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Total Synthesis of (+)-*ent*-Cyclizidine: Absolute Configurational Confirmation of Antibiotic M146791

Stephen Hanessian,* Udaykumar Soma, Stéphane Dorich, and Benoît Deschênes-Simard

Department of Chemistry, Université de Montréal, P.O. Box 6128, Station Centre-ville, Montreal, QC, H3C 3J7, Canada

stephen.hanessian@umontreal.ca

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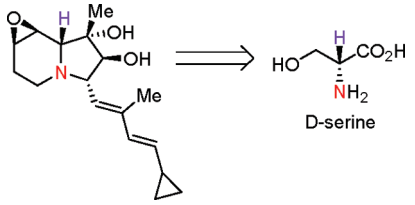
ABSTRACT



The first total synthesis of the enantiomer of the indolizidine alkaloid, cyclizidine, was accomplished from readily available D-serine as the starting chiron. The relevant key reactions involve the stereocontrolled construction of the indolizidine ring system with the required functionality and further elaboration to install the cyclopropyl dienyl side chain. With this total synthesis, the absolute configuration of the natural product based on a redetermination of its X-ray structure has been confirmed.

A soil sample originating from Stretford in the greater Manchester area, U.K., was found to contain an undescribed *Streptomyces* species (NCIB11649). Aerobic fermentation conditions in the laboratory produced a crystalline levorotatory substance that was given the name cyclizidine (antibiotic M146791)[1] (Figure 1). The structure and relative configuration of cyclizidine was unambiguously established in 1982 by X-ray crystallographic and NMR spectroscopic methods.[1] The biosynthesis of cyclizidine was subsequently studied by Leeper and co-workers in 1993.[2]

Analysis of the structure of cyclizidine reveals several unique features that are not shared by other physiologically active hydroxylated indolizidine alkaloids.[3,4] Although it has common features consisting of a C7/C8 epoxide and an extended olefinic appendage with indolizomycin[5,6] (Figure 1), cyclizidine appears to be especially unusual because of the monosubstituted cyclopropyl *trans*-dienic subunit at C3. To the best of our knowledge, cyclizidine appears to be the only representative member of its kind directly isolated from a *Streptomyces* species. Its closest congener, indolizomycin,

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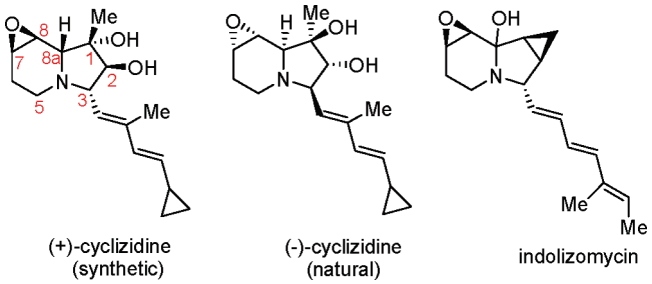

Figure 1. Structures of cyclizidine and indolizomycin.

was the product of a genetically engineered protoplast fusion technique from two microorganisms.[5]

Herein we describe the first total synthesis of (+)-cyclizidine, the enantiomer of the levorotatory natural product (Figure 1). This choice was initially guided by the three-dimensional ORTEP representation portrayed in the originally published report for the levorotatory product.[1]

Analysis of the structural features of cyclizidine reveals a number of challenges that are heightened by the presence of the C7/C8 epoxide, as part of six contiguous stereogenic centers extending to C3 of the indolizidine core structure. In addition, we were aware that the order of introducing the required functional groups in a regio- and stereocontrolled manner with control of absolute stereochemistry on a given core motif was critical. We visualized D-serine as a hidden chiron, which would accommodate the C8a stereochemistry and the position of the nitrogen atom (Figure 2). Key bond forming sequences would be executed starting with a *N*,*O*-protected D-serine ester which would be transformed to a methylketone and further elaborated to the tertiary alcohol *via* an acetylide anion addition. Systematic

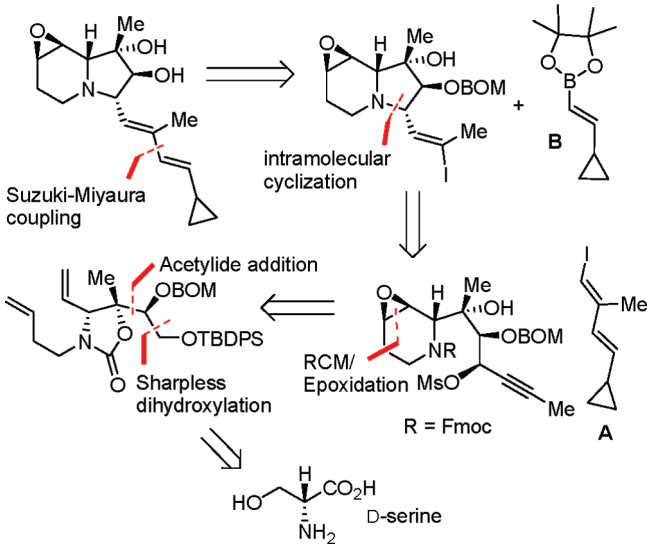

Figure 2. Key disconnections toward cyclizidine.

introduction of intended functionality and the dienic appendage would follow its course as shown in Figure 2. The feasibility of this plan was put to the test while being cognizant of the importance of ensuring orthogonal reactivity and/or compatibility in the choice of reagents and reactions.

The readily available *N*-Boc-D-serine **1** was converted in two steps to the *N*,*O*-protected Weinreb amide derivative[6] **2** in an overall yield of 81% (Scheme 1). Treatment with MeLi led to the methylketone **3**,[8] which was subjected to an acetylide extension according to Joullié and co-workers[9] with the corresponding Grignard reagent to give **4** as the major diastereomer in excellent yield (*dr* > 10:1). Hydroxyl-assisted partial reduction afforded the allylic alcohol **5**, which was dihydroxylated with AD-Mix-β[10] to give the triol **6** as the major diastereomer in 80% yield (*dr* > 5:1). Conversion to the *O*-TBDPS/BOM derivative, followed by separation of isomers, gave intermediate **7** in 78% yield. Treatment with NaHMDS afforded the cyclic carbamate **8** in 81% yield.

Cleavage of the acetal, oxidation of the primary alcohol under Dess−Martin conditions[11] and then treatment with methylenetriphenylphosphorane led to the terminal alkene **9** in an overall yield of 62%. *N*-Alkylation with 3-buten-1-ol triflate ester[12] gave **10** in 78% yield, which was converted to the primary alcohol by treating with TBAF and then subjected to ring closing metathesis with Grubbs' II catalyst[13] to afford **11** in excellent yield.

In order to elaborate the remaining steps, it was necessary to hydrolyze the cyclic carbamate and protect the resulting 3,4-unsaturated piperidine with an Fmoc group to give **12**. Oxone-induced epoxidation[14] gave **13** as the major diastereomer in 83% yield (*dr* > 20:1), which was oxidized to the aldehyde **14** under Dess−Martin conditions.

Our attempts to couple the aldehyde **14** with the entire cyclopropyl diene unit as the vinyl iodide **A** (Figure 2) under Nozaki−Hiyama−Kishi conditions,[15] or by halogen−metal exchange using ^{t}BuLi and then transmetalation with ^{i}PrMgCl[16] and ^{t}BuLi, were not successful, mainly because of the difficulty in the isolation and purification of the

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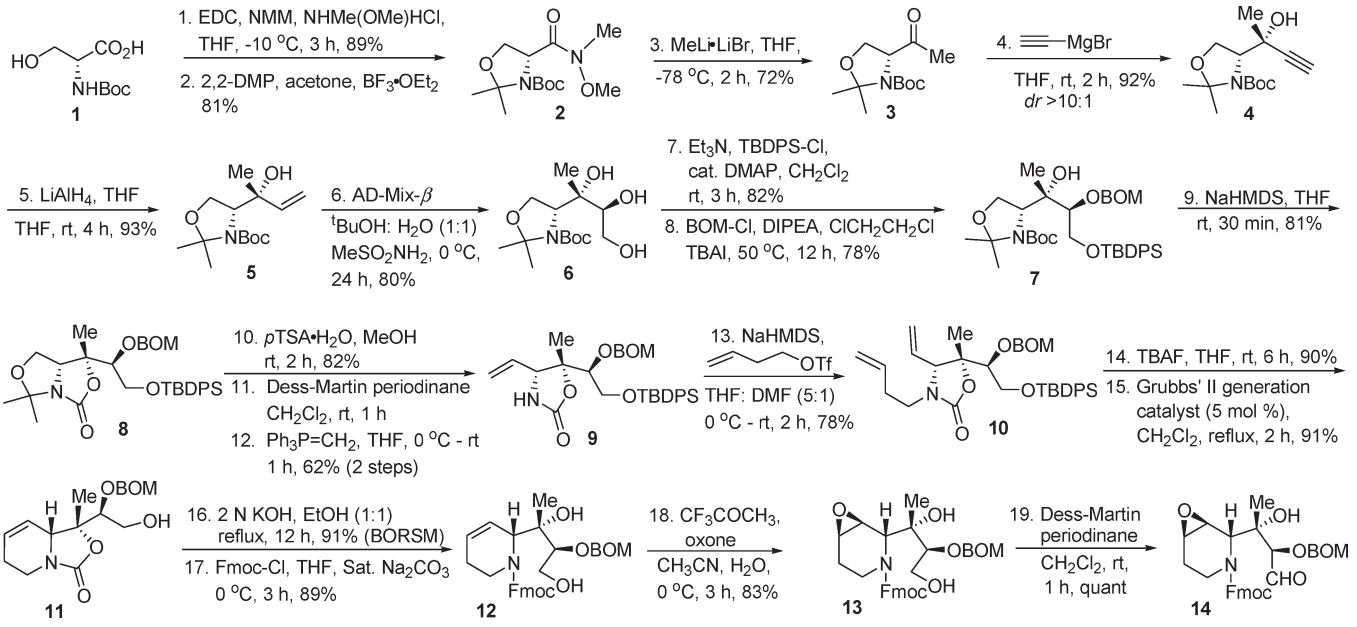
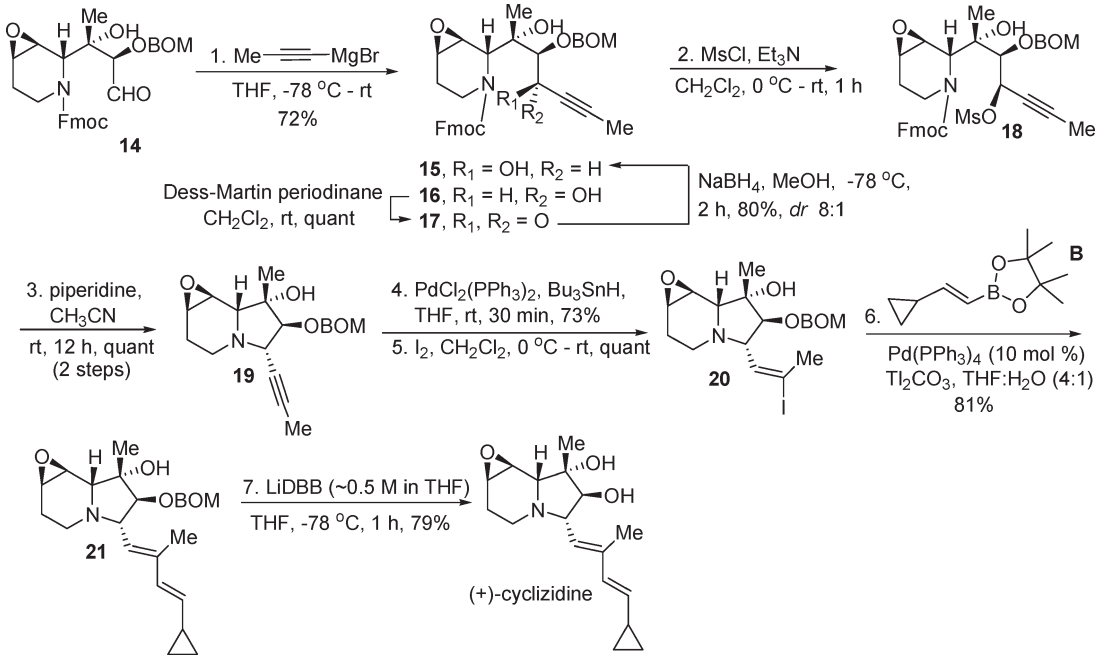
Scheme 1. Synthesis of Key Aldehyde **14** from D-Serine



volatile vinyl iodide. Consequently, we adopted a stepwise approach to construct the cyclopropyl diene unit. Thus, treatment of **14** with *n*-propynylmagnesium bromide led to a 3:2 mixture of alcohols in favor of the desired diastereomer **15** in 72% yield (Scheme 2). Better selectivity (*dr* 4:1) was observed with the corresponding Li-acetylide albeit in lower yield, along with the considerable cleavage of the Fmoc group. The easily separable minor isomer (**16**) from the Grignard reaction could be converted to the desired diastereomer (*dr* 8:1) by oxidation to the ketone **17** with Dess–Martin periodinane, followed by reduction with $NaBH_4$ at −78 °C in an overall yield of 80%.

Scheme 2. Completion of Total Synthesis



Treatment of the mesylate **18** with piperidine resulted in the cleavage of the Fmoc group and cyclization to give bicyclic compound **19** in excellent yield. A Pd-catalyzed hydrostannylation afforded the *E*-vinyl stannane[17] in 73% yield, which, upon treatment with iodine, led to the vinyl iodide **20** quantitatively. We were now poised to attach the vinyl cyclopropyl unit merely using a Suzuki−Miyaura reaction[18] with vinyl cyclopropyl boronate **B**. This led us to the *O*-BOM protected cyclizidine **21** in excellent yield.

Next, there remained the deprotection of the BOM ether under conditions that would not perturb the delicate balance of functional groups in **21**. To this end, a number of deprotection conditions were tried including, catechol bromo- and chloro-boranes,[19] trityl tetrafluoroborate,[20] Na/Li in liquid NH_3,[21] selective hydrogenolysis using different Pd catalysts, and catalytic transfer hydrogenation. These led to either epoxide opening (when Lewis acids were used) or partial or complete reduction of the olefins. Ultimately we overcame this problem by treating **21** with LiDBB[22] (Freeman's reagent) under carefully monitored conditions. Chromatographic purification of the crude solid product and crystallization from ether-hexanes afforded cyclizidine as colorless needles. We were fortunate to receive an original sample of natural cyclizidine from Professor Leeper which was recrystallized in the same manner. The synthetic sample was found to be identical in all respects with the natural product, except for the opposite sign of optical rotation. Lit. value: $[\alpha]_D$ −46.3° (*c* 2.0, MeOH);[1] observed for natural cyclizidine: $[\alpha]_D$ −29.5° (*c* 0.5, MeOH);[8] synthetic cyclizidine: $[\alpha]_D$ +36.1° (*c* 0.5, MeOH). Thus starting with D-serine and based on the original ORTEP representation had led to (+)-cyclizidine, the enantiomer of the natural product.

Having completed the total synthesis of *ent*-cyclizidine, we were intrigued that the X-ray crystal structure of the dextrorotatory synthetic product was identical to the published ORTEP representation in the original publication describing a levorotatory cyclizidine (Figure 3a). Since the synthetic route from D-serine is unambiguous and highly stereocontrolled, it appears that the original authors had arbitrarily chosen to represent the ORTEP structure of

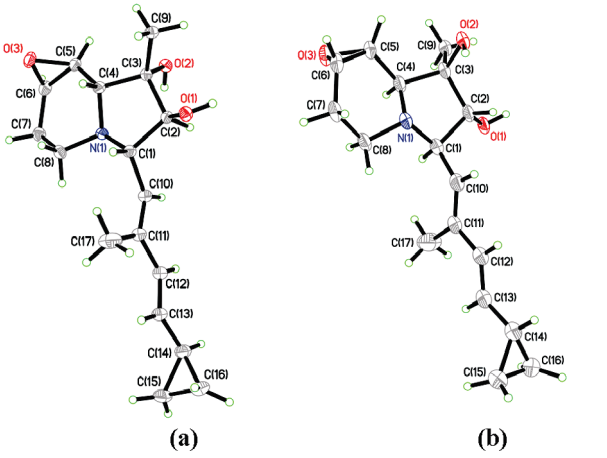


Figure 3. ORTEP diagrams (ellipsoids drawn at 30% probability level) of (a) synthetic (+)-cyclizidine and (b) natural (−)- cyclizidine (this work).

natural cyclizidine as the one that actually corresponds to the enantiomer. They qualified their choice by stating that it represented a relative configuration. Using today's refined crystallographic data acquisition methods,[8] we determined the crystal structure of the original sample of (−)-cyclizidine obtained from Professor Leeper, which corresponds to the product with the correct absolute configuration (Figure 3b). Thanks to the optical rotation measurement, we were able to determine that our synthetic product was in fact (+)-*ent*-cyclizidine. Our synthesis comprises 26 steps (longest linear sequence) starting from D-serine and afforded crystalline *ent*-cyclizidine in an overall yield of 2.7%.

With this knowledge, alternative routes to the levorotatory natural product other than the one starting with L-serine can also be envisaged. Studies toward this objective are in progress.[23]

Acknowledgment. We thank NSERC and FQRNT for financial assistance. We extend our special thanks to Professor Finian Leeper (University Chemical Laboratory, Cambridge, U.K.) for providing us with an authentic sample of cyclizidine of excellent purity in spite of its "age".

Supporting Information Available. Experimental procedures, copies of ^1H and ^{13}C spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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