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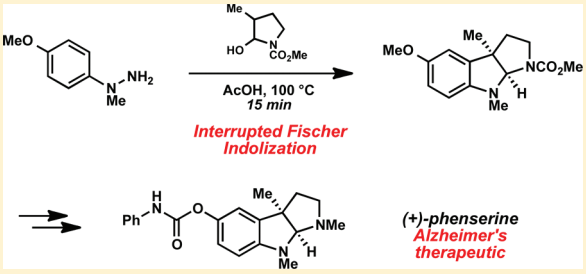
Synthesis of (+)-Phenserine Using an Interrupted Fischer Indolization Reaction

Alex W. Schammel, Grace Chiou, and Neil K. Garg*

Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, California 90095, United States

Supporting Information

ABSTRACT: A concise synthesis of the Alzheimer's therapeutic (+)-phenserine is described. The approach features an interrupted Fischer indolization to construct the pyrrolidinoindoline core, in addition to a classical resolution to arrive at phenserine in enantioenriched form.



Small molecules that possess a pyrrolidinoindoline scaffold have drawn substantial interest from the scientific community.[1] One particular compound that has garnered significant attention is phenserine (**1**, Figure 1),[2,3] first accessed

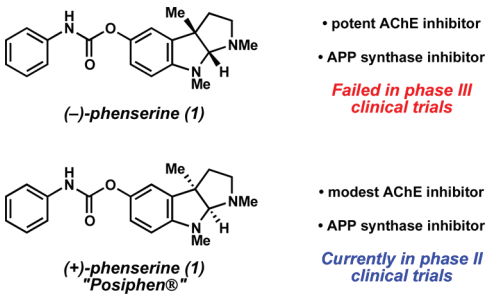


Figure 1. (−)- and (+)-Phenserine (**1**) and potential therapeutic value for the treatment of Alzheimer's disease.

by semisynthesis from the naturally occurring alkaloid physostigmine by Polonovski in 1916.[4] The readily accessible (−)-enantiomer of **1**[5] has been explored as a potential therapeutic for Alzheimer's disease and other neurodegenerative disorders.[1b,6] Despite its promising biological profile, featuring acetylcholinesterase (AChE) inhibition and the inhibition of amyloid precursor protein (APP) expression, (−)-**1** ultimately failed in phase III clinical trials.[6b] The (+)-enantiomer (aka, Posiphen), however, possesses similar activities and is now undergoing clinical trials for the treatment of early phase Alzheimer's disease.[7,8] In phase I/II trials oral Posiphen was found to significantly lower two subtypes of APP by 44% and 45% in patients with mild cognitive impairment.[8] Prompted by this promising data and our own interest in indole-containing compounds,[9] we have developed a concise route to (+)-phenserine (**1**).

Our laboratory has previously reported an efficient approach to pyrrolidinoindolines and related structures (Figure 2).[9a,b]

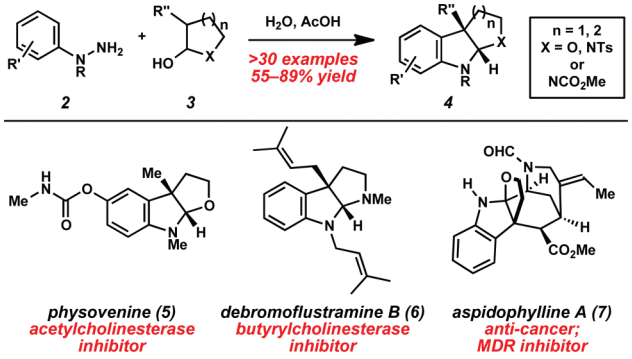


Figure 2. Interrupted Fischer indolization methodology and fused indoline-containing targets.

The method, termed "interrupted Fischer indolization"[10] is broad in scope and has proven useful in the synthesis of physovenine (**5**), debromoflustramine B (**6**), and the complex pentacyclic alkaloid aspidophylline A (**7**), albeit in racemic form.[9b,d] We envisioned that (+)-phenserine (**1**) could also be prepared effectively using this methodology.

In our initial approach, we sought to carry out a diastereoselective variant of the interrupted Fischer indolization using an arylhydrazine bearing a chiral auxiliary. Although the approach provided some diastereoselectivity in furoindoline formation,[9b] the corresponding transformation was less successful in the generation of pyrrolidinoindolines.[11] Thus, an alternative strategy for accessing (+)-phenserine (**1**) was pursued, whereby racemic material would be optically resolved at a late stage. Pyrrolidinone **8**[12] was protected to furnish carbamate **9** (Scheme 1). Subsequent reduction with *i*-Bu_2AlH provided hemiaminal **10**. In the key interrupted Fischer indolization, treatment of hydrazine **11** with hemiaminal **10**

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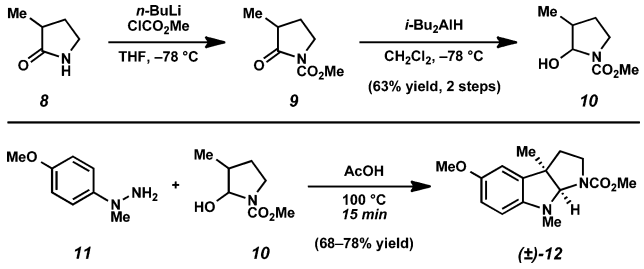
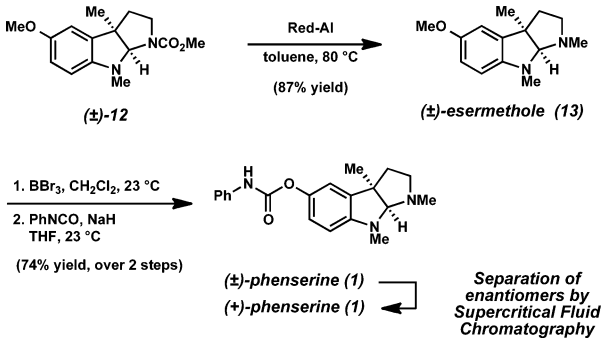
Scheme 1. Synthesis of Hemiaminal 10 and the Key Interrupted Fischer Indolization Reaction



in AcOH delivered pyrrolidinoindoline **12** in 68−78% yield. The transformation is complete in just 15 min at 100 °C and can be performed smoothly on gram scale.

With pyrrolidinoindoline **12** available, completion of the synthesis was achieved as shown in Scheme 2. Reduction of

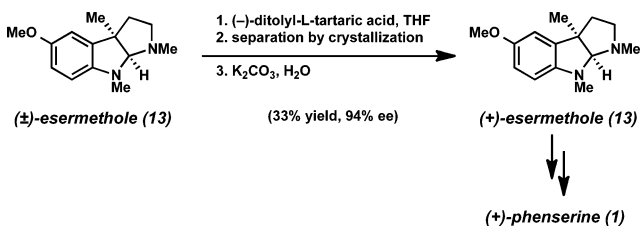
Scheme 2. Synthesis of (+)-Phenserine (1) Using Preparative Chiral SFC for Separation of Phenserine Enantiomers



carbamate **12** with Red-Al gave esermethole (**13**), which is known to serve as a precursor to a variety of unnatural pyrrolidinoindolines.[2g] Using a modification of Overman's procedure,[2f] (±)-phenserine (**1**) was obtained by a deprotection/carbamylation sequence. Resolution of the racemate by preparative supercritical fluid chromatography (SFC) provided the desired (+)-enantiomer of phenserine (**1**), along with its antipode.[13]

As an alternative to SFC separation, we also explored classical resolution of a phenserine precursor. Surprisingly, no reports describing the resolution of esermethole are available. Nonetheless, we found that treatment of (±)-esermethole (**13**) with (−)-ditolyl-L-tartaric acid in THF led to crystallization (Scheme 3).[14] After collecting the filtrate and free-basing the

Scheme 3. Synthesis of (+)-Phenserine by Classical Resolution of Racemic Esermethole



salt with aqueous K_2CO_3, (+)-esermethole (**13**) was obtained in 33% yield (94% ee). Elaboration of (+)-esermethole (**13**) to (+)-phenserine (**1**) proceeded smoothly using the two step procedure described above.

In summary, we have developed a concise and practical synthesis of (+)-phenserine (**1**), a compound currently in clinical trials for the treatment of Alzheimer's disease. The route features an interrupted Fischer indolization to construct the pyrrolidinoindoline core, in addition to a late-stage classical resolution. The strategy requires seven steps from pyrrolidinone **8** and provides efficient access to the desired target. We expect that our route will enable the synthesis of ample quantities of (+)-**1**, along with its derivatives.

EXPERIMENTAL SECTION

Hemiaminal 10. *n*-BuLi (6.82 mL, 7.43 mmol) was added to a solution of methyl pyrrolidinone **8** (670 mg, 6.68 mmol) in THF (30 mL) at −78 °C. The resulting mixture was stirred for 0.5 h, and methyl chloroformate (679 μL, 8.79 mmol) was added. After stirring for 30 min, the mixture was warmed to 23 °C. The reaction was quenched with satd aq NH_4Cl (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was used in the subsequent step without further purification.

To a solution of the crude product in CH_2Cl_2 (24 mL) at −78 °C was added *i*-Bu_2AlH (1.0 M in hexanes, 20 mL) over 1 h via syringe pump. The reaction was stirred for 30 min, quenched with satd aq NH_4Cl (40 mL), and then diluted with EtOAc (50 mL). Saturated aq Na-K tartrate (150 mL) was added, and the resulting mixture was stirred for 0.5 h. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and evaporated under reduced pressure. Purification by flash chromatography (1:1 hexanes/EtOAc) furnished hemiaminal **10** as a yellow oil (745 mg, 63% yield, over 2 steps, 58:42 mixture of diastereomers). R_f 0.2 (1:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, C_6D_6 at 335 K) δ 5.23 (5.01) (s, 1H), 4.40 (4.40) (s, 1H), 3.48 (3.48) (s, 3H), 3.28−3.39 (3.28−3.39) (m, 1H), 3.28−3.33 (2.95−3.07) (m, 1H), 1.65−1.72 (1.99−2.03) (m, 1H), 1.44−1.49 (1.84−1.90) (m, 1H), 1.56−1.65 (1.01−1.09) (m, 1H), 0.96 (0.74) (d, J = 7.0, 3H); ^{13}C NMR (125 MHz, C_6D_6 at 335 K) δ 155.6 (155.4), 82.4 (87.7), 51.4 (51.4), 44.1 (44.8), 37.9 (40.0), 29.4 (29.9), 12.4 (15.9); IR (film) 3421, 2961, 2885, 1683, 1450, 1379, 1121 cm^{-1}; HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_7H_{13}NO_3Na$, 182.0793; found 182.0789.

Pyrrolidinoindoline 12. Hydrazine **11** was freshly prepared before use.[15] A solution of hemiaminal **10** (1.20 g, 6.28 mmol) in acetic acid (12.5 mL) at 23 °C was stirred for 15 min. Phenylhydrazine **11** (1.33 g, 8.70 mmol) was then added, and the resulting reaction mixture was heated to 100 °C for 15 min. The reaction was then cooled to 23 °C and was diluted with EtOAc (20 mL). The reaction mixture was quenched with satd aq $NaHCO_3$ (100 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford crude pyrrolidinoindoline **12**. Purification by flash chromatography (31:1:1 → 23:1:1 benzene/Et_2O/CH_2Cl_2) afforded pyrrolidinoindoline **12** as a red oil (1.36 g, 68% yield); R_f 0.2 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, C_6D_6 at 335 K) δ 6.61−6.64 (m, 2H), 6.18 (d, J = 8.0, 1H), 5.10 (bs, 1H), 3.50−3.60 (m, 1H), 3.50 (s, 3H), 3.46 (s, 3H), 2.95−3.01 (1H), 2.88 (s, 3H), 1.74−1.79 (m, 1H), 1.44−1.50 (m, 1H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6 at 335 K) δ 153.4, 144.9, 135.5, 127.8, 112.7, 109.9, 106.5, 89.6, 55.3, 51.4, 45.9, 38.4, 33.4, 33.4 23.9. Spectral data matches those previous reported.[16]

(±)-Esermethole (13). To a solution of pyrrolidinoindoline **12** (1.66 g, 6.01 mmol) in toluene (30 mL) was added Red-Al (65% in toluene, 5.90 mL) dropwise over 2 min. The resulting reaction mixture was heated to 80 °C. After 1 h, the reaction was cooled to room temperature, diluted with EtOAc (30 mL), and quenched with satd aq Na-K tartrate (40 mL). The resulting mixture was vigorously stirred for 1 h at 23 °C. The layers were separated, and the aqueous layer was

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extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine (75 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (1:1 EtOAc/hexanes with 1% Et_3N) to provide (±)-esermethole (**13**) (1.22 g, 87% yield) as a brown oil. R_f 0.2 (1:9 MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 6.73 (d, J = 2.5, 1H), 6.70 (t, J = 2.5, 1H), 6.29 (d, J = 2.5, 1H), 3.96 (s, 1H), 3.44 (s, 3H), 2.61 (s, 3H), 2.54−2.56 (m, 2H), 2.36 (s, 3H) 1.77−1.85 (m, 2H), 1.32 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) 153.4, 146.9, 138.1, 112.2, 109.7, 107.4, 98.0, 55.1, 52.7, 52.5, 41.1, 37.5, 37.2, 27.2. Spectral data match those previously reported.[16]

(+)-Esermethole (13). To a solution of (±)-esermethole (**13**) (312 mg, 1.35 mmol) in THF (1.3 mL) was added (−)-ditolyl-L-tartaric acid (623 mg, 1.62 mmol) in 1.3 mL of THF. After 1 h, the resulting salt was heated to 80 °C with vigorous stirring for 40 min until the mixture became homogeneous. The solution was cooled to room temperature, while maintaining vigorous stirring for 15 h. A solid precipitate formed, which was collected by filtration and washed with THF (3 × 2 mL) to afford the tartaric salt of (+)-esermethole (**13**). The resulting tartaric salt was suspended in EtOAc (30 mL) and washed with satd aq K_2CO_3 (30 mL) to afford (+)-esermethole (**13**) (131 mg, 33% yield, 94% ee). SFC (CHIRALPAK OD-H, CO_2/MeOH = 19:20 with 0.1% Et_2NH, flow 1.5 mL/min, 23 °C, detection at 254 nm) t_R 5.63 min (minor) and t_R 6.14 min (major); R_f 0.2 (1:9 MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 6.73 (d, J = 2.5, 1H), 6.70 (t, J = 2.5, 1H), 6.29 (d, J = 2.5, 1H), 3.96 (s, 1H), 3.44 (s, 3H), 2.61 (s, 3H), 2.54−2.56 (m, 2H), 2.36 (s, 3H) 1.77−1.85 (m, 2H), 1.32 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 153.4, 146.9, 138.1, 112.2, 109.7, 107.4, 98.0, 55.1, 52.7, 52.5, 41.1, 37.5, 37.2, 27.2; $[\alpha]^{23.8}_D$ +130.0 (c 0.35, C_6H_6). Spectral data match those previously reported.[17]

(+)-Phenserine (1). To a solution of (+)-esermethole (**13**) (74.2 mg, 0.32 mmol) in CH_2Cl_2 (4 mL) was added BBr_3 (0.15 mL, 1.60 mmol) as a solution in CH_2Cl_2 (1.60 mL) over 3 min. The reaction was stirred for 1.5 h and concentrated by purging the reaction with N_2. The residue was dissolved in 5 mL of MeOH, and the resulting solution was stirred for 5 min and was then concentrated. The resulting residue was diluted with H_2O (5 mL) and satd aq $NaHCO_3$ (15 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was used in the subsequent step without further purification.

To a solution of the crude residue in THF (1.4 mL) was added NaH (1.1 mg, 0.03 mmol). The reaction was purged with N_2 for 1 min, and then phenylisocyanate (38 μL, 0.35 mmol) was added dropwise over 5 s. After stirring for 14 h, the reaction was quenched with satd aq $NaHCO_3$ (15 mL), and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (1:1 EtOAc/hexanes with 1% Et_3N) to afford (+)-phenserine (**1**) (79 mg, 81% yield) as a pink foam. R_f 0.3 (1:9 MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 7.37 (d, J = 8.0, 2H), 7.07−7.10 (m, 2H), 6.93−7.01 (m, 1H), 6.89 (s, 1H), 6.81−6.84 (m, 2H), 6.18 (d, J = 3.0, 1H), 3.99 (s, 1H), 2.53 (s, 3H), 2.44−2.50 (m, 2H), 2.30 (s, 3H), 1.71−1.80 (m, 2H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6)) δ 152.2, 150.0, 143.0, 138.2, 137.6, 128.8, 128.8, 123.0, 120.6, 118.5, 116.4, 106.3, 97.7, 52.7, 52.3, 40.9, 40.9, 37.5, 36.4, 26.9; $[\alpha]^{23.8}_D$ +70.0 (c 0.005, $CHCl_3$); mp 138−140 °C. Spectral data match those previously reported.[2g]

(±)-Phenserine (**1**) was also prepared from (±)-esermethole (**13**) using the above procedure (74% yield). The racemic mixture was resolved by Supercritical Fluid Chromotography (SFC). SFC conditions: CHIRALPAK OJ-H (2 cm × 25 cm), CO_2/MeOH (85:15) with 1% Et_2NH, flow 50 mL/min, detection at 220 nm. Analatical detection was conducted under the same conditions, except at a flow rate of 3 mL/min on a 15 cm × 0.46 cm column: t_R 2.26 min ((−)-phenserine (**1**)) and t_R 3.00 min ((+)-phenserine (**1**)).

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra for compounds **10**, **12**, **13**, and **1**, in addition to SFC traces for **13** and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: neilgarg@chem.ucla.edu.

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■ REFERENCES

(1) (a) Takano, S.; Ogasawara, K. *Alkaloids* **1989**, *36*, 225−251. (b) Greig, N. H.; Pei, X.-F.; Soncrant, T. T. *Med. Res. Rev.* **1995**, *15*, 3−31.

(2) For examples of enantiospecific routes to phenserine and closely related pyrrolidinoindolines, see: (a) Schönenberger, B.; Brossi, A.; George, C.; Flippen−Anderson, J. L. *Helv. Chim. Acta* **1986**, *69*, 283−287. (b) Takano, S.; Moriya, M.; Ogasawara, K. *J. Org. Chem.* **1991**, *56*, 5982−5984. (c) Pei, X.-F.; Greig, N. H.; Flippen-Anderson, J. L.; Bi, S.; Brossi, A. *Helv. Chim. Acta* **1994**, *77*, 1412−1422. (d) Node, M.; Hao, X.-J.; Nishide, K.; Fuji, K. *Chem. Pharm. Bull.* **1996**, *44*, 715−719. (e) Yu, Q.-S.; Pei, X.-F.; Holloway, H. W.; Greig, N. H. *J. Med. Chem.* **1997**, *40*, 2895−2901. (f) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500−6503. (g) Yu, Q.-S.; Brossi, A. *Heterocycles* **1988**, *27*, 745−750. (h) Huang, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 14043−14053. (i) Nishida, A.; Ushigome, S.; Sugimoto, A.; Arai, S. *Heterocycles* **2005**, *66*, 181−185. (j) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314−6315. (k) Nakao, Y.; Ebata, S.; Yada, A.; Hiyama, T.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2008**, *130*, 12874−12875. (l) Bui, T.; Syed, S.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2009**, *131*, 8758−8759. (m) Trost, B. M.; Zhang, Y. *Chem.—Eur. J.* **2011**, *17*, 2916−1922.

(3) For a recent synthesis of (±)-phenserine, see: Rigby, J. H.; Sidique, S. *Org. Lett.* **2007**, *9*, 1219−1221.

(4) Polonovski, M. *Bull. Soc. Chim. Fr.* **1916**, *19*, 47.

(5) Yu, Q.-S.; Schönenberger, B.; Brossi, A. *Heterocycles* **1987**, *26*, 1271−1275.

(6) (a) Greig, N. H.; Sambamurti, K.; Yu, Q.-S.; Brossi, A.; Bruinsma, G. B.; Lahiri, D. K. *Curr. Alzeheimer Res.* **2005**, *2*, 281−290. (b) Becker, R. E.; Greig, N. H. *Curr. Alzeheimer Res.* **2010**, *7*, 642−651.

(7) Lahiri, D. K.; Chen, D.; Maloney, B.; Holloway, H. W.; Yu, Q.-S.; Utsuki, T.; Giordano, T.; Sambamurti, K.; Greig, N. H. *J. Pharmacol. Exp. Ther.* **2007**, *320*, 396−396.

(8) QR Pharma, Inc. Home Page. http://www.qrpharma.com/ (accessed September 15, 2011).

(9) (a) Boal, B. W.; Schammel, A. W.; Garg, N. K. *Org. Lett.* **2009**, *11*, 3458−3461. (b) Schammel, A. W.; Boal, B. W.; Zu, L.; Mesganaw, T.; Garg, N. K. *Tetrahedron* **2010**, *66*, 4687−4695. (c) Çelebi-Ölçüm, N.; Boal, B. W.; Huters, A. D.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2011**, *133*, 5752−5755. (d) Zu, L.; Boal, B. W.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 8877−8879. (e) Bronner, S. M.; Goetz, A. E.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 3832−3835. (f) Huters, A. D.; Quasdorf, K. W.; Styduhar, E.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 15797−15799.

(10) For the classic Fischer indole synthesis and select examples of related methodologies to construct fused indolines, see: (a) Fischer,

E.; Jourdan, F. *Berichte* **1883**, *16*, 2241−2245. (b) Fischer, E.; Hess, O. *Ber.* **1884**, *17*, 559−568. (c) Grandberg, I. I.; Zuyanova, T. I.; Afonina, N. I.; Ivanova, T. A. *Dokl. Akad. Nauk SSSR* **1967**, *176*, 583−585. (d) Grandberg, I. I.; Tokmakov, G. P. *Khim. Geterotsikl. Soedin.* **1975**, 207−210. (e) Takano, S.; Moriya, M.; Iwabuchi, Y.; Ogasawara, K. *Chem. Lett.* **1990**, 109−112. (f) Takano, S.; Ogasawara, K.; Iwabuchi, R.; Moriya, M. JP 03112989 A 19910514, 1991. (g) Rosenmund, P.; Gektidis, S.; Brill, H.; Kalbe, R. *Tetrahedron Lett.* **1989**, *30*, 61−62.

(11) Mesganaw, T.; Zu, L.; Garg, N. K. University of California, Los Angeles, CA. Unpublished work, 2010. For a chiral auxilary approach toward (−)-esermethole and other related pyrrolidinoindolines, see ref 2i.

(12) α-Methylpyrrolidinone **8** can be obtained from commercial sources or laboratory preparation; for preparation, see: (a) Menezes, R.; Smith, M. B. *Synth. Commun.* **1988**, *18*, 1625−1636. (b) Mader, M.; Helquist, P. *Tetrahedron Lett.* **1988**, *29*, 3049−3052.

(13) Separation was conducted using an OJ-H column and 15% MeOH (0.1% Et_2NH)/CO_2 solvent.

(14) Dibenzoyltartaric acid has previously been employed to resolve a similar pyrrolidinoindoline; see ref 2e.

(15) Srivastava, S.; Ruane, P. H.; Toscano, J. P.; Sullivan, M. B.; Cramer, C. J.; Chiapperino, D.; Reed, E. C.; Falvey, D. E. *J. Am. Chem. Soc.* **2000**, *122*, 8271−8278.

(16) Tsuji, R.; Nakagawa, M.; Nishida, A. *Heterocycles* **2002**, *58*, 587−594.

(17) Pallavicini, M.; Valoti, E.; Villa, L.; Lianza, F. *Tetrahedron: Asymmetry* **1994**, *5*, 111−116.