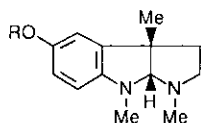


AN ENANTIOCONTROLLED ROUTE TO UNNATURAL (+)-PHYSOSTIGMINE

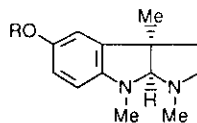
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Abstract — *ent*-Esermethole (**3**), enantiomer of the key intermediate of physostigmine (**1**) and its other congeners, has been synthesized starting from the known optically active dihydronaphthalene (**6**) obtained via lipase mediated asymmetric hydrolysis.

Naturally occurring (–)-physostigmine (**1**), a major alkaloid of the calabar bean (*Physostigma venenosum*), is medically used as an anticholinesterase agent.¹ Since it was recently reported that it significantly improved memory in patients with Alzheimer's disease² as well as its decarbamoyl derivative eseroline (**2**) exhibited morphine-like potent analgetic properties,³ unnatural antipode of the alkaloid is currently required to investigate enantiospecificity on the pharmacological effects in order to alleviate unwanted side effects exhibiting by the natural enantiomer.⁴ We report herein an enantiocontrolled synthesis of (+)-esermethole⁵ (*ent*-**3**), the key intermediate of unnatural (+)-physostigmine (*ent*-**1**) and (+)-eseroline (*ent*-**2**) as well as the other members of the alkaloid family¹ starting from the dihydronaphthalene derivative⁶ (**6**) available from either enantiomers of the dienone (**5**) obtained from racemic dicyclopentadiene (**4**) via lipase mediated asymmetric hydrolysis.^{7,8}

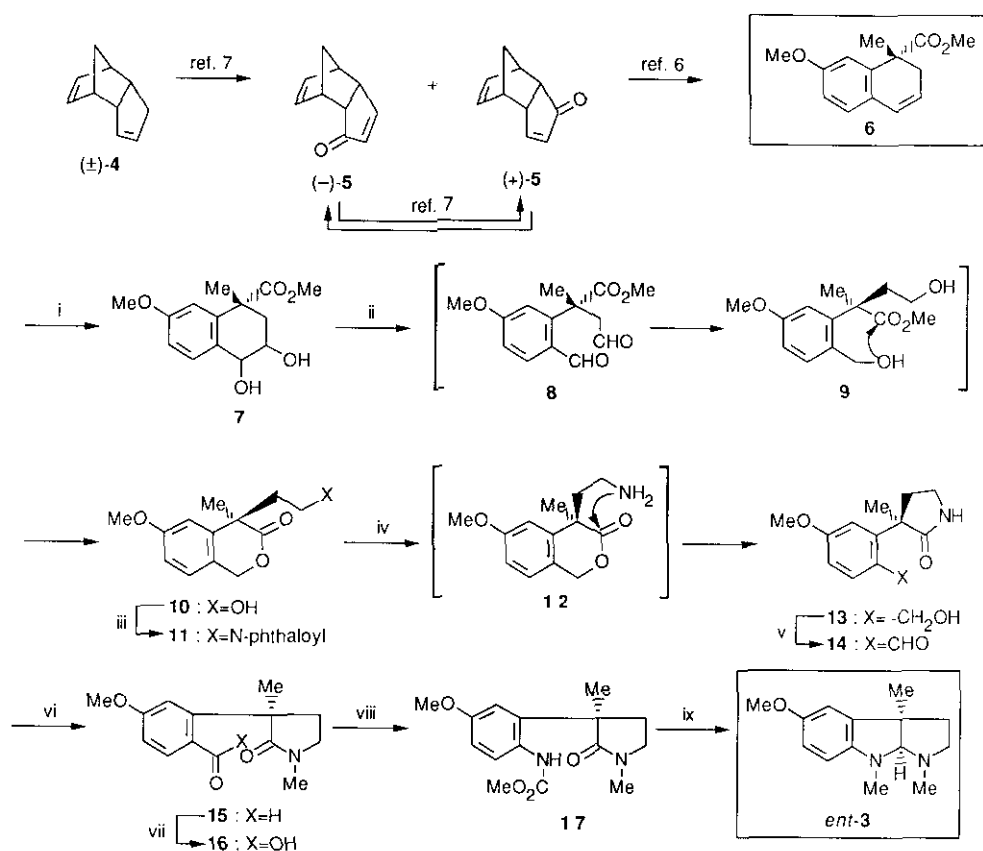


1 : (–)-physostigmine (R=MeNHCO–)
2 : (–)-eseroline (R=H)
3 : (–)-esermethole (R=Me)



ent-**1** : (+)-physostigmine (R=MeNHCO–)
ent-**2** : (+)-eseroline (R=H)
ent-**3** : (+)-esermethole (R=Me)

Fig. 1



Scheme 1

Reagents and conditions: (i) OsO_4 (cat.), 1-methylmorpholine-1-oxide, aq. THF, 0 °C - room temp.; (ii) NaIO_4 , aq. THF, 0 °C, then NaBH_4 ; (iii) phthalimide, $(\text{NCO}_2\text{Pr})_2$, PPh_3 , THF, 0 °C - room temp.; (iv) $(\text{NH}_2)_2 \cdot \text{H}_2\text{O}$, EtOH, reflux; (v) MnO_2 , CH_2Cl_2 , room temp.; (vi) MeI, NaH, DMF, room temp.; (vii) NaClO_2 , $\text{NH}_2\text{SO}_3\text{H}$, aq. BuOH, room temp.; (viii) $(\text{PhO})_2\text{P}(\text{O})\text{N}_3$, Et_3N , benzene, reflux, 1 h, then MeOH, reflux, 3 h; (ix) LiAlH_4 , THF, 0 °C ~ reflux.

Treatment of 6 with a catalytic amount of osmium tetroxide in the presence of 2 equivalents of 1-methylmorpholine 1-oxide⁹ yielded the glycol (7) as a diastereomeric mixture which was treated with sodium periodate followed by sodium borohydride in the same reaction flask to give the δ -lactone (10) as a single product via 8 and 9 by preferential lactonization at the benzylic hydroxy group during the workup stage. Employing the Mitsunobu reaction¹⁰ 10 was next transformed into the phthalimide (11), $[\alpha]_{\text{D}}^{27} +6.43^\circ$ (c 0.67, CHCl_3). Overall yield of the imide (11) from the starting olefin (6) was 44.3%.

On exposure to hydrazine in refluxing ethanol the imide (**11**) afforded the lactam (**13**), $[\alpha]_D^{29} +100.7^\circ$ (c 0.62, CHCl_3), in 73.1% yield via spontaneous cyclization of the initially formed primary amine (**12**). On sequential oxidation, N-alkylation, and oxidation^{11,12} **13** furnished the carboxylic acid (**16**) which was subjected to the Shioiri modification¹³ of the Curtius reaction to afford the lactam carbamate (**17**), $[\alpha]_D^{27} -17.3^\circ$ (c 0.81, CHCl_3), of which racemate has been obtained by Fukumoto and co-workers employing a fundamentally different route.^{12,14} Overall yield of the carbamate (**17**) from the lactam (**13**) was 32.4%. Although a three-step acquisition of esermethole (*rac*-**3**) from *rac*-**17** has been accomplished in the reported racemic synthesis,¹² we found that it could be realized in a single step to give (+)-esermethole (*ent*-**3**), $[\alpha]_D^{29} +126.2^\circ$ (c 0.13, benzene), $[[\alpha]_D -129^\circ$ (c 0.37, benzene)^{5a} for "natural configuration"; $[\alpha]_D^{28.5} +133^\circ$ (c 0.35, benzene)^{5b} for "unnatural configuration"], in 37.8% yield, when **17** was treated with lithium aluminum hydride in THF.

Since we have already obtained the antipode of the starting olefin⁷ (**6**), the present result constitutes the formal synthesis of natural physostigmine (**1**) and its congeners.

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