.2 (OCH(O)CH₃), 14.3 (O(CH₂)₃CH₃); MS m/z 381 [M⁺]; HRMS (+ESI) calcd for C₁₉H₁₉ClN₂O₅ [M⁺] 381.1343, found 381.1339.

Methyl 4-chloro-1-pivaloyloxy-3-[(n-hexyloxy)methyl]-1H-indole-2-carboxylate (1cy)

Use of SnCl₂·2H₂O (82.8 mg, 0.37 mmol, 3.3 eq), n-hexanol (44 μL, 0.22 mmol, 2.0 eq), and 2 (30 mg, 0.11 mmol, 1.0 eq) for 2 h at 40 °C, then use of DBU (233 μL, 1.56 mmol, 14.0 eq)
and pivaloyl chloride (28 µL, 0.22 mmol, 2.0 eq) for 1.5 h in general procedure afforded the title compound 1cy (13.7 mg, 29%) as a pale-yellow solid. Mp 57–58 °C; Rf 0.55 (1:4 EtOAc/hexanes); HPLC tR 36.5 min; UV–Vis (CH3CN-H2O) λmax 235, 296 nm; 1H NMR (300 MHz, CDCl3) δ 7.27–7.18 (m, 2H, Ar), 7.05 (dd, J = 7.9, 0.9 Hz, 1H, Ar), 5.14 (s, 2H, C(3)CH2O), 3.92 (s, 3H, CO2CH3), 3.57 (t, J = 6.6 Hz, 2H, OCH2CH2), 1.68–1.25 (m, 8H, OCH2(CH2)4), 1.47 (s, 9H, C(CH3)3), 0.86 (t, J = 6.6 Hz, 3H, O(CH2)2CH3); 13C NMR (75 MHz, CDCl3) δ 175.6 (NOC(O)), 160.3 (CO2CH3), 137.2, 129.0, 126.9, 125.7, 123.5, 120.5, 118.8, 107.8 (Ar), 70.5 (OCH2CH2), 61.9 (C(3)CH2O), 52.2 (CO2CH3), 38.8 (C(CH3)3), 31.9 (OCH2CH2), 30.0 (O(CH2)2CH2), 27.4 (C(CH3)3), 26.1 (O(CH2)3CH2), 22.8 (O(CH2)4CH2), 14.2 (O(CH2)5CH3); MS m/z 423 [M]+; HRMS (+ESI) calcd for C22H30CINO5 [M]+ 423.1813, found 423.1815.

Methyl 4-chloro-1-benzoyloxy-3-[(n-hexyloxy)methyl]-1H-indole-2-carboxylate (1cz)

Use of SnCl2·2H2O (82.8 mg, 0.37 mmol, 3.3 eq), n-hexanol (44 µL, 0.22 mmol, 2.0 eq), and 2 (30 mg, 0.11 mmol, 1.0 eq) for 2 h at 40 °C, then use of DBU (233 µL, 1.56 mmol, 14.0 eq) and benzoyl chloride (26 µL, 0.22 mmol, 2.0 eq) for 1 h in general procedure afforded the title compound 1cz (14.2 mg, 30%) as a pale-yellow solid. Mp 62–64 °C; Rf 0.44 (1:4 EtOAc/hexanes); HPLC tR 35.4 min; UV–Vis (CH3CN-H2O) λmax 235, 296 nm; 1H NMR (300 MHz, CDCl3) δ 8.21 (d, J = 7.4 Hz, 2H, Ar), 7.72 (t, J = 7.4 Hz, 1H, Ar), 7.57 (t, J = 7.9 Hz, 2H, Ar), 7.28–7.17 (m, 3H, Ar), 5.17 (s, 2H, C(3)CH2O), 3.82 (s, 3H, CO2CH3), 3.60 (t, J = 6.6 Hz, 2H, OCH2CH2), 1.63 (quintet, J = 7.0 Hz, 2H, OCH2CH2), 1.41–1.22 (m, 6H, O(CH2)2(CH2)5), 0.86 (t, J = 6.6 Hz, 3H, O(CH2)2CH3); 13C NMR (75 MHz, CDCl3) δ 164.7 (NOC(O)), 160.4 (CO2CH3), 137.6, 134.9, 130.6, 129.2, 129.0, 127.1, 126.4, 126.0, 123.7, 120.5, 119.3, 108.3 (Ar), 70.7 (OCH2CH2), 61.9 (C(3)CH2O), 52.3 (CO2CH3), 31.9 (OCH2CH2), 30.0 (O(CH2)2CH2), 26.1 (O(CH2)3CH2), 22.9 (O(CH2)4CH2), 14.3 (O(CH2)5CH3); MS m/z 443 [M]+; HRMS (+ESI) calcd for C24H30CINO5 [M]+ 443.1500, found 443.1500.

Methyl 4-chloro-1-butanoxyloxy-3-[(benzyl(oxy)hydroxy)methyl]-1H-indole-2-carboxylate (1du)

Use of SnCl2·2H2O (138 mg, 0.62 mmol, 3.3 eq), benzyl alcohol (38 µL, 0.37 mmol, 2.0 eq), and 2 (50 mg, 0.18 mmol, 1.0 eq) for 2.5 h at 40 °C, then use of DBU (388 µL, 2.60 mmol, 14.0 eq) and butanoyl chloride (38 µL, 0.37 mmol, 2.0 eq) for 2 h in general procedure afforded the title compound 1du (20.4 mg, 26%) as a white solid. Mp 81–83 °C; Rf 0.56 (1:2 EtOAc/hexanes); HPLC tR 30.2 min; UV–Vis (CH3CN-H2O) λmax 214, 234, 297 nm; 1H NMR (300 MHz, CDCl3) δ 7.42–7.20 (m, 7H, Ar), 7.12 (d, J = 7.9 Hz, 1H, Ar), 5.20 (s, 2H, C(3)CH2O), 4.67 (s, 2H, OCH2Ph), 3.82 (s, 3H, CO2CH3), 2.68 (t, J = 7.4 Hz, 2H, OC(O)CH2), 1.86 (sextet, J = 7.4 Hz, 2H, OC(O)CH2CH2), 1.10 (t, J = 7.4 Hz, 3H, OC(O)(CH2)2CH2); 13C NMR (75 MHz, CDCl3) δ 171.2 (NOC(O)), 160.3 (CO2CH3), 138.7, 137.0, 128.9, 128.5, 128.2, 127.7, 127.0, 125.2, 123.6, 120.2, 117.9, 108.0 (Ar), 72.6 (OCH2Ph), 61.7 (C(3)CH2O), 52.3 (CO2CH3), 33.4 (O(C)H2), 18.3 (OC(O)CH2CH2), 13.9 (OC(O)(CH2)2CH2); MS m/z 415 [M]+; HRMS (+ESI) calcd for C22H22CINO5 [M]+ 415.1187, found 415.1184.

Methyl 4-chloro-1-hexanoxyloxy-3-[(benzyl(oxy)hydroxy)methyl]-1H-indole-2-carboxylate (1dv)

Use of SnCl2·2H2O (138 mg, 0.61 mmol, 3.3 eq), benzyl alcohol (38 µL, 0.37 mmol, 2.0 eq), and 2 (50 mg, 0.18 mmol, 1.0 eq) for 2.5 h at 40 °C, then use of DBU (388 µL, 2.60 mmol, 14.0 eq) and hexanoyl chloride (52 µL, 0.37 mmol, 2.0 eq) for 2 h in general procedure afforded the title compound 1dv (23.9 mg, 30%) as a pale-yellow solid. Mp 64–66 °C; Rf 0.62 (1:2 EtOAc/hexanes); HPLC tR 34.0 min; UV–Vis (CH3CN-H2O) λmax 211, 234, 296 nm; 1H NMR (300 MHz, CDCl3) δ 7.41–7.20 (m, 7H, Ar), 7.11 (dd, J = 7.9, 1.2 Hz, 1H, Ar), 5.20 (s, 2H, C(3)CH2O), 4.66 (s, 2H, OCH2Ph), 3.82 (s, 3H, CO2CH3), 2.68 (t, J = 7.5 Hz, 2H, OC(O)CH2), 1.83 (quintet, J = 7.4 Hz, 2H, OC(O)CH2CH2), 1.49–1.34 (m, 4H, OC(O)(CH2)2(CH2)2), 0.94 (t, J = 6.9 Hz, 3H, OC(O)(CH2)3(CH2)); 13C NMR (75 MHz, CDCl3) δ 171.4 (NOC(O)), 160.3 (CO2CH3), 138.7, 137.1, 129.0, 128.5, 128.2, 127.7, 127.0, 125.9, 123.6, 120.3, 118.0, 108.0 (Ar) 72.6 (OCH2Ph), 61.7 (C(3)CH2O), 52.2 (CO2CH3), 31.5 (OC(O)H2), 31.4 (OC(O)CH2CH2), 24.4 (OC(O)(CH2)2CH2), 22.4 (OC(O)(CH2)3CH2), 14.1 (OC(O)(CH2)4CH2); MS m/z 443 [M]+; HRMS (+ESI) calcd for C24H36CINO5 [M]+ 443.1500, found 443.1496.
Methyl 4-chloro-1-hydrocinnamoyloxy-3-[(benzyloxy)methyl]-1H-indole-2-carboxylate (1dw)
Use of SnCl₂·2H₂O (138 mg, 0.61 mmol, 3.5 eq), benzyl alcohol (38 µL, 0.37 mmol, 2.0 eq), and 2 (50 mg, 0.18 mmol, 1.0 eq) for 3 h at 40 °C, then use of DBU (388 µL, 2.60 mmol, 14.0 eq) and hydrocinnamolyl chloride (55 µL, 0.37 mmol, 2.0 eq) for 3 h in general procedure afforded the title compound 1dw (28.6 mg, 32%) as a pale-yellow solid. Mp 103–104 °C; Rf 0.48 (1:2 EtOAc/hexanes); HPLC tR 32.7 min; UV–Vis (CH₂CN-H₂O) λmax 211, 235, 296 nm; 1H NMR (300 MHz, CDCl₃) δ 7.41–7.14 (m, 13H, Ar), 5.19 (s, 2H, C(3)CH₂O), 4.66 (s, 2H, OCH₂Ph), 3.77 (s, 3H, CO₂CH₃), 3.14 (t, J = 7.1 Hz, 2H, (OC(O)CH₂), 3.03 (t, J = 7.1 Hz, 2H, (OC(O)CH₂CH₃); 13C NMR (75 MHz, CDCl₃) δ 170.6 (NO(C(O))), 160.3 (CO₂CH₃), 139.7, 138.7, 137.0, 129.0, 128.8, 128.5, 128.2, 127.7, 127.0, 126.9, 125.2, 125.3, 123.6, 120.2, 118.1, 108.1 (Ar), 72.6 (OCH₂Ph), 61.6 (C(3)CH₂O), 52.2 (CO₂CH₃), 33.3 (OC(O)CH₂), 30.7 (OC(O)CH₂CH₃); MS m/z 477 [M]+; HRMS (+ESI) calcd for C₂₇H₂₅ClNO₃ [M]+ 477.1343, found 477.1345.

Methyl 4-chloro-1-acetoxy-3-[(benzyloxy)methyl]-1H-indole-2-carboxylate (1dx)
Use of SnCl₂·2H₂O (82.8 mg, 0.37 mmol, 3.3 eq), benzyl alcohol (24 µL, 0.22 mmol, 2.0 eq), and 2 (30 mg, 0.11 mmol, 1.0 eq) for 2 h at 40 °C, then use of DBU (233 µL, 1.56 mmol, 14.0 eq) and acetic anhydride (32 µL, 0.22 mmol, 2.0 eq) for 2 h in general procedure afforded the title compound 1dx (13.0 mg, 30%) as a pale-yellow solid. Mp 68–69 °C; Rf 0.31 (1:2 EtOAc/hexanes); HPLC tR 26.6 min; UV–Vis (CH₂CN-H₂O) λmax 236, 299 nm; 1H NMR (300 MHz, CDCl₃) δ 7.42–7.14 (m, 8H, Ar), 5.20 (s, 2H, C(3)CH₂O), 4.67 (s, 2H, OCH₂Ph), 3.82 (s, 3H, CO₂CH₃), 2.42 (s, 3H, OC(O)CH₃); 13C NMR (75 MHz, CDCl₃) δ 168.5 (NO(C(O))), 160.4 (CO₂CH₃), 138.6, 137.0, 129.0, 128.5, 128.2, 127.7, 127.1, 125.0, 123.7, 122.0, 118.0, 108.0 (Ar), 72.6 (OCH₂Ph), 61.7 (C(3)CH₂O), 52.3 (CO₂CH₃), 18.2 (OC(O)CH₃); MS m/z 387 [M]+; HRMS (+ESI) calcd for C₂₉H₂₃ClNO₃ [M]+ 387.0874, found 387.0875.

Methyl 4-chloro-1-pivaloyloxy-3-[(benzyloxy)methyl]-1H-indole-2-carboxylate (1dy)
Use of SnCl₂·2H₂O (82.8 mg, 0.37 mmol, 3.3 eq), benzyl alcohol (24 µL, 0.22 mmol, 2.0 eq), and 2 (30 mg, 0.11 mmol, 1.0 eq) for 2 h at 40 °C, then use of DBU (233 µL, 1.56 mmol, 14.0 eq) and pivaloyl chloride (28 µL, 0.22 mmol, 2.0 eq) for 2 h in general procedure afforded the title compound 1dy (15.7 mg, 33%) as a pale-yellow solid. Mp 80–82 °C; Rf 0.65 (1:2 EtOAc/hexanes); HPLC tR 31.6 min; UV–Vis (CH₂CN-H₂O) λmax 213, 234, 296 nm; 1H NMR (300 MHz, CDCl₃) δ 7.41–7.19 (m, 7H, Ar), 7.06 (d, J = 7.7 Hz, 1H, Ar), 5.22 (s, 2H, C(3)CH₂O), 4.66 (s, 2H, OCH₂Ph), 3.82 (s, 3H, CO₂CH₃), 1.47 (s, 9H, C(CH₃)₃); 13C NMR (75 MHz, CDCl₃) δ 175.7 (NO(C(O))), 160.2 (CO₂CH₃), 138.7, 137.1, 129.0, 128.4, 128.2, 127.7, 126.9, 125.8, 123.6, 120.4, 118.2, 107.8 (Ar), 72.5 (OCH₂Ph), 61.7 (C(3)CH₂O), 52.2 (CO₂CH₃), 38.8 (OC(O)CH₃), 27.4 (OC(CH₃)₂); MS m/z 429 [M]+; HRMS (+ESI) calcd for C₂₃H₂₁ClNO₅ [M]+ 429.1343, found 429.1342.

Methyl 4-chloro-1-benzoxoxy-3-[(benzyloxy)methyl]-1H-indole-2-carboxylate (1dz)
Use of SnCl₂·2H₂O (82.8 mg, 0.37 mmol, 3.3 eq), benzyl alcohol (24 µL, 0.22 mmol, 2.0 eq), and 2 (30 mg, 0.11 mmol, 1.0 eq) for 2 h at 40 °C, then use of DBU (233 µL, 1.56 mmol, 14.0 eq) and benzoyl chloride (26 µL, 0.22 mmol, 2.0 eq) for 2 h in general procedure afforded the title compound 1dz (16.5 mg, 33%) as a pale-yellow solid. Mp 112–114 °C; Rf 0.50 (1:2 EtOAc/hexanes); HPLC tR 35.1 min; UV–Vis (CH₂CN-H₂O) λmax 235, 296 nm; 1H NMR (300 MHz, CDCl₃) δ 8.20 (d, J = 7.9 Hz, 1H, Ar), 7.70 (t, J = 7.5 Hz, 1H, Ar), 7.55 (t, J = 7.9 Hz, 2H, Ar), 7.42–7.17 (m, 8H, Ar), 5.25 (s, 2H, C(3)CH₂O), 4.68 (s, 2H, OCH₂Ph), 3.72 (s, 3H, CO₂CH₃); 13C NMR (75 MHz, CDCl₃) δ 164.6 (NO(C(O))), 160.3 (CO₂CH₃), 138.7, 137.5, 134.9, 130.6, 129.2, 129.0, 128.2, 128.1, 127.7, 127.1, 126.7, 125.6, 123.7, 120.5, 118.6, 108.3 (Ar), 72.6 (OCH₂Ph), 61.7 (C(3)CH₂O), 52.3 (CO₂CH₃); MS m/z 449 [M]+; HRMS (+ESI) calcd for C₂₉H₂₉ClNO₅ [M]+ 449.1034, found 449.1028.

Methyl 4-chloro-1-acetoxy-3-[(phenylethoxy)methyl]-1H-indole-2-carboxylate (1ex)
Use of SnCl₂·2H₂O (82.8 mg, 0.37 mmol, 3.3 eq), 2-phenylethyl alcohol (27 µL, 0.22 mmol, 2.0 eq), and 2 (30 mg, 0.11 mmol, 1.0 eq) for 2 h at 40 °C, then use of DBU (233 µL, 1.56 mmol,
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14.0 eq) and acetic anhydride (32 µL, 0.22 mmol, 2.0 eq) for 2 h in general procedure afforded the title compound 1ex (11.5 mg, 26%) as a pale-yellow solid. Mp 70–71 °C; Rf 0.21 (1:4 EtOAc/hexanes); HPLC tR 27.6 min; UV–Vis (CH3CN-H2O) λmax 211, 235, 296 nm; 1H NMR (300 MHz, CDCl3) δ 7.29–7.13 (m, 8H, Ar), 5.17 (s, 2H, C(3)(CH2)3), 3.89 (s, 3H, CO2CH3), 3.80 (t, J = 7.2 Hz, 2H, OCH2CH2), 2.94 (t, J = 7.4 Hz, 2H, OCH2CH2), 2.42 (s, 3H, OC(O)CH3); 13C NMR (75 MHz, CDCl3) δ 168.5 (NOC(O)), 160.4 (CO2CH3), 139.2, 137.0, 129.1, 129.0, 128.4, 127.0, 126.2, 125.0, 123.7, 120.2, 118.3, 108.0 (Ar), 71.4 (OCH2CH2), 62.1 (C(3)OCH3), 52.4 (CO2CH3), 36.5 (OCH2CH2), 18.2 (OC(O)CH3); MS m/z 401 [M]+; HRMS (+ESI) calcd for C21H26ClNO5 [M]+ 401.1030, found 401.1029.

Methyl 4-chloro-1-pivaloyloxy-3-[(phenylethoxy)methyl]-1H-indole-2-carboxylate (1ey)
Use of SnCl2·2H2O (82.8 mg, 0.37 mmol, 3.3 eq), 2-phenylethyl alcohol (27 µL, 0.22 mmol, 2.0 eq), and 1 (30 mg, 0.11 mmol, 1.0 eq) for 2 h at 40 °C, then use of DBU (233 µL, 1.56 mmol, 14.0 eq) and pivaloyl chloride (28 µL, 0.22 mmol, 2.0 eq) for 1.5 h in general procedure afforded the title compound 1ey (13.1 mg, 27%) as a pale-yellow solid. Mp 83–84 °C; Rf 0.59 (1:4 EtOAc/hexanes); HPLC tR 33.1 min; UV–Vis (CH3CN-H2O) λmax 212, 235, 296 nm; 1H NMR (300 MHz, CDCl3) δ 7.32–7.18 (m, 7H, Ar), 7.05 (d, J = 8.0 Hz, 1H, Ar), 5.20 (s, 2H, C(3)(CH2)3), 3.88 (s, 3H, CO2CH3), 3.80 (t, J = 7.3 Hz, 2H, OCH2CH2), 2.94 (t, J = 7.4 Hz, 2H, OCH2CH2), 1.47 (s, 9H, C(CH3)3); 13C NMR (75 MHz, CDCl3) δ 175.7 (NOC(O)), 160.3 (CO2CH3), 139.3, 137.2, 129.2, 129.0, 128.5, 127.0, 126.4, 125.9, 123.6, 120.4, 118.6, 108.1 (Ar), 71.3 (OCH2CH2), 62.1 (C(3)OCH3), 52.3 (CO2CH3), 38.8 (OC(O)CH3), 36.6 (OCH2CH2), 27.4 (OCH3CH3); MS m/z 443 [M]+; HRMS (+ESI) calcd for C24H26ClNO5 [M]+ 443.1500, found 443.1503.

Methyl 4-chloro-1-benzoyloxy-3-[(phenylethoxy)methyl]-1H-indole-2-carboxylate (1ez)
Use of SnCl2·2H2O (82.8 mg, 0.37 mmol, 3.3 eq), 2-phenylethyl alcohol (27 µL, 0.22 mmol, 2.0 eq), and 1 (30 mg, 0.11 mmol, 1.0 eq) for 1.5 h at 40 °C, then use of DBU (233 µL, 1.56 mmol, 14.0 eq) and benzoyl chloride (26 µL, 0.22 mmol, 2.0 eq) for 2 h in general procedure afforded the title compound 1ez (16.3 mg, 32%) as a pale-yellow solid. Mp 112–113 °C; Rf 0.44 (1:4 EtOAc/hexanes); HPLC tR 32.0 min; UV–Vis (CH3CN-H2O) λmax 235, 296 nm; 1H NMR (300 MHz, CDCl3) δ 8.22 (d, J = 7.2 Hz, 2H, Ar), 7.73 (t, J = 7.4 Hz, 1H, Ar), 7.58 (t, J = 7.7 Hz, 2H, Ar), 7.31–7.18 (m, 8H, Ar), 5.24 (s, 2H, C(3)(CH2)3), 3.84 (t, J = 7.4 Hz, 2H, OCH2CH2), 3.79 (s, 3H, CO2CH3), 2.97 (t, J = 7.4 Hz, 2H, OCH2CH2); 13C NMR (75 MHz, CDCl3) δ 164.6 (NOC(O)), 160.3 (CO2CH3), 139.3, 137.5, 134.9, 130.6, 129.2, 129.1, 129.0, 128.4, 127.1, 126.4, 122.5, 125.3, 123.7, 120.4, 119.0, 108.3 (Ar), 71.4 (OCH2CH2), 62.0 (C(3)OCH3), 52.3 (CO2CH3), 36.5 (OCH2CH2); MS m/z 463 [M]+; HRMS (+ESI) calcd for C26H28ClNO5 [M]+ 463.1188, found 463.1188.

Methyl 4-chloro-1-acetoxy-3-[(cyclohexyloxy)methyl]-1H-indole-2-carboxylate (1fx)
Use of SnCl2·2H2O (82.8 mg, 0.37 mmol, 3.3 eq), cyclohexanol (23 µL, 0.22 mmol, 2.0 eq), and 2 (30 mg, 0.11 mmol, 1.0 eq) for 2 h at 40 °C, then use of DBU (233 µL, 1.56 mmol, 14.0 eq) and acetic anhydride (32 µL, 0.22 mmol, 2.0 eq) for 2 h in general procedure afforded the title compound 1fx (10.2 mg, 24%) as a pale-yellow solid. Mp 80–82 °C; Rf 0.42 (1:2 EtOAc/hexanes); HPLC tR 24.9 min; UV–Vis (CH3CN-H2O) λmax 235, 296 nm; 1H NMR (300 MHz, CDCl3) δ 7.29–7.13 (m, 3H, Ar), 5.14 (s, 2H, C(3)(CH2)3), 3.94 (s, 3H, CO2CH3), 3.51–3.44 (m, 1H, OCH), 2.43 (s, 3H, OC(O)CH3), 2.06–1.25 (m, 10H, CH2(CH2)3); 13C NMR (75 MHz, CDCl3) δ 168.6 (NOC(O)), 160.4 (CO2CH3), 137.1, 129.0, 127.0, 125.0, 123.6, 120.2, 119.0, 108.0 (Ar), 77.9 (OCH), 59.4 (C(3)OCH3), 52.3 (CO2CH3), 32.6, 26.1, 24.6 (OCH2CH2CH2), 18.2 (N(1)OC(O)CH3); MS m/z 379 [M]+; HRMS (+ESI) calcd for C19H22ClNO5 [M]+ 379.1187, found 379.1183.

Methyl 4-chloro-1-pivaloyloxy-3-[(cyclohexyloxy)methyl]-1H-indole-2-carboxylate (1fy)
Use of SnCl2·2H2O (82.8 mg, 0.37 mmol, 3.3 eq), cyclohexanol (23 µL, 0.22 mmol, 2.0 eq), and 2 (30 mg, 0.11 mmol, 1.0 eq) for 2 h at 40 °C, then use of DBU (233 µL, 1.56 mmol, 14.0 eq) and pivaloyl chloride (28 µL, 0.22 mmol, 2.0 eq) for 1.5 h in general procedure afforded the title compound 1fy (13.9 mg, 30%) as a pale-yellow solid. Mp 98–100 °C;
Methyl 4-chloro-1-benzyloxy-3-[(cyclohexyloxy)methyl]-1H-indole-2-carboxylate (1fz)

Use of SnCl$_2$-2H$_2$O (82.8 mg, 0.37 mmol, 3.3 eq), cyclohexanol (23 μl, 0.22 mmol, 2.0 eq), and 2 (30 mg, 0.11 mmol, 1.0 eq) for 2 h at 40 °C, then use of DBU (233 μL, 1.56 mmol, 14.0 eq) and benzyol chloride (26 μL, 0.22 mmol, 2.0 eq) for 2 h in general procedure afforded the title compound 1fz (13.1 mg, 27%) as a pale-yellow solid. Mp 96–97 °C; R$_f$ 0.63 (1:2 EtOAc/hexanes); HPLC $t_R$ 34.7 min; UV–Vis (CH$_3$CN-H$_2$O) $\lambda_{max}$ 212, 234, 296 nm; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.24–7.15 (m, 2H, Ar), 7.01 (d, $J = 7.9$ Hz, 1H, Ar), 5.13 (s, 2H, (C(3)CH$_2$O)), 3.89 (s, 3H, CO$_2$CH$_3$), 3.48–3.41 (m, 1H, OCH), 1.44 (s, 9H, (CH$_3$)$_3$), 2.10–1.23 (m, 10H, (CH$_2$)$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 175.7 (NOC(O)), 160.3 (CO$_2$CH$_3$), 137.2, 129.0, 126.9, 125.7, 125.2, 115.0, 119.3, 107.8 (Ar), 77.7 (OCH), 59.4 (C(3)CH$_2$O), 43.2 (CO$_2$CH$_3$), 38.8 (OC(CH$_3$)$_2$), 32.6, 26.1, 25.4 (OCHCH$_2$CH$_2$CH$_3$), 27.4 (OC(CH$_3$)$_3$); MS m/z: 421 [M$^+$]; HRMS (+ESI) calcd for C$_{22}$H$_{25}$ClNO$_3$ [M$^+$]= 421.1656, found 421.1655.

4. Conclusions

We reported the studies on one-pot synthesis of new 1-acyloxyindoles 1 through four-step reactions. With substrate 2 obtained by a two-step synthetic sequence, we performed the reactions using SnCl$_2$-2H$_2$O as a reducing agent and alcohol (R$^1$OH) as a nucleophile through reduction, intramolecular addition, and nucleophilic 1,5-addition, affording intermediate 1-hydroxyindole 8. Subsequent acylation of 8 using acetic anhydride or acyl chlorides (R$^2$COX) in a basic condition provided target compound 1-acyloxyindoles 1. Optimization of the reaction conditions was established as follows: 1) conjugate ketoester 2 (1.0 eq), SnCl$_2$-2H$_2$O (3.3 eq), and ROH (2.0 eq) in DME at 40 °C; and 2) DBU (14.0 eq) and acetic anhydride or acyl chloride (2.0 eq) at room temperature. Consequently, using the optimized conditions, 21 examples of new 1-acyloxyindole derivatives were successfully synthesized in modest yields (Y = 24–35%) through one-pot reaction of a four-step sequence.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules27196769/s1, The charts for $^1$H- and $^{13}$C-NMR spectroscopies are available online.

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