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Chemo- and regioselective ethynylation of 4,5,6,7-tetrahydroindoles with ethyl 3-halo-2-propynoates

Boris A. Trofimov *, Lyubov' N. Sobenina, Zinaida V. Stepanova, Ol'ga V. Petrova, Igor' A. Ushakov, Al'bina I. Mikhaleva

A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 1 Favorsky St., Irkutsk 664033, Russian Federation

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Abstract

4,5,6,7-Tetrahydroindoles undergo a rapid, facile (rt, 60 min) ethynylation with ethyl 3-halo-2-propynoates upon grinding with solid K_2CO_3 (without solvent) at C-2 of the tetrahydroindole ring to afford ethyl 3-(4,5,6,7-tetrahydroindol-2-yl)-2-propynoates in 62–90% yield.

Keywords: 4,5,6,7-Tetrahydroindoles; Indoles; Active surface; K_2CO_3; Cross-coupling

4,5,6,7-Tetrahydroindoles, due to their easy aromatization, are good intermediates to synthesize indoles.[1] Consequently, 2-functionalized 4,5,6,7-tetrahydroindoles are convenient starting materials for the preparation of 2-functionalized indoles. A number of their representatives are pharmacologically important substances and precursors for a wide variety of alkaloids such as vindoline,[2] vindorosine,[2] ellipticine.[3] Also, 2-functionalized indoles attract attention owing to their usefulness in the total synthesis of polyfunctional complex molecules possessing the indole scaffold.[4] Of special importance are 2-substituted indoles with acetylenic moieties because they are currently employed in the design of numerous indole derivatives[5] due to the rich chemistry of the acetylenic function.

Although methods for the preparation of 3-substituted indoles are well developed, syntheses of 2-substituted indole derivatives still remain less elaborated. Therefore a new simple access to 2-functionalized indoles, particularly 2-ethynylindoles, might further contribute to the chemistry and pharmacology of indole compounds.

Amongst the known syntheses of indoles bearing acetylenic substituents at C-2 are cross-couplings of 2-haloindoles with terminal acetylenes in the presence of palladium, copper and a base in different solvents, performed as a rule, under an inert atmosphere.[6] However, 2-haloindoles are quite unstable, and decompose at room temperature.[7] The cross-coupling of methyl bromopropynoate with 1-SEM-2-tributylstannylindole in the presence of $Pd(PPh_3)_4$[6a] gives the corresponding 2-ethynylindole in 45% yield. Recently, syntheses of 2-ethynylindoles involving simultaneous building of the indole ring have been documented.[8] One of the promising approaches to indoles with an acetylenic group at C-2 could involve aromatization of 3-(4,5,6,7-tetrahydroindol-2-yl)-2-propynoates. Therefore, a search for a versatile general synthesis of 3-(4,5,6,7-tetrahydroindol-2-yl)-2-propynoates is a crucial step in solving the above problem.

Previously, the synthesis of ethyl 3-(4,5,6,7-tetrahydroindol-2-yl)-2-propynoate by the ethynylation of available[9] 4,5,6,7-tetrahydroindole **1a** with ethyl 3-bromo-(**2a**) and ethyl 3-iodo-2-propynoates **2b** on active Al_2O_3 surface has been described.[10] However, this reaction with bromopropynoate was not chemoselective: along with ethyl 3-(4,5,6,7-tetrahydroindol-2-yl)-2-propynoate **3a** (46%) a

* Corresponding author. Tel.: +7 3952 461411/511431; fax: +7 3952 419346.
E-mail address: boris_trofimov@irioch.irk.ru (B. A. Trofimov).

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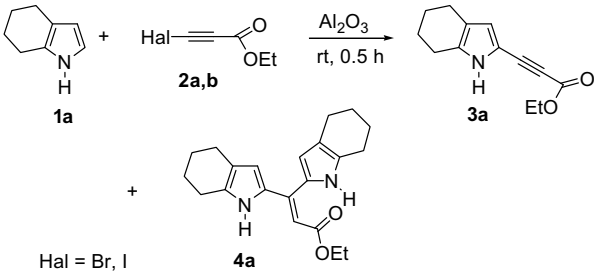
side product, ethyl 3,3-di(4,5,6,7-tetrahydro-1*H*-indol-2-yl)acrylate **4a**, was also formed in 24% yield (Scheme 1). The same reaction of 4,5,6,7-tetrahydroindole with iodopropynoate proceeded to deliver only adduct **4a** (79%).

In this Letter, we report an efficient chemo- and regioselective ethynylation of the known[11] 4,5,6,7-tetrahydroindoles **1a**–**h** with ethyl 3-halo-2-propynoates **2a**,**b** on solid K_2CO_3 as a novel active surface to afford the corresponding 3-(4,5,6,7-tetrahydroindol-2-yl)-2-propynoates **3a**–**h** in 62–90% yields (Table 1).[12]

The reaction proceeded smoothly at room temperature over about 60 min on grinding the reactants with solid K_2CO_3. The reaction was equally efficient in air and under argon. The reaction course (conversion of reactants **1** and **2** and the formation of ethynylation product **3**) was monitored by ^{1}H NMR spectroscopy of $CDCl_3$ extracts from the reaction mixture. Products **3a**–**h** were isolated and purified chromatographically by placing the solid reaction mixture on the top of an Al_2O_3-packed column and eluting with *n*-hexane and diethyl ether. The yields of pyrroles **3a**–**h** were reproducible (within ±5%), also with K_2CO_3 samples from different suppliers.

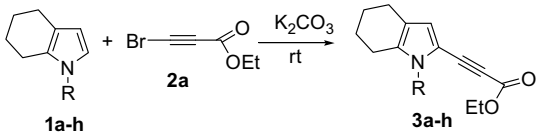
In contrast to the similar reaction on Al_2O_3,[10] in the case of ethyl 3-bromo-2-propynoate **2a** we failed to detect any side products (^{1}H NMR), whereas with ethyl 3-iodo-2-propynoate **2b**, 4,5,6,7-tetrahydroindole **1a** gave minor amounts of 3,3-di(4,5,6,7-tetrahydro-1*H*-indol-2-yl)acrylate **4a** (2–4%). Besides, the latter reaction appeared to be noticeably slower (41% conversion of pyrrole **1a** over 60 min).

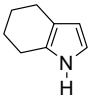
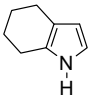
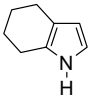
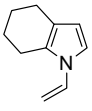
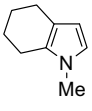
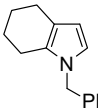
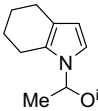
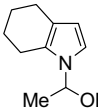
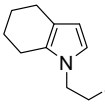
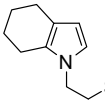
The reaction is chemo- and regioselective. The expected addition products of the type 2-(1-bromo-2-carbethoxyethenyl)-4,5,6,7-tetrahydroindole[10] were not detectable in the reaction mixtures. Also, no traces of corresponding 3-isomers were observed despite the fact that it is common knowledge that bulky and branched substituents at position 1 of the pyrrole nucleus can direct electrophilic attack to position 3.[13] In this reaction, even bulky substituents such as CH(Me)O^{i}Pr and CH(Me)OBu did not affect the regioselectivity, though the reaction time was considerably increased (12 h instead of 60 min) and portion-wise addition of acetylene **2a** to the reaction mixture was required. Obviously, the slow reaction rate in this case results from steric hindrance. Generally, this ethynylation reaction tolerates various N-substituents on the indole (H, Alk, aralkyl, vinyl, acetal and sulfide).



Scheme 1.

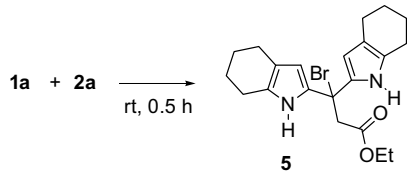
Table 1
Ethynylation of substituted 4,5,6,7-tetrahydroindoles **1a**–**h** with ethyl 3-bromo-2-propynoate **2a** on solid K_2CO_3 (rt, reactants ratio = 1:1)



Entry	4,5,6,7-Tetrahydroindole **1**	Reaction time (h)	Mass excess of K_2CO_3 versus reactants	Product **3** (yield, %)
1	 **1a**	1	2	**3a** (50)
2	 **1a**	1	5	**3a** (55)
3	 **1a**	1	10	**3a** (90)
4[a]	 **1b**	12	10	**3b** (82)
5	 **1c**	1	10	**3c** (80)
6	 **1d**	1	10	**3d** (90)
7[a]	 **1e**	12	10	**3e** (64)
8[a]	 **1f**	12	10	**3f** (62)
9	 **1g**	1	10	**3g** (71)
10	 **1h**	1	10	**3h** (81)

[a] Ratio **1**:**2** = 1:1.5.

Interestingly, the reaction does not occur in solution (diethyl ether, $CHCl_3$) either with and without K_2CO_3. When neat reactants **1a** and ethyl 3-bromo-2-propynoate



Scheme 2.

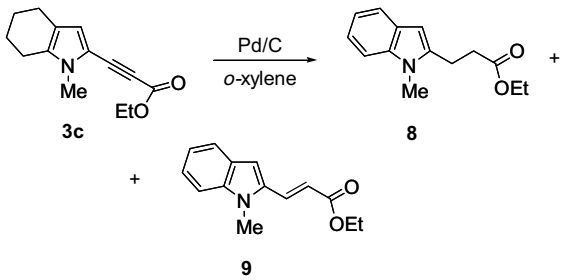
2a were ground together for 30 min only adduct **5** was formed (Scheme 2).[10]

The key effect of the K_2CO_3 active surface on the ethynylation reaction was also supported by the influence of reactants/K_2CO_3 ratio on the product yield. At the 1:10 ratio the yield of **3a** was close to quantitative, while at higher concentrations of reactants (1:2, 1:5) the yields decreased to 50–55%. Meanwhile, the addition of K_2CO_3 (2.5 mol excess) to Al_2O_3 did not change the usual (for Al_2O_3) product ratio significantly—**3a**:**4a** with $Al_2O_3 = 2{:}3$, and with $Al_2O_3 + K_2CO_3 = 3{:}2$.[10] It is noteworthy that as yet, K_2CO_3 has not been mentioned amongst numerous known active surfaces for effecting chemical reactions.[14]

Formally, the ethynylation can be rationalized both as electrophilic substitution on the pyrrole ring and nucleophilic addition of the electron-rich pyrrole ring to the electron deficient triple bond. In both the cases, the one-electron transfer step is plausible. Indeed, in the ESR spectrum of the reaction mixture a singlet ($g = 2.0023$, $\Delta H = 1.8$ mT) was observed, thus confirming a one-electron transfer step.

To check the possibility of aromatization of the ethyl 3-(4,5,6,7-tetrahydroindol-2-yl)-2-propynoates, propynoate **3c** was refluxed in *o*-xylene with Pd/C (10% of Pd) for 12 h to give 2-indolepropanoate **8** and 2-indolylacrylate **9** (4:1 ratio) resulting from the hydrogen redistribution between the cyclohexane ring and the triple bond (Scheme 3).[15] This confirms that the ethyl 3-(4,5,6,7-tetrahydroindol-2-yl)-2-propynoates **3** synthesized are convertible to 2-functionalized indoles.

In conclusion, the facile chemo- and regioselective ethynylation of 4,5,6,7-tetrahydoindoles with 3-halopropynoates upon grinding with solid K_2CO_3 to furnish ethyl 3-(4,5,6,7-tetrahydroindol-2-yl)-2-propynoates has been developed. The reaction proceeds at room temperature under solvent-free conditions in air. This novel approach promises a general and easy access to 2-functionalized indoles. Further systematic investigations of the reaction employing other active surfaces (salts and metal oxides) are underway in this lab.



Scheme 3.

Acknowledgement

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12. General procedures for the ethynylation of 4,5,6,7-tetrahydroindoles. (A). Ethyl 3-bromo-2-propynoate **2a** (1 mmol) was added in small portions (4 portions) with grinding for 10 min (ambient temperature) to 4,5,6,7-tetrahydroindole **1a**,**c**,**d**,**g**,**h** (1 mmol) and K_2CO_3 (2–10-fold amount vs total weight of reactants) in a porcelain mortar. The mixture self-heated up to 30 °C and became bright-yellow in colour. Gradually, the colour changed to brown. The reaction mixture was kept additionally for 50 min under grinding (2–3 min) at regular intervals of 10 min. The reaction mixture was purified through an

Al_2O_3 column eluting with *n*-hexane (*n*-hexane and then diethyl ether for propynoate **3a**) to afford pure ethyl 3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)-2-propynoates **3a**,**c**,**d**,**g**,**h.** Pyrroles **3a** and **3d** were also isolated by filtration of the reaction mixture after dilution with water. (B) Ethyl 3-bromo-2-propynoate **2a** (1 mmol) was added in small portions with grinding for 15 min (ambient temperature) to 4,5,6,7-tetrahydroindole **1b**,**e**,**f** (1 mmol) and K_2CO_3 in a porcelain mortar. The reaction mixture was kept additionally for 6 h under grinding (2–3 min) at regular intervals of 30 min, and ethyl 3-bromo-2-propynoate (0.5 mmol) in small portions was added with grinding for 15 min to the mixture. The reaction mixture was kept additionally for 5.5 h without grinding and then purified by column chromatography over Al_2O_3 eluting with *n*-hexane to afford pure ethyl 3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)-2-propynoates **3b**,**e**,**f**.

The analytical and spectral data of ethyl 3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)-2-propynoate **3a** and ethyl 3-(1-vinyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-2-propynoate **3b** have been reported previously.[10]

Ethyl 3-(1-methyl-4,5,6,7-tetrahydro-1H-indol-2-yl)-2-propynoate (**3c**): White crystals (80%), mp 68–69 °C. IR (KBr) *ν* 1694 (C=O), 2184 (C≡C); ^{1}H NMR (400.13 MHz, $CDCl_3$) *δ* 1.32 (t, *J* = 7.1 Hz, 3H, Me), 1.70 (m, 2H, CH_2-5), 1.82 (m, 2H, CH_2-6), 2.45 (m, 2H, CH_2-4), 2.51 (m, 2H, CH_2-7), 3.52 (s, 3H, NMe), 4.25 (q, *J* = 7.1 Hz, 2H, OCH_2), 6.48 (s, 1H, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 14.2 (Me), 22.4, 22.7, 22.8, 23.2 (CH_2-4,5,6,7), 31.0 (NMe), 61.5 (OCH_2), 81.8 (C≡), 87.9 (≡C), 110.3 (C-2), 118.3 (C-3), 119.0 (C-4), 134.7 (C-5), 154.7 (C=O). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.83; H, 7.22; N, 5.86.

Ethyl 3-(1-benzyl-4,5,6,7-tetrahydro-1H-indol-2-yl)-2-propynoate (**3d**): White crystals (90%), mp 69–70 °C. IR (KBr) *ν* 1697 (C=O), 2180 (C≡C); ^{1}H NMR (400.13 MHz, $CDCl_3$) *δ* 1.29 (t, *J* = 7.1 Hz, 3H, Me), 1.67 (m, 2H, CH_2-5), 1.74 (m, 2H, CH_2-6), 2.39 (m, 2H, CH_2-4), 2.47 (m, 2H, CH_2-7), 4.21 (q, *J* = 7.1 Hz, 2H, OCH_2), 5.11 (s, 2H, CH_2Ph), 6.55 (s, 1H, H-3), 7.06 (m, 2H, H_o), 7.23 (m, 1H, H_p), 7.29 (m, 2H, H_m); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 14.2 (Me), 22.7, 22.8, 22.9, 23.2 (CH_2-4,5,6,7), 48.3 (CH_2), 61.5 (OCH_2), 81.8 (C≡), 87.9 (≡C), 110.6 (C-2), 118.9 (C-3), 119.7 (C-4), 126.9 (C_o), 127.5 (C_p), 128.7 (C_m), 134.7 (C-5), 137.5 (C_i), 154.7 (C=O). Anal. Calcd. for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 77.81; H, 7.01; N, 4.88.

Ethyl 3-[1-(1-isopropoxyethyl)-4,5,6,7-tetrahydro-1H-indol-2-yl]-2-propynoate (**3e**): Yellowish oil (64%). IR (KBr) *ν* 1693 (C=O), 2175 (C≡C); ^{1}H NMR (400.13 MHz, $CDCl_3$) *δ* 0.98 (d, *J* = 6.1 Hz, 3H, MeCH), 1.18 (d, *J* = 5.9 Hz, 3H, MeCH), 1.32 (t, *J* = 7.1 Hz, 3H, CH_2Me), 1.60 (d, *J* = 6.1 Hz, 3H, MeCHN), 1.69–1.84 (m, 4H, CH_2-5,6), 2.47 (m, 2H, CH_2-4), 2.66 (m, 1H, CH_2-7), 2.87 (m, 1H, CH_2-7), 3.43 (m, 1H, OCH), 4.26 (q, *J* = 7.1 Hz, 2H, OCH_2), 5.74 (q, *J* = 6.1 Hz, 1H, NCH), 6.47 (s, 1H, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 14.2 (CH_2Me), 21.1, 22.3 (Me_2CH), 22.7, 23.0, 23.1, 23.2 (CH_2-4,5,6,7), 24.0 (MeCHN), 61.5 (OCH_2), 68.6 (OCH), 80.8 (NCH), 81.4 (C≡), 88.2 (≡C), 110.1 (C-2), 119.3 (C-3), 120.5 (C-4), 134.2 (C-5), 154.7 (C=O). Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.57; H, 8.12; N, 4.23.

Ethyl 3-[1-(1-butoxyethyl)-4,5,6,7-tetrahydro-1H-indol-2-yl]-2-propynoate (**3f**): Yellowish oil (62%). IR (KBr) *ν* 1705 (C=O), 2190 (C≡C); ^{1}H NMR (400.13 MHz, $CDCl_3$) *δ* 0.86 (t, *J* = 6.9 Hz, 3H, Me of Bu), 1.33 (t, *J* = 6.9, 3H, CO_2CH_2Me), 1.49 (m, 2H, CH_2), 1.62 (d, *J* = 6.2 Hz, 3H, MeCH), 1.81 (m, 6H, CH_2-5,6, CH_2), 2.46 (m, 2H, CH_2-4), 2.65 (m, 1H, CH_2-7), 2.80 (m, 1H, CH_2-7), 3.14 (m, 1H, OCH_2), 3.32 (m, 1H, OCH_2), 4.25 (q, *J* = 6.9 Hz, 2H, CO_2CH_2), 5.61 (q, *J* = 6.2 Hz, 1H, NCH), 6.46 (s, 1H, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 13.9, 14.3 (Me), 19.4 (CH_2), 22.0, 23.1, 23.2, 23.3 (CH_2-4,5,6,7), 24.0 (MeCH), 31.5 (CH_2), 61.6 (CO_2CH_2), 67.9 (OCH_2), 81.4 (C≡), 83.7 (NCH), 88.3 (≡C), 110.4 (C-2), 119.5 (C-3), 120.5 (C-4), 134.0 (C-5), 154.7 (C=O). Anal. Calcd. for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.78; H, 8.42; N, 4.60.

Ethyl 3-1-[2-(ethylsulfanyl)ethyl]-4,5,6,7-tetrahydro-1H-indol-2-yl-2-propynoate (**3g**): Colourless oil (71%). IR (KBr) *ν* 1699 (C=O), 2186 (C≡C); ^{1}H NMR (400.13 MHz, $CDCl_3$) *δ* 1.26 (t, *J* = 7.4 Hz, 3H, Me), 1.32 (t, *J* = 7.2 Hz, 3H, Me), 1.70 (m, 2H, CH_2-5), 1.82 (m, 2H, CH_2-6), 2.46 (m, 2H, CH_2-4), 2.56 (m, 4H, SCH_2, CH_2-7), 2.78 (m, 2H, CH_2S), 4.06 (m, 2H, NCH_2), 4.25 (q, *J* = 7.2 Hz, 2H, OCH_2), 6.50 (s, 1H, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 14.0, 14.6 (Me), 22.3, 22.6, 23.0 (CH_2-4,5,6,7), 25.8 (SCH_2), 31.6 (CH_2S), 44.6 (NCH_2), 61.2 (OCH_2), 81.2 (C≡), 87.8 (≡C), 109.4 (C-2), 118.8 (C-3), 119.0 (C-4), 133.9 (C-5), 154.3 (C=O). Anal. Calcd. for $C_{17}H_{23}NO_2S$: C, 66.85; H, 7.59; N, 4.58; S, 10.50. Found: C, 66.78; H, 7.89; N, 4.39, S 10.38.

Ethyl 3-1-[2-(propylsulfanyl)ethyl]-4,5,6,7-tetrahydro-1H-indol-2-yl-2-propynoate (**3h**): Colourless oil (81%). IR (KBr) *ν* 1698 (C=O), 2185 (C≡C); ^{1}H NMR (400.13 MHz, $CDCl_3$) *δ* 0.96 (t, *J* = 7.2 Hz, 3H, Me), 1.32 (t, *J* = 6.9 Hz, 3H, Me), 1.61 (m, 2H, CH_2), 1.70 (m, 2H, CH_2-5), 1.81 (m, 2H, CH_2-6), 2.48 (m, 4H, CH_2-4,7), 2.57 (m, 2H, SCH_2), 2.76 (m, 2H, CH_2S), 4.06 (m, 2H, NCH_2), 4.25 (q, *J* = 6.9 Hz, 2H, OCH_2), 6.48 (s, 1H, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 13.4, 14.3 (Me), 22.6, 22.9, 23.0, 23.3 (CH_2-4,5,6,7, CH_2), 32.2 (SCH_2), 34.3 (CH_2S), 44.9 (NCH_2), 61.5 (OCH_2), 81.6 (C≡), 88.0 (≡C), 109.6 (C-2), 119.1 (C-4), 119.3 (C-3), 134.3 (C-5), 154.6 (C=O). Anal. Calcd. for $C_{18}H_{25}NO_2S$: C, 67.68; H, 7.89; N, 4.38; S, 10.04. Found: C, 67.81; H, 8.24; N, 4.39; S 9.86.

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15. *Ethyl 3-(1-methyl-1H-indol-2-yl)propanoate* (**8**) *and ethyl 3-(1-methyl-1H-indol-2-yl)acrylate* (**9**): Propynoate **3c** (100 mg, 0.42 mmol) was refluxed in *o*-xylene (4 mL) in the presence of 10% of Pd/C (10%) for 12 h. After removing the solvent, the residue (easily sublimated crystals, mp 50–51 °C, 88 mg) was analyzed by ^{1}H NMR (**8**:**9**, 4:1). Fractionation of this mixture by column chromatography (Al_2O_3, *n*-hexane–diethyl ether, 1:1) gave indole **9** (15 mg, purity 90%) only. Indole **8** was not isolated. Compound **8**: ^{1}H NMR (400.13 MHz, $CDCl_3$) *δ* 1.16 (t, *J* = 7.1 Hz, 3H, Me), 2.75 (t, *J* = 7.3 Hz, 2H, CH_2CO), 3.06 (t, *J* = 7.3 Hz, 2H, CH_2), 3.64 (s, 3H, Me), 4.16 (q, *J* = 7.1 Hz, 2H, OCH_2), 6.24 (s, 1H, H-3), 6.96 (m, 1H, H-5), 7.07 (m, 1H, H-6), 7.31 (m, 1H, H-7), 7.43 (m, 1H, H-4); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 14.5 (Me), 22.6 (CH_2), 29.6 (NMe), 33.5 (CH_2CO), 60.8 (OCH_2), 99.2 (C-3), 109.7 (C-7), 119.8 (C-5), 120.4 (C-4), 121.4 (C-6), 128.9 (C-3a), 138.5 (C-7a), 140.6 (C-2), 172.8 (C=O). **9**: ^{1}H NMR (400.13 MHz, $CDCl_3$) *δ* 1.24 (t, *J* = 7.1 Hz, 3H, Me), 3.76 (s, 3H, NMe), 4.28 (q, *J* = 7.1 Hz, 2H, OCH_2), 6.48 (d, *J* = 15.7 Hz, 1H, H_α), 7.05 (m, 1H, H-5), 7.07 (m, 1H, H-3), 7.21 (m, 1H, H-6), 7.43 (m, 1H, H-7), 7.56 (m, 1H, H-4), 7.80 (d, *J* = 15.7 Hz, 1H, H_β).