

PRACTICAL TOTAL SYNTHESSES OF PHYSOSTIGMINES AND OF PHENSERINES: A SYNOPSIS¹⁾

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Abstract- (±)-1,3-Dimethyl-3-cyanomethyl-5-methoxyoxindole (**8**), or (3*S*)-enriched **8** obtained by asymmetric alkylation, separated into the optically pure enantiomers (**8a**) and (**8b**) when chromatographed on a microcrystalline cellulose triacetate (MCTA) column. Asymmetric alkylation of (±)-1,3-dimethyl-5-tetrahydropyranyloxyoxindole (**6**) gave the nitrile (**9**) ((3*S*) 66 % ee) which could not be separated on the MCTA column. Optically pure eseroline (**17a**) was obtained by recrystallization of the fumarate salt (66 % ee) obtained from **9** after reduction with Vitride, reductive *N*-methylation, and treatment with 2*N* HCl.

Physostigmine (**1a**),²⁾ a major alkaloid from *Calabar* beans, is medically used to treat glaucoma and myasthenia gravis, and was found useful to relieve the symptoms of Alzheimer's disease. The alkaloid (**1a**) was prepared by total synthesis by Julian and Piki in 1935, a major accomplishment at that time.^{1, 2} The therapeutic properties of **1a** are vastly improved in phenserine (**2a**) which is a long-acting and selective inhibitor of acetylcholinesterase,³⁻⁵ and in 1-demethylphenserine (*N*¹-norphenserine) (**3a**) which also shows such qualities.⁵ It is, therefore, not surprising that great efforts were made at several places to prepare these compounds by total synthesis. The following is a synopsis on what was achieved by us since 1989⁶ and highlighted here with an efficient resolution of nitrile (**8**).

Since it was found that the (3*aR*)-enantiomer (**1b**) (not shown) of the unnatural series was largely devoid of anticholinesterase activity,^{7,8} synthetic efforts focused on the synthesis of compounds with (3*S*)-configuration. Several new syntheses of natural (-)-physostigmine,⁹⁻¹⁶ and improvements of Julian's total synthesis accomplished by chemical resolution of different intermediates,¹⁷⁻²¹ were recently reported. Further progress, achieved with the asymmetric 3-cyanomethylation of oxindole (**5**), yielding nitrile (**8**) with a 77 % ee of the

1) This paper is dedicated to the memory of the late Dr. Yoshio Ban who was a close friend of the Brossi family.

2) The small letters a, b used in the numbering of compounds refer to optically pure compounds having (3*S*)- and (3*R*)-configurations, respectively. Compounds lacking these prefixes are racemic mixtures.

(3*S*)-enantiomer (**8a**), gave optically pure material only after its reduction and a chemical resolution of the amine with dibenzoyl-*D*-tartaric acid.²² The resolution of this amine with tartaric acid was also reported recently.²³ All these syntheses if evaluated for a technical scale are handicapped by the use of expensive chemicals requiring unpractical reaction conditions, and tedious chemical resolution at later stages to give low yields of the (3*S*)-enantiomers. A practical resolution of intermediates into the enantiomers at an early stage, therefore, remained a challenge.

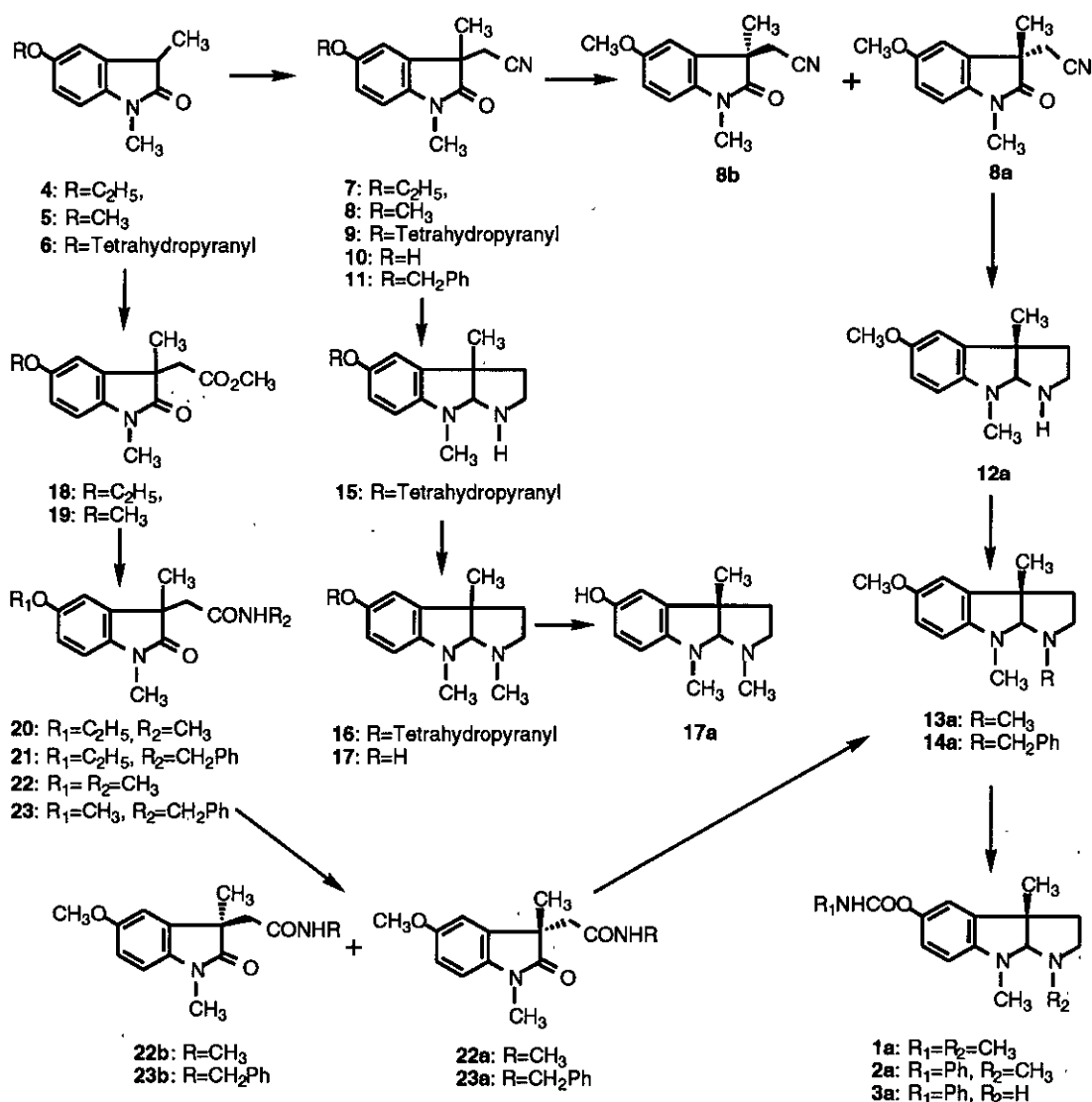


Figure 1: Total Syntheses of Physostigmines and Phenserines

Recently the chromatographic separation of racemic mixtures into the enantiomers on a preparative scale by use of chiral stationary phases (CSPs), especially microcrystalline cellulose triacetate (MCTA, as referred as CTA I), has gained increasing recognition.²⁴ Our preliminary investigations on the chromatographic enantioseparation

of oxindoles with MCTA as CSP showed that the nitrile (**8**) can be resolved into the enantiomers by this technique.²⁵ Optimization of the chromatographic conditions for **8** was explored on an analytical MCTA column. Different mobile phases were tested (Table). Best resolution was obtained with pure EtOH or 96 % EtOH (volume %). While pure MeOH dramatically decreased the retention ($k'_1=1.89$), poor resolution ($R_s<0.4$) was noticed. With H₂O (30 % volume) added to MeOH, the R_s increased, but further increase of the H₂O proportion to 50 % make the nitrile (**8**) so retained ($k'_1=12.4$) that the chromatographic time became too long to be practical. Pure isopropanol also eluted too slowly ($k'_1=7.50$), and made no improvement to the resolution.

Table: Effects of Mobile Phase on the Enantioseparation of Nitrile (8**) on a MCTA Column***

Mobile Phase (V/V)	k'_1	R_s	α
EtOH	3.99	1.17	1.48
EtOH/H ₂ O = 96/4	3.95	1.17	1.46
EtOH/H ₂ O = 70/30	3.84	1.06	1.44
MeOH	1.89	<0.4	1.16
MeOH/H ₂ O = 70/30	3.82	0.86	1.29
MeOH/H ₂ O = 50/50	12.4	1.01	1.34
<i>i</i> -PrOH	7.50	0.90	1.30

* Column: Chiral Triacel (25 cmX0.4 cm i.d.) (MCTA as CSP); Detection: UV 254 nm; Flow-rate: 0.1 ml/min; k'_1 = Capacity factor (for less retained (3*R*)-enantiomer); R_s = Resolution factor; α = Separation factor.

Slower flow-rate gave better resolution (Figure 2), indicating slow kinetics of the adsorption-desorption process. The resolution was greatly improved by decreasing the flow-rate from 0.5 ml/min (Figure 2, (A)) to 0.1 ml/min (Figure 2, (C)), but almost no further improvement was achieved by decreasing the flow-rate to 0.05 ml/min (Figure 2, (D)). Complete baseline resolution was achieved on the analytical MCTA column (0.4 cm i.d.) with a flow-rate of 0.1 ml/min equivalent to 3.9 ml/min on a preparative MCTA column (2.5 cm i.d.). In a preparative run, 270 mg of **8** with a 64 % ee of **8a** was separated into optically pure **8a** and **8b** in 80 % and 15 % yields, respectively, on a column (68 cmX2.5 cm, ca. 80 g of MCTA, flow-rate 0.5 ml/min) with 96 % EtOH as mobile phase (see experimental part). The loading capacity was greater than 3.38 mg per gram of MCTA. The MCTA is reusable and the column was used for 7 runs without obvious loss of efficiency.

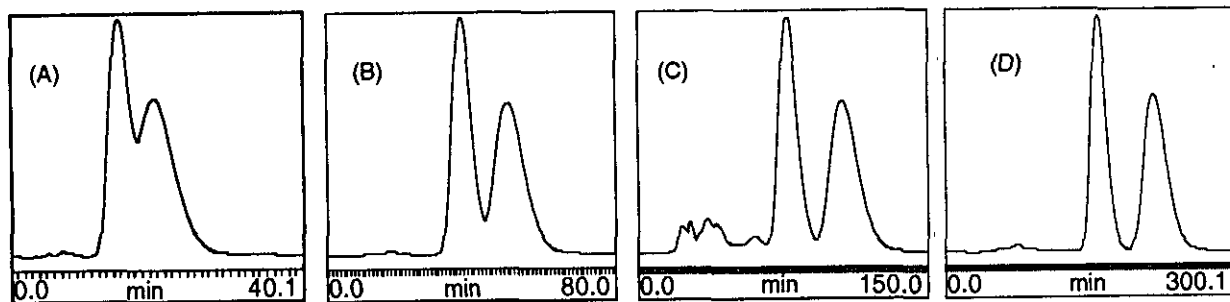


Figure 2: Effect of Flow-rate on the Resolution of (±)-1,3-Dimethyl-3-cyanomethyl-5-methoxyoxindole (**8**)
 Column: Chiral Triacel (25 cmX0.4 cm i.d.); Eluent: 96 % EtOH; Detection: UV 254 nm;
 Flow-rate: (A) 0.50 ml/min; (B) 0.20 ml/min; (C) 0.1 ml/min; (D) 0.05 ml/min.

Small structural modifications of the oxindoles studied gave unexpected results. Separation of the ethyl ether analog (7),² the benzyl ether analog (11) and the tetrahydropyranyl ether analog (9),²⁶ failed to give satisfactory results. The methyl ester (19), used to prepare *Calabar* alkaloids of the racemic series,²⁷ and its ethyl ether analog (18) could not be resolved. However, amides (22) and (23), prepared from the ester (19) by reaction with methylamine and benzylamine, respectively,²⁸ could be resolved on the MCTA column, but their ethyl ether analogs (20) and (21) again failed to separate. While the first eluted was (3*S*)-isomer for amide (22), the (3*R*)-isomers were eluted first for nitrile (8) and amide (23). In preparative runs, racemic 22 (170 mg) and 23 (300 mg) were resolved completely on the same column with the same chromatographic conditions for 8, with loading capacity greater than 2.13 mg and 3.75 mg per gram of MCTA, respectively.

Optically pure 8a, 22a and 23a which have been obtained before by a different route²⁰ on reduction with sodium dihydride-bis(2-methoxyethoxy) aluminate in toluene solution (Vitride),²⁸ yielded the desired *N*¹-noresermethole (12a), esermethole (13a), and *N*¹-benzylnoresermethole (14a). Compound (12a) also could be converted into 13a on *N*-methylation,¹⁸ and into 14a on *N*-benzylation.²⁹ Compounds (13a) and (14a) have already been used to prepare the carbamates (1a-3a).^{5,6,17}

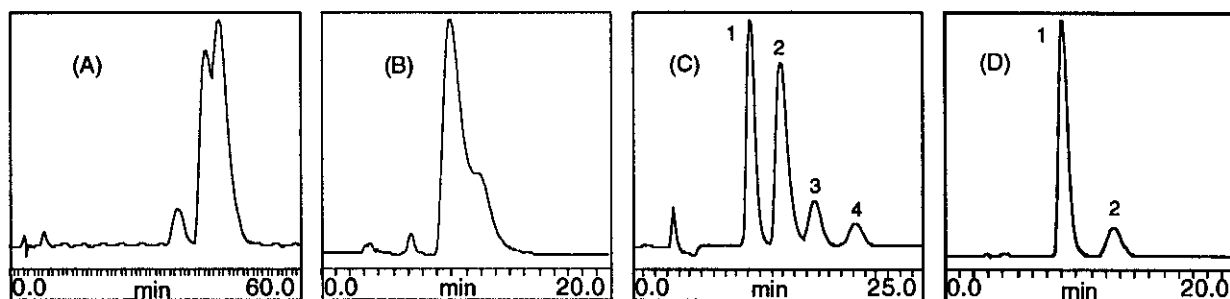


Figure 3: Chromatograms of Compounds 9(A), 15(B), 16(C) and 17(D) with 66 % ee of (3*S*)-Enantiomers.

Column: Chiralcel OD (25 cmX0.46 cm i.d.); Flow-rate: 1.0 ml/min; Detection: UV 254 nm;

Eluent (*i*-PrOH/hexane, V/V): (A) 5/95; (B) 5/95; (C) 0.5/99.5 (D) 10/90.

Some comments are indicated regarding the tetrahydropyranyl ether (6), which was found to be an excellent intermediate to develop the racemic series of the alkaloids.²⁶ Asymmetric 3-cyanomethylation of 6 yielded 9 with an estimated 66 % ee of the desired (3*S*)-enantiomers. Tetrahydropyranyl ether oxindole (9) has two chiral centers and represents four isomers which could not be resolved completely on a Chiralcel OD column by hplc (Figure 3, (A)). The tricyclic amine (15) also could not be resolved completely (Figure 3, (B)). The four isomers of 16, however, could be separated clearly (Figure 3, (C)). It can be speculated that peaks 1 and 2 (Figure 3, (C)) represent isomers with (3*S*)-configuration (total 81.8 %), and that peaks 3 and 4 are isomers with (3*R*)-configuration (total 17.8 %). This was further confirmed by the analysis of the final product eseroline (17) (Figure 3, (D)). It is interesting to note that neither of the two (3*S*)-enantiomers (36.6 %, 45.2 %), nor the two (3*R*)-enantiomers (11.7 %, 6.1 %) were present in equal amounts in 16 (Figure 3, (C)), indicating that chirality in the tetrahydropyranyl moiety interferes with the course of the asymmetric alkylation. It was found that optically pure (3a*S*)-eseroline (17a, 98 % ee) can be obtained by recrystallization of the fumarate of (3a*S*)-enantiomer enriched eseroline (17a, 66 % ee) obtained from 9 (ee 66 %) on reduction with Vitride to amine

(15), followed by *N*-methylation and ether cleavage. Unfortunately the yield in the resolution is low and since it was achieved at the end of the synthesis, this route is not suitable for **1a** and **2a**.

Chromatographic enantioseparation of nitrile (**8**) gave the first optically pure intermediates in high yield in the Julian total syntheses of physostigmine and related compounds. The finding that the reductive cyclization of the nitrile (**8a**) can readily be accomplished with Vitride,²⁸ to replace lithiumaluminum hydride,¹⁹ adds another improvement and now allows to prepare **13a** from **8a** in 4 steps with a total yield of more than 50 %. Esermethole (**13a**) is a key compound in the synthesis of physostigmines and phenserines. The total synthesis of optically pure esermethole (**13a**) from metol,²⁶ including an asymmetric alkylation, and a separation of enantiomers now requires 7 easy steps, and can be accomplished in a total yield exceeding 35 %. The improvements reported here together with simple chemical reactions now allow to make the derived alkaloidal substances (**1a-3a**) by total synthesis on a technical scale.

ACKNOWLEDGEMENT

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EXPERIMENTAL

General: Melting points (uncorrected): *Fisher-Johns* apparatus; Optical rotations ($[\alpha]_D$), Perkin-Elmer-241 MC automatic polarimeter; ir spectra (cm^{-1}): MIDIC FTIR instrument; $^1\text{Hnmr}$ (in CDCl_3 with Me_4Si as internal reference, δ ppm, J Hz): Varian XL-300 MHz spectrometer; MS (m/z) for chemical ionization (CI-ms): Finnigan-1015D mass spectrometer; for electron impact (EI-ms): V.G. Micromass 7070 mass spectrometer; Thin layer chromatography (silica gel GHLF, 250 mm): Analtech Inc.; Column chromatography (silica gel GHLF, 250 mm), Merck 60 (230-400 mesh). hplc: Rainin 81-2XM *Macintosh* Controlled hplc System, Chiralcel OD column (25 cmX0.46 cm i.d.) (Daicel Chemical Industries, Ltd.), Chiral Triacel column (25 cmX0.4 cm i.d.) (Machaney-Nagel GmbH & Co.), UV detector wavelength 254 nm. hplc Grade ethanol, isopropanol and hexane were obtained from Fisher Scientific (Pittsburgh, PA, USA). MCTA was obtained from E. Merck, Germany (Merck, art. No. 16362, 15-25 μm).

Chromatographic Enantioseparation of 1,3-Dimethyl-3-cyanomethyl-5-methoxyoxindole (8): A glass column (75 cm X 2.5 cm i.d.) was slurry packaged (bed height 68 cm) with ca. 80 g of MCTA which was swollen before in 95 % EtOH at 75 °C for 20 min. After removal of excess solvent, the stationary phase was washed (96 % EtOH, 200 ml, flow-rate 0.5 ml/min). The nitrile (**8**) (270 mg) with (3*S*)-isomer ee 64 %²² was dissolved in the eluent (95 % EtOH, 1.5 ml) and injected. Fractions of 3 ml were collected (flow rate 0.5 ml/min) and monitored with a UV detector (254 nm). Fractions with pure (3*R*)- and (3*S*)-enantiomers (optical purity checked by hplc with a Chiralcel OD column, eluent: hexane/*i*-PrOH=80/20, flow-rate: 1.0 ml/ml) were combined separately, and evaporation of solvent under reduced pressure gave pure **8b** (40 mg, 15 %) as a colorless gum, $[\alpha]_D-50.5^\circ$ ($c=0.54$, CHCl_3), and **8a** (215 mg, 80 %) as a colorless gum, $[\alpha]_D+50.6^\circ$ ($c=0.74$, CHCl_3) (lit.²⁰: $[\alpha]_D+57.5^\circ$ (CHCl_3)). Racemic **8** (166 mg) was resolved in the same way to give **8b** (81 mg, 49 %) and **8a** (80 mg, 48 %).

Phase Transfer Catalyzed Asymmetric 3-Cyanomethylation of 1,3-Dimethyl-5-tetrahydropyranyloxyoxindole (6): Oxindole (**6**)²⁶ (262 mg, 1 mmol) was dissolved in toluene (8 ml) and *N*-[(4-trifluoromethyl)benzyl]-cinchoninium bromide (50 mg, 0.1mmol) and 50 % NaOH (3.5 ml) were added. After the mixture was stirred

for 10 min under N_2 , a solution of chloroacetonitrile (109 mg, 0.09 ml, 1.2 mmol) in toluene (8 ml) was added dropwise at 0 °C over 1 h. The mixture was stirred at 0 °C under N_2 and monitored by tlc (silica gel, $CH_2Cl_2/MeOH=20/1$). The reaction was complete in 2-3 h, then ice-cold water (10 ml) was added and the mixture filtered through a small celite pad and the pad rinsed with toluene (10 ml). The combined toluene layers were dried over Na_2SO_4 , evaporated in vacuum to give **9** quantitatively as a colorless crystal: mp 111-113 °C; $[\alpha]_D^{+24}$ ($c=0.5$, $CHCl_3$); (3*S*)-isomers ee=66 % based on the hplc analysis of its derived 5-*O*-tetrahydropyranyl-eseroline (**16**) and of eseroline (**17**) (Figure 3). Spectra are identical with those of racemic **9**.⁶

1,3-Dimethyl-3-cyanomethyl-5-hydroxyoxindole (10): The above tetrahydropyranyl ether (**9**) (90 mg, 0.49 mmol) was shaken with 2*N* HCl (2 ml) for 10 min, then extracted with ether (2X5 ml). The combined ether layers were dried over Na_2SO_4 , evaporated in vacuum to give **10** quantitatively (69 mg) as a colorless crystal: mp: 181-183 °C; ms (CI- NH_3): 217 (M^++1).

1,3-Dimethyl-3-cyanomethyl-5-benzyloxyoxindole (11): The above phenol (**10**) (22 mg, 0.1 mmol) was dissolved in anhydrous anisole (1 ml), and benzyl chloride (12 μ l, 0.1 mmol) and K_2CO_3 (36 mg, 0.26 mmol) were added. The mixture was refluxed with stirring under N_2 for 12 h. After cooling to rt, H_2O (3 ml) was added and the mixture was extracted with ether (2X2 ml). After removal of solvent in vacuum, the residue was chromatographed (silica gel, $CH_2Cl_2/MeOH=20/1$) to give **11** (18 mg, 59 %) as a colorless gum: ir (film): 2930, 2249, 1713, 1601, 1501; ms (CI- NH_3): 307 (M^++1); 1H -nmr: 7.47-7.36 (m, 5H, Ph), 7.18 (d, 1H, $J=2.2$, C4-H), 6.94 (dd, 1H, $J=2.2$, 8.4, C6-H); 6.80 (d, 1H, $J=8.4$, C7-H), 5.06 (s, 2H, CH_2Ph), 3.22 (s, 3H, N1- CH_3), 2.84 (d, 1H, $J=16.7$, $-CH_2CN$, AB), 1.51 (d, 1H, $J=16.7$, $-CH_2CN$, AB).

O-Tetrahydropyranyl-*N*¹-noreseroline (15): Prepared from above tetrahydropyranyl ether (**9**) according to the procedure to prepare the racemic compound (**15**),²⁸ as a colorless gum which could not be resolved completely on the Chiralcel OD column. The content of (3*aS*)-enantiomers (ee=66 %) is based on hplc analysis of its derived 5-*O*-tetrahydropyranyleseroline (**16**), and of eseroline (**17**) (Figure 3).

O-Tetrahydropyranyleseroline (16): The above *O*-tetrahydropyranyl-*N*¹-noreseroline (**15**) (125 mg, 0.43 mmol) was dissolved in MeOH (3 ml) and aqueous formaldehyde (36 %, 0.26 ml) was added. The mixture was stirred under N_2 at rt for 3 h, then cooled to 0 °C, and $NaBH_4$ (71 mg, 1.88 mmol) was added. After stirring at room temperature for 1 h, the solvent was evaporated in vacuum and to the residue was added H_2O (5 ml), and extracted with ether (3X5 ml). The combined ether layers were dried over Na_2SO_4 , evaporated in vacuum. The residue was chromatographed (silica gel, $CH_2Cl_2/MeOH=20/1$) to give **16** (114 mg, 0.38 mmol, 88 %) as a colorless gum: ms (CI- NH_3): 303 (M^++1); 1H -nmr: 6.82 (dd, 1H, $J=2.6$, 8.6, C6-H), 6.76 (d, 1H, $J=2.8$, C4-H), 6.33 (d, 1H, $J=8.4$, C7-H), 5.2-5.3 (1H, m, C2'-H), 4.1-3.9 (2H, m, C6'- H_2), 2.89 (s, 3H, N8- CH_3), 2.8-2.5 (2H, m, C2- H_2), 2.53 (s, 3H, N1- CH_3), 2.01-1.59 (8H, m, $(CH_2)_8$), 1.43 (s, 3H, C3a- CH_3), $[\alpha]_D^{+49.3}$ ($c=0.36$, $CHCl_3$), (3*aS*)-isomers ee=66 % based on hplc analysis (Figure 3(C)).

Eseroline (17): Prepared from the above compound (**15**) as described for the racemic **17**,²⁶ pink crystals, yield 85 %, $[\alpha]_D^{+74.6}$ ($c=0.5$, MeOH), **17a** ee=66 % based on hplc analysis (Figure 3(D)).

Purification of (-)-Eseroline (17a): The above free base (**17**) (180 mg, 0.83 mmol) was dissolved in ether (2 ml), and a saturated ethanolic solution of fumaric acid (96 mg, 0.83 mmol) was added. After standing in a refrigerator overnight, 95 mg of crystals were collected: $[\alpha]_D^{+94}$ ($c=0.5$, MeOH) (ee=86.2 %). The crystals

were recrystallized from MeOH/ether to give pure **17a** fumarate (80 mg, yield 29 %, ee 98 %), mp 197-199 °C, $[\alpha]_D^{107}$ (c=0.5, MeOH) (lit.,³⁰: mp 197-199 °C, $[\alpha]_D^{109.0}$ (c=1, MeOH)), ee based on hplc analysis.

($\pm$)-1,3-Dimethyl-3-methoxycarbonylmethyl-5-ethoxyoxindole (**18**): Prepared from **4** as described for its methyl ether analog (**19**),²⁷ yield 78 %, mp 89-91 °C; ms (CI-NH₃): 278 (M⁺+1).

($\pm$)-1,3-Dimethyl-3-methylaminocarbonylmethyl-5-ethoxyoxindole (**20**): Prepared from **18** as described for its methyl ether analog (**22**),²⁸ yield 52 %, mp 169-171 °C; ms (CI-NH₃): 277 (M⁺+1).

($\pm$)-1,3-Dimethyl-3-benzylaminocarbonylmethyl-5-ethoxyoxindole (**21**): Prepared from **18** as described for its methyl ether analog (**23**),²⁸ yield 92 %, mp 178-179 °C; ms (CI-NH₃): 353 (M⁺+1).

*Chromatographic Enantioseparation of ($\pm$)-1,3-Dimethyl-3-methylaminocarbonylmethyl-5-methoxyoxindole (**22**):* Racemic **22** (170 mg) was resolved into **22a** (80 mg, 47 %, $[\alpha]_D^{37.8}$ (c=1.03, CHCl₃), lit.,²⁰: $[\alpha]_D^{29.6}$ (CHCl₃)) and **22b** (80 mg, 47 %, $[\alpha]_D^{35.4}$ (c=0.95, CHCl₃)) as described for **8**. Optical purities were checked by hplc (Chiralcel OD column, eluent: hexane/i-PrOH=80/20, flow-rate: 1.0 ml/min)

*Chromatographic Enantioseparation of ($\pm$)-1,3-Dimethyl-3-benzylaminocarbonylmethyl-5-methoxyoxindole (**23**):* Racemic **23** (300 mg) was resolved into **23a** (147 mg, 49 %, $[\alpha]_D^{64.2}$ (c=0.66, CHCl₃), lit.,²⁰: $[\alpha]_D^{48.9}$ (CHCl₃)) and **23b** (145 mg, 48 %, $[\alpha]_D^{63.1}$ (c=0.77, CHCl₃)) as described for **8** on the same column. Optical purities were checked by hplc (Chiralcel OD column, eluent: hexane/i-PrOH=80/20, flow-rate: 1.0 ml/min.)

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