One-Pot Synthesis of Highly Functionalized Oxindoles under Swern Oxidation Conditions

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Abstract: The reaction of indole derivatives bearing a 3- or 4-hydroxyalkyl chain with dimethyl sulfoxide and oxalyl chloride under Swern conditions led to a one-pot process involving three different synthetic transformations, namely oxidation of indole to oxindole, introduction of a chlorine substituent at the oxindole C-3 position, and substitution of the hydroxyl group in the side chain by chlorine. In spite of its mechanistic complexity, this synthetically useful process proceeded in good to excellent overall yield.

Key words: indoles, Swern reaction, oxindole synthesis, halogenation, oxidation

The oxindole moiety is present in large number of compounds with pharmaceutical interest, including growth hormone secretagogues,[1] Pgp-450-mediated MDR inhibitors,[2] analgesic[3] and anti-inflammatory[4] compounds, and SNC active compounds, including serotonergics[5] and the anti-Parkinson drug ropirinole.[6] The oxindole motif is also a key structural element in several bioactive natural products,[7] including the antifungal ascidian metabolite cynthichlorine,[8] the cell-cycle inhibitors spirotryprostatin A,[9] and the MDR inhibitor and antimicrotubule agent *N*-methylwelwitindolinone C isothiocyanate (welwistatin, Figure 1).[2,10] Most of these compounds bear a variety of substituents at the oxindole C-3 position and many of them, including spirotryprostatin, speradine, and welwistatin, are also functionalized at the γ-position of the chain attached to C-3.

Dimethyl sulfoxide is widely employed as an oxidant, most notably in the transformation of primary alcohols into aldehydes. The oxidation of indoles into oxindoles by dimethyl sulfoxide under acidic conditions is well known,[11,12] although this transformation is not general due to the low stability of indole derivatives in acidic media. Alternative modes of reaction are known when nucleophilic groups are present in side chains attached to the indole ring. Thus, *N*-acetyltryptophan methyl ester (**1**), upon treatment with the Swern reagent, gives a moderate yield of the tricyclic derivatives **2**, in a transformation that involves the overall oxidation at the C-2 position of indole and that was rationalized as shown in Scheme 1. When the same reaction was performed on cyclo-(L-Trp-L-Pro), a similar cyclization occurred, but a methylthiomethyl group was introduced at C-4 of indole; this side reaction could be prevented by use of DMSO–TFAA–Et_3N and by carrying out the whole procedure at –78 °C, but under these conditions the cyclization proceeded in only 12% yield.[13]

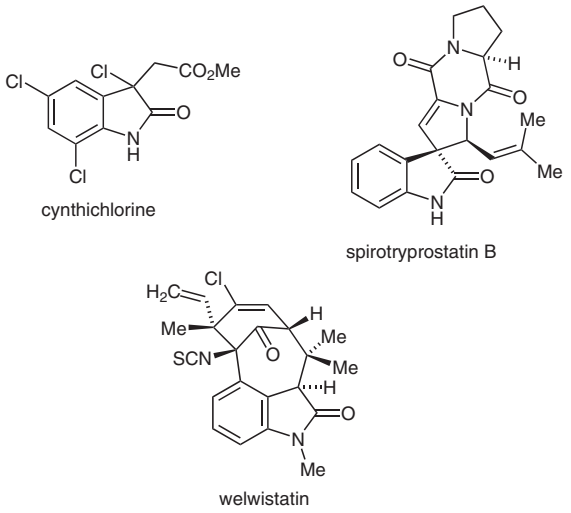
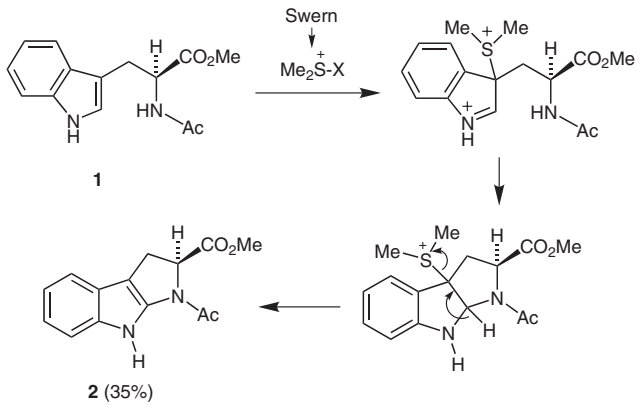


Figure 1 Some bioactive natural oxindoles

In this context, we communicate here our findings on the Swern oxidation of compounds where the side-chain nucleophile is a γ- or δ-hydroxy group and show that a reaction pathway alternative to that in Scheme 1 is possible, leading to the efficient formation of oxindole systems functionalized by chloro substituents at both the oxindole C-3 and the side-chain γ- or δ-positions.

The starting materials for our study were prepared as shown in Scheme 2. Thus, primary alcohols **6a**,**b** were ob-



Scheme 1 Literature precedent for the Swern reaction of tryptamine derivatives

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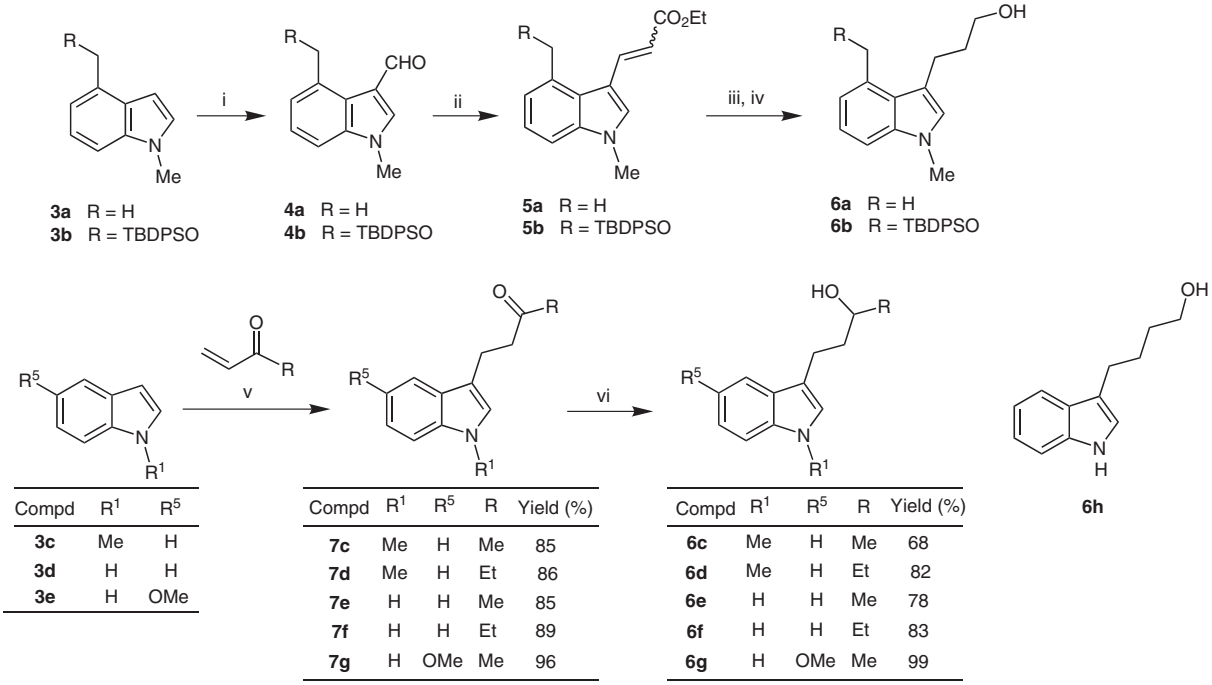


Compd	R^1	R^5
3c	Me	H
3d	H	H
3e	H	OMe

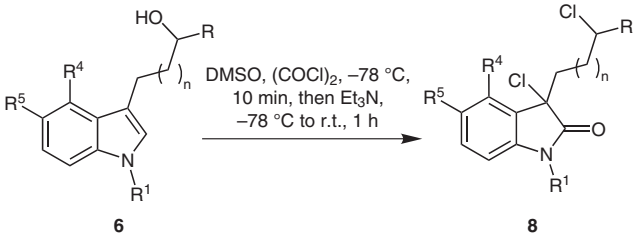
Compd	R^1	R^5	R	Yield (%)
7c	Me	H	Me	85
7d	Me	H	Et	86
7e	H	H	Me	85
7f	H	H	Et	89
7g	H	OMe	Me	96

Compd	R^1	R^5	R	Yield (%)
6c	Me	H	Me	68
6d	Me	H	Et	82
6e	H	H	Me	78
6f	H	H	Et	83
6g	H	OMe	Me	99

Scheme 2 Synthesis of starting materials. *Reagents and conditions*: i) for **3a**: $POCl_3$, DMF, 0 °C, 30 min, 0 °C to r.t., 45 min, then NaOH–H_2O (20%), pH = 8, 60 °C, 30 min, 60%; for **3b**: same conditions (58%); ii) for **4a**: $Ph_3P{=}CHCO_2Et$, EtOH, r.t., 90 min (98%, *E*/*Z* = 4:1); for **4b**: $Ph_3P{=}CHCO_2Et$, EtOH, 110 °C, 48 h (87%, *E*/*Z* = 6:1); iii) for **5a**: H_2, Pd/C, r.t., 4 h (90%); for **5b**: H_2, Pd/C, r.t., 8.5 h (100%); iv) for **5a**: $LiAlH_4$, THF, r.t., 16 h (85%); for **5b**: same conditions (88%); v) $Yb(OTf)_3$, MeCN, r.t., 16 h; vi) $NaBH_4$, EtOH, r.t., 45 min.

tained from the corresponding 3-unsubstituted indoles **3a**,**b** through a Vilsmeier formylation–Wittig olefination–reduction sequence, while the secondary alcohols **6c–g** came from a ytterbium triflate catalyzed Michael reaction[14] of indoles **3c–e** with the corresponding α,β-unsaturated ketones to give compounds **7**,[14] followed by sodium borohydride reduction. 4-(3-Indolyl)butanol **6h** was prepared by a literature method.[15]

As shown in Scheme 3 and Table 1, the reaction between 3-(3-hydroxyalkyl)indole derivatives **6a–g** and dimethyl sulfoxide under Swern conditions gave good to excellent yields of oxindole derivatives **8**, bearing chloro substituents at the C-3 position of the oxindole and at the γ- or δ-positions of the side chain.[16–18] In two examples (**c** and **d**), this product was accompanied by small amounts of the corresponding γ-oxo-3-chlorooxindoles.[19] In the cases where R was different from hydrogen (**b–g**), compounds **8** were obtained as 2:1 to 3:1 diastereomeric mixtures that could not be separated because column chromatography must be very fast in order to avoid the hydrolysis of compounds **8** into the corresponding diols.



Scheme 3 One-pot preparation of chlorooxindole derivatives

Table 1 Yields Obtained in the Chlorooxindole Synthesis

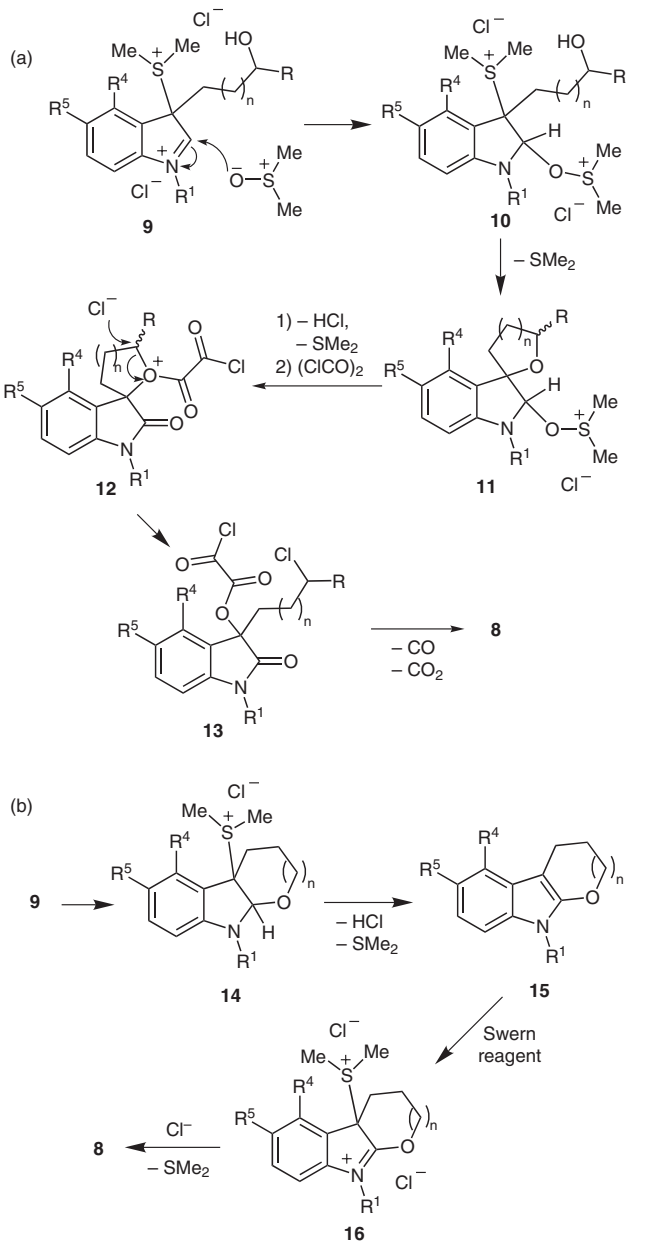
Compd	R^1	R^4	R^5	R	n	Yield (%)	dr
8a	Me	H	H	H	1	82	–
8b	Me	$TBDPSOCH_2$	H	H	1	90	–
8c	Me	H	H	Me	1	71[a]	2:1
8d	Me	H	H	Et	1	73[b]	2:1
8e	H	H	H	Me	1	80	2:1
8f	H	H	H	Et	1	87	2:1
8g	H	H	MeO	Me	1	81	3:1
8h	H	H	H	H	2	85	–

[a] Together with 15% of 3-chloro-1-methyl-3-(3-oxobutyl)oxindole.
[b] Together with 12% of 3-chloro-1-ethyl-3-(3-oxobutyl)oxindole.

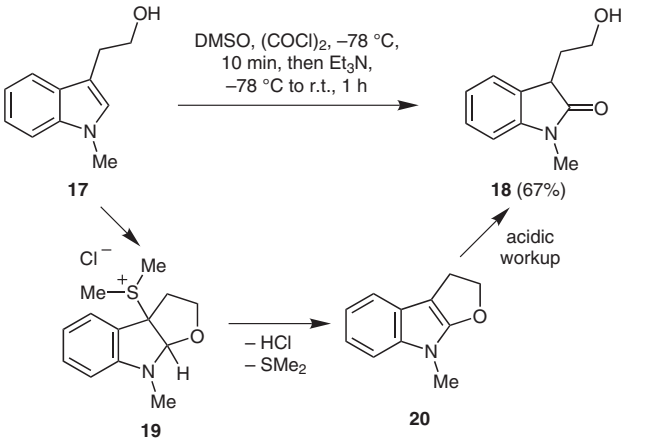
One possible rationalization for the formation of the observed products can be found in Scheme 4, (a). The initial reaction between the nucleophilic C-3 position of indoles **6** and one of the sulfonium species present in the reaction medium leads to iminium derivatives **9**, where the C-2 position is highly electrophilic and is trapped by a second molecule of dimethyl sulfoxide to give intermediates **10**. The latter compounds would yield **11** by spirocyclization,[20] thus protecting the side-chain hydroxyl group from oxidation, and then **11** would be transformed into the corresponding oxindoles by elimination of dimethyl sulfide. Subsequent evolution to the final product may then pro-

ceed by reaction of the tetrahydrofuran oxygen with one of the highly electrophilic species present in the reaction medium (e.g., oxalyl chloride) to give the oxonium derivative **12**, which then would undergo ring opening by attack of chloride anion[21] to the position adjacent to the oxonium group, giving **13**, followed by loss of carbon monoxide and carbon dioxide. An alternative pathway can be proposed [Scheme 4, (b)] involving cyclization of the side-chain oxygen onto the iminium cation function in **9** to give **14**, followed by elimination of dimethyl sulfide furnishing the fused pyrano[2,3-*b*]indole or oxepino[2,3-*b*]indole systems **15**. Further reaction of the indole C-3 position with the Swern reagent to give **16** followed by two final steps involving nucleophilic attack by chloride, namely opening of the oxygenated ring and displacement of a second molecule of dimethyl sulfide, would lead to the observed products **8**. In order to discriminate between these two proposals, we submitted 2-(1-methyl-3-indolyl)ethanol (**17**) to the Swern conditions because in this case the intermediate corresponding to **11** would have a highly strained spirooxetane structure, while that corresponding to **15** would be much more easily formed and indeed it would be an analogue of the species generated from *N*-acetyltryptamine, as previously mentioned.[13] As shown in Scheme 5, this reaction did not give a dichlorooxindole derivative, as would be expected if mechanism b was in operation, but instead afforded the known[22] compound **18** in 67% yield. The formation of **18** can be explained by the generation of **20** (analogous to **2**) by elimination of HCl and dimethyl sulfide from intermediate **19**, followed by opening of the furane ring under the acidic workup conditions. A similar acid-catalyzed ring opening has been described for the 3a-hydroxy analogue of **19**, presumably through **20** as an intermediate,[23] and also for the pyrane analogue of **20**.[18b]

In conclusion, we have developed a general, one-pot method that allows the transformation in good overall yields of 3-(3- or 4-hydroxyalkyl)indoles into oxindole derivatives with additional functionalization (chlorine substituents) at the C-3 position of the oxindole ring and at the γ- or δ-position of the side chain. The method uses Swern chemistry, which involves very mild conditions and simple and inexpensive reagents.



Scheme 4 Proposed rationalization for the chlorooxindole synthesis



Scheme 5 Swern reaction of an indole-3-ethanol derivative

Acknowledgment

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(16) **Representative Experimental Procedure**
To a solution of oxalyl chloride (5 equiv) in anhyd CH_2Cl_2 (10 mL), at –78 °C under an argon atmophere, was added DMSO (7 equiv). The solution was stirred for ca. 10 min, until effervescence ceased. A solution of alcohol **6b** (350 mg, 0.77 mmol) in anhyd CH_2Cl_2 (3 mL) was added dropwise via cannula, and the red solution was stirred for 10 min at –78 °C. Then, Et_3N (10 equiv) was added and the solution was left to warm to r.t. for 20 min, while stirred. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with sat. aq NH_4Cl (3 × 20 mL). The organic layer was dried (Na_2SO_4) and evaporated, and the residue was purified by rapid chromatography on silica gel, eluting with PE–EtOAc mixtures (gradient from 20:1 to 5:1), to yield compound **8b** (357 mg, 90%). Slower chromatographic separation may lead to considerable amounts of decomposition products, specially from hydrolysis of the terminal chloromethylene moiety.
(17) **Data for Representative Compounds 8**
Compound **8b**: IR (film on NaCl): 1731.6 (C=O), 1112.9 (C–O) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.73–7.67 (m, 4 H, H-2″,6″), 7.50–7.35 (m, 8 H, H-5,6,3″,4″,5″), 6.77 (d, 1 H, *J* = 7.6 Hz, H-7), 5.07 (d, 1 H, *J* = 14.2 Hz, CH_2O), 4.90 (d, 1 H, *J* = 14.2 Hz, CH_2O), 3.31–3.13 (m, 2 H, H-3′), 3.21 (s, 3 H, NCH_3), 2.40–2.17 (m, 2 H, H-1′), 1.43–1.28 (m, 2 H, H-2′), 1.12 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 173.2 (C-2), 142.4 (C-7a), 139.1 (C-4), 135.5 (C-2″,6″), 133.0 (C-1″), 130.5 (C-6), 129.9 (C-4″), 127.8 (C-3″,5″), 123.2 (C-3a), 121.6 (C-5), 107.4 (C-7), 64.4 (C-3), 60.9 (CH_2O), 43.6 (C-3′), 35.6 (C-1′), 27.7 (C-2′), 26.85 (NCH_3), 26.75 [$C(CH_3)_3$], 19.3 [$C(CH_3)_3$]. Anal. Calcd for $C_{29}H_{33}Cl_2NO_2Si$: C, 66.15; H, 6.32; N, 2.66. Found: C, 65.97; H, 6.02; N, 2.36.
Compound **8d** (major diastereomer, **8da**; minor diastereomer, **8db**): IR (film on NaCl): 1729.0 (C=O) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 2 H, H-4,6), 7.07 (t, 1 H, *J* = 7.6 Hz, H-5), 6.80 (d, 1 H, *J* = 7.8 Hz, H-7), 3.75–3.60 (m, 1 H, H-3′), 3.18 (m, 3 H, NCH_3), 2.70–2.10 (m, 2 H, H-1′), 1.80–1.35 (m, 4 H, H-2′, CH_2CH_3), 0.95–0.80 (m, 3 H, CH_2CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 174.1 (CO), 143.0 (C-7a, **8da**), 142.9 (C-7a, **8db**), 130.7 (C-4), 129.7 (C-3a, **8da**), 129.5 (C-3a, **8db**), 124.6 (C-6), 124.0 (C-5, **8db**), 123.9 (C-5, **8da**), 109.1 (C-7), 65.1 (C-3′, **8db**), 64.9 (C-3′, **8da**), 64.7 (C-3), 36.8 (C-1′, **8db**), 36.3 (C-1′, **8da**), 33.1 (C-2′, **8db**), 32.7 (C-2′, **8da**), 31.8 (CH_2, **8da**), 31.5 (CH_2, **8db**), 27.1 (NCH_3), 11.3 (CH_2CH_3). Anal. Calcd for $C_{14}H_{17}Cl_2NO$: C, 58.75; H, 5.99; N, 4.89. Found: C, 58.80; H, 5.91; N, 4.99.
Compound **8g** (major diastereomer, **8ga**; minor diastereomer, **8gb**): IR (film on NaCl): 3296.0 (NH), 1718.7 (C=O) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 8.96 (s, 1 H, NH, **8ga**), 8.90 (s, 1 H, NH, **8gb**), 6.96 (d, 1 H, *J* = 2.4 Hz, H-4), 6.88 (d, 1 H, *J* = 8.5 Hz, H-6), 6.82 (dd, 1 H, *J* = 8.5, 2.4 Hz, H-7), 4.05–3.85 (m, 1 H, H-3′), 3.81 (s, 3 H, OCH_3), 2.60–2.40 (m, 2 H, H-1′), 2.40–2.20 (m, 2 H, H-2′), 1.48 (d, 3 H, *J* = 6.5 Hz, CH_3, **8ga**), 1.46 (d, 3 H, *J* = 6.3 Hz, CH_3, **8gb**). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 177.1 (CO), 156.3 (C-5), 141.1 (C-7a), 134.1 (C-3a, **8gb**), 133.8 (C-3a, **8ga**), 115.7 (C-7, **8gb**), 115.5 (C-7, **8ga**), 111.8 (C-4, **8ga**), 111.5 (C-4, **8gb**), 111.3 (C-6), 68.0 (C-3), 58.2 (C-3′, **8gb**), 58.0 (C-3′, **8ga**), 56.2 (OCH_3), 36.9 (C-1′, **8gb**), 36.5 (C-1′, **8ga**), 35.1 (C-2′, **8gb**), 34.8 (C-2′, **8ga**), 25.7 (CH_3, **8gb**), 25.5 (CH_3, **8ga**). Anal. Calcd for $C_{13}H_{15}Cl_2NO_2$: C, 54.18; H, 5.25; N, 4.86. Found: C, 53.95; H, 5.12; N, 4.75.
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(19) **Data for 3-Chloro-1-methyl-3-(3-oxobutyl)oxindole**
IR (film on NaCl): 1728.2, 1717.0 (C=O) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.39 (d, 1 H, *J* = 7.6 Hz, H-4), 7.37 (t, 1 H, *J* = 7.6 Hz, H-6), 7.15 (t, 1 H, *J* = 7.6 Hz, H-5), 6.87 (d, 1 H, *J* = 7.6 Hz, H-7), 3.25 (s, 3 H, NCH_3), 2.65–2.40 (m, 4 H, H-1′,2′), 2.11 (s, 3 H, $COCH_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 206.9 (C-3′), 173.9 (C-2), 142.7 (C-7a), 130.8 (C-4), 129.8 (C-3a), 124.5 (C-6), 123.9 (C-5), 109.2 (C-7), 64.4 (C-3), 38.4 (C-2′), 33.2 (C-1′), 30.4 ($COCH_3$), 27.0 (NCH_3). MS: *m/z* = 251 [M^+]. Anal. Calcd for $C_{13}H_{14}ClNO_2$: C, 62.03; H, 5.61; N, 5.56. Found: C, 62.35; H, 5.81; N, 5.62.

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