PRACTICAL TOTAL SYNTHESES OF PHYSOSTIGMINES AND OF PHENSERINES: A SYNOPSIS[1)]

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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 2N 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 Pikl 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 1989 [6] and highlighted here with an efficient resolution of nitrile (**8**).

Since it was found that the (3a*R*)-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.

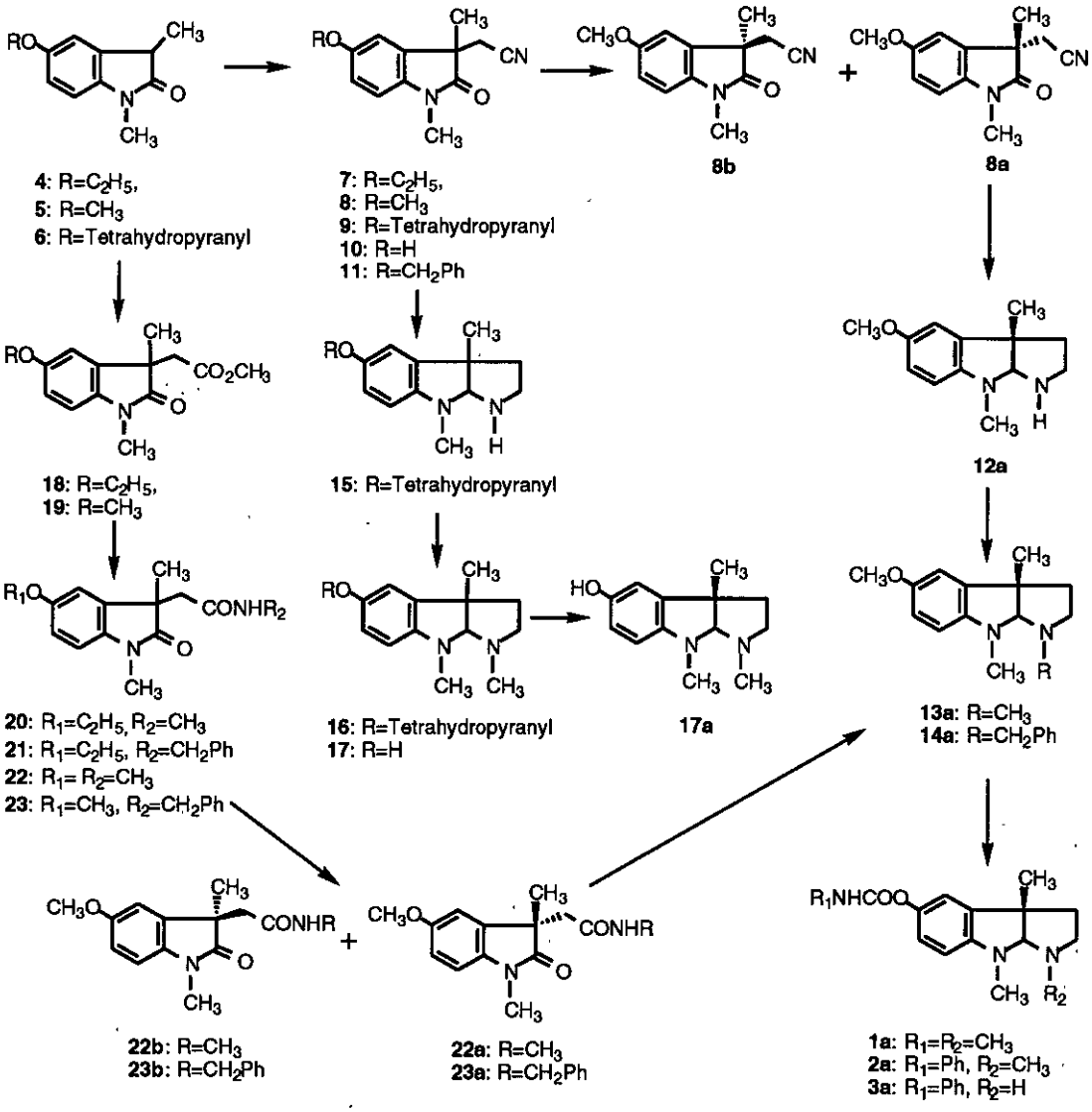

Figure 1: Total Syntheses of Physostigmines and Phenserines

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 (Rs<0.4) was noticed. With H_2O (30 % volume) added to MeOH, the Rs increased, but further increase of the H_2O 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_2O = 96/4	3.95	1.17	1.46
EtOH/H_2O = 70/30	3.84	1.06	1.44
MeOH	1.89	<0.4	1.16
MeOH/H_2O = 70/30	3.82	0.86	1.29
MeOH/H_2O = 50/50	12.4	1.01	1.34
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 (Figure2, (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.

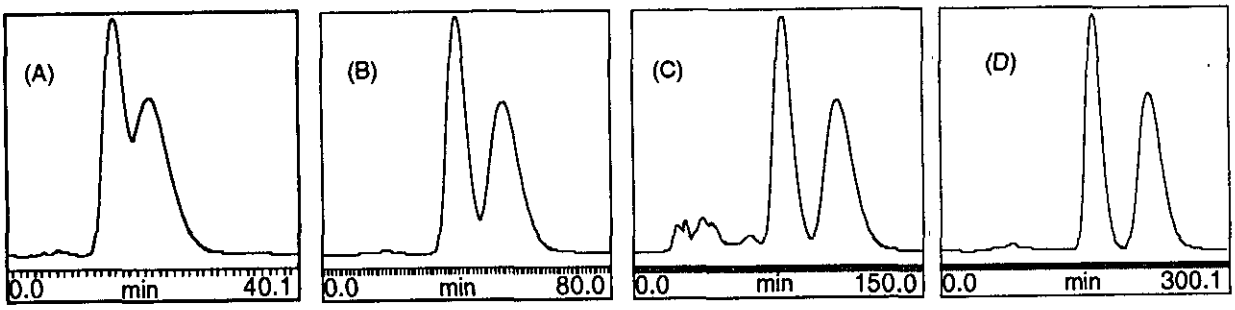

Figure 2: Effect of Flow-rate on the Resolution of (±)-1,3-Dimethyl-3-cyanomethyl-5-methoxyoxindole (**8**) Column: Chiral Triacel (25 cmX0.4 cm i.d.); Eluent: 96 % EtOH; Detection: UV 254 nm; Flow-rate: (A) 0.50 ml/min; (B) 0.20 ml/min; (C) 0.1 ml/min; (D) 0.05 ml/min.

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 route [20] 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]

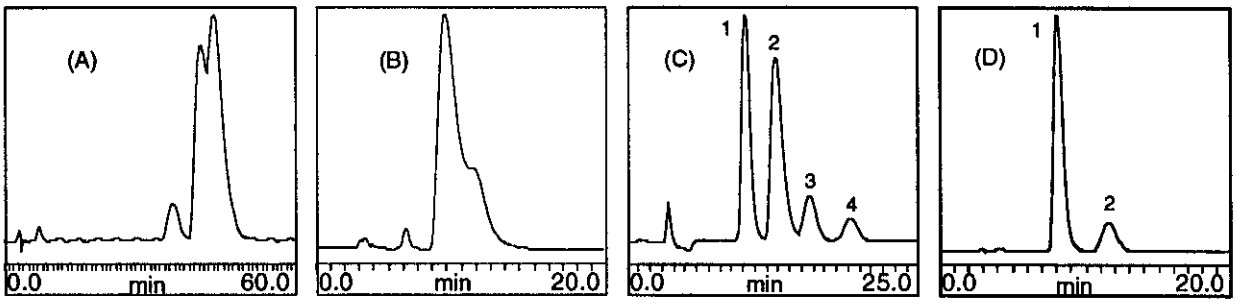

Figure 3: Chromatograms of Compounds **9**(A), **15**(B), **16**(C) and **17**(D) with 66 % ee of (3*S*)-Enantiomers. Column: Chiralcel OD (25 cmX0.46 cm i.d.); Flow-rate: 1.0 ml/min; Detection: UV 254 nm; Eluent (*i*-PrOH/hexane,V/V): (A) 5/95; (B) 5/95; (C) 0.5/99.5 (D) 10/90.

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] addes 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.

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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}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.) (Macheney-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 Chiracel 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° (c=0.54, $CHCl_3$), and **8a** (215 mg, 80 %) as a colorless gum, $[\alpha]_D$+50.6 ° (c=0.74, $CHCl_3$) (lit.,[20]: $[\alpha]_D$+57.5 ° ($CHCl_3$)). 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-triflouromethyl)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 gave **9** quantitavely 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*-tetrahydropryranyl-eseroline (**16**) and of eseroline (**17**) (Figure 3). Spectra are identical with those of reacemic **9**.[6]

1,3-Dimethyl-3-cyanomethyl-5-hydroxyoxindole (10): The above tetrahydropyranyl ether (**9**) (90 mg, 0.49 mmol) was shaken with 2N 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 µl, 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); ^{1}H-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 reacemic compound (**15**),[28] as a colorless gum which could not be resolved completely on the Chiralcel OD column. The content of (3a*S*)-enantiomers (ee=66 %) is based on hplc analysis of its derived 5-*O*-tetrahydropryranyleseroline(**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); ^{1}H-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)), 1.43 (s, 3H, C3a-CH_3), $[\alpha]_D$-49.3 ° (c=0.36, $CHCl_3$), (3a*S*)-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.

(±)-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-NH_3): 278 (M^++1).

(±)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-NH_3): 277 (M^++1).

(±)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-NH_3): 353 (M^++1).

Chromatographic Enantioseparation of (±)-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, $CHCl_3$), lit., [20]: $[\alpha]_D$-29.6° ($CHCl_3$)) and **22b** (80 mg, 47 %, $[\alpha]_D$+35.4° (c=0.95, $CHCl_3$)) 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 (±)-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, $CHCl_3$), lit.,[20]: $[\alpha]_D$-48.9° ($CHCl_3$)) and **23b** (145 mg, 48 %, $[\alpha]_D$+63.1° (c=0.77, $CHCl_3$)) 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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