Catalytic Asymmetric Synthesis of Either Enantiomer of the Calabar Alkaloids Physostigmine and Physovenine

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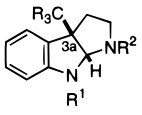
Received March 9, 1998

Abstract: A potentially versatile asymmetric route to hexahydropyrrolo[2,3-*b*]indoles having carbon substituents at C-3a (Scheme 1) is demonstrated through enantioselective total syntheses of the Calabar alkaloids (−)-physostigmine (**2**), (−)-physovenine (**10**), and their enantiomers. The synthesis of enantiopure (−)-physostigmine proceeds from commercially available 2-butyn-1-ol (**11**) and *N*-methyl-*p*-anisidine (**15**) in 15−20% overall yield by way of eight isolated and purified intermediates. The central step is catalytic asymmetric Heck cyclization of (*Z*)-2-methyl-2-butenanilide **17** to form oxindole aldehyde (*S*)-**19** in 84% yield and 95% ee.

Introduction

A hexahydropyrrolo[2,3-*b*]indole ring having a carbon substituent at C-3a (**1**) is the defining structural feature of a diverse collection of natural products. The best known members of



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this group are alkaloids found in seeds of the African Calabar bean,[2] exemplified by (−)-physostigmine (**2**), which was isolated in pure form as early as 1864.[3] Ring system **1** is found throughout the natural products kingdom and is displayed in a wide variety of structural formats.[4] Representative examples include flustramine B (**3**) isolated from a marine bryozoan[4,5] and the 3a-bishexahydropyrrolo[2,3-*b*]indole alkaloids chaetocin (**4**), isolated from a fungus,[6] and quadrigemine C (**5**), isolated from a New Caledonian plant.[7]

Some success has been recorded recently in asymmetric synthesis of pyrroloindolines of this type, either from 3a-unsubstituted pyrrolo[2,3-*b*]indolines[8] or through asymmetric alkylation of 3-substituted oxindoles.[9] We have pursued an alternate strategy in which 3a-substituted pyrroloindolines **1** are prepared from acyclic precursors by a sequence whose central step is an asymmetric intramolecular Heck reaction (Scheme 1).[10] Besides the simplicity of employing achiral aromatic precursors, the catalytic asymmetric approach outlined in Scheme 1 provides convenient access to either pyrrolo[2,3-*b*]-indoline enantiomer and potentially could allow a wide variety of substituents to be incorporated at C-3a, including those not readily introduced through alkylation processes. The use of an intramolecular Heck reaction to assemble a hexahydropyrrolo-[2,3-*b*]indole in racemic form, in this case from cyclization of a pyrroline-2-one aminal, was first reported by Hoffmann.[11]

As our initial natural product targets in this area we chose the Calabar alkaloids, which are the simplest members of this group yet display important pharmacological properties.[4] (−)-

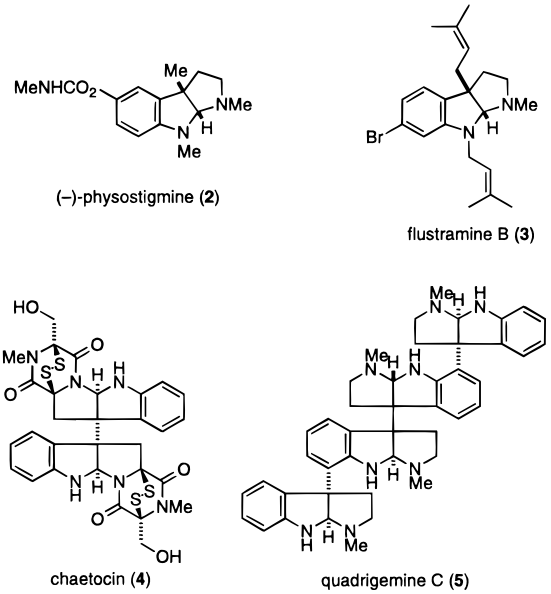

Figure 1. Representative hexahydropyrrolo[2,3-b]indole alkaloids having a quaternary center at C-3a.

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(2) For a review of the Calabar alkaloids, see: Takano, S.; Ogasawara, K. *Alkaloids* **1989**, *36*, 225−251.

(3) Jobst, J.; Hesse, O. *Ann. Chem. Pharm.* **1864**, *129*, 115.

(4) For a review, see: Hino, T.; Nakagawa, M. *Alkaloids* **1989**, *34*, 1−75.

(5) For a review, see: Kobayashi, J.; Ishibashi, M. *Alkaloids* **1992**, *41*, 52−57.

(6) Weber, H. P. *Acta Crystallogr., Sect. B* **1972**, *28*, 2945.

(7) Guéritte-Voegelein, F.; Sévenet, T.; Pusset, J.; Adeline, M. T.; Gillet, B.; Beloeil, J. C.; Guénard, D.; Potier, P. *J. Nat. Prod.* **1992**, *55*, 923.

(8) (a) Bruncko, M.; Crich, D.; Samy, R. *J. Org. Chem.* **1994**, *59*, 5543. (b) Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143.

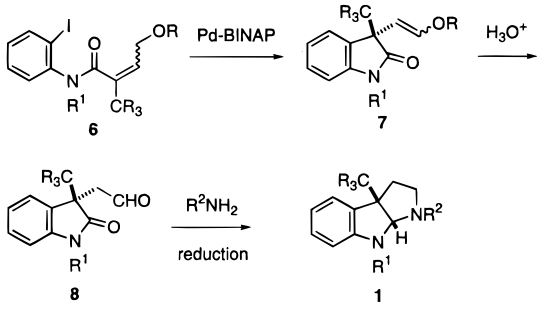
(9) Lee, T. B. K.; Wong, G. S. K. *J. Org. Chem.* **1991**, *56*, 872.

(10) For our initial report of this strategy, see: Ashimori, A.; Overman, L. E. *J. Org. Chem.* **1992**, *57*, 4571.

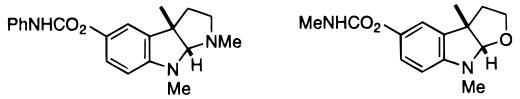
(11) Hoffmann, H. M. R.; Schmidt, B.; Wolff, S. *Tetrahedron* **1989**, *45*, 6113.

S0002-7863(98)00788-4 CCC: $15.00
Published on Web 06/20/1998

Scheme 1



Physostigmine (**2**) is a powerful inhibitor of acetyl cholinesterase and has been an invaluable tool in elucidating pharmacological and physiological mechanisms. Physostigmine is clinically used to reduce intraocular pressure in glaucoma, to treat postoperative intestinal atony and myasthenia gravis, and has recently been found useful for relieving symptoms of Alzheimer's disease.[4,12] However, the therapeutic usefulness of physostigmine is limited by its short duration of action, narrow therapeutic window, and lack of selectivity toward the two subtypes of human cholinesterase enzymes.[12a] A number of physostigmine analogues have recently been evaluated, such as the phenyl carbamate congener, phenserine (**9**), which in promising preclinical studies shows improved phamacokinetic properties, low toxicity, and good selectivity in inhibiting human erythrocyte acetylcholinesterase.[12,13] As is often the case, biological activity of the Calabar alkaloids is highly dependent upon absolute configuration; for example, (+)-*ent*-physostigmine has little effect on acetyl cholinesterase in vitro and is a weak centrally acting cholinergic agonist.[12]

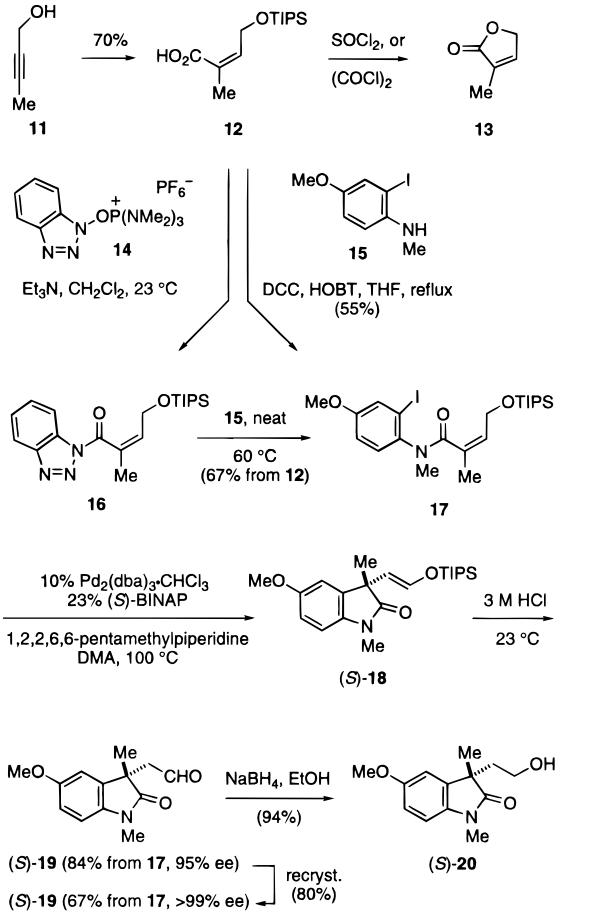


phenserine (**9**) (–)-physovenine (**10**)

In an impressive early accomplishment in alkaloid synthesis, physostigmine was first prepared in racemic form in 1935 by Julian and Pikl.[14] Since then, numerous total syntheses have been accomplished including several asymmetric total syntheses.[4,15,16] Of particular note is the recent success of Brossi, Greig, and co-workers in elaborating and optimizing the Hoechst−Roussel asymmetric modification of the original Julian approach[9] to provide practical access to enantiopure physostigmine (**2**) and phenserine (**9**).[13,17]

In this paper we report full details of our asymmetric total syntheses of (−)- and (+)-physostigmine (**2** and *ent*-**2**)[10] and

Scheme 2



the related hexahydrofurano[2,3-*b*]indole alkaloid (−)- physovenine (**10**) and its enantiomer *ent*-**10**.

Results and Discussion

The key asymmetric intramolecular Heck step of our enantioselective approach to hexahydropyrrolo[2,3-*b*]indoles **1** containing a methyl substituent at C-3a should proceed with high enantioselection if carried out under "neutral" Heck conditions with a (*Z*)-2-methyl-2-butenanilide cyclization precursor.[18,19] Since commercially available *N*-methyl-*p*-anisidine can be converted in one step into *o*-iodo derivative **15**,[20] the (*Z*)-2-butenanilide **17** required for the synthesis of physostigmine was prepared by coupling **15** with (*Z*)-butenoic acid **12** (Scheme 2). This acid was prepared in 70% overall yield from commercially available 2-butyn-1-ol (**11**) through a standard three-step sequence.[19] However, the junction of these components to prepare (*Z*)-butenanilide **17** was not straightforward. Attempted conversion of **12** to the corresponding acid chloride as a prelude to condensation with aniline **15** resulted in cleavage of the triisopropylsilyl (TIPS) group to deliver butenolide **13**.[21] Condensation of **12** and **15** in the presence of dicyclohexylcarbodiimide (DCC) and *N*-hydroxybenzotriazole (HOBT) in refluxing THF provided **17** in 55% yield. The efficiency of

(12) For recent reviews of pharmacology, see: (a) Grieg, N. H.; Pei, X. F.; Soncrant, T. T.; Ingram, D. K.; Brossi, A. *Med. Res. Rev.* **1995**, *15*, 3. (b) Sano, M.; Bell, K.; Marder, K.; Stricks, L. *Clinical Pharm.* **1993**, *16*, 61.

(13) For a review, see: Brossi, A.; Pei, X.-F.; Greig, N. H. *Aust. J. Chem.* **1996**, *49*, 171.

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(15) For asymmetric total syntheses published since Takano's review, see refs 9, 15, 18 and the following: (a) Takano, S.; Moriya, M.; Iwabuchi, Y.; Ogasawara K. *Chem. Lett.* **1990**, 109. (b) Takano, S.; Sato, T.; Inomata, K.; Ogasawara, K. *Heterocycles* **1990**, *31*, 411. (c) Takano, S.; Moriya, M.; Ogasawara K. *J. Org. Chem.* **1991**, *56*, 5982. (d) Node, M.; Itoh, A.; Masaki, Y.; Fuji, K. *Heterocycles* **1991**, *32*, 1705. (e) Marino, J. P.; Bogdan, S.; Kimura, K. *J. Am. Chem. Soc.* **1992**, *114*, 5566. (f) Node, M.; Hao, X., Nishide, K.; Fuji, K. *Chem. Pharm. Bull.* **1996**, *44*, 715.

(16) Ashimori, A.; Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Org. Chem.* **1993**, *58*, 6949.

(17) Pei, X.-F.; Yu, Q.; Lu, B.; Greig, N. H.; Brossi, A. *Heterocycles* **1996**, *42*, 229.

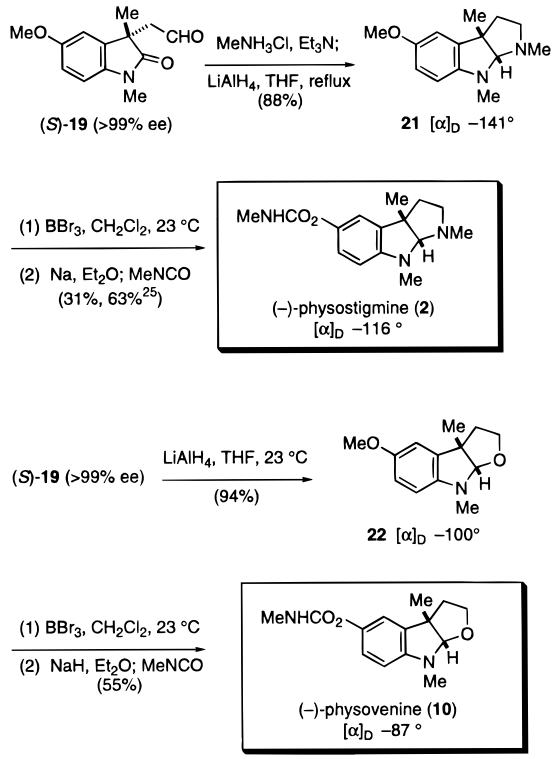
(18) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477−6487.

(19) Ashimori, A.; Bachand, B.; Govek, S.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488−6499.

(20) (a) Horne, S.; Taylor, N.; Collins, S.; Rodrigo, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3047. (b) Katritzky, A. R.; Fan, W.-Q.; Akutagawa, K. *Tetrahedron* **1986**, *42*, 4027.

(21) Kayser, M. M.; Breau, L.; Eliev, S.; Morand, P.; Ip, H. S. *Can. J. Chem.* **1986**, *64*, 104.

Scheme 3



this conversion could be increased to 67% by first condensing **12** with benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) **14**[22] to provide acyloxybenzotriazole derivative **16**, which was isolated in 84% yield after chromatography on silica gel. Subsequent condensation of this derivative with aniline **15** at 60 °C in the absence of solvent provided **17** in 67% overall yield from **12**. The absence of even a trace of a diagnostic signal for the β-vinylic hydrogen of the *E* stereoisomer of **17** in the 500 MHz ^{1}H NMR spectrum suggests that (*Z*)-anilide **17** was >98% isomerically pure.

Asymmetric Heck cyclization[19] of **17** with 20% Pd−(*S*)-BINAP (formed in situ from 10% $Pd_2(dba)_3$·$CHCl_3$ and 23% (*S*)-BINAP)[23] at 100 °C in *N*,*N*-dimethylacetamide (DMA) in the presence of excess 1,2,2,6,6-pentamethylpiperidine (PMP) afforded predominantly (diastereoselectivity = 98:2) the oxindole (*E*)-enoxysilane (*S*)-**18**. This intermediate was isolated by chromatography on silica gel and subsequently hydrolyzed in dilute HCl to provide oxindole aldehyde (*S*)-**19** in 84% yield from **17**. Sodium borohydride reduction of (*S*)-**19** and analysis of the derived primary alcohol (*S*)-**20** by chiral HPLC[24] established that **19** was formed with excellent enantiopurity (95% ee). A single recrystallization of (*S*)-**19** from ethyl acetate−hexane provided enantiopure (*S*)-**19** in 67% overall yield from anilide **17**.

Condensation of enantiopure (*S*)-**19** with methylamine followed by reduction of the derived crude imine with excess $LiAlH_4$ in refluxing THF afforded (−)-esermethole (**21**), $[\alpha]^{25}_D$ −141 ° (*c* 0.4, C_6H_6); lit.[15a] $[\alpha]^{25}_D$ −134 ° (*c* 0.3, C_6H_6), in 88% yield (Scheme 3). Using conditions optimized by Brossi, this intermediate was transformed in two steps (31% overall yield, 63% overall yield is reported on a larger scale[25]) to enantiopure natural (−)-physostigmine (**1**): mp 103−104 °C, $[\alpha]^{25}_D$ −116 ° (*c* 0.4, C_6H_6); salicylate salt $[\alpha]^{25}_D$ −75 ° (*c* 0.5, EtOH).[26] Direct reduction of enantiopure (*S*)-**19** with excess $LiAlH_4$ at room temperature provided tricyclic aminal (*S*)-**22** in 94% yield. This intermediate was transformed in a similar fashion (in 55% yield) to (−)-physovenine (**10**): $[\alpha]^{25}_D$ −87° (*c* 0.3, EtOH); lit.[15a] $[\alpha]^{25}_D$ −90 ° (*c* 0.09, EtOH).

Heck cyclization of (*Z*)-butenanilide **17** with Pd−(*R*)-BINAP in the presence of PMP followed by acid hydrolysis and recrystallization provided enantiopure (*R*)-**19**, which was converted in an identical way to enantiopure (+)-physostigmine (*ent*-**2**) and (+)-physovenine (*ent*-**10**).

Conclusion

The synthesis summarized in Schemes 2 and 3 constitutes an efficient method for preparing either enantiomer of physostigmine. The overall yield from commercially available 2-butyn-l-ol (**11**) and *N*-methyl-*p*-anisidine is 15−20%. The synthesis of (−)-physostigmine proceeds from **11** by way of eight isolated and purified intermediates.[27] At its present refinement, this route to (−)-physostigmine and congeners is less practical than the optimized NIH synthesis.[13,17] Nonetheless, the intramolecular Heck strategy could find wide utility since it will likely be applicable to the asymmetric construction of a variety of 3a-substituted hexahydropyrrolo[2,3-*b*]indoles, including those containing 3a substituents that could not be incorporated by alkylation of an oxindole precursor (e.g., the aryl and tertiary substituents found in **4** and **5**). Efforts to address the total synthesis of more complex hexahydropyrrolo[2,3-*b*]indoles using asymmetric Heck cyclizations as the central step are ongoing and will be reported in due course.

Experimental Section[28]

2′-Iodo-4′-methoxy-*N*-methyl-(*Z*)-4-(triisopropylsiloxy)-2-methyl-2-butenanilide (17). The BOP coupling reagent **14** (448 mg, 1.01 mmol) was added to a solution of (*Z*)-acid **12**[19] (276 mg, 1.01 mmol), Et_3N (0.13 mL, 1 mmol), and CH_2Cl_2 (3 mL) at room temperature. After 30 min, H_2O (6 mL) and two drops of 1 M HCl were added, the organic layer was separated and washed with brine (6 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by sgc (4:1 hexanes−EtOAc) gave acyl benzotriazole **16** (329 mg, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 8.0 Hz, 1H), 7.52−7.62 (m, 1H), 7.44 (t, J = 7.8 Hz, 2H), 6.63−6.71 (m, 1H), 4.70−4.77 (m, 2H), 2.26 (q, J = 1.7 Hz, 3H), 0.99−1.17 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 155.9, 143.5, 128.7, 128.5, 124.8, 120.5, 120.0, 108.2, 62.5, 18.9, 17.9, 11.8; IR (film) 1781, 1643 cm^{-1}; HRMS (CI) *m*/*z* 390.2197 (390.2212 calcd for $C_{20}H_{32}N_3O_3Si$).

(22) Castro, B.; Dormoy, J. R.; Evin, G.; Selve, C. *Tetrahedron Lett.* **1975**, 1219.

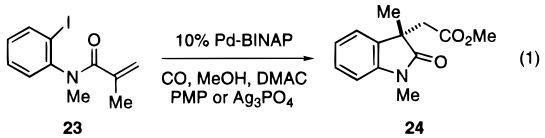
(23) BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl: Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629.

(24) A Diacel Chiralcel OD column (9:1 hexane−*i*-PrOH) provided baseline resolution of enantiomers; chromatograms are provided in the Supporting Information.

(25) Yu, Q.-S.; Brossi, A. *Heterocycles* **1988**, *27*, 745.

(26) Comparison data for authentic (−)-physostigmine obtained from Aldrich Chemical Co., Inc. are mp 104−105 °C.; $[\alpha]^{25}_D$ −117 ° (*c* 0.4, C_6H_6). A rotation of $[\alpha]_D$ +75 ° (*c* 0.5, EtOH) has been reported for the salicylate salt of (+)-physostigmine.[25]

(27) Since 25% of the steps are involved in preparing (*Z*)-siloxybutenoic acid **12**, we investigated Heck cyclizations of anilides prepared from commercially available methacrylic acid. Although carbonylative Heck cyclizations could be realized (eq 1), enantioselection was never satisfactory. Results of these investigations are briefly summarized in the Supporting Information.



(28) General experimental details have been described.[19] Conventional silica gel flash chromatography is abbreviated as sgc.

A mixture of this sample of **16** (329 mg, 0.845 mmol) and *o*-iodoaniline **15**[20] (452 mg, 1.72 mmol) was heated at 60 °C for 4 h. After cooling to room temperature, the crude product was purified by sgc (5:1 hexanes−EtOAc) to give anilide **17** (350 mg, 80%): ^{1}H NMR (300 MHz, $CDCl_3$, a 3:1 mixture of amide rotamers) major rotamer—δ 7.38 (d, J = 2.8 Hz, 1H), 7.25 (d, J = 8.7 Hz, 1H), 6.81 (dd, J = 8.7, 2.8 Hz, 1H), 5.38 (br t, J = 6.5 Hz, 1H), 4.29−4.38 (m, 2H), 3.80 (s, 3H), 3.23 (s, 3H), 1.58 (br s, 3H), 1.02−1.20 (m, 21H); minor rotamer—δ 7.41 (d, J = 2.8 Hz, 1H), 7.09 (d, J = 8.7 Hz, 1H), 6.94 (dd, J = 8.7, 2.8 Hz, 1H), 5.68 (br t, J = 6.6 Hz, 1H), 4.38−4.43 (m, 2H), 3.80 (s, 3H), 3.27 (s, 3H), 2.06 (br s, 3H), 1.02−1.20 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) major rotamer—δ 171.0, 158.9, 137.9, 133.4, 130.6, 128.5, 124.3, 114.6, 98.5, 61.3, 55.4, 36.5, 19.8, 17.9, 11.8; minor rotamer—δ 170.8, 158.8, 137.6, 132.6, 131.4, 129.1, 124.5, 115.4, 97.8, 61.1, 60.1, 38.6, 20.8, 17.9, 11.8; IR (film) 1652, 1594 cm^{-1}; HRMS (CI) m/z 518.1582 (518.1589 calcd for $C_{22}H_{37}INO_3Si$). Anal. Calcd for $C_{22}H_{36}INO_3Si$: C, 51.06; H, 7.01; N, 2.71. Found: C, 51.15; H, 7.02; N, 2.66.

(*S*)-3-(2-Oxoethyl)-1,2-dihydro-5-methoxy-1,3-dimethyl-2-oxo-[3*H*]indole [(*S*)-19]. A mixture of $Pd_2(dba)_3$·$CHCl_3$ (360 mg, 0.347 mmol), (*S*)-BINAP (504 mg, 0.809 mmol), and *N*,*N*-dimethylacetamide (DMA, 21 mL) was stirred at room temperature for 65 min. To the resulting orange solution was added a solution of iodoanilide **17** (1.82 g, 3.51 mmol), 1,2,2,6,6-pentamethylpiperidine (3.2 mL, 18 mmol), and DMA (18 mL), and the reaction was heated at 100 °C for 90 min. The resulting dark solution was poured into half-saturated aqueous $NaHCO_3$ (100 mL) and extracted with ether (3 × 150 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated, and the residue was purified by sgc (9:1 → 1:1 hexanes−EtOAc) to give oxindole enoxysilane (*S*)-**18** (1.29 g, 94%) as a 98:2 mixture of geometric isomers: $[\alpha]^{25}_D$ −81°, $[\alpha]_{405}$ −224°, $[\alpha]_{435}$ −182°, $[\alpha]_{546}$ −98°, $[\alpha]_{577}$ −85°, (*c* 0.61, C_6H_6); ^{1}H NMR (300 MHz, $CDCl_3$) 6.72−6.84 (m, 3H), 6.35 (d, J = 12.0 Hz, 1H), 5.19 (d, J = 12.0 Hz, 1H), 3.80 (s, 3H), 3.17 (s, 3H), 1.44 (s, 3H), 0.99−1.17 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.1, 155.9, 142.9, 136.3, 134.9, 112.2, 110.7, 108.3, 55.7, 47.8, 26.3, 23.7, 17.6, 11.9; IR (film) 1655, 1636, 1600 cm^{-1}; HRMS (CI) m/z 390.2479 (390.2464 calcd for $C_{22}H_{36}NO_3Si$). Anal. Calcd for $C_{22}H_{35}NO_3Si$: C, 67.82; H, 9.05; N, 3.60. Found: C, 67.96; H, 9.19; N, 3.54.

A solution of (*E*)-enoxysilane (*S*)-**18** (1.26 g, 3.23 mmol), 3 M HCl (10 mL), and THF (25 mL) was maintained at room temperature overnight. The reaction was then cooled in an ice bath and poured into saturated aqueous $NaHCO_3$ (100 mL), and the resulting mixture was extracted with EtOAc (2 × 90 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated, and the residue was purified by sgc (4:1 → 1:2 hexanes−EtOAc) to afford pure aldehyde (*S*)-**19** (673 mg, 89%, 96% ee[24]). Recrystallization from EtOAc−hexane provided enantiopure[24] (*S*)-**19** in 80% yield: mp 116−117 °C; $[\alpha]^{25}_D$ +49°, $[\alpha]_{405}$ +151°, $[\alpha]_{435}$ +115°, $[\alpha]_{546}$ +58°, $[\alpha]_{577}$ +50° (*c* 0.67, C_6H_6); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.52 (s, 1H), 6.75−6.85 (m, 3H), 3.79 (s, 3H), 3.24 (s, 3H), 3.00 (dd, J = 17.3, 1.2 Hz, 1H), 2.91 (dd, J = 17.3, 1.9 Hz, 1H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7, 179.1, 156.0, 136.6, 134.0, 112.0, 110.2, 108.5, 55.7, 50.4, 45.3, 26.4, 23.9; IR ($CHCl_3$) 1702, 1601 cm^{-1}; HRMS (CI) m/z 234.1136 (234.1130 calcd for $C_{13}H_{16}NO_3$). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.98; H, 6.54; N, 6.04.

(−)-Esermethole (21). A mixture of enantiopure aldehyde (*S*)-**19** (58 mg, 0.25 mmol), $MeNH_2$·HCl (170 mg, 2.5 mmol), Et_3N (0.35 mL, 2.5 mmol), $MgSO_4$ (170 mg), and THF (6 mL) was stirred at room temperature overnight. Solid $LiAlH_4$ (95 mg, 2.5 mmol) was then added to this suspension, and the resulting mixture was heated at reflux for 1.5 h. After cooling to room temperature, excess hydride was decomposed by adding EtOAc (15 mL) dropwise. Saturated aqueous $NaHCO_3$ (15 mL) was added, the phases were separated, the aqueous layer was extracted with EtOAc (2 × 15 mL), and the combined organic extracts were washed with brine (14 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by sgc (99:1 to 20:1 $CHCl_3$−MeOH) gave (−)-esermethole (**21**, 51.4 mg, 88%, 99%ee[29a]) as a slightly yellow solid: mp 53−54 °C; $[\alpha]^{25}_D$ −141°, $[\alpha]_{405}$ −334°, $[\alpha]_{435}$ −285°, $[\alpha]_{546}$ −171°, $[\alpha]_{577}$ −150° (*c* 0.36, C_6H_6).

(−)-Physostigmine (2). Following the procedure of Brossi,[25] **21** (50.2 mg, 0.261 mmol) was converted to (−)-physostigmine (19 mg, 32% overall): mp 103−104 °C; $[\alpha]^{25}_D$ −116° (*c* 0.4, C_6H_6); (−)-physostigmine salicylate: mp 145−146 °C; $[\alpha]^{25}_D$ −75° (*c* 0.5, EtOH).

(3a*S*)-3,3a,8,8a-Tetrahydro-5-methoxy-3a,8-dimethyl-2*H*-furo-[2,3-*b*]indole (22). A mixture of aldehyde (S)-**19** (151 mg, 0.646 mmol), $LiAlH_4$ (124 mg, 0.328 mmol), and THF (10 mL) was stirred at room temperature for 40 min. Workup as described for the preparation of **21** and sgc (4:1→1:1 hexanes−EtOAc) afforded 133 mg (0.604 mmol, 94%, 100%ee[29b]) of **22**: mp 35.0−35.5 °C; $[\alpha]^{25}_D$ −100°, $[\alpha]_{405}$ −262°, $[\alpha]_{435}$ −220°, $[\alpha]_{546}$ −124°, $[\alpha]_{577}$ −108°, (*c* 0.4, $CHCl_3$).

(−)-Physovenine (10). Following the general procedure of Brossi,[25] **22** (103 mg, 0.467 mmol) was demethylated with BBr_3. A mixture of the resulting phenol (82.7 mg, 0.40 mmol), NaH (60% oil dispersion, 1.6 mg, 0.040 mmol), and THF (5.0 mL) was stirred at room temperature for 5 min, and methylisocyanate (29.0 μL, 0.492 mmol) was added dropwise. After 10 min, the solution was concentrated, and the residue was added to a mixture of EtOAc (10 mL) and saturated aqueous $NaHCO_3$ (5 mL). The phases were separated, the aqueous layer was extracted with EtOAc (8 mL), and the combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by preparative TLC (1:1 hexanes−EtOAc) and recrystallization (hexanes−EtOAc) gave (−)-physovenine (**10**, 63 mg, 60%, 100% ee[30]): mp 125−125.5 °C; $[\alpha]^{26}_D$ −87°(*c* 0.26, EtOH).

Acknowledgment. We wish to thank Atsuyuki Ashimori for his early studies in this area. Support from NIH (GM-30859) and Shionogi & Co. Ltd.are gratefully acknowledged. Additional support from Merck, Pfizer, Roche Biosciences, and SmithKline Beecham is gratefully acknowledged. NMR and mass spectra were determined at UCI using instruments acquired with the assistance of NSF and NIH Shared Instrumentation Programs.

Supporting Information Available: Preparation and characterization data for compound **20**, optical rotation and chiral HPLC data for compounds in the *ent* series, table and experimental details for carbonylative Heck cyclization of **23** → **24**, experimental details for the conversion of **12** → **13** and copies of HPLC traces used to determine enantiomeric purity of crude and pure (*S*)-**19**, **21**-, and *ent*-**21** and **2** and *ent*-**2** (8 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(29) The enantiomeric excess was determined by HPLC analysis on a Diacel Chiralcel OD column using as eluent: (a) 99:1 hexane−*i*-PrOH; (b) 99.5:0.5 hexane-*i*-PrOH.

(30) The enatiomeric excess was determined by HPLC analysis on a Diacel Chiralcel OJ column (85:15 hexane−*i*-PrOH).