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REGIOSELECTIVE SYNTHESIS OF 3-INDOLYL(ALKOXY)ACETATES

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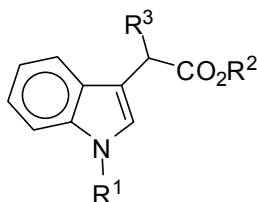
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Abstract – The regioselective synthesis of *N*-carbomethoxy-2-alkoxyindolenines and α -alkoxyindoles is reported. Bromination of indole **5** with NBS/AIBN/CCl₄ gave α -bromoindole **6** which after treatment with ROH/3Å molecular Sieves afforded (*Z*-) and (*E*)-2-alkoxyindolenines **8a-d** as the main products, together with minor amounts of α -alkoxyindoles **9a-d**. The reversed regioselectivity was achieved in the absence of molecular Sieves to give α -alkoxyindoles **9a-d** as the main products, while no traces of *Z*- or *E*-**8a-d** were detected.

INTRODUCTION

Indole-3-acetic acid (**1a**) and its derivatives **1b-e** are plant growth-regulators (auxins), among them α -methoxy derivatives **1c** and **1e** increase the physiological effectiveness and strikingly translocate in plants.¹



1a: R¹ = R² = R³ = H

1b: R¹ = R³ = H, R² = Me

1c: R¹ = H, R² = Me, R³ = OMe

1d: R¹ = Ac, R² = Me, R³ = H

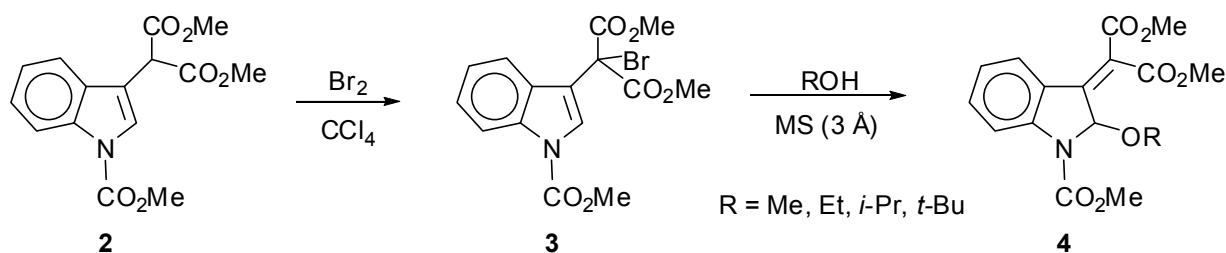
1e: R¹ = Ac, R² = Me, R³ = OMe

Hydroxylation or alkoxylation at α position of **1a,b** is achieved by oxidating reagents like DDQ,² SeO₂³ or FeCl₃,⁴ while δ -alkoxylation of tetrahydro- β -carbolines is attained by means of anodic oxidation with MeOH/HCl.⁵ It is worth noting that DDQ oxidation at α position of indoles affords the corresponding ketones² through the incorporation of hydroxyl or alkoxy groups at the α position due to selection of substrates and reaction conditions.^{2c-f} Another strategy to prepare α -hydroxyl and alkoxy derivatives is Friedel-Crafts reaction of indoles with carbonyl compounds or alkyl halides.⁶ The synthesis of α -hydroxyl indole derivatives has also been achieved by reduction of the corresponding α -carbonylindole derivatives with NaBH₄ and LiAlH₄,⁷ while two less frequently used strategies consist in the hydrolysis of α -bromoalkylindoles⁸ and in deamination or demethoxylation of the α -aminoindolyl acetates or 2-methoxyindolenines.⁹

In continuation with our studies on the bromination of indole derivatives,¹⁰ in this work we describe the easy synthesis of α -alkoxyindole-3-acetates as potential plant growth-regulators through bromination of indoles **1** and **10** with NBS/AIBN/CCl₄ followed by alkoxylation using various alcohols.

RESULTS AND DISCUSSION

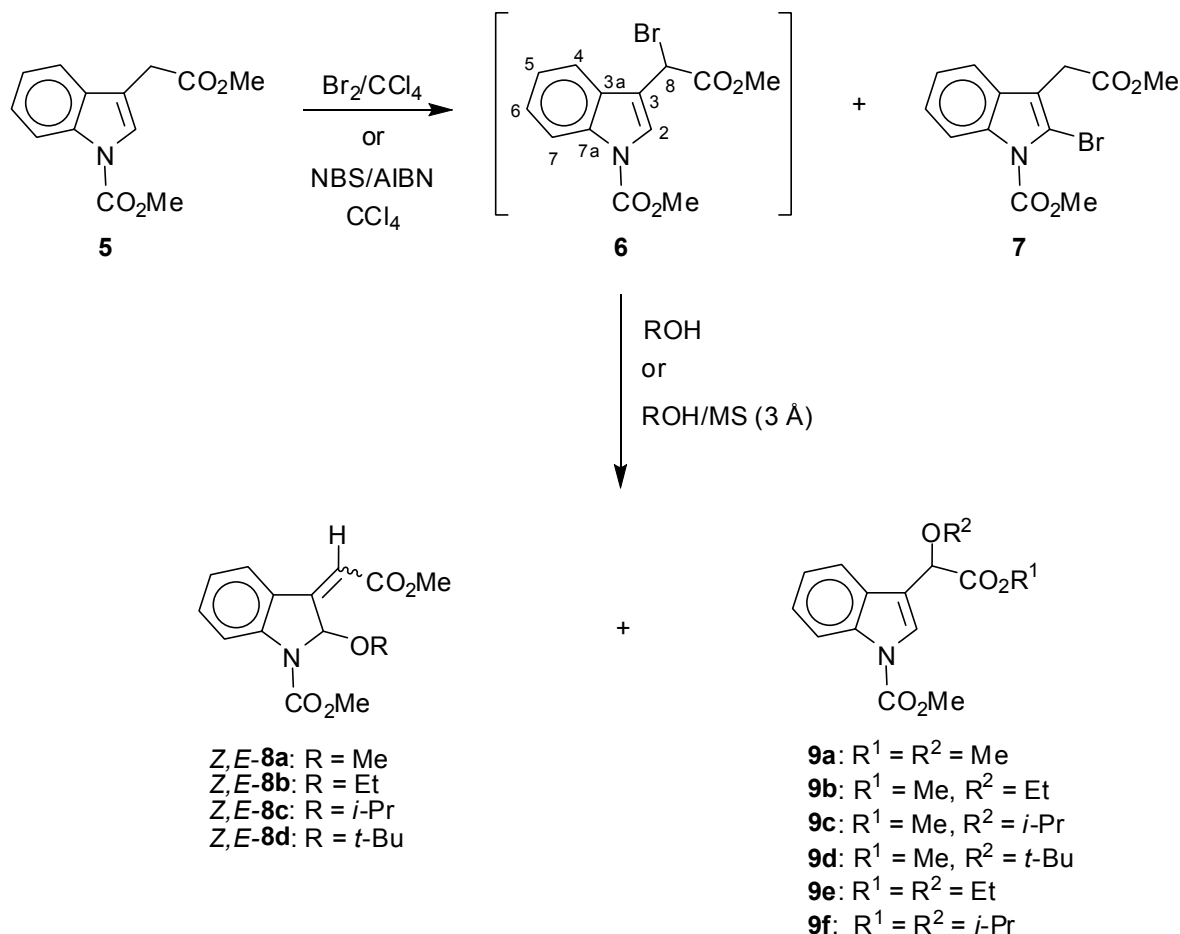
We previously reported^{10a} the bromination of indolylmalonate **2** with Br₂/CCl₄ to give indolylbromomalonate **3**, which on treatment with various alcohols in the presence of 3 Å molecular Sieves (MS) gave 2-alkoxyindolenines **4** in excellent yields through allylic substitution at the C2 position (Scheme 1).



Scheme 1

Thus, we envisioned that the less hindered methyl indolylbromoacetate **6** (Scheme 2) would allow direct substitution of the bromine atom at α position with various alcohols to give α -alkoxyindolylacetates **9**. Thus, treatment of **5** with Br₂/CCl₄ at room temperature afforded indolylbromoacetate **6**, which without isolation was treated with MeOH and 3 Å MS under reflux, whereby expected **9a** was not obtained. Instead a mixture of isomeric 2-methoxyindolenines *Z*-**8a** (26%, $\delta_{H4} = 7.51$) and *E*-**8a** (11%, $\delta_{H4} = 8.80$) was produced together with 2-bromoindolylacetate **7** (33%). This latter compound **7** was formed during

the first step by bromination of **5**. Since it is known that MS affects the reaction outcome, we decided to carry out the methoxylation of **6** in the absence of MS. Under this reaction conditions alkoxyindole **9a** was obtained in 26% yield, together with **7** in 41% yield (Table 2, entry 1). Chromatographic attempts to separate **6** from **7** resulted in decomposition of **6**.



Scheme 2. Synthesis of (*Z*)- and (*E*)-2-alkoxyindolenines **8**, and 3-indolyl(alkoxy)acetates **9**.

It follows from this result that MS promotes nucleophilic attack of MeOH at the C2 position regardless of the steric hindrance at α position in compound **6**. It is known that Faujasite zeolites behave as a nucleophile and/or a base in the presence of alkyl halides and that the Na cation present in this solid assists the C-halogen bond cleavage.¹¹ Such interaction should avoid the nucleophilic attack of MeOH at α of **6**, and as a consequence the nucleophilic attack at C2 is effected.

As the main drawback of this methodology is the low yielding of compounds **8a** or **9a** due to formation of **7** in first step, we decided to apply the bromination methodology described by Cook *et al.*¹² Thus, the use of NBS/AIBN/CCl₄ afforded compound **6**, as the main product, as evidenced by ¹H NMR analysis of the reaction crude. When **6** was reacted with MeOH in the presence of MS, a mixture of

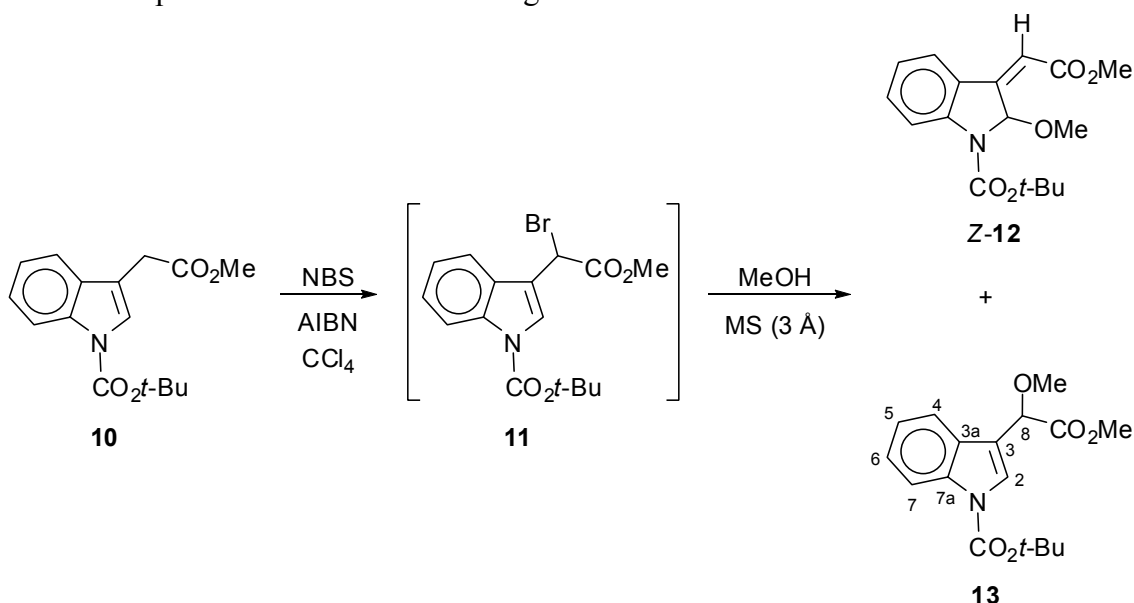
2-methoxyindolenines *Z*-**8a** ($\delta_{\text{H4}} = 7.51$) and *E*-**8a** ($\delta_{\text{H4}} = 8.80$) was obtained in 73% and 12% yield, respectively, together with α -methoxyindole **9a** in 9% yield, while the 2-bromoindolylacetate **7** was detected only in traces (Table 1, entry 2). In a similar way, treatment of **6** with EtOH, *i*-PrOH and *t*-BuOH gave the results as shown in Table 1, entries 3-5. As can be seen, the combined yields for compounds *Z*-**8b-d** and *E*-**8b-d** were gradually decreasing while the yields for compounds **9b-d** were gradually increasing. Thus nucleophilic attack at position C2 or α in indole **6** depends greatly on the steric effect of the used alcohol. As the steric effect of the alcohol increases, the steric interaction with the carbamate group becomes important, thus favoring the nucleophilic attack at position α in **6**. This assumption was demonstrated when **10**, containing the bulkier Boc group, was treated with MeOH in the presence of MS (Scheme 3) giving *Z*-**12** ($\delta_{\text{H4}} = 7.49$) in only 53% yield together with **13** in 20% yield compared to **6** (Table 1, entry 2).

Table 1. Reaction of **5** with NBS/AIBN/CCl₄, ROH/MS

Entry	ROH	Product (%)
1 ^a	MeOH	(<i>Z</i>)- 8a (26), (<i>E</i>)- 8a (11), 7 (33)
2	MeOH	(<i>Z</i>)- 8a (73), (<i>E</i>)- 8a (12), 9a (9), 7 (traces)
3	EtOH	(<i>Z</i>)- 8b (59), (<i>E</i>)- 8a (9), 9b (20)
4	<i>i</i> -PrOH	(<i>Z</i>)- 8c (24), (<i>E</i>)- 8c (16), 9c (50)
5	<i>t</i> -BuOH	(<i>Z</i>)- 8d /(<i>E</i>)- 8d (27, 1.0/0.2 ratio), 9d (41)
6 ^b	MeOH	(<i>Z</i>)- 12 (53), 13 (20)

^aReaction of **5** with Br₂/CCl₄.

^bCompound **10** was used as starting material.



Scheme 3

We next carried out the reaction of intermediate **6** with the same alcohols in the absence of MS to afford the α -alkoxylated products **9** in good yields whereby no 2-alkoxyindolenines *Z*-**8** nor *E*-**8** were detected (Table 2).

Table 2. Reaction of **5** with NBS/AIBN/CCl₄, ROH without MS

Entry	ROH	Product (%)
1 ^a	MeOH	9a (26), 7 (41)
2	MeOH	9a (85)
3	EtOH	9b (16), 9e (62)
4	<i>i</i> -PrOH	9c (50), 9f (39)
5	<i>t</i> -BuOH	9d (52)

^aReaction of **5** with Br₂/CCl₄

These reactions followed the expected reactivity, that is, as bulkier the alcohol is, as longer is the alkoxylation time of **6** (See experimental). The reaction of **6** with MeOH afforded **9a** in 85% yield (entry 2). It is worth noting that reaction of **6** with EtOH gave **9b** in 16% yield together with the transesterified product **9e** in 62% yield (Scheme 2, Table 2, entry 3), while when *i*-PrOH was used, expected **9c** was obtained in 50% yield together with the transesterified product **9f** in 39% yield (entry 4). When **6** was reacted with *t*-BuOH, **9d** was obtained in 52% yield without transesterified product (entry 5).

As described above, for the reaction of α -bromoindolylacetates **6** and **11** with alcohols, in the presence of MS, the corresponding 2-alkoxyindolenines *Z*-**8a-d** are predominantly formed over their respective isomers *E*-**8a-d**.¹³ In order to explain this result the energy characteristics for these *Z*- and *E*- isomers were calculated. A conformational search was carried out by means of systematic and Monte Carlo protocols within the Spartan 04 program¹⁴ from which the mayor conformers were further submitted to geometry optimization using DFT calculations at the B3LYP/6-31G(d) level.¹⁵ The relative energies for the mayor *Z*-**8a-d** and *E*-**8a-d** isomeric pairs are shown in Table 3.

As can be deduced from Table 3 and Figure 1, isomers *Z*-**8a-d** and *Z*-**12** are more stable by 1.58-3.21 kcal/mol, which matches very well with experimental results. On the other hand, the ¹H NMR spectra of alkoxyindolenines *Z*-**8**, *E*-**8** and **12** evidence slow rotation around the *N*-CO₂Me bond,^{10a} giving rise to the two mayor *s-cis* and *s-trans* conformers denoted by the C(7a)-N(1)-C=O torsion angle. For example, both *s-cis* and *s-trans* mayor conformers of *Z*-**12** and *E*-**12** and their DFT energies are shown in Figure 1. Compound **12** gave crystals suitable for X-ray diffraction analysis, the corresponding structure being shown in Figure 2, where it is evident that the *s-cis*-(*Z*)-**12** isomer is preferred in the crystalline state.

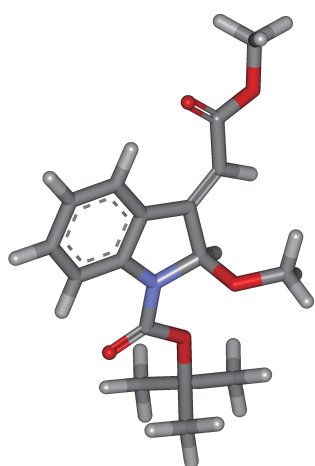
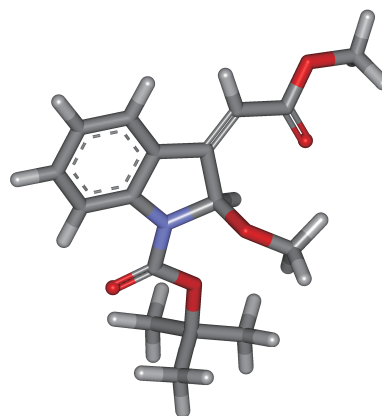
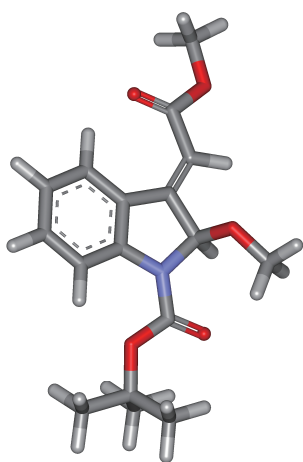
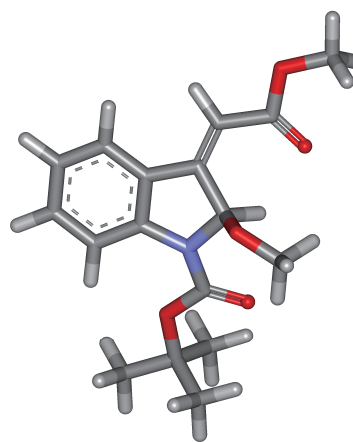
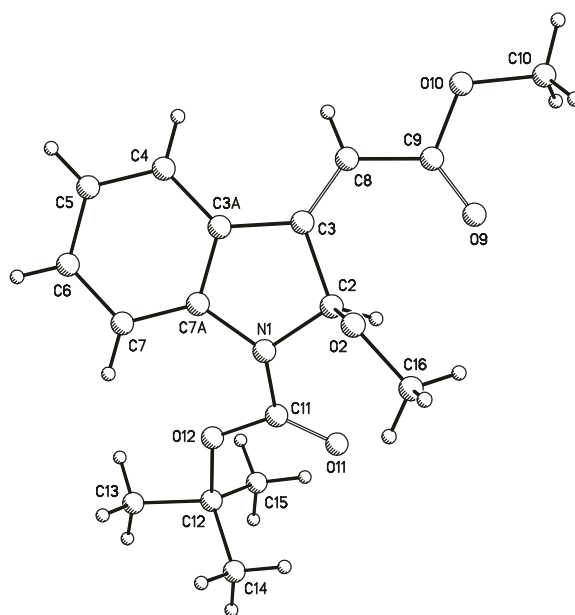
*s-trans-(E)-12* $E_{\text{DFT}} = -1091.34581$ hartree $E_{\text{rel}} = 1.68$ kcal/mol*s-trans-(Z)-12* $E_{\text{DFT}} = -1091.34820$ hartree $E_{\text{rel}} = 0.18$ kcal/mol*s-cis-(E)-12* $E_{\text{DFT}} = -1091.34597$ hartree $E_{\text{rel}} = 1.58$ kcal/mol*s-cis-(Z)-12* $E_{\text{DFT}} = -1091.34848$ hartree $E_{\text{rel}} = 0$ kcal/mol

Figure 1. Optimized geometries, calculated energies (E /kcal/mol), relative energy differences (E_{rel} /kcal/mol) for *E*-12 and *Z*-12 isomers obtained at the DFT B3LYP/6-31G(d) level of theory.

Table 3. Relative energies (kcal/mol) for the *E*- and *Z*-**8a-d** diastereomers

Isomer	<i>E</i> (kcal/mol)	<i>E</i> _{rel} (kcal/mol)
(<i>E</i>)- 8a	-610814.781	1.82
(<i>Z</i>)- 8a	-610816.601	0
(<i>E</i>)- 8b	-635488.076	2.54
(<i>Z</i>)- 8b	-635490.614	0
(<i>E</i>)- 8c	-660160.118	1.64
(<i>Z</i>)- 8c	-660161.753	0
(<i>E</i>)- 8d	-684826.883	3.21
(<i>Z</i>)- 8d	-684830.090	0

**Figure 2.** X-Ray diffraction structure of **12**.

In conclusion, we developed a simple protocol for the synthesis of 3-indolyl(alkoxy)acetates **9a-f** as potential plant growth-regulators. The procedure employs operationally facile reaction conditions, giving good yields and therefore providing advantages over those previously reported.

EXPERIMENTAL

Melting points were determined on a Büchi B-540 apparatus. IR spectra were recorded on a Perkin Elmer 2000 FT-IR spectrophotometer. The ¹H and ¹³C NMR spectra were obtained on a JEOL Eclipse 400 spectrometer using CDCl₃ as solvent and TMS as the internal reference. For complete assignments 2D NMR spectra, HMQC and HMBC were used. Chemical shifts are reported in ppm from TMS. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q =

quartet, sept = septet, br = broad, m = multiplet), coupling constant (Hz) and assignment. Low-resolution mass spectra were recorded at an ionizing voltage of 70 eV on a Hewlett Packard 5989-A spectrometer. High-resolution (HR) mass spectra were measured on a JEOL JMS-SX 102A mass spectrometer at Instituto de Química, UNAM-México. Microanalytical determinations were performed on a Perkin Elmer 2400 series PCII apparatus. Analytical thin-layer chromatography (TLC) was done on silica gel 60 F₂₅₄ coated aluminum sheets (0.25 mm thickness) with a fluorescent indicator. Visualization was accomplished with UV light (254 nm). Flash chromatography was done using silica gel 60 (230-400 mesh) from Aldrich.

General bromination-alkoxylation procedure in the presence of MS

Bromination

Method A: To a solution of **5** (0.1 g, 0.4 mmol) in CCl₄ (5 mL) was added Br₂ (0.8 mmol, 41 μL) and the resulting mixture was stirred at rt for 5 h. The mixture was treated with a saturated aqueous solution of NaHSO₃ (10 mL) and stirred during 30 min. The aqueous phase was separated and extracted with CH₂Cl₂ (10 mL) and the combined organic layer was washed with brine (2 x 10 mL), dried over Na₂SO₄, filtered and evaporated under reduced pressure, yielding a mixture of **6** (55%) and **7** (45%).

Method B: To a solution of **5** (0.25 g, 1.01 mmol) or **10** (0.5 g, 1.73 mmol) in CCl₄ (15-20 mL) were added 2.2 equiv de NBS (0.40 g, 2.22 mmol for **5** and 0.60 g, 3.8 mmol for **10**) and 0.05 equiv de AIBN (8 mg, 0.05 mmol for **5** and 30 mg, 0.19 mmol for **10**). The mixture was heated under reflux in a nitrogen atmosphere for 2 h. After cooling to rt the reaction mixture was washed with brine (2 x 20 mL), dried over Na₂SO₄, filtered and evaporated under reduced pressure. Compound **5** gave **6** (87%) and **7** (13%).

Alkoxylation

To a solution of the appropriate crude products **6** or **11** (Method A or B) in 30 mL of the corresponding alcohol (MeOH, EtOH, *i*-PrOH, *t*-BuOH) was added molecular Sieves (3 Å) (3.75 g for **6** and 7.5 g for **11**) and heated under reflux during 2 h (MeOH), 5 h (EtOH), 10 h (*i*-PrOH) and 16 h (*t*-BuOH) for **6**, and 3 h (MeOH) for **11**. After cooling to rt the mixture was filtrated and concentrated in vacuum. The resultant crude products **Z-8a-d**, **12** and **13** were purified by flash column chromatography on silica gel eluting with EtOAc/hexane 1:4 and with EtOAc/hexane 1:7, respectively.

Methyl Z-(1-carbomethoxy-2-methoxy-3-indolylidene)acetate (8a). Prepared from **5** as white crystals (Method A: 0.03 g, 26%, Method B: 0.204 g, 73.0%); mp 92-94 °C (EtOAc/hexane); ¹H NMR (CDCl₃, 400 MHz) δ 7.91 (1H, brs, H-7), 7.51 (1H, dd, *J* = 7.7, 0.7 Hz, H-4), 7.41 (1H, t, *J* = 7.8 Hz, H-6), 7.07 (1H, t, *J* = 7.7 Hz, H-5), 6.70 (1H, d, *J* = 1.9 Hz, H-2), 6.38 (1H, d, *J* = 1.8 Hz, H-8), 3.92 (3H, s, NCO₂CH₃), 3.82 (3H, s, CO₂CH₃), 3.50 (3H, brs, OCH₃); ¹³C NMR (CDCl₃, 100 MHz) δ 165.8

(CO₂CH₃), 153.1 (NCO₂CH₃), 150.1 (C-3), 144.5 (C-7a), 132.9 (C-6), 125.7 (C-3a), 123.4 (C-5), 121.4 (C-4), 116.0 (C-7), 111.6 (C-8), 88.7 (C-2), 55.7 (OCH₃), 53.0 (NCO₂CH₃), 51.7 (CO₂CH₃); IR (KBr) ν_{\max} 3121, 3000, 2918, 2835, 1954, 1704, 1645, 1598, 1478, 1447 cm⁻¹; EIMS m/z 277 [M⁺] (49), 262 (38), 246 (100), 230 (71), 218 (46), 159 (47), 59 (65); *Anal.* Calcd for C₁₄H₁₅NO₅: C 60.64; H 5.45; N 5.05. Found: C 60.63; H 5.48; N 4.77; FABHMRS m/z 277.0954 (calcd for C₁₄H₁₅NO₅, 277.0950).

Methyl Z-(1-carbomethoxy-2-ethoxy-3-indolylidene)acetate (8b). Prepared from **5** as white crystals (Method B: 0.174 g, 59.0%); mp 100-102 °C (EtOAc/hexane); ¹H NMR (CDCl₃, 400 MHz) δ 7.88 (1H, brs, H-7), 7.49 (1H, d, J = 7.7 Hz, H-4), 7.39 (1H, t, J = 7.9 Hz, H-6), 7.05 (1H, td, J = 7.7, 0.7 Hz, H-5), 6.70 (1H, d, J = 1.9 Hz, H-2), 6.34 (1H, d, J = 1.5 Hz, H-8), 3.91 (3H, s, NCO₂CH₃), 3.85 (2H, br, OCH₂), 3.81 (3H, s, CO₂CH₃), 1.16 (3H, t, J = 6.9 Hz, OCH₃); ¹³C NMR (CDCl₃, 100 MHz) δ 165.9 (CO₂CH₃), 153.3 (NCO₂CH₃), 150.7 (C-3), 144.5 (C-7a), 132.9 (C-6), 125.8 (C-3a), 123.5 (C-5), 121.7 (C-4), 116.4 (C-7), 111.4 (C-8), 88.5 (C-2), 65.5 (OCH₂CH₃), 53.0 (NCO₂CH₃), 51.7 (CO₂CH₃), 15.7 (CH₂CH₃); IR (KBr) ν_{\max} 3089, 2977, 2956, 2899, 1719, 1659, 1471, 1439 cm⁻¹; EIMS m/z 291 [M⁺] (42), 262 (25), 247 (63), 246 (100), 230 (63), 59 (77); *Anal.* Calcd for C₁₅H₁₇NO₅: C 61.85; H 5.88; N 4.81. Found: C 61.83; H 5.95; N 4.67. FABHMRS m/z 291.1109 (calcd for C₁₅H₁₇NO₅, 291.1107).

Methyl Z-(1-carbomethoxy-2-isopropoxy-3-indolylidene)acetate (8c). Prepared from **5** as white solid (Method B: 0.073 g, 24.0%); mp 76-78 °C (EtOAc/hexane); ¹H NMR (CDCl₃, 400 MHz) δ 7.88 (1H, brs, H-7), 7.50 (1H, d, J = 7.7 Hz, H-4), 7.40 (1H, t, J = 7.7 Hz, H-6), 7.06 (1H, t, J = 7.5 Hz, H-5), 6.83 (1H, s, H-2), 6.33 (1H, d, J = 1.5 Hz, H-8), 4.04 (1H, br, OCH(CH₃)₂), 3.88 (3H, s, NCO₂CH₃), 3.78 (3H, s, CO₂CH₃), 1.22 (3H, brs, OCH(CH₃)₂), 1.12 (3H, d, J = 6.2 Hz, OCH(CH₃)₂); ¹³C NMR (CDCl₃, 100 MHz) δ 165.8 (CO₂CH₃), 153.4 (NCO₂CH₃), 150.9 (C-3), 144.5 (C-7a), 132.7 (C-6), 126.4 (C-3a), 123.6 (C-5), 121.8 (C-4), 116.7 (C-7), 111.5 (C-8), 86.8 (C-2), 71.2 (OCH(CH₃)₂), 53.0 (NCO₂CH₃), 51.7 (CO₂CH₃), 23.9 (OCH(CH₃)₂), 22.6 (OCH(CH₃)₂); IR (film) ν_{\max} 2974, 2953, 1719, 1658, 1469, 1441 cm⁻¹; EIMS m/z 305 [M⁺] (28), 262 (13), 246 (100), 188 (36), 144 (13), 59 (8), 43 (3); FABHRMS m/z 305.1266 (calcd for C₁₆H₁₉NO₅, 305.1263).

Methyl Z-(1-carbomethoxy-2-tertbutoxy-3-indolylidene)acetate (8d). Prepared from **5** as a yellow oil (Method B: 86 mg, 27%, obtained as a mixture of *Z*-**8d**/*E*-**8d**, 1.0/0.2 ratio); ¹H NMR (CDCl₃, 400 MHz) δ 8.72 (1H, d, J = 8.1 Hz, H-4), 7.73 (1H, d, J = 8.4 Hz, H-7), 7.38 (1H, t, J = 7.9 Hz, H-6), 7.09 (1H, t, J = 7.7 Hz, H-5), 6.06 (1H, s, H-2), 6.01 (1H, s, H-8), 3.88 (3H, s, NCO₂CH₃), 3.79 (3H, s, CO₂CH₃), 1.35 (9H, s, 3CH₃); ¹³C NMR (CDCl₃, 100 MHz) δ 165.7 (CO₂CH₃), 153.5 (NCO₂CH₃), 152.4 (C-3), 146.0 (C-7a), 132.6 (C-6), 129.2 (C-4), 124.7 (C-3a), 123.6 (C-5), 116.6 (C-7), 114.8 (C-8), 87.4

(C-2), 76.7 ($C(\text{Me})_3$), 52.8 (NCO_2CH_3), 51.6 (CO_2CH_3), 28.5 (3 CH_3); IR (film) ν_{max} 2974, 2953, 2854, 1720, 1659, 1469, 1441 cm^{-1} ; EIMS m/z 319 [M^+] (38), 246 (100), 231 (52), 203 (81), 172 (66), 59 (66); FABHRMS m/z 319.1420 (calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_5$, 319.1420).

Methyl *E*-(1-carbomethoxy-2-terbutoxy-3-indolylidene)acetate (8d). Prepared from **5** as a yellow oil (Method B: 86 mg, 27%, obtained as a mixture of *Z*-**8d**/*E*-**8d**, 1.0/0.2 ratio); ^1H NMR (CDCl_3 , 400 MHz) δ 7.71 (1H, br, H-7), 7.49 (1H, d, $J = 7.7$ Hz, H-4), 7.38 (1H, t, $J = 7.8$ Hz, H-6), 7.06 (1H, t, $J = 7.7$ Hz, H-5), 6.95 (1H, s, H-2), 6.26 (1H, s, H-8), 3.88 (3H, s, NCO_2CH_3), 3.79 (3H, s, CO_2CH_3), 1.35 (9H, s, 3 CH_3); ^{13}C NMR (CDCl_3 , 100 MHz) δ 165.7 (CO_2CH_3), 153.5 (NCO_2CH_3), 152.9 (C-3), 144.4 (C-7a), 132.3 (C-6), 127.5 (C-3a), 123.8 (C-5), 121.9 (C-4), 117.8 (C-7), 110.8 (C-8), 83.8 (C-2), 76.7 ($C(\text{CH}_3)_3$), 52.8 (NCO_2CH_3), 51.6 (CO_2CH_3), 28.5 (3 CH_3); IR (film) ν_{max} 2974, 2953, 2854, 1720, 1659, 1469, 1441 cm^{-1} ; EIMS m/z 319 [M^+] (38), 246 (100), 231 (52), 203 (81), 172 (66), 59 (66); FABHRMS m/z 319.1420 (calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_5$, 319.1420).

Methyl *Z*-(1-terbutoxy-2-methoxy-3-indolylidene)acetate (12). Prepared from **10** as white crystals (0.29 g, 53%); mp 109-111 $^\circ\text{C}$ (EtOAc/hexane); ^1H NMR (CDCl_3 , 400 MHz); δ 7.84 (1H, brs H-7), 7.49 (1H, d, $J = 7.3$ Hz, H-4), 7.38 (1H, td, $J = 8.4, 1.1$ Hz, H-6), 7.03 (1H, td, $J = 7.7, 0.9$ Hz, H-5), 6.60 (1H, d, $J = 1.5$ Hz, H-2), 6.35 (1H, d, $J = 1.5$ Hz, H-8), 3.82 (3H, br, CO_2CH_3), 3.60 (3H, s, OCH_3), 1.61 (9H, s, 3 CH_3); ^{13}C NMR (CDCl_3 , 100 MHz) δ 166.1 (CO_2CH_3), 151.9 ($\text{NCO}_2t\text{-Bu}$), 151.0 (C-3), 145.0 (C-7a), 132.9 (C-6), 125.8 (C-3a), 123.2 (C-5), 121.6 (C-4), 116.4 (C-7), 111.2 (C-8), 89.2 (C-2), 82.4 ($C(\text{Me}_3)$), 57.5 (OCH_3), 51.6 (CO_2CH_3), 28.5 (3 CH_3); IR (KBr) ν_{max} 3093, 2977, 2937, 1725, 1698, 1659, 1601, 1470 cm^{-1} ; EIMS m/z 319 [M^+] (6), 187 (56), 172 (16), 160 (11), 128 (12), 57 (100); *Anal.* Calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_5$: C 63.94; H 6.63; N 4.39. Found: C 64.09; H 6.69; N 4.00.

Methyl-2-(1-carbomethoxy-3-indolyl)-2-tertbutoxyacetate (13). Prepared from **10** as a yellow oil (0.119 g, 22.0%); ^1H NMR (CDCl_3 , 400 MHz) δ 8.16 (1H, d, $J = 8.4$ Hz, H-7), 7.74 (1H, d, $J = 7.7$ Hz, H-4), 7.70 (1H, s, H-2), 7.34 (1H, td, $J = 7.9, 1.3$ Hz, H-6), 7.25 (1H, td, $J = 7.5, 1.1$ Hz, H-5), 5.06 (1H, s, H-8), 3.74 (3H, s, CO_2CH_3), 3.45 (3H, s, OCH_3), 1.67 (9H, s, 3 CH_3); ^{13}C NMR (CDCl_3 , 100 MHz) δ 170.9 (CO_2CH_3), 149.5 ($\text{NCO}_2t\text{-Bu}$), 135.8 (C-7a), 128.3 (C-3a), 125.4 (C-2), 125.0 (C-6), 123.1 (C-5), 120.2 (C-4), 115.9 (C-3), 115.4 (C-7), 84.2 ($C(\text{Me}_3)$), 76.4 (C8), 57.4 (OCH_3), 52.5 (CO_2CH_3), 28.3 (3 CH_3); IR (KBr) ν_{max} 3454, 3104, 3009, 2980, 2956, 2860, 1732, 1458, 1442, 1247 cm^{-1} ; EIMS m/z 319 [M^+] (5), 187 (100), 172 (35), 128 (68), 57 (56).

General procedure for the alkoxylation without MS

A solution of crude **6** in 25 mL of the appropriate alcohol (MeOH, EtOH, *i*-PrOH, *t*-BuOH) was heated

under reflux during 4 h (MeOH), 6 h (EtOH), 12 h (*i*-PrOH) and 36 h (*t*-BuOH). After cooling to rt the mixture was concentrated in vacuum and the resultant crude products were purified by flash column chromatography on silica gel eluting with EtOAc/hexane 1:4.

Methyl 2-(1-carbomethoxy-3-indolyl)-2-methoxyacetate (9a). Prepared from **5** as a pale yellow solid (Method A: 0.029 g, 26%, Method B: 0.238 g, 85.0%); mp 68-69 °C (EtOAc: Et₂O:hexanes); ¹H NMR (CDCl₃, 400 MHz) δ 8.18 (1H, d, *J* = 8.0 Hz, H-7), 7.75 (1H, dd, *J* = 7.9, 0.9 Hz, H-4), 7.72 (1H, s, H-2), 7.36 (1H, td, *J* = 7.9, 1.2 Hz, H-6), 7.28 (1H, td, *J* = 7.5, 1.1 Hz, H-5), 5.05 (1H, s, H-8), 4.04 (3H, s, NCO₂CH₃), 3.74 (3H, s, CO₂CH₃), 3.45 (3H, s, OCH₃); ¹³C NMR (CDCl₃, 100 MHz) δ 170.6 (CO₂CH₃), 151.2 (NCO₂CH₃), 135.7 (C-7a), 128.1 (C-3a), 125.1 (C-6), 124.9 (C-2), 123.3 (C-5), 120.3 (C-4), 116.7 (C-3), 115.2 (C-7), 76.1 (C-8), 57.3 (OCH₃), 53.9 (NCO₂CH₃), 52.4 (CO₂CH₃); IR (film) ν_{max} 3461, 3105, 2956, 2860, 1733, 1607, 1459 cm⁻¹; EIMS *m/z* 277 [M⁺] (11), 218 (100), 159 (28), 116 (13), 59 (13); *Anal.* Calcd for C₁₄H₁₅NO₅: C 60.64; H 5.45; N 5.05. Found: C 60.71; H 5.47; N 4.79. FABHRMS *m/z* 277.0945 (calcd for C₁₄H₁₅NO₅, 277.0950).

Methyl 2-(1-carbomethoxy-3-indolyl)-2-ethoxyacetate (9b). Prepared from **5** as a white solid (Method A: 0.0144 g, 12%, Method B: 0.046 g, 16.0%); mp 68-70 °C EtOAc/hexane; ¹H NMR (CDCl₃, 400 MHz) δ 8.17 (1H, brd, *J* = 8.1 Hz, H-7), 7.76 (1H, d, *J* = 7.7 Hz, H-4), 7.71 (1H, s, H-2), 7.36 (1H, td, *J* = 7.6, 1.1 Hz, H-6), 7.27 (1H, t, *J* = 7.7 Hz, H-5), 5.16 (1H, s, H-8), 4.04 (3H, s, NCO₂CH₃), 3.74 (3H, s, CO₂CH₃), 3.65 (1H, dq, *J* = 9.1, 7.0 Hz, OCH₂CH₃), 3.58 (1H, dq, *J* = 9.0, 7.0 Hz, OCH₂CH₃), 1.28 (3H, t, *J* = 6.9 Hz, OCH₂CH₃); ¹³C NMR (CDCl₃, 100 MHz) δ 171.1 (CO₂CH₃), 151.5 (NCO₂CH₃), 135.8 (C-7a), 128.4 (C-3a), 125.3 (C-6), 124.7 (C-2), 123.5 (C-5), 120.5 (C-4), 117.4 (C-3), 115.3 (C-7), 74.7 (C-8), 65.5 (OCH₂CH₃), 54.0 (NCO₂CH₃), 52.6 (CO₂CH₃), 15.3 (OCH₂CH₃); IR (film) ν_{max} 3119, 2928, 1743, 1455 cm⁻¹; EIMS *m/z* 291 [M⁺] (12), 232 (100), 204 (39), 144 (14), 117 (31), 59 (17); FABHRMS *m/z* 291.1109 (calcd for C₁₅H₁₇NO₅, 291.1107).

Methyl 2-(1-carbomethoxy-3-indolyl)-2-isopropoxyacetate (9c). Prepared from **5** as a yellow oil (Method A: 0.038 g, 31%, Method B: 0.153 g, 50%); ¹H NMR (CDCl₃, 400 MHz) δ 8.17 (1H, brd, *J* = 8.1 Hz, H-7), 7.78 (1H, dd, *J* = 6.6, 0.7 Hz, H-4), 7.70 (1H, s, H-2), 7.35 (1H, td, *J* = 7.8, 1.2 Hz, H-6), 7.27 (1H, td, *J* = 7.6, 0.9 Hz, H-5), 5.26 (1H, d, *J* = 0.7 Hz, H-8), 4.03 (3H, s, NCO₂CH₃), 3.75 (1H, sept, *J* = 6.2 Hz, OCH(CH₃)₂), 3.73 (3H, s, CO₂CH₃), 1.27, 1.22 (6H, 2d, *J* = 6.2 Hz, OCH(CH₃)₂); ¹³C NMR (CDCl₃, 100 MHz) δ 171.4 (CO₂CH₃), 151.3 (NCO₂CH₃), 135.7 (C-7a), 128.3 (C-3a), 125.0 (C-6), 124.4 (C-2), 123.2 (C-5), 120.4 (C-4), 117.8 (C-3), 115.2 (C-7), 72.2 (C-8), 70.9 (OCH(CH₃)₂), 53.9 (NCO₂CH₃), 52.3 (CO₂CH₃), 22.1 (OCH(CH₃)₂), 22.0 (OCH(CH₃)₂); IR (film) ν_{max} 3120, 2972, 1739,

1456 cm^{-1} ; EIMS m/z 305 [M^+] (8), 246 (52), 204 (100), 132 (9), 117 (25); FABHRMS m/z 305.1272 (calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_5$, 305.1263).

Methyl 2-(1-carbomethoxy-3-indolyl)-2-*tert*-butoxyacetate (9d). Prepared from **5** as a pale yellow solid (Method A: 0.02 g, 15%, Method B; 0.167 g 52%); mp 75-77 °C (EtOAc/hexane); ^1H NMR (CDCl_3 , 400 MHz) δ 8.17 (1H, d, $J = 7.7$ Hz, H-7), 7.76 (1H, d, $J = 8.1$ Hz, H-4), 7.69 (1H, s, H-2), 7.35 (1H, td, $J = 7.4, 1.1$ Hz, H-6), 7.28 (1H, td, $J = 7.2, 1.1$ Hz, H-5), 5.32 (1H, s, H-8), 4.03 (3H, s, NCO_2CH_3), 3.72 (3H, s, CO_2CH_3), 1.30 (9H, s, 3CH_3); ^{13}C NMR (CDCl_3 , 100 MHz) δ 172.8 (CO_2CH_3), 151.3 (NCO_2CH_3), 135.7 (C-7a), 128.2 (C-3a), 124.9 (C-6), 123.8 (C-2), 123.1 (C-5), 120.2 (C-4), 119.4 (C-3), 115.2 (C-7), 76.0 ($\text{C}(\text{CH}_3)_3$), 68.0 (C-8), 53.8 (NCO_2CH_3), 52.3 (CO_2CH_3), 27.9 ($\text{C}(\text{CH}_3)_3$); IR (film) ν_{max} 2976, 1743, 1456 cm^{-1} ; EIMS m/z 319 [M^+] (4), 260 (13), 246 (10), 204 (100), 117 (14), 57 (14); *Anal.* Calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_5$: C 63.94; H 6.63; N 4.39. Found: C 63.98; H 6.73; N 4.18. FABHRMS m/z 319.1422 (calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_5$, 319.1420).

Ethyl 2-(1-carbomethoxy-3-indolyl)-2-ethoxyacetate (9e). Prepared from **5** as a pale yellow oil (Method B: 0.192 g, 62.0%); ^1H NMR (CDCl_3 , 400 MHz) δ 8.17 (1H, d, $J = 7.3$ Hz, H-7), 7.78 (1H, d, $J = 8.0$ Hz, H-4), 7.72 (1H, s, H-2), 7.35 (1H, t, $J = 7.9$ Hz, H-6), 7.27 (1H, t, $J = 8.1$ Hz, H-5), 5.14 (1H, s, H-8), 4.24 (1H, dq, $J = 10.8, 7.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.17 (1H, dq, $J = 10.7, 7.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.02 (3H, s, NCO_2CH_3); 3.65 (1H, dq, $J = 9.0, 7.2$ Hz, OCH_2CH_3), 3.58 (1H, dq, $J = 8.9, 7.1$ Hz, OCH_2CH_3), 1.28 (3H, t, $J = 6.9$ Hz, OCH_2CH_3), 1.22 (3H, t, $J = 7.1$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3 , 100 MHz) δ 170.6 (CO_2Et), 151.3 (NCO_2Me), 135.8 (C-7a), 128.4 (C-3a), 125.1 (C-6), 124.6 (C-2), 123.3 (C-5), 120.5 (C-4), 117.5 (C-3), 115.2 (C-7), 74.7 (C-8), 65.3 (OCH_2CH_3), 61.4 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 54.0 (NCO_2CH_3), 15.3 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 14.2 (OCH_2CH_3); IR (film) ν_{max} 3122, 3053, 2937, 2978, 2899, 1746, 1569 cm^{-1} ; EIMS m/z 305 [M^+] (10), 260 (2), 232 (100), 204 (40), 117 (23), 59 (11); FABHRMS m/z 305.1266 (calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_5$, 305.1263).

Isopropyl 2-(1-carbomethoxy-3-indolyl)-2-isopropoxyacetate (9f). Prepared from **5** as a pale yellow oil (Method B: 0.131 g, 39.0%); ^1H NMR (CDCl_3 , 400 MHz); δ 8.17 (1H, brd, $J = 8.5$ Hz, H-7), 7.79 (1H, d, $J = 7.7$ Hz, H-4), 7.70 (1H, s, H-2), 7.34 (1H, td, $J = 7.7, 1.1$ Hz, H-6), 7.26 (1H, td, $J = 7.5, 1.1$ Hz, H-5), 5.20 (1H, s, H-8), 5.07 (1H, sept, $J = 6.2$ Hz, $\text{CO}_2\text{CH}(\text{CH}_3)_2$), 4.02 (3H, s, NCO_2CH_3), 3.77 (1H, sept, $J = 6.1$ Hz, $\text{OCH}(\text{CH}_3)_2$), 1.28, 1.23 (6H, 2d, $J = 6.2$ Hz, $\text{OCH}(\text{CH}_3)_2$), 1.25, 1.14 (6H, 2d, $J = 6.2$ Hz, $\text{CO}_2\text{CH}(\text{CH}_3)_2$); ^{13}C NMR (CDCl_3 , 100 MHz) δ 170.7 ($\text{CO}_2\text{i-Pr}$), 151.4 (NCO_2CH_3), 135.8 (C-7a), 128.5 (C-3a), 125.0 (C-6), 124.3 (C-2), 123.2 (C-5), 120.6 (C-4), 118.2 (C-3), 115.2 (C-7), 72.7 (C-8), 71.1 ($\text{OCH}(\text{CH}_3)_2$), 69.1 ($\text{CO}_2\text{CH}(\text{CH}_3)_2$), 54.0 (NCO_2CH_3), 22.4 ($\text{OCH}(\text{CH}_3)_2$), 22.0 ($\text{OCH}(\text{CH}_3)_2$), 21.9

(CO₂CH(CH₃)₂); 21.7 (CO₂CH(CH₃)₂). IR (film) ν_{\max} 3123, 2977, 2880, 1743, 1570, 1455 cm⁻¹; EIMS m/z 333 [M⁺] (6), 246 (42), 204 (100), 117 (21); FABHRMS m/z 333.1569 (calcd for C₁₈H₂₃NO₅, 333.1576).

Methyl 2-(2-bromo-1-carbomethoxy-3-indolyl)-acetate (7). Prepared from **5** (Method A) as a pale yellow solid and obtained together with alkoxyindole **9a-d** (0.05 g, 41.0%; 0.03 g, 20%, 0.05 g, 37% and 0.02 g, 11%, respectively); ¹H NMR (CDCl₃, 400 MHz) δ 8.03 (1H, d, J = 8.1 Hz, H-7), 7.46 (1H, dt, J = 7.7, 0.7 Hz, H-4), 7.29 (1H, td, J = 7.8, 1.6 Hz, H-6), 7.24 (1H, td, J = 7.4, 1.3 Hz, H-5), 4.05 (3H, s, NCO₂CH₃), 3.76 (2H, s, H-8), 3.68 (3H, s, CO₂CH₃); ¹³C NMR (CDCl₃, 100 MHz) δ 170.3 (CO₂CH₃), 151.1 (NCO₂CH₃), 136.2 (C-7a), 128.7 (C-3a), 124.9 (C-6), 123.4 (C-5), 118.3 (C-4), 117.1 (C-3), 115.5 (C-7), 110.8 (C-2), 53.8 (NCO₂CH₃), 52.2 (CO₂CH₃), 31.3 (C-8); IR (film) ν_{\max} 2955, 2849, 1747, 1449 cm⁻¹; EIMS m/z 326/324 [M⁺] (69), 268/266 (100), 224 (93), 143 (88), 101 (48), 77 (14), 75 (23), 59 (63). FABHRMS m/z 325.0102 (calcd for C₁₃H₁₂BrNO₄, 324.9950).

Single crystal structure determination of 12. Suitable crystals were obtained by slow evaporation of a EtOAc/hexane solution. A crystal measuring 0.30 x 0.24 x 0.20 mm was mounted on a Bruker Smart 6000 CCD diffractometer. The crystal was triclinic, space group *P*-1, with cell dimensions $a = 9.207(2)$, $b = 9.538(2)$, $c = 10.115(3)$ Å, $\alpha = 73.817(6)$, $\beta = 82.253(6)$ and $\gamma = 84.675(6)$, $V = 843.8(4)$ Å³, $\rho_{\text{calc}} = 1.257$ g/cm³ for $Z = 2$, C₁₇H₂₁O₅N, MW = 319.35, and F(000) = 340 e. The total reflections were 5553 (graphite-monochromated Mo K α radiation, $\lambda = 0.71073$ Å), the unique reflections were 1074 and the observed reflections were 1073. The structure was solved by direct methods using SIR2004, the final discrepancy indices, refining 216 parameters, were $R_F = 5.8\%$, $R_w = 15.4\%$, and the highest residual peak in the final difference Fourier map showed an electron density of 0.20 e/Å³. The CCDC deposition number is 764379.

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