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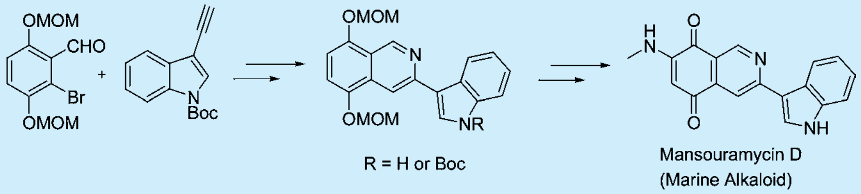
Total Synthesis of the Marine Alkaloid Mansouramycin D

K. S. Prakash and Rajagopal Nagarajan*

School of Chemistry, University of Hyderabad, Hyderabad-500 046, India

Supporting Information



ABSTRACT: Mansouramycin D, a cytotoxic alkaloid was isolated from a marine *Streptomyces* sp. in 2009. The first, simple, and concise route to the total synthesis of Mansouramycin D is reported. The core structure of the isoquinoline ring has been constructed from iminoannulation of 2-alkynylbenzaldehyde followed by oxidation/deprotection and oxidative amination via a three-step sequence from easily accessible starting materials.

Mansouramycin D (**1**), an isoquinoline quinone, was isolated from the ethyl acetate extract of marine *Streptomyces* sp. isolate Mei37 by Laatsch and co-workers in 2009 (Figure 1).[1] The structure of compound **1** has been confirmed as 3-(1*H*-indol-3-yl)-7-methylaminoisoquinoline-5,8-dione by NMR and mass spectrometry. Marine isoquinoline alkaloids have received substantial attention from the scientific community due to their rich biological activities.[1−4] Mansouramycin A−D (**1**−**4**) showed cytotoxicity against cancer cell lines and strong antimicrobial activity. Mansouramycin A−D (**1**−**4**) showed cytotoxicity against 36 cancer cell lines and were found to have significant activity against nonsmall cell lung cancer, breast cancer, melanoma, and prostate cancer cells. Specifically, high cytotoxicity was shown against many human cancer cell lines with an IC_{50} value up to 0.089 μM for lung cancer.[1]

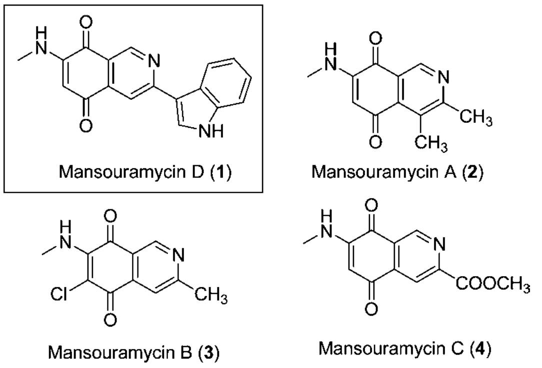
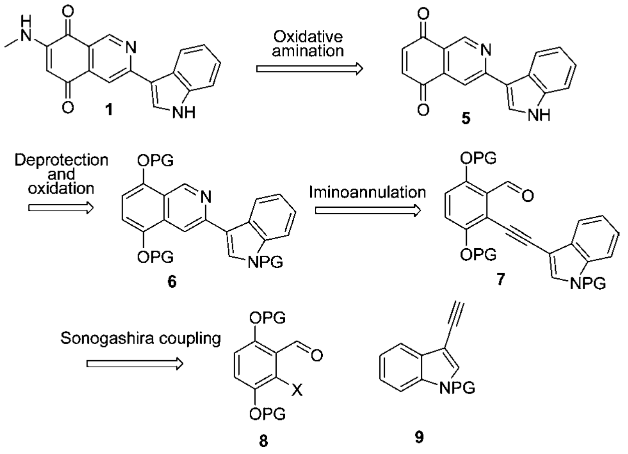

Mansouramycin D (**1**)
Mansouramycin A (**2**)
Mansouramycin B (**3**)
Mansouramycin C (**4**)

Figure 1. Structure of Mansouramycin A−D.

Considering the biological importance of Mansouramycin D and the lack of synthetic methods to date, we focused our interest on its synthesis. There was an unsuccessful attempt to synthesize Mansouramycin D (**1**) involving Pictet−Spengler cyclization.[3] Synthesis of isoquinoline heterocycles has received much attention due to the presence of the isoquinoline skeleton in numerous alkaloids.[5] Synthesis of isoquinoline systems by various methods is known. The classical methods are, mainly, the Bischler−Napieralski reaction,[6] Pomeranz−Fritsch reaction,[7] Pictet−Spengler reaction, and Pictet−Games reaction.[8] Numerous elegant protocols for isoquinoline synthesis have been reported to date.[9]

Herein, we report the first successful and concise total synthesis of Mansouramycin D (**1**) involving intramolecular iminoannulation as a key ring closure step, which resulted in an overall yield of 54.5% to 60.9%. The retrosynthetic disconnection for the synthesis of **1** is depicted in Scheme 1.

Scheme 1. Retrosynthetic Approach to Mansouramycin D (1)



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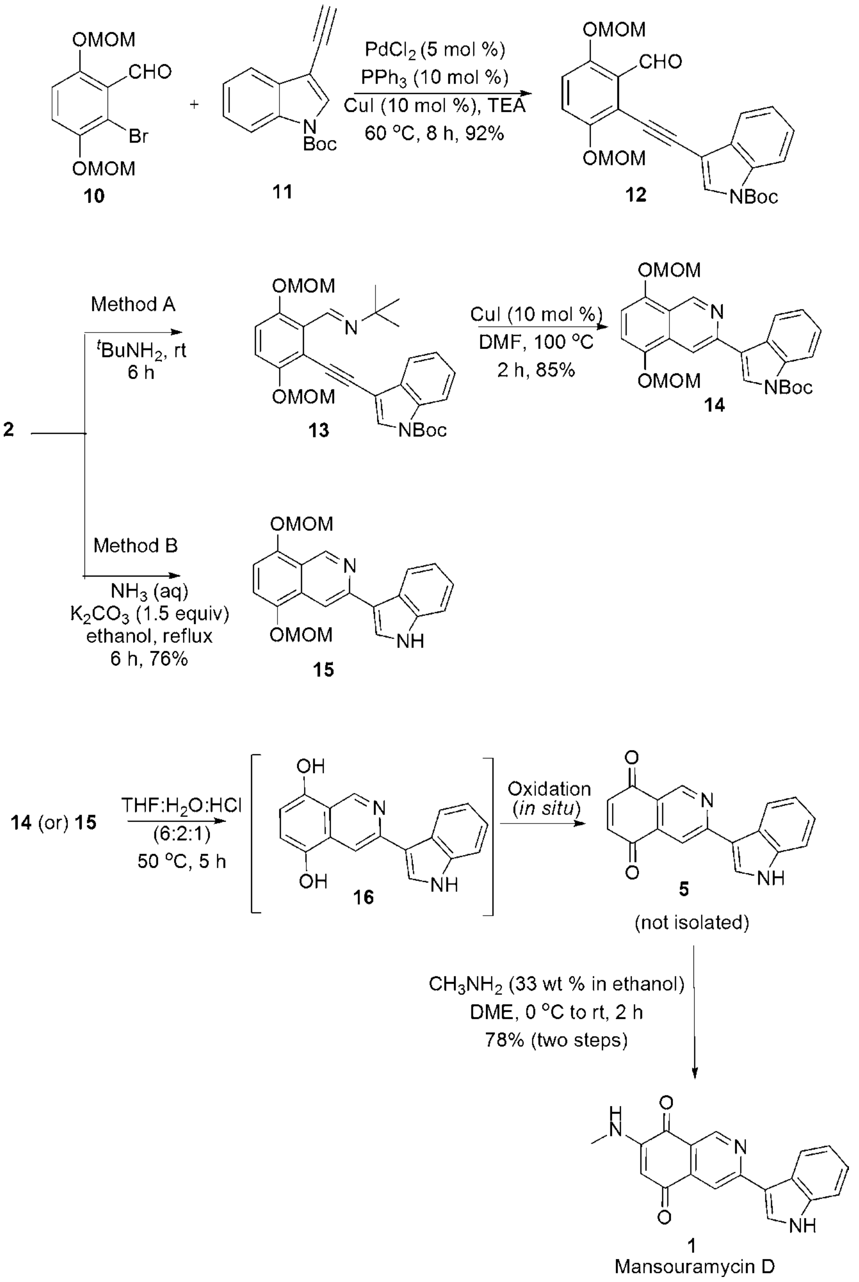
Scheme 2. Total Synthesis of Mansouramycin D (1)



The core structure of **1** contains an isoquinoline moiety substituted with the indole at the third position. Among the reported synthetic methods, iminoannulation (key step) followed by subsequent deprotection, oxidation, and oxidative amination would be the simplest and most concise route to the synthesis of this valuable marine alkaloid, Mansouramycin D (**1**).

At the outset, we focused on Sonogashira coupling of 2-bromo-3,6-dihydroxybenzaldehyde and Boc protected 3-ethynyl-1*H*-indole (**11**).[11] Unfortunately, the expected product was not formed. This might be due to the presence of free hydroxy groups in 2-bromo-3,6-dihydroxybenzaldehyde. Then, both hydroxyl groups of 2-bromo-3,6-dihydroxybenzaldehyde were protected by a MOM group using MOM chloride and diisopropylethylamine (DIPEA) as a base.[10] To our advantage after this modification, the Sonogashira reaction with MOM ether **10** of 2-bromo-3,6-dihydroxybenzaldehyde[10] and *N*-Boc protected 3-ethynyl-1*H*-indole (**11**)[11] using $PdCl_2$ (5 mol %), PPh_3 (10 mol %), CuI (10 mol %), and triethylamine as solvent proceeded smoothly at 60 °C and yielded 92% of coupled product **12** as a brown oil (Scheme 2). If the reaction was carried out at more than 60 °C, the yield of the product was decreased.

The isoquinoline ring closure was accomplished from product **12** via intramolecular iminoannulation. Iminoannulation can be performed in two ways: (i) Larock annulation with ^{t}BuNH$_2$ and (ii) with aqueous ammonia. In method A (Scheme 2), iminoalkyne **13** was synthesized by the treatment of alkynylaldehyde **12** at room temperature with excess *tert*-butylamine for 6 h. After evaporation of *tert*-butylamine, the obtained crude imine **13** was then dissolved in DMF and 10 mol % copper iodide was added as a catalyst. To our delight, the expected product **14** was achieved in 85% yield. In method

B, isoquinoline core **15** was synthesized via ammonia mediated ring closure of **12** with treatment of excess aqueous ammonia and 1.5 equiv of potassium carbonate. A new polar spot was observed by TLC. Surprisingly, during this reaction, the Boc group was removed and the product **15** was obtained in 76% yield.

At this juncture, having the core structure **14** and **15** in hand, we further performed functional group modification, consisting of removal of MOM or Boc using a THF, H_2O, and cond HCl (6:4:1) mixture heating at 50 °C. It is also to be noted that, for **15** having the MOM groups and in the case of **14** having both MOM and Boc groups, the groups are removed under the same conditions. To our surprise, the product **16** underwent oxidation *in situ* without the use of any oxidizing agents and with the complete conversion of the starting material (TLC). It furnished the oxidized product **5**, and we utilized the compound without further purification. Finally, the aminomethylation was accomplished using an ethanolic solution of methylamine (33 wt %) in 1,2-dimethoxyethane at 0 °C. It is noteworthy to mention that the reaction proceeded in a regioselective manner and gave only the final targeted molecule in 78% yield.

Thus, we have completed the first total synthesis of Mansouramycin D in three steps with an overall yield of 54.5% to 60.9%. Spectral data of **1** are fully consistent with those of Mansouramycin D isolated from the natural source.[1] So the structure of **1** is rigorously verified by the present total synthesis.

In summary, we accomplished a concise, first total synthesis of Mansouramycin D in an overall yield of 54.5% to 60.9%. The core isoquinoline ring has been constructed by iminoannulation in two different methods. It will likely find applications for other related alkaloids and provide an inroad to further biological surveys.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Details of experimental procedures, copies of ^1H, ^{13}C NMR and HRMS spectra for compounds **12**, **14**, **15**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rnsc@uohyd.ernet.in; naga_indole@yahoo.co.in.

Notes

The authors declare no competing financial interest.

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