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A Chiral Total Synthesis of (-)-Physostigmine

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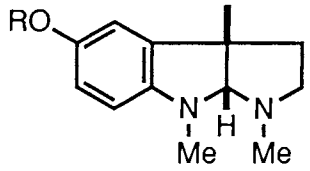
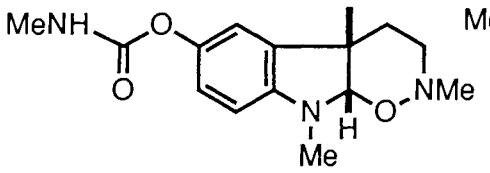
A chiral total synthesis of (-)-physostigmine via (-)-eserethole has been achieved starting from (*S*)-(-)-2-methyl-2-(2'-nitrovinyl)-δ-valerolactone.

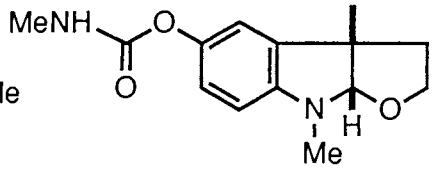
(-)-Physostigmine (**1**), a principal alkaloid of the Calabar bean, has been used clinically for glaucoma, myasthenia gravis, and as an antidote in organophosphate poisoning. Inhibition of acetyl- and butylcholinesterase from electric eel by (-)-physostigmine (**1**) has been reported.[1] Another and most inportant aspect of this alkaloid is a possible candidate for treating Alzheimer's disease.[2] A number of syntheses[3] of racemic and optically active physostigmine reflected the importance of this alkaloid. Total synthesis of naturally occuring (-)-physostigmine (**1**) has been accomplished by Takano *et al.*,[4] Brossi *et al.*,[5] and Julian *et al.*[6] The former utilized a chiral building block, (*S*)-*O*-benzylglycidol, as a starting material, while the latter two involve an optical resolution of racemic intermediate.[7]



1, R = CONHMe : (-)-Physostigmine
2, R = Et : (-)-Eserethole
3, R = H : (-)-Eseroline



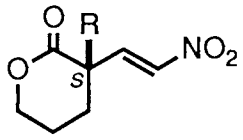
4 : (-)-Geneserine



5 : (-)-Physovenine

Recently, we reported a new method for chiral synthesis of α,α-disubstituted δ-lactones **6** with high enantiomeric excess (ee) through addition-elimination process,[8] and applications to the synthesis of diterpenoids of C-20β series such as podocarpic acid[9] and indole alkaloids[10] of *Aspidosperma*- and *Hunteria*-type from **6a** and **6b**, respectively. Here we report a chiral synthesis

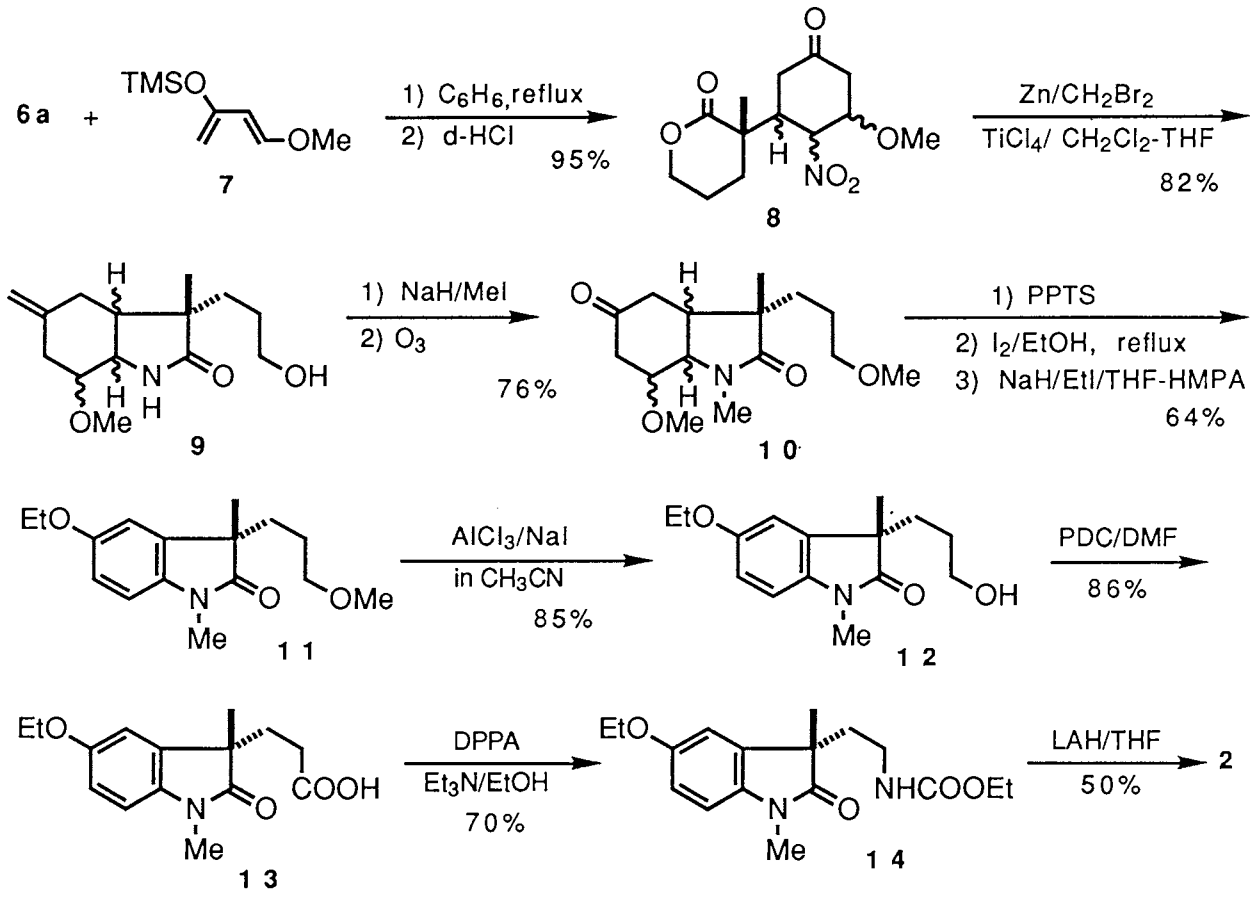
of (-)-physostigmine (**1**), starting from **6a** through a regioselective Diels-Alder reaction as a key reaction.



6a, R = Me
6b, R = Et

The Diels-Alder reaction of optically active nitroolefin **6a** of 87% ee with the Danishefsky diene (**7**) afforded a diastereomeric mixture **8** in good yield. Though a stereochemical control at the newly created asymmetric carbons was poor, a complete regioselectivity was observed in this cycloaddition. The mixture **8** was used for further transformations without separation, because those diastereomers converge into a single compound after aromatization of the resulting 6-membered ring. After a number of unsuccessful attempts to reduce the nitro group in **8** directly or after protection of the carbonyl with trivial protecting groups, we selected methylene for the protection of carbonyl group. Thus, the reaction of **8** with the Nozaki reagent[11] in a 2:1 mixture of tetrahydrofuran (THF) and dichloromethane underwent methylenation concomitant with reductive cyclization to give the lactam **9** in 82% yield in one-pot. A marked feature of this reaction is a role of dichloromethane. The reductive cyclization was completely suppressed in THF only, but addition of dichloromethane into the reaction mixture greatly facilitated both the methylenation and reductive cyclization. Methylation of **9** followed by ozonization afforded **10**. Successive treatment of **10** with pyridinium *p*-toluenesulfonate in refluxing benzene, iodine in refluxing ethanol, and sodium hydride-ethyl iodide in THF-HMPA gave a single compound **11** in 64% yield. Selective demethylation with a combination reagent system of aluminum chloride-sodium iodide[12] converted **11** into the alcohol **12** in 85% yield. Recrystallization from hexane-ethyl acetate afforded optically pure **12**,[13] $[\alpha]^{22}_{D}$ -24° (c 0.87, MeOH); which was oxidized with pyridinium dichromate in dimethylformamide to give the carboxylic acid **13**[14] in good yield. The Curtius degradation of **13** with diphenylphosphoryl azide[15] provided **14**.[16] Exposure of **14** on lithium aluminum hydride in THF afforded (-)-eserethole (**2**), $[\alpha]^{21}_{D}$ -85° (c 0.45, EtOH); lit.[17] $[\alpha]_{D}$ -81° (EtOH), in 50% yield. It is worthy of note that all of the carbons in **6a** have been utilized for this synthesis, because the carbonyl carbon rearranged in the Curtius degradation has been converted into N-Me group. Since (-)-eserethole (**2**) has been converted to (-)-physostigmine (**1**)[18] *via* (-)-eseroline (**3**),[6] total synthesis of optically pure (-)-eserethole (**2**) constitutes a formal synthesis of naturally occuring (-)-physostigmine (**1**). A

formal synthesis of (-)-geneserine (**4**) and (-)-physovenine (**5**) has also been completed, because they were derived from (-)-physostigmine (**1**)[19] and (-)-eserethole (**2**),[20] respectively.



Scheme 1. Synthesis of (-)-physostigmine (**1**).

References

1) A. Brossi, B. Schönenberger, O. E. Clark, and R. Ray, *FEBS Lett.*, **201**, 190 (1986); Q.-S. Yu, J. R. Atack, S. I. Rapoport, and A. Brossi, *ibid.*, **234**, 127 (1988).

2) K. L. Davis and R. C. Mohs, *Am. J. Psychiatry*, **139**, 1421 (1982); P. Hartvig, L. Wiklund, and B. Lindström, *Acta Anesthesiol. Scand.*, **30**, 177 (1986); S. A. Beller, J. E. Overall, and A. C. Swann, *Psychopharmacology*, **87**, 145 (1987).

3) For an extensive review on the synthesis of Calabar bean alkaloids: See, S. Takano and K. Ogasawara, "*The Alkaloids*," ed by A. Brossi, Academic Press, San Diego (1989), Vol. 36, p. 225.

4) S. Takano, E. Goto, M. Hirama, and K. Ogasawara, *Chem. Pharm. Bull.*, **30**, 2641 (1982); S. Takano, M. Moriya, Y. Iwabuchi, and K. Ogasawara, *Chem. Lett.*, **1990**, 109.
5) B. Schönenberger and A. Brossi, *Helv. Chim. Acta*, **69**, 1486 (1986).
6) P. L. Julian and J. Pikl, *J. Am. Chem. Soc.*, **57**, 755 (1935).
7) Unnatural (+)-physostigmine has been synthesized. See, Q.-S. Yu and A. Brossi, *Hetrocycles*, **27**, 745 (1988); S. Takano, T. Sato, K. Inomata, and K. Ogasawara, *ibid.*, **31**, 411 (1990).
8) K. Fuji, M. Node, H. Nagasawa, Y. Naniwa, and S. Terada, *J. Am. Chem. Soc.*, **108**, 3855 (1986); K. Fuji, M. Node, H. Nagasawa, Y. Naniwa, T. Taga, K. Machida, and G. Snatzke, *ibid.*, **111**, 7921 (1989).
9) M. Node, X. Hao, H. Nagasawa, and K. Fuji, *Tetrahedron Lett.*, **30**, 4141 (1989).
10) M. Node, H. Nagasawa, and K. Fuji, *J. Am. Chem. Soc.*, **109**, 7901 (1987); M. Node, H. Nagasawa, and K. Fuji, *J. Org. Chem.*, **55**, 517 (1990).
11) L. Lombardo, *Tetrahedron Lett.*, **23**, 4293 (1982).
12) M. Node, K. Ohta, T. Kajimoto, K. Nishide, E. Fujita, and K. Fuji, *Chem. Pharm. Bull.*, **31**, 4178 (1983).
13) **12**: Mp 151.5-153.5 °C (from EtOAc-MeOH). Anal. Found : C, 67.95; H, 8.05; N, 5.19%. Calcd for $C_{15}H_{21}NO_3$: C, 68.40; H, 8.04; N, 5.32%. ^{1}H NMR ($CDCl_3$) δ : 1.10-1.35 (2H, m), 1.35 (3H, s), 1.41 (3H, t, J = 7 Hz), 1.80 (1H, m), 2.00 (1H, m), 3.18 (3H, s), 3.47 (2H, m), 4.00 (2H, q, J = 7 Hz), 6.73-6.80 (3H, m). IR ($CHCl_3$) ν : 3450, 1690, 1600, 1495 cm^{-1}.
14) **13**: Mp 100-102 °C (from acetone-hexane). High resolution MS : Found : m/e 277.129. Calcd for $C_{15}H_{19}NO_4$ (M^+) : m/e 277.131. ^{1}H NMR ($CDCl_3$) δ : 1.37 (3H, s), 1.41 (3H, t, J = 7 Hz), 1.85-2.30 (4H, m), 3.19 (3H, s), 4.01 (2H, q, J = 7 Hz), 6.71-6.82 (3H, m). IR ($CHCl_3$) ν : 3400, 1700, 1600, 1460 cm^{-1}.
15) W. Haefliger and E. Klöppner, *Helv. Chim. Acta* , **65**, 1837 (1982).
16) **14**: Colorless oil. Anal. Found : C, 63.70; H, 7.55; N, 8.75%. Calcd for $C_{17}H_{24}N_2O_4$: C, 63.44; H, 7.68; N, 8.44%. ^{1}H NMR ($CDCl_3$) δ : 1.21 (3H, t, J = 7 Hz), 1.38 (3H, s), 1.44 (3H, t, J = 7 Hz), 1.85-2.25 (2H, m), 2.95 (2H, m), 3.21 (3H, s), 4.01 (2H, q, J = 7 Hz), 4.04 (2H, q, J = 7 Hz), 6.75-6.87 (3H, m). IR ($CHCl_3$) ν : 3450, 1710, 1700, 1240 cm^{-1}.
17) M. Polonovski, *Bull. Soc. Chim. Fr. Sér. 4,* **17**, 235 (1915).
18) M. Polonovski and C. Nitzberg, *Bull. Soc. Chim. Fr. Sér. 4,* **19**, 33 (1916).
19) M. Polonovski, *Bull. Soc. Chim. Fr. Sér. 4,* **21**, 191 (1917).
20) R. B. Longmore and B. Robinson, *Chem. Ind.*, **1966**, 1638.

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