Total Synthesis of Strychnan and Aspidospermatan Alkaloids. 3. The Total Synthesis of (±)-Strychnine

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Reaction of N^b-benzyl-2-[(methoxycarbonyl)methyl]tryptamine (3) with 4,4-dimethoxybut-2-en-1-al (6) provided, by a new condensation–electrocyclization reaction, the tetracyclic core 2 of strychnine (1). A 13-step elaboration of this compound gave a stereoselective synthesis of the racemic alkaloid.

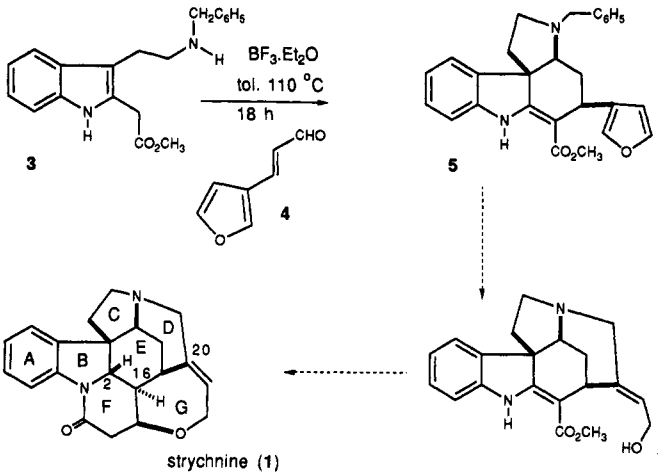
Strychnine! One of the milestones set by the Woodward group in advancements of organic chemistry through synthesis. The heroic ring by ring forging of the original strychnine (1) assembly,[1,2] which required 27 steps, resolution of enantiomers, and the use of three degradation products of the natural alkaloid as relays, now stands as an instructive inspiration for the design of synthetic alternatives. Only very recently was this formidable synthetic challenge met again successfully.[3-5] With the present report,[6] we detail generation of the tetracyclic core of the strychnos alkaloids by a single, stereoselective reaction,[7] and the 13-step conversion of the product (2, Scheme II) into (±)-strychnine (1), to provide a total synthesis of this racemic product, which does not pass through the Wieland–Gumlich aldehyde.[3-5]

In the preceding paper we described how N^b-benzyl-2-[(methoxycarbonyl)methyl]tryptamine (3), readily prepared from N^b,N^b-dibenzyltryptamine, underwent condensation with 3-(3-furyl)acrolein (4) to provide, stereoselectively, the tetracyclic indolenine 5 (Scheme I).[8] While this product contains all but the two, acetate-derived, ring F carbon atoms of strychnine (1), its further elaboration required considerable exploration and discovery of new methodology. Consequently, the synthesis of a simpler tetracyclic intermediate 2 and its advancement to strychnine was undertaken.

Condensation of N^b-benzyl-2-[(methoxycarbonyl)methyl]tryptamine (3) with 4,4-dimethoxybut-2-en-1-al (6) in refluxing toluene (Scheme II), with catalysis by BF_3–etherate, provided the tetracyclic acetal 2 as a single diastereomer.[9] Its hydrolysis with aqueous perchloric acid, at room temperature, gave the corresponding tetracyclic aldehyde 7 in 51% overall yield.

For elaboration of ring D, the aldehyde 7 was added to a THF solution of the ylide obtained by reaction of trimethylsulfonium iodide with *n*-butyllithium (Scheme III). The anticipated epoxide 8 was stirred, without isolation, in tetrahydrofuran, to achieve cyclization. Since the cyclization of unsubstituted epoxides is known to favor formation of the smallest possible ring product,[10-12] formation of a five-membered ring D was expected. Indeed, hydrogenolytic debenzylation of the quaternary salt **9a**, obtained after 2 h at room temperature, gave a primary alcohol 10 (see below for structure proof). However, a minor cyclization product could also be seen. After heating the cyclization mixture in methanol with diazabicycloundecene for 10 h, and hydrogenolysis, only this second product, the six-membered ring D secondary alcohol 11 was obtained. Its corresponding hydroxy epimer, generated in an alternative reaction sequence,[13] could not be detected.

Scheme I



As β-hydroxy ammonium salts are known to form amino epoxides on heating,[14] and, moreover, the cyclization of tertiary amino epoxides was previously found to be favored by protic solvents,[12] the present cyclization reaction is ideally set up for reversibility and equilibration of the products to the more stable six-membered ring quaternary salt **9b**. It may be noted that with ring D in a chair conformation, the hydroxy substituent in the ammonium alcohol **9b** is axial, i.e. not well situated for a ring opening–epoxide reformation reaction. This hydroxy epimer would require a ring D boat conformation for ring fragmentation. Indeed, this boat conformation, which is required for the

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(2) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, *Tetrahedron* **1963**, *19*, 247.

(3) Magnus, P.; Giles, M.; Bonnert, R.; Kim, C. S.; McQuire, L.; Merritt, A.; Vicker, N. *J. Am. Chem. Soc.* **1992**, *114*, 4403.

(4) Stork, G. Lecture at the Ischia School of Organic Chemistry, Ischia Porto, Italy, September 21, 1992.

(5) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1993**, *115*, 9293.

(6) Kuehne, M. E.; Xu, F. National Meeting of the American Chemical Society, Denver, CO, April 1993, ORGN 187.

(7) Parsons, R. P.; Berk, J. D.; Kuehne, M. E. National Meeting of the American Chemical Society, Denver, CO, April 1993, ORGN 186.

(8) Parsons, R. L.; Berk, J. D.; Kuehne, M. E. *J. Org. Chem.* **1993**, *58*, 7482–7489.

(9) For a discussion of the stereochemical course of this reaction see ref 8.

(10) (a) Stork, G.; Cohen, J. F. *J. Am. Chem. Soc.* **1974**, *96*, 5270. (b) Achini, R.; Oppolzer, W. *Tetrahedron Lett.* **1975**, 369.

(11) Kuehne, M. E.; Okuniewicz, F. J.; Kirkemo, C. L.; Bohnert, J. C. *J. Org. Chem.* **1982**, *47*, 1335.

(12) Kuehne, M. E.; Matson, P. A.; Bornmann, W. G. *J. Org. Chem.* **1991**, *56*, 513.

(13) Parsons, R. L. Doctoral dissertation, 1992, Univ. Vermont.

(14) Cope, A. *Org. React.* **1960**, *11*, 317 (see pp 352, 390, 391).

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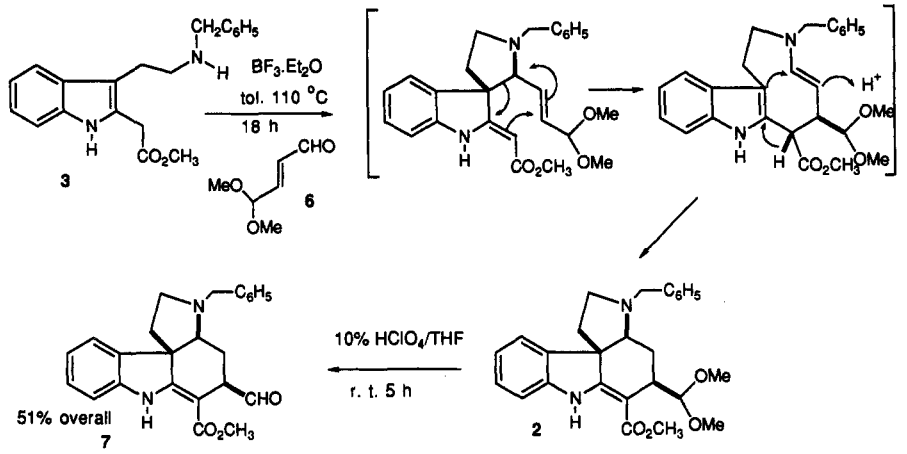
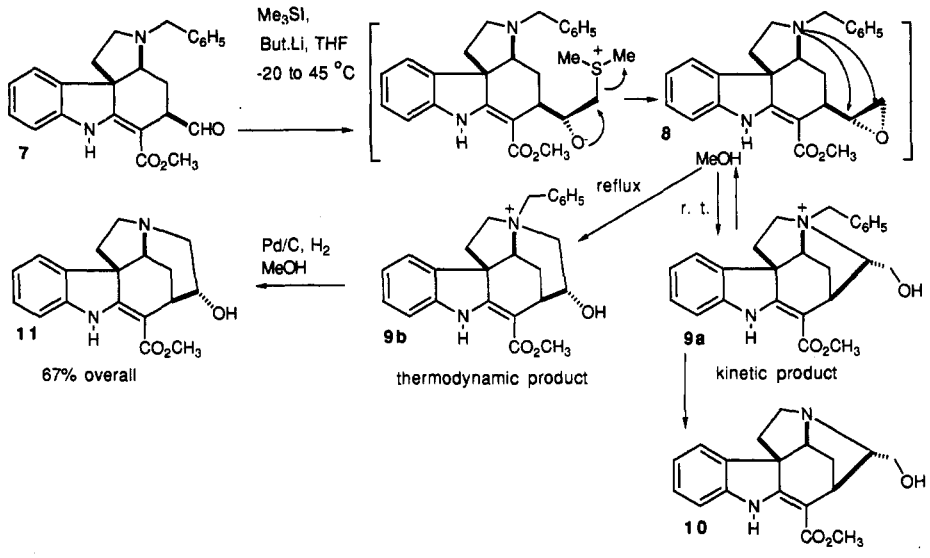
Scheme II



Scheme III



(reversible) formation of the hydroxy product **9b** may be responsible for trapping of the product vs accumulation of the unobserved equatorial hydroxy epimer.

In the closure of ring D, the aminoacrylate double bond was required to ensure proximity of N^b and the electrophilic substituent on ring E.[15] With the cyclization of ring D accomplished, we could now consider reduction of this double bond. Addition of a proton at C-16, on the convex surface of intermediate **11**, could be anticipated but the required introduction of a methine hydrogen at C-2, from the sterically encumbered, concave side of the molecule, was reason for apprehension.[16] However, a reduction with $NaCNBH_3$ in acetic acid provided, exclusively, the desired dihydro product (Scheme IV). This result may be a consequence of a best fit for hydride transfer in an ion pair of the protonated substrate and $CNBH_3^-$. Close association of a protonated N^b ammonium group and the $CNBH_3^-$ anion on the convex (unhindered) side of the molecule will burden the undesired attack of this anion at a more distal iminium C-2 carbon, whereas intimacy of the N^b ammonium and $CNBH_3^-$ ions on the concave face of the receptor facilitates hydride penetration into the cavity, with better proximaty to C-2, and conception of the strychnine stereochemistry. Treatment with acetic anhydride in pyridine, followed by sodium methoxide in methanol at 0 °C, provided the amide alcohol **12** in 83% overall yield from the aminoacrylate **11**.

The five-membered ring D primary alcohol **10**, obtained as kinetic cyclization product of the epoxide **8**, was subjected to the same reduction (**13**) and acylation steps to provide an alcohol amide **14** (Scheme V). Its Swern oxidation gave an aldehyde **15**, thus providing chemical proof of a five-membered ring D formation in the initial cyclization reaction.

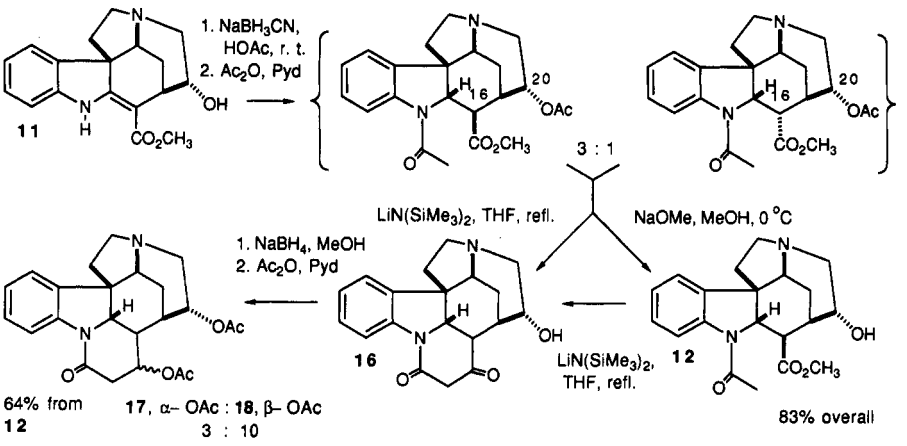
For closure of ring F of strychnine (Scheme IV), the amide ester **12** was heated in tetrahydrofuran with an excess of lithium bis(trimethylsilyl)amide. Reduction of the resulting β-keto lactam **16** with sodium borohydride, and acylation, provided a 3:10 mixture of epimeric acetates (**17**, **18**) in 98% overall yield.

When the epimeric acetates **17**, **18** were heated at 100 °C in aqueous dioxane with an excess of diazabicycloundecene, the olefinic alcohol **19** was obtained in 65% yield (Scheme VI). Swern oxidation of the alcohol **19** resulted in formation of a characterized, but unstable α-amino ketone **20**. Consequently, this crude product was best subjected directly to two alternative reactions for introduction of the last two carbon atoms of the strychnine skeleton.

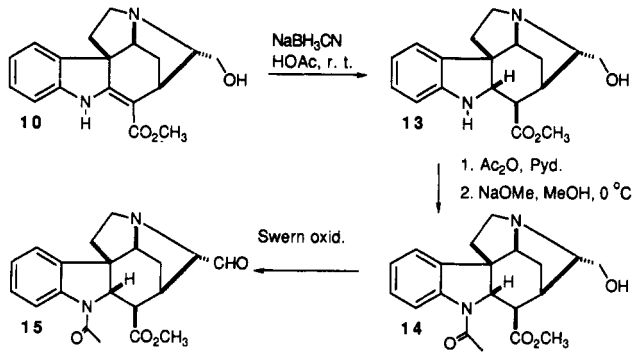
(15) Overman, L. E.; Angle, S. *J. Org. Chem.* **1985**, *50*, 4021.

(16) In the related reduction of a ring F pyridone intermediate in the Woodward synthesis,[2] a 20-hydroxy substituent was used to react with $LiAlH_4$ to guide hydride to the sterically shielded side of the molecule. This avenue was not available to us because of the C-20 epimeric stereochemistry of our hydroxyl group.

Scheme IV



Scheme V



A Wittig–Horner condensation of the ketone **20** with methyl 2-(diethylphosphono)acetate led to a 1:1 mixture of *E*/*Z* acrylates **21**, **22**. On photochemical equilibration this mixture provided a more desirable 8:1 ratio of *E*/*Z* acrylates, which could be separated by chromatography.

For direct formation of isostrychnine (**23**) by reduction of the ester function in the major isomer **21** (Scheme VII), reduction of its lactam carbonyl group had to be avoided. This could be accomplished (87% yield) with DIBALH, in the presence of BF_3, at −78 °C. The final cyclization of racemic isostrychnine (**23**) to racemic strychnine (**1**) with KOH in ethanol at 85 °C was already known from the equilibration of these natural products.[2,17] Strychnine (**1**, 28%) and isostrychnine (**23**, 61%) were then separated (72% yield of strychnine based on recovery of isostrychnine), making this last step the least rewarding one of the synthesis.

In the Woodward synthesis, an alternative series of transformations had been used for conversion of an α-keto lactam, analogous to our unstable ketone **20**, to isostrychnine.[2] Those reactions included the lowest yields of that synthesis (2.6% overall for the penultimate steps). With the hope that more recently developed methodology for such transformations could improve the result, we added vinylmagnesium bromide to the ketone **20** at 0 °C in THF (Scheme VI). The resulting tertiary alcohol **24** (65% yield) was acetylated and the resulting acetate **25**, as its trifluoroacetic acid salt, treated with $PdCl_2(CH_3CN)_2$ in tetrahydrofuran (Scheme VIII). A greatly improved allylic rearrangement (46% vs 12.5% with hydrogen bromide and hydrolysis[2]) was achieved, but the product **26** was found to have only the undesired *Z* configuration.

For adjustment of the double bond stereochemistry, an oxidation–reduction sequence was then required on this alternative path to strychnine. Hydrolysis of the acetate **26** to alcohol **27** and its Swern oxidation provided an aldehyde **28**. Photochemical equilibration resulted in a less favorable 2:1, *E*/*Z*, isomer ratio of aldehydes **29**/**28** than had been found (above) in equilibration of the acrylates **21**, **22**. Finally, reduction of the aldehyde **29** with sodium borohydride and cerric chloride also led to racemic isostrychnine (**23**). A 42% overall yield for the oxidation of the alcohol **27**, photochemical equilibration, and reduction to isostrychnine (**23**) reduced this conversion of the ketone **20** to isostrychnine to 18%.

Conclusion

Use of the readily obtained tetracyclic intermediate **2** has allowed its conversion to (±)-strychnine (**1**) through five major stages of skeletal construction, with supporting adjustments of oxidation levels. Alternatives to the described final ring closure, i.e. earlier closure of the ether ring G, and extensions of our methodology to enantioselective generation of tetracyclic analogues of intermediate **2**, promise to bring further dominance over this classical challenge to organic synthesis.

Experimental Section

General Methods. For usual reaction conditions, chromatographic conditions, and spectroscopic instrumentation see part 1 of this series, except for the NMR data for compound **10**, which were obtained on a Bruker ARX 500 instrument.[18]

(±)-(3a*S,5*R**,11b*R**)-Methyl 5-Formyl-3-(phenylmethyl)-2,3,3a,4,5,7-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (7).** To a solution of methyl 3-[2-[N^b-(phenylmethyl)-amino]ethyl]indole-2-ethanoate (10.0 g, 30.9 mmol) in 250 mL of dry toluene was added freshly activated 4-Å molecular sieves powder (10 g), followed by 4,4-dimethoxy-2-butenal[19] (6.00 g, 46.38 mmol). The flask was equipped with a Dean–Stark separator, which was filled with freshly activated 4-Å molecular sieves. The system was degassed with Ar, and BF_3·Et_2O (267 uL, 2.47 mmol) was added. The reaction mixture was heated at vigorous reflux for 18 h and then cooled to room temperature. The solid was removed by filtration and washed with a solution of MeOH/EtOAc/CH_2Cl_2 (1:1:1). The filtrate was concentrated under reduced pressure. The crude product was used directly for the next step. The product could be purified by column

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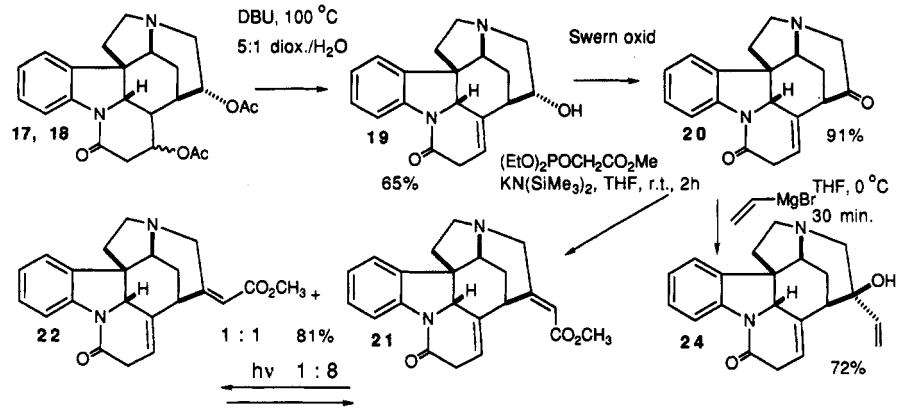
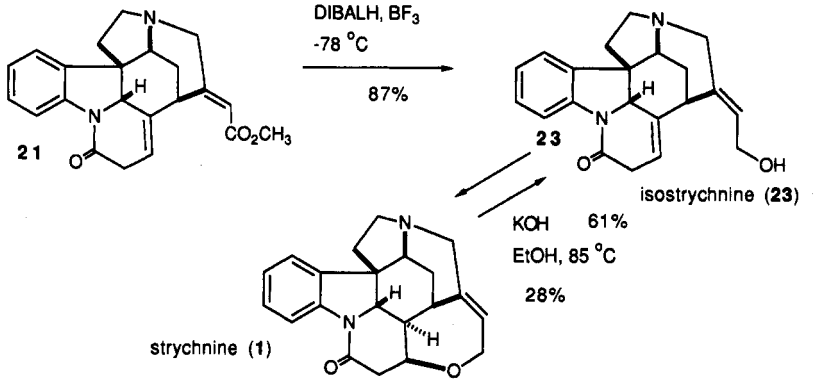
(18) Kuehne, M. E.; Frasier, D. A.; Spitzer, T. D. *J. Org. Chem.* **1991**, *56*, 2696.

(19) Gree, R.; Tourbath, H.; Carrie, R. *Tetrahedron Lett.* **1986**, *27*, 4983.

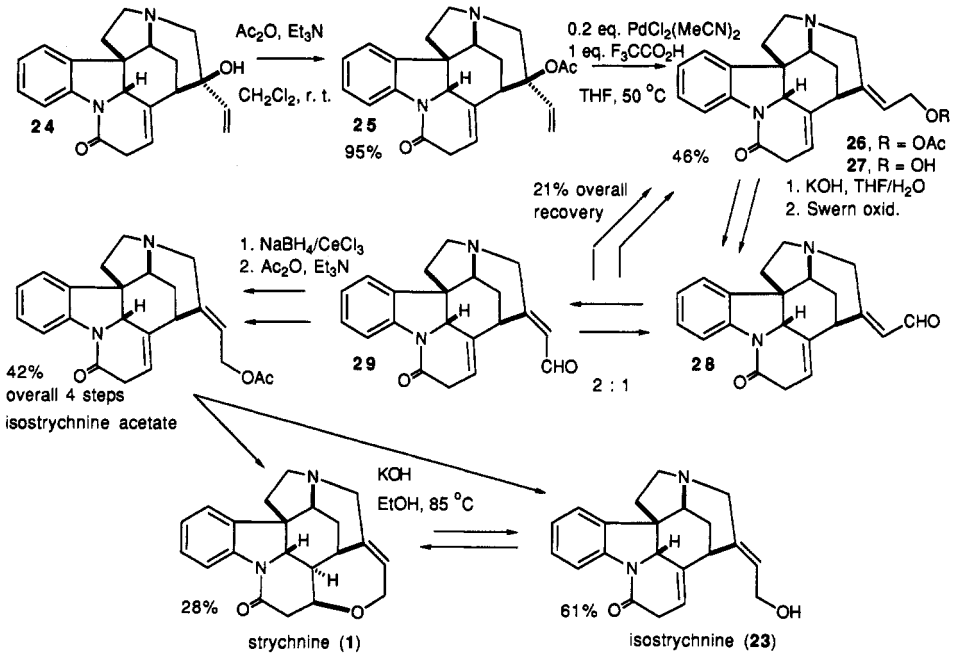
Scheme VI



Scheme VII



Scheme VIII



chromatography, eluting with EtOAc/hex (1:4), to give the acetal **2** as a white foam.

The above crude product **2** was dissolved in 300 mL of THF, and 300 mL of 10% $HClO_4$ was added at 0 °C. The solution was allowed to stir at room temperature for 5 h. (The reaction was monitored by TLC as follows: The reaction solution was basified with saturated sodium bicarbonate solution and then acidified with HOAc. TLC (silica gel, EtOAc/hex 3:7) showed the product **7** (R_f = 0.19) and the starting acetal **2** R_f = 0.08). With ceric ammonium sulfate (CAS), both stained blue; however, the product spot faded faster than the acetal one). The reaction solution was cooled to 0 °C, basified with concd NH_4OH to pH = 10, and extracted with dichloromethane. The residue, obtained upon concentration, was chromatographed on a column, eluting with EtOAc/hex/CH_2Cl_2 (15:80:5), to give 9.1 g of product **7** as a white foam, which crystallized spontaneously, with analytical purity and mp 83–85 °C (51% yield, two steps).

For the dimethyl acetal **2**: TLC R_f = 0.13 (EtOAc/hex, 1:4, CAS blue); UV (EtOH) λ_{max} 324, 296, 224, 204 nm; IR (KBr) ν_{max} 3359, 3048, 3025, 2936, 2823, 1668, 1598, 1471, 1456, 1435, 1372, 1330, 1273, 1238, 1203, 1119, 1069, 955, 730, 703 cm^{-1}.

For the aldehyde **7**: TLC R_f = 0.23 (EtOAc/hex/CH_2Cl_2, 15:80:5, CAS blue); UV(EtOH) λ_{max} 322, 296, 228, 208 nm; IR (KBr) ν_{max} 3361, 3055, 3021, 2942, 2909, 2816, 2789, 1718, 1678, 1610,

1459, 1425, 1279, 1233, 1213, 1139, 1106, 1072, 913, 734 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.89 (s, 1 H), 9.13 (s, 1 H), 7.33 (m, 5 H), 7.17 (m, 2 H), 6.90 (d J = 7 Hz, 1 H), 6.86 (d, J = 8 Hz, 1 H), 4.19 (d, J = 13 Hz, 1 H), 3.76 (s, 3 H), 3.70 (dd, J = 2, 6 Hz, 1 H), 3.57 (d, J = 13 Hz, 1 H), 3.26 (d, J = 4 Hz, 1 H), 2.84 (dd, J = 6, 9 Hz, 1 H), 2.51 (m, 2 H), 1.98 (m, 1 H), 1.58 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 168.15, 167.40, 142.74, 138.38, 137.32, 128.64, 128.49, 128.32, 128.19, 127.99, 127.18, 121.37, 120.81, 109.57, 106.69, 91.77, 65.08, 58.32, 56.11, 51.10, 47.40, 44.49, 30.01; MS m/z (rel inten) 388 (M^+, 0.3), 360 (6), 327 (2), 269 (1), 227 (29), 194 (8), 180 (9), 167 (13), 146 (40), 134 (11), 91 (100). Anal. Calcd for $C_{24}H_{24}N_2O_3$: C, 74.21; H, 6.23; N, 7.21. Found: C, 74.27; H, 6.38; N, 6.98.

(±)-(3a*S,5*S**,11b*R**,12*R**)-Methyl 12-Hydroxy-3,5-ethano-2,3,3a,4,5,7-hexahydro-3*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (11).** To a degassed mixture of Me_3SI (6.10 g, 29.9 mmol) in 50 mL of THF at −20 °C was added nBuLi (2.50 M in hexane, 12.0 mL, 29.9 mmol), dropwise, over 15 min. The mixture was stirred for an additional 30 min at −20 °C. Then, a solution of (±)-(3a*S**,5*R**,11b*R**)-methyl 5-formyl-3-(phenylmethyl)-2,3,-3a,4,5,7-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (7, 3.3 g, 8.54 mmol) in 25 mL of THF was added slowly over 30 min. The reaction mixture was stirred for an additional 30 min at −20 °C, and for 2 h at room temperature. The solvent was removed under reduced pressure. Chromatography on a silica gel column (dichloromethane/methanol, 9:1) afforded a quaternary ammonium salt **9a**, which was dissolved into 200 mL of MeOH. DBU (3.90 mL, 25.6 mmol) was added and the reaction solution was heated at reflux for 10 h and then cooled to room temperature and 1.8 g of 10% Pd–C added. The mixture was hydrogenolyzed under 1 atm of H_2 for 2 h. The residue, obtained on concentration, was purified on a silica gel column, eluting with CH_2Cl_2/MeOH/Et_3N (95:5:1), to obtain 1.86 g of product 11 as a yellow foam (70% yield), which crystallized from EtOAc/MeOH with mp 214–215 °C; TLC R_f = 0.17 (MeOH/CH_2Cl_2, 5:95, SiO_2 plate deactivated with Et_3N, CAS blue); UV (EtOH) λ_{max} 324, 296, 234, 206 nm; IR (KBr) ν_{max} 3355, 2922, 2842, 1672, 1605, 1459, 1432, 1366, 1279, 1233, 1186, 1146, 1093, 1040, 900, 780, 727 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.85 (s, 1 H), 7.17 (t, J = 8 Hz, 1 H), 7.12 (d, J = 8 Hz, 1 H), 6.88 (t, J = 8 Hz, 1 H), 6.82 (d, J = 8 Hz, 1 H), 4.42 (bs, OH, 1 H), 4.03 (s, 1 H), 3.95 (s, 1 H), 3.77 (s, 3 H), 3.05 (m, 3 H), 2.77 (m, 4 H), 2.62 (m, 1 H), 1.86 (m, 1 H), 1.17 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 170.65, 168.14, 144.37, 135.44, 127.66, 121.12, 119.97, 109.69, 100.53, 66.79, 60.40, 57.16, 53.83, 51.80, 51.03, 43.85, 34.53, 23.94; MS m/z (rel inten) 312 (M^+, 53), 295 (2), 281 (8), 239 (11), 225 (98), 213 (20), 194 (39), 180 (30), 167 (61), 154 (20), 149 (24), 140 (21), 129 (14), 127 (14), 115 (11), 111 (24), 97 (20), 87 (100).

(±)-(3a*S,5*S**,11b*R**,12*S**)-Methyl 12-(Hydroxymethyl)-3,5-methano-2,3,3a,4,5,7-hexahydro-3*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (10).** The preceding procedure, but without refluxing in THF and MeOH, was applied to the aldehyde 7. Chromatography on a silica gel column (CH_2Cl_2/MeOH/Et_3N, 97:3:1) gave the title product **10** as a white foam: TLC R_f = 0.44 (MeOH/CH_2Cl_2, 1:9; CAS blue); UV (EtOH) λ_{max} 326, 298, 206 nm; IR (KBr) ν_{max} 3341, 2942, 2869, 1672, 1592, 1459, 1432, 1372, 1292, 1233, 1146, 1100, 1033, 900, 727 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.66 (s, 1 H), 7.23 (d, J = 7.3 Hz, 1 H), 7.15 (t, J = 7.7 Hz, 1 H), 6.93 (t, J = 7.4 Hz, 1 H), 6.83 (d, J = 7.8 Hz, 1 H), 3.88 (d, J = 3.5 Hz, 1 H), 3.77 (s, 3 H), 3.66 (dd, J = 5.2, 10.6 Hz, 1 H), 3.42 (dd, J = 7.8, 10.6 Hz, 1 H), 3.29 (ddd, J = 9.0, 9.0, 12.4 Hz, 1 H), 3.06 (d, J = 4.3 Hz, 1 H), 2.90 (ddd, J = 2.4, 8.4, 12.4 Hz, 1 H), 2.60 (dd, J = 5.2, 7.8 Hz, 1 H), 2.46 (ddd, J = 9.0, 9.0, 13.6 Hz, 1 H), 2.16 (ddd, J = 4.2, 4.2, 11.5 Hz, 1 H), 2.10 (ddd, J = 2.4, 8.4, 13.6 Hz, 1 H), 1.01 (d, J = 11.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 167.35, 167.24, 143.99, 133.64, 127.75, 121.20, 109.52, 103.07, 74.69, 67.26, 65.93, 59.80, 52.12, 51.04, 46.99, 36.31, 36.17; MS m/z (rel inten) 313 (5), 312 (M^+, 27), 294 (23), 281 (24), 249 (15), 239 (27), 226 (63), 221 (43), 207 (12), 202 (23), 194 (60), 182 (21), 180 (24), 167 (86), 156 (16), 154 (15), 149 (50), 142 (99), 128 (67), 112 (11), 93 (100).

(±)-(3a*S,5*R**,6*R**,6a*S**,11b*R**,12*R**)-Methyl 7-Acetyl-12-hydroxy-3,5-ethano-1,2,3a,4,5,6,6a,7-octahydro-3*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (12):** To a solution of (±)-(3a*S**,5*S**,11b*R**,12*R**)-methyl 12-hydroxy-3,5-ethano-1,2,3a,4,5,7-hexahydro-3*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (11, 2.0 g, 6.4 mmol) in 20 mL of HOAc, at room temperature, was added $NaBH_3CN$ (2.0 g, 32 mmol) in several portions. Subsequently, the solution was stirred for 30 min, cooled to 0 °C, and basified with concd NH_4OH. The aqueous solution was extracted with dichloromethane. The residue, obtained on concentration, was dissovled in 20 mL of pyridine and 5 mL of acetic anhydride. The solution was stirred at room temperature for 10 h and then concentrated under reduced pressure. The residue was dissolved in dichloromethane and washed with saturated sodium bicarbonate solution. Concentration and solution of the crude acetamide in 80 mL of methanol and dropwise addition, at 0 °C, of a freshly prepared solution of 589 mg of Na in 20 mL of MeOH was followed by stirring at 0 °C for 40 min. The reaction solution was adjusted with 2 N HCl to pH = 8. Most of solvent was evaporated under reduced pressure, and the residue was dissolved in dichloromethane and washed with water. The crude product was purified on a silica gel column, eluting with CH_2Cl_2/MeOH (3:2) to give 1.9 g of product as a white foam (83% yield), which crystallized from EtOAc/MeOH with mp 248–250 °C; TLC R_f = 0.18 (MeOH/CH_2Cl_2, 2:3, CAS grey); UV (EtOH) λ_{max} 282, 252, 208 nm; IR (KBr) ν_{max} 3348, 2949, 2915, 2875, 1727, 1652, 1593, 1480, 1462, 1434, 1394, 1309, 1284, 1162, 1089, 1018, 910, 727 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.02 (s , br, 1 H), 7.26–7.02 (m, 3 H), 4.77 (m, 1 H), 4.35 (m, 1 H), 3.97 (m, 2 H), 3.52 (m, 2 H), 3.43 (s, 3 H), 3.16 (m, 2 H), 2.83 (m, 1 H), 2.65 (m, 1 H), 2.40 (s, 3 H), 2.30 (m, 3 H), 2.06 (m, 1 H), 1.89 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 171.97, 169.32, 141.81, 127.85, 124.32, 122.21, 122.01, 121.62, 69.33, 66.08, 60.38, 55.56, 53.50, 52.09, 51.56, 46.36, 44.90, 34.77, 23.68, 16.58; MS m/z (rel inten) 356 (M^+, 38), 314 (2), 241 (94), 199 (22), 184 (100), 167 (12), 156 (2), 144 (69), 130 (55), 115 (14). Anal. Calcd for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79; N, 7.86. Found: C, 67.25; H, 6.98; N, 7.76.

(±)-(3a*S,5*R**,6*R**,6a*S**,11b*R**,12*S**)-Methyl 7-Acetyl-12-(hydroxymethyl)-3,5-methano-1,2,3a,4,5,6,6a,7-octahydro-3*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (14).** The preceding procedure was applied to reduction of the aminoacrylate **10**. Chromatography on a silica gel column (CH_2Cl_2) gave the dihydro product **13** as a white foam (99.4% yield): TLC R_f = 0.17 (MeOH/CH_2Cl_2, 1:9; CAS brown faded to green); UV (EtOH) λ_{max} 296, 248, 208 nm; IR (KBr) ν_{max} 3354, 2942, 2922, 2862, 1725, 1598, 1479, 1459, 1244, 1185, 1100, 1020, 755, 727 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.09 (m, 2 H), 6.82 (t, J = 8 Hz, 1 H), 6.63 (d, J = 8 Hz, 1 H), 5.68 (s, br, 1 H), 4.21 (dd, J = 3, 7 Hz, 1 H), 4.09 (s, 1 H), 3.82 (s, 3 H), 3.64 (m, 2 H), 3.40 (m, 1 H), 3.32 (m, 1 H), 2.95 (d, J = 7 Hz, 1 H), 2.85 (dd, J = 5, 9 Hz, 1 H), 2.75 (d, J = 5 Hz, 1 H), 2.63 (m, 1 H), 2.46 (m, 1 H), 2.15 (m, 1 H), 2.01 (m, 1 H), 1.88 (m, 1 H); MS m/z (rel inten) 315 (45), 314 (M^+, 59), 283 (59), 184 (90), 172 (11), 167 (10), 156 (13), 143 (100), 130 (54), 112 (72).

The dihydro product **13** was then acylated, as above, to provide the acetamide **14**. Chromatography on silica gel column (CH_2Cl_2/MeOH, 92:8) gave the product as a white foam: TLC R_f = 0.21 (MeOH/CH_2Cl_2, 8:92, CAS pink); UV (EtOH) λ_{max} 290, 280, 254, 208 nm; IR (KBr) ν_{max} 3388, 2942, 2922, 2882, 1734, 1650, 1596, 1480, 1455, 1394, 1309, 1190, 1161, 1058, 1037, 755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 1 H), 7.10 (m, 3 H), 4.44 (d, J = 9 Hz, 1 H), 4.05 (s, br, OH), 3.65 (m, 2 H), 3.53 (m, 1 H), 3.50 (s, 3 H), 3.32 (m, 1 H), 2.98 (m, 2 H), 2.81 (m, 1 H), 2.41 (s, 3 H), 2.32 (m, 1 H), 2.19 (m, 2 H), 1.95 (m, 1 H), 1.86 (m, 1 H); MS m/z (rel inten) 357 (22), 356 (M^+, 42), 325 (76), 184 (100), 173 (13), 167 (15), 156 (18), 144 (71), 130 (43), 117 (11), 115 (19), 111 (52).

(±)-(3a*S,5*R**,6*R**,6a*S**,11b*R**,12*S**)-Methyl 7-Acetyl-12-formyl-3,5-methano-1,2,3a,4,5,6,6a,7-octahydro-3*H*-pyrrolo-[2,3-*d*]carbazole-6-carboxylate (15).** A Swern oxidation, using the procedure given for oxidation of the secondary alcohol **19**, was applied to preparation of the title aldehdye from 10 mg of the primary alcohol **14**. Chromatography on a silica gel column (CH_2Cl_2/MeOH, 95:5) gave 8 mg of the product **15** as a white foam (81% yield): TLC R_f = 0.43 (MeOH/CH_2Cl_2, 1:9; CAS pink); UV (EtOH) λ_{max} 290, 282, 252, 208 nm; IR (KBr) ν_{max} 2942, 2929, 2876, 1732, 1651, 1480, 1460, 1432, 1389, 1310, 1282, 1193, 1162, 1055, 753 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.64 (s, 1 H), 7.26 (m, 1 H), 7.11 (m, 3 H), 4.39 (d, J = 9 Hz, 1 H), 3.72 (m, 2 H), 3.52 (s, 3 H), 3.44 (m, 1 H), 3.03 (m, 1 H), 2.78 (m, 1 H), 2.60–1.62 (m, 5 H), 2.41 (s, 3 H); MS m/z (rel inten) 354 (M^+, 0.5), 325 (8), 256 (1), 185 (3), 167 (2), 154 (2), 149 (3), 144 (10), 129 (5), 115 (3), 111 (3), 94 (3), 78 (86).

(±)-(3a*R,11*R** and *S**,11a*R**,11b*S**,12*R**,13a*S**,14*R**)-Methyl 11,14-Dihydroxy-9-oxo-12*H*-1,12-ethano-2,3,10,11,-11a,11b,13,13a-octahydro-9*H*-pyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]-carbazole.** To a mixture of (±)-(3a*S**,5*R**,6*R**,6a*S**,11b*R**,12*R**)-Methyl 7-acetyl-12-hydroxy-3,5-ethano-1,2,3a,4,5,6,6a,7-octahydro-3*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (12, 50 mg, 0.14 mmol) in 4 mL of THF was added $LiN(SiMe_3)_2$ (1.0 M in toluene, 448 uL, 0.448 mmol), dropwise, at room temperature. The reaction mixture was heated at reflux for 30 min. Then, the solvents were evaporated. The residue was dissolved in 3 mL of MeOH, and HOAc (32 uL, 0.56 mmol) was added at 0 °C, followed by $NaBH_4$ (21 mg, 0.56 mmol) in several portions. The reaction solution was stirred at 0 °C for an additional 1 h. Ammonium chloride was added to quench the excess $NaBH_4$. Filtration and concentration gave the crude product, which could be used directly for next reaction. The residue also could be chromatographed on a silica gel column, eluting with MeOH, to afford 29 mg of product as white solid (64% yield): TLC R_f = 0.11 (MeOH/CH_2Cl_2, 2:3); UV (EtOH) λ_{max} 282, 254, 206 nm; IR (KBr) ν_{max} 3328, 2922, 1650, 1633, 1594, 1483, 1457, 1403, 1309, 1084, 1054, 1030, 753 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.09 (d, J = 8 Hz, 1 H), 7.18 (m, 3 H), 4.35 (m, 1 H), 4.11 (m, 1 H), 3.90 (m, 1 H), 3.11 (m, 2 H), 3. 00 (m, 2 H), 2.81–0.85 (m, 11 H); MS m/z (rel inten) 326 (M^+, 5.0), 180 (3.3), 167 (9.1), 154 (17.1), 149 (31.4), 143 (11.5), 129 (18.9), 123 (18.6), 115 (13.1), 112 (66.3), 97 (86.6), 83 (100).

(±)-(3a*R,11*R** and *S**,11a*R**,12*R**,11b*S**,13a*S**,14*S**)-Methyl 11,14-Acetoxy-9-oxo-12*H*-1,12-ethano-2,3,10,11,11a,-11b,13,13a-octahydro-9*H*-pyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazole (17, 18).** A solution of (±)-(3a*R**,11*R** and *S**,11a*R**,12*R**,11b*S**,13a*S**,14*S**)-Methyl 11,14-Dihydroxy-9-oxo-12*H*-1,12-ethano-2,3,10,11,11a,11b,13,13a-octahydro-9*H*-pyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazole (20 mg, 0.062 mmol) in 2 mL of pyridine and 0.5 mL of acetic anhydride was stirred at room temperature overnight. The solvents were evaporated under reduced pressure. The residue was dissovled in dichloromethane and washed with saturated soidum bicarbonate solution to give 25 mg of product 17 and 18 (98% yield) after chromatography on a silica gel column, eluting with CH_2Cl_2/MeOH (96:4). The ratio of the two acetoxy epimers was 10:3. For the above three steps, the overall yield was 64%, if the two intermediates were not purified on a silica gel column: TLC R_f = 0.22 (MeOH/CH_2Cl_2, 4:96); UV (EtOH) λ_{max} 290, 280, 254, 210 nm; IR (KBr) ν_{max} 2935, 2876, 1734, 1659, 1478, 1406, 1363, 1234, 1037, 755, 730 cm^{-1}; ^1H NMR ($CDCl_3$) major isomer δ 8.11 (d, J = 8 Hz, 1 H), 7.30–7.13 (m, 4 H), 5.29 (m, 1 H), 4.75 (s, br, 1 H), 4.17 (d, J = 5 Hz, 1 H), 3.19–2.20 (m, 10 H), 2.18 (s, 3 H), 2.11 (s, 3 H), 1.48 (m, 1 H), 0.88 (m, 1 H). Partial data for the minor isomer: δ 8.16 (d, J = 8 Hz, 1 H), 5.22 (m, 1 H), 4.96 (s, br, 1 H), 4.30 (d, J = 6 Hz, 1 H), 2.10 (s, 3 H), 2.09 (s, 3 H); MS m/z (rel inten) 410 (M^+, 0.5), 384 (0.9), 350 (14.9), 291 (1.3), 226 (1.8), 183 (7.6), 167 (2.7), 158 (2.8), 144 (4.2), 107 (30.2), 93 (100).

(±)-(3a*R,11b*S*,13a*S**,14*S**)-Methyl 14-Hydroxy-9-oxo-12*H*-1,12-ethano-2,3,10,11b,13,13a-hexahydro-9*H*-pyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazole (19).** A solution of (±)-(3a*R**,11*R** and *S**,11a*R**,11b*S**,13a*S**,14*S**)-Methyl 11,14-acetoxy-9-oxo-12*H*-1,12-ethano-2,3,10,11,11a,11b,13,13a-octahydro-9*H*-pyrido-[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazole (17, 18, 360 mg, 0.877 mmol) and DBU (656 uL, 8.72 mmol) in 20 mL of 1,4-dioxane and 4 mL of water was heated at reflux for 10 h. The solvents were evaporated, and the residue was dissolved in dichloromethane and washed with saturated sodium bicarbonate solution. Chromatography on a silica gel column, CH_2Cl_2/MeOH (4:1), gave 165 mg of product 19, which crystallized from $CHCl_3$/hexane with mp 219–220 °C (61% yield): TLC R_f = 0.22 (MeOH/CH_2Cl_2, 1:4); UV (EtOH) λ_{max} 286, 256, 208 nm; IR (KBr) ν_{max} 3280, 2949, 2915, 2850, 1669, 1650, 1591, 1481, 1455, 1392, 1284, 1089, 753, 732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.13 (d, J = 8 Hz, 1 H), 7.23 (m, 2 H), 7.12 (m, 1 H), 5.93 (m, 1 H), 4.99 (s, br, OH, 1 H), 4.36 (s, 1 H), 3.90 (s, 1 H), 3.50 (s, 1 H), 3.24 (m, 1 H), 3.19 (m, 1 H), 3.06 (m, 1 H), 2.73 (m, 1 H), 2.57 (m, 1 H), 2.38 (m, 5 H), 1.35 (m, 1 H), 0.88 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 168.29, 141.84, 140.97, 135.66, 128.27, 124.29, 122.32, 122.01, 114.35, 69.98, 69.15, 65.05, 54.32, 52.74, 51.36, 48.02, 38.25, 37.24, 20.24; MS m/z (rel inten) 308 (M^+, 59), 291 (6), 277 (5), 251 (5), 236 (17), 222 (35), 206 (7), 194 (12), 180 (14), 167 (19), 154 (12), 149 (12), 143 (12), 130 (17), 125 (9), 115 (17), 112 (39).

(±)-(3a*R,11b*S**,12*R**,13a*S**,14*S**)-Methyl 14-Hydroxy-14-ethenyl-9-oxo-12*H*-1,12-ethano-2,3,10,11b,13,13a-hexahydro-9*H*-pyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazole (24).** To a solution of $(COCl)_2$ (2.0 M in CH_2Cl_2, 130 ul, 0.26 mmol) in 0.5 mL of CH_2Cl_2 at −78 °C was added, dropwise, DMSO (250 uL, 0.351 mmol). The solution was stirred for an additional 15 min. A solution of (±)-(3a*R**,11b*S**,12*R**,13a*S**,14*R**)-methyl 14-hydroxy-9-oxo-12*H*-1,12-ethano-2,3,10,11b,13,13a-hexahydro-9*H*-pyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazole (19, 20 mg, 0.065 mmol) in 1 mL of CH_2Cl_2 was introduced at −78 °C. The solution was stirred for 1 h. Et_3N (121 uL, 0.871 mmol) was added dropwise, and the solution was stirred for an additional 20 min. Then, the reaction solution was allowed to warm to room temperature and stirred for 15 min. The solution was diluted with dichloromethane and washed with saturated sodium bicarbonate. The solvent was evaporated under reduced pressure. The crude product 20 could be purified on a silica gel column, eluting with CH_2Cl_2/MeOH (95:5), to give 18 mg of the ketone 20 as a white foam (98% yield).

The above crude product 20 was dissolved in 1.5 mL of THF. Vinyl magnesium bromide (1.0 M in THF, 80 uL) was added dropwise at 0 °C. The mixture was stirred for 30 min at 0 °C, diluted with dichloromethane, and washed with saturated sodium bicarbonate. The residue, obtained on concentration, was chromatographed on a silica gel column. Elution with CH_2Cl_2/MeOH (4:1) gave 14 mg of product 24 as a white foam (65% yield). The product crystallized from acetone/hexane with mp 237–239 °C.

For the ketone 20: TLC R_f = 0.29 (MeOH/CH_2Cl_2, 5:95); UV (EtOH) λ_{max} 292, 284, 254, 212 nm; IR (KBr) ν_{max} 2922, 2856, 1718, 1669, 1594, 1483, 1460, 1389, 1285, 755, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.16 (d, J = 8 Hz, 1 H), 7.26 (m, 2 H), 7.11 (t, J = 7 Hz, 1 H), 6.05 (m, 1 H), 4.14 (s, 1 H), 3.96 (m, 1 H), 3.82 (d, J = 16 Hz, 1 H), 3.44 (m, 1 H), 3.24 (s, 1 H), 3.13 (m, 3 H), 2.62 (m, 1 H), 2.41 (m, 1 H), 2.28 (m, 1 H), 1.98 (dd, J = 13, 5 Hz, 1 H), 1.77 (d, J = 14 Hz, 1 H) 1.22 (s, 1 H); MS m/z (rel inten) 307 (6), 306 (M^+, 20), 284 (7), 278 (68), 263 (11), 256 (8), 248 (8), 234 (24), 220 (18), 206 (9), 194 (11), 185 (10), 180 (10), 167 (13), 157 (13), 143 (10), 129 (28), 127 (11), 125 (18), 115 (21), 112 (41).

For the alcohol 24: TLC R_f = 0.26 (MeOH/CH_2Cl_2, 1:4); UV (EtOH) λ_{max} 294, 284, 256, 210 nm; IR (KBr) ν_{max} 3350, 2920, 2852, 1663, 1649, 1592, 1479, 1458, 1392, 1285, 1090, 1027, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.12 (d, J = 8 Hz, 1 H), 7.20 (m, 2 H), 7.09 (t, J = 7 Hz, 1 H), 6.28 (dd, J = 17, 11 Hz, 1 H), 5.97 (m, 1 H), 5.65 (d, J = 17 Hz, 1 H), 5.35 (d, J = 11 Hz, 1 H), 4.39 (s, 1 H), 3.35 (s, 1 H), 3.23 (m, 1 H), 3.14 (m, 2 H), 3.00 (m, 2 H), 2.50 (m, 2 H), 2.36 (m, 1 H), 2.25 (m, 1 H), 2.05 (d, J = 12 Hz, 1 H), 1.47 (d, J = 14 Hz, 1 H), 1.26 (s, OH, 1 H); ^{13}C NMR ($CDCl_3$) δ 168.53, 140.85, 140.69, 140.34, 135.97, 128.17, 124.62, 124.33, 122.29, 116.08, 114.33, 70.93, 70.09, 64.79, 57.71, 54.65, 51.70, 48.27, 43.96, 37.42, 24.06; MS m/z (rel inten) 334 (M^+, 10), 279 (25), 222 (12), 206 (3), 194 (3), 180 (3), 167 (5), 143 (2), 130 (3), 113 (9), 98 (13).

(±)-(3a*R,11b*S**,12*R**,13a*S**)-Methyl 14-(*E* and *Z*)-[(Methoxycarbonyl)methylene]-9-oxo-12*H*-1,12-ethano-2,3,10,11b,-13,13a-hexahydro-9*H*-pyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazole (21 and 22).** To a solution of methyl (diethylphosphono)acetate (205 mg, 0.94 mmol) in 5 mL of THF was added potassium bis(trimethylsilyl)amide (0.5 M in toluene, 1.8 mL, 0.9 mmol), at room temperature, dropwise, and the solution was stirred for additional 30 min. Then, a solution of the ketone 20 (220 mg, 0.72 mmol) in 5 mL of THF was added dropwise. The reaction solution was stirred at room temperature for 2 h. The reaction was quenched with water and the product was extracted with dichloromethane. The residue, obtained on concentration, was chromatographed on a silica gel column, eluting with CH_2Cl_2/hex/Et_3N (10:10:1), to afford 100 mg of the *E*-isomer 21 and 110 mg of the *Z*-isomer 22 as a white foam (81% yield).

A degassed solution of the *Z*-isomer (50 mg, 0.138 mmol) in 50 mL of dry benzene was irradiated by a high-pressure Hg lamp with a Pyrex filter, at room temperature, for 30 min. Concentration and purification on a silica gel column (CH_2Cl_2/hex/Et_3N = 10:10:1) gave 38 mg of the *E*-isomer and 5 mg of the *Z*-isomer (76% yield of *E*-isomer, 84% yield based on recovery of *Z*-isomer).

For the *E*-isomer 21: TLC R_f = 0.24 (CH_2Cl_2/hex/Et_3N, 10:10:1); IR (KBr) ν_{max} 2948, 2915, 2869, 1713, 1673, 1595, 1478,

1457, 1392, 1279, 1213, 1192, 1143, 755, 732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.15 (d, J = 8 Hz, 1 H), 7.24 (m, 2 H), 7.08 (t, J = 7 Hz, 1 H), 5.92 (s, 1 H), 5.89 (m, 1 H), 4.22 (s, 1 H), 4.13 (d, J = 16 Hz, 1 H), 3.96 (d, J = 16 Hz, 1 H), 3.76 (s, 1 H), 3.71 (s, 3 H), 3.26 (m, 2 H), 3.09 (m, 2 H), 2.75 (m, 1 H), 2.22 (m, 2 H), 2.07 (m, 1 H), 1.48 (d, J = 14 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 168.17, 166.29, 158.01, 142.56, 141.55, 133.78, 128.33, 124.01, 122.48, 120.43, 118.25, 114.63, 65.57, 61.90, 52.46, 52.35, 51.11, 46.55, 44.93, 39.40, 36.85, 24.16; MS m/z (rel inten) 363 (23), 362 (M$^+$, 100), 347 (84), 303 (33), 220 (11), 204 (2), 165 (6).

For the Z-isomer **22**: TLC R_f = 0.18 (CH_2Cl_2/hex/Et_3N, 10:10:1); IR (KBr) ν_{max} 2942, 2915, 2876, 1714, 1672, 1594, 1484, 1466, 1393, 1264, 1191, 1154, 1078, 800, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.15 (d, J = 8.1 Hz, 1 H), 7.21 (m, 2 H), 7.09 (t, J = 8 Hz, 1 H), 6.17 (m, 1 H), 5.77 (s, 1 H), 4.77 (s, 1 H), 4.30 (s, 1 H), 3.72 (s, 3 H), 3.62 (m, 2 H), 3.23 (m, 1 H), 3.01 (m, 3 H), 2.31 (m, 2 H), 2.19 (m, 2 H), 1.53 (d, J = 14 Hz, 1 H); ^{13}C NMR ($CDCl_3$): δ 168.34, 165.99, 157.68, 141.30, 141.25, 134.76, 128.24, 124.04, 122.54, 122.32, 115.13, 114.46, 67.77, 63.47, 54.48, 53.59, 52.09, 51.06, 46.73, 37.09, 33.67, 25.67; MS m/z (rel inten) 363 (25), 362 (M$^+$, 84), 347 (100), 331 (6), 303 (14), 273 (4), 258 (5), 246 (5), 232 (5), 220 (16), 218 (8), 204 (9), 192 (5), 180 (6), 167 (11), 165 (36), 154 (5), 134 (16), 130 (11), 128 (21), 119 (29), 115 (11).

(±)-(3a*R,11b*S**,12*R**,13a*S**)-Methyl 14(*E*)-(2-Hydroxyethylidene)-9-oxo-12*H*-1,12-ethano-2,3,10,11b,13,13a-hexahydro-9*H*-pyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazole (Isostrychnine, 23).** To a solution of the E-acrylate **21** (20 mg, 0.055 mmol) in 2 mL of dichloromethane, at −78 °C, was added BF_3·Et_2O (14 uL, 0.11 mol), dropwise. The solution was stirred for an additional 30 min and then DIBAL (171 uL, 0.171 mmol, 1.0 M in hexane) was added dropwise. The solution was stirred at −78 °C for 4 h. The reaction was quenched by adding MeOH at −78 °C, followed by adding saturated sodium potassium tartrate and saturated sodium bicarbonate aqueous solution. The reaction solution was stirred at room temperature for 1 h and then extracted with dichloromethane. The solvent was removed under reduced pressure and the residue dissolved in 10 mL of dichloromethane, 1 mL of triethylamine, and 1 mL of methanol. The solution was heated at reflux for 1 h. The residue, obtained on concentration, was purified on a silica gel column, eluting with CH_2Cl_2/hex/Et_3N (90:10:1), to give 16 mg of the alcohol as a white solid (87% yield): TLC R_f = 0.17 (MeOH CH_2Cl_2, 5:95; SiO_2 plate was deactivated with Et_3N); IR (KBr) ν_{max} 3348, 2922, 2875, 1668, 1591, 1478, 1460, 1392, 1286, 1147, 1011, 906, 755, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.15 (d, J = 8 Hz, 1 H), 7.22 (m, 2 H), 7.09 (t, J = 8 Hz, 1 H), 5.85 (m, 1 H), 5.59 (t, J = 4 Hz, 1 H), 4.29 (m, 2 H), 3.66 (s, 1 H), 3.59 (m, 2 H), 3.20 (m, 1 H), 3.08 (m, 2 H), 2.92 (m, 3 H), 2.23 (m, 3 H), 1.98 (s, br, OH, 1 H), 1.48 (m, 1 H); MS m/z (rel inten) 334 (M$^+$, 1), 316 (2), 303 (1), 101 (26), 86 (100). Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.16; H, 6.77; N, 8.27.

(±)-(3a*R,11b*S**,12*R**,13a*S**,14*S**)-Methyl 14-Acetoxy-14-ethenyl-9-oxo-12*H*-1,12-ethano-2,3,10,11b,13,13a-hexahydro-9*H*-pyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazole (25).** To a solution of (±)-(3a*R**,11b*S**,12*R**,13a*S**,14*S**)-Methyl 14-Hydroxy-14-ethenyl-9-oxo-12*H*-1,12-ethano-2,3,10,11b,13,13a-hexahydro-9*H*-pyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazole (24, 15 mg, 0.045 mmol), triethylamine (125 uL, 0.9 mmol), and one crystal of 4-(*N*,*N*-dimethylamino)pyridine in 2 mL of dichloromethane, at 0 °C, was added acetic anhydride (42 uL, 0.45 mmol) dropwise. The solution was stirred for 24 h at room temperature, 5 mL of half-saturated sodium bicarbonate aqueous solution was added, and the mixture was stirred for 5 min. The solution was extracted with dichloromethane. The residue, obtained on concentration, was chromatographed on a silica gel column. Elution with CH_2Cl_2/MeOH (98:2) afforded the acetate as a white foam: TLC R_f = 0.20 (MeOH/CH_2Cl_2, 2:98); UV (EtOH) λ_{max} 288, 256, 208 nm; IR (KBr) ν_{max} 2955, 2922, 2849, 1732, 1669, 1649, 1596, 1481, 1394, 1236, 1084, 1014, 753, 732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.13 (d, J = 8 Hz, 1 H), 7.23 (m, 3 H), 6.39 (dd, J = 11, 18 Hz, 1 H), 5.88 (m, 1 H), 5.66 (d, J = 18 Hz, 1 H), 5.46 (d, J = 11 Hz, 1 H), 4.41 (s, 1 H), 3.44 (d , J = 12 Hz, 1 H), 3.33 (d, J = 12 Hz, 1 H), 3.23 (m, 1 H), 3.11 (m, 1 H), 2.98 (m, 1 H), 2.48 (m, 1 H), 2.32 (m, 1 H), 2.21 (m, 2 H), 1.96 (s, 3 H), 1.42 (m, 1 H), 1.15 (m, 1 H), 0.88 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 169.30, 168.19, 140.85, 140.21, 137.18, 136.06, 128.08, 124.20, 123.36, 122.21, 118.25, 114.28, 80.77, 70.01, 64.95, 54.73, 54.16, 51.64, 48.47, 39.26, 37.30, 23.57, 21.96; MS m/z (rel inten) 377 (6), 376 (M$^+$,4), 316 (22), 220 (6), 183 (3), 168 (3), 144 (14), 130 (6), 116 (44).

(±)-(3a*R,11b*S**,12*R**,13a*S**)-Methyl 14(*Z*)-(2-acetoxyethylidene)-9-oxo-12*H*-1,12-ethano-2,3,10,11b,13,13a-hexahydro-9*H*-pyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazole (26).** By addition of trifluoroacetic acid to a solution of 50 mg of (±)-(3a*R**,11b*S**,12*R**,13a*S**,14*S**)-methyl 14-acetoxy-14-ethenyl-9-oxo-12*H*-1,2-ethano-2,3,10,11b,13,11a-hexahydro-9*H*-pyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazole (25, 0.133 mmol) in dichloromethane, the amine was converted into its CF_3COOH salt. A degassed solution of this salt and 7.8 mg of $Pd(MeCN)_2Cl_2$ in 4 mL of dry THF was heated at reflux for 3 days. Then, the solution was diluted with dichloromethane and washed with saturated sodium bicarbonate solution. The residue, obtained on evaporating the solvent, was purified on a silica gel column, eluting with CH_2Cl_2/MeOH (95:5), to afford 10 mg of the rearranged acetate **26** as a yellowish solid and 28 mg of starting material (46% yield based on the recovery of **25**): TLC R_f = 0.18 (MeOH/CH_2Cl_2, 5:95); UV (EtOH) λ_{max} 290, 278, 252, 206 nm; IR (KBr) ν_{max} 2922, 2862, 1734, 1673, 1594, 1483, 1460, 1392, 1284, 1230, 1023, 755, 732 c m^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.15 (d, J = 8 Hz, 1 H), 7.19 (m, 2 H), 7.11 (m, 1 H), 5.84 (m, 1 H), 5.63 (t, J = 6 Hz, 1 H), 4.61 (m, 2 H), 4.27 (s, 1 H), 3.69 (m, 2 H), 3.22 (m, 2 H), 3.10 (m, 2 H), 2.21 (m, 3 H), 2.07 (s, 3 H), 1.98 (m, 1 H), 1.48 (m, 1 H); MS m/z (rel inten) 376 (M$^+$, 6), 332 (8), 316 (94), 303 (35), 290 (8), 260 (7), 240 (7), 232 (11), 220 (32), 204 (16), 191 (18), 167 (20), 154 (12), 149 (20), 144 (28), 130 (19), 119 (13), 115 (20).

(●)-(3a*R,11b*S**,12*R**,13a*S**)-Methyl 14(*E* and *Z*)-(2-Hydroxyethylidene)-9-oxo-12*H*-1,12-ethano-2,3,10,11b,13,13a-hexahydro-9*H*-pyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazole (Isostrychnine (23) and Its C14-C1′ Isomer).** A solution of (±)-(3a*R**,11b*S**,12*R**,13a*S**)-methyl 14(*Z*)-(2-(acetoxyethylidene)-9-oxo-12*H*-1,12-ethano-2,3,10,11b,13,13a-hexahydro-9*H*-pyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazole (26, 20 mg, 0.053 mmol) in 2 mL of 2% KOH in MeOH/H_2O (4:1) was heated at reflux (50 °C) for 30 min. The product was extracted with dichloromethane. The residue **27**, obtained on evaporating the solvent, was used directly for the next reaction.

To a solution of $(COCl)_2$ (2.0 M in CH_2Cl_2, 106 uL, 0.212 mmol) in 0.5 mL of CH_2Cl_2 at −78 °C was added, dropwise, DMSO (20 uL, 0.286 mmol). The solution was stirred for an additional 15 min and then a solution of the above allylic alcohol **27** in 1 mL of CH_2Cl_2 was introduced at −78 °C. The solution was stirred for 1 h. Et_3N (51 uL, 0.371 mmol) was then added dropwise and the solution was stirred for an additional 20 min. Then, the reacton solution was allowed to warm to room temperature, diluted with dichloromethane, and washed with saturated sodium bicarbonate. The solvent was evaporated under reduced pressure. The crude product was filtered through a short silica gel column, eluting with CH_2Cl_2/MeOH (97:3).

The resulting aldehyde **28** was dissolved in 15 mL of benzene and degassed with argon. The solution was irradiated for 1 h, at 10 °C, with a high-pressure mercury lamp, through a Pyrex filter.

The photoisomerized products **28** and **29** were dissolved in 2 mL of MeOH, and Ce_3Cl·$7H_2O$ (20 mg, 0.053 mmol) was added. Then, $NaBH_4$ (10 mg, 0.264 mmol) was added in several portions at 0 °C. The solution was stirred for 30 min, 0.5 mL of acetone was added, and the solution was diluted with saturated sodium bicarbonate. The product was extracted with dichloromethane. The residue, obtained on evaporating the solvent, was purified on a silica gel column, eluting with CH_2Cl_2/MeOH/Et_3N (90:10:1), to afford 16 mg (63% yield) of the hydroxy products as a mixture (EZ = 2:1). This mixture could be used for the synthesis of strychnine or converted to the corresponding acetates for chromatographic separation.

(±)-(3a*R,11b*S**,12*R**,13a*S**)-Methyl 14(*E* and *Z*)-(2-Acetoxyethylidene)-9-oxo-12*H*-1,12-ethano-2,3,10,11b,13,13a-hexahydro-9*H*-pyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazole (Isostrychnine Acetate and Its *Z* Isomer).** A solution of 16 mg of (±)-(3a*R**,11b*S**,12*R**,13a*S**)-Methyl 14(*E* and *Z*)-(2-hydroxyethylidene)-9-oxo-12*H*-1,12-ethano-2,3,10,11b,13,13a-hexahydro-9*H*-pyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazole (isostrychnine (**23**) and its Z-isomer **27**), 200 μL of triethylamine, and 100 μL of acetic anhydride in 2 mL of dichloromethane was allowed to stir

at room temperature overnight. Saturated sodium bicarbonate was added and the product was extracted with dichloromethane. The residue, obtained on the concentration, was chromatographed on a silica gel column, eluting with CH_2Cl_2/MeOH (95:5), to give the 11 mg of isostrychnine acetate (61% yield) and 6 mg of the *Z*-isomer **26** (32% yield).

For isostrychnine acetate: TLC R_f = 0.25 (MeOH/CH_2Cl_2, 1:9); UV (EtOH) λ_{max} 292, 286, 254, 206 nm; IR (KBr) ν_{max} 2935, 2882, 1737, 1669, 1560, 1483, 1460, 1389, 1230, 1023, 758, 727 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.15 (d, J = 8 Hz, 1 H), 7.26 (m, 2 H), 7.10 (t, J = 8 Hz, 1 H), 5.93 (m, 1 H), 5.57 (t, J = 7 Hz, 1 H), 4.71 (m, 2 H), 4.31 (s, 1 H), 3.87 (s, 1 H), 3.70 (d, J = 14 Hz, 1 H), 3.64 (s, 1 H), 3.32 (m, 1 H), 3.12 (m, 1 H), 3.07 (m, 1 H), 2.99 (d, J = 14 Hz, 1 H), 2.87 (m, 1 H), 2.30 (m, 1 H), 2.17 (m, 2 H), 2.07 (s, 3 H), 1.50 (d, J = 14 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 170.51, 168.06, 141.28, 141.19, 138.38, 133.50, 128.42, 124.12, 123.11, 122.56, 121.09, 114.51, 66.22, 62.10, 59.62, 52.90, 52.31, 51.96, 45.01, 36.65, 34.41, 24.91, 20.70; MS *m/z* (rel inten) 376 (M^+, 4), 316 (100), 287 (3), 260 (3), 246 (3), 232 (4), 220 (13), 204 (7), 191 (5), 180 (6), 167 (9), 158 (7), 144 (23), 130 (12), 120 (7), 115 (10).

(±)-Strychnine. (a) A solution of 10 mg of isostrychnine acetate in 1 mL of 1.5% EtOH was heated at reflux (85 °C) for 6 h. The solvents were removed under reduced pressure, and the residue was dissolved in dichloromethane and washed with water. Concentration and chromatography on a silica gel column (CH_2Cl_2/MeOH/Et_3N, 90:10:1) gave 2 mg of strychnine and 5 mg of recovered isostrychnine, which was contaminated by α,β-unsaturated lactam.

(a) A solution of 100 mg of isostrychnine (**23**) in 10 mL of 1.5% EtOH was heated at reflux at (85 °C) for 6 h. The solvents were removed under reduced pressure, and the residue was dissolved in dichloromethane and washed with water. Concentration and chromatography on a silica gel column (CH_2Cl_2/MeOH/Et_3N, 90:10:1) gave 28 mg of strychnine and 61 mg of recovered isostrychnine, which was contaminated with α,β-unsaturated lactam (72% yield based on recovered isostrychnine): TLC R_f = 0.30 (MeOH/CH_2Cl_2, 1:9; SiO_2 plate deactivated with Et_3N); UV (EtOH) λ_{max} 288, 286, 254, 206 nm; IR (KBr) ν_{max} 2942, 2895, 2865, 2813, 1666, 1596, 1473, 1453, 1387, 1281, 1187, 1142, 1103, 1047, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.10 (d, J = 8 Hz, 1 H), 7.27 (m, 1 H), 7.16 (d, J = 6 Hz, 1 H), 7.09 (t, 7 Hz, 1 H), 5.89 (t, J = 7 Hz, 1 H), 4.28 (m, 1 H), 4.12 (dd, J = 7, 14 Hz, 1 H), 4.06 (dd, J = 6, 14 Hz, 1 H), 3.94 (s, 1 H), 3.86 (d, J = 11 Hz, 1 H), 3.70 (d, J = 15 Hz, 1 H), 3.15 (m, 3 H), 2.87 (dd, J = 10, 18 Hz, 1 H), 2.72 (d, J = 15 Hz, 1 H), 2.67 (dd, J = 4, 17 Hz, 1 H), 2.36 (m, 1 H), 1.87 (m, 2 H), 1.45 (d, J = 14 Hz, 1 H), 1.27 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 169.15, 142.18, 140.54, 132.74, 128.40, 127.01, 124.06, 122.13, 116.11, 77.53, 64.53, 60.12, 60.04, 52.62, 51.87, 50.25, 48.16, 42.81, 42.38, 31.56, 26.79; MS, *m/z* (rel inten) 335 (20), 334 (M^+, 91), 183 (7), 167 (18), 161 (20), 149 (17), 143 (22), 134 (21), 130 (29), 120 (40), 111 (31), 107 (39).

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Supplementary Material Available: Copies of ^1H NMR spectra for all intermediates (20 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.