Syntheses of Strychnan- and Aspidospermatan-Type Alkaloids. 10. An Enantioselective Synthesis of (−)-Strychnine through the Wieland−Gumlich Aldehyde

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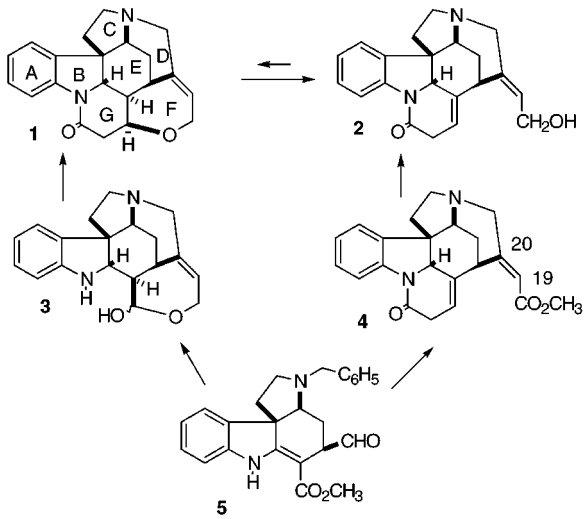
Condensations of L-tryptophan-derived 2-[(methoxycarbonyl)methyl]-3-[2(*S*)-(benzyloxycarbonyl)-2-(*N*^{b}-benzylamino)ethyl]indole (**6**) with 4,4-dimethoxyacrolein or with 2,4-hexadienal, followed by removal of the tryptophanyl ester function, respectively gave the tetracyclic acetal (−)-methyl (2*S*,3a*S*,5*R*,11b*R*)-3-benzyl-2,3,3a,4,5,7-hexahydro-5-(dimethoxymethyl)-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (**10**) or the tetracyclic olefin (−)-methyl (2*S*,3a*S*,5*R*,11b*R*)-3-benzyl-2,3,3a,4,5,7-hexahydro-5-(1-propenyl)-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (**14**). Their respective hydrolysis or oxidation provided, enantioselectively, the tetracyclic aldehyde (−)-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**). Its reaction with tri-*n*-butyl-1-(ethoxy)ethoxymethyltin and *n*-butyllithium, followed by oxidation of the resultant alcohol (−)-methyl (2*S*,3a*S*,5*R*,11b*R*)-3-benzyl-2,3,3a,4,5,7-hexahydro-5-(1ξ-hydroxy-2-((1-ethoxyethoxy))ethyl-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (**16**) and cyclization furnished the pentacyclic ketone (−)-methyl (2*S*,3a*S*,5*R*,11b*R*)-3-benzyl-2,3,3a,4,5,7-hexahydro-3,5-ethano-12-oxo-1*H*-pyrrolo-[2,3-*d*]carbazole-6-carboxylate (**15**). A Horner−Emmons condensation led to the unsaturated esters (−)-methyl (2*S*,3a*S*,5*R*,11b*R*)-3-benzyl-2,3,3a,4,5,7-hexahydro-3,5-ethano-12-(*E* and *Z*)-[(methoxycarbonyl)-methylene]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylates (**19** and **20**) with 17:1 *E*/*Z* selectivity. Reductions of the ester and vinylogous urethane functions in **19** led to the Wieland−Gumlich aldehyde **3** as a 6:1 anomeric hemiacetal mixture. Its condensation with malonic acid provided (−)-strychnine (**1**) in 5.3% overall yield and 14 steps from the tryptophan derivative **6**.

In 1993 we reported a total synthesis of racemic strychnine (**1**).[1] The new tandem condensation, sigmatropic rearrangement, and cyclization sequence on which that synthesis was based[2] was then studied in greater detail.[3] It was also shown to allow the enantioselective generation of ABCE tetracyclic compounds, which could serve as potential intermediates, or as models, for syntheses of *Strychnos* alkaloids.[3] On the basis of those results, we now report an alternative to our earlier synthetic path to strychnine, which now generates the alkaloid with complete enantioselectivity and overcomes the most significant strategic liabilities of our earlier synthesis.

In our first approach, we focused on reaching our goal as expeditiously as possible and succeeded in reducing the number of steps from 28[4] or 27[5] in the then-reported syntheses to 17 steps, and we were able to increase the overall yield from 6×10^{-5}%[4] or 3×10^{-2}%[5] to 1.4% (3% with two recycling steps) from tryptophan.[1] Our initial synthesis lacks, however, the enantioselectivity of the contemporary synthesis by Overman (25 steps, 3% yield),[6] and it is not as efficient as that of Rawal (15 steps, 10% yield).[7]

Scheme 1



As in the first and last reported strychnine syntheses,[4,7] isostrychnine (**2**) was our last intermediate. Its Prelog−Taylor cyclization to strychnine (Scheme 1) suffers from an unfavorable 3:1 equilibration ratio of these compounds.[1,8] From this perspective, the alternative biomimetic route through condensation of the Wieland−Gumlich aldehyde **3** with an acetate equivalent for

(1) Kuehne. M. E.; Xu, F. *J. Org. Chem.* **1993**, *58*, 7490.
(2) Parsons, R. L.; Berk, J. D.; Kuehne, M. E. *J. Org, Chem.* **1993**, *58*, 7482.
(3) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1997**, *62*, 7950.
(4) (a) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749. (b) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *Tetrahedron* **1963**, *19*, 247.
(5) Magnus, P.; Giles, M.; Bonnert, R.; Johnson, G.; McQuire, M. D.; Merritt, A.; Kim, C. S.; Vicker, N. *J. Am. Chem. Soc.* **1993**, *115*, 8116.
(6) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1993**, *115*, 9293; **1995**, *117*, 5776.
(7) Rawal, V, H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685.
(8) Prelog, V.; Battegay, J.; Taylor, W. I. *Helv. Chim. Acta* **1948**, *31*, 2244.

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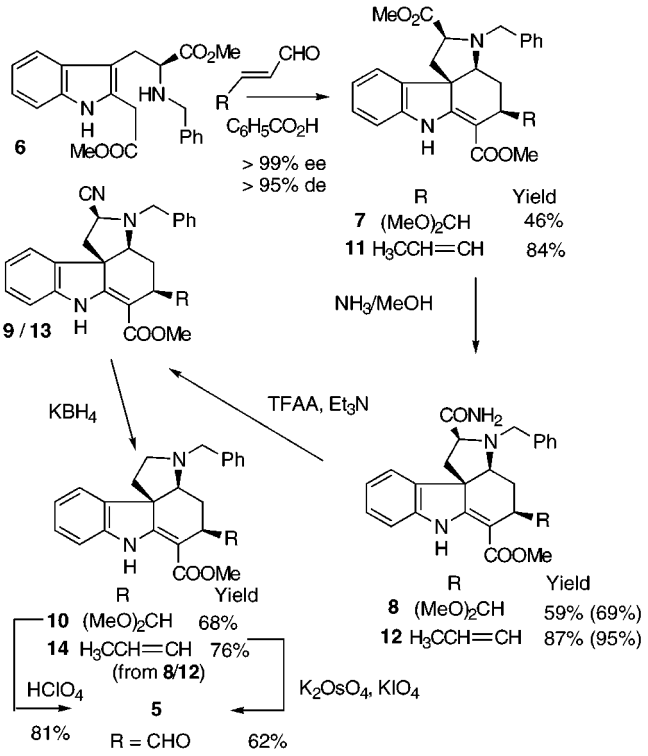
Scheme 2



formation of ring G[5,6,9] is more attractive, and consequently, the present report describes the enantioselective synthesis of this final precursor of (−)-strychnine.

In addition to the lack of enantioselectivity and the unfavorable cyclization in the last step, a third deficiency in our previous strychnine synthesis was encountered in establishment of the C-19−C-20 *E* double bond geometry that is required for cyclization of ring F. While this geometry is exclusively inherent in the Overman and Rawal strategies,[6,7] it was obtained in our initial synthesis by a photochemical equilibration of an unsaturated ester (intermediate **4**),[1] in an acceptable 6:1 *E*/*Z* ratio (it was less favorable for the corresponding unsaturated nitrile, 2:1, *E*/*Z*).[5] A more pleasing 17:1 *E*/*Z* ratio could now be achieved directly in the present synthesis, thus surmounting the third strategic hurdle on the course to strychnine (**1**).

Our first objective toward an enantioselective synthesis of strychnine was the enantioselective generation of the ABCE tetracyclic intermediate aldehyde **5**. This was obtained by condensation of the L-tryptophan-derived 2-[(methoxycarbonyl)methyl]-3-[2(*S*)-(benzyloxycarbonyl)-2-(*N*^{b}-benzylamino)ethyl]indole (**6**) with 4,4-dimethoxyacrolein (Scheme 2),[3] followed by removal of the tryptophanyl ester group in the tetracyclic product **7** by its conversion to an amide (**8**) and then a nitrile (**9**), and subsequent reduction of this α-aminonitrile **9** with potassium borohydride. Acid-catalyzed hydrolysis of the acetal function in the amine **10** provided the aldehyde **5**. No racemic contamination was detectable by complexation of the product with Eu(hfc) chiral shift reagent and NMR comparison with the corresponding racemic compound that was obtained from tryptamine (aldehyde ^{1}H signals at δ 10.24 and 10.10 for the two complexed enantiomers). The overall yield of the aldehyde **5** was 15% over five steps.

(9) Anet, F. A. L.; Robinson, R. *Chem. Ind.* **1953**, 245.

The lability of the acetal function in the precursors to the aldehyde **5**, particularly under the acid conditions of formation of the initial ABCE tetracycle **7**, suggested an alternative reaction sequence starting with condensation of 2,4-hexadienal with the tryptophan-derived diester **6**. Here, the yield of the initial ABCE tetracycle **11** was doubled (relative to formation of the acetal **7**), and the overall yield of the aldehyde **5**, after removal of the tryptophanyl ester function (**11**−**14**) and a final double bond cleavage with potassium osmate and periodate, was 34%. Again, no enantiomeric product could be detected in the aldehyde **5**.

For our next key intermediate, we focused on generation of the ABCDE pentacyclic C-20 ketone **15**. In our earlier racemic strychnine synthesis we had avoided this compound,[1] since oxidation of a corresponding alcohol had given an unstable product. Further structure extension at that center was deferred until after reduction of the vinylogous urethane function in rings B/E.

Our new target, therefore, became the generation of a C-20 ketone functionality prior to cyclization of ring D. To that end, the aldehyde **5** was condensed with tri-*n*-butyl-1-(ethoxy)ethoxymethyltin and *n*-butyllithium as base,[10] at −78 °C, to give an epimeric mixture of C-20 hydroxy compounds **16** in 73% yield. Oxidation of this mixture of alcohols with chloro(dimethyl)sulfonium chloride furnished the C-20 ketone **17** in 94% yield. Cleavage of its C-21 acetal ether function with *p*-toluenesulfonic acid then provided the C-21 alcohol, C-20 ketone **18** in 82% yield, without contamination by any epimeric or enantiomeric products.

Cyclization of the hydroxy ketone **18** with *p*-toluenesulfonic anhydride and *N*^{b}-debenzylation by hydrogenolysis then resulted in a 92% yield of the sensitive ketone **15**.

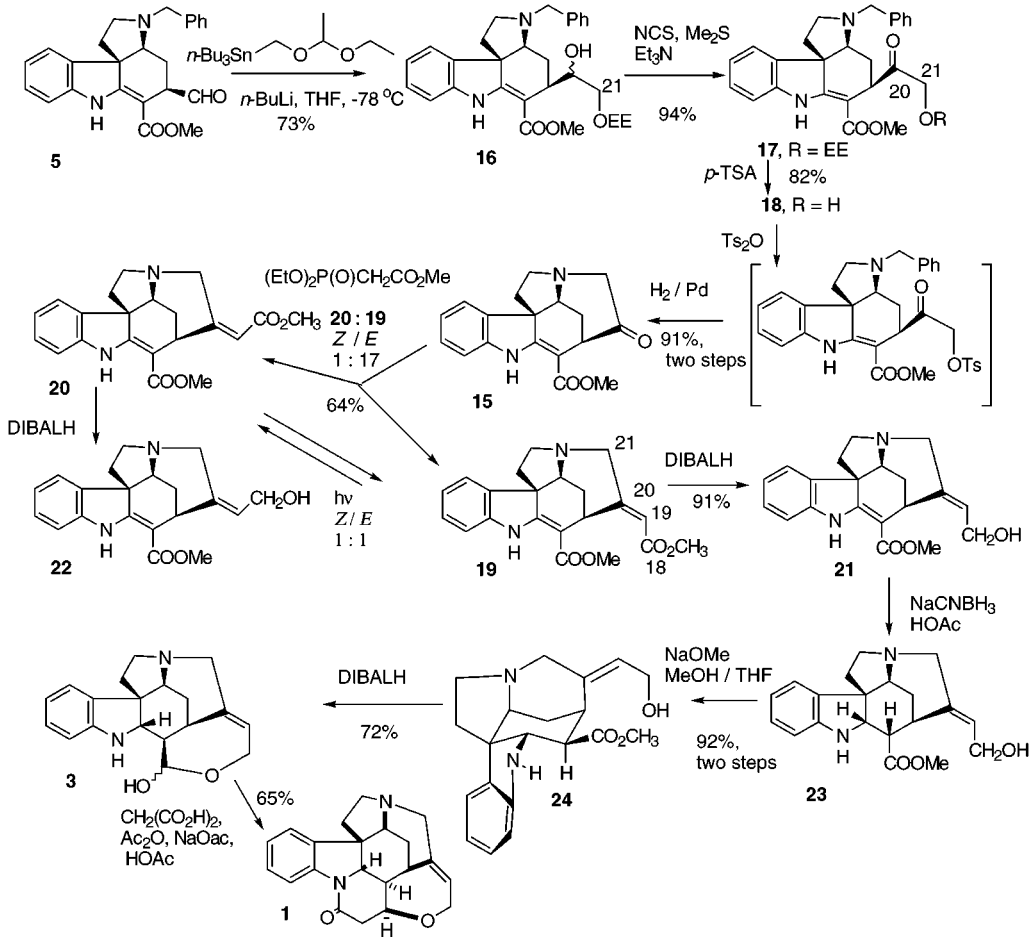
For elaboration of ring F of the Wieland−Gumlich aldehyde **3**, the ketone **15** was subjected to a Horner−Emmons condensation. The olefinic C-19, C-20 *E*/*Z* isomer ratio of the product was found to depend critically on experimental conditions. While in THF/toluene only a 3:2 *E*/*Z* ratio was obtained, a reaction in THF, with potassium hexamethyldisilazane as base, provided a gratifying 17:1 ratio of chromatographically separated isomers **19** and **20**, obtained in 64% yield.[11] It was also found that a photochemical equilibration of these olefins **19** and **20** in benzene resulted in formation of a 1:1 mixture; in contrast to the 6:1 ratio of olefin isomers obtained on irradiation of the corresponding acrylate attached to the saturated pentacycle.[1] ^{1}H NMR NOE interactions of the C-19 vinyl hydrogen at δ 5.75 with the C-21 aminomethylene hydrogens at δ 3.63 and 3.16 established the *E* double bond configuration for isomer **19**.

Reduction of the C-18 ester function in **19** and **20** with diisobutylaluminum hydride and BF_3 then provided the corresponding alcohols **21** and **22**. When the vinylogous urethane **21** was subjected to cyanoborohydride in acetic acid, it was reduced with introduction of both the proton at C-16 and hydride at C-2 on the face of ring E bearing the *N*^{b} substituent.[12] Epimeriztion of the saturated ester

(10) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.

(11) The relative *E*/*Z* ratios are consistent with generation of intermediates having a relative propensity for eclipsed oxyanion and phosphorane substituents in a less polar solvent versus formation of a trans anti-periplanar orientation of these substituents in a more polar solvent.

Scheme 3



product **23** with sodium methoxide then gave the equatorial ester substituent (**24**) with an overall yield of 92% for these two steps.

The Wieland−Gumlich aldehyde **3** was obtained by a DIBALH reduction of the ester **24** (72% yield). A final biomimetic condensation of that product with malonic acid,[5,6,9] acetic anhydride, sodium acetate, and acetic acid provided (−)-strychnine (**1**) with a 5.3% overall yield for the 14-step reaction sequence starting from the tryptophan derivative **6**.

Conclusion. The present synthesis is the shortest and most efficacious enantioselective total synthesis of strychnine. Its methodology and concepts lend themselves to modifications that can provide syntheses of other related alkaloids.[13]

Experimental Section

***N*^{b}-Benzyltryptophan Methyl Ester. Method a.** Tryptophan methyl ester hydrochloride (20.0 g, 0.0785 mol) was converted into the free base by partitioning it between ether and 10% potassium carbonate. The organic solution was dried over sodium sulfate and concentrated, and the resulting amine was dissolved in 250 mL of dichloromethane. Benzaldehyde (8.0 mL, 0.079 mol) and 15 g of $MgSO_4$ were added, and the mixture was stirred for 5 h. Filtration and concentration gave the imine product, which was dissolved in 200 mL of methanol, and 3.29 g of $NaBH_4$ (0.0865 mol) was added in portions at 0 °C. The solvent was evaporated after 1 h at 0 °C, and the residue was dissolved in ether and washed with 5% ammonium hydroxide. Concentration gave the crude benzylation product, which was pure enough for the next reaction. It also could be purified by chromatography on a silica gel column, eluted with Hex/EtOAc (3:2).

Method b. The first step to form the imine intermediate was simplified by using MeOH instead of dichloromethane. After 5 h at room temperature, the reaction solution was cooled to 0 °C, $NaBH_4$ was added as above, and the reaction was then worked up as above. Eu(fad) chiral shift reagent was used to determine the % ee. No racemization was observed: $R_f = 0.27$ (EtOAc/Hex, 2:3, CAS brown); mp 105 °C (EtOAc/Hex); $[\alpha]^{24}_D$ −6.6 (c = 2.0, $CHCl_3$); UV λ_{max} (EtOH) 222, 282, 292 nm; IR (KBr) ν_{max} 3420, 1735 cm^{-1}; ^{1}H NMR δ 8.03 (s, 1 H), 7.57 (d, J = 7.8 Hz, 1 H), 7.32 (d, J = 8.1 Hz, 1 H), 7.24 (m, 5 H), 7.17 (dt, J = 0.9, 8.0 Hz, 1 H), 7.09 (dt, J = 0.8, 7.8 Hz, 1 H), 7.01 (d, J = 2.0 Hz, 1 H), 3.82 (d, J = 13.2 Hz, 1 H), 3.66 (m, 2 H), 3.62 (s, 3 H), 3.22 (dd, J = 6.3, 14.4 Hz, 1 H), 3.14 (dd, J = 6.9, 14.4 Hz, 1 H), 1.82 (s, br, 1 H); ^{13}C NMR δ 175.3, 139.7, 136.2, 128.3, 128.1, 127.6, 127.0, 122.7, 122.1, 119.5, 118.8, 111.5, 111.1, 61.3, 52.1, 51.7, 29.3; MS m/z (rel intensity) 309 (M^++1, 7), 178 (25), 130 (100), 91 (76). Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.46; H, 6.43; N, 8.92.

***N*^{b}-Boc-*N*^{b}-Benzyltryptophan Methyl Ester.** To a solution of the preceding *N*-benzyltryptamine ester and triethylamine (21.9 mL, 0.157 mol) in 300 mL of dichloromethane, at room temperature, was added (t-Boc)$_2$O (17.1 g, 0.075 mol). The the solution was stirred at room temperature overnight.

(12) This stereochemical result is in agreement with the analogous reduction of the less substituted ABCDE pentacycle, discussed in our previous strychnine synthesis.[1] Surprisingly, this reduction had failed in the Overman synthesis, where a lower yielding reduction with zinc was then used.[6]

(13) For syntheses of (−)-lochneridine and its C-20 epimer see the following paper (no. 11 of this series): Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1998**, *63*, 9434.

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

The residue, obtained upon concentration, was purified on a silica gel column, eluted with EtOAc/Hex (1:4), to give 28.5 g (89% yield, two steps) of the title product: $R_f = 0.27$ (EtOAc/Hex, 1:4; CAS, brown); $[\alpha]^{26}_D$ −101 (c = 2.1, $CHCl_3$); UV λ_{max} (EtOH) 222, 284 nm; IR (KBr) ν_{max} 3357, 1740, 1696, 1684, 1674, 1558 cm^{-1}; ^1H NMR δ 7.98 (s, 1 H), 7.45−7.33 (m, 2 H), 7.18 (s, br, 4 H), 7.07 (s, br, 3 H), 6.98−6.76 (m, 1 H), 4.51 (d, br, J = 13.0 Hz, 1 H), 4.35 (d, br, J = 13.5 Hz, 0.4 H), 4.18 (s, br, 0.6 H), 4.02 (d, br, J = 15.4 Hz, 0.4 H), 3.85 (d, br, J = 15.4 Hz, 0.6 H), 3.58 (s, 3 H), 3.47 (m, 1 H), 3.37 (s, br, 0.4 H), 3.21 (s, br, 0.6 H), 1.46 (s, 5.4 H), 1.42 (s, 3.6 H); MS m/z (rel intensity) 409 (2), 408 (M^+, 8), 201 (54), 130 (100), 91 (22).

2-[Bis(methoxycarbonyl)methyl]-3-[2(*S*)-(methoxycarbonyl)-2-[*N*^{b}-*tert*-(butoxycarbonyl)-*N*^{b}-benzylamino]ethyl]indole. To a solution of 32.0 g of the preceding urethane (0.0783 mol) and 12 mL of Et_3N (0.086 mol) in 500 mL of THF, at −78 °C, was added 10.3 mL of *t*-BuOCl (0.0862 mol) dropwise. After the solution was stirred for another 30 min, 15.67 mL of $ZnCl_2$ (0.01567 mol, 1.0 M in ether) was introduced. The reaction solution was stirred for another 10 min; a solution of 13 g of lithium dimethyl malonate (0.094 mol) in 60 mL of THF was then cannulated into the reaction solution. The solution was stirred at −78 °C for 1 h and then at room temperature overnight. Water was added, and the organic layer was separated. The aqueous phase was extracted with ether. Concentration gave the crude product, which was used without further purification. It also could be purified on a silica gel column, eluted with EtOAc/Hex (1:4): $R_f = 0.19$ (EtOAc/Hex, 1:4, CAS, blue fades fast); mp 68−70 °C (EtOAc/Hex); $[\alpha]^{26}_D$ −98 (c = 2.0, $CHCl_3$); UV λ_{max} (EtOH) 220, 284, 294 nm; IR (KBr) ν_{max} 3397, 1737, 1700 cm^{-1}; ^1H NMR δ 8.87 (s, 1 H), 7.33 (d, J = 8.1 Hz, 1 H), 7.16 (m, 5 H), 7.02 (m, 3 H), 5.16 (s, br, 0.4 H), 5.11 (s, br, 0.6 H), 4.41 (d, br, J = 14.6 Hz, 0.6 H), 4.28 (d, br, J = 15.0, 0.4 H), 4.21 (s, br, 0.4 H), 4.07 (s, br, 0.6 H), 3.95 (d, br, J = 15.0 Hz, 0.4 H), 3.80 (d, br, J = 14.6 Hz, 0.6 H), 3.76 (s, 6 H), 3.57 (s, 3 H), 3.50 (m, br, 1 H), 3.42 (s, br, 0.4 H), 3.22 (s, br, 0.6 H), 1.52 (s, 5.4 H), 1.45 (s, 3.6 H); ^{13}C NMR (more peaks observed due to the rotamers) δ 171.4, 167.7, 155.1, 137.1, 136.0, 128.6, 128.0, 127.6, 127.2, 127.0, 126.2, 122.6, 119.6, 118.8, 118.4, 111.3, 111.0, 81.0, 60.6, 59.6, 53.1, 52.4, 52.0, 48.8, 28.3, 25.3; MS m/z (rel intensity) 538 (M^+, 3), 260 (100), 169 (17), 91 (28). Anal. Calcd for $C_{29}H_{34}N_2O_8 \cdot 0.5H_2O$: C, 63.79; H, 6.44; N, 5.11. Found: C, 63.55; H, 6.28; N, 5.03.

2-[(Methoxycarbonyl)methyl]-3-[2-(*S*)-(methoxycarbonyl)-2-[*N*^{b}-(*tert*-butoxycarbonyl)-*N*^{b}-benzylamino]ethyl]indole. The above crude diester was dissolved in 300 mL of wet DMF, and 6.64 g of LiCl (0.157 mol) was added. The solution was heated at 135 °C for 4 h. After the solution was cooled to room temperature, 5% NH_4OH was added. The aqueous phase was extracted with ether several times. The combined organic extract was washed with water and brine. The residue, obtained on drying and concentration, was purified on a silica gel column, eluted with EtOAc/Hex (25:75), to give 33.1 g (88% yield, 2 steps) of the title product: R_f = 0.34 (EtOAc/Hex, 3:7, CAS, green); mp 54−56 °C (EtOAc/Hex); $[\alpha]^{23}_D$ −116 (c = 1.1, $CHCl_3$); UV λ_{max} (EtOH) 208, 222, 284, 292 nm; IR (KBr) ν_{max} 3383, 1740, 1692 cm^{-1}; ^1H NMR δ 8.61 (s, 1 H), 7.36 (m, br, 0.4 H), 7.30 (d, J = 8.0 Hz, 1 H), 7.19 (m, br, 0.6 H), 7.14 (m, 4 H), 7.03 (t, J = 7.4 Hz, 1 H), 6.98 (m, 2 H), 4.43 (d, br, J = 14.5 Hz, 0.6 H), 4.27 (d, br, J = 14.3 Hz, 0.4 H), 4.14 (s, br, 0.4 H), 4.06 (s, br, 0.6 H), 3.87 (d, br, J = 14.3 Hz, 0.4 H), 3.75 (s, br, 2.6 H), 3.73 (s, 3 H), 3.58 (s, 3 H), 3.44 (m, br, 1.4 H), 3.18 (m, br, 0.6 H), 1.52 (s, 5.4 H), 1.44 (s, 3.6 H); ^{13}C NMR δ 171.5, 155.2, 135.7, 128.6, 128., 127.8, 127.2, 121.9, 119.5, 118.0, 110.9, 52.2, 51.8, 3.2, 28.4; MS m/z (rel intensity) 481 (7), 480 (M^+, 1), 203 (100), 142 (24), 91 (16). Anal. Calcd for $C_{27}H_{32}N_2O_6 \cdot 1.5\ H_2O$: C, 63.89; H, 6.95; N, 5.52. Found: C, 64.26; H, 6.35; N, 5.38.

2-[(Methoxycarbonyl)methyl]-3-[2(*S*)-(methoxycarbonyl)-2-(*N*^{b}-benzylamino)ethyl]indole (6). To a solution of 20.0 g of the above urethane (41.62 mmol) and 11.6 mL of Et_3N (83.24 mmol) in 500 mL of dichloromethane, at 0 °C, was added 16.1 mL of TMSOTf (83.24 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 of the combined organic solutions, was purified on a silica gel column, eluted with EtOAc/Hex (2:3), to give 15.4 g (97% yield) of the title product: $R_f = 0.23$ (EtOAc/Hex, 2:3, CAS, yellow/green); $[\alpha]^{23}_D$ −9.3 (c = 2.0, $CHCl_3$); IR (KBr) ν_{max} 3391, 1732 cm^{-1}; ^1H NMR δ 8.59 (s, 1 H), 7.48 (d, J = 8.0 Hz, 1 H), 7.31 (d, J = 8.1 Hz, 1 H), 7.26−7.18 (m, 5 H), 7.15 (t, J = 7.1 Hz, 1 H), 7.07 (t, J = 7.7 Hz, 1 H), 3.82 (d, J = 3.0 Hz, 2 H), 3.77 (d, J = 13.1 Hz, 1 H), 3.68 (s, 3 H), 3.61 (m, 2 H), 3.59 (s, 3 H), 3.11 (m, 2 H), 1.58 (s, br, 1 H); ^{13}C NMR δ 175.4, 171.1, 165.5, 139.8, 135.7, 128.2, 128.1, 128.0, 126.9, 121.9, 119.5, 118.5, 110.7, 108.9, 61.3, 52.3, 52.2, 51.7, 31.6, 28.6; MS m/z (rel intensity) 383 (M^+ + 3, 14), 382 (M^+ + 2, 6), 202 (100), 142 (38), 91 (56).

(−)-Methyl (2*S*,3a*S*,5*R*,11b*R*)-2-(Methoxycarbonyl)-3-benzyl-2,3,3a,4,5,7-hexahydro-5-(dimethoxymethyl)-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (7). A solution of 2-[(methoxycarbonyl)methyl]-3-[2(*S*)−(methoxycarbonyl)-2-(*N*^{b}-benzylamino)ethyl]indole (**6**, 4.00 g, 10.5 mmol), 4,4-dimethoxy-2-butenal[14] (1.64 g, 12.6 mmol), and benzoic acid (1.28 g, 10.5 mmol) in 100 mL of benzene was heated at reflux for 48 h with a Dean−Stark trap to remove the formed water. The solvent was removed under vacuum. The residue was dissolved in EtOAc and washed with saturated sodium bicarbonate. The residue, obtained on concentration, was purified on a silica gel column, eluting with Et_2O/Hex (3:2), to give 2.4 g (46% yield) of the title product: $R_f = 0.2$ (Et_2O/Hex, 3:2, CAS blue); mp 120−122 °C (HCl salt); $[\alpha]^{27}_D$ −256 (c = 1.0, $CHCl_3$); UV λ_{max} (EtOH) 206, 226, 296, 326 nm; IR (KBr) ν_{max} 3364, 1736, 1667, 1609 cm^{-1}; ^1H NMR δ 9.15 (s, 1 H), 7.38 (m, 2 H), 7.34 (m, 3 H), 7.10 (t, J = 7.7 Hz, 1 H), 6.77 (d, J = 7.7 Hz, 1 H), 6.72 (t, J = 7.5 Hz, 1 H), 6.42 (d, J = 7.3 Hz, 1 H), 5.32 (d, J = 9.1 Hz, 1 H), 4.04 (d, J = 13.9 Hz, 1 H), 3.95 (d, J = 13.9 Hz, 1 H), 3.78 (s, 3 H), 3.75 (dd, J = 5.3, 11.6 Hz, 1 H), 3.63 (s, 3 H), 3.56 (s, 3 H), 3.52 (d, J = 5.4 Hz, 1 H), 3.41 (s, 3 H), 3.32 (m, 1 H), 2.28 (d, J = 13.2 Hz, 1 H), 2.22 (dd, J = 11.6, 11.6 Hz, 1 H), 1.97 (dd, J = 5.3, 11.6 Hz, 1 H), 1.23 (ddd, J = 5.4, 5.4, 13.2 Hz, 1 H); ^{13}C NMR δ 172.9, 164.8, 142.7, 137.0, 135.1, 130.6, 128.2, 128.1, 127.6, 121.3, 120.5, 109.3, 106.7, 96.6, 63.6, 62.7, 55.5, 55.4, 55.3, 53.6, 51.7, 51.2, 48.9, 38.4, 29.0; MS m/z 461 (M^+ − OMe, 9), 460 (26), 359 (10), 268 (22), 238 (10), 192 (23), 91 (100).

(−)-Methyl (2*S*,3a*S*,5*R*,11b*R*)-2-(Methoxycarbonyl)-3-benzyl-2,3,3a,4,5,7-hexahydro-5-(1-propenyl)-1*H*-pyrrolo-[2,3-*d*]carbazole-6-carboxylate (11). A solution of 2-[(methoxycarbonyl)methyl]-3-[2(*S*)-(methoxycarbonyl)-2-(*N*^{b}-benzylamino)ethyl]indole (**6**, 10.0 g, 26.3 mmol), sorbic aldehyde (3.67 mL, 31.6 mmol), benzoic acid (3.21 g, 26.3 mmol), and hydroquinone (120 mg, 1.05 mmol) in 300 mL of benzene was heated at reflux for 10 h with a Dean−Stark head to remove the formed water. The solvent was removed under vacuum. The residue was dissolved in EtOAc and washed with half-saturated sodium carbonate. The residue, obtained on concentration, was purified on a silica gel column, eluted with EtOAc/Hex (1:9), to give 10.1 g (84% yield) of the title product: $R_f = 0.5$ (EtOAc/Hex, 1:4, CAS blue); $[\alpha]^{24}_D$ −197 (c = 0.5, $CHCl_3$); UV λ_{max} (EtOH) 208, 228, 298, 326 nm; IR (KBr) ν_{max} 3367, 1734, 1677, 1609 cm^{-1}; ^1H NMR δ 9.09 (s, 1 H), 7.38 (m, 2 H), 7.35 (m, 2 H), 7.25 (m, 1 H), 7.12 (t, J = 7.5 Hz, 1 H), 6.78 (J = 7.5 Hz, 1 H), 6.77 (t, J = 7.5 Hz, 1 H), 6.62 (d, J = 7.3 Hz, 1 H), 6.15 (m, 1 H), 5.46 (m, 1 H), 4.00 (d, J = 13.8 Hz, 1 H), 3.97 (d, J = 13.8 Hz, 1 H), 3.76 (s, 3 H), 3.74 (m, 1 H), 3.64 (apparent s, 1 H), 3.54 (d, J = 5.5 Hz, 1 H), 3.48 (s, 3 H), 2.55 (dd, J = 11.7, 11.7 Hz, 1 H), 1.91 (apparent d, J = 12.2 Hz, 1 H), 1.84 (dd, J = 5.5, 11.7 Hz, 1 H), 1.71 (d, J = 6.4 Hz, 3 H), 1.32 (ddd, J = 5.6, 5.6, 12.2 Hz, 1 H); ^{13}C NMR δ 172.7, 168.8, 164.5, 142.8, 137.2, 137.1, 135.8, 130.0, 128.1, 128.0, 127.3, 123.7, 121.6, 120.5, 109.3, 98.2, 66.1, 64.1, 57.3, 54.3, 51.6, 51.0, 47.4, 36.4, 34.3, 17.9; MS m/z 459 (M^+ + 1, 10), 400 (11), 368 (26), 255 (100), 223 (44), 194 (37), 180 (13), 167 (12), 91 (79).

(−)-Methyl (2*S*,3a*S*,5*R*,11b*R*)-2-(Aminocarbonyl)-3-benzyl-2,3,3a,4,5,7-hexahydro-5-(1-propenyl)-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (12). A solution of of the diester

11 (10.0 g, 21.8 mmol) in 200 mL of dry MeOH, at 0 °C, was saturated with dry NH_3(g). The solution was stirred gently at room temperature for 5 days. The residue, obtained on concentration, was purified on a silica gel column eluted with EtOAc/CH_2Cl_2 (1:9), to give 8.4 g of the title product (87% yield, 95% yield based on recovered starting material) and 900 mg of starting material (9% recovery yield): R_f = 0.38 (EtOAc/CH_2Cl_2, 1:4, CAS blue); mp 180 °C (EtOAc/Hex); $[\alpha]^{24}_D$ −155 (c = 1.1, $CHCl_3$); UV λ_{max} (EtOH) 206, 228, 298, 324 nm; IR (KBr) ν_{max} 3434, 3367, 1684, 1608 cm^{-1}; ^{1}H NMR δ 9.12 (s, 1 H), 7.39 (m, 3 H), 7.30 (m, 2 H), 7.09 (t, J = 7.6 Hz, 1 H), 6.87 (d, J = 4.5 Hz, 1 H), 6.77 (d, J = 7.7 Hz, 1 H), 6.69 (t, J = 7.5 Hz, 1 H), 6.32 (d, J = 7.4 Hz, 1 H), 5.75 (m, 1 H), 5.44 (d, J = 4.5 Hz, 1 H), 5.36 (m, 1 H), 4.03 (d, J = 13.5 Hz, 1 H), 3.85 (d, J = 13.5 Hz, 1 H), 3.74 (s, 3 H), 3.61 (m, 3 H), 2.32 (dd, J = 11.8, 11.8 Hz, 1 H), 1.89 (dd, J = 5.4, 11.8 Hz, 1 H), 1.80 (apparent d, J = 14.1 Hz, 1 H), 1.66 (m, 3 H), 1.36 (ddd, J = 5.8, 5.8, 14.1 Hz, 1 H); ^{13}C NMR δ 175.4, 168.7, 165.1, 142.5, 136.7, 136.3, 135.3, 130.5, 128.7, 128.1, 127.9, 124.2, 121.7, 120.7, 109.3, 96.1, 66.0, 64.7, 56.3, 54.7, 51.1, 48.0, 35.9, 34.4, 18.1; MS m/z (rel intensity) 443 (M^+, 1), 399 (31), 352 (11), 254 (48), 222 (11), 194 (15), 91 (100). Anal. Calcd for $C_{27}H_{29}N_3O_3$: C, 73.11; H, 6.59; N, 9.47. Found: C, 72.89; H, 6.31; N, 9.30.

(−)-Methyl (2*S*,3a*S*,5*R*,11b*R*)-3-Benzyl-2,3,3a,4,5,7-hexahydro-5-(1-propenyl)-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (14). To a solution of the amide **12** (10.5 g, 23.7 mmol) and *i*-Pr_2NEt (19.8 mL, 114 mmol) in 300 mL of dichloromethane, at 0 °C, was added trifloroacetic anhydride (6.69 mL, 47.4 mmol), dropwise. The reaction mixture was stirred at room temperature for 40 min and then washed with saturated sodium bicarbonate. Drying and concentration gave the nitrile **13**, which was used for the next reaction without purification.

To a solution of nitrile **13** in 300 mL of dry EtOH, at room temperature, was added KBH_4 (6.40 g, 119 mmol) in several portions. The reaction mixture was then heated in a 75 °C oil bath for 4 h. The solvent was evaporated under reduced pressure, and 5% NH_4OH was added to the residue. The mixture was extracted with EtOAc. The residue, obtained on concentration, was purified on a silica gel column, eluted with EtOAc/Hex (5:95), to give 7.2 g of the title product (76% yield, two steps): $[\alpha]^{24}_D$ −204 (c = 1.0, $CHCl_3$). The ^{1}H and ^{13}C NMR, MS, IR, TLC, and UV/vis data for this material were indistinguishable from those of its racemic form reported previously.[3]

(−)-Methyl (2*S*,3a*S*,5*R*,11b*R*)-2-(Aminocarbonyl)-3-benzyl-2,3,3a,4,5,7-hexahydro-5-(dimethoxymethyl)-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (8). The acetal diester **7** (2.8 g, 5.69 mmol) was treated with 40 mL of dry MeOH saturated with NH_3(g). Use of the procedure for formation of amide **12** gave 1.6 g (59% yield, 69% yield based on the recovery of diester **7**) of amide **8**, after column chromatography on silica gel (EtOAc/Hex, 4:1), and 400 mg of recovered diester **7**: R_f = 0.27 (EtOAc/Hex, 4:1, CAS blue); mp 178 °C (EtOAc/Hex); $[\alpha]^{24}_D$ −348 (c = 1.0, $CHCl_3$); UV λ_{max} (EtOH) 206, 228, 298, 328 nm; IR (KBr) ν_{max} 3428, 3364, 1683, 1609 cm^{-1}; ^{1}H NMR δ 9.13 (s, 1 H), 7.38 (m, 3 H), 7.34 (m, 3 H), 7.10 (ddd, J = 0.9, 7.7, 7.7 Hz, 1 H), 6.77 (d, J = 7.7 Hz, 1 H), 6.72 (ddd, J = 0.5, 7.5, 7.5 Hz, 1H), 6.42 (d, J = 7.4 Hz, 1 H), 5.42 (d, br, J = 3.6 Hz, 1 H), 4.83 (d, J = 8.6 Hz, 1 H), 4.08 (d, J = 13.5 Hz, 1 H), 3.90 (d, J = 13.5 Hz, 1 H), 3.77 (s, 3 H), 3.70 (dd, J = 6.0, 11.5 Hz, 1 H), 3.60 (d, J = 6.2 Hz, 1 H), 3.33 (m, 1 H), 3.32 (s, 6 H), 2.23 (dd, J = 11.5, 11.5 Hz, 1 H), 2.11 (dd, J = 6.0, 11.5 Hz, 1 H), 1.95 (dd, J = 1.2, 14.4 Hz, 1 H), 1.18 (ddd, J = 6.0, 6.0, 14.4 Hz, 1 H); ^{13}C NMR δ 175.5, 168.8, 164.9, 142.3, 137.1, 135.4, 130.5, 128.5, 128.1, 127.8, 121.4, 120.7, 109.3, 105.1, 95.8, 65.5, 64.4, 56.7, 55.9, 54.2, 51.2, 50.0, 49.3, 36.4, 29.0; MS m/z 463 ($M^+ + 1 -$ Me, 10), 446 (9), 434 (5), 402 (7), 370 (5), 268 (24), 226 (5), 194 (7), 177 (100), 167 (10), 91 (71).

(−)-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). **Method a.** To a mixture of (−)-methyl (2*S*,3a*S*,5*R*,11b*R*)-3-benzyl-2,3,3a,4,5,7-hexahydro-5-(1-propenyl)-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (**14**, 6.0 g, 15 mmol) and KIO_4 (20.7 g, 90 mmol) in 140 mL of THF and 60 mL of H_2O, at 0 °C, was added $K_2OsO_4 \cdot 2H_2O$ in one portion. The mixture was stirred at 0 °C for 4 h. The solid was removed by filtration, and the filtrate was concentrated under reduced pressure. Ethyl ether was added, and the organic phase was washed with water and with saturated sodium bicarbonate. The residue, obtained on concentration, was purified on a silica gel column, eluting with EtOAc/Hex (1:4), to give 3.6 g (62% yield) of the title product.

Method b. Dehydration of the amide **8** and reduction of the nitrile **9**, using the procedures for the preparation of the amine **14**, provided the tetracyclic amine **10**. Its ^{1}H, ^{13}C, MS, UV, and IR spectra and TLC data matched those of the corresponding racemate, reported previously.[1] Hydrolysis of of the dimethyl acetal **10**, as described in the total synthesis of racemic strychnine,[1] gave the above aldehyde **5** in 81% yield; $[\alpha]^{24}_D$ −187 (c = 1.0, $CHCl_3$).

The ^{1}H and ^{13}C NMR, MS, IR, TLC, and UV/vis data for this product were indistinguishable from those of its racemic form, reported previously.[1]

(−)-Methyl (2*S*,3a*S*,5*R*,11b*R*)-3-Benzyl-2,3,3a,4,5,7-hexahydro-5-(1ξ-hydroxy-2-(1-ethoxyethoxy))-ethyl-1*H*-pyrrolo[2,3-*d*]-carbazole-6-carboxylate (16). To a solution of tri-*n*-butyl-(1-(ethoxy)ethoxy)methyltin (9.80 g, 24.9 mmol),[10] in 80 mL of THF at −78 °C, was added *n*-BuLi (8.7 mL, 22 mmol, 2.5 M in Hex) dropwise. The solution was stirred for an additional 30 min. A solution of the aldehyde **5** (2.50 g, 6.44 mmol) in 10 mL of THF was then added dropwise. The reaction solution was stirred for 230 min at −78 °C, and saturated sodium bicarbonate was added. 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 (2:3), to give 3.26 g (73% yield) of the title product **16**: R_f = 0.26 (EtOAc/Hex, 2:3, CAS blue); UV λ_{max} (EtOH) 206, 230, 298, 326 nm; IR (KBr) ν_{max} 3360, 1674, 1607 cm^{-1}; ^{1}H NMR δ 9.35 (s, 0.5 H), 9.34 (s, 0.5 H), 7.36 (m, 4 H), 7.31 (m, 1 H), 7.14 (m, 1 H), 7.02 (m, 1 H), 6.85 (m, 1 H), 6.82 (m, 1 H), 5.91 (s, br, 1 H, OH), 4.81 (m, 1 H), 4.16 (m, 1 H), 3.95 (m, 0.5 H), 3.77 (s, 3 H), 3.72 (m, 2 H), 3.64 (m, 1 H), 3.56 (m, 2 H), 3.41 (m, 0.5 H), 3.31 (m, 1 H), 3.26 (m, 1 H), 2.96 (m, 1 H), 2.61 (m, 2 H), 1.95 (m, 1 H), 1.63 (m, 1 H), 1.58 (m, 1 H), 1.37 (m, 3 H), 1.23 (m, 3 H); MS m/z 493 (1), 492 (M^+, 1), 360 (37), 327 (10), 227 (67), 194 (15), 167 (15), 146 (60), 134 (21), 119 (16), 117 (14), 91 (100).

(−)-Methyl (2*S*,3a*S*,5*R*,11b*R*)-3-Benzyl-2,3,3a,4,5,7-hexahydro-5-(2-(1-ethoxyethoxy)acetyl)-1*H*-pyrrolo[2,3-*d*]-carbazole-6-carboxylate (17). To a stirred mixture of *N*-chlorosuccinimide (4.34 g, 32.5 mmol) in 50 mL of toluene at 0 °C was added Me_2S (2.2 mL, 30 mmol) dropwise. The mixture was stirred for an additional 10 min and then cooled to −20 °C. A solution of the alcohol **16** (3.2 g, 6.5 mmol) in 5 mL of toluene was introduced. The reaction solution was stirred at −20 °C for 30 min, and Et_3N (5.4 mL, 39 mmol) was added. 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 (3:7), to give 3.0 g (94% yield) of the title product **17**: R_f = 0.61 (EtOAc/Hex, 2:3, CAS blue); UV λ_{max} (EtOH) 206, 230, 298, 326 nm; IR (KBr) ν_{max} 3374, 1717, 1681, 1610 cm^{-1}; ^{1}H NMR δ 9.18 (s, 1 H), 7.32 (m, 4 H), 7.26 (m, 1 H), 7.14 (t, J = 7.6 Hz, 1 H), 7.00 (t, J = 6.6 Hz, 1 H), 6.83 (m, 2 H), 4.79 (m, 1 H), 4.55−4.31 (m, 2 H), 4.18 (m, 1 H), 3.98 (m, 1 H), 3.73 (s, 3 H), 3.62 (m, 2 H), 3.49 (m, 1 H), 3.26 (m, 1 H), 2.81 (m, 1 H), 2.69 (m, 1 H), 2.48 (m, 1 H), 1.56 (m, 2 H), 1.36 (m, 3 H), 1.15 (m, 3 H); MS m/z 491 ($M^+ + 1$, 11), 359 (35), 327 (16), 226 (15), 194 (17), 180 (11), 167 (15), 146 (35), 134 (20), 91 (100).

(−)-Methyl (2*S*,3a*S*,5*R*,11b*R*)-3-Benzyl-2,3,3a,4,5,7-hexahydro-5-(2-hydroxyacetyl)-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (18). A solution of the acetal **17** (2.8 g, 5.7 mmol) in 45 mL of THF and 15 mL of H_2O, at room temperature, was added *p*-TSA$\cdot H_2O$ (113.8 mg, 0.6 mmol) in one portion. The solution was stirred for 2 h. Saturated sodium bicarbonate solution was added, and the aqueous solution was

extracted with dichloromethane. The residue, obtained on drying and concentration, was purified on a silica gel column, eluting with EtOAc/Hex (2:3), to give 1.95 g (82% yield) of the title product **18**: $R_f = 0.25$ (EtOAc/Hex, 2:3, CAS blue); $[\alpha]^{25}_D$ −200 ($c = 1.0$, $CHCl_3$); UV λ_{max} (EtOH) 206, 228, 296, 324 nm; IR (KBr) ν_{max} 3473, 3362, 1706, 1683, 1608 cm^{-1}; ^1H NMR δ 9.20 (s, 1 H), 7.34 (m, 2 H), 7.29 (m, 3 H), 7.16 (t, $J = 7.7$ Hz, 1 H), 7.06 (d, $J = 7.3$ Hz, 1 H), 6.87 (m, 2 H), 4.68 (d, $J = 18.0$ Hz, 1 H), 4.39 (d, $J = 18.0$ Hz, 1 H), 4.14 (d, $J = 13.2$ Hz, 1 H), 3.81 (d, $J = 4.1$ Hz, 1 H), 3.75 (s, 3 H), 3.51 (d, $J = 13.2$ Hz, 1 H), 3.26 (d, $J = 3.5$ Hz, 1 H), 2.78 (dd, J 6.8, 8.7 Hz, 1 H), 2.54 (d, $J = 14.3$ Hz, 1 H), 2.45 (ddd, $J = 8.7$, 12.2, 13.6 Hz, 1 H), 2.12 (ddd, $J = 6.8$, 12.2, 12.2 Hz, 1 H), 1.60 (m, 2 H); ^{13}C NMR δ 210.6, 167.9, 142.6, 137.8, 137.2, 128.8, 128.4, 128.0, 127.2, 121.3, 120.9, 109.6, 91.7, 66.7, 65.3, 58.2, 56.0, 51.2, 50.9, 44.1, 43.7, 30.5; MS *m*/*z* 419 (2), 418 (M^+, 6), 359 (21), 159 (12), 146 (39), 134 (15), 112 (14), 91 (100).

(−)-Methyl (2*S*,3a*S*,5*R*,11b*R*)-3-Benzyl-2,3,3a,4,5,7-hexahydro-3,5-ethano-12-oxo-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (15). To a solution of the keto alcohol **18** (200 mg, 0.478 mmol) in 4 mL of 1,2-dichloroethane, at 0 °C, were added Et_3N (133 μL, 0.956 mmol), Ts_2O (187 mg, 0.573 mmol), and DMAP (5.9 mg, 0.048 mmol). The reaction was carefully monitored by TLC. As soon as the starting material had disappeared (ca. 20 min.), 4 mL of MeOH was introduced. The reaction solution was stirred at 0 °C for another 30 min and then heated in a 60 °C oil bath for 1 h. The solvent was evaporated under vacuum, and the residual solid was triturated with ethyl ether.

The resulting quaternary salt was dissolved in 6 mL of MeOH, and $PdCl_2$ (25 mg, 0.143 mmol) was added. Hydrogenolysis was carried out under 1 atm of hydrogen for 3 h. The solid was removed by filtration, and the solvent was evaporated under vacuum. The residue was dissolved in dichloromethane and washed with 5% sodium carbonate. The residue, obtained on drying and concentration, was purified on a silica gel column, eluting with CH_2Cl_2/MeOH (95:5), to afford 135 mg (91% yield) of the title product as a white foam: $R_f = 0.4$ (CH_2Cl_2/MeOH, 95:5, CAS blue); $[\alpha]^{26}_D$ −327 ($c = 0.95$, $CHCl_3$); UV λ_{max} (EtOH) 204, 226, 296, 326 nm; IR (KBr) ν_{max} 3364, 1717, 1673, 1608 cm^{-1}; ^1H NMR δ 8.90 (s, 1 H), 7.27 (d, $J = 8.0$ Hz, 1 H), 7.19 (ddd, $J = 1.0$, 7.7, 7.7 Hz, 1 H), 6.94 (ddd, $J = 0.6$, 7.5, 7.5 Hz, 1 H), 6.86 (d, $J = 7.8$ Hz, 1 H), 4.19 (s, 1 H), 3.87 (d, $J = 17.3$ Hz, 1 H), 3.82 (s, 3 H), 3.72 (dd, $J = 1.6$, 1.6 Hz, 1 H), 3.30 (ddd, $J = 5.6$, 12.0, 12.0 Hz, 1H), 3.02 (d, $J = 17.3$ Hz, 1 H), 2.93 (ddd, $J = 5.6$, 7.8, 12.0 Hz, 1 H), 2.61 (ddd, $J = 1.6$, 3.6, 13.7 Hz, 1 H), 1.95 (m, 2 H), 1.65 (ddd, $J = 1.6$, 1.6, 13.7 Hz, 1 H); ^{13}C NMR δ 212.2, 167.7, 166.9, 143.3, 135.1, 128.4, 121.4, 120.9, 109.9, 97.3, 60.6, 60.2, 57.5, 55.9,. 51.5, 46.7, 40.7, 29.1; MS *m*/*z* 311 (2), 310 (M^+, 11), 215 (10), 183 (11), 156 (40), 154 (11), 115 (11), 109 (100), 95 (32); HRMS calcd for $C_{18}H_{18}N_2O_3$ 310.1317, found 310.1317.

Note: If excess Ts_2O was used, or if MeOH was not added as soon as the keto alcohol **18** was consumed, the corresponding enol tosylate could be isolated in variable yields, depending on reaction conditions: $R_f = 0.41$ (EtOAc/Hex, 2:3, CAS gray); mp 159 °C (EtOAc/Hex) for the racemic compound obtained from racemic **18** in a parallel series of reactions; UV λ_{max} (EtOH) 206, 226, 298, 328 nm; IR (KBr) ν_{max} 3366, 1675, 1603 cm^{-1}; ^1H NMR δ 8.90 (s, 1 H), 7.82 (d, $J = 8.3$ Hz, 2 H), 7.33 (d, $J = 8.3$ Hz, 2 H), 7.22 (d, $J = 7.3$ Hz, 1 H), 7.15 (ddd, $J = 0.9$, 7.7, 7.7 Hz, 1 H), 6.90 (t, $J = 7.4$ Hz, 1 H), 6.81 (d, $J = 7.7$ Hz, 1 H), 5.66 (s, 1 H), 4.01 (d, $J = 2.0$ Hz, 1 H), 3.74 (s, 3 H), 3.49 (d, $J = 1.9$ Hz, 1 H), 3.19 (ddd, $J = 4.8$, 12.4, 12.4 Hz, 1 H), 3.00 (dd, $J = 6.4$, 11.9 Hz, 1 H), 2.46 (s, 3 H), 2.22 (ddd, $J = 6.4$, 12.5, 12.5 Hz, 1 H), 2.13 (ddd, $J = 3.0$, 3.0, 12.7 Hz, 1 H), 1.75 (dd, $J = 4.8$, 11.9 Hz, 1 H), 1.37 (ddd, $J = 2.9$, 2.9, 12.7 Hz, 1 H); ^{13}C NMR δ 167.5, 167.3, 145.0, 143.6, 138.3, 135.4, 133.3, 129.6, 128.5, 128.0, 121.0, 120.1, 109.7, 101.2, 58.8, 58.1, 53.24, 51.1, 46.0, 30.8, 29.5, 21.7; MS *m*/*z* 464 (M^+, 2), 309 (35), 281 (12), 278 (23), 249 (34), 221 (13), 194 (13), 167 (24), 156 (19), 139 (67), 123 (20), 91 (100).

(−)-Methyl (2*S*,3a*S*,5*R*,11b*R*)-3-Benzyl-2,3,3a,4,5,7-hexahydro-3,5-ethano-12-(*E* and *Z*)-[(methoxycarbonyl)methylene]-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylates (19 and 20). To a solution of potassium hexamethyldisilazane (414 mg, 1.97 mmol) in 4 mL of THF, at 0 °C, was added $(EtO)_2P(O)CH_2COOMe$ (388 uL, 2.03 mmol), dropwise. The solution was stirred at room temperature for another 30 min. A solution of the ketone **15** (180 mg, 0.58 mmol) in 2 mL of THF was then cannulated into the above solution. The reaction mixture was stirred at room temperature for 8 h, and the reaction was then quenched with water. The aqueous phase was extracted with dichloromethane. The residue, obtained on drying and concentration, was chromatographed on a silica gel column, eluting with Hex/CH_2Cl_2/Et_3N (60:40:5), to afford 135 mg of the title (*E*)-ester (**19**, 64% yield) and 10 mg of the (*Z*)-ester **20**, contaminated with $(EtO)_2P(O)CH_2COOEt$.

For the (*E*)-ester **19**: $R_f = 0.19$ (Hex/CH_2Cl_2/Et_3N, 60:40:5, CAS blue); $[\alpha]^{26}_D$ −403 ($c = 0.45$, $CHCl_3$); UV λ_{max} (EtOH) 206, 234, 298, 326 nm; IR (KBr) ν_{max} 3368, 1723, 1676, 1607 cm^{-1}; ^1H NMR δ 8.78 (s, 1 H), 7.18 (d, $J = 7.5$ Hz, 1 H), 7.12 (t, $J = 7.6$ Hz, 1 H), 6.88 (t, $J = 7.5$ Hz, 1 H), 6.79 (d, $J = 7.7$ Hz, 1 H), 5.75 (s, 1 H), 4.79 (s, 1 H), 3.98 (s, 1 H), 3.75 (s, 3 H), 3.69 (s, 3 H), 3.63 (d, $J = 14.5$ Hz, 1 H), 3.16 (m, 2 H), 2.91 (dd, $J = 7.0$, 12.2 Hz, 1 H), 2.66 (ddd, $J = 7.0$, 12.4 Hz, 1 H), 2.26 (d, $J = 13.5$ Hz, 1 H), 1.87 (dd, $J = 5.9$, 12.4 Hz, 1 H), 1.46 (d, $J = 13.5$ Hz, 1 H); ^{13}C NMR δ 168.5, 168.2, 165.9, 158.1, 144.0, 135.8, 127.7, 127.6, 120.9, 120.2, 114.9, 109.5, 101.2, 61.3, 57.1, 55.6, 55.0, 51.1, 51.0, 44.6, 30.6, 30.6; MS *m*/*z* 367 (15), 366 (M^+, 38), 334 (12), 307 (11), 216 (21), 202 (15), 180 (10), 169 (12), 165 (100), 156 (26), 152 (10), 137 (22), 133 (16), 123 (17), 115 (10), 109 (18), 106 (18); HRMS calcd or $C_{21}H_{22}N_2O_4$ 366.1580, found 366.1572.

For the (*Z*)-ester **20**: $R_f = 0.28$ (Hex/CH_2Cl_2/Et_3N, 60:40:5, CAS blue); UV λ_{max} (EtOH) 208, 234, 298, 328 nm; selected ^1H NMR data δ 8.86 (s, 1 H), 7.24 (d, $J = 7.7$ Hz, 1 H), 7.16 (t, $J = 7.6$ Hz, 1 H), 6.92 (t, $J = 7.3$ Hz, 1 H), 6.85 (d, $J = 7.7$ Hz, 1 H), 6.02 (s, 1 H), 4.65 (d, $J = 17.4$ Hz, 1 H), 3.88 (apparent s, 1 H), 3.84 (s, 3 H), 3.68 (3, 3 H), 2.40 (m, 1 H), 2.18 (m, 1 H), 1.89 (m, 1 H).

(−)-Methyl (2*S*,3a*S*,5*R*,11b*R*)-3-Benzyl-2,3,3a,4,5,7-hexahydro-3,5-ethano-12-(*E*)-[(hydroxymethyl)methylene]-1*H*-pyrrolo-[2,3-*d*]carbazole-6-carboxylate (18-Hydroxyakuammicine, 21). To a solution of the (*E*)-ester **19** (50 mg, 0.136 mmol) in 2 mL of CH_2Cl_2 at −78 °C was added $BF_3{\cdot}Et_2O$ (34 uL, 0.27 mmol), dropwise. The solution was stirred at −78 °C for 15 min. DIBALH (435 uL, 0.435 mmol, 1.0 M in CH_2Cl_2) was then added dropwise. After 3 h at −78 °C, the reaction was quenched with saturated potassium sodium tartrate at −78 °C. The mixture was then allowed to warm to room temperature and stirred until the two phases were clear (ca. 30 min). The aqueous phase was extracted with dichloromethane. The residue, obtained on drying and concentration, was dissolved in a solution of 0.5 mL of Et_3N, 4 mL of CH_2Cl_2, and 1 mL of MeOH. The solution was heated in a 40 °C oil bath for 1 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 give 42 mg (91% yield) of the title allylic alcohol as a white solid: $R_f = 0.13$ (CH_2Cl_2/MeOH, 95:5, SiO_2 plate, deactivated with Et_3N, CAS blue); mp 146 °C (dec); $[\alpha]^{24}_D$ −550 ($c = 0.3$, $CHCl_3$); UV λ_{max} (EtOH) 206, 234, 298, 328 nm; IR (KBr) ν_{max} 3354, 1673, 1605 cm^{-1}; ^1H NMR δ 8.91 (s, 1 H), 7.24 (d, $J = 7.3$ Hz, 1 H), 7.16 (t, $J = 7.5$ Hz, 1 H), 6.91 (t, $J = 7.4$ Hz, 1 H), 6.84 (d, $J = 7.7$ Hz, 1 H), 5.55 (t, $J = 6.4$ Hz, 1 H), 4.22 (d, $J = 6.4$ Hz, 1 H), 4.07 (s, 1 H), 3.98 (s, 1 H), 3.88 (d, $J = 15.4$ Hz, 1 H), 3.83 (s, 3 H), 3.27 (ddd, $J = 5.6$, 5.6, 12.3 Hz, 1 H), 3.05 (d, $J = 15.4$ Hz, 1 H), 3.01 (m, 1 H), 2.55 (ddd, $J = 6.8$, 6.8, 12.5 Hz, 1 H), 2.38 (apparent d, $J = 13.4$ Hz, 1 H), 1.87 (dd, $J = 5.6$, 12.5 Hz, 1 H), 1.34 (apparent dd, $J = 3.0$, 13.4 Hz, 1 H); ^{13}C NMR δ 168.5, 167.6, 143.3, 140.6, 136.3, 127.9, 125.7, 121.2, 120.7, 109.6, 100.6, 61.5, 58.3, 57.6, 56.1, 55.7, 51.3, 45.8, 30.7, 29.8; MS *m*/*z* 339 (7), 338 (M^+, 20), 180 (9), 149 (31), 137 (100), 121 (10), 119 (10).

(−)-Methyl (2*S*,3a*S*,5*R*,11b*R*)-3-Benzyl-2,3,3a,4,5,7-hexahydro-3,5-ethano-12-(*Z*)-[(hydroxymethyl)methylene]-1*H*-pyrrolo-[2,3-*d*]carbazole-6-carboxylate (22). For confirmation of the structure of isolated ester **20**, contaminated with Wittig reagent, a DIBALH reduction of the (*Z*)-ester, using the preceding procedure, gave the title compound in 65% yield: $R_f = 0.18$ ($CHCl_3$/MeOH, 98:2, CAS blue); UV λ_{max} (EtOH) 206,

230, 298, 330 nm; IR (KBr) ν_{max} 3368, 1675, 1608 cm^{-1}; ^{1}H NMR δ 8.84 (s, 1 H), 7.31 (d, J = 7.4 Hz, 1 H), 7.21 (t, J = 7.6 Hz, 1 H), 6.97 (t, J = 7.4 Hz, 1 H), 6.86 (d, J = 7.7 Hz, 1 H), 5.93 (t, J = 6.0 Hz, 1 H), 4.27 (dd, J = 6.1, 13.9 Hz, 1 H), 4.21 (dd, J = 6.1, 13.9 Hz, 1 H), 4.15 (s, 1 H), 4.02 (s, 1 H), 3.93 (d, J = 15.4 Hz, 1 H), 3.86 (s, 3 H), 3.64 (ddd, J = 6.4, 13.3, 13.3 Hz, 1 H), 3.32 (d, J = 15.4 Hz, 1 H), 3.23 (dd, J = 6.7, 13.3 Hz, 1 H), 2.64 (ddd, J = 6.7, 13.3, 13.3 Hz, 1 H), 2.58 (apparent d, 1 H), 1.94 (dd, J = 6.4, 13.3 Hz, 1 H), 1.34 (d, J = 14.1 Hz, 1 H); MS m/z 339 (3), 338 (M$^+$, 19), 167 (9), 149 (29), 137 (49), 129 (10), 127 (10), 121 (10), 111 (24).

Methyl 18-Hydroxy-2β,16β-cur-19-en-17-oate (23). To a solution of 40 mg of 18-hydroxyakuammicine (**21**, 0.12 mmol) in 2 mL of HOAc at 10 °C was added $NaBH_3CN$ in several portions. After 30 min, the reaction solution was cooled to 0 °C and basified with concentrated NH_4OH to pH 10. The aqueous phase was extracted with dichloromethane. Drying and concentration gave the title product, which was pure enough (as indicated by NMR) for the next reaction: R_f = 0.33 (CH_2Cl_2/MeOH, 9:1, SiO_2 plate, deactivated with Et_3N, CAS brown); UV λ_{max} (EtOH) 208, 248, 298 nm; IR (KBr) ν_{max} 3314, 1734, 1611 cm^{-1}; ^{1}H NMR δ 7.12 (d, J = 7.3 Hz, 1 H), 7.06 (ddd, J = 1.0, 7.6, 7.6 Hz, 1 H), 6.80 (t, J = 7.4 Hz, 1 H), 6.61 (d, J = 7.7 Hz, 1 H), 5.56 (t, J = 6.8 Hz, 1 H), 4.18 (m, 2 H), 4.17 (d, J = 5.3 Hz, 1 H), 3.79 (s, 3 H), 3.72 (d, J = 15.3 Hz, 1 H), 3.61 (apparent s, 1 H), 3.37 (d, J = 3.6 Hz, 1 H), 3.34 (m, 1 H), 3.29 (d, J = 15.3 Hz, 1 H), 3.00 (ddd, J = 7.0, 7.0, 11.3 Hz, 1 H), 2.74 (dd, J = 3.3, 5.1 Hz, 1 H), 2.50 (ddd, J = 7.5, 7.5, 13.7 Hz, 1 H), 2.31 (apparent d, J = 14.1 Hz, 1 H), 2.12 (ddd, J = 6.2, 6.2, 13.7 Hz, 1 H), 1.75 (ddd, J = 2.9, 2.9, 14.1 Hz, 1 H); ^{13}C NMR δ 173.9, 149.3, 141.4, 133.6, 128.3, 125.0, 122.6, 120.0, 110.0, 63.9, 63.6, 57.9, 53.8, 53.6, 52.4, 51.4, 46.8, 37.6, 27.4, 22.4; MS m/z 341 (M$^+$ + 1, 85), 267 (73), 210 (100), 181 (28), 167 (10), 155 (13), 153 (11), 149 (16), 144 (100), 130 (51), 124 (18), 117 (10), 115 (12); HRMS calcd for $C_{20}H_{24}N_2O_3$ 340.1787, found 340.1801.

Methyl 18-Hydroxy-2β,16α-cur-19-en-17-oate (24).To a solution of crude α-methoxycarbonyl compound **23** in 2 mL of THF and 2 mL of MeOH, was added a solution of NaOMe in MeOH (354 μL, 1.0 M). After 2 h at room temperature, the reaction was quenched with 2 N HCl to pH = 9. Most of the solvents were removed under vacuum. The aqueous phase was extracted with dichloromethane. The residue, obtained on drying and concentration, was purified on a silica gel column, eluting with CH_2Cl_2/MeOH/Et_3N (90:10:1) to give 37 mg (92% yield, two steps) of the title β-methoxycarbonyl product: R_f = 0.45 (CH_2Cl_2/MeOH, 9:1, Si_2O plate, deactivated with Et_3N; CAS brown); UV λ_{max} (EtOH) 206, 248, 298 nm; IR (KBr) ν_{max} 3364, 1733, 1607, 1559 cm^{-1}; ^{1}H NMR δ 7.04 (m, 2 H), 6.76 (t, J = 7.4 Hz, 1 H), 6.63 (d, J = 7.7 Hz, 1 H), 5.68 (t, J = 7.1 Hz, 1 H), 4.24 (s, br, 1 H, OH), 4.08 (m, 2 H), 3.94 (d, J = 9.9 Hz, 1 H), 3.75 (s, 3 H), 3.60 (s, 1 H), 3.59 (d, J = 14.1 Hz, 1 H), 3.26 (s, 1 H), 3.24 (m, 1 H), 3.12 (d, J = 14.1 Hz, 1 H), 2.88 (m, 1 H), 2.56 (m, 2 H), 2.10 (apparent d, J = 13.6 Hz, 1 H), 1.80 (m, 2 H); MS m/z 341 (16), 340 (M$^+$, 1), 310 (17), 296 268 (33), 211 (20), 181 (10), 172 (10), 167 (37), 158 (16), 155 (13), 149 (78), 144 (52), 137 (17), 130 (25), 125 (16), 111 (22), 97 (40).

Wieland−Gumlich Aldehyde 3. To a solution of the ester **25** (37 mg, 0.11 mmol) in 1 mL of dichloromethane at −90 °C was added DIBALH, slowly. After 30 min, the reaction was quenched with MeOH at −90 °C. The mixture was then allowed to warm to room temperature and acidified with 1 M HCl. The resulting solution was stirred overnight and then basified with concentrated NH_4OH. Saturated potassium sodium tartrate solution was added, and the solution was stirred for another 1 h. The aqueous phase was extracted with dichloromethane. The residue, obtained on drying and concentration, was purified on a silica gel column, eluting with CH_2Cl_2/MeOH/Et_3N (90:10:1), to give 24 mg (71% yield) of the Wieland−Gumlich aldehyde as an 8:1 mixture of anomers: R_f = 0.4 (CH_2Cl_2/MeOH, 9:1, SiO_2 plate, deactivated with Et_3N, CAS brown); $[\alpha]^{25}_D$ −129 (c = 0.23, MeOH); IR (KBr) ν_{max} 3370, 1605 cm^{-1}; MS m/z 310 (M$^+$, 42), 267 (18), 180 (100), 144 (58), 134 (17), 130 (40), 119 (10), 117 (11), 115 (11).

For the major isomer: ^{1}H NMR δ 7.10 (t, J = 7.5 Hz, 1 H), 7.05 (d, J = 7.7 Hz, 1 H), 6.85 (t, J = 7.4 Hz, 1 H), 6.79 (d, J = 7.8 Hz, 1 H), 5.85 (apparent s, 1 H), 5.01 (s, 1 H), 4.24 (dd, J = 7.0, 14.3 Hz, 1 H), 3.99 (s, 1 H), 3.95 (dd, J = 5.2, 14.3 Hz, 1 H), 3.83 (d, J = 10.7 Hz, 1 H), 3.76 (d, J = 14.7 Hz., 1 H), 3.30 (dd, J = 8.0, 8.0 Hz, 1 H), 2.85 (m, 1 H), 2.71 (d, J = 14.7 Hz, 1 H), 2.69 (s, 1 H), 2.29 (ddd, J = 4.1, 4.1, 14.2 Hz, 1 H), 2.08 (dd, J = 6.3, 12.6 Hz, 1 H), 1.83 (d, J = 10.7 Hz, 1 H), 1.64 (m, 1 H), 1.57 (apparent d, J = 14.2 Hz, 1 H).

(−)-Strychnine (1). Condensation of the Wieland−Gumlich aldehyde **3** with malonic acid according to the procedure of Overman[6] provided (−)-strychnine.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra, compounds marked with an asterisk include COSY spectra and compounds marked with a dagger (†) include NOESY spectra, for compounds **3**, **6**, **7***, **8***,**11***, **15***, **15** enol tosylate, **18***, **19***†, **21***, and **23*** and ^{1}H NMR spectra for compounds **3***, (−)-**5** and (±)-**5** with NMR chiral shift reagent, **16***, **17***, **22***, and **24*** (49 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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