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Tremorgenic Mycotoxins: Synthesis of 6-Demethoxyfumitremorgin C

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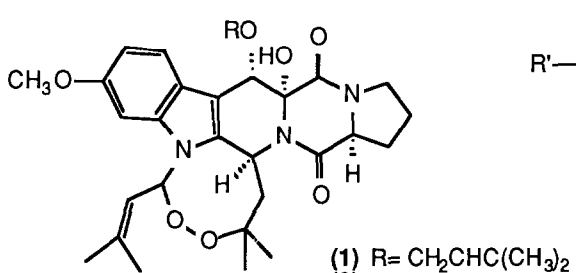
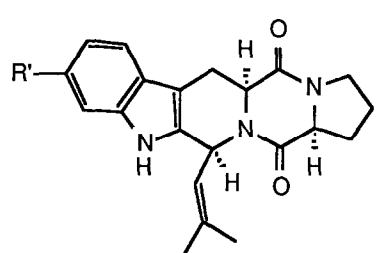
Summary: Synthetic studies directed toward the development of a general route to the fumitremorgin group of mycotoxins are disclosed. A chloroformate-induced cyclization of a L-tryptophan imine afforded a 1,2,3,4-tetrahydro-β-carboline which was elaborated to 6-demethoxyfumitremorgin C.

The fumitremorgins are a group of 6-methoxyindole containing mycotoxins isolated from *Aspergillus fumigatus* and *Penicillium verruculosum* which include fumitremorgin A (**1**), fumitremorgin C (**2**) and verruculogen (**3**).[1] The recent report by Nakagawa[2a] *et al.* in regard to fumitremorgin B is of special significance in this area.[2a-c] We now report the first synthesis of 6-demethoxyfumitremorgin C (**4**), which represents the prototype of the fumitremorgin series as well as a synthetic relay for further functionalization studies.



(1) R= $CH_2CHC(CH_3)_2$
(2) R=H



(3) R'=OCH_3
(4) R'=H

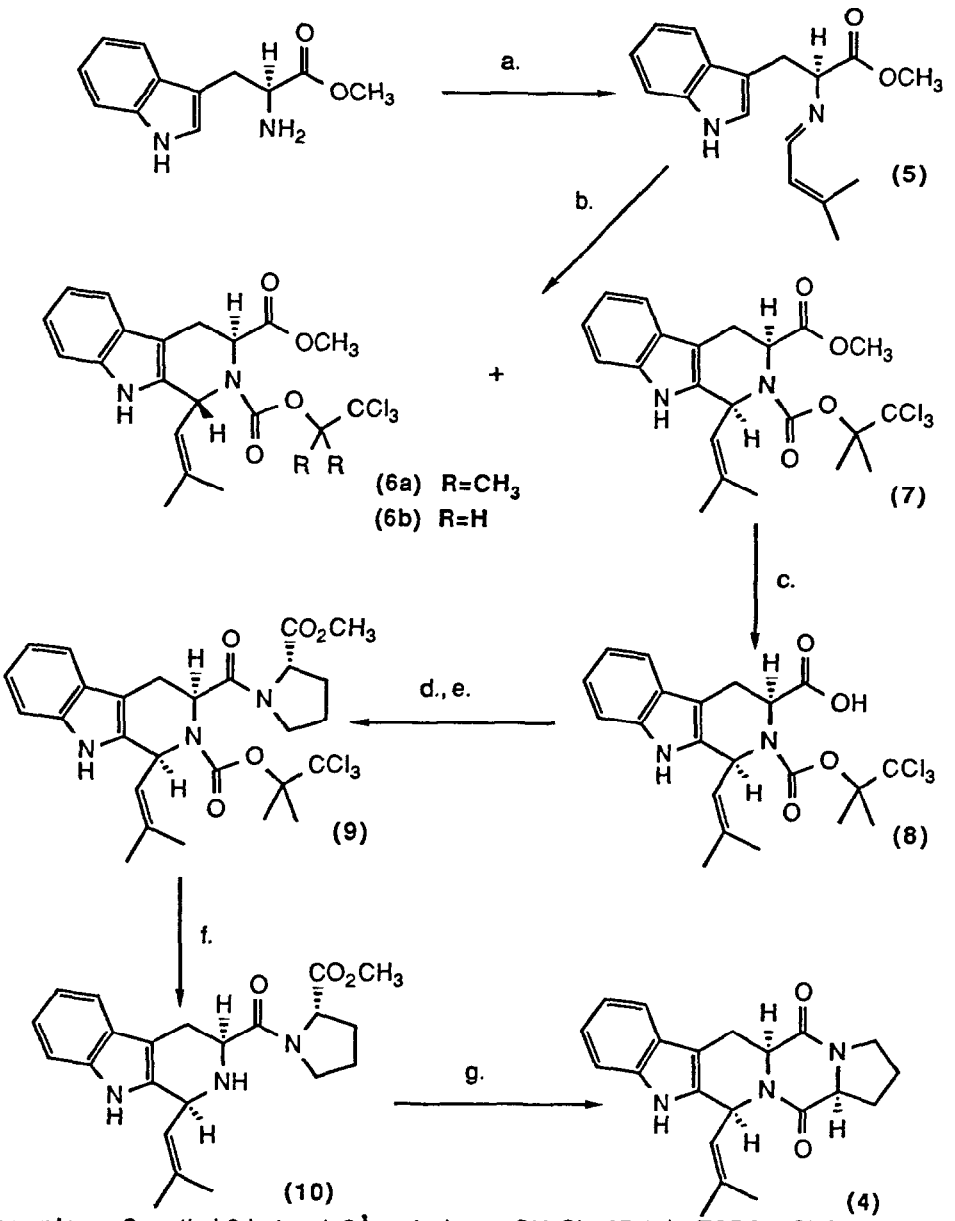
Our initial objective was the preparation of the correct stereoisomer of the 1,2,3,4-tetrahydro-β-carboline portion of the target, which could then be elaborated by coupling with a suitably protected proline derivative. Attempts to effect a Pictet-Spengler condensation between L-tryptophan methyl ester and 3-methyl-2-butenal under either protic or aprotic conditions were unsuccessful.[3]

When L-tryptophan methyl ester was allowed to condense with 3-methyl-2-butenal under aprotic conditions in the presence of molecular sieves, however, the imine was produced in excellent yield.

Following investigations by Cook[4] *et al.* concerning Pictet-Spengler cyclizations of N_b-benzyltryptophan methyl ester in aprotic media in connection with the synthesis of pyridindolol, the use of chloroformates in the Pictet-Spengler-type cyclization of tryptamine imines was reported.[5] Utilization of chiral tryptophan imine derivatives and the question of the stereochemical outcome of the chloroformate-induced Pictet-Spengler type cyclization remained uninvestigated; however, Cook[6] *et al.* demonstrated the stereospecific formation of *trans*-1,3-disubstituted-1,2,3,4-tetrahydro-β-carbolines from the Pictet-Spengler condensation of N_b-benzyltryptophan methyl ester with various aldehydes. When the imine (**5**) was reacted with 2,2,2-trichloro-1,1-dimethylethyl chloroformate in the presence of pyridine, a smooth cyclization occurred to afford a 2:1 mixture of the diastereomeric 1,2,3,4-tetrahydro-β-carbolines (**6a**) and (**7**) which were readily separable by flash chromatography. Interestingly, when 2,2,2-trichloroethyl chloroformate was used under the same reaction conditions only the *trans*-1,2,3,4-tetrahydro-β-carboline (**6b**) was obtained. The assignment of stereochemistry was based on ^{13}C NMR observations using the method of Bailey[7a] and Cook.[7b]

The methyl ester of the *cis*-1,2,3,4-tetrahydro-β-carboline (**7**) could be cleanly hydrolyzed utilizing the *anhydrous hydroxide* method[8] to afford the acid (**8**) without any detectable racemization. The mixed anhydride of the acid was formed using pivaloyl chloride and then coupled with L-proline methyl ester to give the peptide (**9**).[9] Facile deprotection of the 2,2,2-trichloro-1,1-dimethylethyloxycarbonyl (TCBOC)-derivatized amine could be accomplished using our recently introduced tellurolate-anion methodology.[10] The tellurolate anion which is readily obtained in a catalytic cycle by the sodium borohydride reduction of dithienyl ditelluride efficiently and selectively reacts with the TCBOC group to produce the amine (**10**). When the amine (**10**) is heated in refluxing toluene the pentacyclic 6-demethoxyfumitremorgin C

Scheme 1: Synthesis of 6-Demethoxyfumitremorgin C



Reagents: a. 3-methyl-2-butenal, 3Å mol. sieves, CH_2Cl_2, 95%; b. TCBOC-Cl, Pyridine, DMAP, CH_2Cl_2, 0°C, 70%; c. KO^tBu (8eq), H2O (2eq), ether, O°C, 95%; d. pivaloyl chloride, Et_3N, CH_2Cl_2, 0°C; e. L-proline methyl ester, CH_2Cl_2, 0°C, 91%; f. dithienylditelluride, $NaBH_4$, THF, H_20, 58°C, 88%; g. toluene, reflux, 78%

(**4**) is obtained after crystallization from ethanol.[11]

Aspects of this problem which are currently under investigation in our laboratories include functionalization studies on (**4**), preparation of the natural products and introduction of increased stereochemical control in the chloroformate-induced cyclization of chiral tryptophan imine derivatives.

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11. All compounds gave satisfactory ^{1}H NMR, IR, mass spec. values and analytical data.

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