AN ENANTIOCONTROLLED ROUTE TO UNNATURAL (+)-PHYSOSTIGMINE

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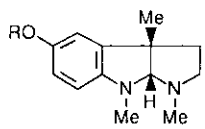
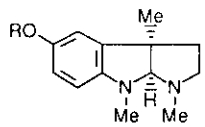
Abstract —— *ent*-Esermethole (**3**), enantiomer of the key intermediate of physostigmine (**1**) and its other congeners, has been synthesized starting from the known optically active dihydronaphthalene (**6**) obtained via lipase mediated asymmetric hydrolysis.

Naturally occurring (–)-physostigmine (**1**), a major alkaloid of the calabar bean (*Physostigma venenosum*), is medicinally used as an anticholinesterase agent.[1] Since it was recently reported that it significantly improved memory in patients with Alzheimer's disease[2] 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 (+)-esermethole[5] (*ent*-**3**), the key intermediate of unnatural (+)-physostigmine (*ent*-**1**) and (+)-eseroline (*ent*-**2**) as well as the other members of the alkaloid family[1] starting from the dihydronaphthalene derivative[6] (**6**) available from either enantiomers of the dienone (**5**) obtained from racemic dicyclopentadiene (**4**) via lipase mediated asymmetric hydrolysis.[7,8]

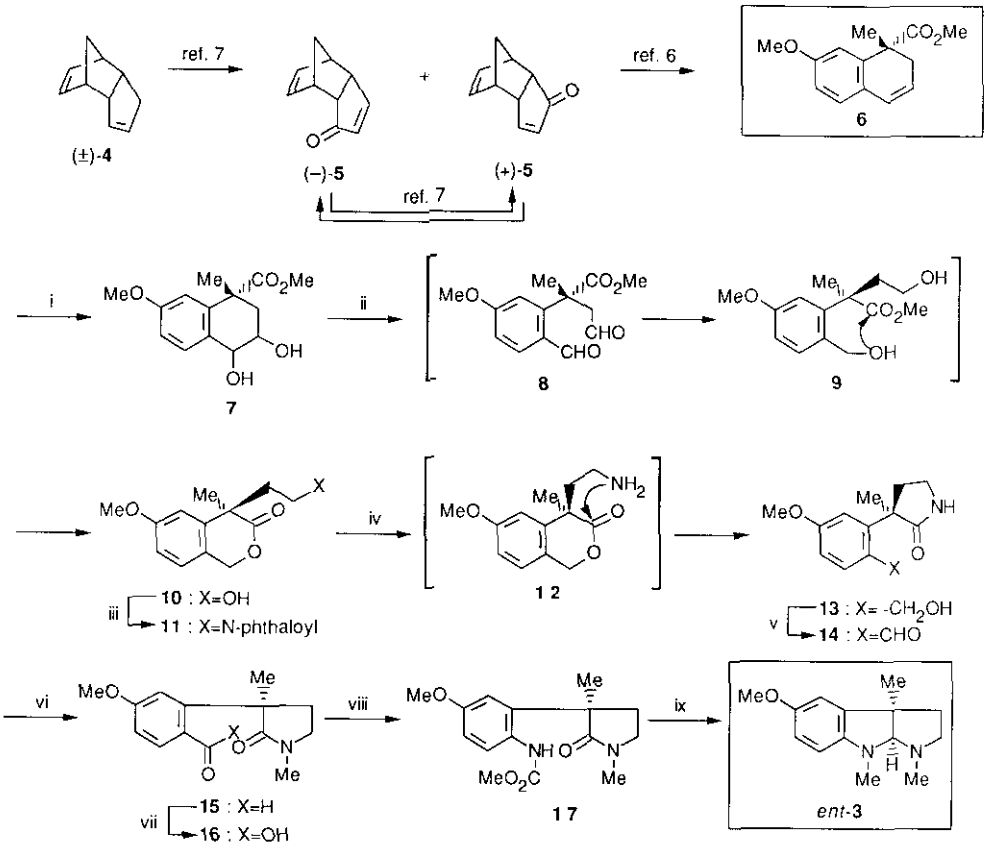


1 : (–)-physostigmine (R=MeNHCO–)
2 : (–)-eseroline (R=H)
3 : (–)-esermethole (R=Me)



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, $(NCO_2Pr^i)_2$, PPh_3, THF, 0 °C - room temp.; (iv) $(NH_2)_2 \cdot H_2O$, EtOH, reflux; (v) MnO_2, CH_2Cl_2, room temp.; (vi) MeI, NaH, DMF, room temp.; (vii) $NaClO_2$, NH_2SO_3H, aq. Bu^tOH, room temp.; (viii) $(PhO)_2P(O)N_3$, 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-oxide[9] 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 reaction[10] **10** was next transformed into the phthalimide (**11**), $[\alpha]_D^{27}$ +6.43° (*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° (*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 modification[13] of the Curtius reaction to afford the lactam carbamate (**17**), $[\alpha]_D^{27}$ –17.3° (*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° (*c* 0.13, benzene), {$[\alpha]_D$ –129° (*c* 0.37, benzene)[5a] for "natural configuration"; $[\alpha]_D^{28.5}$ +133° (*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 olefin[7] (**6**), the present result constitutes the formal synthesis of natural physostigmine (**1**) and its congeners.

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Received, 8th December, 1989