A TOTAL SYNTHESIS OF (-)-PHYSOSTIGMINE

Manabu Node,[a]* Akichika Itoh,[b] Yukio Masaki,[b] and Kaoru Fuji[c]

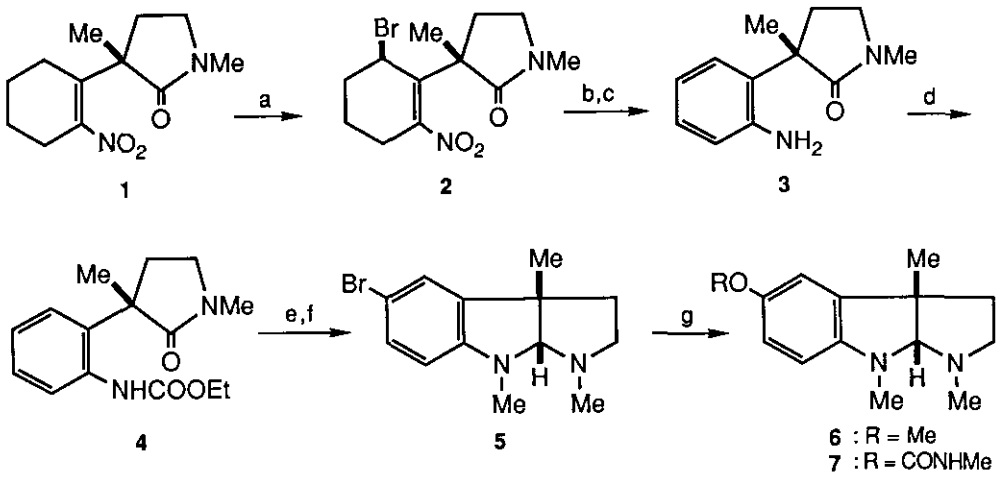
Kyoto Pharmaceutical University,[a] Yamashina-ku, Kyoto 607, Japan; Gifu Pharmaceutical University,[b] Mitahora, Gifu 502, Japan; Institute for Chemical Research, Kyoto University,[c] Uji, Kyoto 611, Japan.

Abstracts - A total synthesis of (-)-physostigmine (**7**) was accomplished from a chiral nitro olefin (**1**).

Enantioselective nitro olefination of active methine group with chiral β-nitro enamines is one of feasible methods for the construction of quaternary centers in optically active form.[1] Resulting nitro olefinic lactones have been used for the chiral syntheses of indole alkaloids[2,3] and diterpenoids.[4,5] We reported that the nitroolefin with a chiral sulfinyl group at the β-position underwent the addition-elimination reaction with the lactam enolates to provide chiral lactams possessing a quaternary carbon center in high enantiomeric excess (ee).[6] Since the absolute configuration of the products remained to be clarified, we planned to synthesize a natural product to identify their absolute stereochemistry. (-)-Esermethol (**6**) was selected as a target molecule, because compound (**1**),[6] which is one of the addition-elimination products, has a carbon frame work totally suitable for the synthesis of **6**. Since (-)-esermethol (**6**) has been converted to (-)-physostigmine (**7**),[7] the total synthesis of (-)-**6** constitutes a synthesis of (-)-physostigmine (**7**) in formal sense. (-)-Physostigmine (**7**) has been used as a clinically important anticholin-esterase agent[8] and more recently received much attention as a possible therapeutic agent for Alzheimer's disease.[9] This is reflected by a number of chiral syntheses of this alkaloid.[7,10]

Our synthetic route is shown in Scheme 1. Bromination of **1** (85% ee) under basic conditions afforded **2** in 83% yield. Crystallization from dichloromethane-ethyl acetate yielded a small amount of crystalline racemate. Examination by ^{1}H-nmr with *(R)*-(+)-1,1'-bi-2-naphthol[11] demonstrated that the residual non-crystalline material was enantiomerically enriched up to >99% ee. The yield of the enantiomerically enriched **2** was 75%. Optically active **2** was converted into the aniline derivative (**3**) by treatment with KO^{t}Bu in dimethyl sulfoxide followed by hydrogenolysis of nitro group. The reaction of **3** with ethyl chlorocarbonate gave **4** in 29% overall yield from **2**. Reduction of **4** with $LiAlH_4$ followed by the bromination afforded a 35% yield of tricyclic amine (**5**), which was

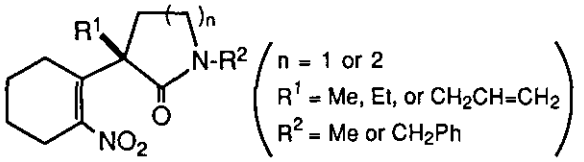
converted to (-)-esermethol (**6**) by the reaction with sodium methoxide with cuprous iodide[12] in 35% yield. The spectral data including optical rotation, $[\alpha]_D$ = -134° (benzene); lit.,[10c] -134° (benzene), were identical with those of the authentic specimen.



[a] Br_2/KO^{t}Bu. [b] KO^{t}Bu/DMSO. [c] H_2/PtO_2. [d] ClCOOEt. [e] $LiAlH_4$. [f] NBS. [g] NaOMe/CuI

Scheme 1

The transformation described above confirmed the absolute configuration of **1** to be of *S*. Though we have no direct chemical evidence for other addition-elimination products (**8**) with different substituents at the quaternary carbon and the amide nitrogen, CD curves indicated the *S*-configuration at the quaternary center for all products, which will be published elesewhere.



8

REFERENCES

1. K. Fuji, M. Node, H. Nagasawa, Y. Naniwa, and S. Terada, *J. Am. Chem. Soc.*, 1986, **108**, 3855; K. Fuji, M. Node, H. Nagasawa, Y. Naniwa, T. Taga, K. Machida, and G. Snatzke, *J. Am. Chem. Soc.*, 1989, **111**, 7921.

2. M. Node, H. Nagasawa, and K. Fuji, *J. Am. Chem. Soc.*, 1987, **109**, 7901; *Idem, J. Org. Chem.*, 1990, **55**, 517.

3. M. Node, X.-J. Hao, and K. Fuji, *Chemistry Lett.*, **1991**, 57.

4. M. Node, X.-J. Hao, H. Nagasawa, and K. Fuji, *Tetrahedron. Lett.*, 1989, **30**, 4141.

5. K. Fuji, S.-Z. Zheng, M. Node, and X.-J. Hao, *Chem. Pharm. Bull.*, 1991, **39**, 202.

6. K. Fuji, M. Node, H. Abe, A. Itoh, Y. Masaki, and M. Shiro, *Tetrahedron Lett.*, 1990, **31**, 2419.

7. S. Takano, E. Goto, M. Hirama, and K. Ogasawara, *Chem. Pharm. Bull.*, 1982, **30**, 2641, and references cited therein. For an extensive review: See, S. Takano and K. Ogasawara ," The Alkaloids," ed., A. Brossi, Academic Press, New York, 1989, Vol. 36, Chapter 5, p. 225.

8. P. Taylor, "The Pharmacological Basis of Therapeutics", ed. L. S. Goodman and A. Gilman, MacMillan,New York, 1985, Chapter 6, p. 110.

9. K. L. Davis and R. C. Mohs, *Am. J. Psychiatry*, 1982, **139**, 1421.

10. (a) P. L. Julian and J. Pikl, *J. Am. Chem. Soc.*, 1935, **57**, 755. (b) B. Schonenberger and A. Brossi, *Helv. Chem. Acta*, 1986, **69**, 1486. (c) S. Takano, M. Moriya, Y. Iwabuchi, and K. Ogasawara, *Chemistry Lett.*, **1990**, 109. (d) T. B. K. Lee and G. S. K. Wong, *J. Org. Chem.*, 1991, **56**, 872.

11. F. Toda, K. Mori, J. Okada, M. Node, A. Itoh, K. Oomine, and K. Fuji, *Chemistry Lett.*, **1988**, 131.

12. K. Saito and Y. Kikugawa, *J. Heterocycl . Chem.*, 1979, **16**, 1325; Y. Kikugawa, Y. Miyake, and M. Kawase, *Chem. Pharm. Bull.*, 1981, **29**, 1231.

Received, 24th June, 1991