TOTAL SYNTHESES OF (±)-ANANTINE AND (±)-ISOANANTINE *VIA* THIYL RADICAL ADDITION-CYCLIZATION REACTION

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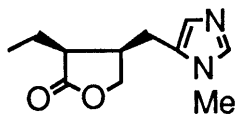
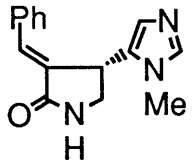
A new stereoselective route to isoanantine (**1**) and anantine (**2**) has been developed by the combination of three key steps: thiyl radical addition-cyclization of dienylamide, construction of the substituted imidazole, and stereoselective construction of the *E*-benzylidene moiety.

KEYWORDS anantine; imidazole alkaloid; radical cyclization; total synthesis; isoanantine; selenenylation

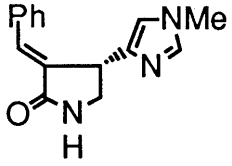
Two imidazole alkaloids,[1] isoanantine (**1**) and anantine (**2**), were isolated from the leaves of *Cynometra* species which have been used as a traditional folk medicine in Africa exhibiting antitussive and analgesic activities.[2-6] Because of their structural similarity to pilocarpine, a muscarinic agonist for the symptomatic treatment of Alzheimer's disease, we focused our attention on developing a general and practical method of synthesizing anantine (**2**) and related alkaloids for the evaluation of their pharmacological activities.



pilocarpine



isoanantine (**1**)



anantine (**2**)

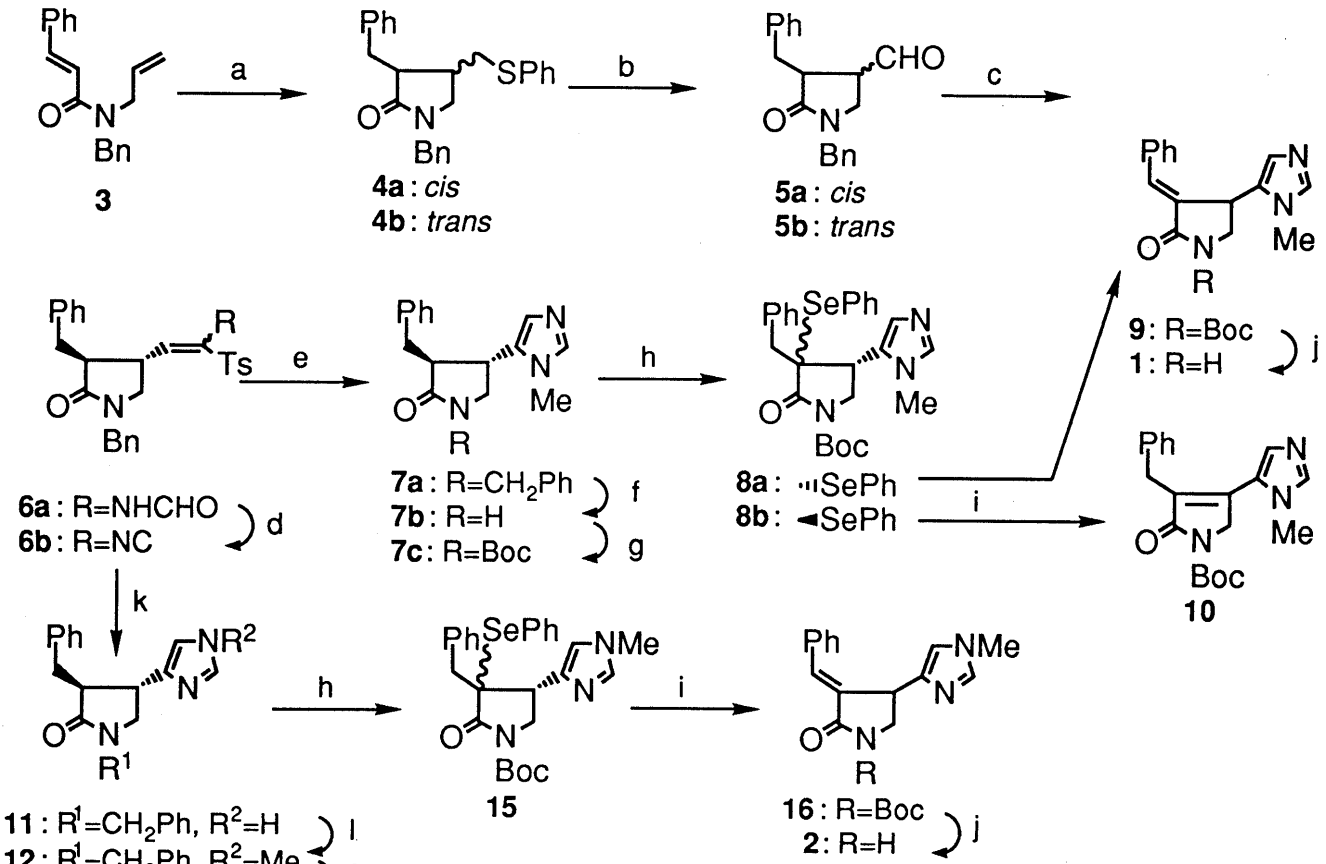
Our synthetic strategy consists of three key steps: [1] construction of 3,4-disubstituted pyrrolidinone ring by thiyl radical addition-cyclization, [2] construction of two types of the substituted imidazoles from a common intermediate, [3] construction of the *E*-benzylidene moiety *via* selenenylation.

According to the previous method,[7] thiyl radical addition-cyclization of *N*-allyl-*N*-benzylcinnamamide (**3**) in the presence of equimolar amounts of diphenyl disulfide and thiophenol proceeded smoothly to give a 1:1 mixture of two stereoisomeric 4-(phenylthiomethyl)pyrrolidinones **4a** and **4b** in 71% yield. Their stereostructures were established by irreversible conversion of the *cis*-isomer **4a** into the *trans*-congener **4b** upon treatment with sodium ethoxide in ethanol.[7,8] Oxidation of the *cis*- and *trans*-sulfides **4a** and **4b** with *m*-chloroperbenzoic acid (mCPBA) at 0°C gave the corresponding sulfoxides, which were respectively subjected to the Pummerer reaction and subsequent hydrolysis to give the desired *cis*- and *trans*-aldehydes **5a** (82%) and **5b** (92%) in three steps from the starting sulfides. Unstable *cis*-aldehyde **5a** was readily isomerized into the *trans*-isomer **5b** during the course of either purification by silica gel chromatography or stirring of the methylene chloride solution in the presence of silica gel.

According to the van Leusen's procedure,[9] treatment of the *trans*-aldehyde **5b** with (*p*-tolylsulfonyl)-methyl isocyanide (TosMIC) in the presence of potassium *t*-butoxide gave the formamide **6a** in 77% yield. The formamide **6a** was dehydrated by phosphorous oxychloride-triethylamine to give the isonitrile **6b** which without purification was treated with methanolic methylamine to afford the desired imidazole **7a** in 55% yield from **6a**. Attempted preparation of the imidazole **7a** *via* the corresponding imine,[10]

prepared by the condensation of the aldehyde **5b** and methylamine, was unsuccessful. Debenzylation of the lactam **7a** under the Birch conditions gave the lactam **7b**, dihydroisoanantine.[2,11]

For the stereoselective synthesis of isoanantine, we have developed a method for stereoselective construction of the *E*-benzylidene group *via* the route involving the introduction of the phenylselenenyl group followed by *syn*-elimination of the corresponding selenoxide. Acylation of the lactam **7b** with *t*-Boc_2O gave the *N*-Boc lactam **7c** in 92% yield, which was then selenenylated[12] at 0°C to give a 3:1 mixture of two selenides **8a** and **8b** in 57% yield along with 12% recovery of the starting lactam **7c**. Treatment of the selenides **8a** and **8b** with mCPBA at 0°C afforded the *exo*- and *endo*-olefins **9** and **10**, respectively, both in 92% yield, as a result of concomitant elimination of the resulting selenoxides. Both products **9** and **10** were readily characterized by their spectral data, and therefore the stereostructures of both selenides **8a** and **8b** were unambiguously established. Removal of the Boc group in **9** by treatment with trifluoroacetic acid gave the lactam **1**,[13] which was identical with isoanantine upon comparisons of the spectral data with those of the authentic sample.[2,11]



The synthetic method for isoanantine described above is also successfully applied to the total synthesis of (±)-anantine. Treatment of the intermediary isonitrile **6b** with methanolic ammonia gave the *N*-

unsubstituted imidazole **11** in 38% yield from **6a**. Alkylation of the imidazole **11** with methyl iodide in the presence of KOH gave a 1:3 mixture of the two products **7a** and **12** in 97% yield, the latter of which was then subjected to the same reaction sequence described for the synthesis of (±)-isoanantine (**1**) to afford the lactam **2**[13] in 30% yield from **12**. The lactam **2** was identical with anantine upon comparisons of the spectral data with those of the authentic sample.[3,4,11]

In conclusion, we have now established a practical synthetic method for anantine and related alkaloids for pharmacological evaluation.

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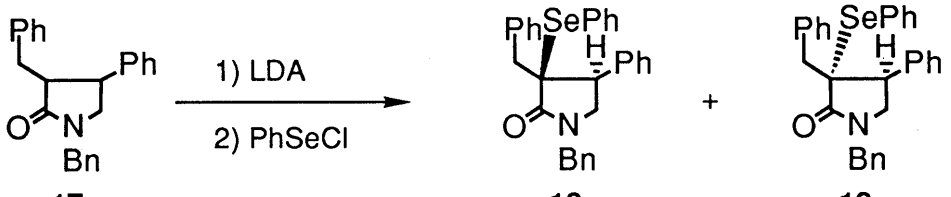
10) A. M. van Leusen, J. Wildeman, and O. H. Oldenziel, *J. Org. Chem.*, **42**, 1153 (1977).
11) At our request for sending authentic samples of natural alkaloids, Dr. F. Khuong-Huu sent us only an authentic sample of isocynometrine. Therefore, we could not directly identify our synthetic samples with natural isoanantine and anantine.
12) As a preliminary experiment, we investigated the selenenylation of lactam **17** with phenylselenenyl chloride and found that ratios of *cis*- **18** and *trans*-selenide **19** were 2:3 at -78°C and 13:1 at 0°C, respectively, depending upon the reaction temperature employed.



17 **18** **19**

13) Lactam **1**: mp 168 - 170 °C (lit. [4] 201 °C), Lactam **2**: mp 204 -206 °C (lit. [4] 179 °C).

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