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Total Synthesis of (±)-Phenserine *via* [4+1] Cyclization of a Bis(alkylthio)carbene and an Indole Isocyanate

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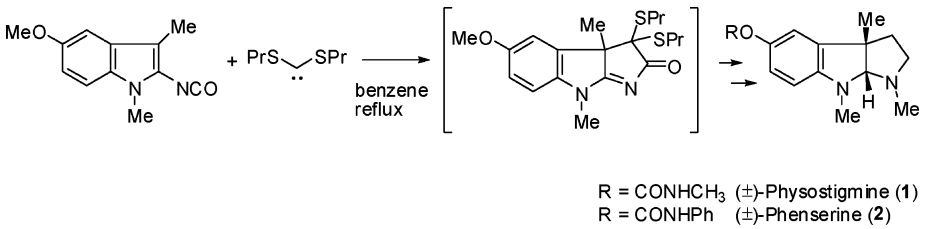
ABSTRACT



A total synthesis of acetylcholine blocking agent, phenserine, has been achieved by employing a [4+1] cyclization between an appropriately substituted indole isocyanate and a bis(alkylthio)carbene.

Alkaloids exhibiting the hexahydropyrrolo[2,3-*b*]indole core are a growing class of natural products that display a broad range of biological activities.[1] Physostigmine (**1**) was first isolated in pure form from the African Calabar bean seeds *Physostigma venenosum* in 1864 by Jobst and Hesse.[2] It is one of the earliest compounds to be identified as an inhibitor of acetyl cholinesterase. (−)-Physostigmine is currently used to treat myasthenia gravis and glaucoma.[3] It was also found to have promise as a therapeutic agent for Alzheimer's disease.[4] However, the major drawbacks of this drug are a low therapeutic window and short duration of action.[5] Phenserine (**2**), the phenylcarbamate analogue of physostigmine (Figure 1), is a more potent and selective inhibitor of

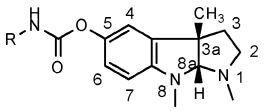


Figure 1. Structures of physostigmine and phenserine.

AChE[6] and inhibits the formation of the β-amyloid precursor protein (β-APP).[7] Consequently, it is an attractive target molecule for synthetic study.

(1) For reviews, see: (a) Anthoni, U.; Christophersen, C.; Nielsen, P. H. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1999; Vol. 13, pp 163. (b) Takano, S.; Ogasawara, K. In *The Alkaloids*; Brossi, A., Ed.; Academic: San Diego, CA, 1989; Vol. 36, pp 225.

(2) Jobst, J.; Hesse, O. *Justus Liebigs Ann. Chem.* **1864**, *129*, 115.

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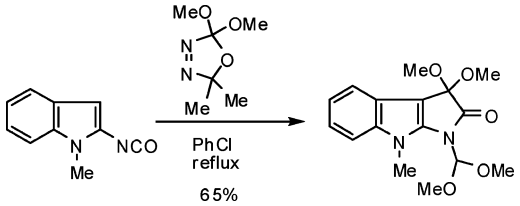
The hexahydropyrrolo[2,3-*b*]indole alkaloids have been the subject of a number of synthetic studies,[1b,8] including several total syntheses of physostigmine.[9] Total synthesis of (−)-phenserine has been reported as well.[10]

The most synthetically challenging feature of both physostigmine and phenserine is the sterically congested all-carbon quaternary center at C_{3a}. Our laboratory had previously reported a method for producing quaternary centers by reacting nucleophilic carbenes with β,β-disubstituted vinyl isocyanates.[11−13] Nucleophilic carbenes[11−15] have emerged as powerful 1,1-dipole equivalents for the construction of highly functionalized nitrogen heterocycles *via* [4+1] cyclization with isocyanates, and the preparation of adducts derived from indole isocyanates and these carbenes was recently reported[16] (Scheme 1).

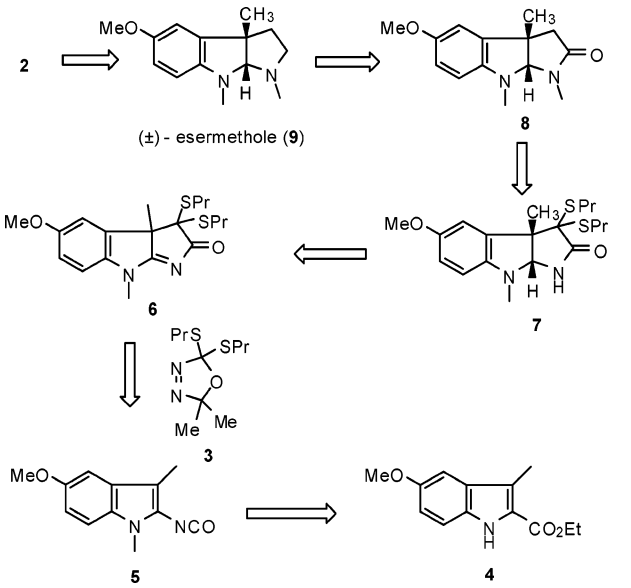
Scheme 1. [4+1] Cyclization between an Indole Isocyanate and Dimethoxycarbene



Inspired by these results, the synthesis of phenserine was envisioned to proceed by the reaction of a suitably substituted indole isocyanate with a nucleophilic carbene. Phenserine possesses a methylene carbon at C_3 (Figure 1), and access to this substitution pattern could be achieved by using a nucleophilic carbene partner that could be readily reduced to the desired oxidation level after the cyclization event. An ideal candidate for achieving this objective is a bis(alkylthio)-carbene,[12,17] the resultant dithioacetal serving as a methylene equivalent *via* postcyclization reductive desulfurization.

Herein, an efficient total synthesis of (±)-phenserine *via* [4+1] cyclization of an indole isocyanate and bis(propylthio)-carbene is disclosed. The proposed retrosynthetic analysis of this target is outlined in Scheme 2. The key transformation

Scheme 2. Retrosynthetic Analysis



in this sequence is the thermal decomposition of the 2,2-bis(propylthio)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**3**)[12] to produce the corresponding carbene in the presence of indole isocyanate **5**, which would be expected to afford adduct **6** on the basis of prior related results.[16]

The synthesis began with the preparation of indole **4** using Cook's procedure.[18] The resulting species was then *N*-methylated and saponified to obtain acid **10** in 61% yield. Treatment of intermediate **10** with diphenylphosphorazidate (DPPA) in the presence of Et_3N generated the requisite acyl azide **11** (Scheme 3). The acyl azide **11** was refluxed in benzene to effect Curtius rearrangement to the indole isocyanate **5**. Excess dithiooxadiazoline **3** was then added, and the solution was refluxed for an additional 30 min to afford adduct **6**. The crude adduct was exposed to $LiAlH_4$ to deliver reduced tricycle **7** in 72% yield for the two steps after purification (Scheme 4). Critical to the success of this approach was the facility by which the quaternary center at C_{3a} was constructed. The efficiency of the carbene/isocyanate

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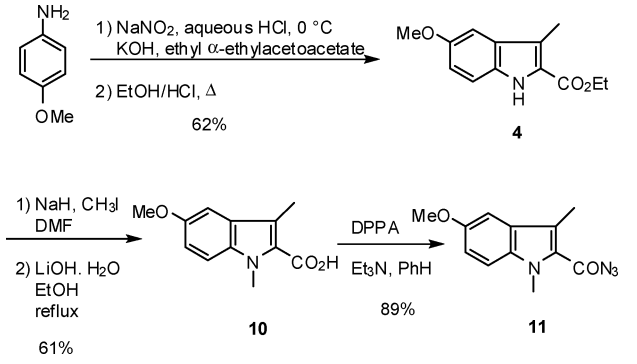
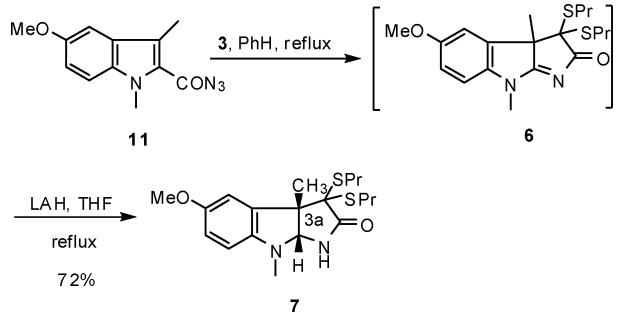
Scheme 3. Preparation of the Acyl Azide



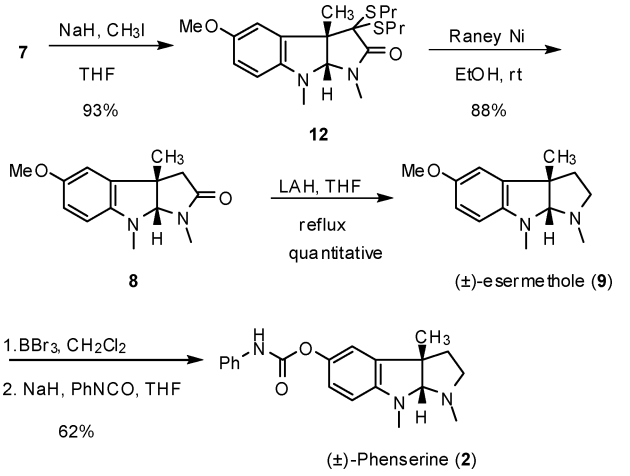
cyclization for making quaternary centers is a noteworthy feature of these reactions that has been exploited previously.[11−13]

With the tricyclic core of phenserine in place, compound **7** was *N*-methylated to furnish **12** in 93% yield. The stage was then set for the reductive cleavage of the carbon−sulfur bonds that were indroduced during the carbene addition step. This was achieved in routine fashion by treatment with Raney Ni. Further reduction of the lactam carbonyl group with

Scheme 4



Scheme 5. Synthesis of Phenserine



$LiAlH_4$ in refluxing THF produced esermethole (**9**) in quantitative yield (Scheme 5).

Finally, using conditions reported by Overman and co-workers,[10d] esermethole was transformed in two steps, and in 62% yield, to (±)-phenserine (**2**). The spectral data of this material were identical with those reported by Overman and co-workers.[10d]

In summary, we have developed a novel and efficient total synthesis of (±)-phenserine *via* a [4+1] cyclization of an indole isocyanate and bis(propylthio)carbene.

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

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