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An Efficient Synthesis of Optically Active Physostigmine from Tryptophan via Alkylative Cyclization

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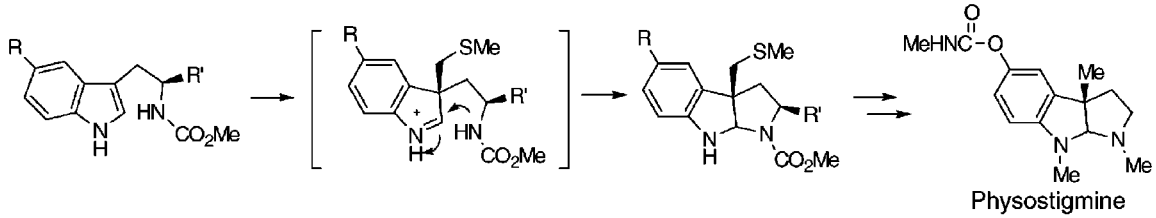
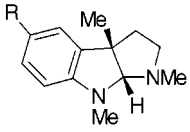
ABSTRACT



A new and efficient synthetic route to physostigmine is described. Corey–Kim reagent reacted with tryptamine or tryptophan carbamates to give 3a-(methylthiomethyl)hexahydropyrrolo[2,3-*b*]indole skeletons. Formal total synthesis of racemic and chiral physostigmine was accomplished in excellent overall yields, in short steps.

Physostigmine[1] (**1**, eserine) is an alkaloid isolated from the seeds of *Physostigma venenosum* (Calabal beans) and has been shown to be a clinically useful anticholinergic drug.[2] More recently, analogues of physostigmine have shown promise as therapeutic agents for Alzheimer's disease,[2] and its enantiomer protects against organophosphate poisoning.[2] Therefore, several syntheses of **1** have been reported.[1e,3]



1: Physostigmine (R=OCONHMe)
2: Esermethole (R=OMe)
3: Desoxyeseroline (R=H)

In this paper, we report a new concise synthesis of chiral physostigmine (**1**) which consists of a one-step construction of the basic tricyclic framework.

We previously reported various reactions of tryptamine and tryptophan derivatives with electrophiles which provide the corresponding tricyclic systems **5** via **4** (Scheme 1), and we succeeded in developing the chemistry of cyclic tautomers and the dye-sensitized photooxidation of tryptamines and tryptophans by this approach.[4] Using this method, we first explored alkylative cyclization reactions of N^b-(methoxycarbonyl)tryptamine (**6**) with alkylating reagents.

(1) For a review of Calabal alkaloids, see: (a) Marion, L. *Alkaloids* **1952**, *2*, 438−450, (b) Coxworth, E. *Alkaloids* **1965**, *8*, 27−45. (c) Robinson, B. *Alkaloids* **1967**, *10*, 383−401. (d) Robinson, B. *Alkaloids* **1971**, *13*, 213−226. (e) Takano, S.; Ogasawara, K. *Alkaloids* **1989**, *36*, 225−251.

(2) For recent reviews of pharmacology, see: Greig, N. H.; Pei. X.-F.; Soncrant, T. T.; Ingram, D. K.; Brossi, A. *Med. Res. Rev.* **1995**, *15*, 3−31.

(3) For asymmetric syntheses reported since ref 1e, see: (a) Takano, S.; Sato, T.; Inomata, K.; Ogasawara, K. *Heterocycles* **1990**, *31*, 411−414. (b) Node, M.; Hao, X.; Fuji, K. *Chem. Lett.* **1991**, 57−60. (c) Takano, S.; Moriya, M.; Iwabuchi, Y.; Ogasawara, K. *Chem. Lett.* **1990**, 109−112. (d) Node, M.; Itoh, A.; Masaki, Y.; Fuji, K. *Heterocycles* **1991**, *32*, 1705−1707. (e) Lee, T. B. K.; Wong, G. S. K. *J. Org. Chem.* **1991**, *56*, 872−875. (f) Takano, S.; Moriya, M.; Ogasawara, K. *J. Org. Chem.* **1991**, *56*. 5982−5984. (g) Marino, J. P.; Bogdan, S.; Kimura, K. *J. Am. Chem. Soc.* **1992**, *114*, 5566−5572. (h) Yu, Q.; Luo, W.; Li, Y.; Brossi, A. *Heterocycles* **1993**, *36*, 1279−1285. (i) Ashimori, A.; Matsuura,; T. Overman, L. E.; Poon, D. J. *J. Org. Chem.* **1993**, *58*, 6949−6951. (j) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500−6503. (k) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488−6499. (l) Pallavicini, M.; Valoti, E.; Villa, L.; Lianza, F. *Tetrahedron: Asymmetry* **1994**, *5*, 111−116. (m) Pallavitini, M.; Valoti, E.; Resta, I. *Tetrahedron: Asymmetry* **1994**, *5*, 363−370. (n) Node, M.; Hao, X.; Nishide, K.; Fuji, K.; *Chem. Pharm. Bull.* **1996**, *44*, 715−719. (o) Fuji, K.; Kawabata, T.; Ohmori, T.; Shang, M.; Node, M. *Heterocycles* **1998**, *47*, 951−964.

(4) For a review, see: Hino, T.; Nakagawa, M. *Alkaloids* **1988**, *34*, 1−75.

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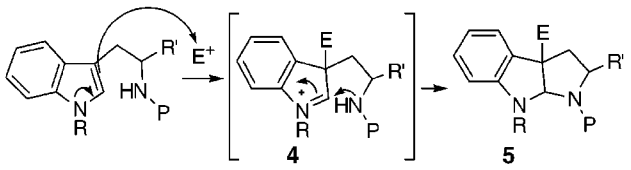
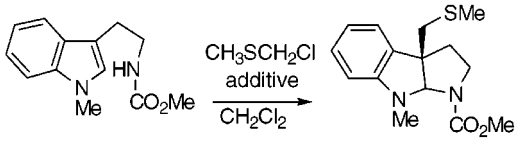
Scheme 1



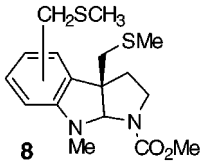
Although direct methylation with MeI, MeOTf, and Me_2SO_4 was not successful under various conditions, methylthiomethyl chloride (MTMCl) reacted with **6** in moderate yield after a long reaction time (Table 1, entry 1). Addition of a

Table 1. Reaction of **6** with CH_3SCH_2Cl



entry	Additive	conditions	yield (%)
1	none	rt, 70 h	46
2	$SnCl_4$	-10 °C, 1 h	29[a]
3	nBu_4NI	rt, 22 h	59

[a] Overalkylated products (**8**) were contaminated.



Lewis acid such as $SnCl_4$ produced inseparable overalkylated products **8** in addition to **7**.[5] The yield of **7** increased up to 59% when *n*-Bu_4NI was added.

Among the sulfonium salts tested, Corey−Kim reagent[6] reacted readily with tryptamine carbamate (**9**) in the presence of *i*-Pr_2NEt to give the pyrroloindole (**10** and **11**) in quantitative yield (Scheme 2). Interestingly, N^a-methyltryptamine (**6**) was not cyclized with Corey−Kim reagent.[7]

Under similar reaction conditions, 5-methoxy-N^b-(methoxycarbonyl)tryptamine (**12**) gave **13** in 88% yield.

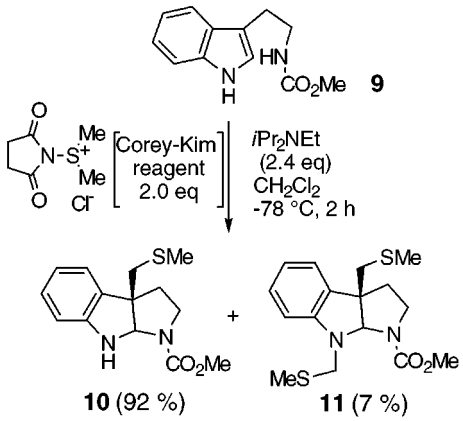
From **10** and **13**, the syntheses of racemic desoxyeseroline ((±)-**3**) and esermethole ((±)-**2**)[3d] were achieved, respectively, in short steps. Reductive methylation and desulfurization of **10** were carried out simultaneously with Raney

(5) Using another Lewis acid such as $EtAlCl_2$, $AlCl_3$, or AgOTf gave the same products.

(6) The reaction of Corey−Kim reagent with 1*H*-indole to give 3,3-disubstituted indolenium compounds has been reported previously. Katayama, S.; Watanabe, T.; Yamauchi, M. *Chem. Pharm. Bull.* **1992**, *40*, 2836−2838.

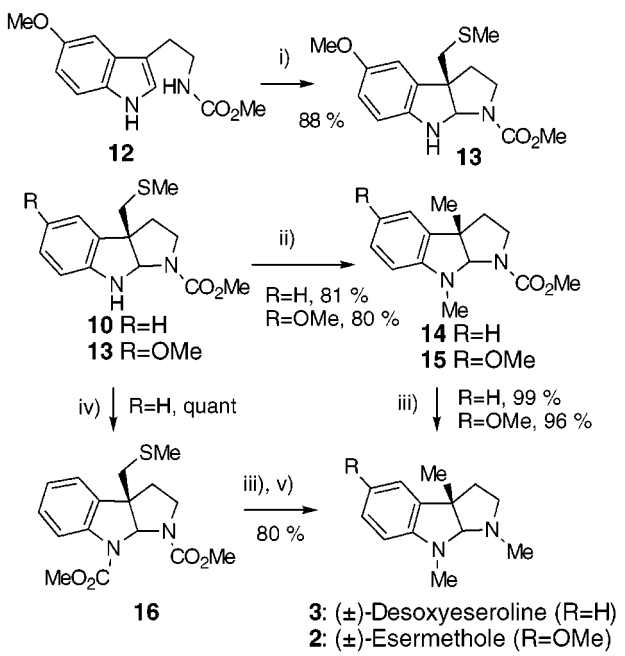
(7) When **6** was treated with Corey−Kim reagent, **7** was obtained in only 7% yield and **6** was recovered in 88% yield.

Scheme 2



Ni (W2) under a H_2 atmosphere in the presence of $HCHO_{aq}$ to give **14**. Reduction of **14** with Red-Al gave (±)-**3**, quantitatively. The synthesis of (±)-esermethole (**2**) was also achieved from **13** via **15** in 77% overall yield (Scheme 3).

Scheme 3[a]

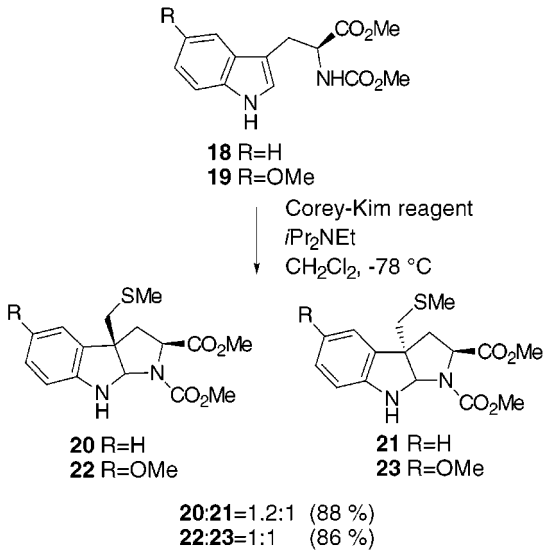


[a] Conditions: (i) Corey−Kim reagent, *i*-Pr_2NEt, −78 °C; (ii) H_2, Raney Ni (W2), $HCHO_{aq}$, EtOH, reflux; (iii) Red-Al, toluene, reflux; (iv) NaH, MeOCOCl, THF; (v) Raney Ni (W2), H_2, EtOH, reflux.

On the other hand, methoxycarbonylation of **10** to **16**, followed by desulfurization and reduction with Red-Al, gave (±)-(**3**) in 80% yield.

Using this strategy, we synthesized optically active esermethole from tryptophan derivatives (Scheme 4). *N*-(Methoxycarbonyl)-L-tryptophan methyl ester (**18**) was treated with Corey−Kim reagent in the presence of *i*-Pr_2NEt to give the

Scheme 4

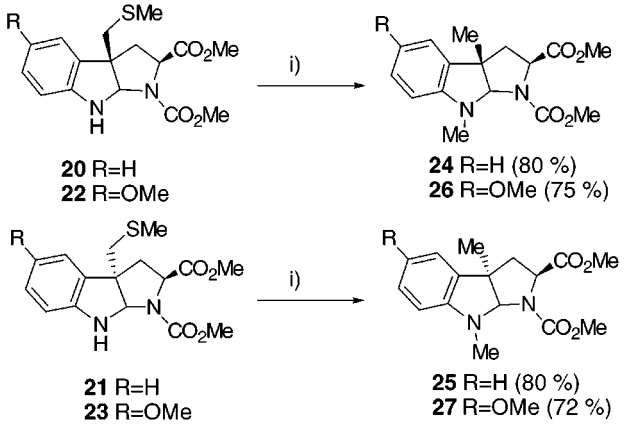


pyrrolo[2,3-*b*]indole skeleton (**20**, **21**) in high yield. Although this product was a mixture of diastereomers (1.2:1), as determined by ^{1}H NMR analysis, they were readily separated by silica gel column chromatography. Likewise, 5-methoxy-*N*-(methoxycarbonyl)-L-tryptophan methyl ester (**19**) gave **22** and **23** as a 1:1 mixture of two diastereomers.

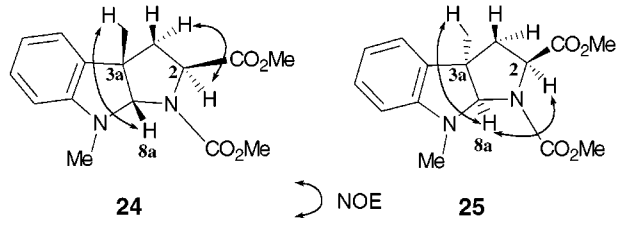
Reductive methylation of **20**, followed by desulfurization as described earlier, gave **24** in 80% yield. Under similar conditions, **21**, **22**, and **23** were converted to the corresponding **25**, **26**, and **27**, respectively. Their stereochemistries were determined by differential NOE experiments, as shown in Scheme 5. No NOE enhancement of **24** was observed between the protons at position 2 (δ 4.22 ppm) and position 8a (δ 5.17 ppm), while in **25** an enhancement in the signal of the proton at position 2 (δ 4.61 ppm) was observed when the proton at position 8a (δ 5.19 ppm) was irradiated.

Reduction of both the carbamate and ester groups of **26** gave the chiral amine (**28**) (Scheme 6). Reduction of **27** gave

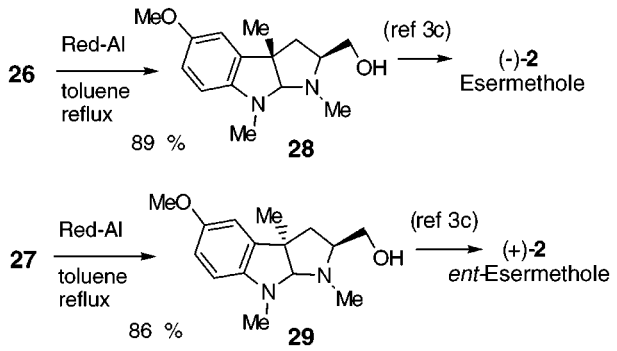
Scheme 5[a]



[a] Conditions: (i) H_2, Raney Ni (W2), 37% $HCHO_{aq}$, EtOH, reflux.

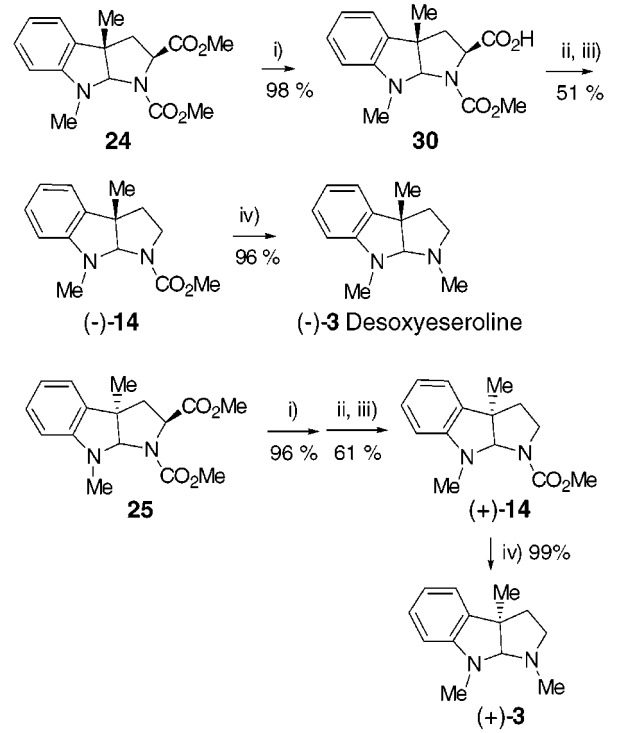


Scheme 6



29. Since the chiral alcohols **28**, $[\alpha]^{29}_D$ −117° (*c* 0.5, $CHCl_3$) [lit. $[\alpha]^{31}_D$ −118° (*c* 0.5, $CHCl_3$)], and **29**, $[\alpha]^{24}_D$ +35.9° (*c*

Scheme 7[a]



[a] Conditions: (i) KOH, MeOH−H_2O; (ii) ^{i}BuOCOCl, *N*-methylmorpholine, THF, then, 2-hydroxythiopyridone, NEt_3; (iii) *hν* (tungsten lamp), PhSH, THF; (iv) Red-Al, toluene, reflux.

0.48, $CHCl_3$) [lit. $[\alpha]_D^{30.5}$ +36.3° (*c* 1.01, $CHCl_3$)], have already been converted into (−)- and (+)-esermethole (**2**), respectively, by Takano et al.,[3c] formal syntheses of (+)- and (−)-esermethole (**2**) were achieved.

Although a formal synthesis was achieved, the previous method for removing the extraneous carbomethoxy group at C2 was not efficient (22%). Therefore, removal of the extraneous carbomethoxy group at C2 using Barton reductive decarboxylation was examined[8] (Scheme 7). Saponification of **24** provided the carboxylic acid (**30**), from which the Barton ester was secured by successive treatment with isobutyl chloroformate and the anion of 2-mercaptopyridine *N*-oxide. The intermediates were converted to (−)-**14** by irradiation with a tungsten lamp in the presence of PhSH. Optically active (−)-**14** was converted to *natural* desoxyeseroline (**3**)[3d,k] as described earlier. Its enantiomer was synthesized from **25** by a similar route. Physostigmine (**1**) has already been synthesized from **3** via **2**.[3j,k]

(8) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901−3924.

In conclusion, we have developed a short synthesis of physostigmine and related compounds from readily available tryptamine and L-tryptophan. Related sequences should allow direct access to either enantiomer of a wide variety of physostigmine analogues.

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Supporting Information Available: Spectral data of new compounds and representative experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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