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Biomimetic Total Synthesis of (+)-Nocardioazine B and Analogs

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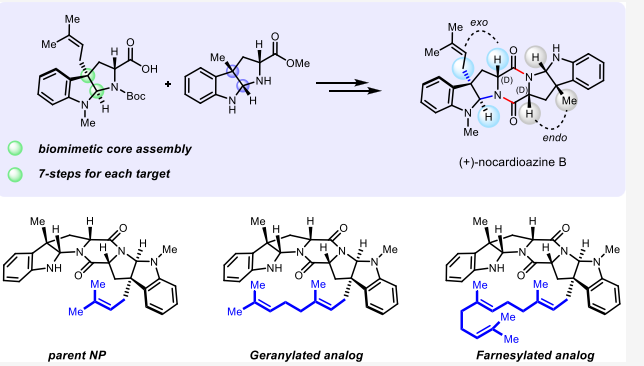
ABSTRACT: Nocardioazines A and B are prenylated, bioactive pyrroloindoline natural products, isolated from *Nocardiopsis*, with a desymmetrized *cyclo*-D-Trp-D-Trp DKP core. Based on our deeper biosynthetic understanding, a biomimetic total synthesis of (+)-nocardioazine B is accomplished in merely seven steps and 23.2% overall yield. This pathway accesses regio- and stereoselectively C3-isoprenylated analogs of (+)-nocardioazine B, using the same number of steps and in similar efficiency. The successful strategy mandated that the biomimetic C3-prenylation step be executed early. The use of an unprotected carboxylic acid of Trp led to high diastereoselectivity toward formation of key intermediates *exo*-**12a**, *exo*-**12b**, and *exo*-**12c** (>19:1). Evidence shows that *N*1-methylation causes the prenylation reaction to bifurcate away to result in a C2-normal-prenylated isomer. Nocardioazine A, possessing an isoprenoidal-epoxide bridge, inhibits P-glycoprotein (P-gp)-mediated membrane efflux, in multidrug-resistant mammalian colon cancer cells. As several P-gp inhibitors have failed due to their toxicity effects, endogenous amino-acid-derived noncytotoxic inhibitors (from the nocardioazine core) are worthy leads toward a rejuvenated strategy against resistant carcinomas. This total synthesis provides direct access to Trp-derived isoprenylated DKP natural products and their derivatives.



INTRODUCTION

Prenylated pyrroloindolines possessing a 2,5-diketopiperazine (DKP) core are significant motifs in natural products and medicinal chemistry.[1] DKP-containing bioactives constitute useful therapeutics as well (e.g., Tadalafil, Retosiban, Bicyclomycin, etc.).[2] Nocardioazines A and B are marine-derived, structurally unique prenylated pyrroloindoline natural products. These were discovered by Raju *et al.* from an actinomycete, *Nocardiopsis* sp. (CMB-M0232), isolated from an ocean sediment near Brisbane, Australia, in 2011.[3] Nocardioazine A, possessing an isoprenoidal-epoxide bridge between the two tryptophan (Trp) units, inhibits P-glycoprotein (P-gp)-mediated membrane efflux in multidrug-resistant (MDR) mammalian colon cancer cells. Structurally similar DKP-containing prenylated pyrroloindolines as noncytotoxic MDR reversal agents, belonging to the amauoramine (Figure 1A) and ardeemin families, were reported earlier by Danishefsky *et al.*[4]

Overexpression of P-gp in most carcinomas is one of the causes toward the development of anticancer drug resistance. Therefore, noncytotoxic, specific P-gp inhibitors are worthy leads toward a rejuvenated strategy against resistant carcinomas.[5] To this end, nocardioazines and their synthetic analogs are reasonable leads toward profiling their P-gp inhibitory activity. Thus far, Ye, Reisman, and Zhang groups have reported three distinct strategies targeting nocardioazine natural products.[6] As briefly illustrated in Figure 1B, the first synthesis of nocardioazine B by the Ye group corrected the absolute configurations of the DKP core to be consisting of the unnatural D-isomer at both α-centers of Trp.[6a] Reisman's approach employed a catalytic asymmetric [3 + 2] cycloaddition reaction between a C3-alkyl indole and an enamide to construct fused pyrroloindolines enantioselectively and resulted in the first total synthesis of nocardioazine A.[6b] The approach reported recently by Zhang's group employed nonindole precursors.[6c]

We have reported detailed biosynthetic studies on the enzymatic assembly of the nocardioazines.[7] The DKP core construction toward nocardioazine biogenesis employs unique cyclodipeptide synthase enzymology.[8] Nature encodes distinct and precisely ordered enzymatic steps, in the form of a prenyltransferase and methyltransferase to execute stereo- and regioselective C3-normal prenylation and dual methylations (N1 and C3′) of Trp DKPs during the course of nocardioazine B biosynthesis. We have recently elucidated this biosynthetic pathway that, in addition to prenyl transfer and methylation reactions, also included an unprecedented isomerase enzyme that converts the L-Trp to its D-version in the DKP form.[9] Further downstream of (+)-nocardioazine B biogenesis, a

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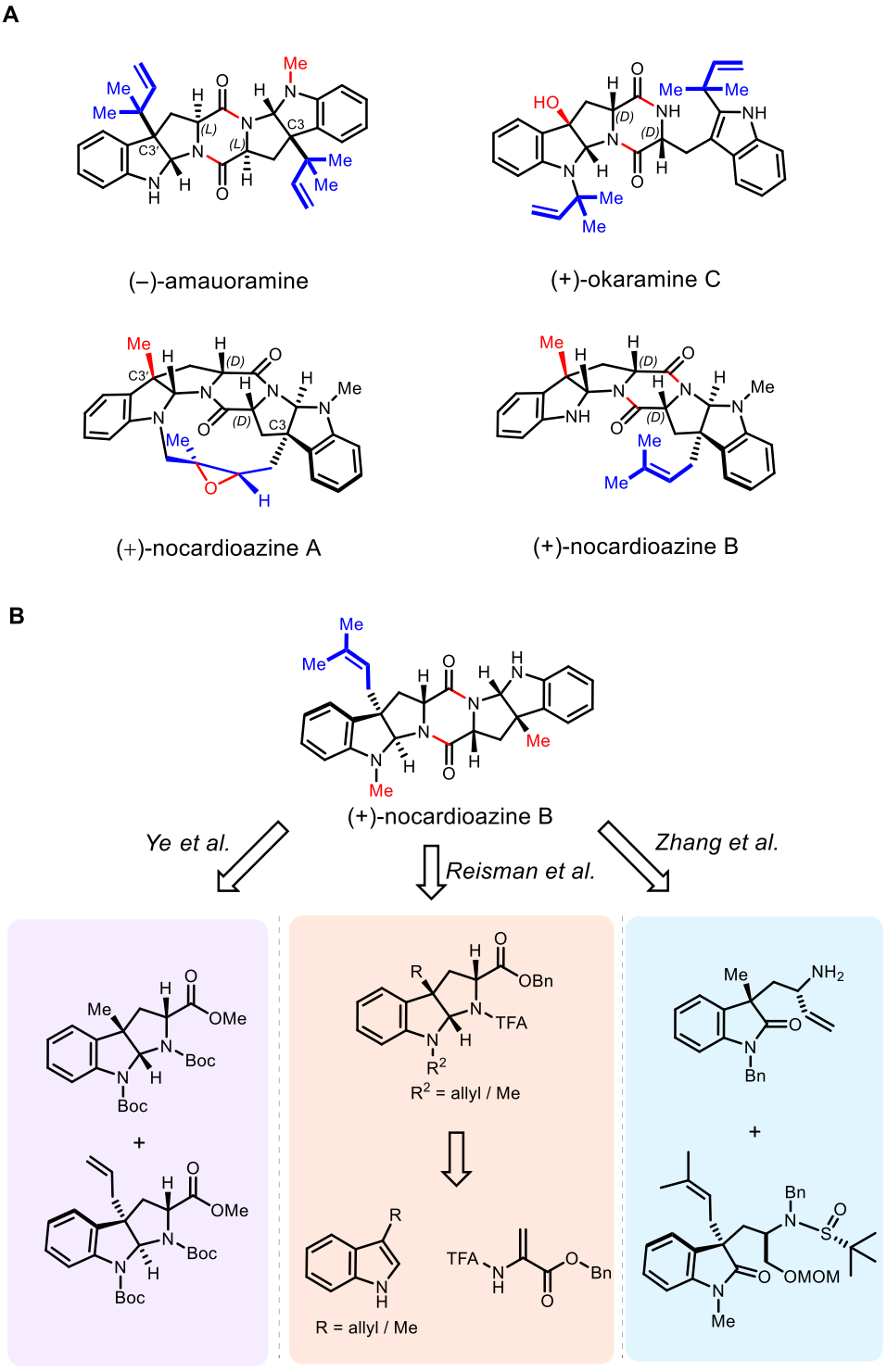

Figure 1. (A) Bioactive prenylated pyrroloindoline DKP natural products. (B) Key disconnections in prior total syntheses of (+)-nocardioazine B.

regioselective terpene oxidation, a macrocyclization tethering the isoprenoid chain, and a stereoselective epoxidation step would yield the bridged (+)-nocardioazine A.[7] We have previously reported a Brønsted acid-promoted regioselective prenylating strategy that is applicable to both monomeric and dimeric L-Trp DKPs as a valuable transformation (Figure 2).

This strategy mimics the fungal and bacterial prenyltransferases and operates as a green synthetic pathway toward pyrroloindolines.[10] In this direction, the *Nocardiopsis* prenyltransferase (NozPT) served as a template for the development of biomimetic regioselective prenylations. *Cyclo*-Trp-Trp-DKPs could be engaged in regioselective C3-isoprenylations, leading to pyrroloindoline building blocks, and furthermore, the reactions are sustainable and work without any protecting group.[11] By tapping into this biomimetic isoprenylation repertoire, we present a robust, enantiospecific total synthesis of (+)-nocardioazine B and its isoprenylated analogs.

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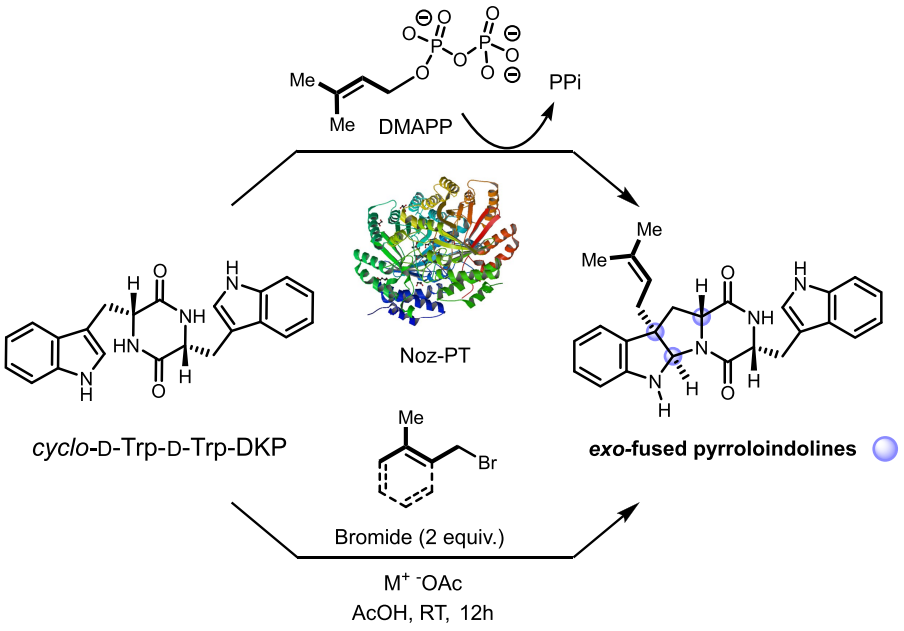
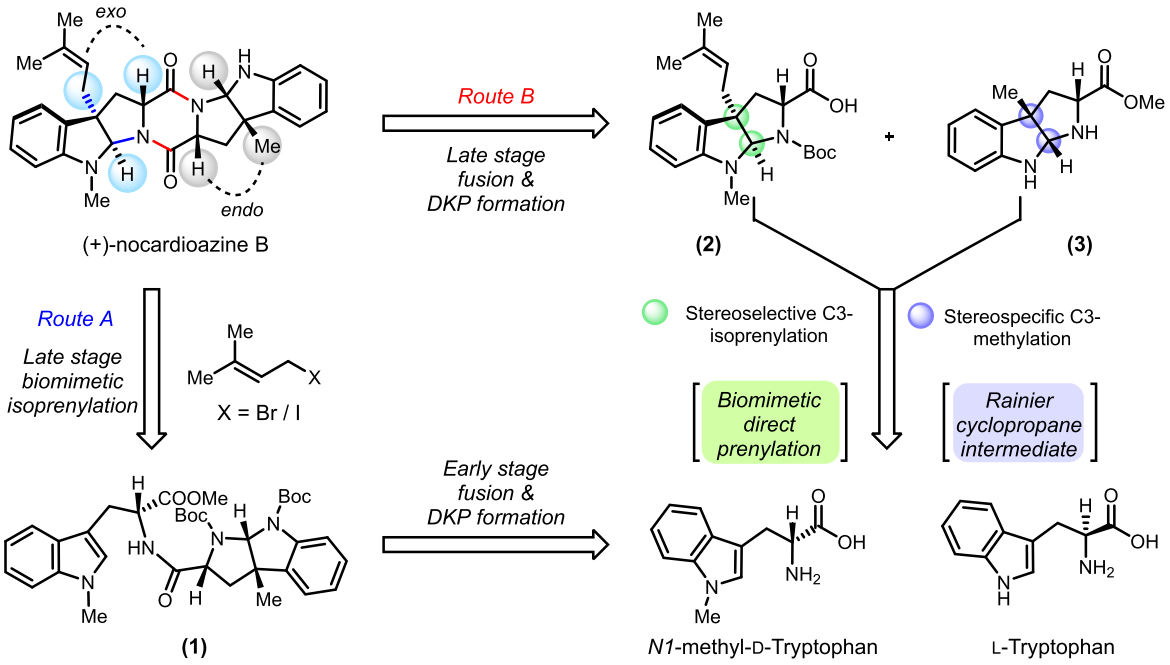


Figure 2. Biomimetic tryptophan-C3-normal-prenylation catalyzed by a prenyltransferase in the biogenesis of the nocardioazines provides a template for this work.

Scheme 1. Retrosynthetic Plans for the Total Synthesis of (+)-Nocardioazine B and Its Analogs



RESULTS AND DISCUSSION

The pseudosymmetric framework of nocardioazine B, featuring a 2,5-diketopiperazine core, is fused with C3′-methyl and C3-prenyl pyrroloindolines and is desymmetrized through their relative *endo* and *exo* configurations of the fused rings. Although nocardioazine biogenesis involves L-Trp as starter units, the presence of appropriate racemases ends up delivering a D-Trp-D-Trp DKP core in nocardioazines A and B, as further evidenced by the structural revision report by Ye *et al.*[6a] and independently verified through enzymology experiments.[9] Guided by the biosynthetic template, we charted two retrosynthetic plans for the total synthesis of (+)-nocardioazine B. As illustrated in Scheme 1, route A would employ a direct C3-prenylation of the dipeptide (**1**), as the end-game, with very minimal protecting group manipulations.

We could envision certain challenges in this strategy as direct prenylations of indoles have traditionally proved to be challenging due to its lack of regioselection.[12] As an alternative, route B, consisting of an early C3-prenylation step, will rely on a late-stage fusion with its C3′-methylated counterpart to complete the total synthesis. The *endo*-C3′-methyl pyrroloindoline (**3**), a common precursor identified for both approaches, was planned to be coupled with either preprenylated *exo*-pyrroloindoline (**2**) or *N*1-Me-D-Trp, for the late-stage indole isoprenylation. We chose Rainier's cyclopropylazetoindoline[13] intermediate, for introducing the C3′-methyl substitution, as it

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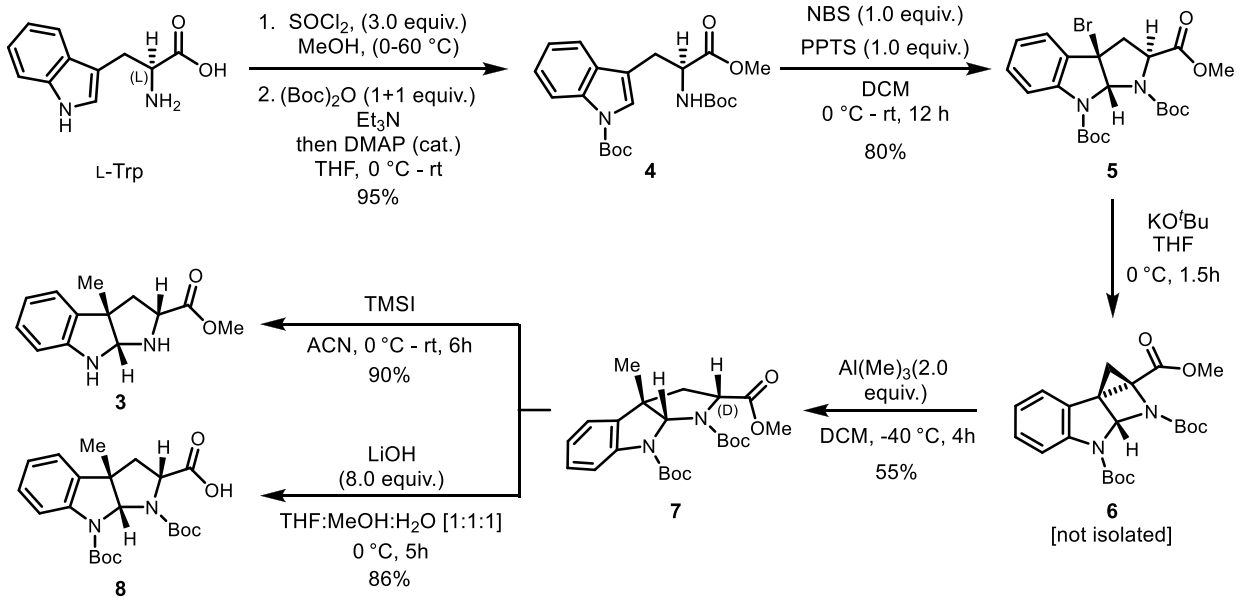
Scheme 2. Synthesis of *Endo*-C3′-Methyl Pyrroloindolines 3 and 8 as Orthogonally Protected Intermediates



would render L-Trp to be a viable starting material in our sequence. Thus, *endo*-C3′-methyl pyrroloindolines (**3** and its orthogonally protected version **8**) were targeted starting from L-Trp, as illustrated in Scheme 2.

Concurring with previous reports,[4,6a,10] the *bis*-Boc-protected Trp methyl ester **4** (obtained from L-Trp) was treated with *N*-bromosuccinimide (NBS, 1 equiv) and pyridinium *p*-toluenesulfonate (PPTS, 1 equiv) to promote a dearomative indole-C3 bromination, resulting in the pyrroloindoline **5**, as a single diastereomer, in 80% yield. KO^{t}Bu-facilitated enolate formation in dry THF, followed by rapid intramolecular displacement of the bromide, afforded cyclopropylazetoindoline **6** as an intermediate that was formed and was further transformed without isolation. This intermediate could be sequenced into the C3-methylation step, as expected by treatment with Lewis acidic trimethylaluminum (2.0 equiv, 2 M solution in toluene) in dichloromethane at −40 °C, enabling a stereospecific cyclopropane ring opening with a methyl nucleophile, affording *endo*-C3′-methyl pyrroloindoline **7**, as a single diastereomer, in good yield. This common intermediate (**7**) was orthogonally deprotected to corresponding pyrroloindoline **3** and acid **8** in straightforward manner. Boc-deprotection of amine and indole functionalities worked well using TMS-iodide in acetonitrile yielding **3** in 90% yield. The ester group of **7** was converted to acid through saponification by excess LiOH (in THF:water:-MeOH), yielding **8** in 86% yield. No epimerization of an α-amino acid stereocenter of **7** was observed under the LiOH conditions, implying that *endo*-**7** is probably the thermodynamically favored diastereomer. This efficient route ensured that the C3′-methyl containing intermediates were flexibly synthesized and were ready for coupling at later stages of the sequence.

Next, we set out to execute our synthetic plan illustrated by route A that will directly access (+)-nocardioazine B. The plan would be through a regio- and stereoselective-C3-normal-prenylation of a dipeptide (**1**) or its cyclized DKP (**9**) that would probably have its *N*-methyl indole side chain undergo this reaction (Scheme 3).

*N*1-Me-D-Trp methyl ester as its TFA salt was therefore prepared from D-Trp using α-*N*-Boc protection (in 96% yield) followed by *N*1-methylation using MeI in THF (85% yield) and then subjecting the product to Boc-deprotection using TFA in quantitative yield (Supporting Information, Spectrum 17). Fragment **8** (consisting of the C3′-Me in its acid form) was therefore coupled to *N*1-methyl-D-Trp-methyl ester TFA salt, and the resulting peptide **1** was isolated in 79% yield. This peptide coupling employing addition of *N*-hydroxybenzotriazole monohydrate followed by HATU in the presence of 2,4,6-collidine as a base gave access to **1** in good yield, albeit as a diastereomeric mixture (**1** and *epi*-**1**, 1.5:1 dr). Epimerization was observed on the α-stereocenter of the C3′-methylated pyrroloindoline moiety. Diastereomeric compounds were unambiguously characterized (see the Supporting Information). The dipeptide **1** was then subjected to the regioselective isoprenylation method, with prenyl bromide (**10a**) (2.0 equiv) in the presence of metal cationic additives, in a manner highly similar to an established protocol from our previous studies.[10,11] It was found that most of the cationic metal additives facilitated the isoprenylation reaction, however, with poor outcomes in terms of the conversion and regioselectivity. Furthermore, the unanticipated C2-isoprenylated indole isomer remained dominant in all reactions even after extensive screening of various conditions (Table S5, Supporting Information). Key observations explaining these outcomes are presented later. While the C3-prenylation of **1** seemed to work very poorly, as was evidenced by TLC, the overall strategy was in question. Furthermore, the formation of the cyclic DKP **9**, which was attempted to be prepared from **1**, using the deprotection-cyclization sequence (with TMSI and Hünig's base) failed to yield **9**. Attempts to directly access the target natural product by prenylation and cyclization to form a DKP core also led to inconclusive results. As the late-stage isoprenylation did not appear to be feasible, we switched our approach to route B. In this path, the *exo*-C3-prenyl pyrroloindoline ring system will get constructed through an early C3-isoprenylation step of **11**. This step, however, presented regio- and stereoselectivity challenges. *N*1-Methyl-*N*α-Boc-D-Trp acid (**11**) was prepared from *N*α-Boc-D-Trp acid using KO^{t}Bu (in THF) and methyl iodide in 65% yield. Similar to our earlier reports,[11] **11** was subjected to NaOAc (2.0 equiv) to induce isoprenylation with prenyl bromide (**10a**, 2.0 equiv) in acetic acid (0.1 M) as a solvent at

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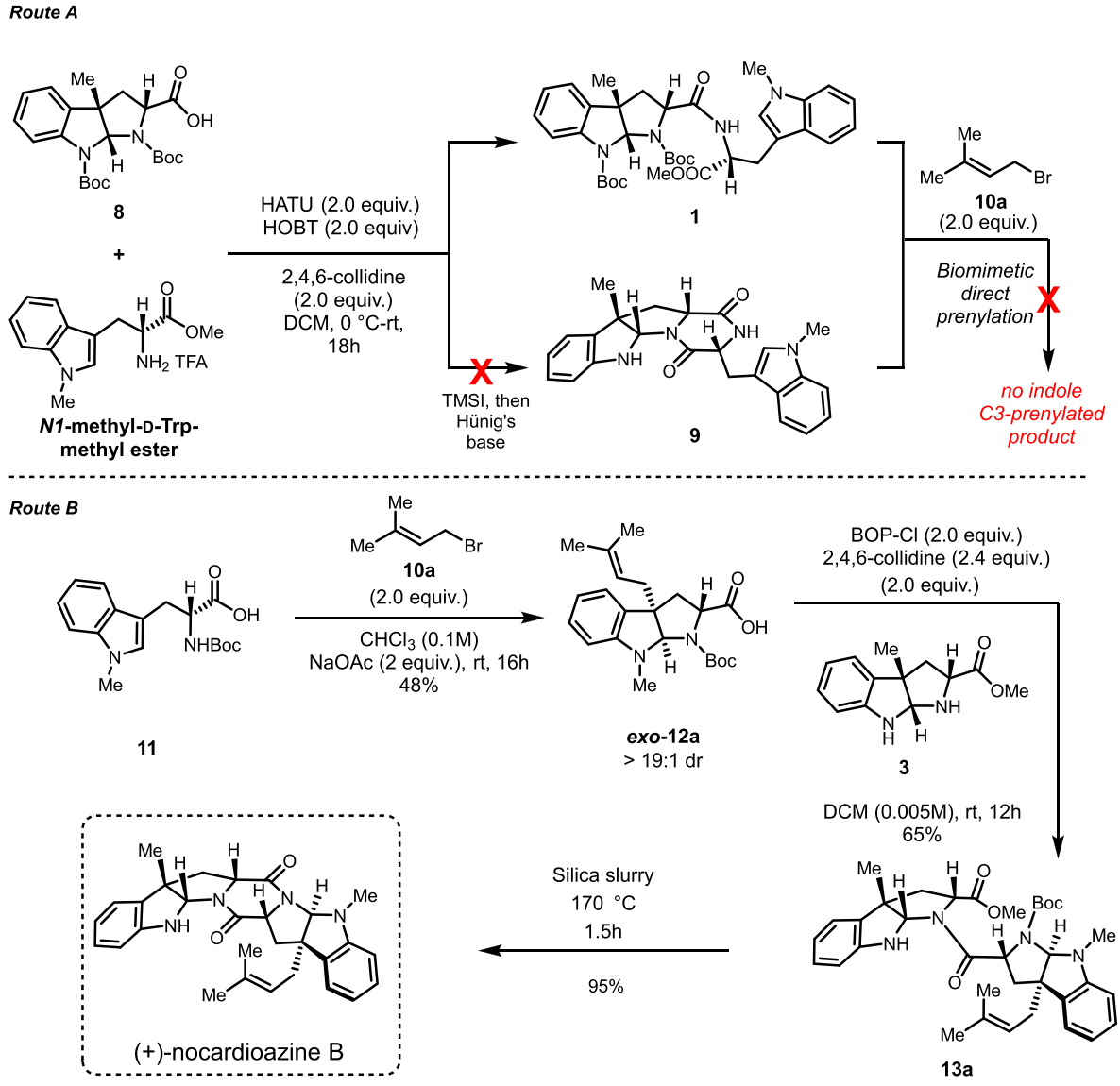
Scheme 3. Stereoselective C3-Prenylation and Completion of Total Synthesis of (+)-Nocardioazine B



room temperature. This approach turned out to be fruitful as the reaction gave *exo*-C3-prenyl pyrroloindoline acid (*exo*-**12a**) as a single diastereomer in noticeable yield (41%, with an additional 23% of the unreacted starting material that was recovered). The product displayed identical NMR spectra (^{1}H and ^{13}C) with data reported earlier by the Zhang group.[6c] This high diastereoselectivity observed for the C3 prenylation (>19:1) is a drastic improvement to our earlier results, wherein the isoprenylation of Trp-OMe afforded three different isomers (C3-*exo*, C3-*endo*, and its rearranged C2-prenyl-regioisomer) with the C3-functionalized products found in nearly a 1:1 ratio.[11] The excellent diastereoselectivity of the C3 prenylation product (*exo*-**12a**) indicated that the α-stereocenter of the amino acid was relaying its chiral influence on to the C3-prenylation process much more effectively. The presence of the free carboxylic acid would be expected to enhance tighter coordination to the incipient prenyl cation, through the coordination of the O atom of carboxylic acid and the carbocationic prenyl unit, in the putative transition state. The presence of the carboxylic acid facilitating the prenyltransfer to the C3 carbon atom with higher diastereoselectivity (stereoselection) is probably concomitantly processed with the sodium ion facilitating the bromide to leave the prenyl chain smoothly. The marvelous work performed by the Toste group[14] demonstrating that chiral anion phase transfer of aryldiazonium cations to form enantioenriched pyrroloindolines perhaps is an analogous mode of selectivity, albeit being an example for the intermolecular version. Correlating to this observation is the fact that when *N*1-Me-D-Trp-OMe was treated with prenyl bromide in the presence of NaOAc, a highly sluggish reaction ensues with the product yield being so low and with no stereoselection, further corroborating to this hypothesis. Results from Ishikawa's studies on L-Trp-OEt under biomimetic prenylation conditions also corroborates with this hypothesis.[12] Along this tighter cation coordination hypothesis, further optimizing conditions in which NaOAc (2.0 equiv) induced isoprenylation in chloroform (at 0.1 M) gave better results (48% yield of *exo*-**12a**, as a single diastereomer, with additional 25% of the recovered unreacted starting material. With *exo*-**12a** in hand, a peptide coupling reaction was executed between this and the 2° amine of fragment **3**, using BOP-chloride (2.0 equiv) and 2,4,6-collidine (2.3 equiv) as the base, in relatively dilute conditions (0.005 M) in

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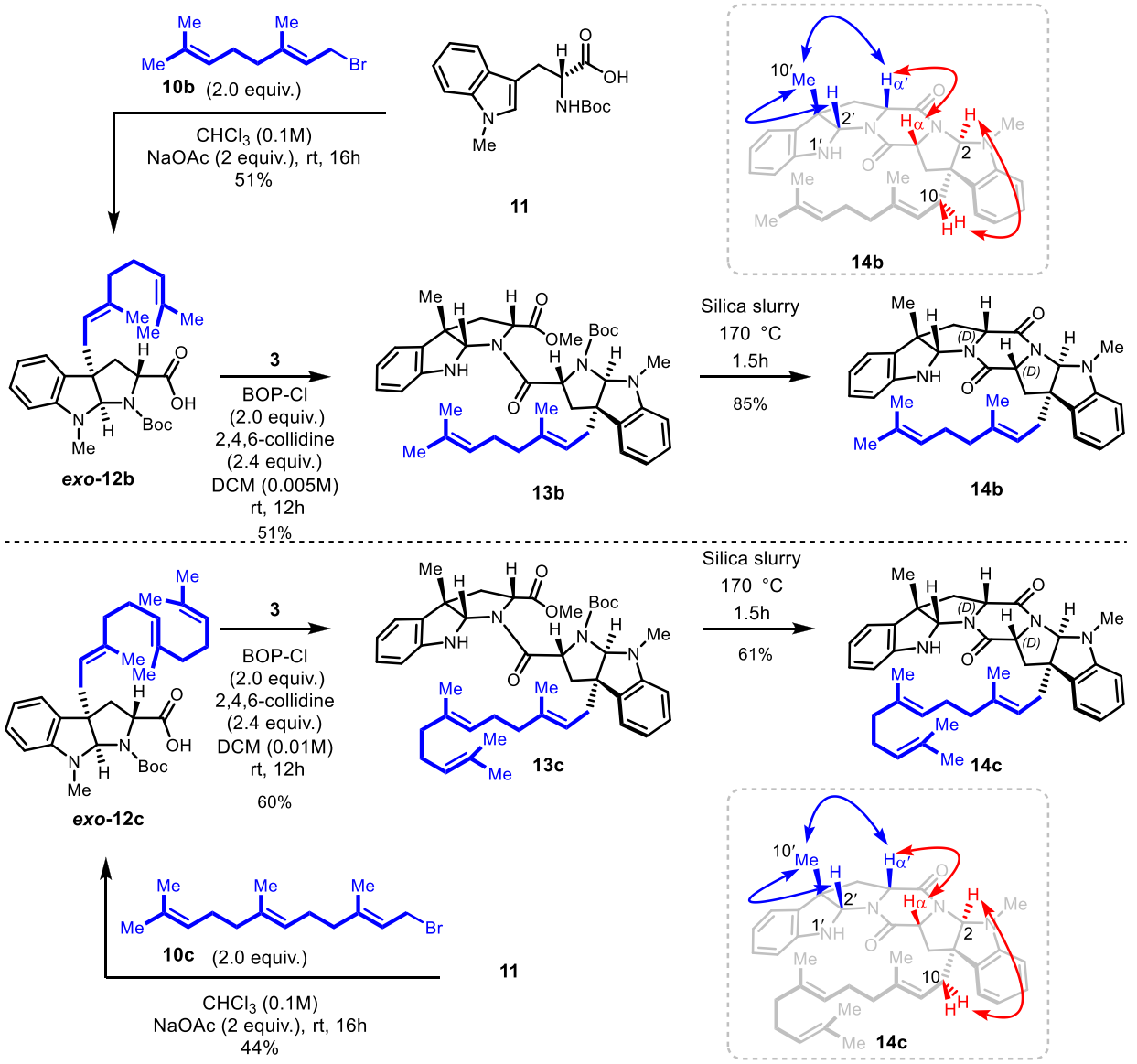
Scheme 4. Total Synthesis of (+)-Nocardioazine B Analogs Using the Direct Biomimetic C3-Isoprenylation Strategy



DCM. It was important to execute a slow addition of acid (*exo*-**12a**) over 14 h, using a syringe pump, to maximize conversion to the desired peptide, ultimately yielding **13a** in 65% yield. The pyrroloindoline 2° amine reacted in preference to the indole N, owing to a greater nucleophilicity. The slow addition and dilute conditions were necessary to prevent dimerization of **3**, among other undesired side products. In the end-game sequence involving deprotection and DKP formation, to our surprise, several classical Boc-deprotection strategies (TFA, TMSOTf, and TMSI, even in the presence of various solvents and promoters) failed to deliver the necessary product (Table S2, Supporting Information). In our hands, these conditions either caused decomposition of the starting dipeptide (**13a**) or otherwise did not react at all. Interestingly, heating the peptide on a silica TLC plate and eluting with ethyl acetate/hexane (30:70) indicated the formation of corresponding acyclic amine and then the natural product nocardioazine B itself (TLC developed with 30:70 ethyl acetate/hexane). Therefore, treatment of the peptide **13a** with mildly acidic silica gel (230−400 mesh) in the form of a slurry, and further heating to 170 °C over 1.5 h, triggered the tandem deprotection-cyclization events and resulted in the formation of (+)-nocardioazine B in 95% yield. The ^{1}H and ^{13}C NMR spectra of our synthesized (+)-nocardioazine B was compared with those reported earlier and were found to be identical (see the Supporting Information).[3,6] The specific optical rotation $[\alpha]_D^{25}$ of +53.4 (in $CHCl_3$, *c* 0.03) also correlated with data reported earlier. High-resolution mass spectrometry further confirmed the target structure. Considering the modularity of our synthetic path, the longest linear sequence consisted of seven steps, with five of them culminating in the synthesis of intermediate C3′-methyl-pylrroloindoline **3**.

Nocardioazine B Analogs. By taking an approach that directly prenylates the Trp unit, in this total synthesis of (+)-nocardioazine B, next, we targeted synthesizing its isoprenyl analogs.

As illustrated in Scheme 4, acid **11** was subjected to NaOAc (2.0 equiv) to promote a C3-geranylation and C3-farnesylation using geranyl bromide (**10b**) (2.0 equiv) and farnesyl bromide (**10c**) (2.0 equiv), respectively. This in turn consistently generated *exo*-C3-isoprenyl pyrroloindoline acid analogs in 51 and 44% yields, respectively. Similar to the synthesis of

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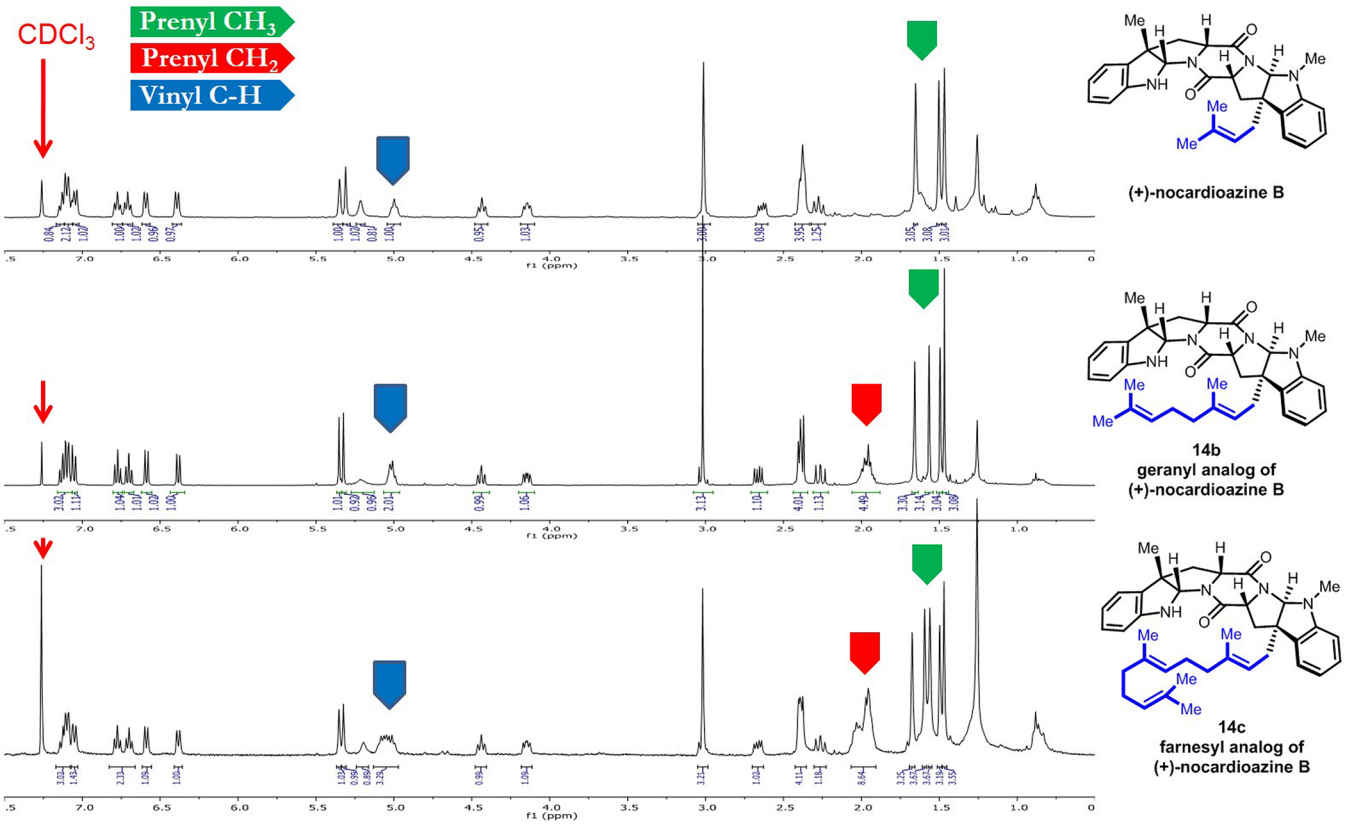

Figure 3. Stacked plot comparing analogs of nocardioazine B to its parent structure.

nocardioazine B, the C3-geranylation and farnesylation resulted in higher stereoselectivities (>19:1), thus yielding single diastereomers, **12b** and **12c**, respectively. Overall productivity of these steps is practical bearing in mind that the strategy works to install isoprenyl chains, directly in a biomimetic fashion, thus avoiding multiple steps and/or protecting groups. Corresponding peptides **13b** and **13c** were synthesized employing a similar protocol to that used for the synthesis of peptide **13a**. Similar to the ^{1}H NMR data corresponding to **13a**, peptides **13b** and **13c** displayed rotamers as indicated in the Supporting Information (Spectra 23, 29, and 43). Finally, the single pot deprotection-cyclization sequence was executed, in each case, resulting in (+)-nocardioazine B analogs, **14b** (geranylated analog) and **14c** (farnesylated analog).

The HRMS analyses of each of the two analogs, **14b** and **14c**, were consistent with the respective molecular masses. The stacked plot of ^{1}H NMR data between nocardioazine and its analogs unambiguously verified the olefinic portion in each target (Figure 3). The structural analogy between (+)-nocardioazine B and its isoprenylated analogs were confirmed with detailed 1D and 2D-NMR spectroscopic data. Characteristic features of the pyrroloindoline ring systems analogous to (+)-nocardioazine B are distinctly visible in the NMR spectra for **14b** and **14c**, respectively. Namely, these are (a) the upfield shifted aromatic C2 proton signal (δ 5.32), (b) signal for the 1-*N*-Me protons (δ 3.02), (c) the multiplet signal for the β-methylene protons (δ 2.26−2.66) on the C3-prenylated half, and (d) an upfield shifted C2 and C3 carbons in the ^{13}C NMR (δ 85.2 and 83.9, respectively) as illustrated in the Supporting Information (Spectra 25, 31, and 45).

The COSY NMR data helped establish the key *J*-coupling correlations of the isoprenyl side chain (for both geranyl and farnesylated derivatives), α(CH), and β(CH2) protons (Supporting Information, Spectra 34 and 48). The ROESY and NOESY spectra as illustrated in the Supporting Information (Spectra 35−37 and 49−52) revealed the absolute and relative configuration of each pyrroloindoline ring system in detail, the summary of which is illustrated in Scheme 4 (above). The strong nOe correlations between α-protons $H_{\alpha'}$ (δ 4.44) with H_{α} (δ 4.15) for **14b** and **14c** indicated D-configuration at α-amino acid centers. The presence of strong nOe *endo*-correlation, $H_{\alpha'}$ (δ 4.44) with C10′-Me (δ 1.47) and *cis*-correlation, C10′-Me (δ 1.47) with C2′-H (δ 5.35) in ROESY and NOESY spectra (Spectra 35−37 and 49−52) can be confirmatory to assign the *exo*-configuration between the α-proton H_{α} (δ 4.15) and the isoprenyl group (C10-protons, δ 2.43−2.33). Moreover, other nOe correlations helped to assign the spatial arrangements of key protons. Furthermore, the heteronuclear correlations drawn from HSQC and HMBC spectra helped to assign the key ^{1}H and ^{13}C chemical shifts of compound **14b** and **14c** as illustrated in the Supporting Information (Spectra 39−40 and 53−54).

Having achieved success in synthesizing nocardioazine B and its analogs, we looked deeper into the probable reasons that caused the crucial prenylation step in route A to fail. Boc-protected dipeptide **1**, consisting of the *N*1-methylated indole side chain (for which the construction was discussed earlier) was investigated further. As illustrated in Scheme 5 (eq. 1), upon subjecting **1** toward C3-prenylation with **10a** under standard conditions, we obtained **16** that was shown to be the C2-prenylated isomer. Various attempts confirmed this observation (Table S5, Supporting Information). The identity of **16** was verified from the absence of the characteristic peak in ^{1}H NMR that belongs to the cyclized pyrroloindoline CH at the C2 position (δ 5.25 ppm, ref. Spectrum 25, Supporting

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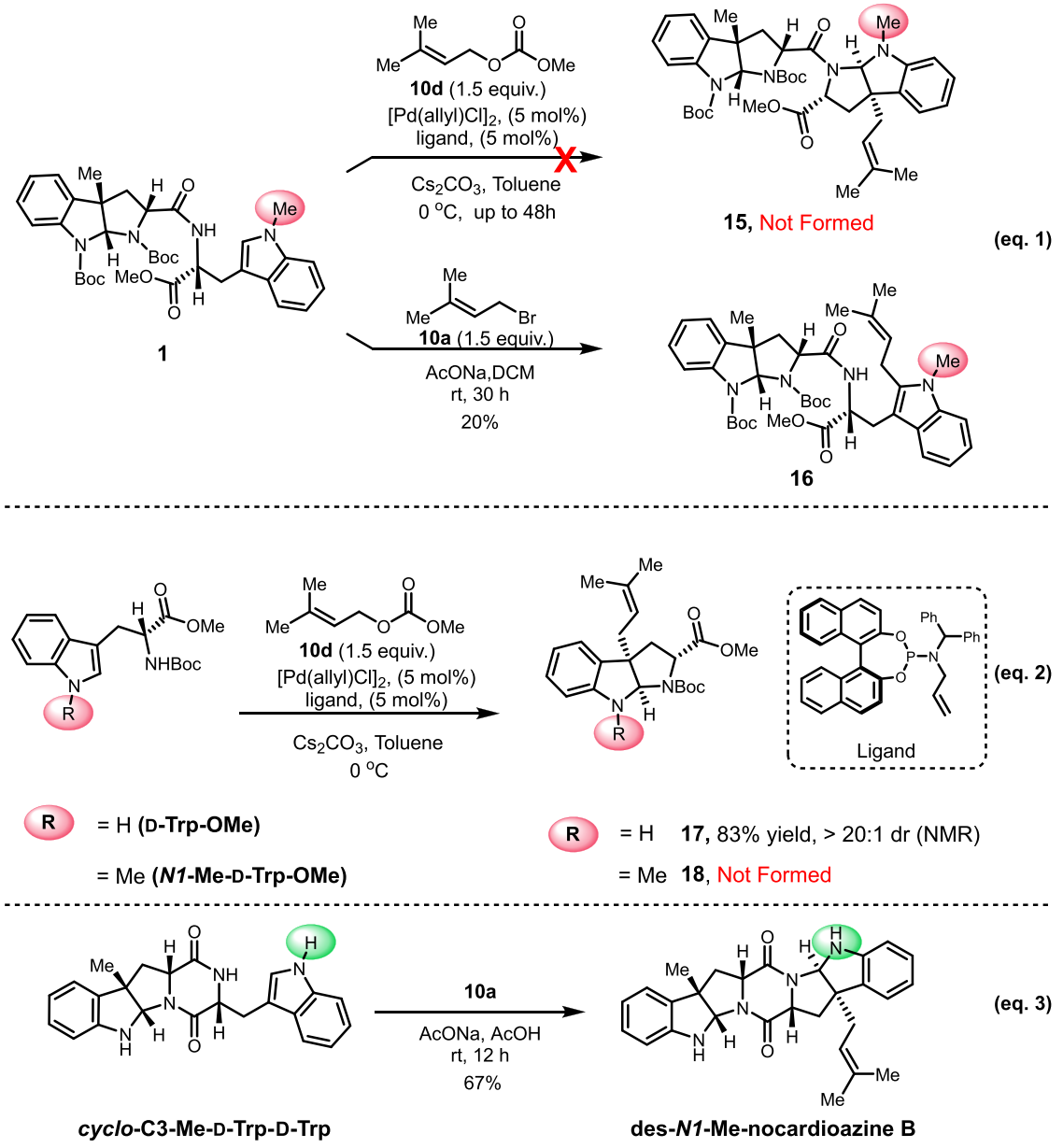
Scheme 5. Comparison between Isoprenylation on *N*1-Methylated and Des-Me-Nocardioazine Precursor



Information). Reproducibly, this prenylation attempt on **1**, which yielded the C2-prenylated product (**16**), offered a chance to create a C2-isoprenyl nocardioazine B analog through a cyclization into the central DKP ring. Interestingly, as a complementary strategy, we noticed that You *et al.* reported a marvelous palladium-catalyzed dearomative indole isoprenylation strategy that afforded excellent conversion to obtain prenylated pyrroloindolines.[15] We tested this alternative method to see if a late-stage prenylation would be effective and feasible per route A.

Thereby, dipeptide **1** was then subjected to isoprenylation by employing prenylcarbonate (**10d**), in the presence of $[allylPdCl]_2$ (10 mol %), BINOL-based ligand (synthesized, Spectra 61−62, Supporting Information), and Cs_2CO_3 as a base, in toluene (0.1 M) at 0 °C. Despite following reported conditions, no C3-prenylated product (**15**) was observed. This observation raised curious questions about probable causes. One possibility was that the *N*1-methylation was probably altering the reactivity of the indole ring at the C3 position and precluding it from undergoing C3-prenylation. Another was perhaps that the steric constraint in the acyclic DKP precursor was forcing the peptide into an unreactive conformation and thereby preventing C3-prenylation. As we put these theories to test, consistent with the report by You *et al.*, when D-Boc-Trp-OMe was isoprenylated using the Pd-based catalytic conditions, the expected C3-prenyl pyrroloindoline **17** was formed in excellent yield (83%) and diastereoselectivity (Scheme 5, eq. 2). Interestingly, isoprenylation of simple *N*1-Me-Boc-Trp-OMe, which would not have any steric strain built-up, did not undergo this reaction, and therefore, not even a trace of **18** was observed. Irrespective of the type of strategy used, methylation of the indole *N* led to a shutdown of this C3-prenylating mode. Consistent with these observations is the fact that *cyclo*-C3′-Me-D-Trp-D-Trp DKP underwent the formation of des-Me-nocardioazine B in 67% yield, upon subjection to our C3-prenylating method (Scheme 5, eq. 3).[10] All these

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observations added evidence to the possibility that under palladium-catalyzed isoprenylation, the *N*1-methyl moiety is subduing the nucleophilicity of the indole ring resulting in no reaction at all. On the other hand, under milder conditions with prenyl bromide (**10a**) and NaOAc, **1** underwent a sluggish biomimetic isoprenylation but instead led to the C2-normal-prenylated product **16**, in 20% yield. However, the same biomimetic reaction conditions using acid **11** (wherein the indole N1 position is methylated) selectively and successfully provided the desired C3-prenylated pyrroloindoline of *exo*-**12a**. As alluded to earlier, the crucial role of the free carboxylic acid of **11** should perhaps be the factor that accelerates the C3-prenylating reaction, perhaps through stabilization of the transition state. Perhaps due to this reason, despite the presence of the *N*1-methylation on **11**, the C3-prenylation is occurring. Overall, these observations channeled our efforts to successfully synthesize (+)-nocardioazine B and its analogs through route B, wherein a biomimetic prenylation was executed on **11**.

CONCLUSIONS

Complex natural products with notable examples from the reverse-prenylated DKPs such as the amauoramines,[4] okaramines,[16] notoamides, and lansai[6b] alkaloids have challenged us to develop newer and sustainable strategies. Their unique structures also have evolved innate bioactivities that are worthy of harnessing, as leads for therapeutics. In the same light, the marine-derived nocardioazines A and B have also been inspiring synthetic targets. A robust convergent total synthetic strategy that gives the access to nocardioazines analogs and devoid of redox and functional group manipulations may lead to further delineation of their full biological efficacy. They have been investigated by us for their biochemical pathways for prospecting unique biocatalysts. While traditionally these DKPs have been documented to originate out of nonribosomal peptide synthetase (NRPS) pathways,[17] the recent decade has offered us biocatalytic pathways involving cyclo dipeptide synthases (CDPS) for their biogenesis. We and others[18] have discovered biocatalysts that selectively synthesize DKPs from two units of L-Trp-charged aminoacyl tRNAs.[8] Earlier work established that L-L-DKP could serve as a plausible precursor to the nocardioazines. Our continued interest in the biogenesis of nocardioazines has recently yielded clarity in terms of the specific types of biochemical steps that are employed. We have elucidated that the biosynthetic pathway employs a unique racemase enzyme and a phytoene synthase-like prenyltransferase that carries out the C3-setereselective normal prenylation. Overall, our biomimetic synthesis of (+)-nocardioazine B and its analogs proceeded in seven steps for each sequence. One of the key observations in this pathway was the use of unprotected carboxylic acid of Trp under C3-prenylating conditions. This led to >19:1 diastereoselectivity toward formation of key intermediates **12a**, **12b**, and **12c**, all as their *exo* isomers. (+)-Nocardioazine B was synthesized in 23.2% overall yield. Its geranyl and farnesyl analogs were synthesized in 16.6 and 13.9%, respectively. By comparison to existing routes to this natural product, the pathways of Ye,[6a] Reisman,[6b] and Zhang[6c] proceeded in 10 steps (11.8%), 9 steps (21%), and 18 steps (9.3%), respectively. By tapping into the biosynthetic template toward the nocardioazine alkaloids, we have created a pathway that mirrors a prenyltransferase enzymatic transformation, considering the regio- and stereoselectivity. We have probed into the feasibility of C3-prenylation conditions and discovered the effect of *N*1-methylation in these C3-prenylation reactions. We have established a concise route to the nocardioazine alkaloids and their analogs. These may potentially have enhanced or altered the biological properties, including a higher affinity toward cell membrane bound targets.

EXPERIMENTAL SECTION

General Methods. *Reagents, Solvents, and Chromatography.* All reactions were carried out under a blanket of nitrogen or under regular atmospheric conditions, using standard syringe-septum and cannulation techniques. Pyridine, KOH, NaOH, Na_2CO_3, $NaHCO_3$, Na_2SO_4, and $Na_2S_2O_3$ were purchased from Merck. Boc anhydride, *N*-bromosuccinimide, DMAP, HOBT, HCl in dioxane, NaOAc, $SOCl_2$, TFA, *p*-toluene sulfonic acid, and triethyl amine were purchased from Spectrochem Chemicals. Allylpalladium chloride dimer, BOP-chloride, S- and R-BINOLs, HATU, LiOH, and L- and D-tryptophan were purchased from TCI Chemicals. $Al(Me)_3$, 2,4,6-collidine, farnesyl bromide, geranyl bromide, prenyl bromide, TMS-I, and TMS-triflate were purchased from Sigma Aldrich. Glacial acetic acid was obtained from Rankem and used without further purification. Dry THF and dichloromethane were purchased from Sigma Aldrich and used without further purification. All other solvents were purified according to standard procedures.[19] Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} precoated aluminum-backed plates (2.5 mm), specifically to monitor the progress of each chemical reaction and used as a guide for purification of the ensuing mixtures. Various combinations of ethyl acetate/hexanes and methanol/DCM were used as eluents. Visualization of spots after TLC was accomplished by exposure to staining agents (iodine vapor, ninhydrin, and/or PMA) and/or UV light (254 nm). All compounds were purified using gravity column chromatography (silica gel grade: 200−400 mesh, 40−63 μm). Yields refer to compounds isolated to analytical purity after chromatography.

Analytical Characterization. NMR spectroscopic analyses (^{1}H NMR, $^{13}C\{^1H\}$ proton decoupled NMR and 2D NMR) were conducted for all new compounds. ^{1}H (400 MHz), $^{13}C\{^1H\}$ (101 MHz), and 2D-NMR (COSY, NOESY, ROESY, HSQC, and HMBC) spectra were recorded on a 400 MHz spectrometer (Bruker AVANCE NEO 400 MHz FT-NMR spectrometer). Pertinent frequency is specifically reported for each spectrum. Chemical shift values (δ) for NMR spectra are reported in parts per million (ppm) relative to the residual (indicated) solvent peak ($CDCl_3$, DMSO-d_6, or CD_3OD). Additional peaks other than the compound in question, if any, are calibrated based on reported values for trace impurities.[20] Coupling constants are reported in hertz (Hz). Data for ^{1}H NMR are reported as follows: chemical shift (δ, ppm), multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, ddd = double double doublet, m = multiplet, and cm = complex multiplet), and integration corresponding to the number of protons followed by coupling constants in Hz. For $^{13}C\{^1H\}$ NMR spectra, the nature of the carbons (C, CH, CH_2, or CH_3) was determined by recording the Distortionless Enhancement by Polarization Transfer (DEPT) experiment, and notations are provided in parentheses. $^{13}C\{^1H\}$ NMR data is reported in parts per million (δ) relative to the residual (indicated) solvent peak. Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments. IR spectroscopic analyses were conducted on a Bruker ALPHA machine. Chiroptical measurements ($[\alpha]_D$) were obtained on a polarimeter (in a 100 × 2 mm cell. High-resolution mass spectra (HRMS) were obtained from an Orbitrap Elite HybridIon Trap-Orbitrap mass spectrometer in electrospray ionization in positive ion mode (ESI+).

Experimental Procedures and Compound Characterization Data. *L-Trp Methyl Ester Hydrochloride (L-Trp-OMe-HCl).* Thionyl chloride (9 mL, 124 mmol, 2.5 equiv) was added dropwise to an ice-cold (0 °C) solution of L-Trp (10.0 g, 48.96 mmol, 1.0 equiv) in excess anhydrous methanol under magnetic stirring. The solution was stirred at 0 °C for 30 min, warmed up to 60 °C (silicone oil bath), and then stirred for an additional 18 h. After evaporation of methanol *in vacuo*, a white solid of hydrochloride salt was obtained, which was used directly in the subsequent transformations (12.5 g, 48.96 mmol, 100% yield).

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Data: mp 204−209 °C. $[\alpha]_D^{20}$ +17.8 (*c* 0.52, CH_3OH). ^1H NMR (400 MHz, CD_3OD) δ 7.54 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.40 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.20 (s, 1H), 7.15 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.07 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 4.33 (dd, *J* = 7.4, 5.5 Hz, 1H), 3.80 (s, 3H), 3.52−3.41 (m, 1H), 3.36 (dd, *J* = 15.2, 7.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, CD_3OD) δ 169.4, 136.9, 126.8, 124.2, 121.6, 118.9, 117.4, 111.3, 106.1, 53.2, 52.3, 26.2. HRMS (ESI) *m*/*z*: $[M]^+$ calcd. for $C_{12}H_{15}N_2O_2$ 219.1134; found 219.1125.

*tert-Butyl (S)-3-(2-((tert-Butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-1H-indole-1-carboxylate (**4**).* To a magnetically stirred ice-cold solution of HCl salt of L-Trp-OMe (8 g, 31.4 mmol, 1.0 equiv) and Et_3N (6.6 mL, 47.4 mmol, 1.5 equiv) in dry DCM (150 mL) was added Boc anhydride (7.3 mL, 31.7 mmol, ∼1.0 equiv) dropwise. The resulting mixture was stirred at room temperature overnight. After 12 h, the solvent was evaporated under reduced pressure. The resultant residue was dissolved in ethyl acetate, washed with 1 N aq. HCl, washed with brine, and finally dried over anhydrous Na_2SO_4. To a magnetically stirred ice-cold solution of the above crude product and DMAP (3.84 g, 31.4 mmol, 2 equiv) in dry THF (100 mL) was added Boc anhydride (7.2 mL, 31.4 mmol, 1.0 equiv) dropwise. The resulting mixture was stirred at room temperature overnight. After 12 h, the solvent was evaporated under reduced pressure. The resultant residue was dissolved in ethyl acetate, washed with 1 N aq. HCl, washed with brine, and finally dried over anhydrous sodium sulfate. The product (**4**) was purified by column chromatography (ethyl acetate/hexanes 10−15%) as thick colorless oil (12.5 g, 29.9 mmol, 95% yield). Data: $[\alpha]_D^{20}$ +2.1 (*c* 0.1, CH_3OH). R_f = 0.66 (50% EtOAc in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.3 Hz, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.39 (s, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 1H), 5.12 (d, *J* = 8.1 Hz, 1H), 4.65 (q, *J* = 6.4 Hz, 1H), 3.69 (s, 3H), 3.22 (qd, *J* = 14.7, 5.6 Hz, 2H), 1.66 (s, 9H), 1.43 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.5, 155.2, 149.7, 135.5, 130.7, 124.6, 124.2, 122.7, 119.0, 115.4, 115.2, 83.8, 80.1, 53.8, 52.5, 28.5, 28.4, 28.0. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd. for $C_{22}H_{30}N_2O_6Na$ 441.1996; found 441.1994.

*1,8-Di-tert-butyl 2-Methyl (2S,3aR,8aR)-3a-Bromo-2,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-1,2,8-tricarboxylate (**5**).* To a magnetically stirred ice-cold solution of di-Boc-L-Trp-OMe (**4**) (10.0 g, 23.9 mmol, 1.0 equiv) in dry dichloromethane (50 mL) were added pyridinium *p*-toluenesulfonate (6.0 g, 23.9 mmol, 1.0 equiv) and *N*-bromosuccinimide (4.25 g, 23.9 mmol, 1.0 equiv). The mixture was stirred at room temperature overnight. After completion of reaction, the solvent was evaporated under reduced pressure, and the product (**5**) was purified by column chromatography (ethyl acetate/hexanes 10−15%) as thick colorless foam (9.5 g, 19.1 mmol, 80% yield). Data: $[\alpha]_D^{20}$ −181.4 (*c* 0.07, $CHCl_3$). R_f = 0.68 (30% EtOAc in hexanes). IR (neat): νmax = 2979, 2933, 1753, 1715, 1604, 1478, 1456, 1437, 1393, 1367, 1330, 1290, 1276, 1255, 1203, 1154, 1133, 1089, 1063, 1017, 957, 904, 867, 848, 789, 751, 732 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.66−7.44 (m, 1H), 7.39−7.28 (m, 2H), 7.12 (td, *J* = 7.5, 1.0 Hz, 1H), 6.39 (s, 1H), 3.89 (dd, *J* = 10.3, 6.3 Hz, 1H), 3.75 (s, 3H), 3.21 (dd, *J* = 12.6, 6.3 Hz, 1H), 2.82 (dd, *J* = 12.6, 10.3 Hz, 1H), 1.59 (s, 9H), 1.40 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.6, 152.3 (C═O × 2, carbamate), 141.6, 132.9 (broad), 130.7, 124.5 (broad), 123.3, 118.5 (broad), 83.9, 82.4, 81.5 (broad), 59.8 (broad), 59.6, 52.5, 42.0 (broad), 28.4, 28.3. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd. for $C_{22}H_{29}BrN_2O_6Na$ 519.1101; found 519.1100.

*1,8-Di-tert-butyl 2-Methyl (2S,3aS,8aR)-3a-Methyl-2,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-1,2,8-tricarboxylate (**7**).* To the ice-cold solution of C3-Br-pyrroloindoline **5** (4.0 g, 8.04 mmol, 1.0 equiv) in dry THF (50 mL) was added KO^{t}Bu (1.08 g in 10 mL dry THF, 9.65 mmol, 1.2 equiv) dropwise over 1 h. After complete addition, the reaction mixture was further stirred for half hour. The reaction was quenched with aq. NH_4Cl (sat., 20 mL), and THF was evaporated on a rotary evaporator. The mixture was diluted with dichloromethane (150 mL), and the organic phase was washed with water, brine, and dried over anhydrous Na_2SO_4. The material obtained as compound **6** was subjected to C3-methylation without any purification.

To a solution of the above compound in dry dichloromethane (40 mL) was added $AlMe_3$ (8.1 mL of a 2.0 M solution in toluene, 16.1 mmol, 2.0 equiv) dropwise over 5 min at −40 °C. The reaction mixture was allowed to warm to 0 °C, over 1 h. The reaction was quenched with 30% Rochelle salt (10 mL), the resulting mixture was diluted with dichloromethane (100 mL), and the two phases were separated by a separating funnel. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The product was purified by column chromatography (ethyl acetate/hexanes 5−10%) as thick colorless foam (1.9 g, 4.4 mmol, 55% yield over two steps). Data: $[\alpha]_D^{20}$ −10.8 (*c* 2.0, $CHCl_3$). R_f = 0.63 (30% EtOAc in hexanes). IR (neat): νmax = 2976, 2930, 2871, 1760, 1706, 1604, 1481, 1455, 1436, 1393, 1366, 1324, 1289, 1256, 1206, 1163, 1149, 1107, 1081, 1028, 1016, 972, 928, 907, 860, 828, 814, 788, 751 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.61−7.47 (m, 1H), 7.18 (td, *J* = 7.8, 1.4 Hz, 1H), 7.05 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.97 (td, *J* = 7.4, 1.0 Hz, 1H), 5.96 (s, 1H), 4.54 (d, *J* = 9.0 Hz, 1H), 3.12 (s, 3H), 2.65 (d, *J* = 12.9 Hz, 1H), 2.33 (dd, *J* = 12.9, 9.1 Hz, 1H), 1.58 (s, 9H), 1.46 (s, 9H), 1.37 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.1, 152.9 (C═O × 2, carbamate), 142.5, 129.7, 128.5, 123.3, 122.8, 115.5, 82.4, 81.6, 80.2, 60.1, 52.0, 40.2, 29.8, 28.6, 28.5, 24.7. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd. for $C_{23}H_{32}N_2O_6Na$ 455.2153; found 455.2151.

*Methyl (2R,3aS,8aR)-3a-Methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carboxylate (**3**).* To the ice-cold solution of *endo*-C3-Me-pyrroloindoline methyl ester **7** (1.1 g, 2.54 mmol, 1.0 equiv) in acetonitrile (40 mL) was added TMS-iodide (2.9 mL, 20.35 mmol, 8.0 equiv). The reaction mixture was stirred for 4 h, at the same temperature. After complete conversion of the starting material, it was added saturated aqueous solution of $Na_2S_2O_3$ (10 mL). Acetonitrile was evaporated on a rotary evaporator, and the crude product was extracted with ethyl acetate (20 mL × 3). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The product was purified by column chromatography (ethyl acetate/hexanes 50−60%) as thick colorless oil (532 mg, 2.29 mmol, 90% yield). Data: $[\alpha]_D^{20}$ −52.2 (*c* 0.5, $CHCl_3$). R_f = 0.34 (5% MeOH in DCM). IR (neat): νmax = 3299, 3051, 2953, 2927, 2867, 2132, 1732, 1608, 1485, 1467, 1449, 1374, 1312, 1212, 1151, 1128, 1103, 1074, 1019, 974, 923, 842, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.05−6.97 (m, 2H), 6.70 (td, *J* = 7.4, 0.8 Hz, 1H), 6.55 (d, *J* = 7.5 Hz, 1H), 4.78 (s, 1H), 3.91 (dd, *J* = 7.7, 4.2 Hz, 1H), 3.5 (s, 2H), 3.38 (s, 3H), 2.47 (dd, *J* = 12.6, 4.2 Hz, 1H), 2.26 (dd, *J* = 12.7, 7.7 Hz, 1H), 1.41 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 174.5, 148.9, 134.8, 128.2, 123.2, 119.0, 109.5, 85.2, 60.2, 53.5, 52.0, 43.4, 25.2. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd. for $C_{13}H_{17}N_2O_2$ 233.1285; found 233.1283.

*(2R,3aS,8aR)-1,8-Bis(tert-butoxycarbonyl)-3a-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carboxylic Acid (**8**).* To the ice-cold solution of C3-Me-pyrroloindoline methyl ester **7** (700 mg, 1.62 mmol, 1.0 equiv) in a THF:MeOH:H_2O (1:1:1) solvent system (9 mL) was added LiOH (310 mg, 12.95 mmol, 8 equiv) portionwise (2 equiv after every half hour) until the starting material is over. After completion of reaction, the maximum amounts of THF and MeOH evaporated on a rotary evaporator and the crude was diluted with ethyl acetate. To this crude mixture was added excess 1 N aq. HCl (approximately 1 pH), and then it was transferred to a separating funnel. The organic layer was separated and washed with brine and then dried over anhydrous Na_2SO_4. The product was purified by column chromatography (ethyl acetate/hexanes 30−40%) as a white solid (582 mg, 1.39 mmol, 86% yield). Data: mp 149−153 °C. $[\alpha]_D^{20}$ +2.0 (*c* 0.2, CH_3OH). R_f = 0.46 (50% EtOAc in hexanes). IR (neat): νmax = 3197, 2975, 2931, 1709, 1604, 1481, 1455, 1396, 1365, 1326, 1254, 1158, 1107, 1019, 916, 860, 750 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.1 Hz, 1H), 7.16 (ddd, *J* = 8.3, 7.5, 1.4 Hz, 1H), 7.08 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.96 (td, *J* = 7.5, 1.0 Hz, 1H), 5.93 (s, 1H), 4.50 (dd, *J* = 9.4, 1.6 Hz, 1H), 2.70 (d, *J* = 13.1 Hz, 1H), 2.33 (dd, *J* = 13.0, 9.4 Hz, 1H), 1.56 (s, 9H), 1.49 (s, 9H), 1.37 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 174.4, 152.8 (C═O × 2, carbamate), 141.7, 135.8, 128.6, 123.6, 122.9, 117.6, 82.7, 82.0 (broad), 81.7, 60.0, 52.0, 39.5

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(broad), 28.5, 28.4, 24.3. HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{22}H_{30}N_2O_6Na$ 441.1996; found 441.2004.

N^{α}-Boc-D-Trp-Acid. To a magnetically stirred clear solution of D-Trp (4 g, 19.6 mmol, 1.0 equiv) in 200 mL of THF-H_2O (1:1) were added Na_2CO_3 (4.9 g, 58.76 mmol, 3.0 equiv) and $NaHCO_3$ (6.24 g, 58.76 mmol, 3.0 equiv). The resulting turbid solution was cooled to 0 °C (H_2O/ice bath) and stirred for 15 min. To this mixture was added Boc Anhydride (4.5 mL, 19.6 mmol, 1.0 equiv) dropwise. The resulting solution was stirred for 15−20 min at 0 °C, the ice bath was removed, and reaction was stirred at room temperature overnight. THF was evaporated by rotary evaporation, and the crude was diluted with EtOAc (100 mL). This mixture was acidified by addition of a 1 N aq. HCl solution. Subsequently, it was transferred to a separating funnel; the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Concentration under reduced pressure gave 5.7 g, (96% yield, 18.73 mmol) as a white solid, which was directly used for the next step without further purification. Data: mp. 143−147 °C. $[\alpha]_D^{20}$ +1.3 (c 0.34, CH_3OH). ^1H NMR (400 MHz, DMSO-d_6) δ 12.53 (s, 1H), 10.82 (s, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.14 (d, J = 2.0 Hz, 1H), 7.08−7.04 (m, 1H), 7.00−6.95 (m, 2H), 4.17−4.11 (m, 1H), 3.13 (dd, J = 14.6, 4.8 Hz, 1H), 2.97 (dd, J = 14.6, 9.3 Hz, 1H), 1.33 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 174.0, 155.4, 136.1, 127.2, 123.6, 120.9, 118.3, 118.1, 111.4, 110.2, 78.0, 54.5, 28.2, 26.8. HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{16}H_{21}N_2O_4$ 305.1496; found 305.1495.

N^{α}-Boc-N1-methyl-D-Trp-methyl Ester. To the ice-cold solution of *N*-Boc-D-Trp-OMe (2.0 g, 6.28 mmol, 1.0 equiv) in THF (60 mL) was added KO^{t}Bu (1.06 g, 9.42 mmol, 1.5 equiv). After 15 min, MeI (1.64 mL, 9.42 mmol, 1.5 equiv) was added dropwise and reaction mixture was stirred for 6 h. After completion, the reaction was quenched with aq. NH_4Cl (sat., 20 mL) and THF was evaporated on a rotary evaporator. The crude product was extracted with DCM (20 mL × 3). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The product was purified by column chromatography (ethyl acetate/hexanes 5−10%) as thick colorless oil (1.77 g, 5.34 mmol, 85% yield). Data: mp 121−124 °C. $[\alpha]_D^{20}$ +0.2 (c 0.7, CH_3OH). R_f = 0.46 (30% EtOAc in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.9 Hz, 1H), 7.27 (t, J = 7.3 Hz, 1H), 7.25−7.19 (m, 1H), 7.10 (t, J = 7.4 Hz, 1H), 6.85 (s, 1H), 5.06 (d, J = 8.3 Hz, 1H), 4.63 (dt, J = 8.5, 5.5 Hz, 1H), 3.74 (s, 3H), 3.68 (s, 3H), 3.27 (d, J = 5.4 Hz, 2H), 1.43 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.9, 155.4, 137.0, 128.3, 127.6, 121.9, 119.2, 119.0, 109.4, 108.7, 79.9, 54.3, 52.4, 32.8, 28.5, 28.0. HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{18}H_{24}N_2O_4Na$ 355.1628; found 355.1632.

N1-Methyl-D-Trp-methyl Ester TFA Salt. To the ice-cold solution of N^{α}-Boc-*N*1-methyl-D-Trp-methyl ester (1 g, 3.0 mmol, 1.0 equiv) in DCM (6.0 mL) was added trifluoroacetic acid (TFA, 6.0 mL). The reaction mixture was stirred for 1 h at the same temperature. After completion of reaction, TFA was evaporated on a rotary evaporator repeatedly (4×) by adding DCM into the reaction mixture and the product obtained as a brown oil (0.93 g, 2.83 mmol, 94% yield). The crude product was used without further purification. Data: $[\alpha]_D^{20}$ +63.2 (c 0.11, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (dt, J = 7.9, 1.0 Hz, 1H), 7.30 (dt, J = 8.3, 1.0 Hz, 1H), 7.25−7.18 (m, 1H), 7.11 (ddd, J = 7.9, 6.9, 1.1 Hz, 1H), 6.93 (s, 1H), 3.82 (dd, J = 7.7, 4.8 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.27 (ddd, J = 14.4, 4.8, 0.8 Hz, 1H), 3.04 (ddd, J = 14.4, 7.7, 0.7 Hz, 1H), 1.72 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 175.9, 137.2, 128.1, 127.8, 121.9, 119.1, 119.0, 109.7, 109.4, 55.2, 52.1, 32.8, 30.7. HRMS (ESI) m/z: $[M + Na]^+$ calcd. for $C_{13}H_{16}N_2O_2Na$ 255.1104; found 255.1106.

*N1-Methyl-Nα-Boc-D-Trp-acid (**11**).* To the ice-cold solution of D-Boc-Trp-OH (2.0 g, 6.57 mmol, 1.0 equiv) in THF was added K^{t}OBu (1.5 g, 13.23 mmol, 2.0 equiv). After 5 min of stirring, it was added MeI (620 μL, 10 mmol, 1.5 equiv) dropwise and the reaction mixture was stirred for 3 h. After completion of reaction, the solvent was evaporated on a rotary evaporator and the remaining residue was transferred to the separating funnel. The crude product was extracted with ethyl acetate (20 mL × 3), washed with brine, and dried over anhydrous Na_2SO_4. The product was purified by column chromatography (silica gel) using an ethyl acetate/hexane (20−50%) solvent system as a white semisolid (65% yield, 1.36 g, 4.27 mmol). Data: $[\alpha]_D^{20}$ −33.2 (c 0.1, $CHCl_3$). IR (neat): νmax = 3321, 3055, 2977, 2932, 1713, 1503, 1476, 1453, 1440, 1394, 1368, 1326, 1250, 1209, 1161, 1060, 1026, 1014, 926, 855, 777, 739 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 12.55 (s, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.18−7.06 (m, 2H), 7.00 (m, 2H), 4.26−3.99 (m, 1H), 3.72 (s, 3H), 3.12 (dd, J = 14.4, 3.8 Hz, 1H), 2.97 (dd, J = 14.1, 9.5 Hz, 1H), 1.33 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 173.8, 155.4, 136.5, 127.9, 127.5, 121.0, 118.5, 118.4, 109.6 (C × 2), 78.0, 54.6, 32.3, 28.2, 26.7. HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{17}H_{23}N_2O_4$ 319.1652; found 319.1654.

*(2R,3aR,8aR)-1-(tert-Butoxycarbonyl)-8-methyl-3a-(3-methylbut-2-en-1-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carboxylic Acid (exo-**12a**).* To the magnetically stirred solution of acid **11** (300 mg, 0.94 mmol, 1.0 equiv) in 10 mL of chloroform were added NaOAc (154.6 mg, 1.88 mmol, 2.0 equiv) and prenyl bromide **10a** (220 μL, 1.9 mmol, 2.0 equiv) at room temperature. The reaction mixture was allowed to stir for 16 h. Then, the solvent was evaporated and reaction mixture was directly loaded for the column chromatography. The product was purified by using 20% ethyl acetate/hexanes (colorless oil, 131 mg, 0.34 mmol, 48% yield based on the 15% recovered starting material). Data: $[\alpha]_D^{20}$ +15.0 (c 0.2, $CHCl_3$). IR (neat): νmax = 3428, 2970, 2925, 2855, 1705, 1608, 1491, 1455, 1428, 1391, 1367, 1328, 1302, 1280, 1161, 1022, 982, 909,850, 796, 771,740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.23−6.95 (m, 2H), 6.76−6.63 (m, 1H), 6.44 (d, J = 7.8 Hz, 1H), 5.30 (s, 1H), 5.06−4.87 (m, 1H), 4.38−4.03 (m, 1H), 3.04 (s, 3H), 2.67−2.19 (m, 4H), 1.76−1.38 (m, 15H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 179.5, 154.4, 150.7, 135.1, 133.0, 128.6, 122.2, 119.7, 118.0, 107.3, 88.2, 81.1, 59.8, 55.4, 41.6, 35.6, 35.4, 28.2, 26.0, 18.1. HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{22}H_{31}N_2O_4$ 387.2278; found 387.2276.

*tert-Butyl (2R,3aR,8aR)-2-((2R,3aS,8aS)-2-(Methoxycarbonyl)-3a-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-1-carbonyl)-8-methyl-3a-(3-methylbut-2-en-1-yl)-3,3a,8,8a-tetrahydropyrrolo-[2,3-b]indole-1(2H)-carboxylate (**13a**).* To the magnetically stirred solution of amine **3** (132 mg, 0.57 mmol, 2.0 equiv) in 50 mL DCM were added 2,4,6-collidine (90 μL, 0.68 mmol, 2.4 equiv) and BOP-Cl (145 mg, 0.57 mmol, 2.0 equiv) at room temperature. To this reaction mixture, acid *exo*-**12a** (110 mg, 0.28 mmol, 1.0 equiv) dissolved in DCM (5 mL) was added slowly using a syringe pump over 14 h. The resulting reaction mixture was allowed to stir for another 6 h. After completion of the reaction, the mixture was quenched with sat. $NaHCO_3$ and then transferred to a 125 mL separating funnel. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The reaction mixture was directly loaded to the column chromatography. The product was purified using a 10−15% ethyl acetate/hexane solvent system (colorless oil, 111 mg, 0.18 mmol, 65%). Data: $[\alpha]_D^{20}$ −19.5 (c 0.1, $CHCl_3$). R_f = 0.46 (30% EtOAc in hexanes). IR (neat): νmax = 3383, 2922, 2853, 1736, 1702, 1671, 1609, 1484, 1455, 1377, 1366, 1301, 1260, 1207, 1166, 1101, 1021, 908, 860, 798, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.14 (dt, J = 13.2, 7.7 Hz, 1H), 7.09−6.93 (m, 3H), 6.72 (dp, J = 30.4, 7.5 Hz, 2H), 6.59 (dd, J = 14.8, 7.7 Hz, 1H), 6.53−6.38 (m, 1H), 5.54−5.36 (m, 1H), 5.34−5.15 (m, 1H), 4.94 (td, J = 14.5, 7.3 Hz, 2H), 4.59−4.28 (m, 1H), 4.21 (d, J = 6.7 Hz, 1H), 3.28 (s, 3H), 3.06−2.90 (m, 3H), 2.92−2.71 (m, 1H), 2.55 (m, 2H), 2.40 (m, 2H), 2.32−2.14 (m, 1H), 1.68−1.56 (m, 6H), 1.49 (d, J = 13.9 Hz, 6H), 1.41 (d, J = 12.0 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, rotamers) δ 172.1, 172.0, 171.1, 170.5, 155.4, 154.3, 150.8, 150.8, 149.3, 147.9, 135.2, 134.9, 133.9, 133.6, 133.2, 133.1, 131.7, 128.9, 128.8, 128.5, 123.1, 122.8, 122.1, 122.0, 120.2, 119.9, 118.9, 118.0, 117.8, 110.3, 109.2, 107.4, 107.3, 89.1, 88.7, 83.4, 83.0, 80.5, 59.3, 58.9, 58.4, 55.6, 54.9, 54.6, 52.4, 52.1, 50.8, 42.6, 42.1, 41.9, 40.3, 35.5, 35.1, 28.6, 28.4, 26.0, 25.9, 25.0, 24.4, 18.3. HRMS (ESI) m/z: $[M + H]^+$ calcd. for $C_{35}H_{45}N_4O_5$ 601.3384; found 601.3381.

(+)-Nocardioazine B. The slurry of peptide **13a** (12 mg, 0.02 mmol, 1.0 equiv) was prepared using 230−400 mesh silica (8 gm) and 20 mL DCM in a 100 mL oven-dried round bottom flask and then magnetically stirred at 170 °C (aluminum heating block) for 1.5 h.

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After completion of reaction, the slurry was directly loaded for column chromatography and the product was purified using a 20% ethyl acetate/hexane solvent system (colorless oil, 8.9 mg, 0.019 mmol, 95%). The data obtained for the product was compared with reports and was confirmed to be identical (Supporting Information, Tables S3 and S4). $[\alpha]_D^{20}$ +53.4 (*c* 0.03, $CHCl_3$). R_f = 0.37 (30% EtOAc in hexanes). IR (neat): νmax = 3347, 2961, 2924, 2854, 1666, 1608, 1487, 1414, 1380, 1341, 1301, 1259, 1199, 1155, 1085, 1015, 864, 792, 743 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 7.6 Hz, 1H), 7.12−7.06 (m, 2H), 7.04 (d, *J* = 7.3 Hz, 1H), 6.77 (t, *J* = 7.3 Hz, 1H), 6.71 (t, *J* = 7.3 Hz, 1H), 6.59 (d, *J* = 7.7 Hz, 1H), 6.39 (d, *J* = 7.8 Hz, 1H), 5.35 (s, 1H), 5.31 (s, 1H), 5.21 (s, 1H), 5.00 (t, *J* = 6.9 Hz, 1H), 4.44 (t, *J* = 8.6 Hz, 1H), 4.18−4.09 (m, 1H), 3.01 (s, 3H), 2.64 (dd, *J* = 12.7, 6.4 Hz, 1H), 2.42−2.34 (m, 4H), 2.30−2.25 (m, 1H), 1.65 (s, 3H), 1.50 (s, 3H), 1.47 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.5, 166.0, 150.8, 147.3, 135.7, 133.6, 132.1, 128.9, 128.6, 123.0, 122.6, 119.4, 118.7, 118.1, 109.5, 106.3, 85.1, 83.9, 60.6, 59.4, 54.9, 51.5, 41.1, 39.8, 36.7, 33.8, 26.1, 23.6, 18.2. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd. for $C_{29}H_{33}N_4O_2$ 469.2598; found 469.2598.

*(2R,3aR,8aR)-1-(tert-Butoxycarbonyl)-3a-((E)-3,7-dimethylocta-2,6-dien-1-yl)-8-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]-indole-2-carboxylic Acid (exo-**12b**).* To the magnetically stirred solution of acid **11** (200 mg, 0.63 mmol, 1.0 equiv) in 6.3 mL of acetic acid were added NaOAc (103 mg, 1.26 mmol, 2.0 equiv) and geranyl bromide **10b** (250 μL, 1.26 mmol, 2.0 equiv) at room temperature. The reaction mixture was allowed to stir for 10 h. Then, the solvent was evaporated and reaction mixture was directly loaded for the column chromatography. The product was purified by using 12−15% ethyl acetate/hexanes (colorless oil, 140 mg, 0.31 mmol, 51% yield based on the 5% recovered starting material). $[\alpha]_D^{20}$ +111.7 (*c* 0.1, $CHCl_3$). IR (neat): νmax = 3456, 3052, 2974, 2928, 1702, 1608, 1489, 1454, 1428, 1391, 1367, 1332, 1301, 1259, 1160, 1108, 1060, 1020, 977, 859, 795, 737 cm^{-1}. **^1H NMR** (400 MHz, $CDCl_3$, rotamers) δ 7.12 (t, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 7.3 Hz, 1H), 6.70 (q, *J* = 7.0 Hz, 1H), 6.44 (d, *J* = 7.7 Hz, 1H), 5.30 (s, 1H), 4.99 (dt, *J* = 13.7, 6.9 Hz, 2H), 4.22 (dd, *J* = 8.9, 5.7 Hz, 1H), 3.05 (s, 3H), 2.63−2.35 (m, 3H), 2.25 (dd, *J* = 13.1, 6.1 Hz, 1H), 2.07−1.88 (m, 4H), 1.68−1.64 (m, 3H), 1.64−1.53 (m, 6H), 1.47 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, rotamers) δ 179.7, 178.2, 154.3, 150.7, 150.4, 150.1, 138.7, 138.6, 132.9, 132.5, 131.7, 131.6, 128.8, 128.6, 124.3, 124.1, 122.7, 122.3, 122.2, 120.1, 119.6, 118.3, 118.0, 107.4, 107.3, 88.2, 88.1, 81.5, 81.1, 59.8, 56.6, 55.5, 41.5, 41.1, 40.0, 35.6, 35.5, 35.3, 34.7, 28.5, 28.2, 26.7, 26.7, 25.8, 17.8, 17.8, 16.5, 16.4. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd. for $C_{27}H_{39}N_2O_4$ 455.2904; found 455.2921.

*tert-Butyl (2R,3aR,8aR)-3a-((E)-3,7-Dimethylocta-2,6-dien-1-yl)-2-((2R,3aS,8aS)-2-(methoxycarbonyl)-3a-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-1-carbonyl)-8-methyl-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (**13b**).* To the magnetically stirred solution of amine **3** (41 mg, 0.18 mmol, 2.0 equiv) in 13 mL DCM were added 2,4,6-collidine (27 μL, 0.20 mmol, 2.3 equiv) and BOP-Cl (51.5 mg, 0.20 mmol, 2.3 equiv) at room temperature. To this reaction mixture, acid *exo*-**12b** (40 mg, 0.09 mmol, 1.0 equiv) dissolved in DCM (5 mL) was added slowly using a syringe pump over 14 h. The resulting reaction mixture was allowed to stir for another 6 h. After completion of reaction, the reaction mixture was quenched with sat. $NaHCO_3$ and then transferred to a separating funnel. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Then, it was directly loaded to the column chromatography using silica (100−200 mesh). The product was purified by using a 18% ethyl acetate/hexane solvent system (colorless oil, 30 mg, 0.04 mmol, 51%). Data: $[\alpha]_D^{20}$ −15.7 (*c* 0.15, $CHCl_3$). R_f = 0.84 (50% EtOAc in hexanes). IR (neat): νmax = 3052, 2975, 2927, 1703, 1608, 1491, 1454, 1428, 1367, 1328, 1301, 1241, 1160, 1060, 1021, 979, 905, 858, 794, 772, 737 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.15 (t, *J* = 7.7 Hz, 1H), 7.09−6.95 (m, 3H), 6.81−6.54 (m, 3H), 6.51−6.40 (m, 1H), 5.52−5.37 (m, 1H), 5.35−5.18 (m, 1H), 5.03−4.89 (m, 3H), 4.52 (dt, *J* = 12.2, 5.9 Hz, 1H), 4.21 (dd, *J* = 10.2, 3.6 Hz, 1H), 3.28 (s, 3H), 3.07−2.93 (m, 3H), 2.92−2.72 (m, 1H), 2.65−2.24 (m, 5H), 2.04−1.90 (m, 4H), 1.64−1.64 (m, 9H), 1.55−1.46 (m, 6H), 1.42−1.38 (m, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, rotamers) δ 172.1, 172.0, 171.5, 171.1, 170.4, 155.3, 154.3, 150.8, 150.6, 149.3, 147.9, 138.7, 138.4, 133.8, 133.2, 131.7, 131.4, 131.3, 128.9, 128.8, 128.6, 128.5, 124.4, 124.2, 123.1, 122.8, 122.2, 122.1, 120.2, 120.1, 119.9, 118.9, 118.0, 117.8, 110.3, 110.2, 109.2, 107.4, 107.3, 89.3, 88.8, 88.5, 83.3, 83.0, 80.5, 59.3, 58.9, 58.4, 56.7, 55.6, 54.9, 54.6, 52.4, 52.1, 52.0, 50.8, 42.6, 42.3, 41.9, 40.3, 39.9, 35.5, 35.2, 34.7, 29.8, 28.6, 28.4, 26.8, 25.8, 25.0, 24.3, 22.8, 17.8, 17.7, 16.5. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd. for $C_{40}H_{53}N_4O_5$ 669.4010; found 669.4009.

*C3-Geranyl (+)-Nocardioazine B (**14b**).* The slurry of peptide **13b** (15 mg, 22.4 μmol, 1.0 equiv) was prepared using 230−400 mesh silica (3 gm) and 3 mL DCM in a 50 mL oven-dried round bottom flask and then magnetically stirred at 170 °C (aluminum heating block) for 1.5 h. After complete conversion of peptide, as evidenced through TLC, the slurry was directly loaded for column chromatography and the product was purified by using a 22% ethyl acetate/hexane solvent system (colorless oil, 10.2 mg, 19 μmol, 85%). Configurational assignments were established using HSQC, HMBC, and NOESY experiments as illustrated in the copies of spectra. Data: $[\alpha]_D^{20}$ +102.6 (*c* 0.05, $CHCl_3$). R_f = 0.35 (30% EtOAc in hexanes). IR (neat): νmax = 3347, 3052, 2923, 2853, 1665, 1608, 1487, 1467, 1446, 1415, 1380, 340, 1301, 1265, 1229, 1199, 1155, 1102, 1085, 1062, 1043, 1019, 1001, 977, 932, 892, 781, 739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.15−7.07 (m, 3H), 7.05 (dd, *J* = 7.4, 1.3 Hz, 1H), 6.77 (td, *J* = 7.4, 1.0 Hz, 1H), 6.70 (td, *J* = 7.4, 1.0 Hz, 1H), 6.59 (dt, *J* = 7.8, 0.8 Hz, 1H), 6.38 (d, *J* = 7.8 Hz, 1H), 5.35 (s, 1H), 5.32 (s, 1H), 5.22 (s, 1H), 5.07−4.96 (m, 2H), 4.44 (td, *J* = 9.3, 8.9, 1.9 Hz, 1H), 4.15 (ddd, *J* = 10.9, 6.4, 1.8 Hz, 1H), 3.02 (s, 3H), 2.66 (dd, *J* = 12.8, 6.4 Hz, 1H), 2.43−2.33 (m, 4H), 2.26 (dd, *J* = 12.8, 10.8 Hz, 1H), 1.91−1.99 (m, 4H), 1.66 (s, 3H), 1.57 (s, 3H), 1.49 (s, 3H), 1.47 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.5 (C═O), 166.0 (C═O), 150.8 (C), 147.3 (C), 139.1 (C), 133.5 (C), 131.8 (C), 131.6 (C), 128.9 (CH), 128.6 (CH), 124.3 (CH), 123.1 (CH), 122.6 (CH), 119.4 (CH), 118.6 (CH), 118.0 (CH), 109.5 (CH), 106.2 (CH), 85.2 (CH), 83.9 (CH), 60.6 (CH), 59.4 (CH), 54.8 (C), 51.4 (C), 41.1 (CH_2), 40.1 (CH_2), 40.0 (CH_2), 36.8 (CH_2), 33.7 (N−CH_3), 26.8 (CH_2), 25.8 (CH_3), 23.5 (CH_3), 17.8 (CH_3), 16.5 (CH_3). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd. for $C_{34}H_{41}N_4O_2$ 537.3224; found 537.3224.

*(2R,3aR,8aR)-1-(tert-Butoxycarbonyl)-8-methyl-3a-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carboxylic Acid (exo-**12c**).* To the magnetically stirred solution of acid **11** (50 mg, 0.16 mmol, 1.0 equiv) in 2 mL of chloroform were added NaOAc (25.8 mg, 0.31 mmol, 2.0 equiv) and farnesyl bromide **10c** (85.2 μL, 0.31 mmol, 2.0 equiv) at room temperature. The reaction mixture was allowed to stir for 16 h. Then, the solvent was evaporated and reaction mixture was directly loaded for the column chromatography. The product was purified by using 24% ethyl acetate/hexanes (colorless oil, 32 mg, 0.061 mmol, 44% yield based on the 11% recovered starting material). Data: $[\alpha]_D^{20}$ +68.2 (c 0.1, CHCl3). IR (neat): νmax = 3438, 2924, 2854, 1704, 1608, 1490, 1454, 1428, 1390, 1367, 1301, 1279, 1248, 1160, 1021, 978, 903, 858, 795, 772, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.12 (t, *J* = 7.1 Hz, 1H), 7.00 (d, *J* = 7.5 Hz, 1H), 6.70 (d, *J* = 6.8 Hz, 1H), 6.43 (d, *J* = 7.2 Hz, 1H), 5.30 (s, 1H), 5.18−4.92 (m, 3H), 4.30−4.17 (m, 1H), 2.99 (s, 3H), 2.60−2.25 (m, 4H), 2.06−1.90 (m, 8H), 1.67 (s, 3H), 1.57 (m, *J* = 12.8, 11.3 Hz, 15H), 1.42 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 179.2, 154.4, 150.7, 138.9, 135.2, 131.4, 128.6, 124.5, 122.7, 122.4, 120.0, 119.6, 118.3, 118.0, 107.3, 88.3, 81.1, 59.7, 55.5, 41.6, 40.1, 39.9, 35.6, 29.8, 28.5, 28.2, 26.9, 25.8, 17.8, 16.6, 16.5, 16.1. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd. for $C_{32}H_{47}N_2O_4$ 523.3530; found 523.3524.

*tert-Butyl (2R,3aR,8aR)-2-((2R,3aS,8aS)-2-(Methoxycarbonyl)-3a-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-1-carbonyl)-8-methyl-3a-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (**13c**).* To the magnetically stirred solution of amine **3** (18 mg, 0.08 mmol, ∼2.0 equiv) in 5 mL DCM were added 2,4,6-collidine (12 μL, 0.09 mmol, 2.4 equiv) and BOP-Cl (19.5 mg, 0.08 mmol, 2.0 equiv) at room

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temperature. To this reaction mixture, acid *exo*-**12c** (20 mg, 0.04 mmol, 1.0 equiv) dissolved in DCM (3 mL) was added slowly using a syringe pump over 14 h. The resulting reaction mixture was allowed to stir for another 6 h. After completion of reaction, the reaction mixture was quenched with sat. $NaHCO_3$ and then transferred to a 125 mL separating funnel. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The reaction mixture was directly loaded for column chromatography. The product was purified by using a 28% ethyl acetate/hexane solvent system (colorless oil, 17 mg, 0.02 mmol, 60% yield). Data: $[\alpha]_D^{20}$ −11.6 (c 0.1, CHCl3). R_f = 0.68 (50% EtOAc in hexanes). IR (neat): νmax = 3379, 2927, 2869, 1737, 1708, 1640, 1484, 1435, 1366, 1332, 1312, 1261, 1229, 1164, 1101, 1057, 1019, 865, 803, 736 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.17−6.96 (m, 4H), 6.80−6.54 (m, 3H), 6.46 (m, 1H), 5.49−5.39 (m, 1H), 5.31−5.22 (m, 1H), 5.09−4.91 (m, 4H), 4.69−4.48 (m, 1H), 4.38−4.17 (m, 1H), 3.21 (s, 3H), 3.05−2.95 (m, 3H), 2.73−2.49 (m, 2H), 2.48−2.26 (m, 3H), 2.03−1.91 (m, 9H), 1.67 (s, 3H), 1.63−1.59 (m, 9H), 1.54−1.51 (m, 3H), 1.47 (s, 3H), 1.44−1.37 (m, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, rotamers) δ 172.2, 172.0, 171.1, 170.5, 157.4, 154.3, 150.7, 148.0, 138.9, 138.7, 135.2, 135.0, 131.7, 131.4, 128.9, 128.8, 128.5, 124.6, 124.5, 124.2, 123.1, 122.8, 122.2, 122.1, 120.2, 120.1, 119.9, 118.9, 118.3, 118.1, 117.9, 115.8, 110.4, 109.3, 107.4, 89.3, 83.4, 83.1, 83.0, 80.5, 59.3, 59.3, 58.9, 58.5, 55.0, 54.7, 52.4, 52.2, 50.8, 42.7, 41.9, 40.1, 40.1, 39.9, 35.6, 35.3, 34.8, 28.7, 28.4, 26.9, 25.8, 25.0, 24.4, 17.8, 16.6, 16.1. HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{45}H_{61}N_4O_5$ 737.4636; found 737.4625.

*C3-Farnesyl (+)-Nocardioazine B (**14c**).* The slurry of peptide **13c** (10 mg, 0.01 mmol, 1.0 equiv) was prepared using 230−400 mesh silica (8 gm) and 20 mL DCM in a 100 mL oven-dried round bottom flask and then magnetically stirred at 170 °C (aluminum heating block) for 1.5 h. After completion of the reaction, the slurry was directly loaded for column chromatography and the product was purified by using 32% ethyl acetate/hexanes solvent system (colorless oil, 5 mg, 0.01 mmol, 61%). Configurational assignments were established using HSQC, HMBC, and NOESY experiments as illustrated in the copies of spectra. Data: $[\alpha]_D^{20}$ +30 (c 0.05, CHCl3). R_f = 0.33 (30% EtOAc in hexanes). IR (neat): νmax = 3369, 2923, 2852, 1686, 1655, 1611, 1468, 1400, 1371, 1340, 1260, 1200, 1149, 1099, 1019, 800, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.15−7.07 (m, 3H), 7.05 (d, *J* = 7.7 Hz, 1H), 6.77 (t, *J* = 7.4 Hz, 1H), 6.70 (t, *J* = 7.2 Hz, 1H), 6.59 (d, *J* = 7.8 Hz, 1H), 6.38 (d, *J* = 8.0 Hz, 1H), 5.35 (s, 1H), 5.32 (s, 1H), 5.19 (s, 1H), 5.13−4.96 (m, 3H), 4.44 (t, *J* = 8.5 Hz, 1H), 4.15 (dd, *J* = 10.7, 7.1 Hz, 1H), 3.02 (s, 3H), 2.66 (dd, *J* = 12.9, 6.4 Hz, 1H), 2.43−2.35 (m, 4H), 2.26 (dd, *J* = 12.8, 10.8 Hz, 1H), 2.07−1.92 (m, 8H), 1.67 (s, 3H), 1.59 (s, 3H), 1.56 (s, 3H), 1.50 (s, 3H), 1.47 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.5 (C═O), 166.0 (C═O), 150.9 (C), 147.3 (C), 139.3 (C), 135.3 (C), 133.5 (C), 131.8 (C), 131.4 (C), 128.9 (CH), 128.6 (CH), 124.5 (CH), 124.2 (CH), 123.1 (CH), 122.6 (CH), 119.4 (CH), 118.6 (CH), 118.1 (CH), 109.5 (CH), 106.2 (CH), 85.2 (CH), 83.9 (CH), 60.6 (CH), 59.4 (CH), 54.9 (C), 51.5 (C), 41.1 (CH_2), 40.1 (CH_2), 40.1 (CH_2), 39.8 (CH_2), 36.8 (CH_2), 33.8 (N−CH_3), 26.9 (CH_2), 26.9 (CH_2), 25.8 (CH_3), 23.5 (CH_3), 17.8 (CH_3), 16.6 (CH_3), 16.1 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{39}H_{49}N_4O_2$ 605.3850; found 605.3846.

*Di-tert-butyl (2R,3aS,8aR)-2-(R)-1-Methoxy-3-(1-methyl-1H-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)-3a-methyl-2,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-1,8-dicarboxylate (**1**).* C3-Me pyrroloindoline acid **8** (500 mg, 1.19 mmol, 1.0 equiv) and *N*1-methyl-D-Trp-methyl ester TFA salt (Spectrum 17) (787 mg, 2.39 mmol, 2.0 equiv) were suspended in anhydrous dichloromethane (6 mL). The suspension was cooled to 0 °C in an ice−water bath. This was followed by addition of 2,4,6-collidine (315 μL, 2.39 mmol, 2.0 equiv). Subsequently, *N*-hydroxybenzotriazole monohydrate (365 mg, 2.39 mmol, 2.0 equiv) was added to the reaction mixture, followed by addition of HATU (910 mg, 2.4 mmol, 2.0 equiv). The reaction was allowed to stir at room temperature for 18 h. The reaction mixture was washed with saturated citric acid solution in a separatory funnel, followed by washing with saturated sodium bicarbonate solution. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The product was purified by column chromatography (ethyl acetate/hexanes 25−35%) as colorless oil (600 mg, 0.98 mmol, 79% yield, 1.5:1 dr). Data: Major isomer: 356 mg, 0.56 mmol. $[\alpha]_D^{20}$ −6.3 (*c* 0.12, CH_3OH). R_f = 0.28 (30% EtOAc in hexanes). **IR (neat)**: νmax = 3415, 3052, 2975, 2928, 1741, 1712, 1674, 1616, 1605, 1511, 1479, 1466, 1454, 1389, 1366, 1322, 1289, 1254, 1216, 1150, 1105, 1080, 1040, 1027, 1013, 965, 927, 889, 860, 828, 816, 788, 737 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.0 Hz, 1H), 7.36 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.23−7.14 (m, 4H), 7.07−7.01 (m, 2H), 6.80 (s, 1H), 6.45 (d, *J* = 8.1 Hz, 1H), 6.03 (s, 1H), 4.42 (dd, *J* = 9.5, 1.4 Hz, 1H), 4.19 (ddd, *J* = 8.2, 6.3, 3.9 Hz, 1H), 3.72 (s, 3H), 3.45 (s, 3H), 3.08−2.88 (m, 2H), 2.36−2.23 (m, 2H), 1.63 (s, 9H), 1.37 (s, 3H), 1.20 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.9, 170.8, 154.1, 153.1, 141.5, 137.1, 136.7, 128.6, 127.8, 127.6, 124.0, 123.7, 121.9, 119.2, 118.9, 117.0, 109.2, 108.1, 83.7, 82.1, 81.6, 62.0, 52.1, 51.7, 51.3, 38.9, 32.8, 28.5, 27.8, 27.5, 24.8. HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{35}H_{45}N_4O_7$ 633.3283; found 633.3276. Data: minor isomer (*epi*-1): 244 mg, 0.39 mmol. $[\alpha]_D^{20}$ +19.7 (*c* 1.6, $CHCl_3$). R_f = 0.26 (30% EtOAc in hexanes). IR (neat): νmax = 3420, 2930, 1708, 1679, 1510, 1480, 1391, 1354, 1256, 1162, 1109, 1016, 858, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 7.2 Hz, 1H), 7.20 (d, *J* = 8.1 Hz, 1H), 7.16−7.09 (m, 2H), 7.08−6.99 (m, 2H), 6.99−6.93 (m, 1H), 6.87 (s, 1H), 6.57 (d, *J* = 6.2 Hz, 1H), 6.00 (s, 1H), 4.52 (d, *J* = 9.1 Hz, 1H), 4.00 (q, *J* = 5.7 Hz, 1H), 3.69 (s, 3H), 3.49 (s, 3H), 3.09 (dd, *J* = 14.8, 5.6 Hz, 1H), 2.99 (dd, *J* = 14.9, 5.0 Hz, 1H), 2.83 (d, *J* = 13.4 Hz, 1H), 2.29 (dd, *J* = 13.1, 9.4 Hz, 1H), 1.54 (s, 9H), 1.38 (s, 9H), 1.36 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.1, 170.7, 154.6, 152.7, 141.2, 136.7, 136.4, 128.1, 128.0, 128.0, 123.7, 123.3, 121.4, 118.8, 118.6, 117.2, 109.1, 108.0, 83.4, 81.7, 81.5, 62.2, 53.1, 52.0, 51.9, 38.7, 32.7, 28.3, 28.2, 27.4, 24.6. HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{35}H_{45}N_4O_7$ 633.3283; found 633.3278.

*Di-tert-butyl (2R,3aS)-2-(((R)-1-Methoxy-3-(1-methyl-2-(3-methylbut-2-en-1-yl)-1H-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)-3a-methyl-2,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-1,8-dicarboxylate (**16**).* To the magnetically stirred solution of peptide **1** (50 mg, 79 μmol, 1.0 equiv) in 1 mL of DCM were added NaOAc (13 mg, 158 μmol, 2.0 equiv) and prenyl bromide **10a** (120 μL, 154 μmol, 2.0 equiv) at room temperature. The reaction mixture was allowed to stir for 16 h. Then, the solvent was evaporated and reaction mixture was directly loaded for the column chromatography. The product was purified using 20% ethyl acetate/hexanes as a colorless oil (11 mg, 16 μmol, 20% yield). Data: $[\alpha]_D^{20}$ +0.7 (*c* 0.05, $CHCl_3$). R_f = 0.38 (30% EtOAc in hexanes). IR (neat): νmax = 3418, 2957, 2925, 2854, 1706, 1603, 1511, 1480, 1455, 1389, 1366, 1323, 1290, 1254, 1211, 1150, 1107, 1080, 1027, 1015, 962, 916, 894, 860, 829, 789, 738 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 8.1 Hz, 1H), 7.16−7.10 (m, 2H), 7.05 (t, *J* = 7.5 Hz, 2H), 6.95 (t, *J* = 7.3 Hz, 1H), 6.53 (d, *J* = 7.4 Hz, 1H), 6.05 (s, 1H), 5.12−4.99 (m, 1H), 4.49−4.46 (m, 1H), 4.24−4.19 (m, 1H), 3.59 (s, 3H), 3.35 (s, 3H), 2.91−2.88 (m, 1H), 2.46−2.40 (m, 2H), 2.37−2.25 (m, 1H), 2.04 (s, 2H), 1.77 (s, 3H), 1.72 (s, 3H), 1.61 (s, 9H), 1.43 (s, 9H), 1.37 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.5, 170.9, 152.8, 151.8, 148.2, 141.5, 137.6, 136.8, 136.5, 132.7, 128.6, 127.8, 123.9, 123.4, 121.3, 121.0, 119.3, 118.2, 108.7, 105.2, 83.8, 82.0, 81.7, 62.5, 61.2, 53.5, 52.0, 51.8, 39.7, 29.9, 29.8, 28.4, 28.3, 25.8, 24.9, 18.2. Mono-Boc deprotected, HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{35}H_{45}N_4O_5$ 601.3384; found 601.3392. Di-Boc deprotected, HRMS (ESI) *m/z*: $[M + H]^+$ calcd. for $C_{30}H_{37}N_4O_3$ 501.2860; found 501.2864.

*Methyl 1-Methyl-N$^{\alpha}$-((2R,3aS,8aR)-3a-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carbonyl)-D-tryptophanate (bis-Boc-deprotected-dipeptide-**1**).* To the ice-cold solution of Boc-protected dipeptide **1** (20 mg, 31.6 μmol, 1.0 equiv) in acetonitrile (1 mL) was added TMS-iodide (18 μL, 126.4 μmol, 4.0 equiv). The reaction mixture was stirred for 4 h, at the same temperature. After complete conversion of the starting material, it was added saturated aqueous solution of $Na_2S_2O_3$ (0.5 mL). Acetonitrile was evaporated on a rotary evaporator, and the crude product was extracted with ethyl acetate (5 mL X 3). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The product was purified by column

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chromatography (methanol in DCM 4%) as colorless oil (8 mg, 18.5 μmol, 59% yield). Data: $[\alpha]_D^{25}$ −47.1 (*c* 0.06, $CHCl_3$). R_f = 0.32 (5% MeOH in DCM). IR (neat): νmax = 3344, 2954, 2925, 1739, 1657, 1509, 1485, 1467, 1260, 1210, 1076, 1017, 802, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.5 Hz, 1H), 7.53 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.30−7.26 (m, 1H), 7.22 (ddd, *J* = 8.1, 6.8, 1.1 Hz, 1H), 7.09 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 7.02 (ddd, *J* = 7.4, 1.3, 0.6 Hz, 1H), 6.95 (td, *J* = 7.6, 1.3 Hz, 1H), 6.77 (s, 1H), 6.69 (td, *J* = 7.4, 1.0 Hz, 1H), 6.31 (dt, *J* = 7.7, 0.8 Hz, 1H), 4.82 (s, 1H), 4.37 (dt, *J* = 7.6, 6.6 Hz, 1H), 3.94 (dd, *J* = 8.7, 5.2 Hz, 1H), 3.64 (s, 3H), 3.57 (s, 3H), 2.86 (dd, *J* = 6.6, 0.8 Hz, 2H), 2.41 (dd, *J* = 12.9, 5.2 Hz, 1H), 2.27 (dd, *J* = 12.9, 8.7 Hz, 1H), 1.75 (s, 2H), 1.34 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 174.1, 173.0, 148.0, 136.9, 134.8, 128.1, 128.1, 127.6, 123.2, 121.8, 119.3, 119.1, 118.9, 109.4, 109.3, 109.0, 86.7, 61.9, 53.8, 53.1, 52.2, 43.6, 32.7, 27.9, 24.5. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd. for $C_{25}H_{29}N_4O_3$ 433.2234; found 433.2248.

Attempt for the Synthesis of (+) Nocardioazine B through Late-Stage Prenylation and Cyclization Sequence. To the magnetically stirred solution peptide *bis*-Boc-deprotected-dipeptide-**1** (6 mg, 18.5 μmol, 1.0 equiv) in 0.2 mL of glacial acetic acid were added NaOAc (3.0 mg, 37 μmol, 2.0 equiv) and prenyl bromide **10a** (4.0 μL, 35 μmol, ∼2.0 equiv) at room temperature The reaction was allowed to stir at the same temperature, and the progress of the reaction was monitored by TLC (developed with 50% EtOAc in hexanes). We observed a complex TLC pattern showing formation of a trace amount of expected nocardioazine B, among several (>7) other products.

(11bS)-N-Allyl-N-benzhydryldinaphtho[2,1-d:1′,2′-f][1,3,2]-dioxaphosphepin-4-amine (Ligand). To a flame-dried 100 mL Schlenk flask were added PCl_3 (0.5 mL, 5.73 mmol, 1.0 equiv) and toluene (15 mL) under an argon atmosphere (Schlenk line), and the solution was cooled at 0 °C. Another 100 mL flame-dried Schlenk flask was charged with amine (1.28 g, 5.73 mmol, 1.0 equiv), Et_3N (1.0 mL, 7.17 mmol, 1.25 equiv), and toluene (5 mL). This mixture was added dropwise to the solution of PCl_3 in toluene at 0 °C. After complete addition, the reaction mixture was heated at 80 °C (silicone oil bath) for 8 h and then cooled to 0 °C. Then, a solution of (*S*)-BINOL (2.0 g, 7.0 mmol, 1.2 equiv) and Et_3N (1.9 mL, 13.75 mmol, 2.4 equiv) in THF (5 mL) was added slowly. The reaction mixture was stirred at room temperature overnight. After completion, the reaction mixture was filtered through a Celite pad with EtOAc washing. The filtrate was concentrated on a rotary evaporator to get crude, which was loaded for the column chromatography on silica gel, and the product was purified using an ethyl acetate/hexane (2−5%) solvent system in 64% yield as a white solid (1.98 g, 3.68 mmol). Data: $[\alpha]_D^{20}$ +140.4 (*c* 0.2, $CHCl_3$). R_f = 0.74 (30% EtOAc in hexanes). IR (neat): νmax = 3358, 3061, 3028, 2954, 2922, 2853, 1638, 1619, 1590, 1506, 1495, 1463, 1432, 1403, 1368, 1328, 1269, 1258, 1230, 1214, 1203, 1155, 1127, 1096, 1067, 1029, 982, 951, 938, 865, 851, 821, 798, 790, 780, 749 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.8 Hz, 1H), 7.87 (d, *J* = 5.0 Hz, 1H), 7.85 (d, *J* = 4.9 Hz, 1H), 7.80 (d, *J* = 8.7 Hz, 1H), 7.52−7.39 (m, 5H), 7.42−7.27 (m, 8H), 7.32−7.15 (m, 5H), 5.72−5.55 (m, 2H), 5.00 (dt, *J* = 10.0, 1.4 Hz, 1H), 4.88 (dd, *J* = 17.1, 1.5 Hz, 1H), 3.37 (dddt, *J* = 15.0, 5.5, 4.1, 1.4 Hz, 1H), 3.14 (ddd, *J* = 15.1, 7.3, 3.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 150.2, 150.1, 149.7, 141.1, 141.0, 140.9, 140.8, 136.1, 132.9, 132.8, 131.5, 130.7, 130.3, 130.0, 129.4, 129.4, 128.6, 128.5, 128.4, 128.3, 127.6, 127.5, 127.2, 126.1, 124.9, 124.6, 124.1, 124.1, 122.4, 122.3, 122.3, 122.1, 118.1, 64.9, 64.7, 48.7. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd. for $C_{36}H_{29}NO_2P$ 538.1930; found 538.1930.

*1-(tert-Butyl) 2-Methyl (2R,3aR,8aR)-3a-(3-Methylbut-2-en-1-yl)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1,2(2H)-dicarboxylate (**17**).* To a flame-dried 25 mL Schlenk flask were added $[Pd(allyl)Cl]_2$ (5.8 mg, 15.7 μmol, 5 mol %), phosphoramidite ligand (8.5 mg, 15.7 μmol, 5 mol %), Cs_2CO_3 (153.5 mg, 471.2 μmol, 1.5 equiv), and D-Boc-Trp-OMe (100 mg, 314.1 μmol, 1.0 equiv). The flask was evacuated (10 min) and refilled with argon (tree times), freshly distilled 3 mL toluene was added, and then the flask was cooled at 0 °C. The carbonate **10d** was added after 5 min at 0 °C, and the reaction mixture was allowed to stir for 12 h at the same temperature. After completion of reaction, the crude was directly loaded to the column chromatography on silica gel and the product purified using an ethyl acetate/hexane (5−10%) solvent system in 83% yield as a colorless oil (101 mg, 261 μmol); Data: $[\alpha]_D^{20}$ +226.6 (*c* 0.18, CH_3OH). R_f = 0.55 (30% EtOAc in hexanes). IR (neat): νmax = 3397, 3053, 2975, 2930, 1749, 1690, 1609, 1483, 1466, 1455, 1436, 1392, 1366, 1356, 1332, 1317, 1258, 1198, 1172, 1151, 1094, 1048, 1031, 992, 898, 849, 813, 779, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.10−1.02 (m, 2H), 6.74 (td, *J* = 7.4, 1.0 Hz, 1H), 6.63 (dt, *J* = 7.8, 0.8 Hz, 1H), 5.36 (s, 1H), 5.24 (s, 1H), 5.18−5.06 (m, 1H), 4.01 (dd, *J* = 8.8, 7.6 Hz, 1H), 3.72 (s, 3H), 2.55 (dd, *J* = 12.7, 7.5 Hz, 1H), 2.44−2.25 (m, 2H), 2.18 (dd, *J* = 12.8, 8.8 Hz, 1H), 1.69 (s, 3H), 1.52 (s, 3H), 1.37 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.7, 153.9, 148.8, 135.5, 132.3, 128.5, 123.3, 118.9, 118.8, 109.8, 81.2, 80.9, 59.5, 56.2, 52.1, 39.2, 35.4, 28.3, 26.1, 18.0. HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd. for $C_{22}H_{30}N_2O_4Na$ 409.2098; found 409.2102.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c01120.

Detailed procedures for the synthetic sequence and preparation of each natural product analog, copies of all 1-D and 2-D NMR spectra (^1H; $^{13}C\{^1H\}$; COSY, NOESY, ROESY, HSQC, and HMBC), and HRMS data for intermediates, target natural product, and their analogs-(PDF)

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Author Contributions

R.V. designed the project. R.V., T.M.K., and A.L.L. contributed to editing various sections of the manuscript. T.M.K, K.A., and D.M.V. performed the experiments and generated data.

Notes

The authors declare no competing financial interest.

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