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Synthesis of (-)-Trichoviridin

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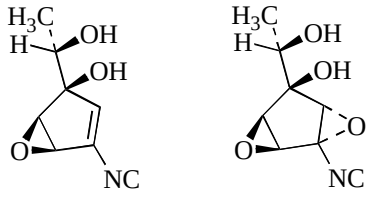
Abstract: The highly-strained cyclopentadiene monoepoxide ring of isonitrin B can be formed efficiently by the intramolecular C-H insertion of an intermediate alkylidene carbene.

Isonitrin B (**1**) and trichoviridin (**2**) are two representatives of a small family of isonitrile antibiotics (ref 1, 2) having compact but highly functionalized (and highly reactive) cyclopentane rings. The current rapid rise in bacterial infections that do not respond to antibiotic therapy makes it urgent that leads such as these be pursued. Although isonitrin B was first described more than twenty-five years ago, only one synthesis, of the racemate, has appeared (ref 2). We report a synthesis of (-)-isonitrin B, using a strategy that should be generally applicable to this family of antibiotics.



1 **2**

The conventional approach to the assembly of highly functionalized ring systems has been to first construct the ring(s), and then to elaborate the functional groups. We proposed to invert this strategy, by first preparing the fully-oxygenated ketone **3**, and then cyclizing it to **4**. The key question was whether the generation and cyclization of the alkylidene carbene from this highly functionalized substrate could proceed smoothly to form the strained bicyclic product **4**. The key to this analysis is the observation that intramolecular C-H insertion of an alkylidene carbene proceeds with retention of the absolute configuration (ref 3).

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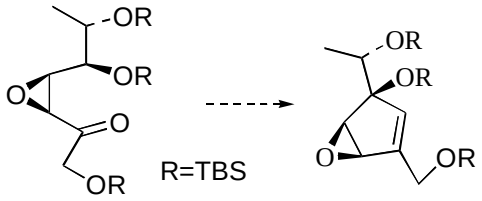
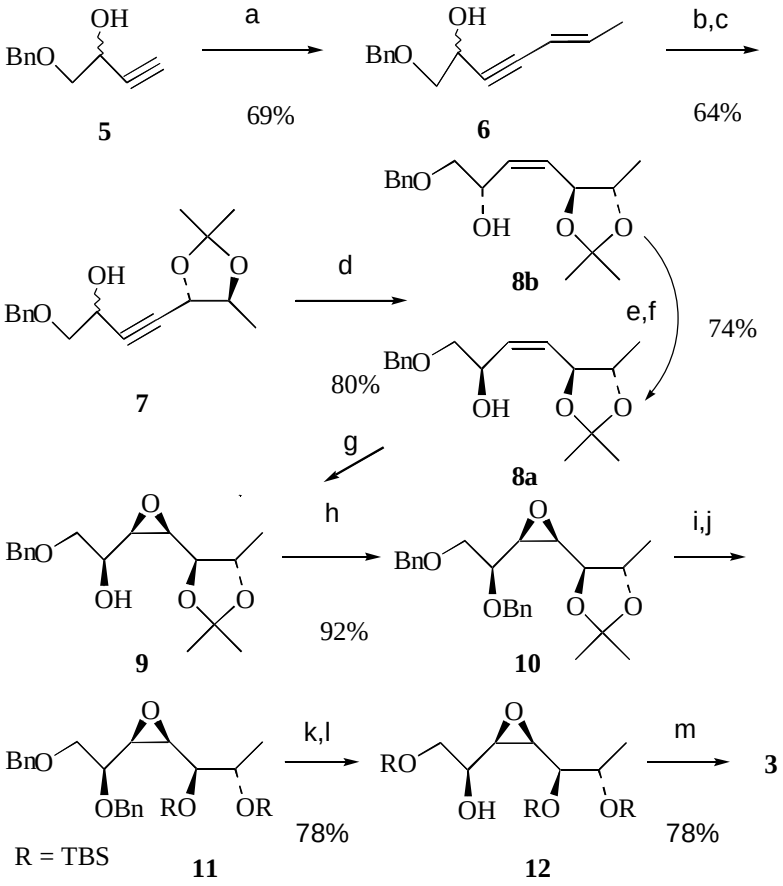


3 **4**

The construction of the required cyclization precursor **3 (Scheme 1)** began with the racemic alkyne **5** (ref 4). Palladium-mediated coupling with E-1-bromo-l-propene led to the alcohol **6**. Sharpless asymmetric dihydroxylation of **6** followed by protection resulted in the inseparable acetonides **7**. Hydrogenation (P-2 nickel) gave the corresponding Z-alkenes as a pair of diastereomers (**8a** and **8b**) which were readily separable on silica gel. The relative configuration of the correct intermediate **8a** was established by X-ray crystallographic analysis of the 4-bromophenylurethane of **8b**. The alcohol **8b** was inverted to **8a** by Mitsunobu coupling followed by hydrolysis (ref 5). Threo-selective MCPBA epoxidation of **8a** (ref 6) then gave the two diastereomeric epoxides in a 4:1 ratio, favoring the expected epoxide **9**. After protecting group interchange (ref 7), alcohol **12** was oxidized (PCC) to the cyclization precursor, ketone **3.**

Scheme 1

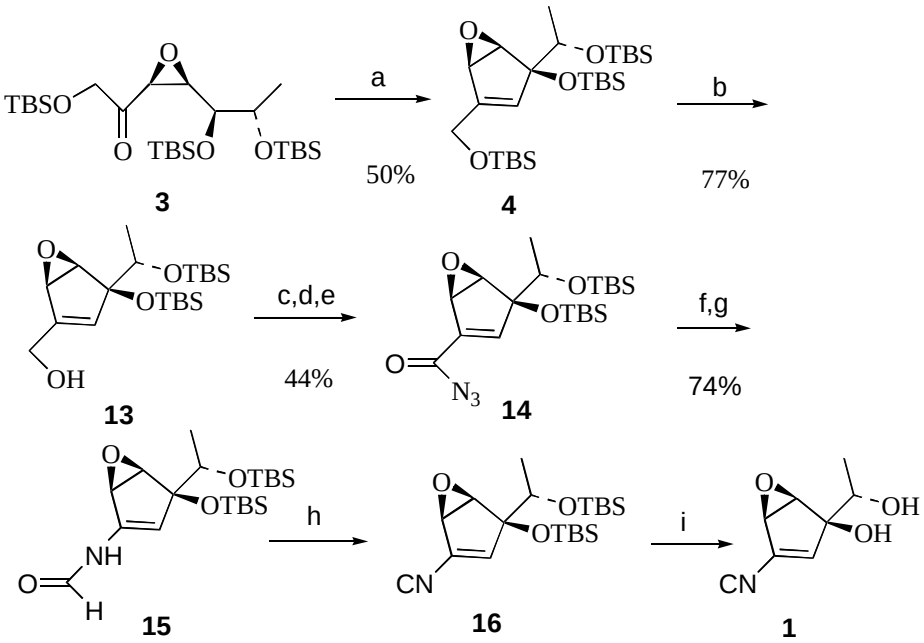


Alkylidene carbenes can be generated from a variety of precursors. Unlike alkyl carbenes, alkylidene carbenes do not need support from either a transition metal or an electron-withdrawing group to undergo efficient intramolecular insertion into a C-H bond to form the new C-C bond (ref 8).

Several reagents have been used to convert ketones into the corresponding alkylidene carbenes (ref 8). In our hands, the most efficient protocol has been our modification of the Ohira procedure (ref 9). We were delighted to observe that treatment of the ketone **3** with the anion of (trimethylsilyl)diazomethane in DME gave clean conversion to the cyclized product **4 (Scheme 2).**

Selective deprotection of the primary silyl group of **4** under the very neutral conditions of HF/piridine (ref 10) gave the acid-sensitive alcohol **13**, which was converted to the aldehyde by Dess-Martin oxidation (ref 11). The aldehyde was then oxidized to the acid with sodium chlorite (ref 12). Treatment of the acid with NaH and $(PhO)_2P(O)N_3$ (ref 13) gave the acyl azide **14**. Thermolysis of the acyl azide gave the unstable isocyanate, which was reduced directly to the formamide **15** using a new reagent combination we have developed, $NaBH_4$ in *t*-BuOH and water (ref 14). Dehydration of the formamide **15** (ref 15) followed by desilylation (TBAF buffered with solid NH_4Cl) then gave the natural product isonitrin B (**1**). Synthetic isonitrin B was identical (^{1}H NMR) with the natural product. As isonitrin B (**1**) has been converted to trichoviridin (**2**) (ref 2), this also constitutes a formal total synthesis of trichoviridin (**2**).

Scheme 2



3 **4** **13** **14** **15** **16** **1**

It is encouraging that the strained bicyclic skeleton of **1** can be formed directly by alkylidene carbene insertion. The approach outlined here should pave the way for the construction of other members of this family of isonitrile antibiotics.

ACKNOWLEDGMENT

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