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Towards a Unified Total Synthesis of the Xiamycin and Oridamycin Families of Indolosesquiterpenes

Adam H. Trotta

Tri-Institutional PhD Program in Chemical Biology, Laboratory for Bioorganic Chemistry, Chemical Biology Program, Sloan Kettering Institute for Cancer Research, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, New York 10065, United States

Abstract

A unified synthetic strategy towards the oridamycin and xiamycin families of natural products was designed, aiming to access several natural products from a common synthetic intermediate readily prepared from geranyl acetate. Part of this strategy was successfully realized, culminating in the synthesis of oridamycin A and oridamycin B. Key steps include a Mn(III)-mediated oxidative radical cyclization to construct the *trans*-decalin ring, and a 6 π -electrocyclization/aromatization sequence to produce the 2,3-fused carbazole. Oridamycin B was accessed through a late-stage, C-H oxidation that converted the C16 methyl to a hydroxymethyl. A variety of strategies were explored to form a chelated radical intermediate en route to xiamycin A, including enolate SET oxidation, oxo-vanadium oxidation, and atom-transfer cyclization. Unfortunately, none of these strategies provided the desired C16-epimeric *trans*-decalin. Exploratory studies on photoredox-catalyzed radical cyclizations yielded interesting results, including the formation of a bicyclic lactone arising from oxidative termination of the photoredox-catalyzed radical cyclization, and a double 6-*endo* cyclization with catalyst loadings as low as 0.01 mol%.

Graphical Abstract

INTRODUCTION

The oridamycins (**1** & **2**) are pentacyclic natural products derived from a soil-dwelling actinomycete, *Streptomyces* sp. strain KS84 (Figure 1).¹ They are the first

ahtrotta@gmail.com

Supporting Information. ¹H and ¹³C NMR spectra of all new compounds, and HSQC and NOE for **54**.

indolosesquiterpenes to be isolated from a prokaryote, as previous indolosesquiterpenes were extracted from plants or fungi. The isolation and structural elucidation of xiamycin A (**3**), extracted from an endophyte (*Streptomyces* sp. GT20021503) found on the stems of mangrove trees, was reported several months later.² Additionally, the biosynthetic precursor of xiamycin A, indospene (**4**), has been discovered,³ along with several other monomers,^{4,5} most of which are oxidized variants of xiamycin A.

During heterologous expression of the *xia* gene cluster in *Streptomyces albus*, the *N-N* linked, atropdiastereomeric dimers dixiamycin A/B (**5a/5b**) were isolated.⁶ Several C-N linked dimers have also been reported,⁷ along with sulfone-bridged dimers.⁸ All of the dimeric family members are homodimers of xiamycin A (**3**).

Oridamycin A (**1**) has shown modest biological activity against *Saprolegnia parasitica*, a common protozoan that infects freshwater fishes.¹ Xiamycin A (**3**) and the dimers have shown more promising activity. Specifically, these compounds have demonstrated modest antiviral activity and potent antibacterial activity, including activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE),⁷ while exhibiting minimal cytotoxicity towards mammalian cells.

Structurally, these pentacyclic compounds are composed of a carbazole fused to a *trans*-decalin ring containing four contiguous stereocenters, including two quaternary carbons. Interestingly, oridamycin A (**1**) and xiamycin A (**3**) are epimeric at C16, where oridamycin A bears an equatorial methyl substituent and an axial carboxylic acid, while xiamycin A harbors an axially disposed methyl group and an equatorial carboxylic acid. Notably, the axial substituent on both molecules is engaged in a sterically demanding 1,3-diaxial interaction with the C12 methyl.

Perhaps not surprisingly, the promising biological activity and interesting molecular architecture of these compounds have attracted the interest of the synthetic community. The first synthesis was reported by Baran and coworkers, who elegantly constructed xiamycin A through a cationic polyolefin cyclization, subsequently accessing dixiamycin B through an electrochemical dimerization of xiamycin A.⁹ Next, Li et al. disclosed an impressive biomimetic synthesis of sespenine, employing a reductive, epoxide-opening radical cyclization and a biomimetic skeletal rearrangement to construct the natural product.¹⁰ Li and coworkers subsequently published a remarkable report detailing the synthesis of oridamycin A, oridamycin B, xiamycin A, indospene, and dixiamycin C.¹¹ Their efforts were virtually concurrent with my own work towards the oridamycins, which was published as a communication shortly after their report.¹² Interestingly, their strategy for the oridamycins closely resembles my own, sharing several key transformations. More recently, the Krische group reported a concise and efficient synthesis of oridamycin A using their direct alcohol C-H functionalization transfer hydrogenation methodology.¹³

RESULTS AND DISCUSSION

The close structural relationship between the oridamycins and the xiamycins prompted the development of a unified synthetic strategy designed to produce oridamycin A (**1**),

oridamycin B (**2**), xiamycin A (**3**), indosespene (**4**), and the dimers (**5a/5b**) from a common synthetic precursor (Scheme 1). Since *trans*-decalin rings are common structural motifs in terpenoid natural products, there are myriad methods for their construction (e.g., Robinson annulation,^{14,15} Diels–Alder cycloaddition,^{16,17} polyolefin cyclization^{18,19}). A biomimetic strategy employing a polyolefin cyclization would be a concise entry to the family, allowing for the formation of multiple rings and stereocenters in a single operation. Specifically, it was envisioned that an oxidative radical cyclization of β -keto ester **6** would generate *trans*-decalin **8** with an oxidation state closely resembling that of the natural products.^{20–25} In fact, the Mn(III)-mediated oxidative free-radical cyclization developed by Snider has been shown to produce *trans*-decalin rings resembling those of the oridamycins, with an axial carboxy substituent and an equatorial methyl group.²¹ The observed stereochemistry of **8** arises from a conformation with the ester group oriented anti to the ketone, an orientation that minimizes the net dipole of the molecule. Furthermore, the smaller steric penalty of the C16 ester relative to the C16 methyl could also contribute, inducing a conformation that minimizes interaction with the proximal C12 methyl by placing the ester in the axial position.

To access xiamycin A from the same β -keto ester **6**, a chelated radical cyclization was envisioned. It was hypothesized that a Lewis acid could tether the carbonyls to generate chelated radical **9** en route to *trans*-decalin **10** which resembles xiamycin A (**3**). Based on prior literature, it seemed likely that the free-radical cyclization towards the oridamycins would be more straightforward than the chelated radical cyclization towards xiamycin A. Accordingly, the initial focus was on the oridamycins to validate the late stage transformations before attempting to develop the chelated cyclization.

Retrosynthetically, the C16 acid could arise from the saponification of an ester, and the C15 alcohol could be derived from the reduction of a suitable ketone (Scheme 2). The 2,3-fused carbazole of **11** could be generated through a biomimetic process, entailing oxidation at indole C3, aza-Prins cyclization, dehydration, and aromatization.²⁶ Bicycle **12** could be produced through alkylation with indole, while bicyclic alcohol **8a** could arise from the key oxidative radical cyclization of a linear substrate readily derived from geranyl acetate and methyl acetoacetate.

Synthesis of Oridamycin A

In the forward direction, known linear alcohol **6a**^{27–29} was readily synthesized from geranyl acetate, and subsequently treated with Mn(OAc)₃ and Cu(OAc)₂ in AcOH to produce bicyclic alcohol **8a** in 50% yield as a single diastereomer and as a single olefin isomer (Scheme 3A). This key step converted a simple, linear compound into a functionalized *trans*-decalin ring bearing four contiguous stereocenters, closely resembling the *trans*-decalin found in the oridamycins. Next, indole attachment was required. After several unsuccessful attempts at converting bicyclic alcohol **8a** into the corresponding bromide, indole attachment was eventually achieved through Grignard addition of indole **14** into the bicyclic aldehyde to yield secondary alcohol **13** as an inconsequential mixture of diastereomers. To access biomimetic cyclization precursor **12** (Scheme 2), a deoxygenation of secondary alcohol **13** was necessary (Scheme 3B). It was envisioned that the *tert*-butyl carbamate could be removed with TFA, increasing the electron density at the indole nitrogen, and facilitating

acid-induced dehydration to form extended iminium **16**, which could be trapped with a silane reductant to form desired compound **12a**. Surprisingly, addition of TFA cleanly afforded triene **17** without a trace of the deprotected material (Scheme 3C).

In light of the unexpected dehydration, a new strategy was adopted. It was anticipated that triene **17** could be induced to undergo a 6π -electrocyclization/aromatization sequence to construct the carbazole.³⁰ Pleasingly, heating triene **17** in PhMe successfully provided the *tert*-butyl carbamate protected carbazole in 66% yield. Subsequent addition of TFA at 45 °C cleaved the *tert*-butyl carbamate to furnish carbazole **11a**. The three preceding operations seemed primed for adaptation to a telescoped protocol (Scheme 3D). Initiation of the one-pot process involved addition of TFA to secondary alcohol **13** in CH₂Cl₂ at room temperature. Upon completion, the solution was concentrated *en vacuo*, removing solvent and acid. The resulting residue was dissolved in PhMe, transferred to a pressure tube, and heated to 135 °C. After completion, the solution was cooled to 45 °C and TFA was added to yield carbazole **11a** in 52% yield from secondary alcohol **13**. Ultimately, the serendipitous dehydration increased the efficiency of the synthesis, improving upon the original proposal.

Now, only two operations separate carbazole **11a** from oridamycin A (**1**): reduction and saponification. Treatment of carbazole **11a** with NaBH₄ successfully delivered hydride from the less hindered face to selectively produce equatorial alcohol **18** (Scheme 4).

Saponification was less straightforward. Initial efforts employing various hydroxide salts were unsuccessful, even at elevated temperature. It seemed likely that formation of the requisite tetrahedral intermediate en route to the desired acid was disfavored due to the sterically demanding relationship between the C16 ester and the C12 methyl (Scheme 4, **19**).

³¹ To avoid this interaction an alternative strategy was employed, in which a nucleophile engages the ester alkyl substituent in an S_N2 fashion to generate the free acid (Scheme 4, **20**). This Krapcho-inspired dealkylation protocol allows the carbonyl to remain planar, precluding the formation of a sterically encumbered tetrahedral intermediate. Indeed, treatment of equatorial alcohol **18** with NaCN in DMSO at 120 °C successfully provided pure oridamycin A in 86% yield. Overall, oridamycin A was accessed in six steps from known linear alcohol **6a** (nine steps from geranyl acetate) in 4.7% overall yield.

Synthesis of Oridamycin B

To access oridamycin B (**2**), the equatorial C16 methyl of oridamycin A (**1**) must be oxidized to a hydroxymethyl. Initially, it was thought that the C15 secondary alcohol could direct an Ir-catalyzed C-H silylation/Tamao oxidation sequence developed by the Hartwig group.³² When these conditions were employed, trace amounts of the desired silacycle were detected by UPLC-MS, but the reaction was procedurally demanding and complicated by side products, inspiring investigation of other avenues.

As an alternative, an oxime-directed, Pd(II)-catalyzed C-H oxidation was explored. Initial attempts were focused on a method developed by Sanford in which an *in situ* generated *O*-acetyloxime serves as the directing group for palladium (Scheme 5A).³³ The *O*-acetyloxime was used because it can be cleaved under milder conditions than commonly employed *O*-alkyloximes. When oxime **21** was treated with PhI(OAc)₂ and catalytic Pd(OAc)₂, trace

oxidized *O*-acetyloxime **22** could be detected by UPLC-MS. Unfortunately, this compound could not be readily isolated, as the reaction was complicated by various side products arising from partial carbamate deprotection, incomplete oxime acetylation, and incomplete C-H oxidation. To minimize side products, a more robust protecting group and oxime were used. Specifically, an *O*-methyloxime was employed along with a tosyl protecting group. The tosyl protecting group was viewed as a temporary strategy, as it would introduce several unnecessary manipulations into the sequence. Successful C-H oxidation conditions discovered on the tosyl protected series would be subsequently applied to the *tert*-butyl carbamate protected series, as the *tert*-butyl carbamate is already present on secondary alcohol **13**. Gratifyingly, subjection of tosyl protected *O*-methyloxime **23** to the standard C-H oxidation conditions produced oxidized *O*-methyloxime **24** in 50% yield (Scheme 5B).³⁴

With successful C-H oxidation conditions in hand, attention was turned back to the carbamate protected series. Although the standard C-H oxidation conditions partially cleaved the carbamate protecting group, it was found that lowering the temperature and increasing the reaction time provided acetoxymethyl **27** in good yield from *O*-methyloxime **25** (Scheme 5C). Only three steps remained to access oridamycin B (**2**): deprotection, reduction, and ester dealkylation. For deprotection, the *O*-methyloxime, acetate, and carbamate could all be cleaved with aqueous acid. Mild conditions were competent to cleave the acetate and carbamate, but the *O*-methyloxime was recalcitrant. Dozens of conditions were screened, and it was ultimately found that the desired diol **28** could be obtained after treating acetoxymethyl **27** with a mixture of aqueous 1M HCl and acetone at 80 °C, directly followed by treatment of the crude material with NaBH₄. Finally, the nucleophilic ester cleavage protocol used for oridamycin A was applied to diol **28** to yield pure oridamycin B (**2**) after HPLC purification. Overall, oridamycin B (**2**) was accessed in nine steps from known linear alcohol **6a** (twelve steps from geranyl acetate) in 0.37% overall yield. The late-stage deprotection and ester dealkylation steps are largely responsible for the significantly reduced overall yield relative to oridamycin A.

Initial Experiments Towards Xiamycin A

With the successful synthesis of oridamycin A and oridamycin B, the next challenge was to develop conditions to produce chelated radical intermediate **9** en route to xiamycin A (Scheme 6). One of the simplest strategies would be to add a Lewis acid to the Mn(III)-mediated oxidative radical cyclization (Scheme 6A). In fact, this has been demonstrated by the Yang group, who employed stoichiometric Yb(OTf)₃ to produce a *trans*-decalin containing two axially disposed methyl groups, albeit in modest yield (18%).³⁵ It was hoped that this could be a starting point towards xiamycin A. Unfortunately, applying their optimized conditions to linear alcohol **6a** was unsuccessful. Several variations to the reported conditions were made, with different Lewis acids (MgCl₂, Mg(ClO₄)₂), additives (Cu(OAc)₂), solvents, and temperatures, but none of these provided the desired *trans*-decalin (not shown). The Yang group reported that TFE was the optimal solvent for their Lewis acid chelated cyclization, but using TFE in the present system was prohibitive. In fact, the same conditions that successfully furnished bicycle **8a** from linear alcohol **6a**, except with TFE replacing AcOH, caused complete decomposition of the starting material.

When considering the mechanism of the chelated Mn(III)-mediated oxidative cyclization, it seems unlikely that a free radical intermediate would exist long enough to allow for the Lewis acid to intercept it prior to cyclization, implying that the Lewis acid must interact with the substrate prior to oxidation, and throughout the oxidation process, in order to produce the desired chelated radical intermediate. Generating a substrate bound to two different transition metal complexes while producing a highly reactive radical intermediate seemed like a difficult construct to engineer and optimize, so this avenue was abandoned in favor of a simpler solution.

Enolate Oxidation Towards Xiamycin A

An alternate strategy would be to perform a single electron transfer (SET) oxidation of the enolate **31**, derived from linear alcohol **6a**, to generate a chelated radical cation (Scheme 6B). If the enolate counterion were an effective Lewis acid, then the resultant radical cation **32** could cyclize to produce the desired stereochemistry. Prior work by Schmittel has demonstrated that the radical cation formed from SET oxidation of titanium enolates dissociates relatively slowly ($k_{\text{Ti-O}} = \sim 3 \times 10^{-2} \text{ s}^{-1}$ in CH_2Cl_2), allowing for the possibility of a chelated cyclization prior to radical cation decomposition.³⁶ To avoid disruption of the Lewis acid-substrate interaction, outer sphere oxidants were used (i.e. $[\text{Cp}_2\text{Fe}]\text{PF}_6$,^{37–39} $\text{Fe}(\text{phen})_3(\text{PF}_6)_2$,^{40–43} $\text{Cu}(\text{OTf})_2$,⁴⁴ CAN).⁴⁵ Unfortunately, SET oxidation experiments with titanium enolates derived from Cp_2TiCl_2 , TiCl_4 ,^{46,47} or $\text{Ti}(\text{O-}i\text{-Pr})_4$ did not yield any of the desired *trans*-decalin (not shown). Long reaction times and high temperatures were required to consume substrate when titanium was used as the counterion, indicating that the highly delocalized radical was perhaps too stable to be productively intercepted by the alkene. Exploratory studies on lithium enolates (derived from LDA, LiHMDS, or *n*-BuLi), zinc enolates (derived from $\text{Zn}(\text{OTf})_2$), magnesium enolates (derived from $\text{EtMgBr}/i\text{-Pr}_2\text{NH}$), and ytterbium enolates (derived from $\text{Yb}(\text{OTf})_3$) also failed to produce the desired *trans*-decalin (not shown). ^1H NMR analysis of the crude material resulting from oxidation of lithium enolates occasionally revealed small amounts of bicycle **8a** (or its protected derivative), indicating that the radical was forming, but that the radical cation was decomposing prior to cyclization. However, most of the conditions outlined above resulted in decomposition of the substrate, producing a complex mixture of products that resisted analysis.

Alternatively, an inner sphere oxidant could be used that would also function as a Lewis acid to produce the desired chelated radical **9** (Scheme 6C). Following oxidation of **33**, the oxidant would maintain an interaction with the substrate to produce chelated radical **9** en route to *trans*-decalin **10**. Promisingly, there are reports from the Hirao group of oxo-vanadium complexes that simultaneously act as both Lewis acids and oxidants.^{48,49} Importantly, they have demonstrated that these complexes can oxidize β -keto esters.^{50,51} For exploratory studies, the oxo-vanadium complex described by Livinghouse was employed ($\text{V}(\text{O})\text{Cl}_2(\text{OTFE})$), which has been shown to be more reactive and selective than the alkoxy variants.⁵² Using conditions based on Hirao's work, the substrate decomposed (Entry 1, Table 1).⁵⁰ It was hypothesized that the HCl generated during the reaction was deleterious, therefore 2,4,6-tri-*tert*-butylpyridine was added to buffer the reaction (Entry 2). Unfortunately, this only returned starting material. It seems possible that adventitious HCl activates the oxo-vanadium complex through interaction with the $\text{V}=\text{O}$ moiety, as evidenced

by previous reports detailing improved reactivity of oxo- vanadium complexes when AgOTf or TMSOTf are added.⁵³ Indeed, upon addition of TMSOTf the starting material was consumed (Entry 3). There were intriguing signals in the alkene region of the crude ¹H NMR spectrum, but the resultant mixture of compounds proved inseparable. Other Lewis acids were screened in an attempt to activate the oxo-vanadium complex (Zn(OTf)₂, TMSCl, AgOTf, CuCl₂, Cu(OAc)₂), but no conditions could be found that provided the desired *trans*-decalin (not shown). Interestingly, addition of Cu(OTf)₂ to the reaction provided the α -chlorinated product **36** (Entry 4). Largely due to the difficulty in preparing and handling the oxo-vanadium complexes, this avenue was abandoned.

Atom-Transfer Cyclization Towards Xiamycin A

After the failure of enolate oxidations to provide the desired chelated radical intermediate, atom-transfer cyclization conditions were explored (Scheme 6D). Previous studies have suggested that chelated atom-transfer cyclizations would be a productive avenue, with the Yang group reporting conditions for bromine and selenium transfer under the influence of Lewis acids.^{54,55} Unfortunately, when the reported conditions were employed on α -seleno β -keto ester **37** there was no reaction (Scheme 7). Other radical initiators, substrates, and Lewis acids were examined, but these also proved fruitless. Inspired by the work of Guindon and coworkers, atom-transfer experiments with α -bromo β -hydroxy ester **45** were conducted (Scheme 8).^{56,57} They were able to generate aluminum chelated radical intermediates with AlMe₃ and trapped them with Bu₃SnH or allylTMS/allylSnBu₃ to generate reduced or allylated products with excellent diastereoselectivity. These conditions were employed, without addition of the reductant/nucleophile, on α -bromo β -hydroxy ester **45** to generate the aluminum chelated intermediate. Surprisingly, these experiments returned starting material. When the more electrophilic EtAlCl₂ was used, the substrate was consumed, but an inseparable mixture of products was generated.⁵⁸

Before further investigation of atom-transfer cyclization conditions, a model system was developed. There are many possible products from atom-transfer cyclizations (i.e. monocyclic and bicyclic products, bromide diastereomers, olefin isomers) that can complicate purification and analysis, so a model system was devised that would simplify the potential product mixture. Allylic acetate **48** was synthesized, effectively removing a prenyl unit from α -bromo β -keto ester **45**, modeling both the initiation and termination, but limiting the number of possible products. Once again, applying the conditions reported by Guindon to truncated allylic acetate **48** returned mostly starting material (not shown). Using EtAlCl₂ resulted in decomposition. To test whether the desired radical was being formed, Bu₃SnH was added. Indeed, the reduced product **49** was formed in 41% yield, indicating that the desired radical forms, but does not cyclize (Scheme 9). It seems likely that the olefin is deactivated by the allylic acetate, precluding cyclization onto the electrophilic radical intermediate. A new model system was developed that lacked the allylic acetate (Scheme 10, **50**). This model system would more accurately model the first 6-*endo* cyclization of α -bromo β -keto ester **45**, with a more electron-rich trisubstituted olefin. The chelated aluminum intermediate was generated in the usual way (addition of AlMe₃ to **50**), and fluorinated phenols (F₅PhOH, 3,5-CF₃PhOH) were added to generate a more electrophilic aluminum species.⁵⁹ A variety of initiators were used (Et₃B/O₂, CuBr/PMDA,⁶⁰ *fac*-

Ir(ppy)₃,⁶¹ Bu₃SnSnBu₃/*hν*), but the desired product(s) **51a/51b/51c/52** could not be isolated (Scheme 10). These results are surprising considering the literature precedent strongly implying the formation of an aluminum chelated radical intermediate.

Photoredox Catalyzed Cyclizations

Due to the difficulties encountered during exploration of atom-transfer cyclizations on α -bromo β -hydroxy ester substrates, a new strategy was sought. The recent success of photoredox catalysis inspired investigation of ruthenium and iridium photocatalysts for the desired radical cyclization. Previous reports have demonstrated that these catalysts are capable of reductively cleaving the C-Br bond in α -bromo β -dicarbonyl substrates to generate an electrophilic radical.⁶² Three termination modes have been reported: reductive,⁶² atom-transfer,⁶³ or oxidative.⁶⁴ It was hoped that atom-transfer or oxidative termination would be operant in the present system to allow for further functionalization. Initial experiments aimed to optimize the unchelated cyclization prior to introduction of a Lewis acid. It was hoped that sequential optimization campaigns would prove more fruitful than prior efforts attempting to optimize all variables simultaneously. Pleasingly, treatment of model α -bromo β -keto ester **53** with *fac*-Ir(ppy)₃ and 2,6-lutidine in CH₂Cl₂ with irradiation from blue LEDs produced lactone **54** (Scheme 11A). A reasonable mechanism for this transformation can be surmised (Scheme 11B).⁶³ First, an electron of the Ir(III) is promoted from the ground state to an excited state from visible light irradiation to generate photoexcited Ir(III)*. The excited catalyst reductively cleaves the C-Br bond of **53** to generate Ir(IV), bromide anion, and the desired radical **55**.

The radical undergoes a 6-*endo* cyclization to produce tertiary radical **56**, which is oxidized by Ir(IV) to close the catalytic cycle. Cation **57** can either be captured by the proximal ester to generate lactone **54** or eliminated to produce one of three possible olefins. Indeed, the crude ¹H NMR spectrum revealed several new signals in the alkene region, leading to the hypothesis that some of the remaining mass balance was a mixture of monocyclic olefin isomers. Isolation of these products was elusive, so HCl was added upon completion of the reaction in an attempt to funnel these products to the lactone. Pleasingly, the yield of the lactone increased (Table 2, Entries 2–4). Further screening of bases revealed that DABCO was optimal (Entry 5). Notably, when trialkyl amines are employed as bases, it is likely that the mechanism differs from the one depicted above (Scheme 11B).⁶³ The photoexcited catalyst is reductively quenched through oxidation of the amine, producing a nitrogen-centered radical cation and a reduced catalyst. The reduced catalyst generates the desired radical **55**, which undergoes cyclization to produce lactone **54**.

With improved conditions in hand, exploratory studies were initiated on substrate **38**. Surprisingly, these conditions decomposed the substrate. Interestingly, when the linear alcohol **58** was subjected to the same conditions, *trans*-decalin **8a** was produced. Efforts to optimize this reaction began with varying the concentration, with higher dilution increasing the yield (Entries 1–3, Table 3). Changing the solvent did not improve the yield, though it was found that MeCN gave comparable results (Entry 4). Further experiments were conducted in MeCN, as it is better able to solubilize a wide array of photocatalysts. Using other photocatalysts failed to improve the yield, though they were all able to provide some

of the desired product (Entries 5–8). Finally, the catalyst loading was varied, but the yield could not be improved (Entries 9–11). Impressively, the reaction proceeded even when the catalyst loading was lowered to 0.01 mol%. Since considerable optimization efforts for the photoredox catalyzed radical cyclization were not successful (not shown), this avenue was ultimately abandoned.

CONCLUSION

A unified synthetic strategy was devised that could access the oridamycin and xiamycin families from a common synthetic precursor. Part of the strategy was successfully realized, culminating in the synthesis of oridamycin A and oridamycin B. The free-radical cyclization of the common linear precursor yielded a *trans*-decalin ring that corresponded to the oridamycins, with an axial ester and equatorial methyl. This key intermediate was elaborated through a Grignard addition that connected the bicyclic ring system to indole, followed by a 6π -electrocyclization/aromatization sequence to produce the 2,3-fused carbazole. The synthesis of oridamycin A was completed with a Krapcho-inspired, nucleophilic ester dealkylation to overcome difficulties with standard saponification conditions, providing the natural product in nine steps from geranyl acetate. The hydroxymethyl substituent found in oridamycin B was installed through a late-stage, oxime-directed C-H oxidation, ultimately producing oridamycin B in twelve steps from geranyl acetate. To access xiamycin A, a variety of strategies were explored to produce a chelated radical intermediate that would cyclize to the C16-epimeric *trans*-decalin. Addition of a Lewis acid to the Mn(III)-mediated cyclization proved fruitless, and would be a difficult method to optimize due to the difficulty in generating a substrate bound to two different transition metal complexes while producing a highly reactive radical intermediate. An alternate strategy was explored that entailed SET oxidation of an enolate with a chelating counterion to generate a chelated radical cation intermediate. Experiments using a variety of outer-sphere oxidants, enolate counterions, and bases were unable to provide the desired *trans*-decalin. Exploratory studies with oxo-vanadium compounds that served as both oxidants and Lewis acids were also unsuccessful. Atom-transfer cyclizations were also explored, leading to the development of a model system to simplify reaction analysis. A variety of conditions using traditional radical initiators (e.g. Et₃B/O₂, AIBN, Bu₃SnSnBu₃/h ν) failed to produce cyclized products. The recent success of photoredox catalysts for a wide variety of transformations prompted their exploration in the current study. Pleasingly, photoredox catalysis provided a bicyclic lactone derived from oxidative termination of the radical cascade, boding well for its use in synthesizing xiamycin A. When photoredox conditions were explored for the desired double 6-*endo* cyclization, the unchelated product was produced. Unfortunately, extensive optimization efforts were unable to increase the yield. However, it was found that the reaction could be conducted with catalyst loadings as low as 0.01 mol%.

While the initial goal of a unified synthetic strategy was not completed in its entirety, the synthesis of the oridamycins was accomplished. Hopefully, the various findings from exploratory studies towards xiamycin A can guide future chemists in their own endeavors on related terpene natural products.

EXPERIMENTAL SECTION

General Experimental Procedures.

All solvents were reagent or HPLC grade. Anhydrous solvents were purchased from Sigma-Aldrich and were used without further purification. All reactions were carried out under an argon atmosphere unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using EMD Millipore silica gel 60 F₂₅₄ plates (250 μ m thickness) and visualized by UV fluorescence quenching and KMnO₄ staining. Preparative thin-layer chromatography (PTLC) separations were performed with EMD Millipore silica gel 60 F₂₅₄ plates (1000 μ m or 500 μ m thickness). Flash column chromatography was performed using Silicycle silica gel 60 (40–63 μ m). Yields refer to chromatographically and spectroscopically pure compounds. Infrared measurements were performed on a JASCO FT/IR 6100 spectrometer. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance DRX-600 MHz at ambient temperature unless otherwise stated. Chemical shifts are reported in parts per million relative to residual solvent CDCl₃ (¹H, 7.26 ppm, ¹³C, 77.16 ppm) or CD₃OD (¹H, 3.31 ppm, ¹³C, 49.00 ppm). Multiplicities are reported as follows: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, td = triplet of doublets, tt = triplet of triplets, m = multiplet, q = quartet, app. = apparent, br. s = broad singlet. Diastereomeric ratio (dr) was determined by ¹H NMR analysis. High-resolution mass spectral analyses were performed by the MSKCC core facility staff.

Allylic Alcohol **S1**. SeO₂ (15.5 g, 140 mmol, 0.7 equiv.) was added to a solution of geranyl acetate (157, 39.2 g, 200 mmol, 1.0 equiv.) in anhydrous EtOH (500 mL) and was heated under a reflux condenser (oil bath = 105 °C) for 24 h. After cooling to room temperature, the solution was filtered through a celite pad and condensed. The resultant orange oil was dissolved in EtOH (100 mL) and Et₂O (360 mL) and cooled to 0 °C. Next, solid NaBH₄ (7.6 g, 200 mmol, 1.0 equiv.) was added in three equal portions and the solution was allowed to stir for 1 h at 0 °C. More NaBH₄ (3.0g, 79 mmol, 0.39 equiv.) was added, and the solution was allowed to stir 3 h at 0 °C. Upon completion, ice cold H₂O (300 mL) was slowly added to quench the reaction, which was allowed to slowly warm to room temperature and was stirred overnight. Sat. aqueous NaHCO₃ was added, the layers were separated, and the aqueous layer was extracted 3x with Et₂O. The combined organic layers were washed 2x with H₂O and 1x with brine, dried over MgSO₄, filtered, and condensed to yield a yellow oil that was distilled (1.0 mbar, product in fraction collected between oil bath temperatures 175 °C → 205 °C) to yield the allylic alcohol **S1** as a pale-yellow oil (23.3 g, 55 % yield).

S9: The spectroscopic data matched the literature;⁶⁵ ¹H NMR (600 MHz, CDCl₃) δ 5.38 – 5.26 (m, 2H), 4.56 (d, J = 7.1 Hz, 2H), 3.96 (s, 2H), 2.18 – 2.11 (m, 2H), 2.09 – 2.04 (m, 2H), 2.03 (s, 3H), 1.68 (s, 2H), 1.64 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 171.3, 141.8, 135.4, 125.3, 118.7, 68.9, 61.5, 39.2, 25.8, 21.1, 16.5, 13.8.

Allylic Bromide **S2**. A solution of allylic alcohol **S1** (9.88 g, 46.6 mmol, 1.0 equiv.) in anhydrous THF (150 mL) was cooled to $-40\text{ }^{\circ}\text{C}$ in a dry ice/acetone bath. MsCl (4.7 mL, 60.6 mmol, 1.3 equiv.) was added in one portion, followed by dropwise addition of Et₃N (12.9 mL, 93.2 mmol, 2.0 equiv.) and the contents were allowed to slowly warm to $-20\text{ }^{\circ}\text{C}$ over the course of 1 h. Next, a solution of LiBr (16.2g, 186.4 mmol, 4.0 equiv.) in THF (50 mL) was slowly added and the solution was slowly allowed to warm to $0\text{ }^{\circ}\text{C}$ over the course of 1.5 h. After stirring at $0\text{ }^{\circ}\text{C}$ for 1 h, the solution was quenched with H₂O, the aqueous was extracted 3x with Et₂O, the combined organics were washed with sat. aq. NaHCO₃, brine, dried over MgSO₄, filtered, and condensed to yield pure allylic bromide **S2** as an orange-yellow oil (11.52 g, 90% yield).

S2: Spectroscopic data was in agreement with the literature;²⁹ ¹H NMR (600 MHz, CDCl₃) δ 5.55 (t, $J = 7.1\text{ Hz}$, 1H), 5.32 (tq, $J = 7.1, 1.3\text{ Hz}$, 1H), 4.57 (d, $J = 7.1\text{ Hz}$, 2H), 3.95 (s, 2H), 2.15 (q, $J = 7.3\text{ Hz}$, 2H), 2.07 (t, $J = 7.8\text{ Hz}$, 2H), 2.04 (s, 3H), 1.74 (s, 3H), 1.69 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 171.2, 141.4, 132.6, 130.5, 119.0, 61.4, 41.7, 38.7, 26.5, 21.2, 16.5, 14.8.

Linear Alcohol **6a**. NaH (60% dispersion in mineral oil, 9.3 g, 234 mmol, 5.0 equiv.) was added to a flame-dried flask, followed by the addition of anhydrous THF (540 mL) and HMPA (15 mL) and the solution was cooled to $0\text{ }^{\circ}\text{C}$. Next, neat methyl 2-methyl-3-oxobutanoate (prepared according to the literature,⁶⁶ 30.3 g, 234 mmol, 5.0 equiv.) was added slowly, causing the gas evolution and the grey suspension to thicken. The solution was stirred at $0\text{ }^{\circ}\text{C}$ for 30 min. A solution of *n*-BuLi (2.37M in hexanes, 98 mL, 234 mmol, 5.0 equiv.) was added dropwise at $0\text{ }^{\circ}\text{C}$, and the suspension became soluble and turned orange. Crude allylic bromide **S2** (12.8 g, 46.7 mmol, 1.0 equiv.) in THF (50 mL) was then added rapidly in one portion. The reaction was allowed to slowly warm to room temperature and was stirred for 16 h. Upon completion, the reaction was quenched with sat. aq. NH₄Cl, the aqueous layer was extracted 3x with CH₂Cl₂, dried over MgSO₄, filtered, and condensed. The resultant orange oil was purified via flash column chromatography (silica gel, gradient of hexanes/EtOAc 20/3 $\rightarrow$ 4/1 $\rightarrow$ 3/1 $\rightarrow$ 20/7) to yield linear alcohol **6a** as a pale orange oil (10.73 g, 82% yield).

6a: Spectroscopic data was in agreement with the literature;²⁸ ¹H NMR (600 MHz, CDCl₃) δ 5.38 – 5.26 (m, 2H), 4.56 (d, $J = 7.1\text{ Hz}$, 2H), 3.96 (s, 2H), 2.18 – 2.11 (m, 2H), 2.09 – 2.04 (m, 2H), 2.03 (s, 3H), 1.68 (s, 2H), 1.64 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ

205.6, 171.2, 139.3, 133.7, 124.7, 123.8, 59.5, 52.8, 52.5, 40.1, 39.4, 33.2, 26.2, 16.3, 16.2, 12.9.

Bicyclic Alcohol **8a**. Linear alcohol **6a** (2.82 g, 10.0 mmol, 1.0 equiv.) was dissolved in PhMe (~100 mL) and trace water was removed via azeotropic distillation, then it was dissolved in AcOH (110 mL) and degassed with two freeze-pump-thaw cycles (Note: as has been previously noted for related transformations, it was vital to thoroughly degass the solution prior to cyclization to obtain reasonable yields).⁶⁷ Next, Mn(OAc)₃•2H₂O (5.9 g, 22 mmol, 2.2 equiv.) and Cu(OAc)₂•H₂O (2.0 g, 10 mmol, 1.0 equiv.) were added simultaneously, and the dark brown suspension was stirred at room temperature under an Argon atmosphere for 16 h. The suspension was condensed, then taken up in EtOAc, to which H₂O and sat. aqueous NaHSO₃ were added. The phases were separated and the aqueous layer was extracted 2x with EtOAc. The combined organic layers were washed 2x with brine, then dried over Na₂SO₄, filtered, and condensed. The orange oil was purified via flash column chromatography (silica gel, hexanes/Et₂O 3/7) to yield bicyclic alcohol **8a** as a crystalline white solid (1.41 g, 50% yield).

8a: R_f = 0.67 (silica gel, Et₂O); IR (film): ν_{max} 3444, 2951, 1711, 1457, 1223, 1024, 891 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 5.04 (s, 1H), 4.73 (s, 1H), 3.85 (d, J = 6.7 Hz, 2H), 3.66 (s, 3H), 2.95 (td, J = 14.8, 6.3 Hz, 1H), 2.52 – 2.43 (m, 2H), 2.09 (ddd, J = 13.3, 6.4, 2.7 Hz, 1H), 2.03 – 1.91 (m, 4H), 1.67 (td, J = 14.1, 4.3 Hz, 1H), 1.63 – 1.54 (m, 1H), 1.43 (d, J = 5.8 Hz, 1H), 1.37 (s, 3H), 0.85 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 208.2, 173.9, 146.1, 107.9, 58.9, 57.6, 57.3, 52.3, 39.1, 38.8, 37.8, 37.1, 26.0, 21.4, 13.4; HRMS (ESI-TOF, m/z) calcd for C₁₆H₂₄O₄Na [M+Na]⁺ 303.1572, found 303.1572.

Bicyclic Aldehyde **S3**. Bicyclic alcohol **8a** (1.31 g, 4.7 mmol, 1.0 equiv.) was dissolved in anhydrous CH₂Cl₂ (50 mL) and cooled to 0 °C. Dess–Martin periodinane (3.97 g, 9.4 mmol, 2.0 equiv.) was added and the cloudy white suspension was stirred at 0 °C for 30 min. The reaction was quenched with 1:1 sat. aqueous NaHCO₃: sat. aqueous Na₂S₂O₃ at 0 °C, then removed from the ice bath and allowed to stir at room temperature until both layers were transparent. The aqueous layer was extracted 3x with CH₂Cl₂, and the combined organic layers were washed with 1:1 sat. aqueous NaHCO₃: sat. aqueous Na₂S₂O₃, and brine, then dried over MgSO₄, filtered, and condensed. The resultant yellow oil was purified via flash column chromatography (silica gel, hexanes/acetone 85/15) to yield bicyclic aldehyde **S3** as a crystalline white solid (0.95 g, 73% yield).

S3: R_f = 0.48 (silica gel, hexanes/Et₂O 1/1); IR (film): ν_{max} 2953, 1717, 1457, 1223, 1143, 1097, 896 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 9.88 (d, J = 4.0 Hz, 1H), 5.03 (s, 1H), 4.59 (s, 1H), 3.69 (s, 3H), 2.98 (td, J = 14.9, 6.1 Hz, 1H), 2.53 – 2.48 (m, 2H), 2.45 (ddd, J = 14.8, 4.5, 2.7 Hz, 1H), 2.07 – 1.93 (m, 3H), 1.62 – 1.55 (m, 2H), 1.49 (dd, J = 11.7, 3.2 Hz, 1H), 1.38 (s, 3H), 1.21 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 207.5, 203.2, 173.6, 143.1, 110.9, 66.1, 57.6, 56.4, 52.4, 38.9, 38.7, 36.9, 36.7, 25.2, 21.4, 13.9; HRMS (ESI-TOF, m/z) calcd for C₁₆H₂₃O₄ [M+H]⁺ 279.1596, found 279.1583.

Secondary Alcohol **13**. Trace water was removed from *tert*-butyl 3-iodoindole-1-carboxylate (prepared according to the literature,⁶⁸ 5.87 g, 17.1 mmol, 5.0 equiv.) via azeotropic distillation with PhMe. Then, it was dissolved in anhydrous THF (90 mL) and cooled to 0 °C. A solution of EtMgBr (3.0 M in Et₂O, 5.6 mL, 16.9 mmol, 4.95 equiv.) was added dropwise. The solution was stirred at 0 °C for 20 min, then it was removed from the ice bath and stirred at room temperature for 35 min. During this time, a solution of aldehyde **S3** (0.95 g, 3.42 mmol, 1.0 equiv.) was prepared as follows: Trace water was removed from aldehyde **S3** via azeotropic distillation with PhMe. Then it was dissolved in THF (60 mL) and cooled to 0 °C. The solution of *tert*-butyl 3-iodoindole-1-carboxylate and EtMgBr was re-cooled to 0 °C, then cannulated dropwise into the solution containing aldehyde **S3** over the course of 15 min at 0 °C. The resulting solution was allowed to stir at 0 °C for 30 min before being quenched with sat. aqueous NH₄Cl. The aqueous layer was extracted 3x with EtOAc, and the combined organic layers were dried over MgSO₄, filtered, and condensed. The orange yellow oil was purified via flash column chromatography (silica gel, hexanes/acetone 4/1) to yield secondary alcohol **13** as a pale-yellow powder (1.68 g, 99% yield). The diastereomers were not separated and were characterized together (approximate *dr* = 4:1).

13: R_f = 0.45 (silica gel, hexanes/Et₂O 1/1); IR (film): $\nu_{\max}$ 3535, 2982, 2951, 1711, 1454, 1367, 1252, 1223, 1155, 735 cm⁻¹; ¹H NMR (600 MHz, CDCl₃): Selected Peaks, *Major Diastereomer* δ 7.53 (s, 1H), 7.49 (d, J = 7.8 Hz, 1H), 5.51 (t, J = 3.7 Hz, 1H), 5.28 (s, 1H), 5.06 (s, 1H), 3.01 (td, J = 14.7, 6.1 Hz, 1H), 2.41 (ddd, J = 14.7, 4.5, 2.8 Hz, 1H), 1.24 (s, 3H). *Minor Diastereomer*: δ 7.57 (d, J = 7.8 Hz, 1H), 7.46 (s, 1H), 5.40 (dd, J = 7.5, 3.4 Hz, 1H), 4.83 (s, 1H), 4.58 (s, 1H), 2.83 (ddd, J = 13.8, 6.1, 2.8 Hz, 1H), 2.54 (d, J = 7.4 Hz, 1H), 1.20 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) *Both Diastereomers*: δ 208.9, 208.5, 173.9, 173.8, 149.8, 147.2, 144.2, 135.7, 128.8, 125.6, 124.7, 124.5, 124.0, 123.8, 122.8, 122.7, 122.6, 119.5, 115.6, 115.6, 111.7, 110.3, 83.9, 68.3, 66.6, 58.9, 58.3, 58.2, 58.2, 58.0, 57.6, 52.2, 52.2, 42.0, 40.6, 39.9, 39.1, 38.9, 38.2, 37.4, 37.2, 28.3, 28.3, 26.5, 26.4, 21.6, 21.4, 14.6, 13.7; HRMS (ESI-TOF, m/z) calcd for C₂₉H₃₇NO₆Na [M+Na]⁺ 518.2519, found 518.2521.

Triene **17**. Secondary alcohol **13** (25 mg, 50 μ mol, 1.0 equiv.) was dissolved in 1 mL CH₂Cl₂ and cooled to 0 °C. TFA (8 μ L, 100 μ mol, 2.0 equiv.) was added dropwise, and the solution was stirred for 40 min at 0 °C. The reaction was removed from the ice bath and allowed to warm to room temperature over 2 h. The reaction was diluted with EtOAc and H₂O, and the aqueous layer was extracted 3x with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and condensed. The resultant material was purified via flash column chromatography (silica gel, 10% EtOAc/hexanes) to yield triene **17** as a clear oil (20 mg, 83% yield).

17: R_f = 0.25 (silica gel, 10% EtOAc/hexanes); IR (film): $\nu_{\max}$ 1727, 1453, 1370, 1224, 1155, 1082, 907, 732 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 8.07 (s, 1H), 7.71 (s, 1H), 7.49 (d, J = 7.7 Hz, 1H), 7.29 (t, J = 7.8 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 6.20 (s, 1H), 5.02 (s, 1H), 4.80 (s, 1H), 3.71 (s, 3H), 3.13 (td, J = 14.8, 5.8 Hz, 1H), 2.69 – 2.54 (m, 2H), 2.25 – 2.00 (m, 5H), 1.74 (dd, J = 12.2, 3.3 Hz, 1H), 1.66 (s, 10H), 1.40 (s, 3H), 1.21 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 208.3, 173.7, 152.1, 145.2, 124.4, 123.3, 122.5, 119.2, 117.3, 115.3, 114.2, 109.8, 57.9, 56.2, 52.3, 41.7, 37.5, 37.2, 36.8, 28.4, 25.6, 21.6, 18.6; HRMS (ESI-TOF, m/z) calcd for C₂₉H₃₆NO₅ [M+H]⁺ 478.2593, found 478.2574.

Boc Carbazole **11b**. *Preparation 1*. Triene **17** (17 mg, 36 μmol , 1.0 equiv.) was dissolved in 600 μL PhMe and transferred to a pressure tube. The solution was heated to 140 $^{\circ}\text{C}$ for 2 h and 20 min before being condensed. The crude material was purified via flash column chromatography (silica gel, 12% to 15% EtOAc/hexanes) to yield Boc carbazole **11b** as a pale-yellow oil (11.3 mg, 66% yield).

Boc-Carbazole **11b**. *Preparation 2*. Secondary alcohol **13** (260 mg, 0.52 mmol, 1.0 equiv.) was dissolved in anhydrous CH_2Cl_2 (9 mL) and cooled to 0 $^{\circ}\text{C}$. TFA (80 μL , 1.05 mmol, 2.0 equiv.) was added in one portion, and the solution was stirred at 0 $^{\circ}\text{C}$ for 20 min. The flask was removed from the ice bath and was allowed to warm to room temperature, and was stirred at room temperature for 2.5 h. The solvent was removed under reduced pressure, then azeotropically distilled with PhMe, dissolved in anhydrous PhMe (9 mL), and heated to 140 $^{\circ}\text{C}$ for 2 h and 20 min. Upon completion, the reaction was condensed to yield a brown foam, which was purified by flash column chromatography (silica gel, hexanes/acetone 9/1) to yield Boc carbazole **11b** as a beige foam (168 mg, 68% yield).

11b: R_f = 0.22 (silica gel, hexanes/acetone 9/1); IR (film): ν_{max} 2976, 1723, 1456, 1359, 1226, 1156, 769 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 8.22 (d, J = 8.4 Hz, 1H), 8.04 (s, 1H), 7.92 (d, J = 7.3 Hz, 1H), 7.87 (s, 1H), 7.42 (ddd, J = 8.4, 7.3, 1.3 Hz, 1H), 7.32 (td, J = 7.5, 1.0 Hz, 1H), 3.73 (s, 3H), 3.24 – 3.16 (m, 2H), 3.09 – 3.00 (m, 1H), 2.78 (ddd, J = 13.3, 6.3, 2.5 Hz, 1H), 2.64 (ddd, J = 14.7, 4.5, 2.4 Hz, 1H), 2.29 – 2.21 (m, 2H), 1.95 – 1.85 (m, 2H), 1.75 (s, 9H), 1.50 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 208.1, 174.2, 151.3, 141.6, 138.8, 137.3, 134.7, 126.9, 125.9, 124.5, 123.1, 119.4, 116.4, 116.2, 84.0, 57.7, 54.2, 52.4, 39.8, 38.4, 37.7, 32.9, 28.5, 23.4, 21.8, 21.1; HRMS (ESI-TOF, m/z) calcd for $\text{C}_{29}\text{H}_{33}\text{NO}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 498.2256, found 498.2239.

Carbazole **11a**. *Preparation 1*. Boc-carbazole **11b** (11.3 mg, 24 μmol , 1.0 equiv.) was dissolved in 400 μL CH_2Cl_2 . TFA (18 μL , 240 μmol , 10.0 equiv.) was added, and the solution was heated to 45 $^{\circ}\text{C}$ for 2.5 h. The solution was condensed and the resultant material was purified via flash column chromatography (silica gel, 15% acetone/hexanes) to yield carbazole **11a** as a white foam (5.5 mg, 61% yield).

Carbazole **11a**. *Preparation 2*. Secondary alcohol **13** (1.42 g, 2.87 mmol, 1.0 equiv.) was dissolved in anhydrous CH_2Cl_2 (48 mL) and cooled to 0 $^{\circ}\text{C}$. TFA (440 μL , 5.74 mmol, 2.0 equiv.) was added dropwise, and the solution was allowed to stir at 0 $^{\circ}\text{C}$ for 10 min, at which point it was removed from the ice bath and allowed to warm to room temperature. The solution was stirred at room temperature for 3 h, then it was condensed, azeotropically distilled with PhMe to remove trace TFA and H_2O , dissolved in anhydrous PhMe (48 mL), transferred to a pressure tube, heated to 135 $^{\circ}\text{C}$, and stirred for 2 h. The solution was allowed

to cool to room temperature, then TFA (2.2 mL, 28.7 mmol, 10.0 equiv.) was added dropwise, the solution was heated to 45 °C, and the mixture was stirred for 2.5 h. The solution was condensed and the resultant brown oil was purified by flash column chromatography (silica gel, acetone/hexanes 4/1) to yield carbazole **11a** as a brown foam (561 mg, 52% yield).

11a: R_f = 0.63 (silica gel, hexanes/EtOAc 2/1); IR (film): $\nu_{\max}$ 3410, 2956, 1705, 1467, 1322, 1239, 1097, 735 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 8.00 (d, J = 7.8 Hz, 1H), 7.98 (s, 1H), 7.87 (s, 1H), 7.37 (d, J = 3.5 Hz, 1H), 7.20 (dt, J = 8.0, 3.8 Hz, 1H), 7.11 (s, 1H), 3.73 (s, 3H), 3.25 – 3.12 (m, 2H), 3.08 – 2.99 (m, 1H), 2.82 (ddd, J = 13.3, 6.3, 2.5 Hz, 1H), 2.64 (ddd, J = 14.7, 4.6, 2.4 Hz, 1H), 2.31 – 2.19 (m, 2H), 1.94 (td, J = 14.0, 4.5 Hz, 1H), 1.89 (dd, J = 11.4, 2.7 Hz, 1H), 1.50 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 208.4, 174.3, 140.2, 138.5, 138.3, 133.6, 125.8, 123.5, 122.4, 120.1, 119.4, 116.9, 110.7, 110.0, 57.7, 54.5, 52.3, 40.1, 38.4, 37.8, 32.7, 23.6, 21.8, 21.2; HRMS (ESI-TOF, m/z) calcd for $\text{C}_{24}\text{H}_{26}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 376.1913, found 376.1913.

Equatorial Alcohol **18**. Carbazole **11a** (100 mg, 0.27 mmol, 1.0 equiv.) was azeotropically distilled with PhMe to remove trace H_2O , then dissolved in anhydrous MeOH (6 mL) and cooled to 0 °C. NaBH_4 (31 mg, 0.80 mmol, 3.0 equiv.) was added in one portion, and the reaction was stirred for 3 h. Upon completion, the reaction was quenched with H_2O , then diluted with EtOAc. The aqueous phase was extracted 3x with EtOAc, and the combined organic layers were dried over MgSO_4 , filtered, and condensed. The resultant oil was purified by flash column chromatography (silica gel, EtOAc/hexanes 3/7) to yield equatorial alcohol **18** as a pink foam (72 mg, 72% yield).

18: R_f = 0.42 (silica gel, hexanes/EtOAc 7/3); IR (film): $\nu_{\max}$ 3410, 2951, 1701, 1467, 1236, 1027, 735 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 8.02 (d, J = 7.8 Hz, 1H), 7.97 (s, 1H), 7.92 (s, 1H), 7.38 (t, J = 7.4 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.00 (s, 1H), 3.72 (s, 3H), 3.65 (d, J = 11.9 Hz, 1H), 3.24 (td, J = 11.9, 4.4 Hz, 1H), 3.10 (dd, J = 16.6, 4.3 Hz, 1H), 3.05 – 2.95 (m, 1H), 2.56 (dt, J = 13.3, 3.6 Hz, 1H), 2.34 – 2.20 (m, 2H), 2.11 – 2.01 (m, 2H), 1.64 (td, J = 13.6, 4.1 Hz, 1H), 1.56 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 178.7, 140.2, 139.6, 138.3, 133.7, 125.6, 123.6, 122.3, 120.1, 119.3, 117.2, 110.6, 109.8, 78.3, 53.0, 51.4, 49.2, 39.1, 38.5, 33.2, 29.4, 23.9, 23.8, 21.5; HRMS (ESI-TOF, m/z) calcd for $\text{C}_{24}\text{H}_{28}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 378.2069, found 378.2057.

Oridamycin A (**1**). Alcohol **18** (50 mg, 0.135 mmol, 1.0 equiv.) was dissolved in DMSO (3 mL) and solid NaCN (132 mg, 2.7 mmol, 20.0 equiv.) was added in one portion. The resulting solution was heated to 120 °C and stirred for 2 h and 40 min before it was allowed to cool to room temperature. The amber solution was diluted with EtOAc, washed 4x with a solution of 5:3 brine:1M HCl (Beware! Forms HCN, highly toxic! Keep in fume hood!), dried over MgSO₄, filtered, and condensed. The resultant amber solid was found to be pure Oridamycin A (**1**) (42 mg, 86% yield) and no further purification was necessary.

Oridamycin A (**1**): IR (film): ν_{max} 3411, 2962, 1693, 1611, 1466, 1321, 1243, 1026, 937, 737 cm⁻¹; ¹H NMR (600 MHz, CD₃OD) δ 7.98 – 7.94 (m, 2H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 7.05 (s, 1H), 3.24 (dd, *J* = 12.2, 4.6 Hz, 1H), 3.07 (ddd, *J* = 16.9, 5.5, 1.9 Hz, 1H), 3.00 – 2.92 (m, 1H), 2.58 (dt, *J* = 13.2, 3.6 Hz, 1H), 2.32 (dq, *J* = 13.6, 3.6 Hz, 1H), 2.26 – 2.19 (m, 1H), 2.13 (dt, *J* = 12.9, 5.4 Hz, 1H), 1.96 – 1.90 (m, 1H), 1.59 (dt, *J* = 13.6, 3.9 Hz, 1H), 1.52 (d, 12.3 Hz, 1H), 1.49 (s, 3H), 1.27 (s, 3H); ¹³C NMR (150 MHz, CD₃OD) δ 181.0, 142.0, 140.3, 140.1, 134.5, 126.1, 124.6, 123.2, 120.6, 119.3, 117.5, 111.4, 110.7, 79.1, 54.1, 48.7, 40.0, 39.6, 34.0, 30.3, 24.8, 24.6, 22.5; HRMS (ESI-TOF, *m/z*) calcd for C₂₃H₂₅NO₃Na [M+Na]⁺ 386.1732, found 386.1724.

Oxime **21**. Boc carbazole **11b** (70 mg, 150 μ mol, 1.0 equiv.) was dissolved in 1 mL pyridine, and NH₂OH•HCl (14 mg, 200 μ mol, 1.35 equiv.) was added. The solution was heated to 80 °C and stirred for 40 min before being cooled to room temperature and diluted with EtOAc. The solution was washed 3x with 20% aqueous AcOH, sat. aqueous NaHCO₃, brine, dried over MgSO₄, filtered, and condensed. The resultant material was purified via flash column chromatography (silica gel, 20% EtOAc/hexanes) to yield oxime **21** as a yellow oil (58 mg, 78% yield).

21: R_f = 0.27 (silica gel, 20% ethyl acetate/hexanes); IR (film): ν_{max} 3462, 3272, 2977, 1720, 1358, 1325, 1225, 1153, 941, 766, 733 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 8.22 (d, *J* = 8.3 Hz, 1H), 8.01 (s, 1H), 7.92 (d, *J* = 7.3 Hz, 1H), 7.86 (s, 1H), 7.45 – 7.39 (m, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 3.72 (s, 3H), 3.59 (ddd, *J* = 15.0, 4.7, 2.5 Hz, 1H), 3.16 (dd, *J* = 16.8, 4.7 Hz, 1H), 3.07 – 2.98 (m, 1H), 2.61 (ddd, *J* = 13.1, 5.5, 2.6 Hz, 1H), 2.43 (td, *J* =

14.8, 5.4 Hz, 1H), 2.31 (dd, $J = 13.8, 6.2$ Hz, 1H), 2.21 – 2.10 (m, 1H), 1.80 (dd, $J = 12.2, 1.9$ Hz, 1H), 1.75 (s, 9H), 1.65 (td, $J = 13.5, 4.8$ Hz, 1H), 1.57 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 175.6, 161.5, 151.3, 142.4, 138.8, 137.2, 135.0, 126.8, 126.1, 124.4, 123.0, 119.4, 116.4, 116.3, 83.9, 54.1, 52.3, 50.8, 38.6, 38.6, 33.0, 28.5, 23.4, 22.4, 21.4, 19.8; HRMS (ESI-TOF, m/z) calcd for $\text{C}_{29}\text{H}_{35}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ 491.2546, found 491.2547.

Tosyl Carbazole **S4**. Carbazole **11a** (30 mg, 80 μmol , 1.0 equiv.) was dissolved in 800 μL DMF and degassed with Ar for 10 min. NaH (60% dispersion in mineral oil, 3.5 mg, 90 μmol , 1.1 equiv.) was added and the solution was stirred at room temperature for 1 h. *p*-TsCl (30 mg, 160 μmol , 2.0 equiv.) was added, and the solution was heated to 50 $^\circ\text{C}$ and stirred for 6 h. The solution was removed from heat, diluted with EtOAc, and quenched with sat. aqueous NH_4Cl . The aqueous layer was extracted 3x with EtOAc, and the combined organic layers were washed 3x with brine, dried over MgSO_4 , filtered and condensed. The resultant material was purified using PTLC (silica gel, 0.5mm thickness, 5% acetone, 45% hexanes, 50% PhMe) to yield tosyl carbazole **S4** as a clear oil (16 mg, 38% yield).

S4: $R_f = 0.27$ (silica gel, 25% ethyl acetate/hexanes); IR (film): ν_{max} 2952, 1713, 1451, 1368, 1171, 1092, 995, 812, 747, 658 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 8.25 (d, $J = 8.3$ Hz, 1H), 8.00 (s, 1H), 7.83 (d, $J = 7.7$ Hz, 1H), 7.79 (s, 1H), 7.72 – 7.68 (m, 2H), 7.46 – 7.41 (m, 1H), 7.32 (td, $J = 7.5, 1.0$ Hz, 1H), 7.12 (d, $J = 8.0$ Hz, 2H), 3.73 (s, 3H), 3.22 (dt, $J = 16.7, 3.5$ Hz, 1H), 3.17 (td, $J = 14.7, 6.3$ Hz, 1H), 3.10 – 3.01 (m, 1H), 2.71 (ddd, $J = 13.2, 6.2, 2.5$ Hz, 1H), 2.62 (ddd, $J = 14.7, 4.6, 2.4$ Hz, 1H), 2.28 (s, 3H), 2.27 – 2.21 (m, 2H), 1.90 – 1.84 (m, 1H), 1.49 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 207.9, 174.1, 144.9, 142.5, 138.7, 137.1, 135.3, 135.3, 129.8, 127.2, 126.7, 126.5, 124.9, 123.9, 119.7, 116.7, 115.2, 115.0, 57.7, 54.0, 52.4, 39.7, 38.4, 37.6, 32.9, 23.4, 21.7, 21.7, 21.1; HRMS (ESI-TOF, m/z) calcd for $\text{C}_{31}\text{H}_{32}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$ 530.2001, found 530.1992.

Tosyl Protected *O*-Methyloxime **23**. Tosyl carbazole **S4** (29 mg, 50 μmol , 1.0 equiv.) was dissolved in 250 μL pyridine. $\text{MeONH}_2\cdot\text{HCl}$ (7 mg, 80 μmol , 1.5 equiv.) was added, and the

solution was stirred at room temperature for 21 h. The solution was diluted with EtOAc and added to 20% aqueous AcOH. The organic layer was washed 3x with 20% aqueous AcOH, 3x with sat. aqueous NaHCO₃, dried over MgSO₄, filtered and condensed. The resultant material was purified via flash column chromatography (silica gel, 20% EtOAc/hexanes) to yield tosyl protected *O*-methyloxime **23** as a pale-yellow oil (29 mg, 95% yield).

23: R_f = 0.25 (silica gel, 20% ethyl acetate/hexanes); IR (film): $\nu_{\max}$ 3421, 2936, 1727, 1453, 1370, 1238, 1173, 1115, 1049, 907, 732, 666, 582 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 8.28 (d, J = 8.3 Hz, 1H), 8.00 (s, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.79 (s, 1H), 7.72 (d, J = 8.5 Hz, 2H), 7.48 – 7.42 (m, 1H), 7.34 (td, J = 7.5, 1.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 2H), 3.89 (s, 3H), 3.73 (s, 3H), 3.48 (dq, J = 15.0, 4.6, 2.5 Hz, 1H), 3.22 (dd, J = 16.8, 5.2 Hz, 1H), 3.11 – 3.01 (m, 1H), 2.72 (s, 1H), 2.53 (dq, J = 13.0, 5.4, 2.6 Hz, 1H), 2.48 – 2.32 (m, 2H), 2.30 (s, 3H), 2.22 – 2.12 (m, 1H), 1.80 (dd, J = 12.3, 1.8 Hz, 1H), 1.60 (s, 4H), 1.26 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 175.8, 159.6, 144.9, 143.4, 138.7, 136.9, 135.6, 135.3, 129.8, 127.1, 126.7, 124.8, 123.9, 119.7, 116.8, 115.2, 114.8, 61.6, 54.0, 52.2, 50.6, 38.7, 38.6, 33.0, 23.3, 22.4, 21.7, 21.4, 20.5; HRMS (ESI-TOF, m/z) calcd for C₃₂H₃₅N₂O₅S [M + H]⁺ 559.2267, found 559.2250.

Oxidized *O*-Methyloxime **24**. *O*-Methyloxime **23** (9.4 mg, 17 μ mol, 1.0 equiv.) was dissolved in 200 μ L of 1:1 AcOH: Ac₂O at room temperature. PhI(OAc)₂ (11 mg, 34 μ mol, 2.0 equiv.) and Pd(OAc)₂ (376 μ g, 1.68 μ mol, 10 mol%) were added, and the solution was heated to 80 °C for 4 h. The solution was cooled, diluted with EtOAc, washed 2x with sat. aqueous NaHCO₃, brine, dried over MgSO₄, filtered, and condensed. The resultant crude material was purified via PTLC (silica gel, 25% EtOAc/hexanes) to yield oxidized *O*-methyloxime **24** as a white foam (3.9 mg, 37% yield).

24: R_f = 0.29 (silica gel, 25% ethyl acetate/hexanes); IR (film): $\nu_{\max}$ 3414, 2945, 1731, 1368, 1225, 1171, 1045, 908, 729, 664 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 8.25 (d, J = 8.4 Hz, 1H), 7.98 (s, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.80 (s, 1H), 7.71 (d, J = 8.3 Hz, 2H), 7.47 – 7.41 (m, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.13 (d, J = 8.2 Hz, 2H), 4.66 (d, J = 10.7 Hz, 1H), 4.55 (d, J = 10.7 Hz, 1H), 3.84 (s, 3H), 3.74 (s, 3H), 3.28 – 3.21 (m, 1H), 3.17 (dd, J = 17.0, 5.4 Hz, 1H), 3.08 – 3.00 (m, 1H), 2.59 – 2.49 (m, 2H), 2.28 (s, 3H), 2.18 – 2.10 (m, 2H), 2.06 – 1.97 (m, 4H), 1.67 – 1.58 (m, 1H), 1.27 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 172.5, 170.8, 156.0, 144.9, 143.0, 138.6, 137.0, 135.3, 135.2, 129.8, 127.2, 126.7, 126.5, 124.8, 123.9, 119.7, 116.7, 115.1, 114.9, 65.7, 62.0, 54.4, 52.4, 46.8, 38.1, 36.7, 32.3, 23.5, 21.7, 21.2, 21.2, 20.8; HRMS (ESI-TOF, m/z) calcd for C₃₄H₃₇N₂O₇S [M + H]⁺ 617.2321, found 617.2298.

O-Methyloxime **25**. Boc carbazole **11b** (168 mg, 0.35 mmol, 1.0 equiv.) was dissolved in anhydrous pyridine (6 mL), to which MeONH₂•HCl (73 mg, 0.88 mmol, 2.5 equiv.) was added in one portion. The reaction was heated to 70 °C and stirred at that temperature for 3.5 h. Upon completion, the mixture was diluted with EtOAc, washed 4x with sat. aqueous NH₄Cl, washed with 1M HCl, dried over MgSO₄, filtered, and condensed. The resulting yellow oil was purified by flash chromatography (silica gel, hexanes/acetone 19/1) to yield *O*-methyloxime **25** as a yellow foam (160 mg, 90% yield).

25: R_f = 0.40 (silica gel, hexanes/acetone 9/1); IR (film): ν_{max} 2976, 1725, 1490, 1359, 1228, 1158, 1049, 769, 736 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 8.22 (d, *J* = 8.3 Hz, 1H), 8.01 (s, 1H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.84 (s, 1H), 7.41 (ddd, *J* = 8.5, 7.3, 1.3 Hz, 1H), 7.31 (td, *J* = 7.5, 1.0 Hz, 1H), 3.87 (s, 3H), 3.71 (s, 3H), 3.48 (ddd, *J* = 15.0, 4.7, 2.5 Hz, 1H), 3.15 (dd, *J* = 16.9, 4.3 Hz, 1H), 3.02 (ddd, *J* = 17.4, 12.6, 6.2 Hz, 1H), 2.57 (ddd, *J* = 13.0, 5.5, 2.6 Hz, 1H), 2.40 (td, *J* = 14.8, 5.3 Hz, 1H), 2.31 (dd, *J* = 13.8, 6.1 Hz, 1H), 2.14 (qd, *J* = 12.9, 5.3 Hz, 1H), 1.79 (dd, *J* = 12.3, 1.8 Hz, 1H), 1.75 (s, 10H), 1.68 – 1.61 (m, 1H), 1.58 (s, 3H), 1.26 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 175.8, 159.8, 151.3, 142.5, 138.8, 137.1, 135.0, 126.8, 126.1, 124.4, 123.0, 119.4, 116.4, 116.3, 116.2, 83.9, 61.6, 54.2, 52.2, 50.6, 38.7, 38.6, 33.0, 28.6, 28.5, 23.4, 22.4, 21.4, 20.5; HRMS (ESI-TOF, *m/z*) calcd for C₃₀H₃₇N₂O₅ [M+H]⁺ 505.2702, found 505.2706.

Acetoxymethyl **27**. *O*-Methyloxime **25** (152 mg, 0.3 mmol, equiv) was dissolved in 1:1 Ac₂O: AcOH (3 mL). PhI(OAc)₂ (193 mg, 0.6 mmol, 2.0 equiv.) and Pd(OAc)₂ (7 mg, 0.03 mmol, 0.1 equiv.) were added sequentially and the contents were heated to 70 °C and stirred at that temperature for 16 h. Upon completion, the mixture was diluted with EtOAc, washed 3x with sat. aqueous NaHCO₃, dried over MgSO₄, filtered, and condensed. The resultant brown oil was purified by flash chromatography (silica gel, hexanes/acetone 20/3) to yield acetoxymethyl **27** as a yellow oil (116 mg, 69% yield).

27: R_f = 0.42 (silica gel, hexanes/acetone 4/1); IR (film): $\nu_{\max}$ 2973, 1727, 1491, 1360, 1227, 1154, 1051, 769, 736 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 8.23 (d, J = 8.3 Hz, 1H), 8.02 (s, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.88 (s, 1H), 7.42 (t, J = 7.4 Hz, 1H), 7.32 (t, J = 7.2 Hz, 1H), 4.67 (d, J = 10.7 Hz, 1H), 4.56 (d, J = 10.7 Hz, 1H), 3.85 (s, 3H), 3.74 (s, 3H), 3.32 – 3.24 (m, 1H), 3.14 (dd, J = 16.9, 5.4 Hz, 1H), 3.03 (ddd, J = 17.4, 12.3, 6.4 Hz, 1H), 2.62 – 2.52 (m, 2H), 2.18 (d, J = 11.5 Hz, 1H), 2.12 (dd, J = 13.3, 6.2 Hz, 1H), 2.05 – 1.96 (m, 4H), 1.75 (s, 9H), 1.69 – 1.61 (m, 1H), 1.30 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 172.5, 170.7, 156.1, 151.3, 142.2, 138.9, 137.2, 134.7, 126.9, 126.0, 124.4, 123.1, 119.4, 116.4, 116.4, 116.2, 83.9, 65.7, 62.0, 54.4, 52.4, 46.9, 38.0, 36.8, 32.4, 28.5, 23.5, 21.2, 21.1, 20.8; HRMS (ESI-TOF, m/z) calcd for $\text{C}_{32}\text{H}_{39}\text{N}_2\text{O}_7$ $[\text{M}+\text{H}]^+$ 563.2757, found 563.2762.

Diol **28**. Acetoxymethyl **27** (20 mg, 0.036 mmol, 1.0 equiv.) was dissolved in acetone (540 μL) and aqueous 1M HCl (180 μL) was added. The contents were heated to 80 $^\circ\text{C}$ and maintained at that temperature for 13 h. Upon completion, the reaction mixture was diluted with CH_2Cl_2 , washed with H_2O and sat. aqueous NaHCO_3 , dried over Na_2SO_4 , filtered, and condensed. The crude material was immediately taken up in MeOH (720 μL) and cooled to 0 $^\circ\text{C}$. NaBH_4 (4 mg, 0.11 mmol, 3.0 equiv.) was added, and the solution was stirred at 0 $^\circ\text{C}$ for 40 min. The reaction was diluted with EtOAc, quenched with aqueous 1M HCl, and stirred at room temperature for 15 min to quench excess reagent. Additional H_2O and EtOAc were added, the aqueous was extracted 2x with EtOAc, the combined organic layers were washed 2x with sat. aqueous NaHCO_3 , dried over Na_2SO_4 , filtered, and condensed. The resultant material was purified via flash column chromatography (silica gel, hexanes/acetone 5/2) to yield diol **28** as a brown foam (4.0 mg, 25% yield).

28: R_f = 0.35 (silica gel, hexanes/acetone 3/2); IR (film): $\nu_{\max}$ 3408, 2926, 1706, 1492, 1240, 1071, 735 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.99 (d, J = 7.7 Hz, 1H), 7.95 (s, 1H), 7.83 (s, 1H), 7.37 (d, J = 3.9 Hz, 2H), 7.20 (dq, J = 8.0, 4.4 Hz, 1H), 7.07 (s, 1H), 4.38 (t, J = 10.6 Hz, 1H), 3.96 (d, J = 10.4 Hz, 1H), 3.84 – 3.81 (m, 2H), 3.80 (s, 4H), 3.69 (td, J = 12.0, 4.6 Hz, 1H), 3.09 (dd, J = 16.5, 5.3 Hz, 1H), 3.05 – 2.95 (m, 1H), 2.59 (dt, J = 13.4, 3.6 Hz, 1H), 2.35 (qd, J = 13.2, 3.9 Hz, 1H), 2.14 (dd, J = 14.0, 6.0 Hz, 1H), 2.08 – 1.99 (m, 2H), 1.70 – 1.63 (m, 2H), 1.22 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 176.4, 140.2, 139.2, 138.3, 133.5, 125.7, 123.6, 122.4, 120.1, 119.4, 117.1, 110.6, 109.8, 79.6, 72.0, 53.4, 51.9, 47.5, 38.8, 38.3, 32.7, 29.4, 24.2, 21.3; HRMS (ESI-TOF, m/z) calcd for $\text{C}_{24}\text{H}_{28}\text{NO}_4$ $[\text{M}+\text{H}]^+$ 394.2018, found 394.2006.

Oridamycin B (**2**). Diol **28** (1.3 mg, 3.3 μ mol, 1.0 equiv.) was dissolved in *m*DMSO (70 μ L) and solid NaCN (3.2 mg, 70 μ mol, 21 equiv.) was added in one portion. The reaction was heated to 120 $^{\circ}$ C and was stirred at that temperature for 2 h. Upon completion, the amber solution was diluted with EtOAc, washed 4x with a solution of 5:3 brine:1M HCl (Beware! Forms HCN, highly toxic! Keep in fume hood!), dried over Na₂SO₄, filtered, and condensed. The crude material was purified by semi-preparative HPLC (7 injections, Varian Microsorb 300–5 C18 column, 5 μ m, 250 x 4.6 mm) using MeCN/H₂O (30/70 to 80/20, 0.6 mL/min) as eluent to give pure oridamycin B (**2**), as a white powder (t_R = 10.39 min, 0.30 mg, 24% yield). NOTE: While the ¹H NMR spectrum of purified **2** corroborated the proposed structure (splitting, J values, relative chemical shifts, etc.), notable differences were found in the chemical shift of several protons relative to the isolated material. However, it was found that upon treatment with excess TFA the ¹H NMR spectrum matched that of the natural isolate, and the tabulated data from both spectra are provided below (for more detailed information see reference 12).

Oridamycin B (**2**): IR (film): $\nu_{\max}$ 3391, 2931, 2856, 1695, 1607, 1494, 1340, 1266, 1026, 740 cm^{-1} ; ¹H NMR (600 MHz, CD₃OD) δ 7.97 (s, 1H), 7.96 (d, J = 7.9 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.27 (dt, J = 7.6, 1.3 Hz, 1H), 7.07 (dt, J = 7.6, 1.2 Hz, 1H), 7.05 (s, 1H), 4.04 (d, J = 10.9 Hz, 1H), 3.95 (d, J = 10.9 Hz, 1H), 3.61 (dd, J = 12.1, 4.7 Hz, 1H), 3.06 – 2.99 (m, 2H), 2.55 (dt, J = 13.0, 3.6 Hz, 1H), 2.45 (dq, J = 12.5, 3.9 Hz, 1H), 2.27 – 2.22 (m, 2H), 1.95 – 1.88 (m, 1H), 1.84 – 1.78 (m, 1H), 1.55 (td, J = 13.4, 3.7 Hz, 1H), 1.36 (s, 3H), 1.34 – 1.27 (m, 1H); ¹³C NMR (150 MHz, CD₃OD) δ 180.6 (assigned from HMBC), 142.0, 141.2, 140.0, 135.2, 125.9, 124.7, 123.0, 120.5, 119.2, 117.6, 111.3, 110.6, 73.1, 64.7, 56.1, 46.9, 40.3, 39.5, 34.0, 30.8, 25.7, 22.6; HRMS (ESI-TOF, *m/z*) calcd for C₂₃H₂₅NO₄ [M-H][–] 378.1705, found 378.1723.

Linear Acetate **6b**. Linear alcohol **6a** (2.9 g, 10.4 mmol, 1.0 equiv.) was dissolved in 70 mL CH₂Cl₂ at room temperature. Pyridine (2.0 mL, 25.0 mmol, 2.4 equiv.) was added, followed by Ac₂O (1.47 mL, 15.6 mmol, 1.5 equiv.). The solution was allowed to stir for 21 h at room temperature. DMAP (9 mg, 73 μ mol, 0.7 mol%) was added, and the solution was allowed to stir for an additional 5 h. Upon completion, the reaction mixture was diluted with CH₂Cl₂, and quenched with sat. aqueous NaHCO₃. The layers were separated and the organic layer was washed with H₂O and brine, then dried over Na₂SO₄, filtered, and condensed. The

resultant material was purified via flash column chromatography (silica gel, 15% EtOAc/hexanes) to yield linear acetate **6b** as a pale-yellow oil (2.52 g, 75% yield).

6b: R_f = 0.58 (silica gel, 20% ethyl acetate/hexanes); IR (film): $\nu_{\max}$ 2916, 1739, 1716, 1437, 1368, 1232, 1070, 1024 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 5.33 (t, J = 7.0 Hz, 1H), 5.10 (t, J = 6.3 Hz, 1H), 4.58 (d, J = 7.1 Hz, 2H), 3.73 (s, 3H), 3.54 (q, J = 7.2 Hz, 1H), 2.71 – 2.55 (m, 2H), 2.26 (t, J = 7.7 Hz, 2H), 2.14 – 2.08 (m, 2H), 2.05 (s, 3H), 2.05 – 1.99 (m, 2H), 1.70 (s, 3H), 1.59 (s, 3H), 1.34 (d, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 205.6, 171.3, 171.2, 142.1, 134.0, 124.6, 118.6, 61.5, 52.9, 52.5, 40.3, 39.5, 33.4, 26.3, 21.2, 16.6, 16.2, 13.0; HRMS (ESI-TOF, m/z) calcd for $\text{C}_{18}\text{H}_{28}\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 347.1834, found 347.1820.

α -Chlorinated Product **36**. Linear acetate **6b** (50 mg, 150 μmol , 1.0 equiv.) was dissolved in 16 mL PhMe, to which 2,4,6-tri-*tert*-butylpyridine (148 mg, 600 μmol , 4.0 equiv.) and $\text{Cu}(\text{OTf})_2$ (163 mg, 45 μmol , 3.0 equiv.) were added. The solution was freeze-pump-thawed 3x to remove trace O_2 . The reaction was cooled to -55°C and $\text{V}(\text{O})\text{Cl}_2(\text{OTFE})$ was added (prepared according to the literature).⁵² The solution was stirred and slowly allowed to warm to -25°C over the course of 2.5 h, at which point the reaction was diluted with EtOAc and quenched with aqueous 1M HCl. The aqueous layer was extracted 2x with EtOAc, and the combined organic layers were washed with sat. aqueous NH_4Cl , sat. aqueous NaHCO_3 , brine, dried over MgSO_4 , filtered, and condensed. The resultant material was purified via flash column chromatography (silica gel, 10% EtOAc/hexanes) to yield α -chlorinated product **36** as a clear oil (30 mg, 56% yield).

36: R_f = 0.26 (silica gel, 10% ethyl acetate/hexanes); IR (film): $\nu_{\max}$ 2923, 2855, 1735, 1447, 1372, 1232, 1117, 1027, 733 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 5.33 (t, J = 7.0 Hz, 1H), 5.13 (t, J = 7.0 Hz, 1H), 4.58 (d, J = 7.1 Hz, 2H), 3.82 (s, 3H), 2.92 – 2.84 (m, 1H), 2.77 – 2.69 (m, 1H), 2.28 (t, J = 7.7 Hz, 2H), 2.11 (q, J = 7.4 Hz, 2H), 2.07 – 2.02 (m, 5H), 1.83 (s, 3H), 1.70 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 201.1, 171.3, 168.8, 142.1, 133.7, 124.9, 118.6, 70.9, 61.5, 53.90, 39.5, 36.5, 33.9, 26.3, 24.7, 21.2, 16.6, 16.2; HRMS (ESI-TOF, m/z) calcd for $\text{C}_{18}\text{H}_{27}\text{O}_5\text{ClNa}$ $[\text{M}+\text{Na}]^+$ 381.1445, found 381.1440.

α -eleno β -Keto Ester **37**. Linear acetate **6b** (50 mg, 150 μmol , 1.0 equiv.) was dissolved in 1.5 mL THF and cooled to -78°C . *t*-BuOK (26 mg, 230 μmol , 1.5 equiv.) was added and the solution was stirred at -78°C for 50 min. PhSeCl (44 mg, 230 μmol , 1.5 equiv.) was

added, and the solution was stirred at -78°C for 3.5 h. The reaction was diluted with EtOAc and quenched with sat. aqueous NH_4Cl . The aqueous layer was extracted 3x with EtOAc, and the combined organic layers were dried over MgSO_4 , filtered, and condensed. The resultant material was purified via flash column chromatography (silica gel, 5% acetone/hexanes) to yield α -seleno β -keto ester **37** as a clear oil (71 mg, 98% yield).

37: $R_f = 0.24$ (silica gel, 10% acetone/hexanes); IR (film): ν_{max} 3450, 2942, 1737, 1700, 1633, 1303, 1233, 1104, 917, 737, 692 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.57 – 7.51 (m, 2H), 7.27 – 7.24 (m, 3H), 5.30 (t, $J = 7.1$ Hz, 1H), 4.55 (qd, $J = 12.5, 7.0$ Hz, 2H), 3.67 (s, 3H), 3.10 – 2.98 (m, 3H), 2.52 – 2.43 (m, 1H), 2.31 – 2.19 (m, 2H), 2.09 (ddd, $J = 12.8, 9.2, 7.9$ Hz, 1H), 2.05 (s, 3H), 1.97 (ddd, $J = 12.8, 8.8, 5.7$ Hz, 1H), 1.72 (t, $J = 1.6$ Hz, 3H), 1.70 – 1.63 (m, 4H), 1.42 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 171.2, 169.9, 169.8, 141.2, 134.0, 130.9, 129.4, 127.7, 119.6, 97.4, 92.0, 61.4, 55.3, 51.0, 38.0, 35.8, 31.2, 29.4, 22.0, 21.2, 16.4, 11.5; HRMS (ESI-TOF, m/z) calcd for $\text{C}_{24}\text{H}_{33}\text{O}_5\text{Se}$ $[\text{M}+\text{H}]^+$ 481.1493, found 481.1482.

Linear α -Bromo Acetate **38**. Linear acetate **6b** (960 mg, 2.96 mmol, 1.0 equiv.) was azeotropically distilled 2x with PhMe to remove trace H_2O , dissolved in 60 mL THF, and cooled to -78°C . NaH (60% dispersion in mineral oil, 130 mg, 3.26 mmol, 1.1 equiv.) was added, and the solution was removed from the cold bath and allowed to warm to room temperature over the course of 1.17 h. The solution was re-cooled to -78°C and NBS (632 mg, 3.55 mmol, 1.2 equiv.) was added. The solution was allowed to stir for 40 min at -78°C before being diluted with EtOAc and quenched with a 1:1 solution of brine: aqueous 1M HCl. The aqueous layer was extracted 3x with EtOAc, and the combined organic layers were washed with sat. aqueous NaHCO_3 , brine, dried over MgSO_4 , filtered, and condensed. The resultant material was purified via flash column chromatography (silica gel, gradient: 5% to 7.5% EtOAc/hexanes) to yield linear α -bromo acetate **38** as a pale-yellow oil (877 mg, 74 % yield).

38: $R_f = 0.26$ (silica gel, 10% ethyl acetate/hexanes); IR (film): ν_{max} 2920, 2851, 1731, 1443, 1379, 1228, 1117, 1024, 737 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 5.33 (t, $J = 7.1$ Hz, 1H), 5.14 (t, $J = 6.1$ Hz, 1H), 4.58 (d, $J = 7.1$ Hz, 2H), 3.82 (s, 3H), 2.98 – 2.88 (m, 1H), 2.83 – 2.74 (m, 1H), 2.30 (t, $J = 7.7$ Hz, 2H), 2.15 – 2.08 (m, 2H), 2.07 – 2.03 (m, 5H), 1.99 (s, 3H), 1.70 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 200.5, 171.3, 169.1, 142.2, 133.8, 124.9, 118.6, 62.7, 61.5, 54.0, 39.5, 37.1, 34.4, 26.3, 25.6, 21.2, 16.6, 16.2; HRMS (ESI-TOF, m/z) calcd for $\text{C}_{18}\text{H}_{27}\text{NaBrO}_5$ $[\text{M}+\text{Na}]^+$ 425.0940, found 425.0921.

Linear α -Bromo β -Hydroxy Acetate **45**. Linear α -bromo acetate (397 mg, 990 μ mol, 1.0 equiv.) was dissolved in 20 mL MeOH and cooled to -78 $^{\circ}$ C. NaBH₄ (75 mg, 1.97 mmol, 2.0 equiv.) was added, and the solution was allowed to stir for 30 min at -78 $^{\circ}$ C. Upon completion, the reaction was diluted with EtOAc, and quenched with 1M HCl. The aqueous layer was extracted 3x with EtOAc, and the combined organic layers were washed 1x with 1M HCl, 1x with sat. aqueous NaHCO₃, and 1x with brine. The organic layers were dried over MgSO₄, filtered, and condensed. The resultant crude material was purified via flash column chromatography (silica gel, gradient: 8% to 10% to 12% to 15% EtOAc/hexanes) to yield linear α -bromo β -hydroxy acetate **45** as a clear oil (278 mg, 70% yield).

45: R_f = 0.13 (silica gel, 15% EtOAc/hexanes); IR (film): $\nu_{\max}$ 3479, 2934, 1731, 1443, 1235, 1024, 912, 733 cm^{-1} ; ^1H NMR (600 MHz, CDCl₃) δ 5.35 (t, J = 6.8 Hz, 1H), 5.17 (t, J = 6.5 Hz, 1H), 4.59 (d, J = 7.2 Hz, 2H), 4.07 (ddd, J = 10.6, 5.9, 1.5 Hz, 1H), 3.81 (s, 3H), 2.61 (d, J = 6.0 Hz, 1H), 2.29 – 2.22 (m, 1H), 2.18 – 2.10 (m, 3H), 2.07 (t, J = 7.9 Hz, 2H), 2.05 (s, 3H), 2.02 – 1.94 (m, 1H), 1.86 (s, 3H), 1.71 (s, 4H), 1.63 (s, 3H), 1.51 – 1.44 (m, 1H); ^{13}C NMR (150 MHz, CDCl₃) δ 171.9, 171.3, 142.2, 134.7, 124.9, 118.6, 75.0, 63.3, 61.6, 53.4, 39.6, 36.4, 29.0, 26.2, 22.0, 21.2, 16.5, 16.0; HRMS (ESI-TOF-TOF, m/z) calcd for C₁₈H₂₉O₅NaBr [M+Na]⁺ 427.1096, found 427.1099.

Truncated Linear Alcohol **S5**. (E)-4-hydroxy-3-methylbut-2-en-1-yl acetate (prepared according to the literature,⁶⁹ 3.57g, 24.8 mmol, 1.0 equiv.) was azeotropically distilled with PhMe to remove trace H₂O, and was subsequently dissolved in 83 mL THF. The solution was cooled to -78 $^{\circ}$ C and MsCl (2.5 mL, 32.2 mmol, 1.3 equiv.) and Et₃N (6.9 mL, 49.6 mmol, 2.0 equiv.) were added. The solution was slowly allowed to warm to -15 $^{\circ}$ C over 3 h. A solution of Lil (13.3 g, 99.2 mmol, 4.0 equiv.) in 50 mL THF was added, and the resultant solution was stirred for 50 min, slowly warming from -15 $^{\circ}$ C to -10 $^{\circ}$ C. The resultant solution was diluted with Et₂O, quenched with sat. aqueous NaHCO₃, extracted 3x with Et₂O, washed with 10% aqueous NaHSO₃, sat. aqueous NH₄Cl, H₂O, and brine. The combined organic layers were dried over MgSO₄, filtered, and condensed to yield the corresponding allylic iodide (5.2 g, 83% yield). The resultant crude material was used directly in the next step.

A suspension of NaH (60% dispersion in mineral oil, 4.1 g, 102.5 mmol, 5.0 equiv.) in 256 mL THF was cooled to 0 °C, and neat methyl 2-methyl-3-oxobutanoate (prepared according to the literature,⁶⁶ 13.3 g, 102.5 mmol, 5.0 equiv.) was slowly added and the solution was allowed to stir for 35 min. *n*-BuLi (2.28M/hexanes, 45 mL, 102.5 mmol, 5.0 equiv.) was slowly added at 0 °C and the solution was allowed to stir for 45 min before being cooled to -78 °C. A solution of the allylic iodide (5.2 g, 20.5 mmol, 1.0 equiv.) in 40 mL THF was slowly added and the solution was stirred for 45 min. The resultant solution was diluted with EtOAc, and quenched with H₂O and sat. aqueous NH₄Cl. The aqueous layer was extracted 3x with EtOAc, and the combined organic layers were washed with brine, dried over MgSO₄, filtered, and condensed. The resultant crude material was purified via flash column chromatography (silica gel, 10% to 15% to 25% to 35% to 50% EtOAc/hexanes) to yield truncated linear alcohol **S5** as a yellow oil (2.82 g, 64% yield). Truncated linear acetate **S6** was also isolated as a yellow oil (500 mg, 10% yield).

S5: R_f = 0.19 (silica gel, 40% ethyl acetate/hexanes); IR (film): $\nu_{\max}$ 3418, 2920, 1739, 1710, 1437, 1268, 1207, 1070, 999 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 5.40 (t, J = 6.9 Hz, 1H), 4.15 (d, J = 6.9 Hz, 2H), 3.74 (s, 3H), 3.55 (q, J = 7.2 Hz, 1H), 2.77 – 2.69 (m, 1H), 2.68 – 2.60 (m, 1H), 2.31 (d, J = 7.5 Hz, 2H), 1.68 (s, 3H), 1.35 (d, J = 7.1 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 205.2, 171.1, 138.1, 124.2, 59.4, 52.9, 52.6, 39.7, 33.0, 16.6, 13.0; HRMS (ESI-TOF, m/z) calcd for C₁₁H₁₈O₄Na [M+Na]⁺ 237.1103, found 237.1096.

Truncated Linear Acetate **S6**. Truncated linear alcohol **S5** (1.44 g, 5.6 mmol, 1.0 equiv.) was dissolved in 5.6 mL CH₂Cl₂ at room temperature. Ac₂O (1.32 mL, 14 mmol, 2.5 equiv.) was added, followed by DMAP (17 mg, 140 μ mol, 2.5 mol%), and the solution was stirred at room temperature for 1.25 h before MeOH was added. After stirring for an additional 10 min, the solution was added to H₂O/hexanes, and the layers were separated. The organic layer was washed 2x with H₂O, 2x with sat. aqueous NaHCO₃, brine, dried over MgSO₄, filtered, and condensed to yield truncated linear acetate **S6** as a pale-yellow oil (1.57 g, 91% yield). The resultant material was pure enough to be used in subsequent operations without purification.

S6: R_f = 0.26 (silica gel, 20% ethyl acetate/hexanes); IR (film): $\nu_{\max}$ 3336, 2923, 1739, 1716, 1454, 1433, 1368, 1232, 1024, 610 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 5.33 (t, J = 7.0 Hz, 1H), 4.57 (d, J = 7.1 Hz, 2H), 3.74 (s, 3H), 3.54 (q, J = 7.0 Hz, 1H), 2.77 – 2.69 (m, 1H), 2.67 – 2.60 (m, 1H), 2.33 (t, J = 7.7 Hz, 2H), 2.05 (s, 3H), 1.71 (s, 3H), 1.35 (d, J = 7.2 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 205.0, 171.2, 171.1, 140.6, 119.2, 61.3, 52.9, 52.6, 39.6, 33.0, 21.2, 16.8, 13.0; HRMS (ESI-TOF, m/z) calcd for C₁₃H₂₀O₅Na [M+Na]⁺ 279.1208, found 279.1196.

Truncated α -Bromo Acetate **S7**. Truncated linear acetate **S6** (1.57 g, 6.13 mmol, 1.0 equiv.) was azeotropically distilled 2x with PhMe to remove trace H₂O, dissolved in 125 mL THF, and cooled to 0 °C. NaH (60% dispersion in mineral oil, 270 mg, 6.74 mmol, 1.1 equiv.) was added, and the solution was stirred for 1.17 h at 0 °C. The solution was cooled to -78 °C and NBS (1.2 g, 6.74 mmol, 1.1 equiv.) was added. The solution was stirred at -78 °C for 1 h before being diluted with EtOAc and quenched with aqueous. 1M HCl. The aqueous layer was extracted 3x with EtOAc, and the combined organic layers were washed with sat. aqueous NaHCO₃, brine, and dried over MgSO₄, filtered, and condensed. The resultant material was purified via flash column chromatography (silica gel, 15% EtOAc/hexanes) to yield truncated α -bromo acetate **S7** as a pale-yellow oil (1.53 g, 75% yield).

S7: R_f = 0.50 (silica gel, 20% ethyl acetate/hexanes); IR (film): $\nu_{\max}$ 1728, 1443, 1367, 1230, 1118, 1073, 1022, 957, 736, 607 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 5.36 (t, J = 7.0 Hz, 1H), 4.58 (d, J = 7.0 Hz, 2H), 3.83 (s, 3H), 3.03 – 2.94 (m, 1H), 2.88 – 2.79 (m, 1H), 2.37 (t, J = 7.7 Hz, 2H), 2.05 (s, 3H), 1.99 (s, 3H), 1.72 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 200.2, 171.2, 169.0, 140.3, 119.4, 62.4, 61.3, 54.0, 36.5, 34.1, 25.6, 21.2, 16.7; HRMS (ESI-TOF, m/z) calcd for C₁₃H₁₉O₅NaBr [M+Na]⁺ 357.0314, found 357.0311.

Allylic Acetate **48**. Truncated α -bromo acetate **S7** (270 mg, 810 μ mol, 1.0 equiv.) was azeotropically distilled 2x with PhMe to remove trace H₂O, and was then dissolved in 16 mL MeOH. The solution was cooled to -78 °C, and NaBH₄ (61 mg, 1.61 mmol, 2.0 equiv.) was added. The solution was stirred for 50 min before being diluted with EtOAc and quenched with aqueous 1M HCl. The aqueous layer was extracted 3x with EtOAc, and the combined organic layers were washed with sat. aqueous NaHCO₃, brine, dried over MgSO₄, filtered, and condensed. The resultant material was purified via flash column chromatography (silica gel, 15% EtOAc/hexanes) to yield allylic acetate **48** as a pale-yellow oil (130 mg, 48% yield).

48: R_f = 0.23 (silica gel, 20% ethyl acetate/hexanes); IR (film): $\nu_{\max}$ 3497, 2959, 2934, 1739, 1713, 1447, 1383, 1232, 1114, 1052, 1020, 737, 625 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 5.42 (t, J = 7.2 Hz, 1H), 4.60 (dd, J = 7.1, 3.0 Hz, 2H), 4.07 (ddd, J = 10.6, 6.1,

1.6 Hz, 1H), 3.83 (s, 3H), 2.53 (d, $J = 6.0$ Hz, 1H), 2.38 – 2.31 (m, 1H), 2.20 – 2.14 (m, 1H), 2.06 (s, 3H), 2.04 – 1.98 (m, 1H), 1.87 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 171.9, 171.3, 141.5, 119.3, 75.2, 63.1, 61.5, 53.5, 36.4, 29.0, 22.0, 21.2, 16.6; HRMS (ESI-TOF, m/z) calcd for $\text{C}_{13}\text{H}_{21}\text{O}_5\text{NaBr}$ $[\text{M}+\text{Na}]^+$ 359.0470, found 359.0458.

Reduced Product **49**. *Preparation 1*. Allylic acetate **48** (25 mg, 74 μmol , 1.0 equiv.) was azeotropically distilled 2x with PhMe to remove trace water, and was subsequently dissolved in 3.7 mL of CH_2Cl_2 and cooled to -45°C under an O_2 balloon. AlMe_3 (2M/hexanes, 111 μL , 222 μmol , 3.0 equiv.) was added and the solution was stirred for 35 min. Bu_3SnH (36 μL , 133 μmol , 1.8 equiv.) was added, and syringe pump addition (0.08 mL/h) of Et_3B (1M/hexanes, 148 μL , 148 μmol , 2.0 equiv.) was initiated. After stirring for 4 h, the solution was diluted with EtOAc, and quenched with H_2O , aqueous 1M HCl, and solid potassium sodium tartrate tetrahydrate. The solution was allowed to stir for 30 min before sat. aqueous NaHCO_3 was added until the layers were clear. The aqueous layer was extracted 3x with EtOAc, and the combined organic layers were washed with sat. aqueous NaHCO_3 , brine, dried over MgSO_4 , filtered, and condensed. The resultant crude material was purified via flash column chromatography (silica gel, 25% EtOAc/hexanes) to yield reduced product **49** as a clear oil (7.8 mg, 41% yield).

Reduced Product **49**. *Preparation 2*. Truncated linear acetate **S6** (80 mg, 240 μmol , 1.0 equiv.) was dissolved in 5 mL MeOH and cooled to 0°C . NaBH_4 (18 mg, 480 μmol , 2.0 equiv.) was added, and the solution was stirred at 0°C for 25 min before being diluted with EtOAc and quenched with aqueous 1M HCl. The aqueous layer was extracted 3x with EtOAc, and the combined organic layers were washed with sat. aqueous NaHCO_3 , brine, dried over MgSO_4 , filtered, and condensed. The resultant material was purified via flash column chromatography (silical gel, gradient: 20% to 25% EtOAc/hexanes) to yield reduced product **49** as a clear oil (57 mg, 70% yield).

49: $R_f = 0.29$ (silica gel, 30% ethyl acetate/hexanes); IR (film): ν_{max} 3467, 2947, 1731, 1439, 1368, 1231, 1025 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) *Major Diastereomer* δ 3.67 – 3.61 (m, 1H), 1.22 (d, $J = 7.2$ Hz, 3H), *Minor Diastereomer* δ 3.86 (ddd, $J = 8.4, 4.0$ Hz, 1H), 1.19 (d, $J = 7.3$ Hz, 1H), *Shared Peaks* δ 5.37 (t, $J = 7.2$ Hz, 1H), 4.58 (d, $J = 7.1$ Hz, 2H), 3.71 (s, 3H), 2.60 (d, $J = 6.8$ Hz, 1H), 2.58 – 2.52 (m, 1H), 2.51 (d, $J = 4.7$ Hz, 0H), 2.30 – 2.22 (m, 1H), 2.17 – 2.06 (m, 1H), 2.05 (s, 3H), 1.71 (s, 3H), 1.68 – 1.47 (m, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 176.6, 176.5, 171.3, 142.0, 141.9, 118.9, 118.8, 73.1, 71.5, 61.5, 61.4, 52.0, 51.9, 45.3, 44.5, 36.0, 35.6, 32.8, 31.8, 21.2, 16.6, 16.6, 14.5, 11.0; HRMS (ESI-TOF, m/z) calcd for $\text{C}_{13}\text{H}_{22}\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 281.1365, found 281.1363.

Truncated β -Keto Ester **S8**. (E)-2-Methylbut-2-en-1-ol (prepared according to the literature,⁷⁰ 1.84 g, 21.4 mmol, 1.0 equiv.) was dissolved in 72 mL THF and cooled to -78°C . MsCl (2.2 mL, 27.8 mmol, 1.3 equiv.) and Et_3N (6.0 mL, 42.8 mmol, 2.0 equiv.) were added and the solution was slowly allowed to warm to -40°C over the course of 3.5 h. A solution of LiI (11.5 g, 85.6 mmol, 4.0 equiv.) in 36 mL THF was added, and the resultant solution was stirred for 1 h. The reaction was diluted with Et_2O and quenched with sat. aqueous NaHCO_3 , H_2O , and 10% aqueous NaHSO_3 . The aqueous layer was extracted 3x with Et_2O , and the combined organic layers were washed with sat. aqueous NH_4Cl , H_2O , and brine. The organic layers were dried over MgSO_4 , filtered, and condensed (bath temperature = 0°C) to yield the corresponding iodide, which was used without further purification in the next step.

A suspension of NaH (60% dispersion in mineral oil, 2.57 g, 64.2 mmol, 3.0 equiv.) in 250 mL THF was cooled to 0°C , and neat methyl 2-methyl-3-oxobutanoate (prepared according to the literature,⁶⁶ 8.35 g, 64.2 mmol, 3.0 equiv.) was slowly added, and the resultant solution was allowed to stir for 30 min. *n*-BuLi (2.28M/hexanes, 28 mL, 64.2 mmol, 3.0 equiv.) was slowly added, and the resultant solution was allowed to stir for 35 min. A solution of (E)-2-methylbut-2-en-1-ol (assuming quantitative yield from previous step, 21.4 mmol, 1.0 equiv.) in 40 mL THF was added, and the reaction was removed from the cold bath and allowed to stir at room temperature for 2.5 h. The resultant solution was diluted with EtOAc and quenched with sat. aqueous NH_4Cl , H_2O , and 10% aqueous NaHSO_3 . The aqueous layer was extracted 3x with EtOAc, and the combined organic layers were washed with brine, dried over MgSO_4 , filtered, and condensed. The resultant crude material was purified via flash column chromatography (silica gel, 2.5% to 5% to 7.5% Et_2O /hexanes) to yield truncated β -keto ester **S8** as a pale-yellow oil (2.5 g, 59% yield over 2 steps).

S8: $R_f = 0.44$ (silica gel, 10% ethyl acetate/hexanes); IR (film): ν_{max} 2948, 1745, 1713, 1437, 1200, 1174, 1120, 1070 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 5.20 (q, $J = 6.6$ Hz, 1H), 3.73 (s, 3H), 3.54 (q, $J = 7.1$ Hz, 1H), 2.70 – 2.54 (m, 2H), 2.26 (t, $J = 7.7$ Hz, 2H), 1.59 (s, 3H), 1.56 (s, 3H), 1.33 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 205.7, 171.2, 134.2, 119.4, 52.9, 52.5, 40.3, 33.4, 15.8, 13.5, 13.0; HRMS (ESI-TOF, m/z) calcd for $\text{C}_{11}\text{H}_{17}\text{O}_3$ $[\text{M}-\text{H}]^-$ 197.1178, found 197.1185.

α -Bromo β -Keto Ester **53**. Truncated β -keto ester **S8** (300 mg, 1.52 mmol, 1.0 equiv.) was azeotropically distilled 2x with PhMe to remove trace H₂O, then dissolved in 30 mL MeOH and cooled to 0 °C. NaH (60% dispersion in mineral oil, 67 mg, 1.67 mmol, 1.1 equiv.) was added and the solution was allowed to stir for 35 min at 0 °C. The solution was cooled to –78 °C, then NBS (297 mg, 1.67 mmol, 1.1 equiv.) was added and the solution was allowed to stir for 40 min at –78 °C. Upon completion, the solution was diluted with EtOAc and quenched with aqueous 1M HCl. The aqueous layer was extracted 3x with EtOAc, and the combined organic layers were washed with sat. aqueous NaHCO₃, brine, dried over MgSO₄, filtered, and condensed. The resultant material was purified via flash column chromatography (silica gel, gradient: 2% to 3% to 4% EtOAc/hexanes) to yield α -bromo β -keto ester **53** as a clear oil (270 mg, 64% yield). NOTE: This compound is unstable at room temperature and should be stored in a freezer.

53: R_f = 0.63 (silica gel, 10% ethyl acetate/hexanes); IR (film): $\nu_{\max}$ 2959, 2920, 2862, 1760, 1724, 1443, 1268, 1117, 1074, 974, 737 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 5.25 (q, J = 6.6 Hz, 1H), 3.82 (s, 3H), 2.97 – 2.89 (m, 1H), 2.82 – 2.73 (m, 1H), 2.30 (t, J = 7.6 Hz, 2H), 1.99 (s, 4H), 1.61 (s, 3H), 1.57 (d, J = 6.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 200.6, 169.1, 134.0, 119.7, 62.8, 54.0, 37.1, 34.4, 25.6, 15.8, 13.5; HRMS (ESI-TOF, m/z) calcd for C₁₁H₁₈O₃Br [M+H]⁺ 277.0439, found 277.0436.

Truncated α -Bromo β -Hydroxy Ester **50**. Truncated α -bromo β -keto ester **53** (270 mg, 980 μ mol, 1.0 equiv.) was dissolved in 20 mL MeOH and cooled to –78 °C. NaBH₄ (75 mg, 1.96 mmol, 2.0 equiv.) was added and the solution was stirred at –78 °C for 40 min. Another portion of NaBH₄ (37 mg, 980 μ mol, 1.0 equiv.) was added and the solution was stirred for 20 min at –78 °C. The reaction was diluted with EtOAc, and quenched with aqueous 1M HCl. The aqueous layer was extracted 3x with EtOAc, and the combined organic layers were washed with sat. aqueous NaHCO₃, brine, dried over MgSO₄, filtered, and condensed. The resultant material was purified via flash column chromatography (silica gel, gradient: 5% to 10% EtOAc/hexanes) to yield truncated α -bromo β -hydroxy ester **50** as a clear oil (190 mg, 70% yield).

50: R_f = 0.32 (silica gel, 15% ethyl acetate/hexanes); IR (film): $\nu_{\max}$ 3439, 2925, 1727, 1446, 1268, 1119, 1057, 910, 736 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 5.30 (q, J = 6.8 Hz, 1H), 4.07 (ddd, J = 10.5, 6.1, 1.6 Hz, 1H), 3.82 (s, 3H), 2.47 (d, J = 6.2 Hz, 1H), 2.31 – 2.23 (m, 1H), 2.16 – 2.08 (m, 1H), 2.02 – 1.94 (m, 1H), 1.86 (s, 3H), 1.63 (s, 3H), 1.59 (d, J = 6.7, 1.1 Hz, 3H), 1.53 – 1.44 (m, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 171.9, 135.1, 119.6, 75.4, 63.4, 53.4, 36.6, 29.3, 22.2, 15.7, 13.5; HRMS (ESI-TOF, m/z) calcd for $\text{C}_{11}\text{H}_{20}\text{O}_3\text{Br}$ $[\text{M}+\text{H}]^+$ 279.0596, found 279.0586.

Lactone **54**. Truncated α -bromo β -keto ester **53** (58 mg, 210 μmol , 1.0 equiv.) was dissolved in 2.1 mL CH_2Cl_2 , and 2,6-lutidine (49 μL , 420 μmol , 2.0 equiv.) and *fac*-Ir(ppy)₃ (3.4 mg, 5.3 μmol , 2.5 mol%) were added at room temperature. Two strips of blue LEDs were turned on (purchased from Creative Lighting Solutions, creativelightings.com, Product Code: CL FRS5050–12WP-12V, Model: Sapphire Blue LED Flex Strip) and the reaction was stirred for 1 h at room temperature. Upon completion, the solution was condensed and purified via PTLC (silica gel, 25% EtOAc/hexanes) to yield lactone **54** as a clear oil (3.8 mg, 10% yield).

54: R_f = 0.39 (silica gel, 30% ethyl acetate/hexanes); IR (film): $\nu_{\max}$ 2926, 1778, 1720, 1451, 1383, 1243, 1146, 1056, 927, 740 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 2.72 – 2.59 (m, 2H), 2.35 (qd, J = 13.9, 8.8, 1.4 Hz, 1H), 2.29 (q, J = 7.0 Hz, 1H), 1.99 (ddd, J = 14.1, 10.4, 8.0 Hz, 1H), 1.49 (s, 3H), 1.22 (s, 3H), 1.03 (d, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 201.5, 175.0, 84.4, 63.0, 48.6, 36.5, 35.4, 21.3, 11.1, 10.6; HRMS (ESI-TOF, m/z) calcd for $\text{C}_{10}\text{H}_{14}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 205.0841, found 205.0847.

Linear α -Bromo Alcohol **58**. Linear alcohol **6a** (250 mg, 890 μ mol, 1.0 equiv.) was dissolved in 18 mL THF and cooled to 0 °C. NaH (60 % dispersion in mineral oil, 35 mg, 890 μ mol, 1.0 equiv.) was added and the solution was stirred for 2h at 0 °C. The solution was cooled to -78 °C and NBS (173 mg, 980 μ mol, 1.1 equiv.) was added. The solution was stirred for 1 h at -78 °C before being diluted with Et₂O and quenched with sat. aqueous NaHCO₃. The aqueous layer was extracted 3x with Et₂O, and the combined organic layers were washed 2x with H₂O, brine, dried over MgSO₄, filtered, and condensed. The resultant material was used without further purification, yielding linear α -bromo alcohol **58** as a yellow oil (320 mg, 99% yield).

58: R_f = 0.29 (silica gel, 30% ethyl acetate/hexanes); IR (film): ν_{max} 3391, 2921, 1723, 1442, 1250, 1119, 994, 736 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 5.40 (t, J = 7.0 Hz, 1H), 5.14 (t, J = 6.7 Hz, 1H), 4.15 (d, J = 6.9 Hz, 2H), 3.82 (s, 3H), 2.97 – 2.89 (m, 1H), 2.81 – 2.74 (m, 1H), 2.30 (t, J = 7.5 Hz, 2H), 2.11 (q, J = 7.3 Hz, 2H), 2.06 – 2.01 (m, 2H), 1.99 (s, 4H), 1.67 (s, 3H), 1.61 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 200.5, 169.1, 139.5, 133.6, 125.1, 123.8, 62.7, 59.6, 54.0, 39.4, 36.96, 34.3, 26.3, 25.6, 16.4, 16.2; HRMS (ESI-TOF, m/z) calcd for C₁₆H₂₅O₄NaBr [M+Na]⁺ 383.0834, found 383.0846.

Representative Photoredox-Catalyzed Cyclization

Linear α -bromo alcohol **58** (26 mg, 72 μ mol, 1.0 equiv.) was dissolved in 3.6 mL CH₂Cl₂. DABCO (16 mg, 145 μ mol, 2.0 equiv.) and *fac*-Ir(ppy)₃ (240 μ g, 360 nmol, 0.5 mol%) were added, and two strips of blue LEDs were turned on (purchased from Creative Lighting Solutions, creativelightings.com, Product Code: CL FRS5050-12WP-12V, Model: Sapphire Blue LED Flex Strip). After 1.5 h the lights were turned off, the reaction was diluted with Et₂O, several drops of aqueous 1M HCl were added (to precipitate DABCO), the solution was dried over MgSO₄, filtered through celite, and condensed. The crude product mixture was analyzed using an internal standard (0.02M 1,3,5- trimethoxybenzene in CDCl₃) revealing bicyclic alcohol **8a** (14% yield).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
The oridamycin and xiamycin families of indolosesquiterpenes.

Scheme 1.

Unified Synthetic Strategy Towards the Xiamycin and Oridamycin Families

Scheme 2.
Retrosynthesis of Oridamycin A

A. Indole Attachment **B. Proposed Reductive Deoxygenation** **C. Carbazole Synthesis** **D. One Pot Process**

Scheme 3.
Construction of Carbazole 11a

Scheme 4.
Synthesis of Oridamycin A

A. O-Acetyloxime Directed C-H Oxidation **B. O-Methyloxime Directed C-H Oxidation** **C. Completion of Oridamycin B**

Scheme 5.
Synthesis of Oridamycin B

A. Inner Sphere Oxidation with Separate Lewis Acid **B. Outer Sphere Enolate Oxidation with Chelating Counterion** **C. Combination Oxidant and Lewis Acid** **D. Chelated Atom-Transfer Cyclization**

Scheme 6.
Strategies Towards Xiamycin A

Scheme 7. Attempted Atom-Transfer Cyclizations of α -Functionalized β -Keto Esters

Scheme 8. Attempted Atom-Transfer Cyclizations of α -Bromo β -Hydroxy Ester **45**

Scheme 9. Failure of Radical Derived from Allylic Acetate **48** to Cyclize

Scheme 10. Attempts to Cyclize Model α -Bromo β -Hydroxy Ester **50**

A. Initial Hit for Photoredox Catalyzed Cyclization **B. Proposed Mechanism** **Scheme 11.**Photoredox Catalyzed Cyclization of Model α -Bromo β -Keto Ester **53**

Table 1.

Oxidation with Oxo-Vanadium Complexes

Entry	Additive (equiv.)	Temp. (°C)	Time	Result
1 ^A	—	0	2h	decomp.
2	—	−40 to rt	18h	no rxn.
3	TMSOTf (3.0)	−78 to rt	22h	complex mixture
4	Cu(OTf) ₂ (3.0)	−55 to −25	2.5h	36 (56%)

Std. conditions: V(O)Cl₂(OTf) (3.0 equiv.), 2,4,6-tri-*tert*-butylpyridine (4.0 equiv.), PhMe (0.02M).

^AUsed CH₂Cl₂ as solvent, no base was added.

Table 2.Photoredox Catalyzed Cyclization of Model α -Bromo β -Keto Ester 53

Entry	Base	(equiv.)	Time	Yield 54
1 ^A		2,6-lutidine (2.0)	1h	10%
2		Et ₃ N (2.0)	2h	8%
3		DABCO (2.0)	1.5h	8%
4 ^B		Et ₃ N (2.0)	1h	17%
5 ^B		DABCO (2.0)	1h	28%

Std. conditions: fac-Ir(ppy)₃ (2.5 mol%), CH₂Cl₂ (0.1M), room temperature, blue LEDs. Yield determined by internal standard (1,3,5-trimethoxybenzene, 0.02M/CDCl₃).

^A Isolated yield.

^B After rxn., added HCl (2M/Et₂O, 2.0 equiv.), stirred for 18h.

Table 3.

Photoredox Catalyzed Cyclization of α -Bromo β -Keto Ester 58

Entry	Solvent	Catalyst (equiv.)	Base (equiv.)	Time	Yield 8a
1	CH ₂ Cl ₂ (0.1M)	fac-Ir(ppy) ₃ (0.5 mol%)	DABCO (2.0)	1.5h	7%
2	CH ₂ Cl ₂ (0.05M)	fac-Ir(ppy) ₃ (0.5 mol%)	DABCO (2.0)	1.5h	8%
3	CH ₂ Cl ₂ (0.02M)	fac-Ir(ppy) ₃ (0.5 mol%)	DABCO (2.0)	1.5h	14%
4	MeCN (0.02M)	fac-Ir(ppy) ₃ (0.5 mol%)	DABCO (2.0)	3.5h	13%
5	MeCN (0.02M)	Ir(ppy) ₂ (dtbpy)PF ₆ (1.0 mol%)	DABCO (2.0)	0.5h	10%
6	MeCN (0.02M)	Ir(dF-ppy) ₃ (1.0 mol%)	DABCO (2.0)	0.5h	8%
7	MeCN (0.02M)	Ir(dF-ppy) ₂ (dtbpy)PF ₆ (1.0 mol%)	DABCO (2.0)	0.5h	10%
8	MeCN (0.02M)	Ru(bpy) ₃ (PF ₆) ₂ (1.0 mol%)	DABCO (2.0)	0.5h	13%
9	MeCN (0.02M)	Ru(bpy) ₃ (PF ₆) ₂ (0.5 mol%)	DABCO (2.0)	0.5h	12%
10	MeCN (0.02M)	Ru(bpy) ₃ (PF ₆) ₂ (0.1 mol%)	DABCO (2.0)	0.5h	11%
11	MeCN (0.02M)	Ru(bpy) ₃ (PF ₆) ₂ (0.01 mol%)	DABCO (2.0)	0.5h	10%

Std. conditions: Room temperature, blue LEDs. Yield determined by internal standard (0.02M 1,3,5-trimethoxybenzene in CDCl₃).