Syntheses of Strychnan- and Aspidospermatan-Type Alkaloids. 11. Total Syntheses of (−)-Lochneridine and (−)- and Racemic 20-*epi*-Lochneridine

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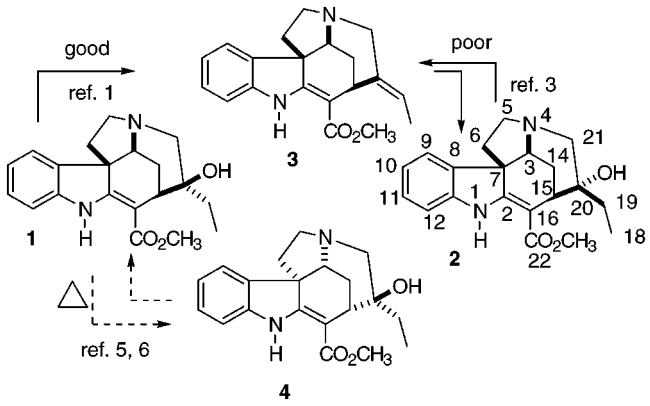
Enantioselective syntheses of (−)-lochneridine (**1**) and (−)-*epi*-lochneridine (**2**) were obtained by two alternative C-20 diastereoselective syntheses of the respective pentacyclic (3a*S*,5*S*,11b*R*)-methyl 12-oxo-3,5-ethano-2,3,3a,4,5,7-hexahydro-3*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate ((−)-**8**) and tetracyclic methyl (2*S*,3a*S*,5*R*,11b*R*))-3-benzyl-2,3,3a,4,5,7-hexahydro-5-(2-(1-butenyl))-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate ((−)-**12b**) precursors from tryptophan derived 2-[(methoxycarbonyl)methyl]-3-[2(*S*)-(methoxy or benzyloxycarbonyl)-2-(N^b-benzyl)aminoethyl]indole (**15** or **16**). While a modified Grignard reaction of the ketone (−)-**8** provided (−)-lochneridine (**1**), dihydroxylation and cyclization of the olefin (−)-**12b** gave its C-20 epimer (**2**).

The alkaloid (−)-lochneridine (**1**)[1] was isolated from *Catharanthus roseus*[2] and its 20-hydroxy epimer (**2**) has been obtained by oxidation of the C-19,20 double bond in akuammicine (**3**).[3] The enantiomer of that oxidation product, (+)-20-*epi*-lochneridine (3,7,15-*epi*-lochneridine, **4**), an alkaloid isolated from *Tabernaemontana pandacaqui*,[4] represents an interesting example of a natural skeletal enantiomerism in strychnan-type alkaloids that has been synthetically achieved in analogous examples by their thermal isomerization.[5,6] The present paper describes enantioselective total syntheses of (−)-lochneridine (**1**) and (−)-20-*epi*-lochneridine (**2**), and since the former (easily)[1] and the latter (sparingly)[3] have been shown to undergo dehydration to akuammicine (**3**), these syntheses also provide enantioselective routes to that alkaloid (Scheme 1).

Scheme 1



Synthetic access to (−)-lochneridine (**1**) and its C-20 epimer (**2**) seemed relatively simple by extension of transformations of the tetracyclic aldehyde **5**[7] to an ethyl ketone **6**, i.e., by its reaction with a sulfur ylide and cyclization of a resulting epoxide followed by N^b-debenzylation. An analogous construction of a ring D C-20 alcohol had been obtained directly from the aldehyde **5** in our first synthesis of racemic strychnine.[7] However, the ring D annelation starting from the ketone **6** could not be realized, and we were also not able to cyclize an N^b-(phenylthio)methyl ketone **7** (Scheme 2).

Consequently, we turned to the sensitive pentacyclic ketone intermediate (−)-**8** (Scheme 2) of our second strychnine synthesis.[8] Its reaction with ethylmagnesium bromide led only to destruction of the starting material, and no substantial amounts of characterizable products were obtained. However, softening of the Grignard reagent by addition of ceric chloride, with a reaction at −78 °C, resulted in a 73% yield of a tertiary alcohol with complete diastereoselection for the formation of (−)-lochneridine (**1**). ^{1}H NMR NOE interaction of a C-14 methylene bridge hydrogen at δ 2.10 with the C-19 methylene hydrogens of the ethyl substituent at δ 1.80 established the stereochemistry of the C-20 alcohol.

To obtain the relative stereochemistry of 20-*epi*-lochneridine (**2**), a new synthetic pathway was required. This was established in reaction sequences leading to racemic and to (−)-20-*epi*-lochneridine (Scheme **4**).

From the foregoing results, it seemed desirable to generate a tetracyclic intermediate that incorporates all carbon atoms of the final alkaloid skeleton and that would allow stereoselective introduction of the C-20 hydroxyl function. To that end, 2-ethylacrolein was converted by a Horner−Emmons condensation (Scheme 3) to 1-(ethoxycarbonyl)-3-ethylbutadiene (**9**).[9] Its reduction to the corresponding allylic alcohol and a PCC oxidation provided the diene aldehyde **10**. A condensation

(1) (a) Nakagawa, Y.; Wilson, J. M.; Budzikiewicz, H.; Djerassi, C. *Chem. Ind.* **1962**, 1986. (b) Djerassi, C.; Nakagawa, Y.; Wilson, J. M.; Budzikiewicz, H.; Gilbert, B.; Antonaccio, L. D. *Experientia* **1963**, *19*, 467.

(2) Svoboda, G, H.; Gorman, M.; Neuss, N.; Barnes, A. J., Jr. *J. Pharm. Sci.* **1961**, *50*, 409.

(3) Mirand, C.; Massiot, G.; Le Men-Olivier, L.; Lévy, J. *Tetrahedron Lett.* **1982**, *23*, 1257.

(4) Lathuillere, P.; Olivier, L.; Lévy, J.; Le Men, J. *Ann. Pharm. Fr.* **1966**, *24*, 547.

(5) For C-3,7,15-epimerization of 19,20-dihydroakuammicine, see: Scott, A. I.; Yeh, C. L. *J. Am. Chem. Soc.* **1974**, *96*, 2273.

(6) Kuehne, M. E.; Frasier, D. A.; Spitzer, T. D. *J. Org. Chem.* **1991**, *56*, 6, 2696.

(7) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1993**, *58*, 7490.

(8) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1998**, *63*, 9427.

(9) Sundberg, R. J.; Bukowick, P. A.; Holcombe, F. O. *J. Org. Chem.* **1967**, *32*, 2938.

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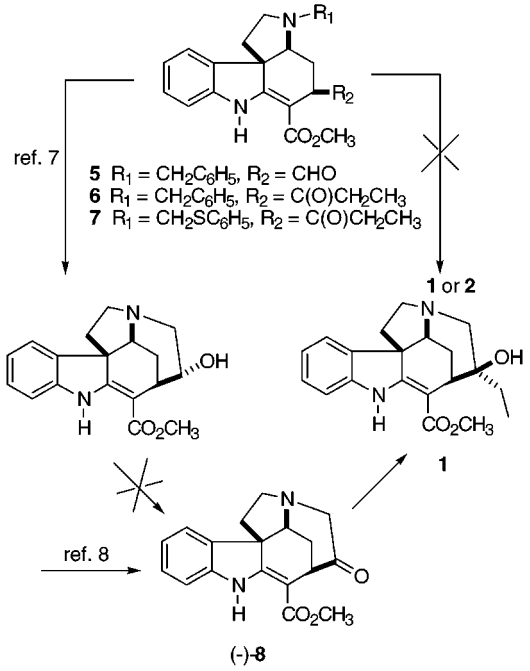
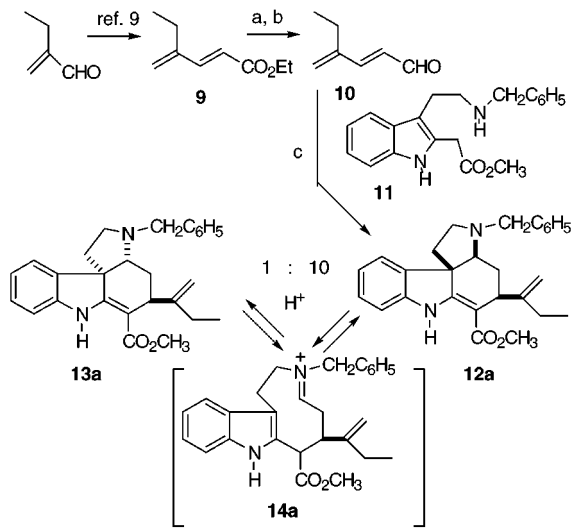
Scheme 2

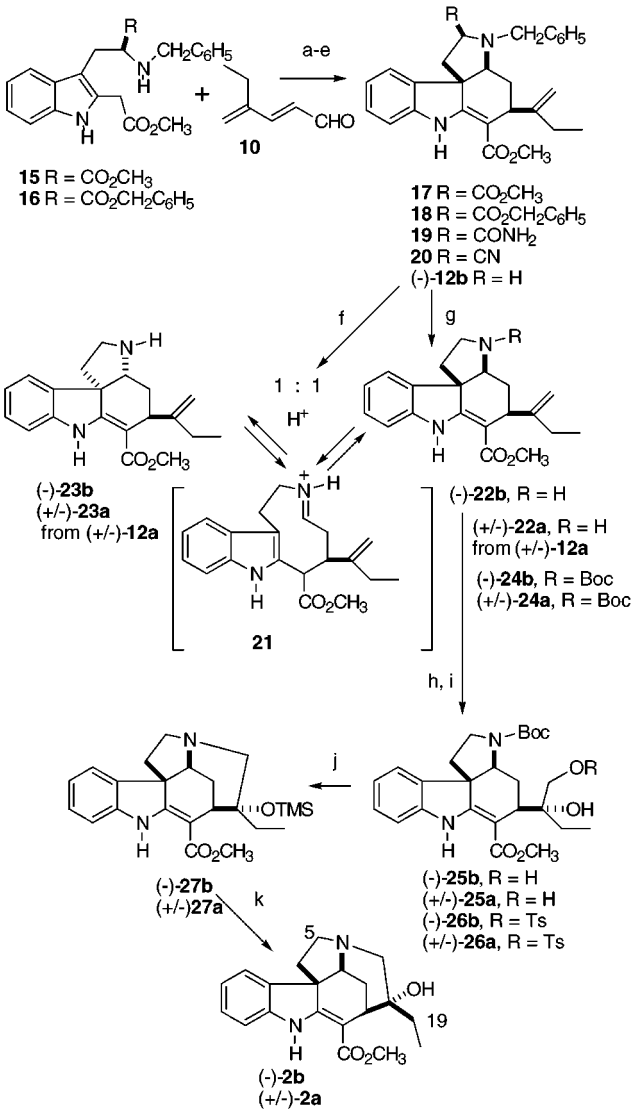


Scheme 3[a]



[a] Key: (a) LAH, 90%; (b) PCC, 80%; (c) benzene, benzoic acid, 75 °C, 18 h, 57%.

Scheme 4[a]



[a] Key: (a,b) benzoic acid, benzene, reflux 10 h/18 h, 79%/70%; (c) MeOH, NH_3, rt, 5 d, 75%; (d) TFAA, CH_2Cl_2, 0 °C to rt, 40 min; (e) KBH_4, EtOH, 75−80 °C, 4 h, 74% for d + e; (f) H_2/Pd, HOAc, 91%; (g) HCO_2NH_4, Pd/C, MeOH, EtOAc, reflux 2 h; (h) $(t\text{-Boc})_2O$, THF, aqueous K_2CO_3, 92%; (i) OsO_4, pyridine, 0 °C, $NaHSO_3$, Ts_2O, Et_3N, rt, 3 h, 62%; (j) TMSOTf, Et_3N, rt, 1 h, MeOH, 50−60 °C, 2 h, 85%; (k) *n*-Bu_4NF, THF, 2 h, rt, 94%.

of this aldehyde **10** with 2-(methoxycarbonylmethyl)-N^b-benzyltryptamine (**11**),[10] catalyzed by benzoic acid, provided a 10:1 mixture of racemic tetracyclic vinylogous urethanes **12a** and **13a**. Formation of the minor isomer **13a** appears to be the result of epimerization through the imonium salt **14a** since the minor epimer **13a** was formed, in the same relative ratio, on subjecting the major tetracyclic product **12a** to the initial acidic reaction conditions.

For an enantioselective synthesis of this tetracyclic urethane (−)-**12b**, the aldehyde **10** was condensed with tryptophan derived 2-[(methoxycarbonyl)methyl]-3-[2(*S*)-(methoxy or benzyloxycarbonyl)-2-(N^b-benzyl)aminoethyl]indole (Scheme 4, **15** or **16**).[8,11] Conversion of the product tetracyclic urethane esters **17** or **18** to an amide **19**, its dehydration to a nitrile **20**, and final reduction with potassium borohydride, furnished the tetracyclic urethane (−)-**12b**. The tetracyclic products **17** and **18** were obtained without evidence of alternative stereoisomers. Their relative stereochemistry was evident from an NOE interaction of a vinyl hydrogen with the methylene β-hydrogen on the pyrrolidine ring, confirming the cis configuration of these structural moieties.[12]

Hydrogenolysis of the tetracyclic N^b-benzylamines (±)-**12a** or (−)-**12b** with Pd/C in acetic acid gave a secondary amine product without reduction of the terminal double bond. However, under these acidic conditions, epimerization arose through the imonium salt **21**, and the respective secondary amines (±)-**22a** or (−)-**22b** and (±)-**23a** or (+)-**23b** were formed formed in equal amounts.

(10) Parsons, R. L.; Berk, J. D.; Kuehne, M. E. *J. Org. Chem.* **1993**, *58*, 7482.

(11) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1997**, *62*, 7950.

(12) For ^1H NMR signal assignments see supplemental spectra, **17**, and ref 11.

However, hydrogenolysis of the N^b-benzyl substituent with Pd/C and ammonium formate in methanol and ethyl acetate furnished the secondary amines (±)-**22a** or (−)-**22b**, respectively, without epimerization.

Protection of the secondary amine function in (±)-**22a** or (−)-**22b** with $(t\text{-Boc})_2O$ and oxidation of the resulting olefinic urethane (±)-**24a** or (−)-**24b** with osmium tetroxide led to the stereoselective formation of a diol (±)-**25a** or (−)-**25b**. Its monotosylation at the primary hydroxyl group ((±)-**26a** or (−)-**26b**), silylation of the tertiary alcohol and cyclization on heating, provided the pentacyclic TMS ether (±)-**27a** or (−)-**27b**. Cleavage of the silyl ether function with fluoride completed the syntheses of racemic (**2a**) and (−)-20-*epi*-lochneridine ((−)-**2b**). ^{1}H NMR NOE interactions of the C-19 methylene hydrogen of the ethyl substituent at δ 1.39 with a C-5 hydrogen of the pyrrolidine ring at δ 3.18 established the C-20 tertiary alcohol stereochemistry.

An elegant, very different synthesis of racemic 20-*epi*-lochneridine (**2a**) was recently reported.[13]

Experimental Section

(−)-Lochneridine (1). To anhydrous $CeCl_3$ (148 mg, 0.58 mmol) in 1 mL of THF at −78 °C was added EtMgBr (129 μL, 0.388 mmol, 3.0 M in Et_2O) dropwise. The mixture was stirred for 30 min. A solution of (3a*S*,5*S*,11b*R*)-methyl 12-oxo-3,5-ethano-2,3,3a,4,5,7-hexahydro-3*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate ((−)-**8**,[8] 30 mg, 0.097 mmol) in 1 mL of THF was cannulated into the above mixture. The mixture was stirred for another 30 min at −78 °C and then warmed to room temperature. The reaction was quenched by adding 5% NH_4OH. The aqueous phase was extracted with dichloromethane several times. The residue, obtained on drying and concentration, was chromatographed on a silica gel column, eluting with CH_2Cl_2/MeOH (9:1) to afford 24 mg (73% yield) of (−)-lochneridine: R_f = 0.29 (CH_2Cl_2/MeOH, 9:1, CAS blue); mp 209−211 °C (lit.[4] mp 211−214 °C); $[\alpha]^{24}_D$ −614 (*c* = 0.09, $CHCl_3$), (lit.[4] $[\alpha]_D$ −608); UV λ_{max} (EtOH) 206, 230, 298, 328 nm; IR (KBr) ν_{max} 3365, 1671, 1599 cm^{-1}; ^{1}H NMR δ 8.82 (s, 1 H), 7.19 (d, *J* = 7.4 Hz, 1 H), 7.15 (t, *J* = 7.7 Hz, 1 H), 6.92 (t, *J* = 7.4 Hz, 1 H), 6.84 (d, *J* = 7.8 Hz, 1 H), 3.93 (s, 1 H), 3.82 (s, 3 H), 3.12 (ddd, *J* = 6.8, 6.8, 10.5 Hz, 1 H), 3.06 (s, 1 H), 2.99 (m, 1 H), 2.85 (d, *J* = 12.1 Hz, 1 H), 2.84 (m, 1 H), 2.64 (s, br, 1 H, OH), 2.44 (d, *J* = 12.1 Hz, 1 H), 2.10 (ddd, *J* = 3.1, 3.1, 13.6 Hz, 1 H), 1.88 (ddd, *J* = 2.2, 6.8, 13.2 Hz, 1 H), 1.80 (m, 2 H), 1.30 (ddd, *J* = 1.0, 1.0, 13.6 Hz, 1 H), 1.03 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR δ 169.0, 144.1, 135.1, 127.8, 121.3, 120.1, 109.8, 98.3, 71.2, 59.7, 57.8, 55.8, 53.9, 51.5, 43.7, 37.5, 31.9, 27.6, 7.0; MS *m*/*z* 341 (46), 340 (M$^+$, 100), 283 (56), 241 (27), 226 (72), 208 (33), 194 (84), 184 (26), 180 (40), 167 (88), 156 (18), 154 (30), 149 (30), 139 (19), 126 (19), 115 (25), 111 (21). Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.57; H, 7.11; N, 8.23. Found: C, 70.30; H, 7.14; N, 8.22.

Methyl (2*S*,3a*S*,5*R*,11b*R*)-2-(Methoxycarbonyl)-3-benzyl-2,3,3a,4,5,7-hexahydro-5-(2-(1-butenyl))-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate and Methyl (2*S*,3a*S*,5*R*,11b*R*)-2-(Benzyloxycarbonyl)-3-benzyl-2,3,3a,4,5,7-hexahydro-5-(2-(1-butenyl))-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (17 and 18). A solution of 4.8 g (0.12 mmol) of lithium aluminum hydride in 15 mL of ether was added to 15.5 g (0.10 mmol) of ethyl 4-ethyl-2,4-pentadienoate,[9] in 20 mL of ether, with stirring at 0 °C. After the reaction was warmed to room temperature, 10% aqueous sodium hydroxide was added, and the resulting solution was extracted with ether and concentrated, 10.0 g (90% yield) of 4-ethyl-2,4-pentadienol was obtained.

The crude alcohol (3.00 g, 26.8 mmol) in 25 mL of dichloromethane was added dropwise, with stirring at 0 °C, to 11.5 g (53.6 mmol) of pyridinium chlorochromate in 50 mL of dichloromethane. After warming to room temperature and continued stirring for 30 min, the reaction mixture was diluted with ether and filtered through Florisil. Concentration and chromatography on a silica gel column, eluting with ether/hexane, 5:95, provided 2.4 g (80% yield) of 4-ethyl-2,4-pentadienal (**10**) with R_f = 0.35 (silica gel, ether/hexane, 5:95, detection UV), which was used directly in the following condensation.

A solution of 2-[(methoxycarbonyl)methyl]]-3-[2-(*S*)-(methoxycarbonyl)-2-(N^b-benzylamino)ethyl]indole (**15**,[8] 1.2 g, 3.15 mmol), 4-ethyl-penta-(2,4)-dienal (**10**, 382 mg, 3.47 mmol), benzoic acid (385 mg, 3.154 mmol), and 10 mg of dihydroquinone in 25 mL of benzene was heated at reflux with a Dean−Stark trap. After 5 h, 181 mg of the aldehyde **10** (1.78 mmol) was introduced again. The reaction mixture was cooled to room temperature after a total of 10 h. The organic phase was washed with 5% sodium carbonate. The residue, obtained on drying and concentration, was purified on a silica gel column, eluted with Et_2O/Hex (3:7), to give 1.18 g of the title product **17** (79% yield): R_f = 0.39 (Et_2O/Hex, 3:7, CAS blue); $[\alpha]^{25}_D$ −195 (*c* = 1.0, MeOH); UV λ_{max} (EtOH) 200, 228, 298, 328 nm; IR (KBr) ν_{max} 3363, 1748, 1673, 1607 cm^{-1}; ^{1}H NMR δ 9.25 (s, 1 H), 7.36 (m, 5 H), 7.11 (t, *J* = 7.6 Hz, 1 H), 6.79 (d, *J* = 7.7 Hz, 1 H), 6.74 (t, *J* = 7.4 Hz, 1 H), 6.46 (d, *J* = 7.4 Hz, 1 H), 4.79 (s, 1 H), 4.71 (s, 1 H), 4.80 (d, *J* = 15.2 Hz, 1 H), 4.70 (d, *J* = 15.2 Hz, 1 H), 3.74 (s, 3 H), 3.73 (m, 2 H), 3.58 (s, 3 H), 3.53 (d, *J* = 5.7 Hz, 1 H), 2.74 (dd, *J* = 11.6, 11.6 Hz, 1 H), 2.57 (qd, *J* = 7.4, 14.8 Hz, 1 H), 2.21 (m, 2 H), 1.72 (dd, *J* = 5.5, 11.6 Hz, 1 H), 1.27 (ddd, *J* = 6.1, 6.1, 14.1, Hz, 1 H), 1.14 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR δ 172.7, 168.8, 164.2, 153.7, 142.8, 137.2, 136.2, 130.3, 128.2, 127.9, 127.4, 121.7, 120.5, 109.2, 108.4, 97.4, 65.2, 63.2, 56.5, 54.3, 51.5, 51.0, 45.2, 39.17, 3.4, 27.3, 12.0; MS *m*/*z* 473 (4), 472 (M$^+$, 12),414 (11), 381 (15), 268 (34), 236 (18), 212 (11), 208 (25), 202 (10), 194 (12), 180 (14), 167 (11), 91 (100).

The benzyl ester **18** could be prepared by the same procedure from 2-[(methoxycarbonyl)methyl]-3-[2-(*S*)-(benzyloxycarbonyl)-2-(N^b-benzylamino)ethyl]indole (**16**)[11] in 70% yield after 18 h of reflux in benzene and purification on a silica gel column (EtOAc/Hex, 1:9): R_f = 0.33 (Et_2O/Hex, 1:4, CAS blue); UV λ_{max} (EtOH) 202, 226, 298, 328 nm; IR (KBr) ν_{max} 3364, 1734, 1672, 1608 cm^{-1}; ^{1}H NMR δ 9.22 (s, 1 H), 7.36−7.23 (m, 10 H), 7.09 (t, *J* = 7.3 Hz, 1 H), 6.77 (d, *J* = 7.6 Hz, 1 H), 6.71 (t, *J* = 7.3 Hz, 1 H), 6.43 (d, *J* = 7.3 Hz, 1 H), 5.06 (d, *J* = 12.1 Hz, 1 H), 4.98 (d, *J* = 12.1 Hz, 1 H), 4.65 (s, 2 H), 4.04 (d, *J* = 13.4 Hz, 1 H), 3.95 (d, *J* = 13.4 Hz, 1 H), 3.74 (m, 2 H), 3.71 (s, 3 H), 3.53 (m, 1 H), 2.73 (dd, *J* = 11.6, 11.6 Hz, 1 H), 2.42 (m, 1 H), 2.16 (m, 1 H), 2.12 (m, 1 H), 1.74 (dd, *J* = 5.5, 11.6 Hz, 1 H), 1.24 (m, 1 H), 1.04 (t, *J* = 7.4 Hz, 3 H); MS *m*/*z* 473 (4), 472 (M$^+$, 1).

Racemic Methyl (3a*S,5*R**,11b*R**)-3-Benzyl-2,3,3a,4,5,7-hexahydro-5-(2-(1-butenyl))-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (12a) and Methyl (3a*R**,5*R**,11b*S**)-3-Benzyl-2,3,3a,4,5,7-hexahydro-5-(2-(1-butenyl))-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (13a).** A solution of 2-[(methoxycarbonyl)methyl]]-3-[2-(N^b-benzylamino)ethyl]indole (**11**, 1.1 g, 3.42 mmol),[10] 4-ethylpenta-(2,4)-dienal (**10**, 451 mg, 4.1 mmol), benzoic acid (42 mg, 0.34 mmol), $MgSO_4$ (2 g), and 10 mg of dihydroquinone, in 25 mL of benzene, was heated in a 75 °C oil bath. After 5 h, 451 mg of additional aldehyde (4.1 mmol) was introduced. The reaction mixture was cooled to room temperature after a total of 18 h. The organic phase was then washed with 5% sodium carbonate. The residue, obtained on drying and concentration, was purified on a silica gel column, eluted with Et_2O/Hex (7:93), to give 720 mg of the title product (**12a**, 51% yield) and 80 mg of its epimer (**13a**, 6% yield).

For the major isomer **12a**: R_f = 0.22 (Et_2O/Hex, 3:97, CAS blue); UV λ_{max} (EtOH) 204, 226, 300, 326 nm; IR (KBr) ν_{max} 3366, 1674, 1609 cm^{-1}; ^{1}H NMR δ 9.28 (s, 1 H), 7.34 (m, 4 H), 7.26 (m, 1 H), 7.14 (m, 2 H), 6.86 (t, *J* = 7.5 Hz, 1 H), 6.82 (d, *J* = 7.9 Hz, 1 H), 4.81 (s, 1 H), 4.76 (s, 1 H), 4.17 (d, *J* = 13.5

(13) Bonjoch, J.; Solé, D.; Garcia-Rubio, S.; Bosch, J. *J. Am. Chem. Soc.* **1997**, *119*, 7230.

Hz, 1 H), 3.74 (s, 3 H), 3.61 (m, 1 H), 3.60 (d, J = 13.5 Hz, 1 H), 3.28(d, J = 3.8 Hz, 1 H), 2.82 (dd, J = 6.5, 8.5 Hz, 1 H), 2.55−2.41 (m, 3 H), 2.28 (m, 1 H), 2.21 (dq, J = 15.0, 7.4 Hz, 1 H), 1.54 (m, 1 H), 1.42 (ddd, J = 5.6, 5.6, 11.7 Hz, 1 H), 1.14 (t, J = 7.4 Hz, 3 H); ^{13}C NMR δ 169.0, 166.0, 154.1, 143.2, 139.3, 138.4, 128.5, 128.3, 127.7, 126.8, 121.9, 120.3, 109.1, 107.7, 96.9, 66.5, 58.4, 55.6, 51.0, 50.7, 42.6, 39.5, 29.2, 27.6, 12.16; MS m/z 415 (M^+ + 1, 15), 146 (32), 143 (8), 91 (100). Anal. Calcd for $C_{27}H_{30}N_2O_2\cdot 0.33\ H_2O$: C, 77.11; H, 7.35; N, 6.66. Found: C, 77.62; H, 7.19; N, 6.46.

For the minor isomer **13a**: R_f = 0.16 (Et_2O/Hex, 3:97, CAS blue); UV λ_{max} (EtOH) 204, 226, 298, 328 nm; IR (KBr) ν_{max} 3368, 1676, 1609 cm^{-1}; ^{1}H NMR δ 9.05 (s, 1 H), 7.41 (m, 2 H), 7.35 (m, 3 H), 7.27 (m, 1 H), 7.15 (t, J = 7.5 Hz, 1 H), 6.89 (t, J = 7.5 Hz, 1 H), 6.82 (d, J = 7.7 Hz, 1 H), 4.69 (s, 1 H), 4.58 (s, 1 H), 3.95 (d, J = 13.2 Hz, 1 H), 3.84 (d, J = 13.2 Hz, 1 H), 3.68 (s, 3 H), 3.42 (dd, J = 5.5, 5.5 Hz, 1 H), 3.32 (dd, J = 5.4, 5.4 Hz, 1 H), 2.82 (m, 2 H), 2.22 (m, 1 H), 2.08 (q, J = 7.3 Hz, 2 H), 1.88 (ddd, J = 5.4, 5.5, 11.3 Hz, 1 H), 1.80 (m, 1 H), 1.62 (ddd, J = 5.4, 5.5, 11.3 Hz, 1 H), 1.08 (t, J = 7.3 Hz, 3 H); ^{13}C NMR δ 169.1 165.8, 155.7, 143.7, 139.6, 137.5, 128.6, 128.2, 127.6, 126.9, 122.4, 120.5, 109.2, 107.3, 97.3, 61.2, 56.7, 55.2, 50.42, 49.2, 43.4, 38.8, 31.8, 28.1, 12.5; MS m/z 415 (M^++1, 42), 146 (53), 143 (16), 91 (100).

Isomerization of the C-15 epimers **12a** and **13a**: A solution of epimer **12a** (50 mg, 0.12 mmol) and benzoic acid (1.5 mg, 0.012 mmol) in 5 mL of benzene was heated in a 75 °C oil bath for 6 h. Workup and purification, as above, gave 35 mg of the epimer **12a** (70% yield) and 4 mg of epimer **13a** (8% yield).

Methyl (2*S*,3a*S*,5*R*,11b*R*)-2-(Aminocarbonyl)-3-benzyl-2,3,3a,4,5,7-hexahydro-5-(2-(1-butenyl))-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (19). Method a: A solution of 1.00 g (2.12 mmol) of the dimethyl ester **17** in 30 mL of of dry methanol, at 0 °C, was saturated with dry NH_3(g). The solution was stirred at room temperature for 5 days and then the solvent was evaporated under vacuum. The residue was chromatographed on a silica gel column, eluted with Hex/EtOAc (1:1), to afford 725 mg (75% yield) of amide **19** as a white solid.

Method b: A solution of the ester **17** in methanol was saturated with with dry NH_3(g) and heated in a sealed tube for 17 h at 110 °C. Concentration and purification as above gave a 52% yield of the amide **19**.

The benzyl ester **18** was converted into amide **19** by the same procedure. Data for **19**: R_f = 0.33 (EtOAc/Hex, 1:1, CAS blue); $[\alpha]^{24}_D$ −211 (c = 1.0, $CHCl_3$); UV λ_{max} (EtOH) 206, 228, 298, 328 nm; IR (KBr) ν_{max} 3440, 3369, 1683, 1608 cm^{-1}; ^{1}H NMR δ 9.17 (s, 1 H), 7.39 (m, 3 H), 7.28 (m, 2 H), 7.08 (t, J = 7.6 Hz, 1 H), 6.77 (d, J = 7.7 Hz, 1 H), 6.68 (t, J = 7.5 Hz, 1 H), 6.61 (d, br, J = 3.8 Hz, 1 H), 6.28 (d, J = 7.3 Hz, 1 H), 5.44 (d, br, J = 3.8 Hz, 1 H), 4.84 (s, 1 H), 4.79 (s, 1 H), 3.99 (d, J = 13.5 Hz, 1 H), 3.85 (d, J = 13.5 Hz, 1 H), 3.72 (s, 3 H), 3.60 (m, 2 H), 3.57 (dd, J = 5.3, 11.7 Hz, 1 H), 2.43 (dd, J = 11.7, 11.7 Hz, 1 H), 2.40 (qd, J = 7.4, 14.9 Hz, 1 H), 2.23 (qd, J = 7.4, 14.9 Hz, 1 H), 2.15 (d, J = 14.5 Hz, 1 H), 1.83 (dd, J = 5.3, 11.7 Hz, 1 H), 1.29 (ddd, J = 5.9, 5.9, 14.5 Hz, 1 H), 1.12 (t, J = 7.4 Hz, 3 H); ^{13}C NMR δ 175.4, 168.6, 165.2, 153.0, 142.6, 136.8, 134.5, 130.7, 128.5, 128.0, 127.9, 121.5, 120.7, 109.7, 109.3, 96.4, 65.7, 64.3, 55.7, 54.5, 51.1, 47.3, 39.1, 29.7, 27.7, 12.3; MS m/z 458 (2), 457 (M^+, 5), 413 (27), 268 (20), 236 (11), 208 (15), 194 (12), 167 (14), 91 (100). Anal. Calcd for $C_{28}H_{31}N_3O_3$: C, 73.50; H, 6.83; N, 9.18. Found: C, 73.47; H, 6.44; N, 9.38.

Methyl (2*S*,3a*S*,5*R*,11b*R*)-3-Benzyl-2,3,3a,4,5,7-hexahydro-5-(2-(1-butenyl))-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate ((−)-12b). To a solution of the amide **19** (460 mg, 1.005 mmol) and Et_3N (697 μL, 5.0 mmol) in 10 mL of dichloromethane, at 0 °C, was added TFAA (282 μL, 2.0 mmol), dropwise. The solution was stirred at room temperature for 40 min, and saturated sodium bicarbonate was added to quench the reaction. The organic phase was extracted with dichloromethane. The nitrile **20**, obtained on drying and concentration, was dissolved in 10 mL of dry EtOH. KBH_4 (271 mg, 5.03 mmol) was added in several portions at room temperature. The reaction mixture was then heated in a 75−80 °C bath for 4 h. The solvent was evaporated under vacuum. The residue was dissolved in dichloromethane, and the solution washed with 5% NH_4OH. Concentration and chromatography on a silica gel column, eluted with Hex/EtOAc (5:95), afforded 308 mg (74% yield) of the tetracyclic amine (−)-**12b** as a white solid: $[\alpha]^{23}_D$ −230 (c = 0.8, $CHCl_3$); mp 104−6 °C (from EtOAc/Hex). Anal. Calcd for $C_{27}H_{30}N_2O_2\cdot 0.2\ H_2O$: C, 77.58; H, 7.26; N, 6.70. Found: C, 77.62; H, 7.19; N, 6.46.

(±)-Methyl (2*S,3a*S**,5*R**,11b*R**)-2,3,3a,4,5,7-Hexahydro-5-(2-(1-butenyl))-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (22a) and Its 2,3,11-Epimer (23a).** A mixture of the N^b-benzyl tetracyclic amine **12a** (100 mg, 0.24 mmol) and 10% Pd−C (26 mg, 0.024 mmol), in 5 mL of HOAc, was stirred under an atmosphere of hydrogen for 1.5 h. The solid was removed by filtration, and the filtrate was basified with concentrated NH_4OH at 0 °C. The aqueous phase was extracted with dichloromethane. The residue, obtained on concentration, was purified on a silica gel column that was eluted with MeOH/CH_2Cl_2 (5:95) to give 36 mg of the title product (±)-**22a** (46% yield) and 35 mg of its C-2,3,11-epimer (±)-**23a** (45% yield). For **22a**: R_f = 0.31 (MeOH/CH_2Cl_2, 5:95, CAS blue); mp 102 °C; UV λ_{max} (EtOH) 204, 228, 298, 326 nm; IR (KBr) ν_{max} 3360, 1674, 1607 cm^{-1}; ^{1}H NMR δ 9.30 (s, 1 H), 7.23 (d, J = 7.4 Hz, 1 H), 7.15 (t, J = 7.2 Hz, 1 H), 6.88 (t, J = 7.5 Hz, 1 H), 6.84 (d, J = 7.7 Hz,1 H), 4.87 (s, 1 H), 4.85 (s, 1 H), 3.77 (s, 1 H), 3.72 (s, 1 H), 3.59 (s, 1 H), 3.09 (dd, J = 6.3, 11.6 Hz, 1 H), 2.96 (ddd, J = 5.3, 11.6, 11.6 Hz, 1 H), 2.31 (qd, J = 7.4, 14.7 Hz, 1 H), 2.25 (m, 2 H), 2.14 (ddd, J = 3.1, 0.31, 14.5 Hz, 1 H), 1.77 (dd, J = 5.3, 12.2 Hz, 1 H), 1.66 (ddd, J = 6.4, 6.4, 14.7 Hz, 1 H), 1.14 (t, J = 7.4, 3 H); ^{13}C NMR δ 168.8, 166.7, 154.0, 143.2, 137.9, 127.9, 121.3, 120.7, 109.5, 109.2, 96.2, 63.0, 51.0, 46.3, 45.9, 39.5, 30.9, 27.6, 12.6; MS m/z 326 (23), 325 (M^+, 100), 324 (90), 280 (10), 268 (34), 265 (38), 254 (27), 242 (76), 236 (29), 226 (13), 222 (27), 210 (49), 208 (55), 194 (33), 180 (33), 167 (30), 159 (34), 154 (16), 144 (8). Anal. Calcd for $C_{20}H_{24}N_2O_2\cdot 0.5H_2O$: C, 72.05; H, 7.56; N, 8.12. Found: C, 71.93; H, 7.32; N, 8.40.

For the C-2,3,11-epimer (±)-**23a**: R_f = 0.19 (MeOH/CH_2Cl_2, 5:95, CAS blue); UV λ_{max} (EtOH) 202, 226, 294, 328 nm; IR (KBr) ν_{max} 3364, 1682, 1609 cm^{-1}; ^{1}H NMR δ 9.15 (s, 1 H), 7.32 (d, J = 7.3 Hz, 1 H), 7.16 (t, J = 7.6 Hz, 1 H), 6.88 (t, J = 7.4 Hz, 1 H), 6.84 (d, J = 7.8 Hz, 1 H), 5.62 (s, br, 1 H), 4.67 (s, 1 H), 4.39 (s, 1 H), 3.66 (s, 3 H), 3.64 (m, 1 H), 3.34 (m, 2 H), 3.22 (m, 1 H), 2.34 (m, 1 H), 2.10 (m, 2 H), 1.91 (m, 2 H), 1.84 (m, 1 H), 1.06 (t, J = 7.4 Hz, 3 H); ^{13}C NMR δ 168.8, 163.7, 155.4, 144.0, 135.7, 128.1, 121.9, 120.7, 109.6, 107.9, 96.4, 55.5, 50.7, 42.9, 42.7, 39.3, 33.6, 29.7, 28.8, 12.5; MS m/z 325 (M^+, 63), 324 (13), 242 (29), 236 (12), 210 (11), 208 (32), 194 (16), 180 (27), 167 (25), 91 (55).

Methyl (2*S*,3a*S*,5*R*,11b*R*)-3-(*tert*-Butoxycarbonyl)-2,3,-3a,4,5,7-hexahydro-5-(2-(1-butenyl))-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate ((−)-24b) and Its Racemate (24a). A mixture of the tetracyclic N^b-benzylamine (−)-**12b** (370 mg, 0.893 mmol), ammonium formate (281 mg, 4.46 mmol), and 10% Pd−C (95 mg, 0.089 mmol), in 8 mL of MeOH and 2 mL of EtOAc, was heated at reflux for 2 h. The solid was removed by filtration, and the solvents were evaporated under vacuum. The residue was dissolved in dichloromethane, and the solution was washed with saturated $NaHCO_3$. The product **22b**, obtained on drying and concentration, was pure enough for the next reaction but it also could be purified on a column eluted with MeOH/CH_2Cl_2 (5:95) to afford the amine as a white solid.

The above crude product **22b** was dissolved in 6 mL of THF and 3 mL of water, and 247 mg of potassium carbonate (1.79 mmol) was added, followed by (t-Boc)$_2$O (234 mg, 1.07 mmol), in several portions. The solution was stirred at room temperature for 1 h, and then the aqueous layer was extracted with dichloromethane. The residue, obtained on drying and concentration, was purified on a silica gel column, eluted with EtOAc/Hex (1:9), to afford 350 mg (92% yield) of urethane (−)-**24b** as a white solid: R_f = 0.24 (EtOAc/Hex, 1:9, CAS blue); mp 150−151 °C (MeOH); $[\alpha]^{24}_D$ −259 (c = 0.35, $CHCl_3$); UV λ_{max} (EtOH) 204, 226, 298, 326 nm; IR (KBr) ν_{max} 3361, 1697, 1683, 1609 cm^{-1}; ^{1}H NMR δ 9.29 (s, 1 H), 7.15 (t, br, J = 7.1

Hz, 1 H), 7.07 (d, J = 7.1 Hz, 1 H), 6.87 (t, J = 7.1 Hz, 1 H), 6.83 (d, J = 7.8 Hz, 1 H), 4.79 (s, 1 H), 4.78 (s, 1 H), 4.26 (s, br, 0.5 H), 4.13 (s, br, 0.5 H), 3.72 (s, 3 H), 3.58 (m, 1 H), 3.50 (s, br, 1 H), 2.48 (m, 1 H), 2.30 (m, br, 0.5 H), 2.16 (qd, J = 7.3, 14.5, Hz, 1 H), 2.12 (qd, J = 7.3, 14.5 Hz, 1 H), 2.0 (m, br, 0.5 H), 1.77 (s, br, 1 H), 1.60 (m, 1 H), 1.52 (s, 9 H), 1.09 (t, J = 7.3 Hz, 2.5 H), 0.89 (t, J = 7.3 Hz, 0.5 H); ^{13}C NMR (more peaks observed due to the rotameres) δ 168.9, 155.0, 154.9, 154.1, 143.0, 138.5, 136.3, 136.1, 128.1, 121.4, 120.77, 109.2, 109.2, 107.3, 79.6, 59.8, 50.9, 50.8, 44.1, 43.6, 40.0, 39.7, 39.6, 38.7, 32.1, 31.1, 28.5, 27.3, 14.8, 13.4, 12.3; MS m/z: 425 (M^+ + 1, 19), 370 (46314 (74), 287 (100), 269 (11), 254 (11), 242 (11), 237 (19), 226 (16), 222 (12), 209 (19), 202 (10), 194 (43), 180 (16), 167 (20), 155 (18), 91 (23). Anal. Calcd for $C_{25}H_{32}N_2O_4 \cdot 0.5H_2O$: C, 69.26; H, 7.67; N, 6.46. Found: C, 69.66; H, 7.55; N, 6.35.

The racemate **24a**, obtained by the same procedure from racemic **12a**, had a mp of 145 °C (MeOH) and the same spectroscopic data.

Methyl (2*S*,3a*S*,5*R*,11b*R*)-3-(*tert*-Butoxycarbonyl)-2,3,-3a,4,5,7-hexahydro-5-(2-((1-tosyloxy-2-hydroxy)butenyl))-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate ((−)-26b and its Racemate 26a). To a solution of the urethane (−)-**24b** (230 mg, 0.542 mmol) in 8 mL of pyridine, at 0 °C, was added OsO_4 (145 mg, 0.569 mmol) in one portion. The solvent was evaporated in a vacuum after 4 h at 0 °C. The residue was dissolved in 20 mL of dichloromethane, and 10 mL of 10% $NaHSO_3$ solution was added. The mixture was stirred for 30 min and basified with saturated $NaHCO_3$. The aqueous layer was extracted with dichloromethane. The residue, obtained on drying and concentration, was passed through a short silica gel column, eluted with MeOH/CH_2Cl_2 (2:98), to afforded the crude diol (−)-**25b**, which was dissolved in 10 mL of CH_2Cl_2. Triethylamine (91 uL, 0.65 mmol) and Ts_2O (194 mg, 0.596 mmol) were added at 0 °C, and the solution was stirred at 0 °C for 3 h. The solvent was evaporated in a vacuum, and the residue was purified on a silica gel column, eluted with Hex/EtOAc (7:3), to afford 205 mg (62% yield) of the tosylate (−)-**26b** as a white solid: R_f = 0.26 (EtOAc/Hex, 3:7, CAS blue); $[\alpha]^{24}_D$ −166 (c = 0.8, $CHCl_3$); UV λ_{max} (EtOH) 204, 228, 296, 326 nm; IR (KBr) ν_{max} 3358, 1683, 1607 cm^{-1}; ^{1}H NMR δ 9.51 (s, 1 H), 7.78 (d, J = 8.1 Hz, 2 H), 7.33 (d, J = 8.1 Hz, 2 H), 7.16 (t, J = 7.6 Hz, 1 H), 7.05 (d, J = 7.4 Hz, 1 H), 6.88 (t, J = 7.4 Hz, 1 H), 6.83 (d, J = 7.7 Hz, 1 H), 4.21 (d, J = 9.9 Hz, 1 H), 4.10 (dd, J = 6.1, 6.1 Hz, 1 H), 3.88 (d, J = 9.9 Hz, 1 H), 3.70 (s, 3 H), 3.56 (dd, J = 3.6, 9.6 Hz, 2 H), 3.31 (dd, J = 4.4, 8.4 Hz, 1 H), 2.75 (m, 1 H), 2.43 (s, 3 H), 2.27 (s, 1 H, OH), 2.04 (m, 1 H), 1.90 (m, 1 H), 1.69 (m, 2 H), 1.59 (m, 1 H), 1.50 (s, 9 H), 0.83 (t, J = 7.5 Hz, 3 H); ^{13}C NMR δ 168.8, 154.6, 144.8, 142.3, 136.7, 132.9, 129.8, 128.1, 128.0, 121.4, 121.2, 109.4, 92.5, 80.0, 75.8, 73.5, 60.2, 54.0, 51.1, 44.8, 44.6, 37.7, 29.6, 28.7, 28.5, 28.4, 26.5, 21.6, 8.5; MS m/z 441 (M^+ − TsOH, 3), 427 (12), 370 (21), 314 (28), 299 (32), 281 (12), 269 (6), 226 (10), 194 (42), 186 (50), 182 (11), 180 (13), 167 (14), 155 (50), 107 (16), 91 (100).

The racemate **26a** was prepared by the same procedure from racemic urethane **24a**. It matched the above compound in spectroscopic data.

(−)-20-*epi*-Lochneridine Trimethylsilyl Ether (−)-(27b) and Its Racemate 27a. To a solution of 65 mg of the tosylate alcohol (−)-**26b** (0.11 mmol) and 59 μL of Et_3N (0.42 mmol) in 1.5 mL of dichloromethane at 0 °C was added 61 μL of TMSOTf (0.32 mmol), dropwise. After the solution was stirred at room temperature for 1 h, the reaction was quenched by adding saturated sodium bicarbonate. The aqueous phase was extracted with dichloromethane. The residue, obtained on drying and concentration, was dissolved in 10 mL of dry MeOH, and the solution was heated in a 50−60 °C oil bath for 2 h. Concentration and dissolution of the residue in dichloromethane, washing with 10% sodium carbonate, and concentration gave the cyclized product (−)-**27b**, which could be purified on a silica gel column, eluted with EtOAc/Hex (4:1), to afford 37 mg (85% yield) of product: R_f = 0.5 (EtOAc/Hex, 4:1, CAS blue); $[\alpha]^{24}_D$ − 586 (c = 0.25, $CHCl_3$); UV λ_{max} (EtOH) 204, 230, 296, 328 nm; IR (KBr) ν_{max} 3351, 1669, 1592 cm^{-1}; ^{1}H NMR δ 9.02 (s, 1 H), 7.16 (d, J = 7.3 Hz, 1 H), 7.03 (t, J = 7.5 Hz, 1 H), 6.88 (t, J = 7.4 Hz, 1 H), 6.79 (d, J = 7.7 Hz, 1 H), 3.86 (s, 1 H), 3.76 (s, 3 H), 3.05 (m, 1 H), 3.04 (s, 1 H), 2.86 (m, 2 H), 2.74 (dd, J = 7.1, 11.7 Hz, 1 H), 2.61 (ddd, J = 3.0, 3.0, 12.8 Hz, 1 H), 2.15 (d, J = 12.5 Hz, 1 H), 1.79 (dd, J = 6.7, 13.3 Hz, 1 H), 1.69 (qd, J = 7.5, 15.0 Hz, 1 H), 1.39 (qd, J = 7.5, 15.0 Hz, 1 H), 1.08 (ddd, J = 2.9, 2.9, 12.8 Hz, 1 H), 0.91 (t, J = 7.5 Hz, 3 H), 0.23 (s, 9 H); ^{13}C NMR δ 171.7, 168.7, 144.3, 136.1, 127.4, 121.0, 119.8, 109.5, 101.0, 75.8, 60.7, 56.9, 54.6, 54.2, 51.0, 43.1, 37.6, 32.7, 26.1, 7.2, 2.5; MS m/z 413 (M^+ + 1, 30), 314 (25), 268 (100), 240 (8), 238 (10), 236 (21), 226 (34), 209 (59), 194 (23), 180 (25), 167 (38), 97 (13).

The racemate **27a** was prepared by the same procedure from the racemic tosylate **26a**. It matched the above compound in spectroscopic data.

(−)-20-*epi*-Lochneridine (2b) and Its Racemate 2a. A solution of the silyl ether (−)-**27b** (18 mg, 0.0436 mmol) and n-Bu_4NF (87 μL, 1.0 M in THF, 0.087 mmol) in 2 mL of THF was stirred at room temperature for 2 h. Concentration and chromatography on a silica gel column (MeOH/CH_2Cl_2/Et_3N, 5:95:1) afforded 14 mg (94% yield) of (−)-20-*epi*-lochneridine (**2b**): R_f = 0.31 (MeOH/CH_2Cl_2, 5:95, SiO_2 plate was deactivated with Et_3N, CAS blue); mp 205−6 °C (lit.[3] mp 205−6 °C); $[\alpha]^{24}_D$ −716 (c = 0.2, MeOH); UV λ_{max} (EtOH) 204, 234, 296, 328 nm; IR (KBr) ν_{max} 3353, 1666, 1596 cm^{-1}; ^{1}H NMR δ 9.04 (s, 1 H), 7.18 (d, J = 7.3 Hz, 1 H), 7.12 (ddd, J = 1.0, 7.7, 7.7 Hz, 1 H), 6.90 (ddd, J = 0.8, 7.6, 7.6 Hz, 1 H), 6.80 (d, J = 7.7 Hz, 1 H), 3.99 (s, 1 H), 3.76 (s, 3 H), 3.18 (m, 1H), 3.05 (s, 1 H), 2.86 (m, 3 H), 2.73 (ddd, J = 3.1, 3.1, 13.5 Hz, 1 H), 2.40 (d, J = 12.6 Hz, 1 H), 1.91 (m, 1 H), 1.61 (qd, J = 7.5, 15.0 Hz, 1 H), 1.39 (qd, J = 7.5, 15.0 Hz, 1 H), 1.19 (ddd, J = 2.8, 2.8, 13.5 Hz, 1 H), 0.98 (t, J = 7.5 Hz, 3 H); ^{13}C NMR δ 170.9, 168.5, 144.3, 135.1, 127.8, 121.3, 119.8, 109.8, 101.5, 70.8, 60.6, 6.16, 54.5, 53.8, 51.1, 42.4, 36.5, 32.4, 25.7, 6.7; MS m/z 341 (45), 340 (M^+, 17), 283 (79), 241 (38), 226 (69), 209 (31), 194 (69), 184 (20), 182 (32), 180 (37), 167 (100), 156 (10), 154 (29), 149 (60), 138 (36), 130 (12), 126 (14), 115 (41).

The racemate **2a** was prepared by the same procedure from the racemic silyl ether **27a**. It matched the above compound in spectroscopic data.

(±)-Methyl (2*S*,3a*S*,5*R*,11b*R*)-3-benzyl-2,3,3a,4,5,7-hexahydro-5-(1-propionyl)-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (6). To a solution of (±)-methyl (2*S**,3a*S**,5*R**,11b*R**)-3-benzyl-2,3,3a,4,5,7-hexahydro-5-formyl-1*H*-pyrrolo[2,3-*d*]-carbazole-6-carboxylate (**5**)[7] (1.4 g, 3.6 mmol) in 30 mL of THF at −20 °C was added EtMgBr (3.0 M in Et_2O, 2.64 mL, 7.93 mmol), dropwise. The reaction solution was stirred for 30 min at −20 °C and then 30 min at 0 °C. The reaction was quenched by adding water, and the aqueous phase was extracted with dichloromethane. Purification on a silica gel column, eluted with EtOAc/Hex (1:4), gave 1.3 g (86% yield) of an inseparable mixture (6:4 in favor of isomer A) of two alcohols. For the major isomer A: R_f = 0.4 (EtOAc/Hex, 3:7, CAS blue fades fast); UV λ_{max} (EtOH) 206, 236, 296, 326 nm; IR (KBr) ν_{max} 3360, 1670, 1606 cm^{-1}; ^{1}H NMR (250 MHz) δ 9.31 (s, 1 H), 7.37 (m, 5 H), 7.14 (t, J = 7.1 Hz, 1 H), 7.05 (d, J = 7.8 Hz, 1 H), 6.84 (t, J = 7.6 Hz, 1 H), 6.80 (d, J = 7.7 Hz, 1 H), 5.78 (s, br, 1 H), 4.22 (d, J = 13.0 Hz, 1 H), 3.78 (m, 1 H), 3.76 (s, 3 H), 3.61 (d, J = 13.0 Hz, 1 H), 3.31 (d, J = 4.8 Hz, 1 H), 3.19 (m, 1 H), 2.96 (m, 1 H), 2.62 (m, 2 H), 1.95 (d, J = 14.8 Hz, 1 H), 1.75 (m, 1 H), 1.63 (m, 2 H), 1.43 (m, 1 H), 1.05 (t, J = 7.4 Hz, 3 H); ^{13}C NMR δ 169.2, 150.8, 142.8, 129.2, 128.6, 127.9, 120.6, 120.3, 109.3, 95.6, 76.3, 65.6, 58.6, 51.6, 50.9, 43.8, 40.1, 32.4, 28.6, 11.1; MS m/z 419 (M^+ + 1, 1), 361 (23), 228 (68), 194 (13), 180 (12), 167 (22), 146 (66), 134 (22), 117 (12), 91 (100).

For the minor isomer B: selected data of ^{1}H NMR (250 MHz) spectrum δ 9.18 (s, 1 H), 4.26 (d, J = 12.9 Hz, 1 H), 3.77 (s, 3 H), 3.55 (d, J = 12.9 Hz, 1 H), 3.09 (m, 1 H), 2.94 (m, 1 H), 2.58 (m, 2 H), 2.30 (d, J = 14.8 Hz, 1 H), 1.07 (t, J = 7.5 Hz, 3 H).

To a stirred mixture of *N*-chlorosuccinimide (1.92 g, 14.4 mmol) in 15 mL of toluene, at 0 °C, was added Me_2S (1.5 mL, 20 mmol), dropwise. The mixture was stirred for an additional 10 min and cooled to −20 °C. A solution of the above mixture of alcohols A and B (1.20 g, 2.87 mmol) in 5 mL of toluene

was introduced. The reaction solution was stirred at −25 °C for 3 h. Et_3N (2.4 mL, 17 mmol) was added, and after 10 min, the solution was allowed to warm to room temperature and stirred for 30 min. Saturated sodium bicarbonate was added, and the aqueous phase was extracted with dichloromethane. The residue, obtained on drying and concentration, was purified on a silica gel column, eluting with EtOAc/Hex (1:4) to give 1.1 g (92% yield) of the title ketone **6**: $R_f = 0.32$ (EtOAc/Hex, 1:4, CAS blue); mp 103−105 °C; UV λ_{max} (EtOH) 208, 298, 326 nm; IR (KBr) ν_{max} 3373, 1701, 1683, 1610 cm^{-1}; ^1H NMR δ 9.11 (s, br, 1 H), 7.35−7.25 (m, 5 H), 7.15 (t, J = 7.6 Hz, 1 H), 7.05 (d, J = 7.4 Hz, 1 H), 6.84 (m, 2 H), 4.13 (d, J = 13.3 Hz, 1 H), 3.77 (dd, J = 2.2, 5.9 Hz, 1 H), 3.74 (s, 3 H), 3.57 (d, J = 13.3 Hz, 1 H), 3.26 (d, J = 4.1 Hz, 1 H), 2.81 (m, 1 H), 2.76 (m, 1 H), 2.61 (m, 1 H), 2.55 (m, 1 H), 2.49 (m, 1 H), 2.23 (ddd, J = 6.5, 6.5, 12.0 Hz, 1 H), 1.58 (m, 2 H), 1.10 (t, J = 7.3 Hz, 3 H); ^{13}C NMR δ 211.9, 142.1, 138.2, 137.7, 128.9, 128.3, 127.8, 127.1, 121.5, 120.6, 109.4, 65.6, 58.2, 55.9, 51.1, 50.9, 46.8, 43.7, 33.2, 30.6, 8.2; MS m/z 417 (4), 416 (M^+, 10), 359 (49), 327 (12), 226 (12), 194 (13), 180 (9), 167 (12), 146 (30), 134 (21), 91 (100). Anal. Calcd for $C_{26}H_{28}N_2O_3 \cdot 1H_2O$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.50; H, 6.75; N, 6.22.

To a solution of the title ketone **6** (700 mg, 1.68 mmol) in 15 mL of MeOH, at 0 °C, was added $NaBH_4$ (127 mg, 3.36 mmol) in several portions. The solution was stirred for another 30 min, the solvent was evaporated in a vacuum, and 5% NH_4OH was added. The aqueous mixture was extracted with dichloromethane. The residue, obtained on concentration, was purified on a silica gel column, eluted with EtOAc/Hex (1:4), to give 695 mg (99% yield) of the above alcohol as a single isomer A.

Racemic Methyl (3a*S,5*R**,11b*R**)-3-((Phenylthio)-methyl)-2,3,3a,4,5,7-hexahydro-5-(propionyl))-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (7) and Methyl (3a*S**,-5*R**,11b*R**))-3-Methyl-2,3,3a,4,5,7-hexahydro-5-(propionyl))-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate.** A mixture of methyl (3a*S**,5*R**,11b*R**)-3-benzyl-2,3,3a,4,5,7-hexahydro-5-(propionyl)-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (**6**, 200 mg, 0.48 mmol), HCO_2NH_4 (152 mg, 2.4 mmol), and 10% Pd−C (50 mg, 0.05 mmol) in 8 mL of MeOH was heated at reflux for 3 h. The solid was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was taken into dichloromethane and washed with saturated sodium bicarbonate. The residue, obtained on drying and concentration, was purified on a silica gel column, eluting with CH_2Cl_2/MeOH (9:1), to give 105 mg (67% yield) of the corresponding secondary amine product: $R_f = 0.31$ ($MeOH/CH_2Cl_2$, 1:9, CAS blue); UV λ_{max} (EtOH) 204, 228, 296, 328 nm; ^1H NMR δ 9.33 (s, 1 H), 7.26 (d, J = 7.4, 1 H), 7.17 (t, J = 7.6 Hz, 1 H), 6.90 (t, J = 7.5 Hz, 1 H), 6.86 (d, J = 7.8 Hz, 1 H), 3.87 (dd, J = 2.4, 5.6 Hz, 1 H), 3.81 (s, 4 H), 3.07 (m, 2 H), 2.70 (m, 1 H), 2.60 (m, 1 H), 2.42 (d, J = 14.4 Hz, 1 H), 1.69 (m, 2 H), 1.56 (ddd, J = 6.4, 6.4, 14.4 Hz, 1 H), 1.05 (t, J = 7.3 Hz, 3 H); ^{13}C NMR δ 213.9, 168.2, 167.2, 142.7, 137.6, 127.9, 121.8, 121.1, 109.4, 93.5, 61.2, 56.9, 51.3, 47.2, 45.2, 33.4, 30.9, 29.7, 8.0.

To 40 mg (0.123 mmol) of the secondary amine, dissolved in 2 mL of dichloromethane, were added NaI (110 mg, 0.74 mmol), Na_2CO_3 (260 mg, 2.46 mmol), and $ClCH_2SPH$ (100 μL, 0.738 mmol). The reaction mixture was stirred at room temperature overnight. Water was then added, and the mixture was extracted with dichloromethane. The residue, obtained on drying and concentration, was purified on a silica gel column, eluting with EtOAc/Hex (1:4), to give 45 mg (80% yield) of the title product **7**: $R_f = 0.24$ (EtOAc/Hex, 1:4; CAS blue); UV λ_{max} (EtOH) 206, 226, 296, 324 nm; ^1H NMR δ 9.06 (s, 1 H), 7.51 (m, 3 H), 7.28 (m, 2 H), 7.19 (m, 2 H), 6.94 (t, J = 7.6 Hz 1 H), 6.84 (d, J = 7.8 Hz, 1 H), 7.75 (d, J = 13.2 Hz, 1 H), 4.68 (d, J = 13.2 Hz, 1 H), 4.73 (m, 1 H), 4.72 (s, 3 H), 3.19 (m, 1 H), 2.68 (dd, J = 7.0, 8.7 Hz, 1 H), 2.47 (m, 1 H), 2.45 (m, 1 H), 2.43 (d, J = 14.4 Hz, 1 H), 2.19 (m, 1H), 1.58 (dd, J = 5.2, 11.9 Hz, 1 H), 1.42 (dd, J = 5.4, 5.4, 14.4 Hz, 1 H), 1.05 (t, J = 7.3 Hz, 3 H); ^{13}C NMR δ 211.5, 167.8, 142.5, 131.5, 129.2, 127.9, 126.7, 121.9, 120.9, 109.4, 60.9, 60.8, 51.1, 49.3, 46.7, 43.2, 32.7, 29.8, 8.4.

To a solution of the phenylthiomethylamine **7** (200 mg, 0.446 mmol) in 8 mL of benzene, at 80 °C, was added a solution of $^nBu_3SnH$ (600 μL, 2.23 mmol) and AIBN (8 mg) in 2 mL of benzene, via a syringe pump, in 1 h. The reaction mixture was then heated at reflux for 1 h. The residue, obtained on concentration, was purified on a silica gel column, eluting with EtOAc/Hex (3:7), to obtain 130 mg (72% yield) of the N^b-methylamine, contaminated with tin compounds: $R_f = 0.36$ (EtOAc/Hex, 3:7, CAS blue); UV λ_{max} (EtOH) 206, 298, 326 nm; IR (KBr) ν_{max} 3371, 1710, 1682, 1610 cm^{-1}; ^1H NMR δ 9.06 (s, br, 1 H), 7.15 (m, 2 H), 6.87 (t, J = 7.3 Hz, 1 H), 6.83 (d, J = 8.0 Hz, 1 H), 3.73 (s, 3 H), 3.69 (dd, J = 2.4, 5.5 Hz, 1 H), 2.93 (d, J = 3.0 Hz, 1 H), 2.83 (dd, J = 6.7, 8.6 Hz, 1 H), 2.65 (m, 1 H), 2.49 (m, 3 H), 2.43 (s, 3 H), 2.22 (m, 1 H), 1.57 (dd, J = 4.9, 11.8 Hz, 1 H), 1.49 (ddd, J = 4.4, 4.4, 14.2 Hz, 1 H), 1.07 (t, J = 7.3 Hz, 3 H).

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Supporting Information Available: ^1H and ^{13}C NMR spectra, compounds marked with an asterisk include COSY spectra and compounds marked with a dagger (†) include NOESY spectra, for compounds **1***†, **2b***†, pre **6** isomer **A***, **6**, pre **7**, **7**, **12b***, **17***†, **19***, **23b***, **24b***, **26b***, **27b***†, and ^1H NMR spectra for compounds **13a***†, **22b***† (46 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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