A Synthesis of (±)-Yohimbine

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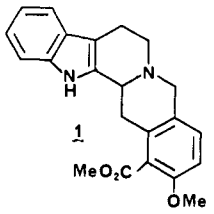
Abstract: The condensation of methyl acetoacetate with 1-tryptophyl-3-formylpyridinium bromide is described. The transformation of the unusual product into hexadehydroyohimbine by two operations is presented. In view of a previous conversion of the latter into (±)-yohimbine the three-step reaction sequence to the hexadehydro product represents a short, formal synthesis of the alkaloid.

Kametani and co-workers reported recently a 14-step conversion of *m*-methoxybenzaldehyde into *O*-methylhexadehydroyohimbine (**1**)[1] and subsequently transformed the latter into the racemic



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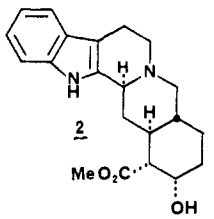

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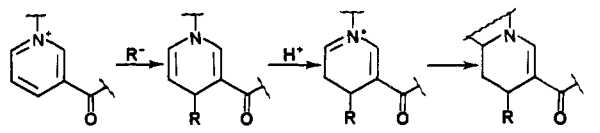
alkaloid yohimbine (**2**).[1,2] The present paper outlines a synthesis of the intermediate **1** by a new route in four operations.[3]

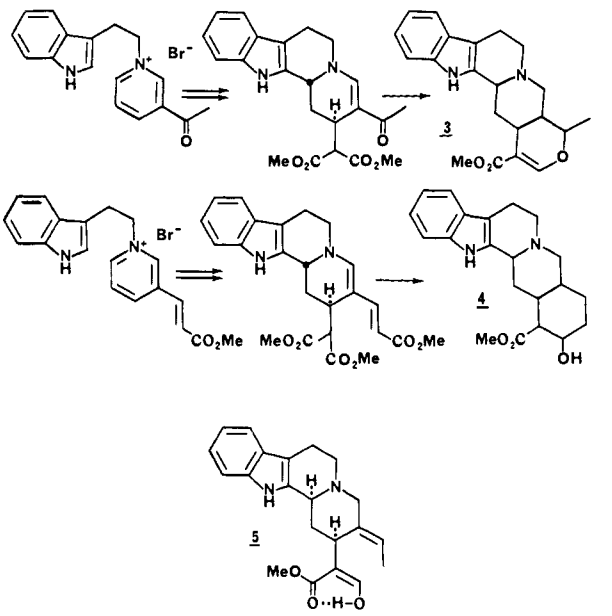
For some time the two-step, addition–condensation route, operating on 1-alkyl-3-acylpyridinium salts, portrayed in Scheme I has served as the conceptual basis for the synthesis of a variety of indole alkaloids. Thus various heteroyohimbines (**3**) were the products of a short reaction scheme starting with β-acetylpyridine,[4] nicotinaldehyde was the starting material for the production of various yohimbines (**4**),[3d] and both starting pyridines could be used for the synthesis of corynanthoid alkaloids such as geissoschizine (**5**)[5] (SchemeII). In each of these syntheses dimethyl sodiomalonate had been the nucleophile adding to the γ center of the pyridinium salt (i.e., R in Scheme I). It now became of interest to learn whether the nucleophilic agent could be varied without undue effect on the overall scheme of alkaloid synthesis. Since the elements of acetoacetic ester and a nicotinaldehyde-based pyridinium salt combine ideally to form the molecular framework of a yohimboid skeleton, the two compounds were chosen as starting materials for the new study.

Exposure of the pyridinium salt **6**, prepared by the N-alkylation of nicotinaldehyde with tryptophyl bromide,[6] to methyl sodioacetoacetate and subsequent treatment of the products with acid under the conditions used earlier in the malonic ester cases[3d-5] yielded two unexpected products. The minor product could be identified as tetracycle **8a**, i.e., the product of 1,4-reduction of the nicotinaldehyde derivative **6** and subsequent acid-induced

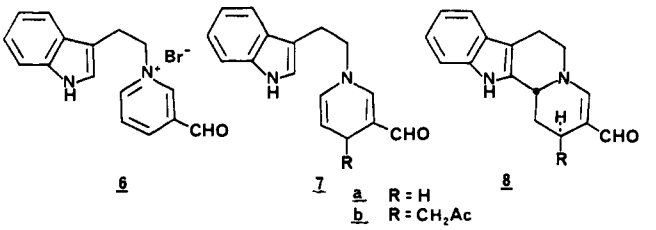
Scheme I



Scheme II



cyclization of the resultant dihydronicotinaldehyde **7a**. The major product could be shown by preliminary analysis to incorporate the acetoacetic ester moiety, but not to have undergone the traditional acid-catalyzed ring closure. In view of this fact, the interaction between methyl sodioacetoacetate and salt **6** was executed without follow-up acid treatment. This change improved the yield of the major product and led to **7a** as the minor product.



6 **7** **a** R = H **b** R = CH_2Ac **8**

The major product appeared by its molecular formula of $C_{21}H_{18}O_3N_2$ to be the product of addition of acetoacetic ester anion to the pyridinium salt minus the elements of water and hydrogen. Its yellow color and ultraviolet spectra [λ_{max}^{EtOH} 224 nm (log ε 4.67), 245 (4.48), 272 (4.29), 355 (4.24); $\lambda_{max}^{EtOH/HCl}$ 220 nm (log ε 4.69),

(1) Kametani, T.; Hirai, Y.; Kajiwara, M.; Takahashi, T.; Fukumoto, K. *Chem. Pharm. Bull.* **1975**, *23*, 2634. Szántay, C.; Honty, K.; Töke, L.; Buzas, A.; Jacquet, J. P. *Tetrahedron Lett.* **1971**, 4871.
(2) Kametani, T.; Hirai, Y.; Fukumoto, K. *Chem. Pharm. Bull.* **1976**, *24*, 2500.
(3) For other yohimbine syntheses, see: (a) van Tamelen, E. E.; Shamma, M.; Burgstahler, A. W.; Wolinsky, J.; Tamm, R.; Aldrich P. E. *J. Am. Chem. Soc.* **1969**, *91*, 7315. (b) Töke, L.; Honte, K.; Szántay, C. *Chem. Ber.* **1969**, *102*, 3248. (c) Stork, G.; Guthikonda, R. N. *J. Am. Chem. Soc.* **1972**, *94*, 5109. (d) Wenkert, E.; Halls, T. D. J.; Kunesch, G.; Orito, K.; Stephens, R. L.; Temple, W. A.; Yadav, J. S. *Ibid.* **1979**, *101*, 5370.
(4) Wenkert, E.; Chang, C.-J.; Chawla, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orito, K. *J. Am. Chem. Soc.* **1976**, *98*, 3645.
(5) Wenkert, E.; Vankar, Y. D.; Yadav, J. S. *J. Am. Chem. Soc.* **1980**, *102*, 7971.
(6) Wenkert, E.; Dave, K. G.; Haglid, F.; Lewis, R. G.; Oishi, T.; Stevens, R. V.; Terashima, M. *J. Org. Chem.* **1968**, *33*, 747.

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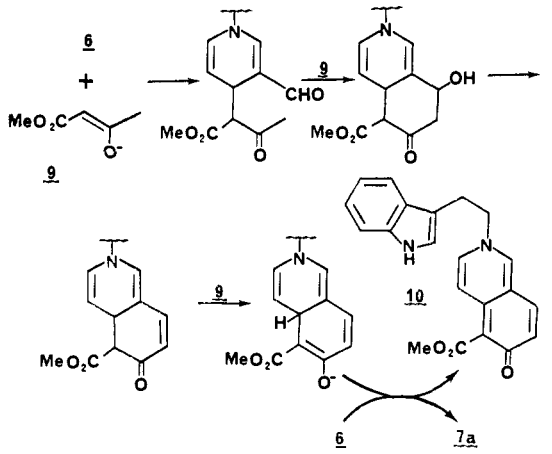
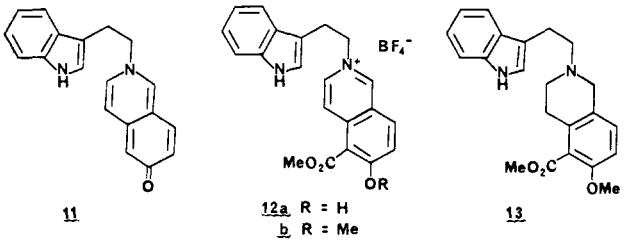
237 (4.46), 255 (4.59), 280 (3.97), 290 (3.98), 315 (3.94)] revealed an extended chromophore and hence the presence of a complex system of conjugated multiple bonds. Its infrared spectrum [ν_{max}^{KBr} NH 3150 (w), C=O 1720 (s), 1705 (s), 1640 (s), 1600 (s) cm^{-1}] exhibited indole N–H, ester carbonyl, and vinylogous amide carbonyl absorption bands. Its low-resolution mass spectrum showed *m/e* 144 and 130 fragments, characteristic of β-indolylethyl and β-indolylmethyl cations, respectively, suggesting that the β-indolylethyl moiety of the starting compound had remained unperturbed in the product. In the face of these spectral data, the ^1H and ^{13}C NMR spectra,[7] and the following, possible mechanism for the formation of the substance as well as **7a**, formula **10** could be suggested as the structure of the new compound.



Thus instead of the simple γ-addition of malonic ester anion to 1-alkyl-3-acylpyridinium salts,[3d-5] the γ-addition of acetoacetic ester anion to the nicotinaldehyde derivative (**6**) had been followed by sequential intramolecular aldol condensation, dehydration, and dehydrogenation. The last reaction, an interesting example of the oxidation of a dehydropyridine by a pyridinium salt and hence of possible import to the chemistry of the NAD–NADH respiratory enzyme system, had precedents.[8] However, the aldolization was somewhat unusual, since the formyl group, being part of a vinylogous amide moiety, is only a weak electrophilic site. Hence it was of interest to test the aldol condensation on some model under the conditions of the reaction which had led to tetracycle **10**. Ketone **7b** was chosen as the model compound for the study. It had been an intermediate in the reported synthesis of tetracycle **8b** by base-induced condensation of acetone with pyridinium salt **6** and acid treatment of the intermediate.[9]

Treatment of ketone **7b** with sodium hydride in tetrahydrofuran produced tetracycle **11** in 42% yield, indicating the vinylogous



formamide to be capable of acting as an electrophile in intramolecular aldol condensations.[10,11]

Exposure of ester **10** to trimethyloxonium tetrafluoroborate in nitromethane solution yielded a mixture of O-protonated salt **12a**,[12] from which starting material could be reliberated, and O-methylated salt **12b**. Reduction of the latter with a minimal amount of sodium borohydride in tetrahydrofuran led to a dihydrointermediate whose treatment with trifluoroacetic acid afforded pentacycle **1**.[13]

The **6** → **10** → **12b** → **1** reaction sequence represents a short synthesis of the Kametani intermediate and a formal total synthesis of (±)-yohimbine (**2**) in view of the earlier **1** → **2** conversion.[1,2]

Experimental Section

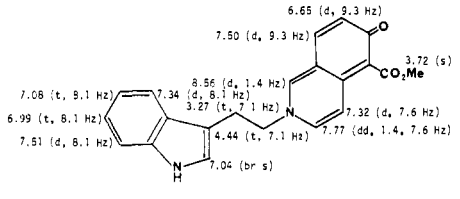
Melting points were determined on a Reichert micro hot stage and are uncorrected. Infrared spectra were recorded on Beckman IR-9 and IR-18 spectrophotometers and ultraviolet spectra on Cary 17 and Kontron Uvikon 810 spectrophotometers. ^1H NMR spectra of deuteriochloroform solutions (unless noted otherwise) with Me_4Si as internal standard (δ = 0 ppm) were taken on a Varian E-390 spectrometer and on a 360-MHz instrument with a highly modified Varian HR-220 console, an Oxford magnet, and a Nicolet 1180-E computer system. ^{13}C NMR spectra were recorded on a Varian XL-100-15 spectrometer operating at 25.2 MHz in the Fourier transform mode. All organic extracts of crude products were washed with water and dried over magnesium sulfate.

The carbon shifts on formula **10**[7] are in parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(Me_2SO\text{-}d_6) + 39.5$ ppm. Asterisked numbers may be interchanged. The carbon shifts on formulas i and ii[14] are in parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm.

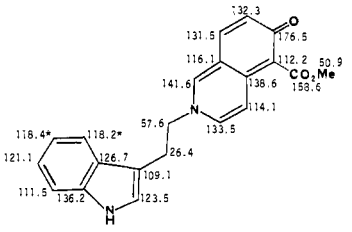
Condensation of Methyl Acetoacetate with 3-Formyl-1-tryptophylpyridinium Bromide (6). Methyl acetoacetate, 8.30 mL (76.8 mmol), was added to a stirring suspension of 3.69 g (76.8 mmol) of sodium hydride (50% in mineral oil) in 110 mL of dry tetrahydrofuran over a 0.5-h period at 0 °C under a stream of argon. After hydrogen evolution had ceased, 5.26 g (16.5 mmol) of salt **6** was added and the mixture stirred at room temperature for 24 h. It then was evaporated under vacuum and the residue treated with a mixture of 200 mL of methylene chloride and 50 mL of saturated ammonium chloride solution. The resultant precipitate was filtered and washed successively with methylene chloride and water, leaving a brown solid. The combined filtrate and washings were separated and the organic layer washed, dried, and evaporated, leaving a brown syrup. Chromatography of the solid on 25 g of silica gel and elution with 16:1 methylene chloride–methanol yielded 1.68 g (29%) of a solid, whose crystallization from methanol gave 1.20 g of yellow, crystalline ester **10**, mp 238 °C. Anal. ($C_{21}H_{18}O_3N_2$) C, H, N.

Medium-pressure column chromatography of the brown syrup on 42 g of silica gel and elution with benzene–acetic ester gave two products. From the fractions, whose TLC analysis (2.3:1 ethyl acetate–benzene) gave a R_f 0.33 spot, there emerged 288 mg (7%) of pale yellow, syrupy vinylogous formamide **7a**: IR ($CHCl_3$) NH 3500 (m), C=O, C=C 1670 (m), 1635 (s), 1580 (s) cm^{-1}; ^1H NMR δ 2.85 (t, 2, *J* = 6 Hz, benzyl H_2), 2.90 (d, 2, *J* = 4 Hz, 2 H-4), 3.32 (t, 2, *J* = 6 Hz, NCH_2), 4.85 (dt, 1, *J* = 7, 4 Hz, H-5), 5.65 (dq, 1, *J* = 7, 1 Hz, H-6), 6.25 (d, 1, *J* = 1 Hz, H-2), 6.90 (d, 1, *J* = 2, Hz, indole α-H), 6.9–7.5 (m, 4, indole Hs), 8.70 (s, 1, CHO); *m/e* 252 (M^+, 70%), 144 (94), 143 (91), 130 (base), 123 (31), 122 (59), 115 (30). Exact mass: *m/e* 252.1250

(7) ^1H NMR spectral data:



^{13}C NMR spectral data:



(8) van Eikeren, P.; Grier, D. L. *J. Am. Chem. Soc.* **1977**, *99*, 8057, and references therein. Piepers, O.; Kellogg, R. M. *J. Chem. Soc., Chem. Commun.* **1980**, 1154, and references therein.

(9) Wenkert, E.; Reynolds, G. D. *Synth. Commun.* **1973**, *3*, 241.

(10) In this case the cause of the dehydrogenation remains unexplained.

(11) The condensation of acetone and the nicotinaldehyde salt **6** over sodium hydride in tetrahydrofuran also produced tetracycle **11**, albeit in only low yield.

(12) Methylation of the solvent by the Meerwein reagent yields methyl methanenitronate, which can act as a proton source.

(13) Reduction of salt **12b** with excess sodium borohydride led to the tetrahydro product **13**.

(calcd for $C_{16}H_{16}ON_2$, 252.1263).[14]

The fractions, whose TLC analysis (2.3:1 ethyl acetate–benzene) gave a R_f 0.15 spot, yielded 28 mg (1%) of colorless needles of tetracycle **8a**, mp 125–127 °C: IR (KBr) NH 3250 (m), C=O, C=C 1580 (s) cm^{-1}; UV (EtOH) λ_{max} 219 nm (log ϵ 4.48), 302 (4.62); ^1H NMR δ 1.2–4.7 (m, 9, $4CH_2$, CH), 7.0–7.5 (m, 5, indole, vinyl Hs), 8.92 (s, 1, CHO), *m/e* 252 (M^+, base), 251 (48%), 223 (43), 156 (60), 32 (99), 28 (99). Exact mass: *m/e* 252.1250 (calcd for $C_{16}H_{16}ON_2$, 252.1263).[14]

A solution of 157 mg of vinylogous formamide **7a** in 7 mL of glacial acetic acid was left at room temperature for 7 h. It was poured into ice-cold, saturated sodium bicarbonate solution and extracted with methylene chloride. The extract was washed, dried, and evaporated under vacuum. Thick-layer chromatography on silica gel (two developments with 4:1 ethyl acetate–benzene) yielded a solid, whose crystallization from methanol produced 55 mg (35%) of tetracycle **8a**, identical in all respects with the above sample.

Vinylogous Amide 11. Dry acetone (4.96 mL, 67.1 mmol), and 1.36 mL (9.8 mmol) of dry triethylamine were added to a suspension of 3.27 g (10.3 mmol) of salt **6** in 20 mL of dimethyl sulfoxide and the mixture stirred under argon at room temperature for 72 h. It then was poured onto ice and extracted with methylene chloride. The extract was washed, dried, and evaporated. Chromatography of the residue on 5 g of alumina (activity IV) and elution with chloroform gave 356 mg of a syrup, whose thick-layer chromatography on silica gel (1.5:1 benzene–ethyl acetate, two developments) yielded three substances: 40 mg (1%) of semisolid **7a**, 18 mg of a ketone of undetermined constitution, and 42 mg (1%) of semisolid ketone **7b**: IR ($CHCl_3$) NH 3480 (m), C=O, C=C 1708 (s), 1668 (m), 1635 (s), 1580 (s) cm^{-1}; UV (MeOH) λ_{max} 232 nm (log ϵ 3.42), 284 (3.90), 292 (3.93), 364 (3.72); ^1H NMR δ (CD_2Cl_2) 2.04 (s, 3, Me), 2.38 (dd, 1, *J* = 16, 9 Hz, α-CO H), 2.70 (dd, 1, *J* = 16, 4 Hz, α-CO H), 3.02 (t, 2, *J* = 7 Hz, 2 benzyl H), 3.52 (t, 2, *J* = 7 Hz, NCH_2), 3.43 (m, 1, H-4), 4.96 (dd, 1, *J* = 8, 4 Hz, H-5), 5.81 (d, 1 *J* = 8 Hz, H-6), 6.41 (s, 1, H-2), 7.0–7.6 (m, 5, indole Hs), 8.79 (s, 1, CHO).

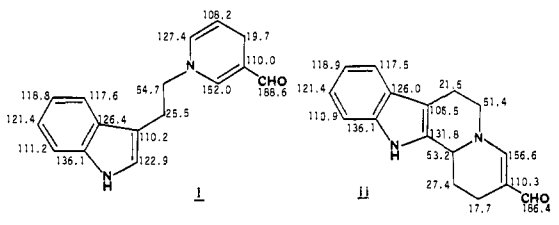
A solution of 38 mg (0.12 mmol) of ketone **7b** in 3 mL of dry tetrahydrofuran was added to a stirring suspension of 18 mg (0.38 mmol) of sodium hydride (50% in mineral oil) in 4 mL of dry tetrahydrofuran at 0 °C under a stream of argon, and the mixture was stirred at room temperature for 72 h. After evaporation of the solvent to dryness, 20 mL of methylene chloride and 7 mL of saturated ammonium chloride were added. The resultant precipitate was filtered, washed, and chromatographed on 5 g of silica gel. Elution with 12:1 methylene chloride–methanol led to a solid, whose crystallization from acetone gave 15 mg (42%) of yellow, crystalline tetracycle **11**, mp 245–247 °C: IR (KBr) NH 3300 (br m), C=O, C=C 1643 (s), 1600 (s) cm^{-1}; UV (MeOH) λ_{max} 244 nm (log ϵ 3.87), 271 (4.30), 342 (3.92), 372 (4.06); ^1H NMR δ (MeOH-d_4) 3.37 (t, 2 *J* = 6 Hz, 2 benzyl H), 4.57 (t, 2, *J* = 6 Hz, NCH_2), 6.69 (br s, 1, α-keto H), 6.82 (s, 1, indole H-2), 6.97 (t, 1, *J* = 8 Hz, H-5), 7.02 (br d, 1, *J* = 9 Hz, α-keto H), 7.09 (t, 1, *J* = 8 Hz, H-6), 7.33 (d, 1, *J* = 8 Hz, H-7), 7.38 (d, 1, *J* = 7 Hz, β-eneamino H), 7.46 (d, 1, *J* = 8 Hz, H-4), 7.60 (d, 1, *J* = 9 Hz, β-keto H), 7.65 (d, 1, *J* = 7 Hz, α-enamino H), 8.32 (s, 1, α-enamino H). Exact mass: *m/e* 288.1284 (calcd for $C_{19}H_{16}ON_2$, 288.1258).

Isoquinoline Salt 12b. Trimethyloxonium tetrafluoroborate, 85 mg (0.57 mmol), was added to a stirring suspension of 181 mg (0.52 mmol) in 18 mL of dry nitromethane; stirring was continued at room temperature under argon for 36 h. The mixture was evaporated under vacuum at room temperature and the solid residue, 194 mg, subjected to thick-layer chromatography on silica gel. Development with 43:8:1 methylene chloride–methanol–water led to two substances, crystallization of the first of which from methanol yielded 114 mg (49%) of pale yellow, crystalline salt **12b**, mp 184 °C: IR (KBr) NH 3420 (s), C=O 1720 (s), C=C 1643 (s), 1605 (s), 1570 (m) cm^{-1}; UV (MeOH) λ_{max} 257 nm (log ϵ 4.40), 274 (3.91), 282 (3.92), 291 (3.92), 326 (3.92); ^1H NMR δ (CD_3CN) 3.45 (t, 2, *J* = 6 Hz, 2 benzyl H), 4.00, 4.11 (s, 3 each, 2 OMe) 4.81 (t, 2, *J* = 6 Hz, NCH_2), 6.9–7.5 (m, 5, indole Hs), 7.81 (d, 1, *J* = 9 Hz, H-7), 8.04 (d, 1 *J* = 6 Hz, H-3), 8.14 (d, 1 *J* = 6 Hz, H-4), 8.28 (d, 1, *J* = 9 Hz, H-8), 9.00 (s, 1, H-1). Anal. ($C_{22}H_{21}O_3N_2BF_4$) C, H, N.

The second substance was pale yellow, crystalline salt **12a**, mp 183 °C: IR (KBr) NH 3420 (m), C=O 1660 (s), 1640 (s), C=C 1580 (s) cm^{-1}; UV (MeOH) 252 nm (log ϵ 4.10), 270 (4.32), 350 (4.24); ^1H NMR δ (Me_2SO-d_6) 3.43 (t, 2, *J* = 6 Hz, 2 benzyl H), 3.96 (s, 3, OMe), 4.85 (t, 2, *J* = 6 Hz, NCH_2), 7.0–7.6 (m, 5, indole Hs), 7.63 (d, 1, *J* = 9 Hz, H-7), 8.19 (d, 1, *J* = 7 Hz, H-3), 8.31 (d, 1, *J* = 9 Hz, H-8), 8.54 (d, 1, *J* = 7 Hz, H-4), 9.62 (s, 1, H-1). A suspension of 171 mg of the latter in 100 mL of saturated sodium bicarbonate solution was stirred at room temperature for 5 min. Filtration of the insoluble material and washing with water led to 120 mg (88%) of **10**, identical in all respects with authentic sample above.

***O*-Methyl-15,16,17,18,19,20-hexadehydroyohimbine (1).** Sodium borohydride, 4 mg (0.11 mmol), was added to a stirring suspension of 50 mg of salt **12b** in 4 mL of dry tetrahydrofuran at 0 °C under argon; stirring was continued at room temperature for 15 min. The mixture was evaporated under vacuum at room temperature. A trifluoroacetic acid solution, 5 mL, of the residue was kept at room temperature for 17 h and then neutralized with saturated sodium bicarbonate solution. The mixture was extracted with methylene chloride and the extract washed, dried, and evaporated. Thick-layer chromatography of the residue on silica gel (25:1 methylene chloride–methanol, two developments) led to three bands, one of which yielded 10 mg (25%) of pale yellow, crystalline ester **1**, mp 179–180 °C (lit.[1] mp 185 °C): UV (MeOH) λ_{max} 234 nm (log ϵ 3.55), 283 (3.93), 2.91 (3.89); ^1H NMR δ 2.6–3.2 (m, 7. 3 CH_2, CH), 3.49 (s, 3, CO_2Me), 3.57 (d, 1, *J* = 14 Hz, H-21), 3.96 (s, 3, OMe), 4.02 (d, 1, *J* = 14 Hz, H-21), 6.65 (d, 1, *J* = 9 Hz, H-18), 7.08 (d, 1, *J* = 9 Hz, H-19), 7.0–7.5 (m, 4, indole Hs). Exact mass: *m/e* 362.1625 (calcd for $C_{22}H_{22}O_3N_2$, 362.1630).

(14) The carbon shifts of **7a** and **8a** are listed on formulas i and ii, respectively.



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Registry No. (±)-**1**, 58649-69-7; (±)-**2**, 24252-70-8; **6**, 42907-66-4; **7a**, 81011-86-1; (±)-**7b**, 81011-87-2; (±)-**8a**, 81011-88-3; **10**, 81011-89-4; **11**, 81011-90-7; **12a**, 81011-92-9; **12b**, 81011-94-1; methyl acetoacetate, 105-45-3.