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Reinvestigating the Synthesis and Characterization of Ethyl 3-[5-(2-Ethoxycarbonyl-1-methylvinyloxy)-1-methyl-1*H*-indol-3-yl]-but-2-enoate

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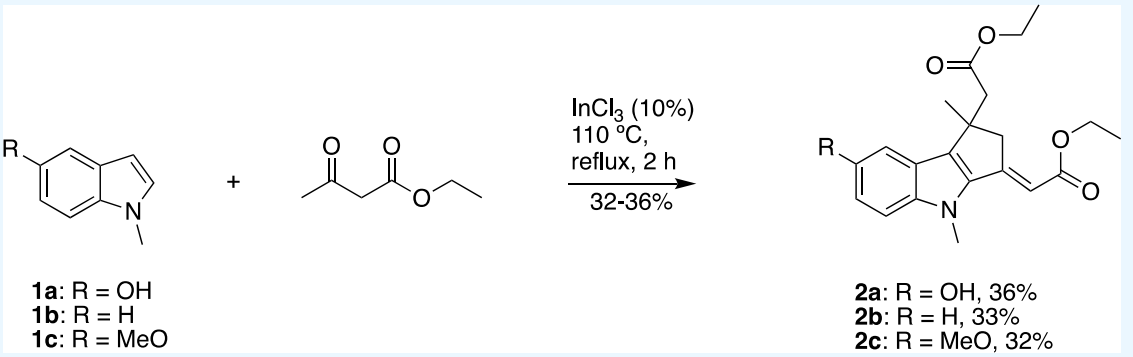

ABSTRACT: We reinvestigated the reported method for the synthesis of ethyl 3-[5-(2-ethoxycarbonyl-1-methylvinyloxy)-1-methyl-1*H*-indol-3-yl]-but-2-enoate (MIBE), which was obtained by the reaction of 5-hydroxy-1-methyl-1*H*-indole with excess ethyl acetoacetate catalyzed by indium(III) chloride. Based on the NMR and MS data, we assigned the structure of the isolated product as (3*E*)-3-(2-ethoxy-2-oxoethylidene)-1,2,3,4-tetrahydro-7-hydroxy-1,4-dimethylcyclopent[*b*]indole-1-acetate (**2a**) rather than the reported MIBE.

INTRODUCTION

The indole moiety is an important structural subunit of many natural and synthetic molecules with significant biological activity.[1−4] Accordingly, the synthesis and application of indole derivatives for drug discovery have received much attention.[5] Ethyl 3-[5-(2-ethoxycarbonyl-1-methylvinyloxy)-1-methyl-1*H*-indol-3-yl]-but-2-enoate (MIBE) was reportedly synthesized as an active antagonist ligand of both estrogen receptor α (ER_a) and GPER in breast cancer cells.[6] The compound was previously synthesized and evaluated for its inhibition of NO production, antioxidant activity, and also for its ability to inhibit in vitro the growth of human tumor cell lines.[7] In 2009, Sinicropi et al. reported the synthesis of MIBE by the reaction of 5-hydroxy-1-methyl-1*H*-indole with an excess amount of ethyl acetoacetate in the presence of catalytic amount of indium(III) chloride at reflux for 2 h (Scheme 1).[7] However, we repeated the synthesis and found that the structure of the product, deduced previously on the basis of IR, ^{1}H NMR, and MS data only,[7] was assigned incorrectly. Here, we characterize the reaction product using both 1D and 2D NMR techniques and high-resolution mass spectrometry (HRMS). The data indicate that the product is a newly substituted cyclopenta[*b*]indole derivative.

RESULTS AND DISCUSSION

Following the literature procedure,[7] we carried out the reaction of 5-hydroxy-1-methyl-1*H*-indole (**1a**) with excess amount of ethyl acetoacetate in the presence of catalytic amount of indium(III)chloride at 110 °C for 2 h. Scheme 2 shows the reaction. We obtained the main product **2a** in 36% yield and assigned the structure (Figure 1) on the basis of the following NMR data.

In the ^{1}H NMR (DMSO-d_6) of **2a**, we assigned the peak at δ 8.92 (s, 1H) as the hydroxyl proton as this peak disappeared when a few drops of D_2O were added (see the Supporting Information). ^{13}C NMR (DMSO-d_6) of **2a** showed 21 different carbons (Figure 2a); the δ 40.30 peak overlaps with the peaks of (DMSO-d_6). DEPT 135 (Figure 2b) showed four CH_2 carbons (negative peaks; C2, C14, C16, and C20), eight CH or CH_3 carbons (positive peaks; CH = C5, C6, C8, C18; CH_3 = C4, C13, C17, C21), and nine carbons without directly bonded

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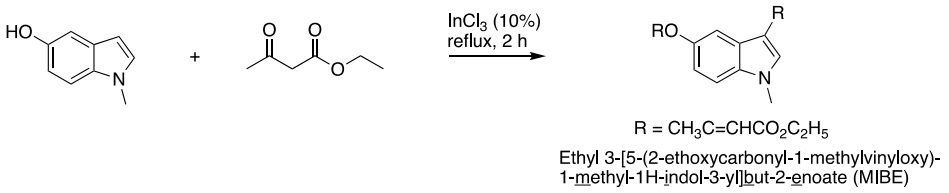
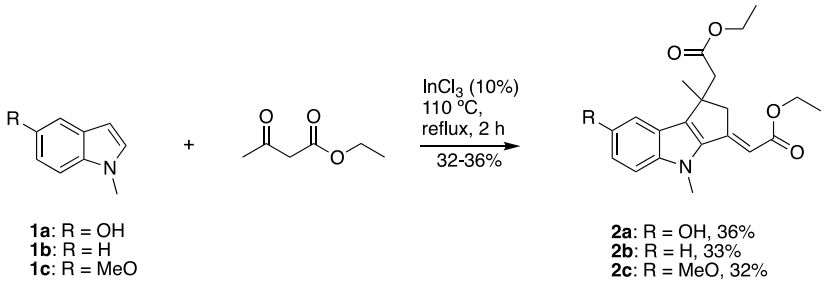
Scheme 1. The Reported Synthetic Approach to MIBE



Scheme 2. New Synthtic Approach to Substituted Cyclopenta[*b*]indole Derivatives



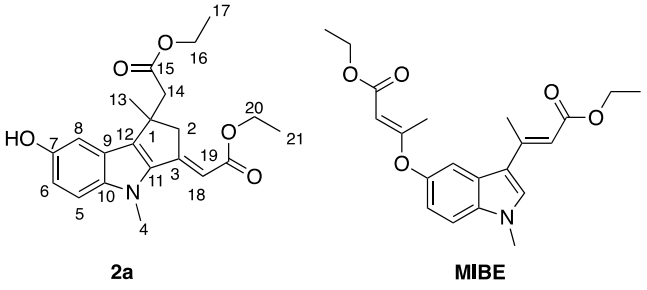


Figure 1. Structures of **2a** and the reported MIBE.

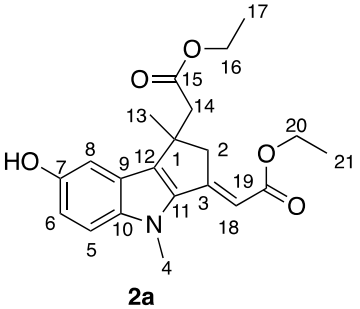
protons (absent peaks, C1, C3, C7, C9, C10, C11, C12, C15, and C19). In contrast, the reported MIBE structure would be expected to lack a D_2O-exchangeable OH proton and contain two CH_2, five CH_3, six CH, and eight carbons (C) without a directly bonded proton (Figure 1). Thus, the data support the structure assignment as **2a** but not as MIBE. COSY of **2a** (Figure 2c) indicated coupling interactions between the vinyl proton 18-H δ 6.08−6.03 (m) and methylene protons 2-H δ 3.82−3.73 (m) and 3.33−3.23 (m). We also observed a small coupling interaction between 8-H δ 6.90 (d) and 6-H δ 6.81 (dd). We recorded the C−H HMQC of **2a** and assigned all the peaks for carbons that have CH bonds (see the Supporting Information). We also recorded the C−H HMBC of **2a** and assigned peaks to the carbons that lack directly bonded protons but interact with protons within two or three bond distances (see the Supporting Information). NOSEY of **2a** (Figure 2d) revealed NOEs between 4-CH_3 δ 3.79 (s) and 5-H δ 7.32 (d); between 4-CH_3 δ 3.79 (s) and 18-H δ 6.08−6.03 (m); between 13-CH_3 δ 1.45 (s) and 8-H δ 6.90 (d); between 13-CH_3 δ 1.45 (s) and 2-H δ 3.33−3.23 (m); and between 13-CH_3 δ 1.45 (s) and 14-H δ 2.74 (d), 2.65 (d). These data confirmed the structure assignment of **2a** as depicted in Figure 1.

To test whether the hydroxyl group contributes to the formation of the observed reaction product, we carried out reactions using 1-methyl-1H-indole (**1b**) and 5-methoxy-1-methyl-1H-indole (**1c**) as starting materials and indeed obtained the corresponding cyclopenta[*b*]indole **2b** and **2c** in 33 and 32%, respectively. The structure of compound **2b** was also assigned by 1D NMRs (^{1}H, ^{13}C, DEPT 135) and 2D NMRs (COSY, HMQC, HMBC, and NOSEY). The NMRs of compound **2c** were assigned by comparison to the NMRs of compound **2a**. These results indicate that the formation of the cyclopenta[*b*]indole scaffold does not require the hydroxyl group.

Other reactions of 1-methyl-1*H*-indole with ethyl acetoacetate have been reported. Ultrasound irradiation in the presence of sulfonic acid-functionalized ionic liquids as the catalyst under solvent-free conditions gave a *bis*(indol-3-yl) derivative when excess 1-methyl-1*H*-indole was used,[8] and the same reaction catalyzed by trifluoromethanesulfonic acid gave 3-acetylindole when excess ethyl acetoacetate was used.[9] In contrast, the current reaction using indium (III) chloride as the catalyst gives a substituted cyclopenta[*b*]indole derivative. Many biologically active substances, both natural and synthetic, possess the cyclopenta[*b*]indole scaffold, which has been investigated extensively as a synthetic target.[10,11] Our results offer a new approach for synthetic access to this important scaffold.

A hypothetical mechanism for the formation of **2a** may be proposed in Scheme 3. The first step is the $InCl_3$-catalyzed 3-substitution of indole by nucleophilic addition to the carbonyl group of ethyl acetoacetate to form **I**, followed by elimination to form **II**. **II** subsequently serves as an electrophile for a nucleophilic attack by the enolate of ethyl acetoacetate to form **III**. Intramolecular nucleophilic addition to the carbonyl group followed by tandem elimination reactions form compound **2a**.

EXPERIMENTAL SECTION



2a

Ethyl (3*E*)-3-(2-Ethoxy-2-oxoethylidene)-1,2,3,4-tetrahydro-7-hydroxy-1,4-dimethylcyclopent[*b*]indole-1-ac-

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ACS Omega 2023, 8, 31941−31945

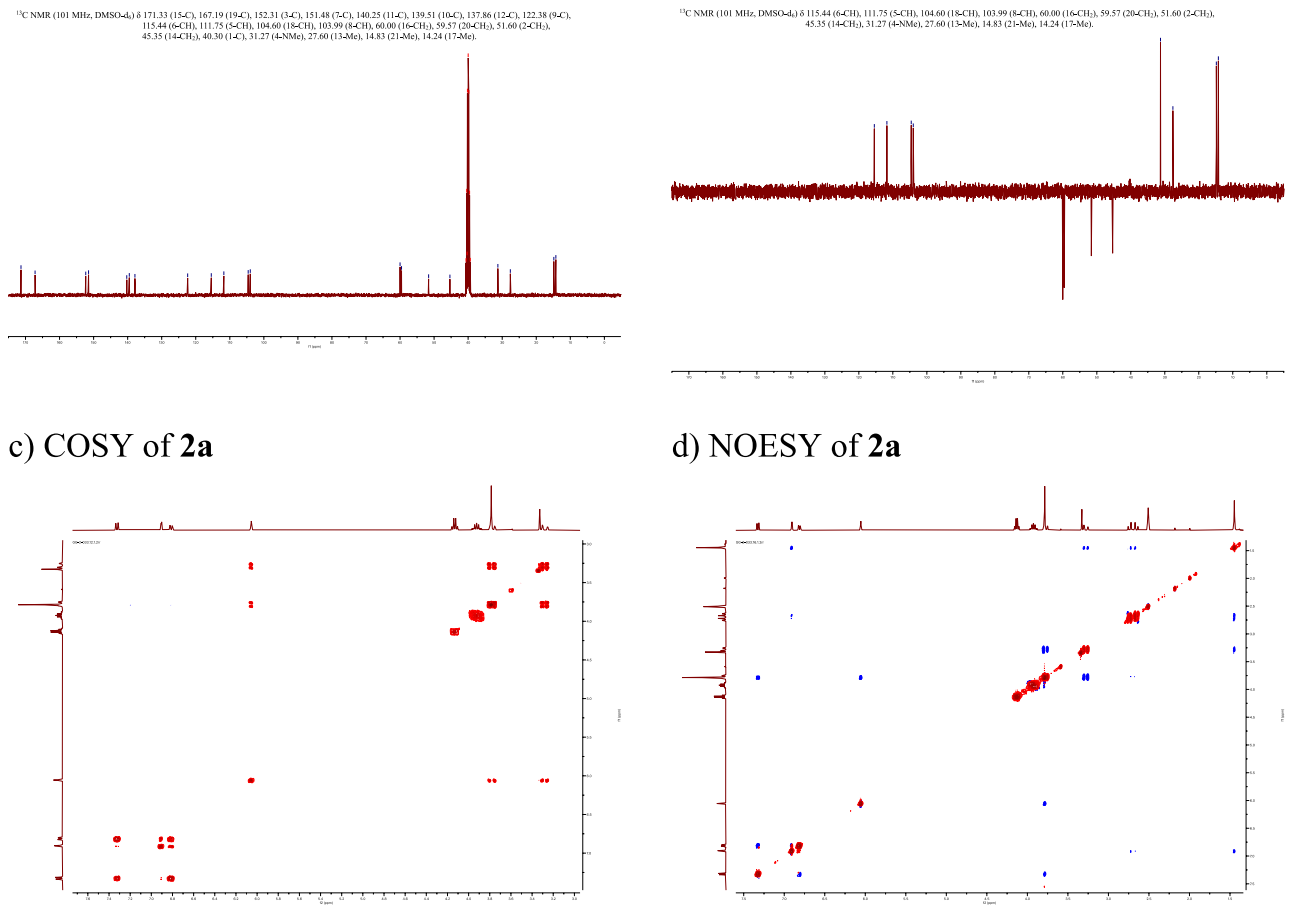
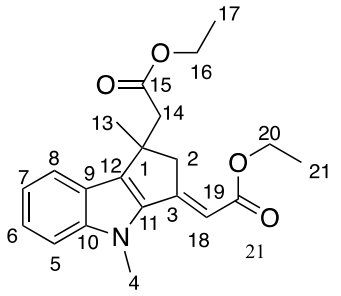


Figure 2. ^{13}C NMR (DMSO-d_6), DEPT 135, COSY, and NOESY of **2a**.

etate (2a). Indium(III)chloride (19 mg, 0.085 mmol) was added under argon to a mixture of 5-hydroxy-1-methyl-1*H*-indole (125 mg, 0.85 mmol) and ethyl acetoacetate (0.27 mL, 2.13 mmol). The reaction mixture was heated under reflux (∼110 °C) for 2 h. After it was left to cool to room temperature, ice water was added and then the reaction mixture was extracted by ethyl acetate. The organic layers were collected and washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The solid residue was further purified by silica gel chromatography, eluting with 20% ethyl acetate to give compound **2a** as an off white solid: 114 mg (36% yield). mp 178−180 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.92 (s, 1H, 7-OH), 7.32 (d, J = 8.9 Hz, 1H, 5-H), 6.90 (d, J = 2.3 Hz, 1H, 8-H), 6.81 (dd, J = 8.9, 2.3 Hz, 1H, 6-H), 6.08−6.03 (m, 1H, 18-H), 4.13 (q, J = 7.1 Hz, 2H, 20-H), 4.01−3.84 (m, 2H, 16-H), 3.82−3.73 (m, 4H, 2-H, 4-NCH_3), 3.33−3.23 (m, 1H, 2-H), 2.74 (d, J = 14.1 Hz, 1H, 14-H), 2.65 (d, J = 14.1 Hz, 1H, 14-H), 1.45 (s, 3H, 13-Me), 1.25 (t, J = 7.1 Hz, 3H, 21-Me), 0.97 (t, J = 7.1 Hz, 3H, 17-Me); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 171.33 (15-C), 167.19 (19-C), 152.31 (3-C), 151.48 (7-C), 140.25 (11-C), 139.51 (10-C), 137.86 (12-C), 122.38 (9-C), 115.44 (6-CH), 111.75 (5-CH), 104.60 (18-CH), 103.99 (8-CH), 60.00 (16-CH_2), 59.57 (20-CH_2), 51.60 (2-CH_2), 45.35 (14-CH_2), 40.30 (1-C), 31.27 (4-NMe), 27.60 (13-Me), 14.83 (21-Me), 14.24 (17-Me). HRMS (TOF, ESI/APCI) calcd for $C_{21}H_{26}NO_5$ [MH^+], 372.1811; found, 372.1810.



2b

Ethyl (3*E*)-3-(2-Ethoxy-2-oxoethylidene)-1,2,3,4-tetrahydro-1,4-dimethylcyclopent[*b*]indole-1-acetate (2b). Indium(III)chloride (84 mg, 0.38 mmol) was added under argon to a mixture of 1-methyl-1*H*-indole (500 mg, 3.80 mmol) and ethyl acetoacetate (1.2 mL, 9.5 mmol). The reaction mixture was heated under reflux (∼110 °C) for 2 h. After it was left to cool to room temperature, ice water was added and then the reaction mixture was extracted by ethyl acetate. The organic layers were collected and washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel chromatography, eluting with 10% ethyl acetate to give compound **2b**: 452 mg (33% yield). mp 112−114 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (dt, J = 8.0, 1.0 Hz, 1H, 8 H), 7.36−7.21 (m, 2H, 5-H, 6-H), 7.10 (dt, J = 8.0, 4.0 Hz, 1H, 7-H), 6.08 (t, J = 2.2 Hz, 1H, 18-H), 4.22 (q, J = 7.1 Hz, 2H, 20-H), 4.08−3.94 (m, 2H, 16-H), 3.94−3.87 (m, 1H, 2-H), 3.84 (s,

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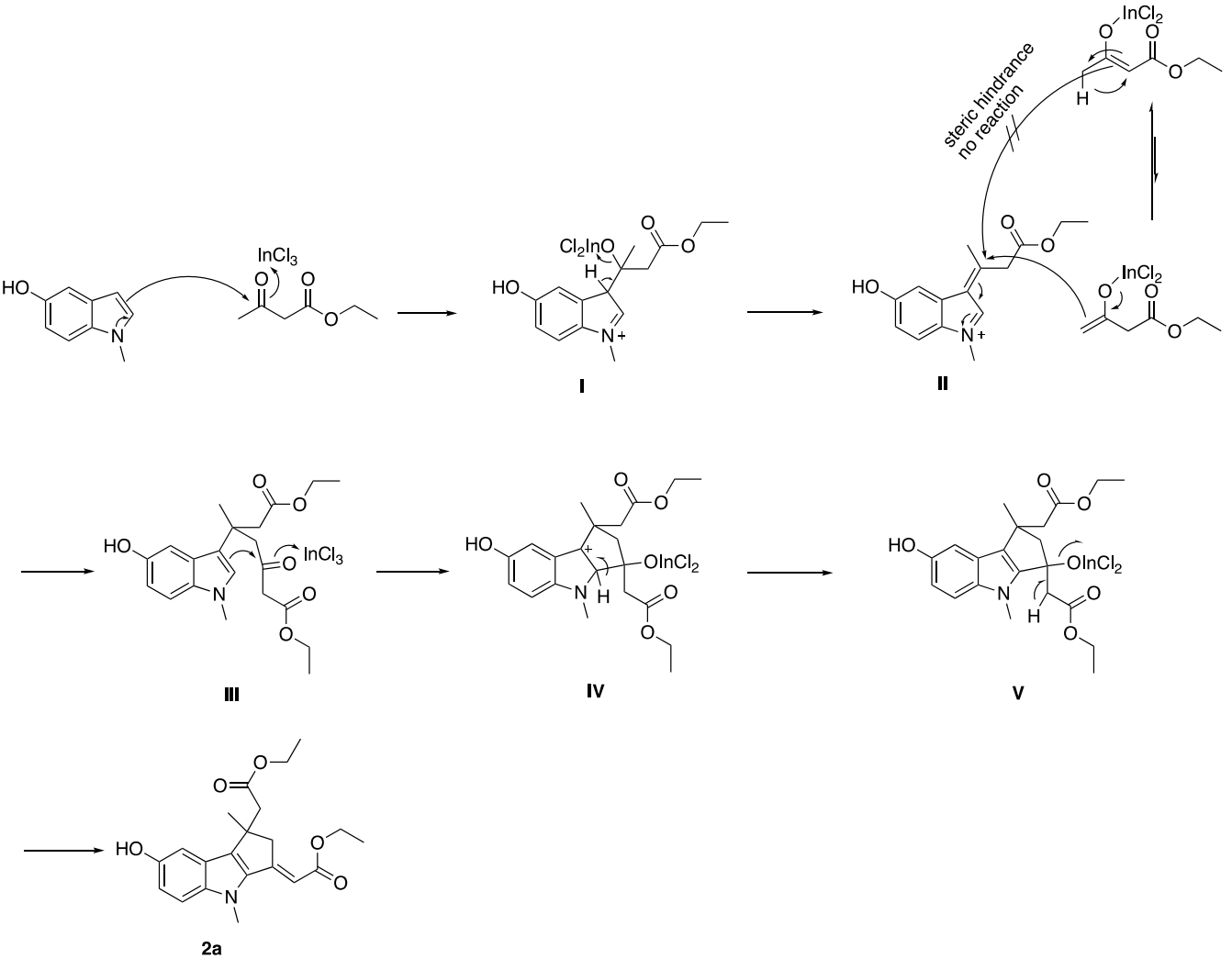
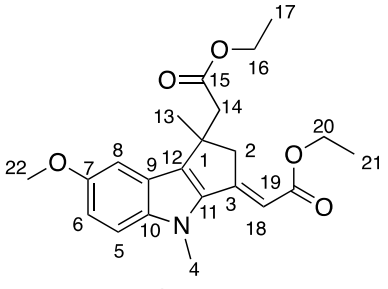
ACS Omega 2023, 8, 31941−31945

Scheme 3. A Proposed Mechanism To Form the Substituted Cyclopenta[*b*]indole Derivative



3H, 4-NMe), 3.50−3.39 (m, 1H, 2-H), 2.81 (d, J = 14.1 Hz, 1H, 14-H), 2.70 (d, J = 14.1 Hz, 1H, 14-H), 1.57 (s, 3H, 13-Me), 1.33 (t, J = 7.1 Hz, 3H, 21-Me), 1.05 (t, J = 7.1 Hz, 3H, 17-Me); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 171.44 (15-C), 167.61 (19-C), 152.24 (3-C), 144.42 (10-C), 140.25 (11-C), 139.20 (12-C), 124.41 (6-CH) 122.10 (9-C), 120.46 (8-CH), 119.87 (7-CH), 110.06 (5-CH), 105.23 (18-CH), 60.15 (16-CH_2), 59.74 (20-CH_2), 51.71 (2-CH_2), 45.82 (14-CH_2), 40.62 (1-C), 30.98 (4-NMe), 27.47 (13-Me), 14.54 (21-Me), 14.03 (17-Me). HRMS (TOF, ESI) calcd for $C_{21}H_{26}NO_4$ [MH^+], 356.1862; found, 356.1860.



2c

Ethyl (3*E*)-3-(2-Ethoxy-2-oxoethylidene)-1,2,3,4-tetrahydro-7-methoxy-1,4-dimethylcyclopent[*b*]indole-1-acetate (2c). Indium(III)chloride (15 mg, 0.068 mmol) was added under argon to a mixture of 5-methoxy-1-methyl-1*H*-indole (110 mg, 0.68 mmol) and ethyl acetoacetate (0.22 mL, 1.73 mmol). The reaction mixture was heated under reflux (∼110 °C) for 2 h. After it was left to cool to room temperature, ice water was added and then the reaction mixture was extracted by ethyl acetate. The organic layers were collected and washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel chromatography, eluting with 2% ethyl acetate in dichloromethane to give compound **2c**: 83 mg (32% yield). mp 72−74 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.22−7.15 (m, 1H, 5-H), 7.01 (d, J = 2.4 Hz, 1H, 8-H), 6.96 (dd, J = 9.0, 2.5 Hz, 1H, 6-H), 6.05 (t, J = 2.2 Hz, 1H, 18-H), 4.22 (q, J = 7.1 Hz, 2H, 20-H), 4.12−3.94 (m, 2H, 16-H), 3.93−3.86 (m, 1H, 2-H), 3.86 (s, 3H, 22-OMe), 3.82 (s, 3H, 4-NMe), 3.48−3.39 (m, 1H, 2-H), 2.80 (d, J = 14.0 Hz, 1H, 14-H), 2.69 (d, J = 14.1 Hz, 1H, 14-H), 1.57 (s, 3H, 13-Me), 1.33 (t, J = 7.1 Hz, 3H, 21-Me), 1.09 (t, J = 7.1 Hz, 3H, 17-Me); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 171.52 (15-C), 167.64 (19-C), 154.05 (3-C), 152.18 (7-C), 140.66 (11-C), 139.91 (10-C), 138.43 (12-C), 122.17 (9-C), 114.98 (6-CH), 110.83 (5-CH), 104.99 (18-CH), 101.61 (8-CH), 60.16 (16-CH_2), 59.71 (20-CH_2), 55.92(22-OMe), 51.73 (2-CH_2), 45.75 (14-CH_2), 40.49 (1-C), 31.07 (4-NMe), 27.24 (13-Me), 14.51 (21-Me), 14.05 (17-Me). HRMS (TOF, ESI/APCI) calcd for $C_{22}H_{28}NO_5$ [MH^+] 386.1967, found 386.1967.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c03686.

^{1}H NMR and ^{13}C NMR of **2a**, **2b**, and **2c**. DEPT 135, COSY, C−H HSQC, C−H HMBC, and NOSEY of **2a** and **2b** (PDF)

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Notes

The authors declare no competing financial interest.

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