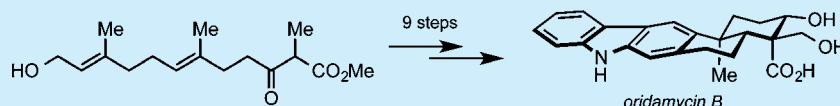


Total Synthesis of Oridamycins A and B

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S Supporting Information



ABSTRACT: The total synthesis of both oridamycin A and oridamycin B was accomplished starting from a common synthetic intermediate readily prepared from geranyl acetate. The sequence utilizes an oxidative radical cyclization to construct the *trans*-decalin ring system, setting three of four contiguous stereocenters in one operation. The carbazole nucleus was forged through a one-pot process entailing acid-promoted dehydration followed by 6π -electrocyclization/aromatization.

The xiamycin family of indolosesquiterpenes comprises bioactive compounds recently isolated from several strains of *Streptomyces*.¹ Among the family members are xiamycin A (3), its biosynthetic precursor indospene (4), and the homodimers dixiamycin A/B (5), isolated as a mixture of atropisomers about the N–N linkage (Figure 1). These

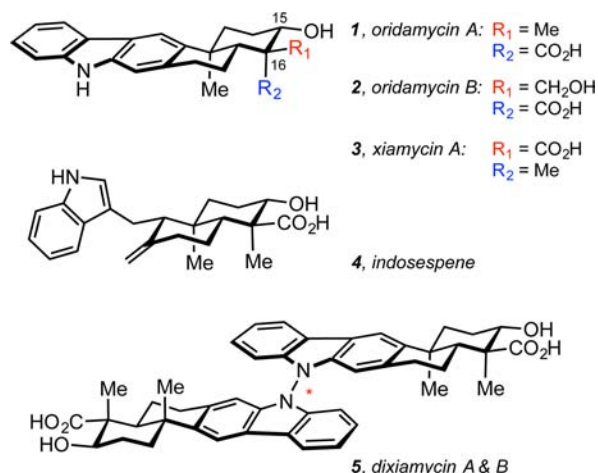


Figure 1. Selected members of the oridamycin and xiamycin families.

compounds display a range of interesting activities, including antiviral and antibacterial properties.¹ Notably, the N-linked dimers dixiamycin A/B (5) are potent agents against both methicillin resistant *Staphylococcus aureus* 134/94 and vancomycin resistant *Enterococcus faecalis* 1528 R10.^{1c} The closely related monomers oridamycin A (1) and oridamycin B (2) were isolated from *Streptomyces* sp. KS84 during screening for activity against *Saprolegnia* spp., a water mold that infects freshwater fish, including those raised in commercial aquaculture.² These compounds have elicited significant interest within the synthetic community; efficient total syntheses of xiamycin A (3) and dixiamycin B (5) have been reported by

Baran and co-workers, employing a cationic cyclization to construct the monomer and a novel electrochemical dimerization to generate the N–N linkage.³ Elegant syntheses of xiamycin A (3), indospene (4), sespenine, oridamycin A (1), oridamycin B (2), and dixiamycin C have been reported by the Li group, utilizing powerful radical cascades to construct the *trans*-decalin ring systems.⁴

Structurally, these pentacyclic molecules possess a carbazole nucleus fused to a *trans*-decalin ring system containing four contiguous stereocenters, including two quaternary centers. The major difference between the family members manifests at the C16 quaternary center; oridamycin A (1) and oridamycin B (2) each bear an axial carboxylic acid and an equatorial methyl/hydroxymethyl, while xiamycin A (3), indospene (4), and dixiamycin A/B (5) contain an axially disposed methyl and an equatorial acid (Figure 1). Biosynthetically, it is known that xiamycin A (3) arises from precursor 6 through a selective enzymatic oxidation mediated by *XiaM* (Figure 2A).⁵ It seems plausible that intermediate 6 is also the biosynthetic precursor of the oridamycins, likely proceeding through an analogous methyl oxidation. Drawing inspiration from nature, we anticipated utilizing a common synthetic intermediate to access congeners from both the oridamycin and xiamycin families (Figure 2B). Anticipating that biomimetic methyl oxidation of intermediate 6 would be difficult to replicate in the flask, we envisioned imparting the requisite oxidation pattern on a linear precursor that would be cyclized under two distinct sets of conditions to yield both of the desired C16 epimers. Employing an oxidative radical cyclization cascade under standard conditions would yield the stereochemistry associated with the oridamycins, proceeding through transition state 10 to produce intermediate 8 (Figure 2C).⁶ To access the C16 stereoisomer relevant to the xiamycin family, we envisioned that introduction of a Lewis acid could invert the selectivity via

Received: June 3, 2015

Published: June 12, 2015

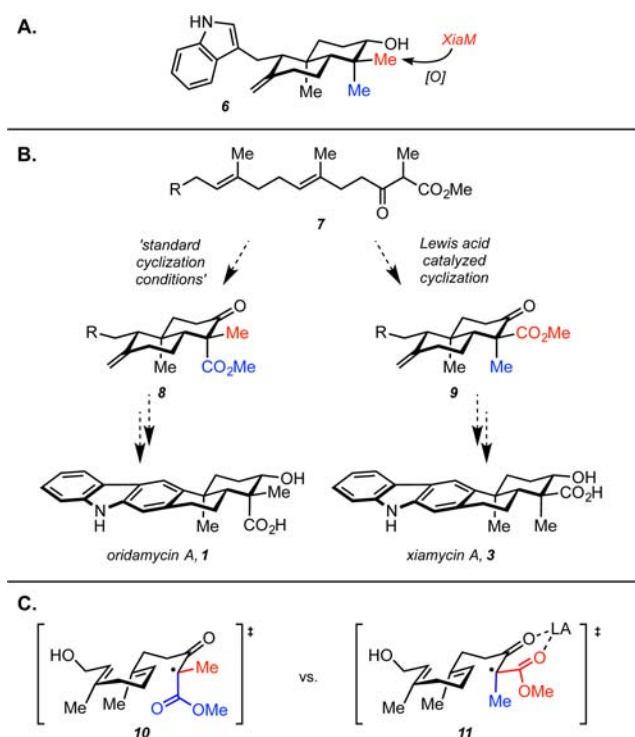
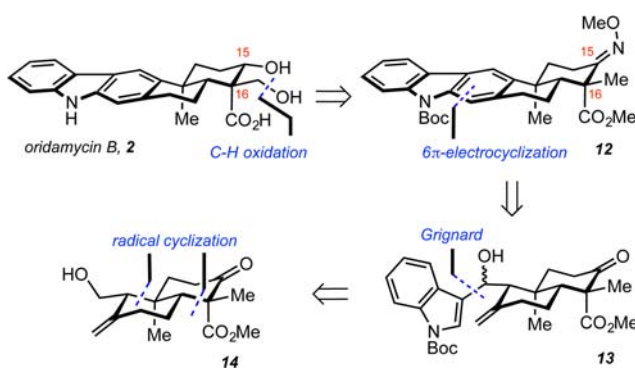


Figure 2. (A) Biosynthetic precursor for the xiamycin family, and proposed precursor for the oridamycin family. (B) General strategy to access both the xiamycin and oridamycin families from a common linear precursor. (C) Proposed radical transition states for the cyclization reactions.

chelation of the β -keto ester, producing transition state **11** en route to intermediate **9**.⁷

We reasoned that it would be expeditious to initiate our synthetic efforts with the oridamycins, allowing for validation of late-stage transformations before attempting to invert the selectivity of the radical cyclization. Retrosynthetically, we anticipated that the C16 hydroxymethyl of oridamycin B (**2**) could arise from an oxime-directed, palladium-catalyzed C–H oxidation of substrate **12** (Scheme 1).⁸ The C15 alcohol would

Scheme 1. Retrosynthesis of Oridamycin B



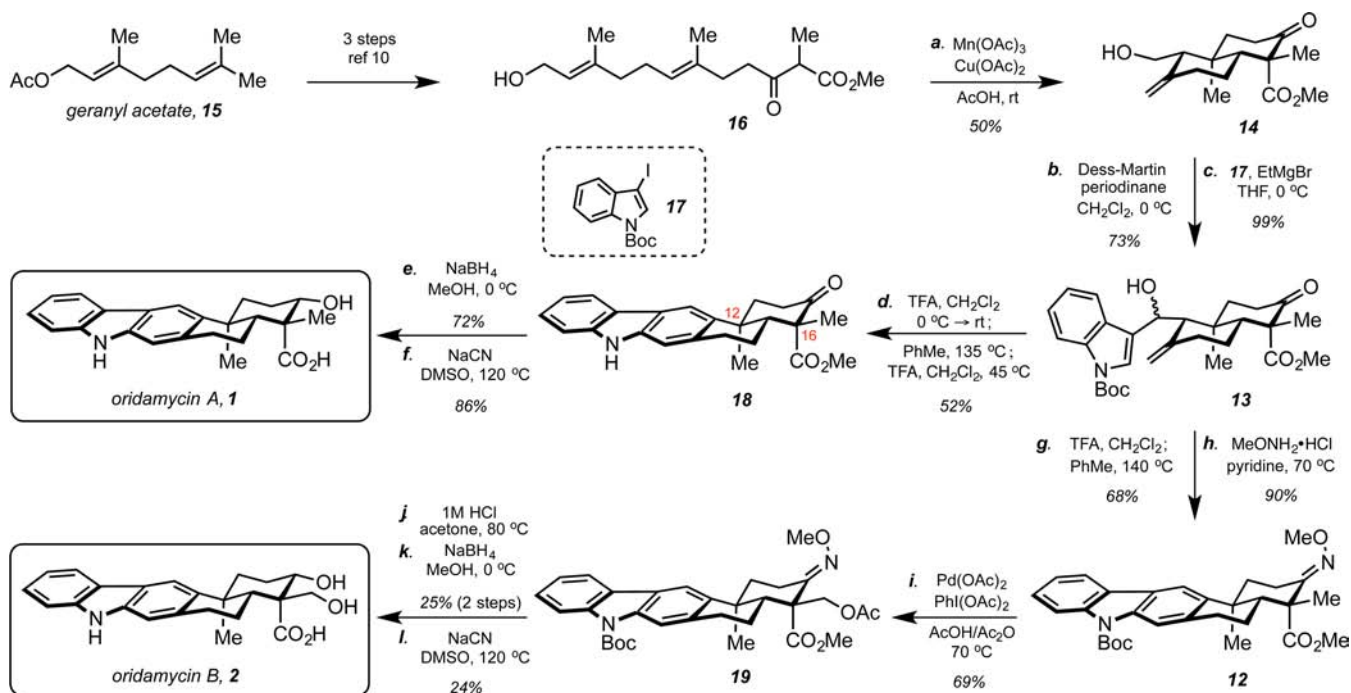
arise via axial hydride delivery onto a suitable ketone precursor. The carbazole nucleus could be forged through 6π -electrocyclization/aromatization of an indole moiety appended to a diene system, which would itself arise from dehydration of a homoallylic alcohol such as **13**.⁹ Grignard addition of a Boc-protected indole onto a suitable aldehyde would provide compound **13**, containing all the requisite carbon atoms of the

natural products. Finally, the *trans*-decalin ring system of **14** would be forged through an oxidative radical cyclization of a linear precursor readily derived from geranyl acetate.¹⁰ Oridamycin A (**1**) would be synthesized in an analogous fashion without requiring the C–H oxidation sequence.

In the forward direction, known compound **16** was readily obtained from geranyl acetate in multigram quantities in three operations (Scheme 2).¹⁰ Oxidative radical cyclization proceeded smoothly under the standard conditions to give alcohol **14** as a single diastereomer.¹¹ Subsequent oxidation with Dess–Martin periodinane afforded the corresponding aldehyde, which was coupled with the Grignard reagent generated from **17** to produce **13** as an inconsequential mixture of diastereomers.^{9,12} Next, when considering the dehydration of intermediate **13**, we hypothesized that the alcohol would be more prone to elimination if the Boc group were removed, allowing for the electron-rich indole to more readily participate in the process. To that end, substrate **13** was treated with TFA, and to our surprise, the secondary alcohol was cleanly eliminated to form a triene intermediate with the Boc group still intact. Thus, this interesting result became the foundation of a one-pot process to forge the free carbazole directly from intermediate **13**. In the event, treatment of a solution of **13** in CH_2Cl_2 with TFA formed the desired triene, which was not isolated but concentrated to remove solvent and acid. Next, this material was dissolved in toluene and heated to $135\text{ }^\circ\text{C}$ to induce a thermal 6π -electrocyclization/aromatization sequence under aerobic conditions.⁹ Upon completion, TFA was added at $45\text{ }^\circ\text{C}$ to remove the Boc group, yielding free carbazole **18**. A stereoselective reduction using NaBH_4 proceeded uneventfully, yielding oridamycin A methyl ester (*d.r.* > 20:1). The final remaining operation entailed conversion of the C16 axial methyl ester into the free acid. Initial attempts at saponification using various hydroxide sources were unproductive, likely due to the 1,3-diaxial relationship between the C12 methyl and the C16 ester—reminiscent of podocarpic acid¹³—which may impede formation of the requisite tetrahedral intermediate.¹⁴ Accordingly, we utilized a nucleophilic cleavage protocol, allowing for successful dealkylation of the ester. Thus, upon treatment with NaCN in DMSO at elevated temperature, oridamycin A (**1**) was produced in 86% yield, cleanly affording characterization quality material.¹⁵

To access oridamycin B (**2**), the route to oridamycin A (**1**) was diverted from intermediate **13**. The same sequence of dehydration and electrocyclization was employed, but the Boc group was preserved to produce the protected carbazole. The ketone was smoothly converted into *O*-methyloxime derivative **12** as a prerequisite for the selective, late-stage C–H oxidation. Upon treatment with $\text{PhI}(\text{OAc})_2$ and catalytic $\text{Pd}(\text{OAc})_2$ at elevated temperature, compound **19** was cleanly produced in 69% yield. Next, global deprotection using a 3:1 mixture of aq 1 M HCl/acetone at $80\text{ }^\circ\text{C}$ cleaved the acetate, removed the Boc group, and hydrolyzed the *O*-methyloxime. A variety of conditions were screened for this transformation, most of which produced a significant amount of a presumed retro-Aldol product, which was largely suppressed through the use of acetone as a cosolvent. However, the elevated temperature required to cleave the *O*-methyloxime appeared to cause a significant amount of nonspecific decomposition, resulting in diminished recovery. The product of the global deprotection was unstable to silica, requiring reduction of the crude material to produce oridamycin B methyl ester. Finally, treatment of this compound with NaCN produced oridamycin B (**2**). Interest-

Scheme 2. Synthesis of Oridamycin A and B



ingly, it was found that the ^1H NMR spectrum of **2** was pH dependent (see Supporting Information).

With the successful synthesis of the oridamycins, the next phase of our program is aimed at accessing epimeric intermediate **9** via Lewis acid chelation of the radical intermediate during cyclization (see Figure 2).⁷ Realization of this strategy could provide access to the xiamycin family from the same linear precursor **7** used to generate the oridamycins. Furthermore, we are optimistic that this transformation could be rendered asymmetric through the use of a suitable chiral ligand.¹⁶ Efforts are ongoing in our laboratory to validate these assertions.

In conclusion, both oridamycin A and B were synthesized from known compound **16** in six and nine steps, respectively. The synthesis was diverted from common intermediate **13** harboring all of the carbon atoms contained within each natural product. The successful construction of the oridamycins lays the foundation for a unified synthetic strategy for this entire class of indolosesquiterpenes.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data (including spectra for new compounds). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01629.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Prof. Samuel J. Danishefsky (MSKCC) is foremost acknowledged for his intellectual mentorship. This material is based upon work supported by the National Science Foundation Graduate Research Fellowship under Grant No. 2014157713. The MSKCC core facility is also acknowledged for mass spectrometric assistance and for providing the necessary instrumentation.

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