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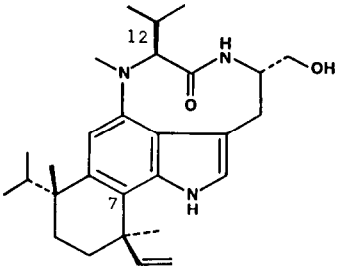
A MODEL STUDY FOR THE SYNTHESIS OF THE TUMOR PROMOTING AGENTS LYNGBYATOXIN A AND TELEOCIDIN B---FURTHER ASPECTS OF A NEW ISOXAZOLINE-BASED INDOLE SYNTHESIS.

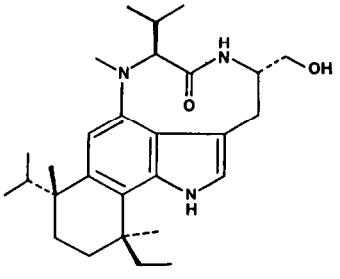
Alan P. Kozikowski* and X.-M. Cheng
Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260

Summary: A new indole synthesis developed in our laboratories has been shown to be applicable to the preparation of 4-amino-7-carbon substituted indoles, a result of some relevance to the preparation of the title compounds.

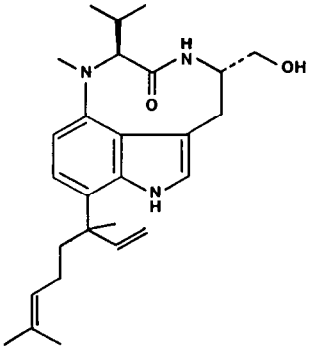
Teleocidin B and lyngbyatoxin A have been shown to induce ornithine decarboxylase activity in mouse skin,[1] a test which has been used to screen environmental agents for their tumor promoting activity.[2] Dihydroteleocidin B, a hydrogenation product of teleocidin, has in fact been found to be comparable in its tumor promoting activity to that of 12-O-tetradecanoylphorbol 13-acetate (TPA).[1]



teleocidin B



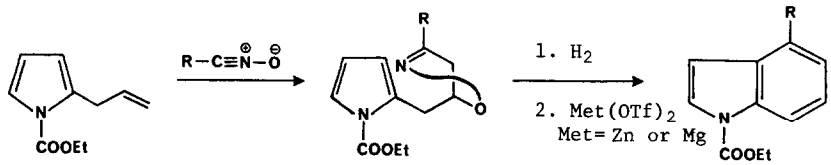
dihydroteleocidin B



lyngbyatoxin A

In devising a total synthesis approach to these structurally intriguing products,[3] which may prove of additional value to assaying the structure/activity relationships required for tumor promotion, we have sought to further explore a new indole synthesis developed recently in our laboratories.[4] This strategy, which is summarized in Scheme 1, is based on the dipolar cycloaddition reaction of an α- (or β-) allylpyrrole with a nitrile oxide. Hydrogenation of the intermediate isoxazoline to β-hydroxy ketone,[5] and zinc or magnesium triflate promoted cyclization then afford the 4- (or 7-) substituted indole.

Scheme 1. The General Indole Synthesis

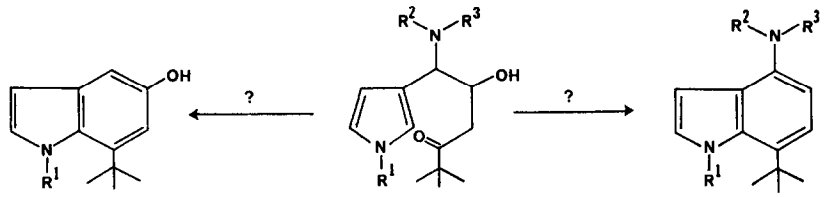


1 2 3

We felt that our indole synthesis might, in contrast to the more classical methods of indole preparation, be especially well suited to the construction of these natural products for the following reasons: a) such a strategy might easily allow us to employ the amino acid valine as one of the building blocks so that the C-12 stereocenter is properly set; and b) a chiral nitrile oxide hosting a quaternary carbon-center might additionally be used in the scheme so that the asymmetric center borne by the aromatic ring at C-7 could be installed in the proper relative stereochemical relationship to the C-12 center.

To probe these notions, we decided to examine the ring closure annotated in Scheme 1 with an intermediate of general structure type **4**. There did exist at the outset of this work certain concerns in our mind regarding whether the $R^2(R^3)N$- group or the OH group would be lost in the benzene annulation step (Scheme 2).

Scheme 2.

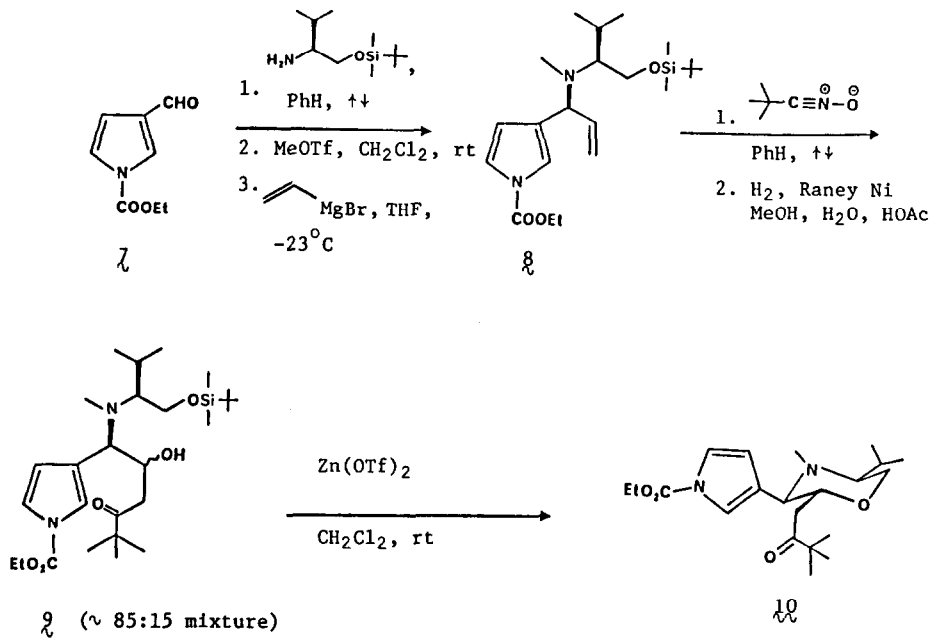


5 4 6

The allylpyrrole required to carry out this study was prepared in a novel fashion from N-carboethoxy-3-formylpyrrole (7) (generated in turn from N-triisopropylsilyl-3-bromopyrrole by a halogen-metal exchange sequence).[6] Imine formation between 7 and the silyl ether derivative of L-valinol was followed by N-methylation (MeOTf), and addition of vinylmagnesium bromide to the intermediate iminium salt. The allylamine so produced was isolated as nearly a single stereoisomer (1,3-asymmetric induction).[7] While reaction of this alkene with 2,2-dimethylpropionitrile oxide was uneventful, subsequent hydrogenation and zinc triflate promoted cyclization led **unfortunately** not to the desired indole, but to a product which has been assigned the morpholine structure **10** (stereochemistry should be considered tentative).[8] This product apparently results from competing desilylation under the reaction conditions, followed by dehydration of the β-

hydroxy ketone to enone, and a 6-exo-trig ring closure.[9] Attempts to induce the further conversion of **10** to the desired indole have not been favorable.

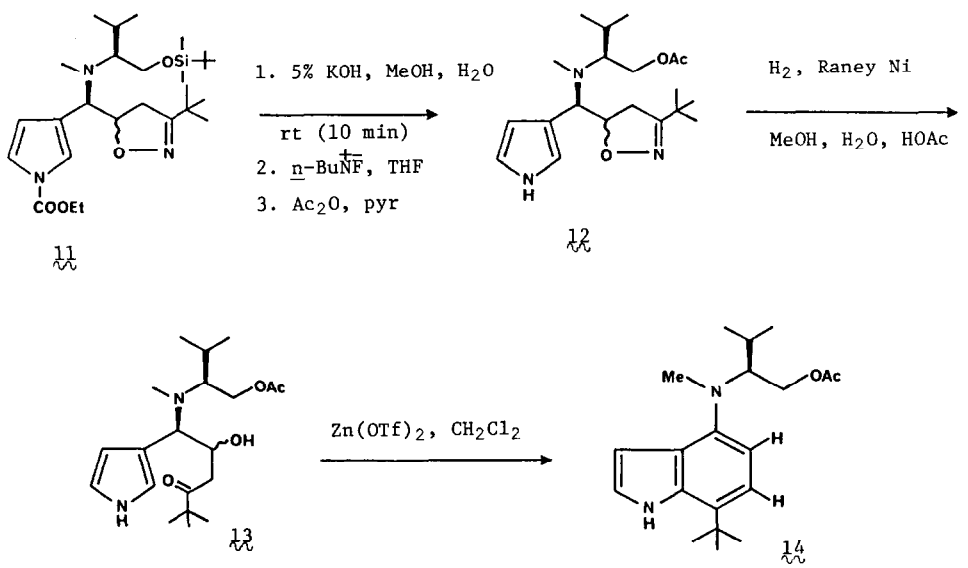
Scheme 3.



7 8 9 (~ 85:15 mixture) 10

To avoid the above side reaction, and to additionally render the pyrrole more reactive toward electrophilic substitution, the N-carboethoxy group was removed from **11**, and the silyl ether protecting group replaced by acetate. This time

Scheme 4.



11 12 13 14

cyclization from **13** did, in fact, proceed readily at room temperature to afford the desired 4,7-disubstituted indole **14** (51% yield, $[\alpha]_D$-20.4° (c 0.265, $CHCl_3$). The assignment of structure to **14** was easily made by observing: (a) the two doublets present for the aromatic protons (δ = 6.48 and 6.97, J = 8.1 Hz); and (b) the large downfield shift of the N-methyl group in going from **13** to **14** (2.30 ppm → 2.87 ppm), a result characteristic of the transformation of an aliphatic amine to an aromatic amine. The chemical shift and coupling patterns of **14** are, in fact, very similar to those reported by Cardellina, Marner and Moore for lyngbyatoxin A.[1]

In summary, we believe that the present model study bodes well for the development of a total synthesis approach to lyngbyatoxin A and teleocidin B. The present indole synthesis allows for the incorporation of both diverse functionality and centers of chirality about the periphery of the indole nucleus, features which allow us in turn to readily make use of the "chiral pool"[10] in selecting the building blocks for our synthesis.

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