Facile Preparation of (3*S*)-1,3-Dimethyl-3-cyanomethyl-5-ethoxyoxindole from Julian's Nitrile Enriched in the (3*S*)-Enantiomer

Xue-Feng Pei [a]* and Arnold Brossi [b]

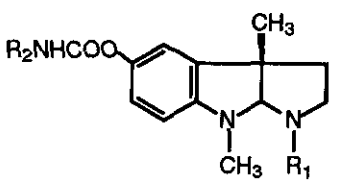
[a] *Laboratory of Bioorganic Chemistry*, NIDDK, NIH, Bldg. 8, Rm. 1A-20, Bethesda, MD 20892-0820, USA

[b] Department of Chemistry, Georgetown University, Washington, DC 20057, and Scientist Emeritus NIH, USA

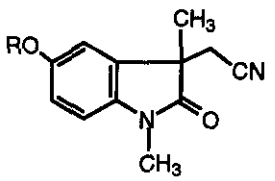
Abstract- (3*S*)-1,3-Dimethyl-3-cyanomethyl-5-ethoxyoxindole (**4a**) was prepared in high optical purity from a **4a** enriched enantiomeric mixture obtained by asymmetric 3-cyanomethylation of oxindole (**11**) by removal of the racemate with a single recrystallization.

Physostigmine (**1a**), [1] a major alkaloid from *Calabar* beans, was recently found useful to relieve the symptoms of *Alzheimer*'s disease. The therapeutic properties of **1a** are vastly improved in *phenserine* (**2a**) which is a long-acting and selective inhibitor of acetylcholinesterase, [2-4] and in 1-demethylphenserine (N^1-norphenserine) (**3a**) which also shows such qualities. [3] Since it was found that the (3a*R*)-enantiomer (**1b**) (not shown) of the unnatural series was largely devoid of anticholinesterase activity, [5,6] synthetic efforts focused on the synthesis of compounds with (3*S*)-configuration. The alkaloid (**1a**) was prepared by total synthesis by Julian and Pikl in 1935, [7, 8] with nitrile (**4**) as the key intermediate, and a chemical resolution of the amine (**9**) obtained from **4** on reduction and methylation. Several improvements in the Julian total synthesis, accomplished by chemical resolution of different intermediates, [9-13] were recently reported. Further progress, achieved by asymmetric 3-cyanomethylation of oxindole with a chiral phase transfer catalyst (CPTC), yielding nitrile (**5**) with a 77 % ee of the (3*S*)-enantiomer (**5a**), gave optically pure material only after its reduction to amine (**10**) and a chemical resolution of **10** with dibenzoyl-*D*-tartaric acid. [14] The resolution of **10** with tartaric acid was also reported recently. [15] We recently reported chromatographic enantioseparation of **5** in high yield with cellulose triacetate as stationary phase on preparative scale, [16] but similar technique didn't work with Julian's nitrile (**4**), and other nitriles (**6-8**). In this paper, we describe a simple and efficient procedure to prepare optically pure **4a** as the key intermediate in the total synthesis of physostigmine and its analogs.

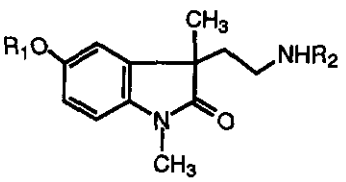
* To whom correspondence should be addressed.



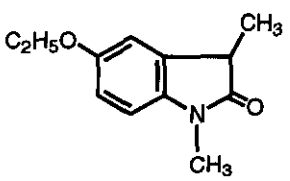
1a: $R_1=R_2=CH_3$
2a: $R_1=CH_3$, $R_2=Ph$
3a: $R_1=H$, $R_2=Ph$



4: $R=C_2H_5$
5: $R=CH_3$
6: $R=CH_2Ph$
7: R=H
8: R=tetrahydropyranyl

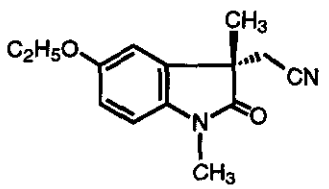


9: $R_1=C_2H_5$, $R_2=CH_3$
10: $R_1=CH_3$, $R_2=H$

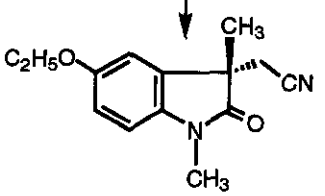


11

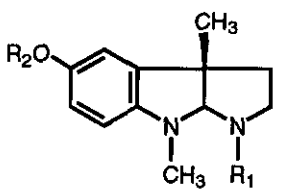
1) $ClCH_2CN$/Toluene
/50 % NaOH/CPTC, room temperature, 1 h
2) Flash Chrom.



4a (ee 70 %)



4a (ee>97 %)



12a: $R_1=H$, $R_2=C_2H_5$
13a: $R_1=CH_3$, $R_2=C_2H_5$
14a: $R_1=CH_2Ph$, $R_2=C_2H_5$
15a: $R_1=CH_3$, $R_2=H$
16a: $R_1=CH_2Ph$, $R_2=H$

It was found that (3*S*)-enantiomer (**4a**) could be obtained in high optical purity from a **4a** (ee = 70 %) enriched enantiomeric mixture obtained by asymmetric 3-cyanomethylation of oxindole (**11**),[14] by removal of the racemic product with a single recrystallization using *i*-PrOH as the solvent. [17] The racemic **4** was easier to be crystallized, and the (3*S*)-enantiomer (>97 % ee) remained in the filtrate. [18] Other solvents such as EtOH and isopropyl ether also were effective. The ethyl group on 5-O position of the nitrile (**4**) seemed to be crucial for the optical purification by recrystallization. A similar procedure failed to give satisfactory results with nitriles (**5-8**).

Optically pure **4a**, on reduction with sodium dihydride-bis(2-methoxyethoxy)aluminate in toluene solution (Vitride), [19] yielded the desired N^1-noreserethole (**12a**). Compound (**12a**) could be converted into eserethole (**13a**) on *N*-methylation, [10] and into N^1-benzylnoreserethole (**14a**) on *N*-benzylation, [20] following the procedures to making their 5-*O*-methyl analogues. Deethylation of **13a** and **14a** could be effected with $AlCl_3$ in boiling petroleum ether to afford eseroline (**15a**) and

N^1-benzylnoreseroline (**16a**). [8] Eseroline (**15a**) and N^1-benzylnoreseroline (**16a**) have already been used to prepare the carbamates (**1a-3a**). [4]

No special resolving reactions, reagents or devices are needed for the optical purification of **4a** reported here. It is obviously more advantageous than the chemical optical purification after asymmetric 3-cyanomethylation of oxindole,[14] in which further reduction of the nitrile (**5**) to the amine (**10**), and a chemical resolution of the amine (**10**) with dibenzoyl-*D*-tartaric acid were needed. When combined with *asymmetric 3-cyanomethylation of oxindole* (**11**), the optical purification of **4a** by recrystallization is the most efficient procedure to prepare optical pure intermediate for the total synthesis of natural physostigmine and its analogs.

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*; hplc: Rainin 81-2XM *Macintosh* Controlled hplc System, Chiralcel OD column (25 cmX0.46 cm i.d.) (Daicel Chemical Industries, Ltd.), uv detector wavelength 254 nm. Hplc grade ethanol, isopropanol and hexane were obtained from Fisher Scientific (Pittsburgh, PA, USA).

Chiral Phase Transfer Catalyzed Asymmetric 3-Cyanomethylation of 1,3-Dimethyl-5-ethyloxyoxindole (9) : [14] Oxindole (**9**) [7] (650 mg, 3.17 mmol) was dissolved in toluene (25 ml) and *N*-(4-triflouromethylbenzyl)cinchoninium bromide (159 mg, 0.32 mmol) and 50 % NaOH (10 ml) were added. After the mixture was stirred for 10 min under N_2, a solution of chloroacetonitrile (346 mg, 0.29 ml, 3.8 mmol) in toluene (25 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 (30 ml). The combined toluene layers were dried over Na_2SO_4, evaporated in vacuum. The residue was flash chromatographed on silica gel column to gave **4a** (736 mg, 95 %) as a colorless crystal, (3*S*)-enantioomer (**4a**) ee=70 % based on the hplc analysis. [18] The spectra are identical with standard racemic sample. [7]

Optical Purificcation of (3S)-1,3-Dimethyl-3-cyanomethyl-5-ethyloxyoxindole (4a) by Recrystallization. The above **4a** enriched nitrile (736 mg, 3.01 mmol) was dissolved in *i*-PrOH (25 ml) with heating. The solution was let to cool, and stand at room temperature for 1 h, and filtered to give 222 mg of crystal (30 %), with **4a** *ee* = 15.5 % based on hplc analysis. [18] The filtrate was evaporated under reduced pressure to give **4a** (487 mg, 66 %), ee > 97 %, mp 86 °C, $[\alpha]_D$+57.4 ° (c=0.61, $CHCl_3$). The above crystal **4a** (222 mg, ee=15.5 %) was recrystallized once more with *i*-PrOH (9 ml) to give racemic **4** (180 mg) as colorless crystal, mp 109 °C (lit.,[7]: mp 109 °C), and a filtrate enriched in **4a** (40 mg, ee=81 %) which could be recycled.

REFERENCES AND NOTES

1. 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.
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18. Optical purity was analysized with chiral hplc: Chiralcel OD column (25 cm X 0.46 cm i.d.); eluent: *i*-PrOH/Hexane=20/80 (v/v); flow-rate: 1.00 ml/min; detection: uv 254 nm; retention time: **4b**: 11.101 min, **4a**: 14.888 min.
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Received, 28th July, 1995