Chapter 3

Enantioselective Total Synthesis of (+)-Nocardioazines A and B[†]

3.1 INTRODUCTION

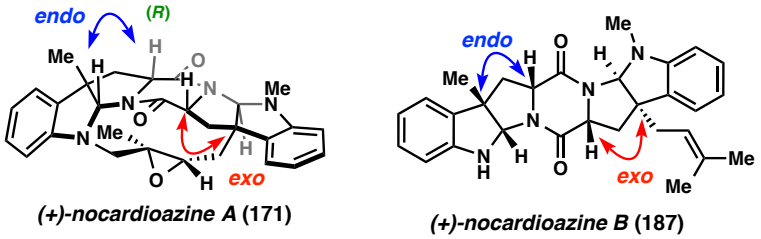
Having accomplished the first total synthesis of (–)-lansai B (**169**), which illustrated the utility of our enantioselective formal (3 + 2) cycloaddition strategy in accessing related pyrroloindolines,[1,2] we turned our attention to structurally related diketopiperazine-containing bis(pyrroloindoline) natural products (+)-nocardioazines A (**171**) and B (**187**). Both of these natural products were isolated in 2011 by Capon and coworkers as a new class of prenylated diketopiperazines from the Australian marine sediment-derived isolate, *Nocardiopsis* sp. (CMB-M0232).[3] Nocardioazine A (**171**) has been found to be a potential multidrug resistance reversal candidate due to its P-glycoprotein binding property.[3]

Although these natural products appear quite similar structurally, close analysis reveals subtle differences in the relative stereochemistry of the pyrroloindoline units.

[†] Part of this chapter was published as the following communications: Wang, H.; Reisman, S. E. *Angew. Chem. Int. Ed.* **2014**, *53*, 6206.

Whereas lansai B (**169**) is composed of two *exo*-pyrroloindolines, **171** and **187** each possess one *endo*- and one *exo*-pyrroloindoline. Moreover, the *endo*- and *exo*-pyrroloindolines are in the opposite enantiomeric series, which is necessary to geometrically accommodate the macrocycle of **171**.

Figure 3.1. *Structures of (+)-nocardioazines A and B*



***(+)-nocardioazine A* (171)** ***(+)-nocardioazine B* (187)**

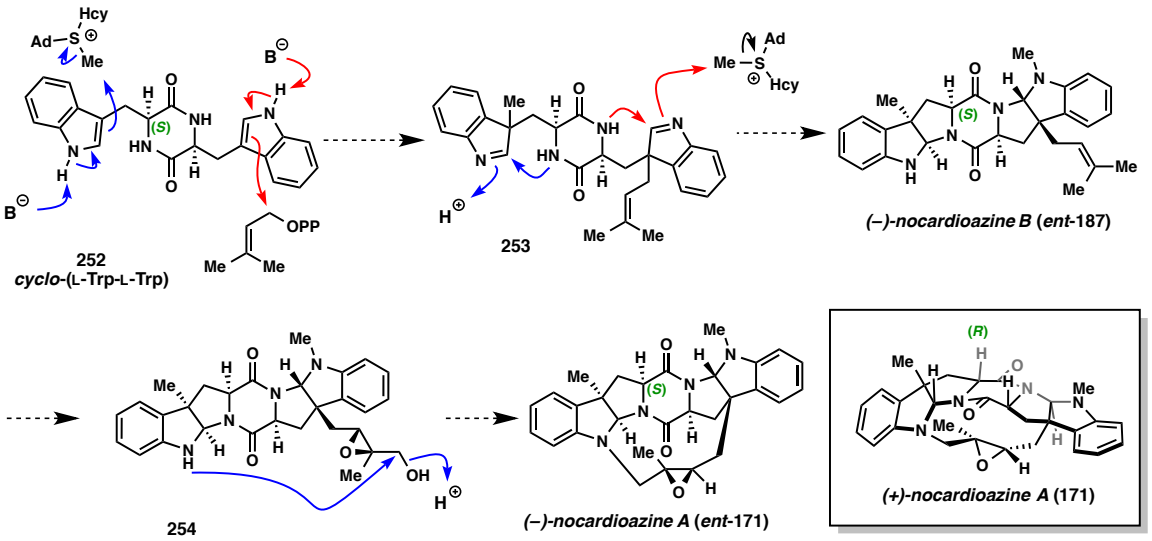
3.1.1 Proposed Biosynthesis of Nocardioazines A and B

Biosynthetically, it is proposed that both nocardioazines A and B are synthesized in bacteria from L-tryptophan cyclic dimer **252** (Scheme 3.1), which is alkylated at both C3 positions with either a methyl or a prenyl group to provide imine intermediate **253**.[3] The diketopiperazine (DKP) nitrogen atoms would then cyclize to form the pyrroloindoline core, providing nocardioazine B (*ent*-**187**). *ent*-**187** is proposed to undergo two subsequent oxidation reactions to produce hydroxyl-epoxide **254**. The elimination of water facilitated by the indoline nitrogen then forms nocardioazine A (*ent*-**171**).

It is important to note that the naturally abundant L-tryptophan series dictates the absolute stereochemistry at the DKP core to be of the (*S*)-configuration, as proposed in the isolation paper.[3] Our total synthesis work, as will be described in this chapter, and related studies by Ye and coworkers[4] have corrected the absolute stereochemistry to be of

the (*R*)-configurations, indicating that the nocardioazine family are derived from the rare D-tryptophan series. In alignment with this claim, Capon and coworkers co-isolated cyclo-(L-Trp-L-Trp) and cyclo-(L-Trp-D-Trp) along with the nocardioazines.[3] It is suggested that cyclo-(L-Trp-D-Trp) could be the biosynthetic precursor of nocardioazines A and B; however, such a hypothesis requires that the L-Trp fragment undergoes epimerization at some point during the biological pathway.

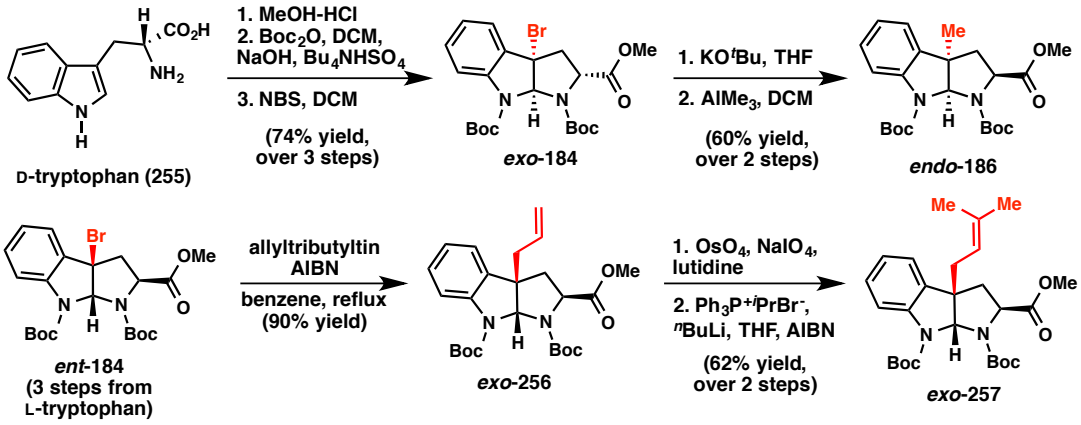
Scheme 3.1. *Proposed biosynthetic origins of nocardioazines A and B*



3.1.2 The Total Synthesis of (–)-Nocardioazine B by Ye

At the outset of our endeavor toward nocardioazines A (**171**) and B (**187**) in 2011, there were no reported total syntheses of these diketopiperazine-containing pyrroloindoline natural products. Only a year afterwards, Ye and coworkers accomplished the first total synthesis of (–)-nocardioazine B (*ent*-**187**).[4]

Scheme 3.2. *Preparation of nocardioazine B fragments from tryptophans by Ye*

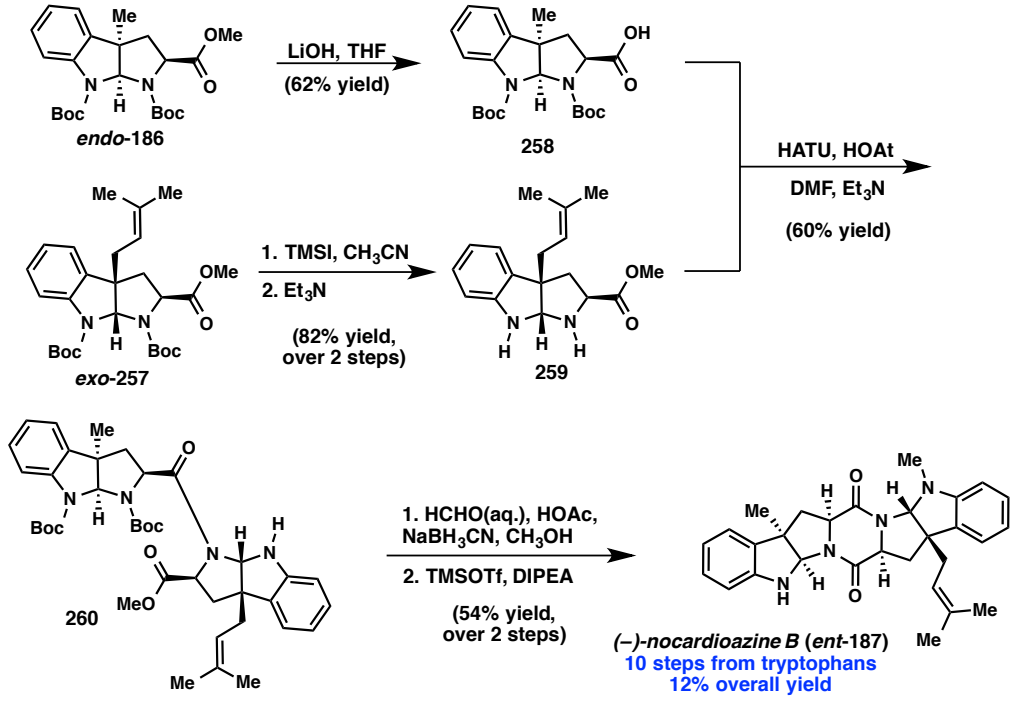


Starting from D-tryptophan (**255**), a well-established three-step procedure provided *exo*-Br-pyrroloindoline **184** in good yield (Scheme 3.2). Utilizing methodology developed by Rainier and coworkers,[5] the bromide of pyrroloindoline *exo*-**184** was converted to a methyl group via a highly strained cyclopropane intermediate (See Chapter 2, Scheme 2.3 for detailed discussion), which provided the *endo*-pyrroloindoline fragment *endo*-**186**. In order to assemble the eastern fragment of the natural product, L-tryptophan was converted to *ent*-**184** following the same procedure, and was subjected to a Keck radical alkylation, as utilized by the Danishefsky group.[6] The allyl group in **256** was subjected to a Johnson-Lemieux oxidation to form the corresponding aldehyde, which underwent a Wittig olefination reaction to provide the prenyl group of the pyrroloindoline fragment *exo*-**257**.

After preparation of both fragments, a step-wise peptide coupling strategy was pursued to form the DKP core (Scheme 3.3): *endo*-**186** was hydrolyzed to give acid **258**, and the Boc groups in *exo*-**257** were then removed to provide amine **259**. Carboxylic acid **258** and amine **259** were treated with peptide coupling reagent HATU to form dipeptide **260**, which was subsequently methylated at the aniline nitrogen under reductive

amination conditions. Upon removal of the two Boc protecting groups, the resulting secondary amine intermediate cyclized *in situ* to provide the central DKP and completed the total synthesis of (–)-nocardioazine B (*ent*-**187**). Through *de novo* exercise, Ye and coworkers were able to correct the originally proposed absolute stereochemistry of the natural product by comparison of the optical rotation signs, confirming that (+)-nocardioazine B (**187**, Figure 3.1) is the naturally occurring form. The question left unanswered was the absolute configuration of nocardioazine A (**171**), although it was presumed that it carried the same absolute configuration as **187**.

Scheme 3.3. *Endgame of (–)-nocardioazine B synthesis by Ye*



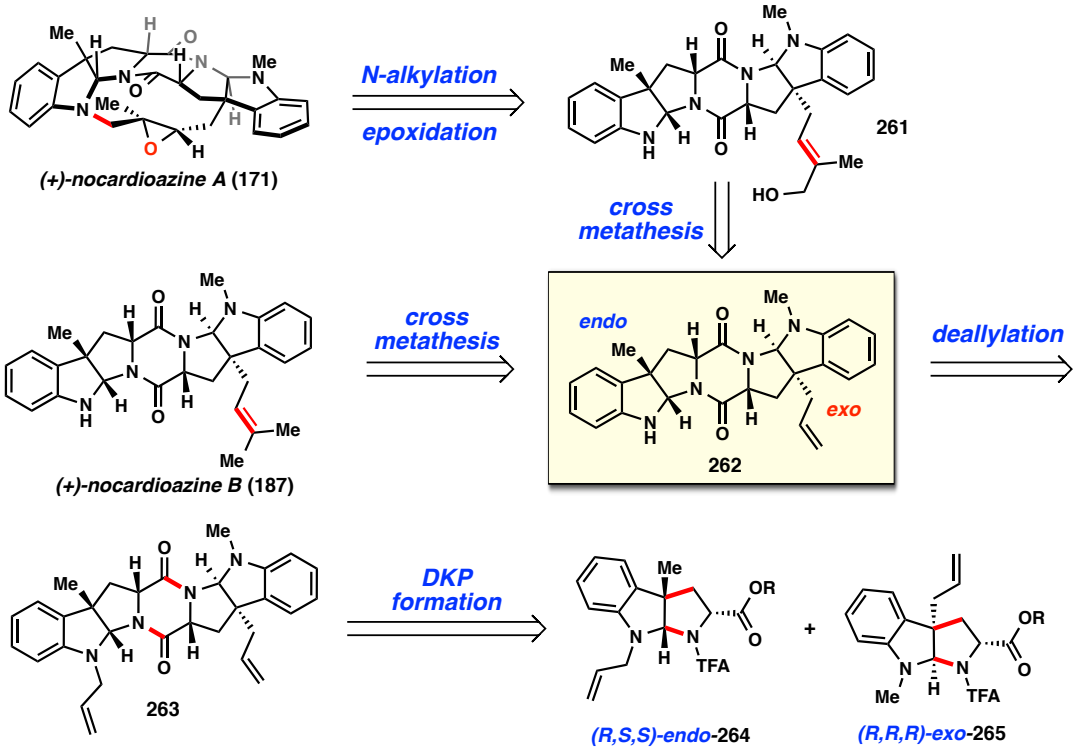
3.1.3 Retrosynthetic Analysis

The total synthesis reported by the Ye group, albeit a short synthesis, relied entirely on the chiral information obtained from D/L-tryptophan building blocks to control

the construction of subsequent stereocenters. However, we believed that a more efficient synthesis of **171** and **187** could be born by harnessing the power of asymmetric catalysis and starting from achiral starting materials.

We took particular note of the fact that the *endo*- and *exo*-pyrroloindolines are of the opposite enantiomeric series, a structural element that is necessary to geometrically accommodate the macrocycle of **171**. This interesting stereochemical relationship makes **171** and **187** appealing synthetic targets for asymmetric catalysis, where selection of the appropriate enantiomer of catalyst dictates the absolute stereochemistry of the pyrroloindoline building blocks.

Scheme 3.4. *Retrosynthetic analysis of (+)-nocardioazines A and B*



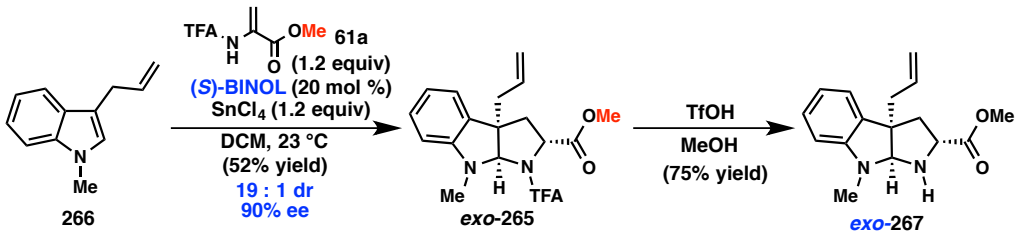
Thus, it was envisioned that both **171** and **187** could be accessed from DKP **262** (Scheme 3.4). A simple cross metathesis with isobutene would provide nocardioazine B

(**187**). On the other hand, cross metathesis with methacrolein and subsequent reduction would generate allylic alcohol **261**, which provides a suitable handle for cyclization and sets the stage for a final epoxidation event to complete the total synthesis of nocardioazine A (**171**). The divergent intermediate **262** is proposed to be accessed by coupling pyrroloindolines *endo*-**264** and *exo*-**265**. In previous studies we have demonstrated that the *exo*-diastereomer can be epimerized to the corresponding *endo*-diastereomer, thus the preparation of both *endo*-**264** and *exo*-**265** would provide a path forward.[1]

3.2 TOTAL SYNTHESIS OF (+)-NOCARDIOAZINE B

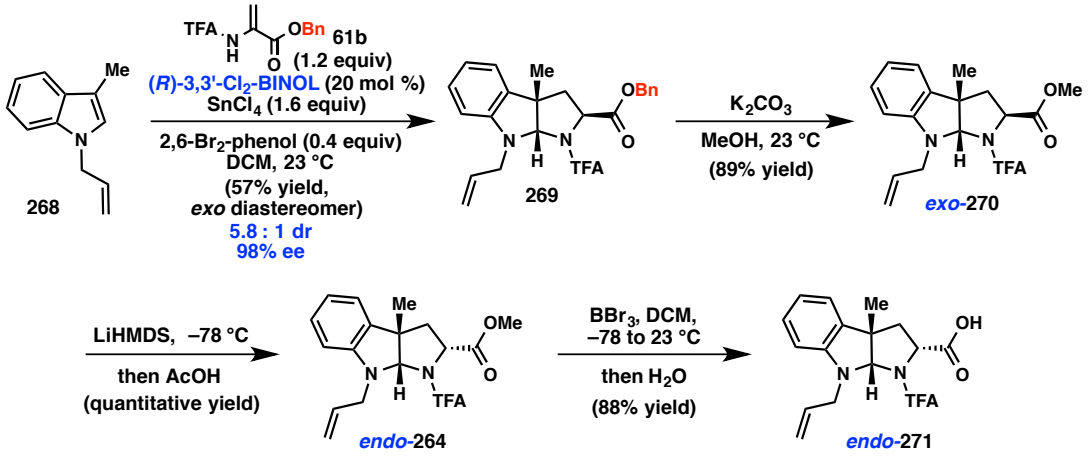
In the forward sense, treatment of a solution of *N*-methyl-3-allyl indole (**266**) and acrylate **61a** with (*S*)-BINOL (20 mol %) and $SnCl_4$ (1.2 equiv) delivered *exo*-pyrroloindoline **265** in 52% yield and 90% ee (Scheme 3.5). These conditions were highly diastereoselective for *exo*-**265** (19:1); however, the yield is modest due to allyl migration from C3 to C2 of the indole under the reaction conditions.[7] Neither addition of 2,6-dibromophenol nor use of other catalysts improved the yield of **265**. Cleavage of the TFA group using TfOH in anhydrous methanol provided, upon basic workup, *exo*-amine **267**.

Scheme 3.5. *Preparation of exo-pyrroloindoline **267** fragment*



On the other hand, treatment of *N*-allylindole **268** and benzyl trifluoroacetamidoacrylate (**61b**) with (*R*)-3,3'-dichloro-BINOL (20 mol %), $SnCl_4$ (1.6 equiv), and 2,6-dibromophenol (0.4 equiv) furnished *exo*-pyrroloindoline **269** in 57% yield and 98% ee (Scheme 3.6). It is noteworthy that additive 2,6-dibromophenol significantly improves the ee of this reaction, compared to the observed 92% ee without it.[2] The modest yield of *exo*-**269** results from the moderate diastereoselectivity (5.8:1) of the transformation. In this case, benzyl acrylate **61b** was employed instead of methyl acrylate **61a** because the dr was improved and the *exo*- and *endo*- diastereomers were more readily separated. In order to prepare the corresponding carboxylic acid **271**, benzyl ester was first converted to methyl ester **270** using K_2CO_3 in methanol. Treatment of *exo*-**270** with LiHMDS at low temperatures followed by acetic acid quench provided the thermodynamically favored *endo* diastereomer **264**, which was deprived of the methyl ester with BBr_3 to deliver *endo*-pyrroloindoline acid **271**.

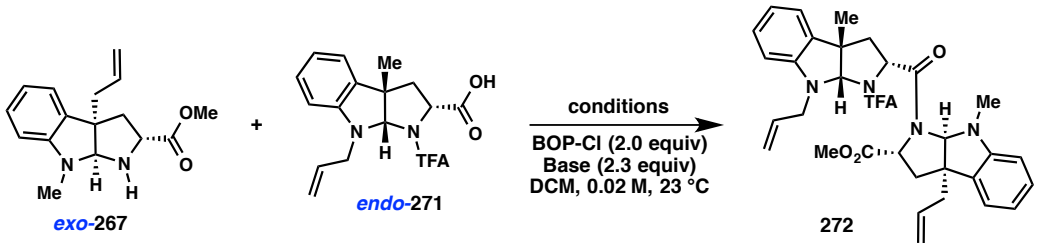
Scheme 3.6. *Preparation of endo-pyrroloindoline **271** fragment*



With access to *endo*-acid **271** and *exo*-amine **267**, we were poised to prepare key DKP **263** (Scheme 3.4). In contrast to our unsuccessful efforts to couple *exo*-

pyrroloindolines in the lansai B (**169**) synthesis (Chapter 2), mixing of *endo*-acid **271** and *exo*-amine **267** in the presence of BOP-Cl furnished the desired dipeptide **272**, albeit in low yield due to side reactions including epimerization and decomposition of **271** (entry 1, Table 3.1). After considerable optimization, we discovered that the nature of the base in the peptide coupling plays a key role in determining the reactivity. When DMAP or pyridine was used, the major product was the anhydride derived from dimerization of acid **271**. Fortunately, 2,4,6-collidine was found to be effective in favoring product formation over anhydride production to provide 45% yield of product (entry 4). The yield was further improved to 81% by slow addition of acid **271** to 2.0 equiv amine **267** (entry 6). Importantly, the unreacted amine **267** could be recovered by silica gel chromatography. When compared to the challenges encountered in the coupling of *exo*-pyrroloindolines, the ability to couple *exo*-**267** and *endo*-**271** reveals that, in addition to the identity of the *N*-substituents, the relative stereochemistry of the pyrroloindoline coupling partners is a key determinate in the ease of peptide formation.

Table 3.1. *Peptide coupling between exo-**267** and endo-**271***

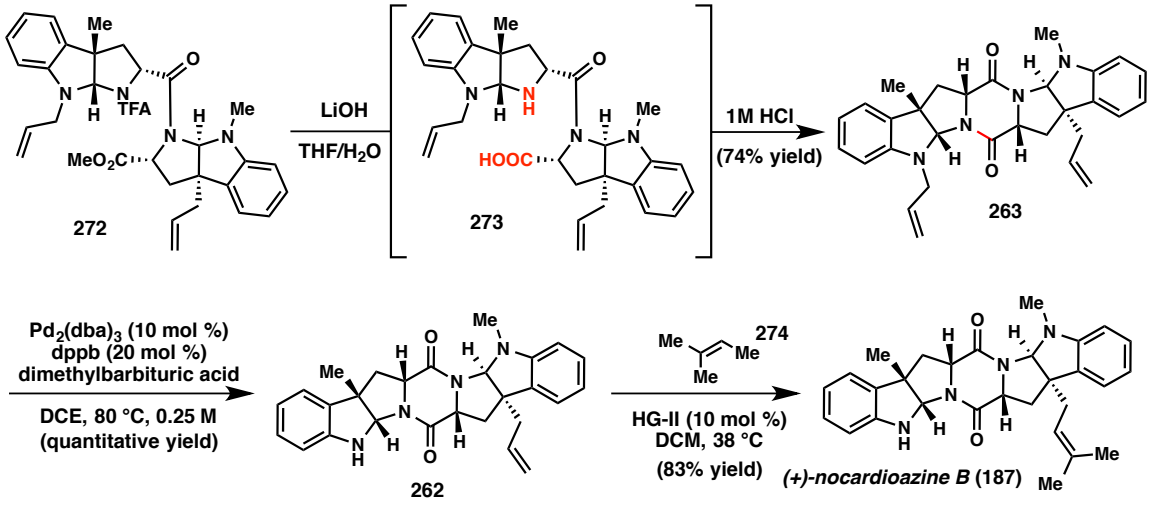


entry	*exo*-267 (equiv)	Base	Results[a]
1	1.0	DIPEA	26% yield of product + diastereomer + *N*-allyl indole
2	1.0	DMAP	anhydride
3	1.0	pyridine	anhydride
4	1.0	2,4,6-collidine	product : anhydride = 1 : 1, 45% yield
5	2.0	2,4,6-collidine	product : anhydride = 1.4 : 1, 57% yield
6[b]	2.0	2,4,6-collidine	product : anhydride = 4 : 1, 81% yield

[a] ratio determined by LCMS. [b] slow addition of *endo*-271 into reaction.

Saponification of **272** with LiOH generated amino acid **273**, which could be detected by LC-MS (Scheme 3.7). Interestingly, acidification of the reaction mixture with 1M HCl delivered DKP **263**, which represents an unusually facile DKP cyclization. Subsequent palladium-catalyzed deallylation of **263** in the presence of 1,3-dimethylbarbituric acid as the allyl scavenger gave free amine **262**.[8] Cross metathesis of **262** with 2-methyl-2-butene (**274**) provided (+)-nocardioazine B (**187**).[9] Thus, the enantioselective total synthesis of (+)-**187** was completed in nine linear steps and 21% overall yield from 3-methylindole.

Scheme 3.7. *Endgame of (+)-nocardioazine B synthesis*



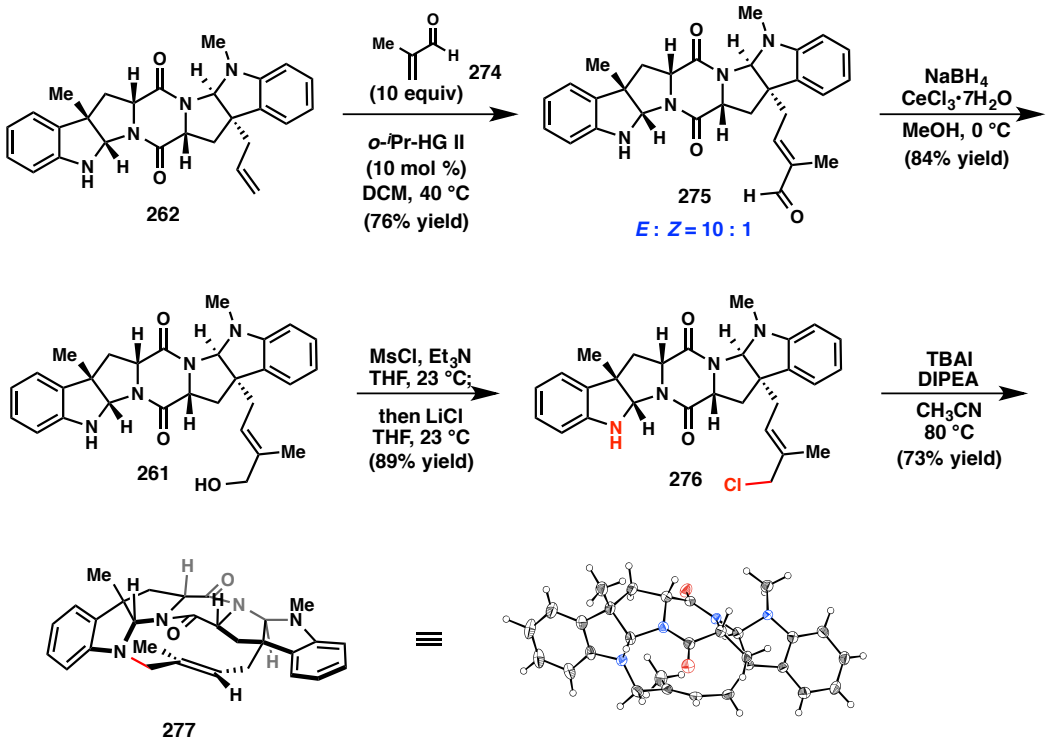
3.3 TOTAL SYNTHESIS OF (+)-NOCARDIOAZINE A

3.3.1 A Late-stage Epoxidation Strategy

At this stage, our focus shifted to advancing amine **262** to (+)-nocardioazine A (**171**). Exposure of **262** to excess methacrolein (**274**) and *ortho*-isopropyl Hoveyda-Grubbs II catalyst (10 mol %) delivered enal **275** in 76% yield as a 10 : 1 *E*/*Z* mixture

(Scheme 3.8).[10] Luche reduction followed by Finkelstein chlorination provided allyl chloride **276**. Gratifyingly, treatment of **276** with tetrabutylammonium iodide (TBAI) and base in acetonitrile at 80 °C promoted intramolecular *N*-alkylation, furnishing macrocycle **277**. Interestingly, the base was found to be important in this S_N2 process: use of a less bulky base like triethylamine provided lower yields due to competing displacement of chloride to form an ammonium salt. Interestingly, the ^{1}H NMR spectra of alkene **277** revealed two interconverting conformations, adding difficulties to the elucidation of its structure. Eventually, the structure of this unusual macrocycle **277** was confirmed by X-ray crystallography, setting the stage for the final epoxidation step.

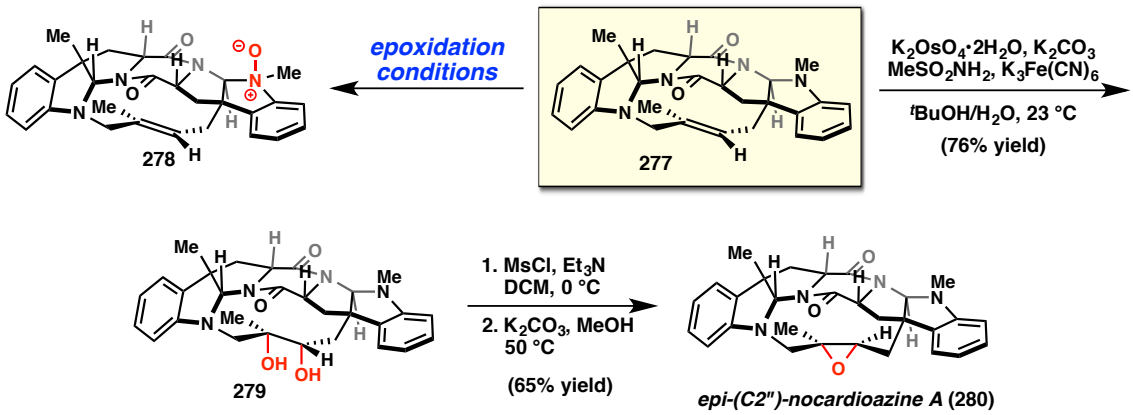
Scheme 3.8. *Preparation of macrocyclic alkene* ***277***



Unfortunately, exposure of **277** to a wide variety of epoxidation conditions, including dimethyldioxirane, *m*-chloroperoxybenzoic acid, and Jacobsen epoxidation

catalysts, failed to produce the natural product; instead, the major product was unstable *N*-oxide **278** (Scheme 3.9), which was characterized by a significant downfield shift of the *N*-methyl group in the ^{1}H NMR. Use of excess oxidant or efforts to isolate **278** and resubject it to epoxidation conditions were also unsuccessful, revealing that the trisubstituted alkenes of **277** and **278** are remarkably inert toward epoxidation. The origin of this effect is unclear; however, inspection of the crystal structure of alkene **277** suggests that it is not simply steric shielding of the double bond.

Scheme 3.9. *Attempts to install the epoxide*

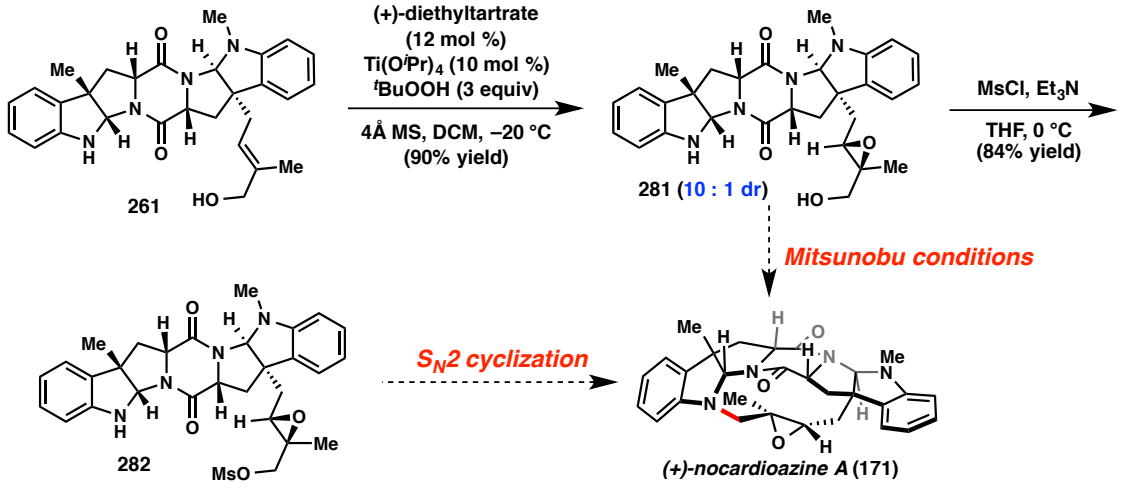


Alternatively, it was possible to diastereoselectively dihydroxylate alkene **279** using potassium osmate.[11] Selective mesylation of the secondary alcohol and exposure of the resulting mesylate to potassium carbonate in methanol closed the epoxide to form *epi*-(C2")-nocardioazine A (**280**). Unfortunately, attempts to correct the stereochemistry by double inversion strategies or oxidation/reduction sequences were unsuccessful.

Fully aware of the challenges associated with epoxidizing the macrocyclic alkene **277**, a strategy involving switching the order of epoxidation and cyclization was pursued. Epoxidation of allylic alcohol **261** proceeded smoothly under Sharpless asymmetric epoxidation conditions (Scheme 3.10).[12] However, intramolecular Mitsunobu reaction did

not occur, presumably due to the lower acidity of the aniline *N*-H in **281**. Alternatively, the primary alcohol could be converted to the mesylate (**282**). Unfortunately, either epimerization or no reaction was observed when treating **282** with a wide array of base. Other leaving groups including iodide and triflate were also explored, but no cyclization product was detected in either case. The lower reactivity toward cyclization of epoxide **282** versus alkene **277** is not entirely surprising due to the loss of reactivity gained from the allylic halide in **277**.

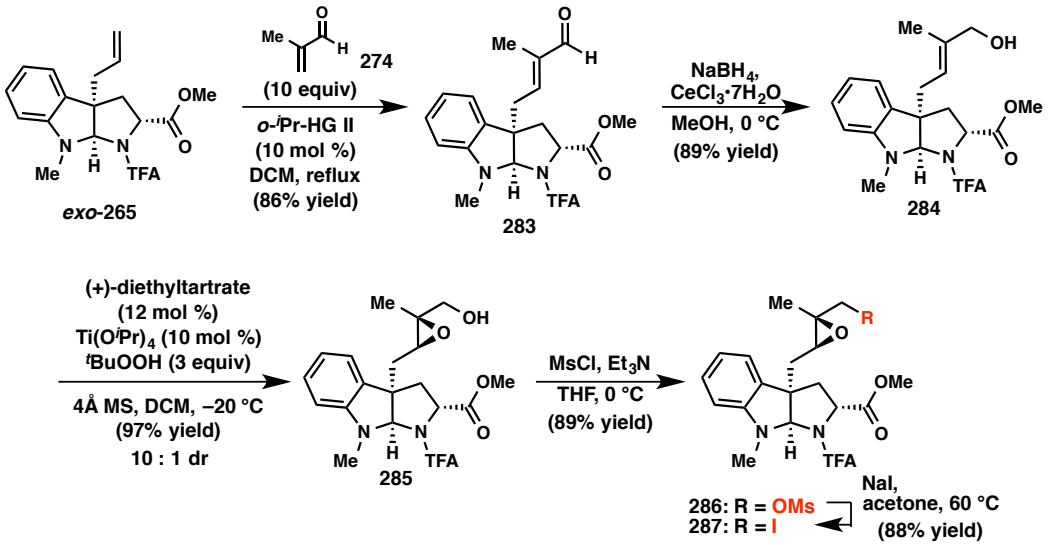
Scheme 3.10. *Attempts to promote the last-stage cyclization*



3.3.2 An Early-stage Epoxide Installation Approach

Given the challenges encountered in attempting to epoxidize late-stage intermediate **277**, a revised strategy utilizing an early-stage epoxidation and diketopiperazine-forming macrocyclization was pursued (Scheme 3.11). Thus, 3a-allyl pyrroloindoline *exo*-**265** was transformed into aldehyde **283** via cross metathesis with **274**. Luche reduction and Sharpless asymmetric epoxidation using (+)-diethyltartrate delivered epoxy alcohol **285** in 10:1 dr,[12] which was converted to mesylate **286** by

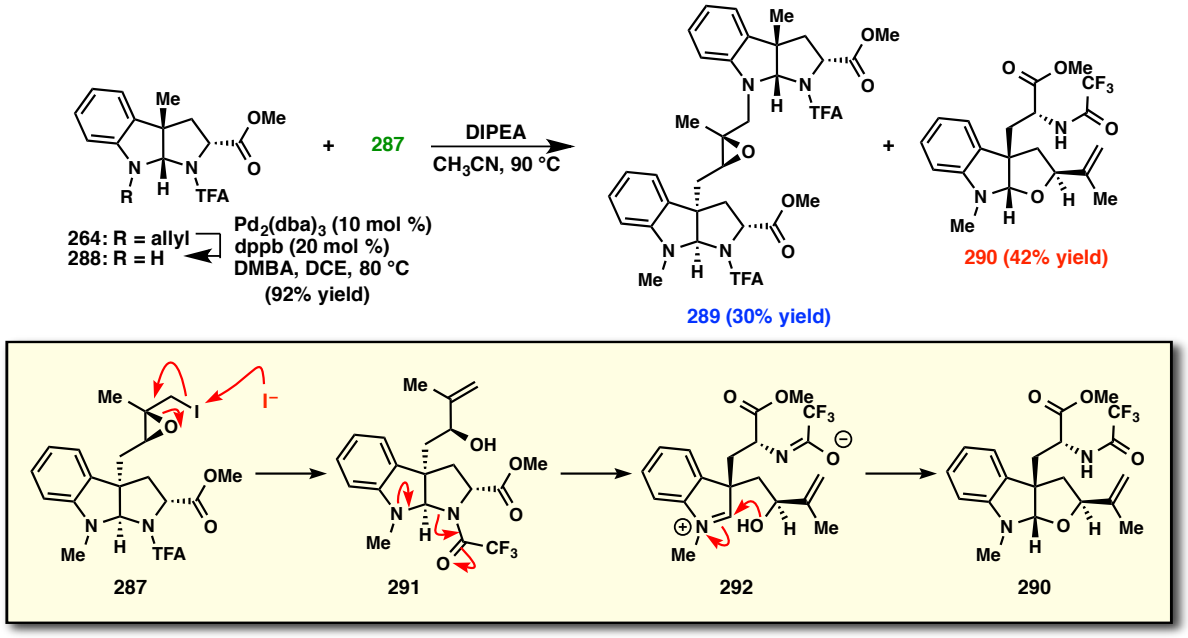
Scheme 3.11. *Early incorporation of epoxide*



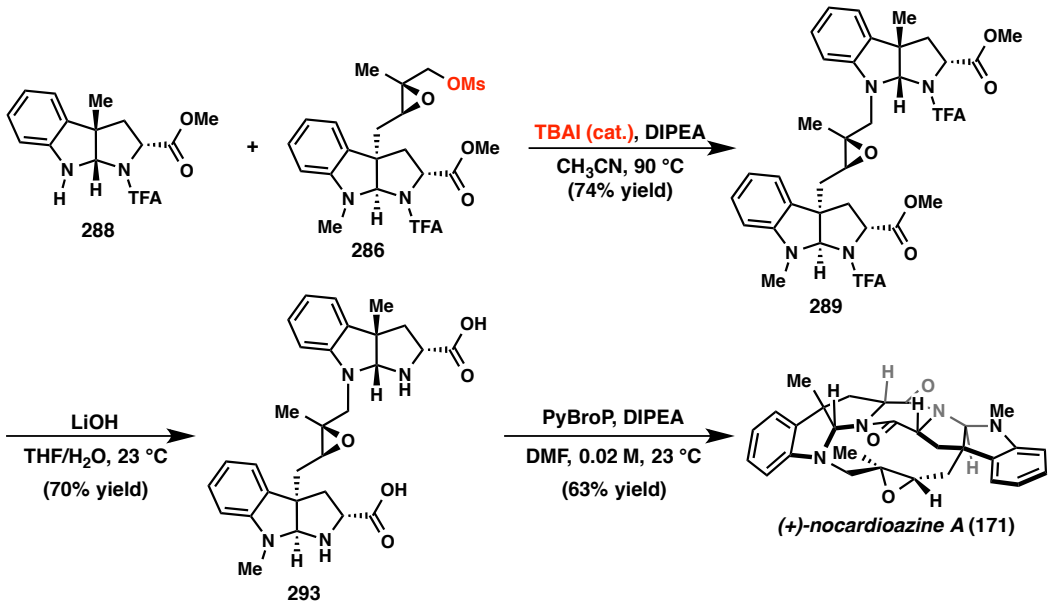
treatment with mesyl chloride. The corresponding epoxy iodide **287** could also be prepared by subjecting mesylate **286** to NaI in acetone. Concomitantly, amine **288** was prepared from *endo*-pyrroloindoline **264** by Pd-catalyzed deallylation (Scheme 3.12). Both epoxide nucleophiles **286** and **287** were exposed to amine **288** and Hünig's base in acetonitrile at high temperatures. Interestingly, mesylate **286** showed no reactivity, while iodide **287** afforded desired coupled product **289** in 30% yield. However, epoxide **289** was accompanied with the formation of side product **290** in 42% yield, which was proposed to arise from iodide-triggered epoxide opening followed by pyrroloindoline ring-opening and intramolecular trapping with the secondary alcohol.

In order to harness the reactivity of epoxide iodide and minimize the undesired rearrangement side pathway, it was proposed that the addition of a catalytic amount of an iodide source to mesylate **286** could generate epoxide iodide **287** *in situ*, thus the lower concentration of iodide would suppress the undesired side reaction pathway. Indeed, after

Scheme 3.12. *Intermolecular alkylation attempts*



Scheme 3.13. *Endgame of (+)-nocardioazine A synthesis*



considerable optimization, it was observed that treatment of amine **288** and mesylate **286** with 0.2 equivalent of TBAI and Hünig's base in acetonitrile at 90 °C delivers bis(pyrroloindoline) **289** in 74% yield (Scheme 3.13). Exposure of **289** to excess LiOH

resulted in saponification of the methyl esters and hydrolysis of the TFA groups to give bis(amino acid) **293**. We were pleased to find that subjection of **293** to bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP, a peptide coupling reagent) in DMF promoted intramolecular DKP formation to afford (+)-nocardioazine A (**171**). The synthesis of (+)-**171** requires only nine steps and proceeds in 11% overall yield from 3-allylindole. Moreover, these findings establish the viability of macrocyclization by intramolecular DKP formation.

Through this process, we also established that the naturally isolated nocardioazine A (**171**) possesses the same absolute stereo configurations as nocardioazine B (**187**), suggesting that both natural products might be produced from the same biological source, namely cyclo-(L-Trp-D-Trp).

3.4 CONCLUDING REMARKS

In summary, the enantioselective total syntheses of the diketopiperazin-containing pyrroloindoline natural products (+)-nocardioazine A (**171**) and B (**187**) were accomplished. These studies demonstrate the utility of enantioselective formal (3 + 2) cycloaddition reactions to prepare highly functionalized pyrroloindolines for applications in total synthesis. In addition, subtle changes in the relative stereochemistry and nitrogen substitution patterns of pyrroloindolines were shown to significantly influence the ability to prepare bis(pyrroloindolines) by DKP formation. Further investigations of **171** as an inhibitor of P-glycoprotein are ongoing with collaboration with the Chang laboratory in UC San Diego.

3.5 EXPERIMENTAL SECTION

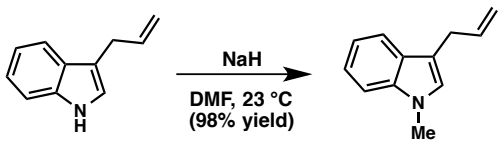
3.5.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), acetonitrile (MeCN), dimethylformamide (DMF), and toluene (PhMe) were dried by passing through activated alumina columns. Unless otherwise stated, chemicals and reagents were used as received. *N,N*-Diisopropylethamine (DIPEA) was distilled over calcium hydride prior to use. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, *p*-anisaldehyde, or $KMnO_4$ staining. Flash column chromatography was performed either as described by Still et al.[13] using silica gel (particle size 0.032-0.063) purchased from Silicycle or using pre-packaged RediSep®Rf columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 MR (at 400 MHz and 101 MHz, respectively), a Bruker 400 equipped with a cryoprobe (at 400 MHz and 101 MHz, respectively), a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), or a Varian Inova 600 (at 600 MHz and 150 MHz, respectively), and are reported relative to internal $CHCl_3$ (^{1}H, δ = 7.26), $CHDCl_2$ (^{1}H, δ = 5.32), CD_2HOD (^{1}H, δ = 3.31), MeCN-*d2* (^{1}H, δ = 1.94), or DMSO-*d5* (^{1}H, δ = 2.50), and $CDCl_3$ (^{13}C, δ = 77.0), CD_2Cl_2 (^{13}C, δ = 54.0), CD_3OD (^{13}C, δ = 49.0), MeCN-*d3* (^{13}C, δ = 118.3), or DMSO-*d6* (^{13}C, δ = 40.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet,

q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM) ionization mode. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing Chiralpak AD or Chiralcel OD-H columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd with visualization at 254 nm. Preparative HPLC was performed with an Agilent 1100 Series HPLC utilizing an Agilent Eclipse XDB-C18 5μm column (9.4 x 250 mm) or an Agilent Zorbax RX-SIL 5μm column (9.4 x 250 mm). Melting points were determined using a Büchi B-545 capillary melting point apparatus and the values reported are uncorrected.

3.5.2 Preparative Procedures and Spectroscopic Data

Preparation of *N*-methyl-3-allylindole 266

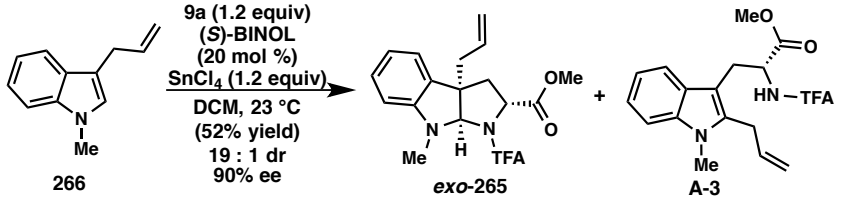


A-2 **266**

To a 500 mL flame-dried flask was added NaH (60%, 4.94 g, 123.6 mmol, 1.5 equiv) and DMF (120 mL). Commercially aviallable 3-allylindole **A-2** (12.95 g, 82.4 mmol, 1.0 equiv) was transferred to the reaction flask via DMF (40 mL). After 90 minutes, methyl iodide (7.7 mL, 123.6 mmol, 1.5 equiv) was added slowly, while the reaction flask was cooled using an ice-bath. After 1 hour, the reaction was diluted with EtOAc (100 mL) and carefully quenched with distilled water (300 mL). The mixture was separated and the aqueous layer was then extracted with EtOAc (2 x 200 mL). Combined

organic layers were washed with brine (3 x 300 mL) to get rid of DMF. It was dried over Na_2SO_4, filtered and concentrated down to a yellow oil. Flash chromatography (0% to 10% EtOAc in hexanes) afforded *N*-methyl-3-allylindole **266**, as a yellow oil (13.77 g, 80.4 mmol, 98% yield). Spectral data matches that reported in the literature.[14]

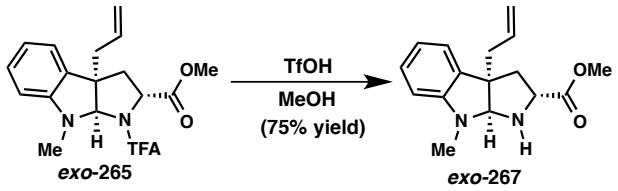
Preparation of *N*-methyl-3-allyl pyrroloindoline 265



To a flame-dried flask was added *N*-methyl-3-allylindole **266** (1.0 g, 5.80 mmol, 1.0 equiv), methyl acrylate **61a** (1.15 g, 5.80 mmol, 1.0 equiv), (*S*)-BINOL (334 mg, 1.20 mmol, 0.2 equiv), and DCM (30 mL). The reaction flask was covered with aluminum foil. $SnCl_4$ (1M solution in DCM, 9.34 mL, 9.34 mmol, 1.6 equiv) was added at last. The reaction mixture was allowed to stir at room temperature for 24 hours. The solution was diluted with acetonitrile (12 mL) and quenched with 1M HCl (12 mL), followed by addition of distilled water (60 mL). The mixture was separated and the aqueous layer was extracted with EtOAc (3 x 60 mL). Combined organic layers were washed with saturated $NaHCO_3$ solution (75 mL) and then brine (75 mL). It was dried over Na_2SO_4, filtered and concentrated down to give an orange oil. Flash chromatography (0% to 20% EtOAc in hexanes) afforded 3-allyl-pyrroloindoline **265** (19 : 1 mixture of *exo*:*endo* diastereomers by ^1H NMR), as a thick orange oil (1.10 g, 2.99 mmol, 52% yield); **A-3** was isolated as the major side product, resulting from C3 to C2 rearrangement. The mixture of diastereomers was further purified by flash chromatography (0% to 10% EtOAc in hexanes) to give major diastereomer **265** for characterization purposes. The enantiomeric

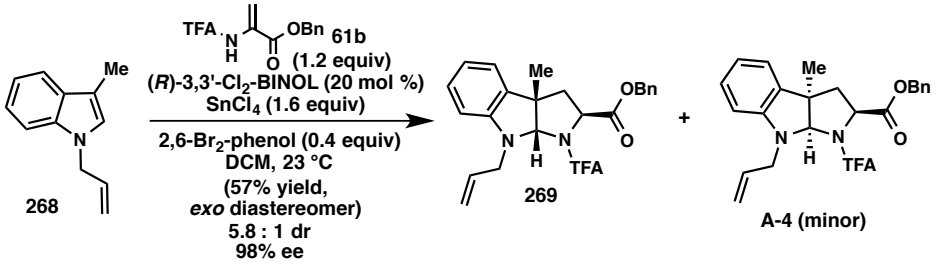
excess of *exo*-**265** was determined to be 90% by chiral SFC analysis (AD, 2.5 mL/min, 3% IPA in CO_2, λ = 254 nm): t_R(major) = 3.2 min, t_R(minor) = 6.5 min. $[\alpha]_D^{25}$ = +112° (*c* = 0.96, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 2.0:1 mixture of rotamers the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.17 (t, *J* = 7.7 Hz, 1H*, 1H§), 7.05 (d, *J* = 7.3 Hz, 1H*, 1H§), 6.84 (t, *J* = 8.1 Hz, 1H§), 6.77 (t, *J* = 7.5 Hz, 1H*), 6.58 (d, *J* = 7.2 Hz, 1H§), 6.52 (d, *J* = 7.9 Hz, 1H*), 5.62 (s, 1H*), 5.60 – 5.45 (m, 1H*, 1H§), 5.44 (s, 1H§), 5.15 – 5.04 (m, 2H*, 2H§), 4.64 (d, *J* = 5.5 Hz, 1H*), 4.38 – 4.31 (m, 1H§), 3.81 (s, 3H*), 3.76 (s, 3H§), 3.10 (s, 3H*), 2.89 (s, 3H§), 2.64 (dd, *J* = 13.6, 9.3 Hz, 1H*), 2.62 – 2.57 (m, 1H§), 2.54 (dd, *J* = 14.0, 6.7 Hz, 1H*, 1H§), 2.52 – 2.47 (m, 1H§), 2.46 – 2.40 (m, 1H*), 2.32 (dd, *J* = 13.9, 8.4 Hz, 1H*), 2.19 – 2.11 (m, 1H§); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5*, 170.5§, 158.8* (q, *J* = 37.1 Hz), 157.5§ (q, *J* = 38.0 Hz), 150.2*§, 133.2*, 132.2§, 129.0§, 128.8*, 122.1*, 120.0§, 119.1*, 118.7§, 116.0* (q, *J* = 288.4 Hz), 115.8§ (app d, *J* = 285.2 Hz), 109.9§, 108.2*, 90.4*, 89.0§, 60.6§, 59.5*, 57.3§, 53.4*, 52.9*, 52.4§, 42.1*, 41.6*, 41.0§, 39.0§, 36.8*, 35.4§ (both ^{1}H and ^{13}C spectra were taken using the enantiomer of **23**); FTIR (NaCl, thin film): 3076, 3053, 3008, 2955, 2918, 2848, 2829, 1751, 1693, 1641, 1608, 1490, 1435, 1357, 1302, 1203, 1158, 1061, 1023, 994, 952, 925, 875, 854, 810, 795, 746 cm^{-1}; HRMS (MM) calc'd for $C_{18}H_{20}F_3N_2O_3$ $[M+H]^+$ 369.1421, found 369.1432.

Preparation of *exo*-pyrroloindoline amine 267



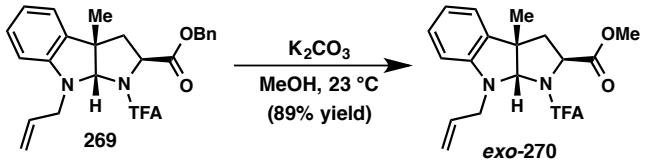
To a 200 mL flame-dried flask was added *exo*-3-allyl-pyrroloindoline **265** (6.57 g, 17.8 mmol, 1.0 equiv) and dissolved with MeOH (90 mL). Triflic acid (15.7 mL, 178.4 mmol, 10.0 equiv) was added slowly into reaction flask. The dark purple mixture was allowed to stir at room temperature for 50 hours. The solution was cautiously quenched with saturated $NaHCO_3$ solution (150 mL). The mixture was separated and the aqueous layer was extracted with DCM (3 x 150 mL). Combined organic layers were dried over Na_2SO_4, filtered and concentrated down to give an orange oil. Flash chromatography (0% to 60% EtOAc in hexanes) afforded 3-allyl-pyrroloindoline amine *exo*-**267** as a thick orange oil (3.60 g, 13.2 mmol, 75% yield). $[\alpha]_D^{25}$ = +43° (*c* = 0.95, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (td, *J* = 7.6, 1.3 Hz, 1H), 6.98 (dd, *J* = 7.4, 1.2 Hz, 1H), 6.61 (td, *J* = 7.4, 1.0 Hz, 1H), 6.31 (d, *J* = 7.8 Hz, 1H), 5.67 (dddd, *J* = 16.7, 10.1, 7.9, 6.4 Hz, 1H), 5.08 – 4.99 (m, 2H), 4.68 (s, 1H), 3.64 (s, 3H), 3.62 (dd, *J* = 10.4, 6.1 Hz, 1H), 2.78 (s, 3H), 2.67 (s, 1H), 2.51 (ddt, *J* = 13.9, 6.5, 1.4 Hz, 1H), 2.41 (ddt, *J* = 13.7, 8.0, 1.1 Hz, 1H), 2.34 (dd, *J* = 12.1, 6.1 Hz, 1H), 1.95 (dd, *J* = 12.2, 10.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 150.8, 134.0, 132.2, 127.9, 122.6, 117.6, 116.4, 104.9, 88.0, 58.9, 56.0, 51.5, 44.1, 42.5, 30.9; FTIR (NaCl, thin film): 3344, 3073, 3050, 3024, 3003, 2950, 2916, 1738, 1639, 1606, 1493, 1449, 1437, 1383, 1354, 1328, 1300, 1267, 1236, 1206, 1166, 1140, 1121, 1105, 1073, 1019, 998, 973, 948, 918, 889, 817, 790, 741 cm^{-1}; HRMS (MM) calc'd for $C_{16}H_{21}N_2O_2$ $[M+H]^+$ 273.1598, found 273.1067.

Preparation of *N*-allyl pyrroloindoline 269



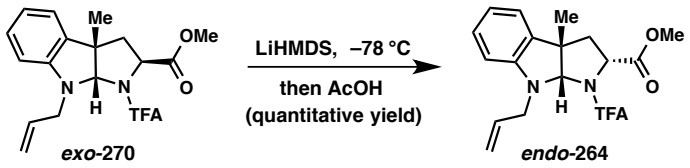
To a flame-dried flask was added *N*-allylindole **268**[15] (815 mg, 4.76 mmol, 1.0 equiv), benzyl acrylate **61b**[16] (1.56 g, 5.71 mmol, 1.2 equiv), (*R*)-3,3'-Cl_2-BINOL (338 mg, 0.95 mmol, 0.2 equiv), 2,6-dibromo-phenol (480 mg, 1.90 mmol, 0.4 equiv) and DCM (35 mL). $SnCl_4$ (1M solution in DCM, 7.62 mL, 7.62 mmol, 1.2 equiv) was added at last. The orange mixture was allowed to stir at room temperature for 42 hours. The solution was diluted with acetonitrile (12 mL) and quenched with 1M HCl (12 mL), followed by addition of distilled water (60 mL). The mixture was separated and the aqueous layer was extracted with ether (3 x 60 mL). Combined organic layers were washed with 3M NaOH solution (3 x 75 mL). It was dried over $MgSO_4$, filtered and concentrated down to give yellow mixture of oil and solid. Flash chromatography (1% to 8% EtOAc in hexanes) afforded major diastereomer *exo*-pyrroloindoline **269** as a thick orange oil (1.19 g, 2.68 mmol, 57% yield); minor diastereomer *endo*-pyrroloindoline **A-4** was also isolated as a thick orange oil (204 mg, 0.46 mmol, 10% yield). The enantiomeric excess of **269** was determined to be 98% by chiral SFC analysis (OJ, 2.5 mL/min, 6% IPA in CO_2, λ = 254 nm): t_R(major) = 5.7 min, t_R(minor) = 4.4 min. The enantiomeric excess of **A-4** was determined to be 93% by chiral SFC analysis (OJ, 2.5 mL/min, 2% IPA in CO_2, λ = 254 nm): t_R(major) = 5.7 min, t_R(minor) = 4.4 min. Spectral data of both diastereomers matches that reported in the literature.[2]

Preparation of *N*-allyl pyrroloindoline methyl ester 270



N-Allyl pyrroloindoline benzyl ester **269** (1.11 g, 2.51 mmol, 1.0 equiv) was dissolved in dry methanol (25 mL); then K_2CO_3 (70 mg, 0.50 mmol, 0.2 equiv) was added as one portion. After running at room temperature for 6 hours, the reaction was quenched with 1M HCl (50 mL), and extracted with EtOAc (3 x 40 mL). Combined organic layer was washed with sodium bicarbonate saturated solution (50 mL) and then dried over Na_2SO_4, filtered and concentrated down to give yellow oil. Flash chromatography (0% to 15% EtOAc in hexanes) afforded corresponding methyl ester **270**, as a white solid (818 mg, 2.22 mmol, 89% yield). Spectral data matches that reported in the literature.[3]

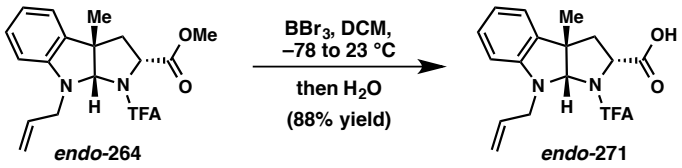
Preparation of *endo-N*-allyl pyrroloindoline 264



N-Allyl pyrroloindoline methyl ester **270** (700 mg, 1.90 mmol) was dissolved in dry THF (16 mL) and brought to –78 °C. LiHMDS solution (1M in THF, 2.85 mL, 2.85 mmol, 1.5 equiv) was added slowly to substrate in THF. After 1 hour, the reaction was quenched with acetic acid (1 mL) and warmed to room temperature. Then the reaction was quenched carefully with sodium bicarbonate saturated solution (40 mL). The aqueous layer was then extracted with EtOAc (3 x 50 mL). Combined organic layer was washed with brine (50 mL). It was then dried over Na_2SO_4, filtered, and concentrated

down to give a yellow oil. Flash chromatography (0% to 10% EtOAc in hexanes) afforded corresponding epimerized *endo* pyrroloindoline methyl ester **264**, as a yellow oil (700 mg, 1.90 mmol, quantitative yield). $[\alpha]_D^{25} = -200°$ (*c* = 1.62, $CHCl_3$); spectral data matches that the corresponding enantiomer reported in the literature.[3]

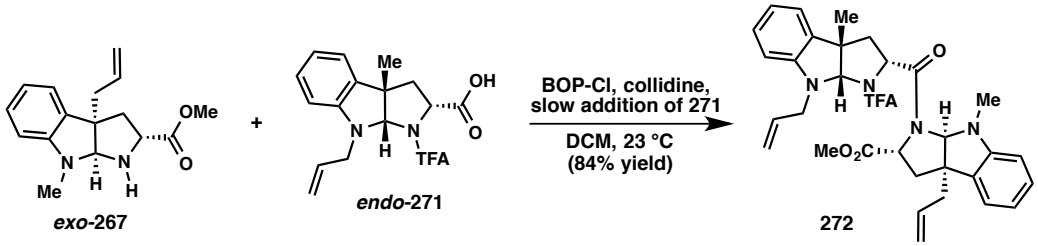
Preparation of *endo-N*-allyl pyrroloindoline carboxylic acid 271



endo-N-Allyl pyrroloindoline methyl ester **264** (1.50 g, 4.07 mmol, 1.0 equiv) was added to a flame-dried 100 mL flask and dissolved in DCM (36 mL). The flask was then cooled to –78 °C and freshly prepared BBr_3 in DCM solution (BBr_3: 1.15 mL, 12.22 mmol, 3.0 equiv; DCM: 12 mL) was added slowly into reaction flask. After 5 minutes, the reaction was allowed to warm to room temperature and stirred for 90 minutes. It was then quenched carefully with addition of distilled water (10 mL), then followed by addition of pH = 2.5 acidic buffer (40 mL, prepared by acidifying a 10% NaH_2PO_4 aqueous solution by $KHSO_4$ until pH reaches 2.5). The aqueous layer was extracted with EtOAc (4 x 40 mL). Combined organic layer was washed with brine (80 mL). It was then dried over Na_2SO_4, filtered, and concentrated down to give a yellow oil. Flash chromatography (0% to 20% EtOAc in hexanes, with 1% acetic acid) afforded corresponding pyrroloindoline carboxylic acid *endo*-**271**, as a brown foam (1.26 g, 3.56 mmol, 88% yield). $[\alpha]_D^{25} = -179°$ (*c* = 1.39, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$; compound exists as a 8.0 : 1 mixture of rotamers the major rotamer is denoted by *, minor rotamer denoted by §) δ 10.90 (s, 1H*, 1H§), 7.11 (td, *J* = 7.7, 1.3 Hz, 1H§), 7.07

(dd, J = 7.4, 1.2 Hz, 1H[§]), 6.99 (td, J = 7.7, 1.3 Hz, 1H*), 6.95 (dd, J = 7.5, 1.2 Hz, 1H*), 6.75 (td, J = 7.4, 1.0 Hz, 1H[§]), 6.57 (td, J = 7.4, 0.9 Hz, 1H*), 6.50 (d, J = 7.9 Hz, 1H[§]), 6.39 (d, J = 7.9 Hz, 1H*), 5.85 (ddt, J = 17.3, 10.6, 5.4 Hz, 1H*), 5.81 – 5.72 (m, 1H[§]), 5.59 (s, 1H*), 5.55 (d, J = 1.9 Hz, 1H[§]), 5.29 (dq, J = 17.2, 1.7 Hz, 1H*), 5.22 – 5.20 (m, 1H[§]), 5.20 – 5.17 (m, 1H[§]), 5.15 (dq, J = 10.2, 1.5 Hz, 1H*), 5.06 (dd, J = 9.9, 5.4 Hz, 1H[§]), 4.73 (dt, J = 8.7, 1.5 Hz, 1H*), 4.13 (qdt, J = 16.7, 5.1, 1.7 Hz, 2H*), 3.91 – 3.69 (m, 2H[§]), 2.76 (dd, J = 13.2, 1.4 Hz, 1H*), 2.42 (dd, J = 13.1, 8.8 Hz, 1H*), 2.39 – 2.34 (m, 1H[§]), 2.29 (dd, J = 13.4, 9.9 Hz, 1H[§]), 1.45 (s, 3H[§]), 1.43 (s, 3H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.3[§], 175.2*, 156.8 (q, $J_{C\text{-}F}$ = 37.0 Hz), 156.6 (q, $J_{C\text{-}F}$= 37.5 Hz), 149.1*, 147.3[§], 133.8*, 133.1[§], 132.4[§], 131.8*, 128.9*, 128.5[§], 122.2*, 121.4[§], 118.7[§], 118.0*, 117.1[§], 116.3*, 116.0* (q, $J_{C\text{-}F}$ = 288.5 Hz), 108.1[§], 107.1*, 88.9[§], 88.3*, 59.8[§], 59.6* (q, $J_{C\text{-}F}$ = 3.1 Hz), 52.2[§], 50.4*, 48.8*, 46.2[§], 42.3*, 41.1[§], 25.2*, 22.0[§]; FTIR (NaCl, thin film): 3079, 3057, 3026, 2963, 2928, 2870, 2647, 2560, 1729, 1696, 1608, 1491, 1448, 1352, 1314, 1253, 1210, 1184, 1145, 1106, 1093, 1083, 1027, 992, 942, 921, 888, 854, 742 cm^{-1}; HRMS (APCI) calc'd for $C_{17}H_{18}F_3N_2O_3$ $[M+H]^+$ 355.1264, found 355.1275.

Preparation of dipeptide 272

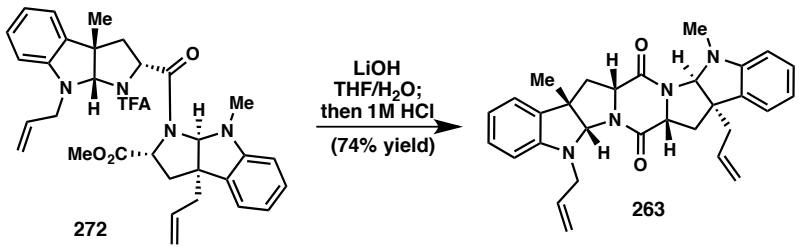


To a 250 mL flame-dried flask was added 3-allyl-amine *exo*-**267** (1.94 g, 7.11 mmol, 2.0 equiv), BOP-Cl (1.81 g, 7.11 mmol, 2.0 equiv) and dissolved with DCM (93

mL), followed by addition of 2,4,6-collidine (1.08 mL, 8.18 mmol, 2.3 equiv). Carboxylic acid *endo*-**271** (1.26 g, 3.56 mmol, 1.0 equiv) was dissolved in DCM (47 mL) and the resulting solution was added slowly into the reaction flask using a syringe pump over 12 hours. The resulting reaction solution was allowed to stir at room temperature for another 10 hours. The reaction was quenched with saturated $NaHCO_3$ solution (200 mL). The mixture was separated and the aqueous layer was extracted with EtOAc (3 x 150 mL). Combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered and concentrated down to give an orange oil. The crude material was left in the flask for 36 hours to allow the hydrolysis of anhydride formed under reaction conditions. Flash chromatography (0% to 60% EtOAc in hexanes) afforded dipeptide **272** as a pink foam (1.81 g, 2.97 mmol, 84% yield). $[\alpha]_D^{25}$ = +18° (*c* = 1.22, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6, compound exists as a 1.4 : 1 : 1 mixture of rotamers) complicated spectrum, please see the attached ^{1}H NMR spectrum; ^{13}C NMR (126 MHz, DMSO-d_6, compound exists as a mixture of rotamers) δ 173.0, 171.6, 171.5, 170.8, 170.2, 168.7, 157.7 (q, $J_{C\text{-}F}$ = 36.5 Hz), 157.0 (q, $J_{C\text{-}F}$ = 36.3 Hz), 156.6 (q, $J_{C\text{-}F}$ = 36.4 Hz), 151.0, 150.6, 149.6, 149.2, 148.3, 147.2, 135.1, 134.9, 134.6, 134.5, 134.4, 134.3, 134.0, 133.9, 133.0, 132.5, 129.1, 128.7, 128.6, 128.4, 128.4, 123.1, 122.6, 122.4, 122.0, 121.3, 120.5, 119.0, 118.7, 118.6, 118.1, 118.0, 117.9, 117.9, 117.1, 117.0, 116.5, 116.3 (q, $J_{C\text{-}F}$ = 288.6 Hz), 116.3 (q, $J_{C\text{-}F}$ = 288.6 Hz), 116.3 (app d, $J_{C\text{-}F}$= 287.3 Hz), 111.5, 108.0, 107.9, 107.5, 107.5, 106.9, 91.1, 89.5, 89.3, 89.1, 87.9, 87.7, 62.2, 61.1, 60.1, 60.0, 58.8, 58.1, 55.7, 53.2, 53.1, 52.6, 52.0, 50.2, 49.9, 49.5, 49.2, 46.0, 43.4, 42.8, 42.1, 41.6, 41.5, 40.8, 38.5, 37.7, 37.6, 36.1, 32.8, 26.5, 23.4, 19.4; FTIR (NaCl, thin film): 3075, 3052, 3016, 2954, 2869, 1744, 1696, 1681, 1638, 1607, 1491, 1448, 1437, 1406, 1357, 1298, 1282, 1210,

1184, 1145, 1106, 1022, 992, 922, 847, 742 cm^{-1}; HRMS (APCI) calc'd for $C_{33}H_{36}F_3N_4O_4$ $[M+H]^+$ 609.2683, found 609.2683.

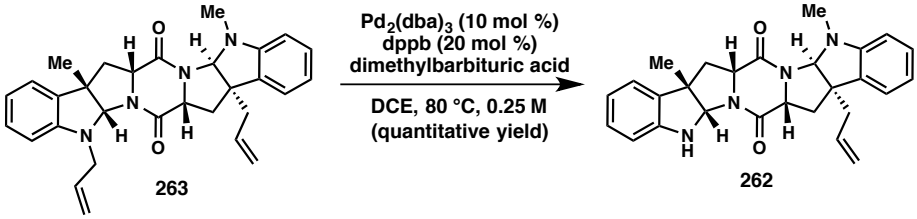
Preparation of bis(allyl)-diketopiperazine 263



To a 200 mL flask was added dipeptide **272** (1.81 g, 2.97 mmol, 1.0 equiv) and it was dissolved with THF (50 mL). LiOH (428 mg, 17.84 mmol, 6.0 equiv) was dissolved in distilled water (50 mL) and the resulting aqueous solution was added into the reaction flask. The reaction was allowed to stir at room temperature for 12 hours. 1M HCl (20 mL) was then added into the reaction, and the reaction was stirred for another 40 minutes. The mixture was extracted with EtOAc (3 x 50 mL). Combined organic layers were washed with saturated $NaHCO_3$ (150 mL) and brine (150 mL). It was dried over Na_2SO_4, filtered and concentrated down to give a yellow oil. Flash chromatography (0% to 50% EtOAc in hexanes) afforded diketopiperazine **263** as a white solid (1.05 g, 2.18 mmol, 74% yield). $[\alpha]_D^{25}$ = +90° (*c* = 1.13, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (app tdd, *J* = 7.8, 6.6, 1.3 Hz, 2H), 7.07 (app ddd, *J* = 7.0, 5.6, 1.2 Hz, 2H), 6.75 (td, *J* = 7.5, 1.0 Hz, 1H), 6.73 (td, *J* = 7.5, 0.9 Hz, 1H), 6.48 (d, *J* = 7.9 Hz, 1H), 6.40 (d, *J* = 7.7 Hz, 1H), 5.86 (dddd, *J* = 16.5, 10.4, 6.1, 4.3 Hz, 1H), 5.61 (dddd, *J* = 16.7, 10.1, 7.9, 6.4 Hz, 1H), 5.42 (s, 1H), 5.41 (s, 1H), 5.27 (dq, *J* = 17.1, 1.9 Hz, 1H), 5.13 (dq, *J* = 10.3, 1.6 Hz, 1H), 5.11 – 5.08 (m, 1H), 5.07 (q, *J* = 1.7 Hz, 1H), 4.40 (ddd, *J* = 9.9, 8.3, 1.5 Hz, 1H), 4.29 (ddt, *J* = 16.8, 4.2, 1.9 Hz, 1H), 4.16 (ddd, *J* = 10.5, 6.7, 1.4 Hz, 1H), 4.09 – 3.98 (m,

1H), 3.03 (s, 3H), 2.69 (dd, *J* = 12.9, 6.7 Hz, 1H), 2.52 (ddt, *J* = 13.8, 6.5, 1.4 Hz, 1H), 2.40 (ddt, *J* = 13.7, 8.0, 1.0 Hz, 1H), 2.36 – 2.29 (m, 3H), 1.45 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 166.3, 150.6, 148.4, 133.9, 133.8, 133.1, 131.3, 128.9, 128.5, 122.8, 121.3, 118.9, 118.3, 117.9, 116.4, 107.8, 106.1, 87.9, 84.6, 60.8, 59.7, 54.2, 51.0, 50.8, 42.7, 40.5, 40.4, 33.6, 22.1; FTIR (NaCl, thin film): 3336, 3075, 3053, 3008, 2978, 2956, 2927, 2891, 2873, 2836, 1676, 1608, 1489, 1465, 1447, 1407, 1335, 1304, 1278, 1219, 1193, 1160, 1123, 1093, 1050, 1026, 999, 978, 922, 846, 800, 746, 707 cm^{-1}; HRMS (MM) calc'd for $C_{30}H_{33}N_4O_2$ $[M+H]^+$ 481.2598, found 481.2612.

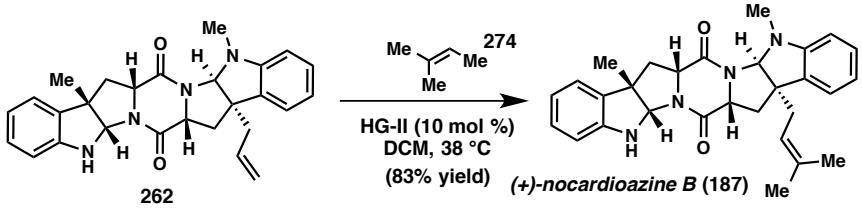
Preparation of diketopiperazine 262



To a 25 mL flame-dried screw-cap Schlenk flask was added bis(allyl)-diketopiperazine **263** (650 mg, 1.35 mmol, 1.0 equiv) and dimethylbibarturic acid (DMBA, 634 mg, 4.06 mmol, 3.0 equiv). The Schlenk flask was then evacuated and backfilled with argon three times. The solids were then dissolved in dry DCE (3.7 mL). In the meantime, in a 1-dram vial, mixed $Pd_2(dba)_3$ (62 mg, 0.068 mmol, 5 mol %) and 1,4-bis(diphenylphosphino)butane (dppb, 58 mg, 0.135 mmol, 10 mol %) in DCE (1.7 mL) and it was allowed to stir at room temperature for one hour; then the resulting solution was added into Schlenk flask. The reaction was heated to 80 °C. After 42 hours, the reaction was cooled to room temperature and quenched with saturated Na_2CO_3 aqueous solution (40 mL). The mixture was extracted with EtOAc (3 x 40 mL). Combined organic layers were washed with brine (100 mL). It was dried over Na_2SO_4,

filtered and concentrated down to give a brown oil. Flash chromatography (0% to 40% EtOAc in hexanes) afforded diketopiperazine **262**, which was contaminated with phosphine oxide formed from the dppb ligand. The mixture was then subjected to preparative reverse phase HPLC (40% to 90% CH_3CN in H_2O in 10 minutes, t_R=7.4-7.8 min), to give pure product **262** as a yellow foam (596 mg, 1.35 mmol, quantitative yield). $[\alpha]_D^{25}$ = +71° (*c* = 0.49, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (td, *J* = 7.7, 1.3 Hz, 1H), 7.12 – 7.04 (m, 3H), 6.78 (td, *J* = 7.4, 1.0 Hz, 1H), 6.72 (td, *J* = 7.4, 1.0 Hz, 1H), 6.59 (dt, *J* = 7.7, 0.8 Hz, 1H), 6.39 (d, *J* = 7.8 Hz, 1H), 5.56 (dddd, *J* = 16.8, 10.1, 8.0, 6.5 Hz, 1H), 5.38 (s, 1H), 5.34 (s, 1H), 5.27 (br s, 1H), 5.08 – 5.04 (m, 1H), 5.03 (dtd, *J* = 2.8, 1.8, 1.1 Hz, 1H), 4.44 (ddd, *J* = 10.1, 7.4, 1.8 Hz, 1H), 4.15 (ddd, *J* = 10.7, 6.5, 1.8 Hz, 1H), 3.01 (s, 3H), 2.65 (dd, *J* = 12.9, 6.5 Hz, 1H), 2.50 (ddt, *J* = 13.8, 6.6, 1.3 Hz, 1H), 2.46 – 2.34 (m, 3H), 2.28 (dd, *J* = 12.9, 10.7 Hz, 1H), 1.47 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 165.8, 150.7, 147.0, 133.3, 133.1, 131.2, 128.8, 128.4, 122.9, 122.4, 119.2, 118.9, 117.9, 109.3, 106.1, 84.7, 83.7, 60.2, 59.2, 54.1, 51.3, 42.8, 40.7, 40.2, 33.5, 23.4; FTIR (NaCl, thin film): 3346, 3074, 3052, 3007, 2976, 2955, 2925, 2896, 2871, 2834, 1666, 1608, 1487, 1468, 1414, 1341, 1300, 1252, 1198, 1161, 1122, 1091, 1059, 1048, 1018, 1000, 978, 921, 887, 824, 746 cm^{-1}; HRMS (MM) calc'd for $C_{27}H_{29}N_4O_2$ $[M+H]^+$ 441.2285, found 441.2294.

Preparation of (+)-nocardioazine B (187)



To a 25 mL flame-dried flask was added diketopiperazine **262** (8.4 mg, 0.019 mmol, 1.0 equiv), which was then co-evaporated with benzene (2 x 1 mL), and dried under high vacuum. Hoveyda-Grubbs II catalyst (1.2 mg, 0.002 mmol, 10 mol %) was added, followed by 2-methyl-2-butene (4.5 mL). The flask was equipped with a condenser and heated to 38 °C for 10 hours. The reaction was then quenched with ethyl vinyl ether (0.1 mL) and filtered through a silica gel plug, eluting with 50% EtOAc in hexanes. The filtrate was concentrated down to give a light brown oil. Flash chromatography (5% to 50% EtOAc in hexanes) afforded (+)-nocardioazine B (**187**) as a light grey solid (7.4 mg, 0.016 mmol, 83% yield). $[\alpha]_D^{25}$ = +65° (*c* = 0.36, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 – 7.09 (m, 2H), 7.09 (td, J = 7.7, 1.2 Hz, 1H), 7.04 (dd, *J* = 7.3, 1.2 Hz, 1H), 6.78 (td, *J* = 7.4, 1.0 Hz, 1H), 6.71 (td, *J* = 7.4, 1.0 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 (br s, 1H), 5.00 (tq, *J* = 4.9, 1.6 Hz, 1H), 4.44 (ddd, *J* = 9.8, 7.7, 1.8 Hz, 1H), 4.15 (ddd, *J* = 10.7, 6.5, 1.8 Hz, 1H), 3.01 (s, 3H), 2.64 (dd, *J* = 12.8, 6.5 Hz, 1H), 2.47 – 2.32 (m, 4H), 2.28 (dd, *J* = 12.8, 10.7 Hz, 1H), 1.65 (s, 3H), 1.50 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3, 165.9, 150.6, 147.1, 135.5, 133.4, 131.9, 128.7, 128.5, 122.8, 122.4, 119.3, 118.6, 118.0, 109.3, 106.2, 84.9, 83.7, 60.4, 59.3, 54.7, 51.3, 40.9, 39.6, 36.5, 33.6, 25.9, 23.4, 18.0; FTIR (NaCl, thin film): 3348, 3051, 2956, 2925, 2870, 2855, 1667, 1608, 1487, 1468, 1445, 1415, 1381, 1342, 1301, 1261, 1232, 1200, 1156, 1099, 1085, 1065, 1042, 1019, 1000, 976, 942, 890, 850, 822, 802, 781, 744 cm^{-1}; HRMS (MM) calc'd for $C_{29}H_{33}N_4O_2$ $[M+H]^+$ 469.2598, found 469.2604.

Table 3.2. *Comparison of ^{1}H NMR data for natural vs. synthetic (+)-nocardioazine B (**187**)*

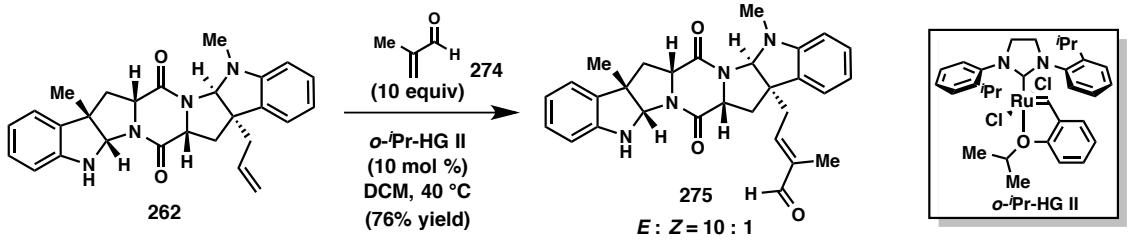
Raju et al. Report,[3] Natural (+)-nocardioazine B ^{1}H NMR, 600 MHz, $CDCl_3$	This Work, Synthetic (+)-nocardioazine B ^{1}H NMR, 500 MHz, $CDCl_3$
δ 7.11 (ddd, *J* = 7.7, 7.4, 1.1 Hz, 1H)	δ 7.16 – 7.09 (m, 2H)
7.08 (ddd, *J* = 7.7, 7.4, 1.0 Hz, 1H)	-
7.06 (dd, *J* = 7.4, 1.0 Hz, 1H)	7.09 (td, J = 7.7, 1.2 Hz, 1H)
7.02 (dd, *J* = 7.4, 1.1 Hz, 1H)	7.04 (dd, *J* = 7.3, 1.2 Hz, 1H)
6.75 (ddd, *J* = 7.4, 7.4, 0.9 Hz, 1H)	6.78 (td, *J* = 7.4, 1.0 Hz, 1H)
6.69 (ddd, *J* = 7.4, 7.4, 0.9 Hz, 1H)	6.71 (td, *J* = 7.4, 1.0 Hz, 1H)
6.57 (dd, *J* = 7.7, 0.9 Hz, 1H)	6.59 (d, *J* = 7.7 Hz, 1H)
6.38 (dd, *J* = 7.7, 0.9 Hz, 1H)	6.39 (d, *J* = 7.8 Hz, 1H)
5.33 (s, 1H)	5.35 (s, 1H)
5.29 (s, 1H)	5.31 (s, 1H)
5.18 (s, 1H)	5.21 (br s, 1H)
4.98 (m, 1H)	5.00 (tq, *J* = 4.9, 1.6 Hz, 1H)
4.42 (ddd, *J* = 9.8, 7.6, 1.8 Hz, 1H)	4.44 (ddd, *J* = 9.8, 7.7, 1.8 Hz, 1H)
4.13 (ddd, *J* = 10.7, 6.5, 1.7 Hz, 1H)	4.15 (ddd, *J* = 10.7, 6.5, 1.8 Hz, 1H)
2.99 (s, 3H)	3.01 (s, 3H)
2.62 (dd, *J* = 12.9, 6.5 Hz, 1H)	2.64 (dd, *J* = 12.8, 6.5 Hz, 1H)
2.37 (m, 2H)	2.47 – 2.32 (m, 4H)
2.35 (m, 2H)	–
2.25 (dd, *J* = 12.9, 10.7 Hz, 1H)	2.28 (dd, *J* = 12.8, 10.7 Hz, 1H)
1.63 (s, 3H)	1.65 (s, 3H)
1.48 (s, 3H)	1.50 (s, 3H)
1.45 (s, 3H)	1.47 (s, 3H)

Table 3.3. *Comparison of ^{13}C NMR data for natural vs. synthetic (+)-nocardioazine B (**187**)*

Raju et al. Report,[3] Natural (+)-nocardioazine B ^{13}C NMR, 150 MHz, $CDCl_3$	This Work, Synthetic (+)-nocardioazine B ^{13}C NMR, 126 MHz, $CDCl_3$	Chemical Shift Difference, Δδ
δ 167.1	δ 167.3	0.2
NR	165.9	–
150.6	150.6	0.0
146.9	147.1	0.2
135.5	135.5	0.0
133.3	133.4	0.1
132.0	131.9	0.1
128.8	128.7	0.1
128.5	128.5	0.0
122.8	122.8	0.0

122.4	122.4	0.0
119.2	119.3	0.1
118.6	118.6	0.0
117.9	118.0	0.1
109.4	109.3	0.1
106.2	106.2	0.0
85.0	84.9	0.1
83.7	83.7	0.0
60.4	60.4	0.0
59.3	59.3	0.0
54.6	54.7	0.1
51.2	51.3	0.1
41.0	40.9	0.1
39.8	39.6	0.2
36.7	36.5	0.2
33.7	33.6	0.1
26.0	25.9	0.1
23.4	23.4	0.0
17.9	18.0	0.1

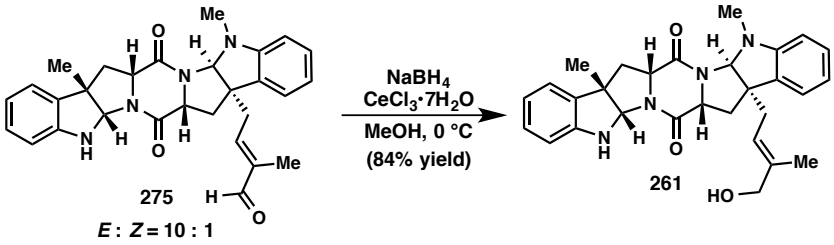
Preparation of enal 275



To a 50 mL flame-dried flask was added diketopiperazine **262** (431 mg, 0.98 mmol, 1.0 equiv) and DCM (9 mL), followed by methacrolein **274** (95%, 0.85 mL, 9.78 mmol, 10 equiv). *ortho*-^{i}Pr-Hoveyda-Grubbs II catalyst (61.3 mg, 0.10 mmol, 10 mol %) was added as a DCM solution (0.1 mL) at last. The flask was equipped with a condenser and heated to 40 °C for 18 hours. The reaction was then quenched with ethyl vinyl ether (0.5 mL) and filtered through a silica gel plug, eluting with EtOAc. The filtrate was concentrated down to give a brown oil. Flash chromatography (10% to 80% EtOAc in hexanes) afforded enal **275** as a light grey foam (*E* : *Z* = 10 : 1 mixture, 356 mg, 0.74

mmol, 76% yield). The mixture of isomers was further purified by flash chromatography (10% to 80% EtOAc in hexanes) to give (*E*)-**275** for characterization purposes. $[\alpha]_D^{25}$ = +77° (*c* = 0.96, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.17 (td, *J* = 7.5, 1.2 Hz, 1H), 7.13 – 7.02 (m, 3H), 6.82 – 6.71 (m, 2H), 6.60 (d, *J* = 7.5 Hz, 1H), 6.42 (d, *J* = 7.9 Hz, 1H), 6.25 (ddd, *J* = 8.7, 6.7, 1.5 Hz, 1H), 5.38 (s, 1H), 5.35 (s, 1H), 5.20 (br s, 1H), 4.47 (ddd, *J* = 9.7, 8.0, 1.8 Hz, 1H), 4.19 (ddd, *J* = 10.7, 6.5, 1.9 Hz, 1H), 3.01 (s, 3H), 2.83 – 2.71 (m, 3H), 2.41 (d, *J* = 2.4 Hz, 1H), 2.38 (s, 1H), 2.32 (dd, *J* = 12.8, 10.6 Hz, 1H), 1.66 – 1.65 (m, 3H), 1.47 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.6, 166.7, 165.8, 150.4, 147.6, 146.9, 141.6, 133.2, 130.0, 129.3, 128.4, 122.5, 122.3, 119.2, 118.2, 109.3, 106.3, 84.7, 83.6, 60.2, 59.1, 53.7, 51.2, 40.7, 40.3, 37.3, 33.1, 23.2, 9.4; FTIR (NaCl, thin film): 3351, 3051, 3013, 2953, 2929, 2872, 2716, 1670, 1607, 1486, 1468, 1446, 1412, 1339, 1302, 1262, 1235, 1200, 1157, 1126, 1099, 1083, 1040, 1019, 1000, 978, 932, 883, 809, 747 cm^{-1}; HRMS (MM) calc'd for $C_{29}H_{31}N_4O_3$ $[M+H]^+$ 483.2391, found 483.2410.

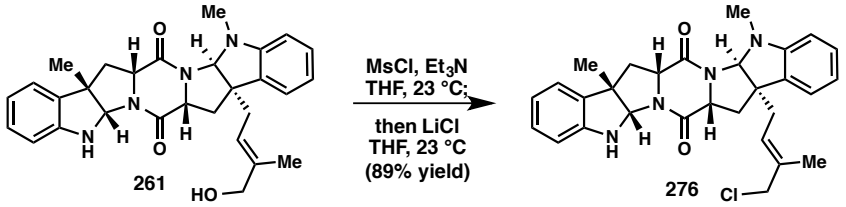
Preparation of allylic alcohol 261



To a 50 mL flask was added aldehyde **275** (*E* : *Z* = 10 : 1 mixture, 159 mg, 0.33 mmol, 1.0 equiv) and methanol (12 mL). Sonicator was used to facilitate **275** to dissolve in solution. Then, cerium chloride heptahydrate (307 mg, 0.82 mmol, 2.5 equiv) was dissolved in methanol (2 mL), while $NaBH_4$ (25 mg, 0.66 mmol, 2.0 equiv) was dissolved

in methanol (2 mL). The reaction was cooled to 0 °C. The previously prepared methanol solution of cerium chloride was added into the reaction flask, quickly followed by the addition of $NaBH_4$ methanol solution. After reacting at 0 °C for 40 minutes, the reaction was quenched with saturated ammonium chloride solution (30 mL), followed by EtOAc (30 mL). The mixture was separated and aqueous layer was extracted with EtOAc (3 x 30 mL). Combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated down to give a grey oil. Flash chromatography (20% to 90% EtOAc in hexanes) afforded allylic alcohol **261** as a white foam (133 mg, 0.27 mmol, 84% yield). $[\alpha]_D^{25}$ = +68° (*c* = 0.51, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (td, *J* = 7.7, 1.3 Hz, 1H), 7.11 – 7.06 (m, 2H), 7.05 (dd, *J* = 7.4, 1.2 Hz, 1H), 6.78 (td, *J* = 7.4, 1.0 Hz, 1H), 6.71 (td, *J* = 7.4, 1.0 Hz, 1H), 6.59 (dt, *J* = 7.6, 0.8 Hz, 1H), 6.40 (d, *J* = 7.8 Hz, 1H), 5.36 (s, 1H), 5.35 (br s, 2H), 5.29 (ddt, *J* = 9.5, 6.7, 1.5 Hz, 1H), 4.44 (ddd, *J* = 9.9, 8.4, 1.8 Hz, 1H), 4.16 (ddd, *J* = 10.1, 7.0, 1.8 Hz, 1H), 3.90 (s, 2H), 3.00 (s, 3H), 2.61 (dd, *J* = 13.0, 7.0 Hz, 1H), 2.51 – 2.39 (m, 2H), 2.39 – 2.30 (m, 3H), 2.15 (s, 1H), 1.56 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 165.8, 150.4, 147.0, 138.8, 133.3, 131.8, 128.8, 128.4, 122.6, 122.3, 119.3, 119.2, 118.0, 109.5, 106.2, 85.2, 83.6, 68.2, 60.3, 59.3, 54.2, 51.3, 40.8, 39.4, 35.9, 33.5, 23.2, 13.9; FTIR (NaCl, thin film): 3367, 3051, 3004, 2929, 2872, 1664, 1607, 1486, 1468, 1420, 1341, 1301, 1251, 1199, 1155, 1099, 1085, 1065, 1039, 1018, 1002, 978, 943, 892, 824, 746 cm^{-1}; HRMS (MM) calc'd for $C_{29}H_{33}N_4O_3$ $[M+H]^+$ 485.2547, found 485.2554.

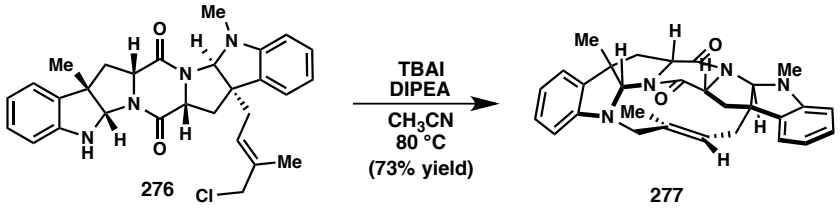
Preparation of allylic chloride 276



To a 10 mL flame-dried flask was added allylic alcohol **261** (60 mg, 0.12 mmol, 1.0 equiv) and THF (1.2 mL). The reaction was cooled to 0 °C. Mesyl chloride (MsCl, 11 μL, 0.14 mmol, 1.1 equiv) was added into the reaction solution, followed by Et_3N (35 μL, 0.25 mmol, 2.0 equiv). After 1.5 hours, the reaction was filtered through a plug of Kimwipes and washed with THF. The filtrate was concentrated down and co-evaporated with benzene. The crude material was re-dissolved in THF (1 mL), and LiOH (52.5 mg, 1.24 mmol, 10 equiv) in THF (0.2 mL) was transferred into the reaction flask. The resulting white slurry was allowed to stir at room temperature for 1.5 hours before it was quenched with saturated $NaHCO_3$ (10 mL). The mixture was extracted with EtOAc (3 x 10 mL). Combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated down to give a yellow liquid. Flash chromatography (10% to 50% EtOAc in hexanes) afforded allylic chloride **276** as a light yellow foam (55 mg, 0.11 mmol, 89% yield). $[\alpha]_D^{25}$ = +68° (*c* = 1.30, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (td, *J* = 7.6, 1.3 Hz, 1H), 7.12 – 7.06 (m, 2H), 7.05 (dd, *J* = 7.4, 1.2 Hz, 1H), 6.78 (td, *J* = 7.4, 1.0 Hz, 1H), 6.72 (td, *J* = 7.4, 1.0 Hz, 1H), 6.60 (dt, *J* = 7.7, 0.8 Hz, 1H), 6.40 (d, *J* = 7.8 Hz, 1H), 5.36 (t, *J* = 6.8 Hz, 1H), 5.35 (s, 1H), 5.31 (s, 1H), 5.23 (br s, 1H), 4.45 (ddd, *J* = 9.7, 8.1, 1.8 Hz, 1H), 4.16 (ddd, *J* = 10.6, 6.5, 1.8 Hz, 1H), 3.98 – 3.87 (m, 2H), 3.01 (s, 3H), 2.69 (dd, *J* = 12.8, 6.5 Hz, 1H), 2.45 (d, *J* = 7.5 Hz, 2H), 2.42 – 2.35 (m, 2H), 2.27 (dd, *J* = 12.8, 10.6 Hz, 1H), 1.63 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (126 MHz,

$CDCl_3$) δ 167.1, 165.9, 150.5, 147.0, 135.3, 133.3, 130.9, 129.0, 128.5, 124.7, 122.9, 122.4, 119.3, 118.1, 109.4, 106.2, 85.0, 83.7, 60.3, 59.2, 54.2, 51.8, 51.3, 40.9, 40.0, 36.6, 33.5, 23.4, 14.5; FTIR (NaCl, thin film): 3345, 3051, 3006, 2954, 2928, 2871, 1667, 1607, 1486, 1468, 1414, 1341, 1302, 1262, 1199, 1157, 1110, 1100, 1083, 1062, 1019, 1001, 977, 932, 746 cm^{-1}; HRMS (MM) calc'd for $C_{29}H_{32}ClN_4O_2$ $[M+H]^+$ 503.2208, found 503.2221.

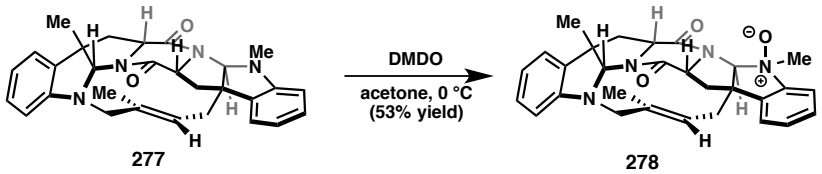
Preparation of macrocyclic alkene 277



To a 25 mL flame-dried Schlenk flask with a screw cap was added allylic chloride **276** (20 mg, 0.04 mmol, 1.0 equiv), tetra-*n*-butylammonium iodide (TBAI, 294 mg, 0.80 mmol, 20.0 equiv), and acetonitrile (4 mL). DIPEA (8.3 μL, 0.048 mmol, 1.2 equiv) was added at last from freshly prepared DIPEA stock solution. The Schlenk flask was sealed and heated to 80 °C for 24 hours. It was then cooled to room temperature and quenched with saturated $NaHCO_3$ aqueous solution (20 mL). The mixture was extracted with EtOAc (3 x 15 mL). Combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated down to give a yellow liquid. Flash chromatography (5% to 50% EtOAc in hexanes) afforded macrocyclic alkene **277** as a white solid (13.5 mg, 0.029 mmol, 73% yield). $[\alpha]_D^{25}$ = +45° (*c* = 0.47, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3CN) δ 7.16 – 7.09 (m, 3H), 7.07 (td, *J* = 7.7, 1.4 Hz, 1H), 6.72 (td, *J* = 7.5, 1.0 Hz, 1H), 6.65 (t, *J* = 7.4 Hz, 1H), 6.52 (d, *J* = 7.7 Hz, 1H), 6.46 (d, *J* = 7.9 Hz, 1H), 5.51 (s, 1H), 5.48 (s, 1H), 5.28 (br s, 1H), 4.57 (t, *J* = 8.8 Hz, 1H), 4.37 (d, *J* = 10.7

Hz, 1H), 4.02 (d, *J* = 16.1 Hz, 1H), 3.47 (d, *J* = 16.1 Hz, 1H), 2.89 (br s, 1H), 2.83 (s, 3H), 2.42 – 2.22 (m, 3H), 1.55 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) 149.3, 128.6, 128.6, 121.7, 121.4, 118.5, 110.0, 107.7, 91.9, 61.9, 59.2, 53.0, 34.0 (Presumably, at room temperature, the alkene in macrocyclic olefin **277** quickly underwent rotation, resulting in ^{1}H NMR signals broadening and not all carbon signals showing up); ^{1}H NMR (500 MHz, CD_3CN, 70 °C) δ 7.17 – 7.10 (m, 3H), 7.09 (td, *J* = 7.8, 1.4 Hz, 1H), 6.73 (td, *J* = 7.4, 1.0 Hz, 1H), 6.67 (td, *J* = 7.4, 1.0 Hz, 1H), 6.52 (d, *J* = 7.7 Hz, 1H), 6.46 (d, *J* = 7.9 Hz, 1H), 5.51 (s, 1H), 5.49 (s, 1H), 5.30 (t, *J* = 8.4 Hz, 1H), 4.58 (t, *J* = 8.7 Hz, 1H), 4.38 (dd, *J* = 11.2, 2.3 Hz, 1H), 4.03 (d, *J* = 16.3 Hz, 1H), 3.52 (d, *J* = 16.3 Hz, 1H), 2.92 (d, *J* = 13.9 Hz, 1H), 2.90 – 2.82 (m, 1H), 2.86 (s, 3H), 2.41 (dd, *J* = 13.4, 8.8 Hz, 1H), 2.34 (d, *J* = 8.8 Hz, 1H), 2.30 (dd, *J* = 11.0, 7.0 Hz, 1H), 2.19 (dd, *J* = 13.7, 11.3 Hz, 1H), 1.60 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (126 MHz, CD_3CN, 70 °C) δ 171.8, 170.5, 151.0, 149.5, 138.3, 136.1, 135.5, 129.7, 123.0, 122.9, 122.8, 122.7, 119.5, 118.7, 108.6, 108.6, 106.6, 106.5, 92.9, 92.9, 90.3, 63.2, 60.3, 60.3, 56.4, 54.3, 52.3, 41.9, 39.5, 34.7, 34.5, 34.4, 21.7, 15.2; FTIR (NaCl, thin film): 3051, 3008, 2954, 2923, 2870, 2856, 1670, 1609, 1485, 1465, 1450, 1429, 1391, 1348, 1304, 1259, 1216, 1186, 1156, 1142, 1122, 1096, 1065, 1023, 1001, 978, 921, 881, 789, 742 cm^{-1}; HRMS (MM) calc'd for $C_{29}H_{31}N_4O_2$ $[M+H]^+$ 467.2442, found 467.2450.

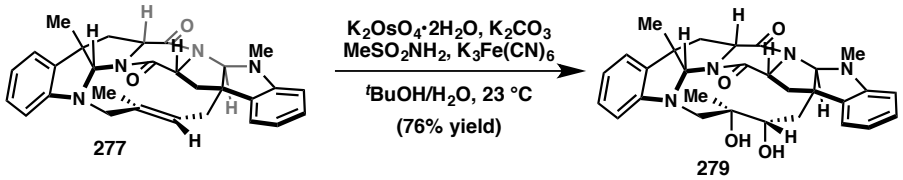
Preparation of *N*-oxide 278



277 278

To a 0.5-dram vial was transferred macrocyclic olefin **277** (2.2 mg, 0.0047 mmol, 1.0 equiv), which was dissolved in acetone (0.35 mL). The reaction was cooled to 0 °C. Freshly prepared DMDO acetone solution (0.050 M, 104 μL, 0.0052 mmol, 1.1 equiv) was added. The reaction was allowed to stir for 15 minutes before being concentrated down to give a light yellow solid. Preparative thin layer chromatography (10% MeOH in DCM) afforded *N*-oxide **278** as a white solid (1.2 mg, 0.0025 mmol, 53% yield); starting material **277** was also isolated (0.8 mg). $[\alpha]_D^{25}$ = +78° (*c* = 0.12, CH_2Cl_2); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.54 – 7.49 (m, 1H), 7.49 – 7.42 (m, 2H), 7.42 – 7.34 (m, 1H), 7.09 (app ddd, *J* = 7.3, 4.4, 3.0 Hz, 2H), 6.69 (t, *J* = 7.4 Hz, 1H), 6.40 (d, *J* = 8.1 Hz, 1H), 5.75 (s, 1H), 5.56 (s, 1H), 4.99 – 4.82 (m, 1H), 4.68 (t, *J* = 8.8 Hz, 1H), 4.00 (d, *J* = 16.5 Hz, 1H), 3.62 (s, 3H), 3.58 (d, *J* = 16.5 Hz, 1H), 2.89 (br s, 1H), 2.72 (t, *J* = 11.9 Hz, 1H), 2.59 – 2.49 (m, 1H), 2.37 (t, *J* = 11.4 Hz, 1H), 2.28 (br s, 1H), 1.86 (br s, 4H), 1.52 (s, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 70.2, 138.0, 130.5, 130.0, 129.0, 124.4, 122.1, 117.6, 99.1, 66.5, 59.6, 56.4, 52.5, 51.6, 41.1 (Presumably, at room temperature, the alkene in macrocyclic olefin **278** quickly underwent rotation, resulting in ^{1}H NMR signals broadening and not all carbon signals showing up); FTIR (NaCl, thin film): 3047, 2955, 2907, 1681, 1607, 1482, 1449, 1432, 1388, 1305, 1270, 1225, 1201, 1156, 1142, 1119, 1094, 1064, 1050, 1022, 1004, 962, 932, 917, 884, 832, 816, 805, 780, 741 cm^{-1}; HRMS (MM) calc'd for $C_{29}H_{31}N_4O_3$ $[M+H]^+$ 483.2391, found 483.2388.

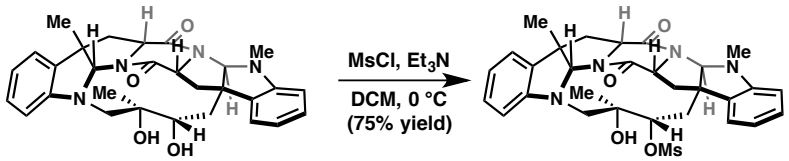
Preparation of diol 279



To a 0.5-dram vial was added $K_3Fe(CN)_6$ (10.4 mg, 0.032 mmol, 3.0 equiv), K_2CO_3 (4.5 mg, 0.033 mmol, 3.1 equiv) and $K_2OsO_4 \bullet 2H_2O$ (1.2 mg, 0.003 mmol, 30 mol %), followed by addition of distilled water (240 μL) and methanesulfonamide (3.0 mg, 0.032mmol, 3.0 equiv). 1,4-Diazabicyclooctane (DABCO, 0.6 mg, 0.005 mmol, 0.5 equiv) was added as a *t*-butanol solution (10 μL). At last, macrocyclic alkene **277** (4.8 mg, 0.010 mmol, 1.0 equiv) was added as *tert*-butanol solution (240 μL; additional heat was required to increase the solubility of **277** in *tert*-butanol; there is a small time window where **277** is completely soluble in *tert*-butanol after it cools down to room temperature, which marks the time to add it to the reaction flask). The reaction turned into a brown homogeneous solution, which was stirred for 12 hours. It was then quenched with solid Na_2SO_3, followed by addition of 2N KOH (0.5 mL). It was stirred for another two hours before it was diluted with EtOAc (2 mL). The mixture was separated and the aqueous layer was extracted with EtOAc (3 x 2 mL). Combined organic layers were washed with brine (3 mL), dried over Na_2SO_4, filtered, and concentrated down to give a white solid. Flash chromatography (5% to 50% EtOAc in hexanes) afforded diol **279** as a white solid (3.9 mg, 0.008 mmol, 76% yield). $[\alpha]_D^{25}$ = +36° (*c* = 0.33, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (tt, *J* = 7.7, 1.5 Hz, 2H), 7.08 (ddd, *J* = 7.4, 2.4, 1.2 Hz, 2H), 6.89 (d, *J* = 7.9 Hz, 1H), 6.82 (td, *J* = 7.4, 0.9 Hz, 1H), 6.79 (td, *J* = 7.5, 1.0 Hz, 1H), 6.52 (d, *J* = 7.7 Hz, 1H), 5.77 (s, 1H), 5.65 (s, 1H), 4.60 (dd, *J* = 10.0, 8.1 Hz, 1H), 4.47 (d, *J* = 8.7 Hz, 1H), 3.52 (d, *J* = 15.4 Hz, 1H), 3.31 (d, *J* = 15.4 Hz, 1H), 3.25 (d, *J* = 10.5 Hz, 1H), 2.96 (d, *J* = 12.6 Hz, 1H), 2.92 (s, 3H), 2.75 (dd, *J* = 13.4, 10.1 Hz, 1H), 2.49 (dd, *J* = 12.7, 8.8 Hz, 1H), 2.48 (s, 1H), 2.27 (dd, *J* = 13.4, 8.1 Hz, 1H), 2.17 (dd, *J* = 15.5, 10.5 Hz, 1H), 1.99 (d, *J* = 15.6 Hz, 1H), 1.86 (s, 1H), 1.49 (s, 3H), 1.09 (s, 3H); ^{13}C NMR

(126 MHz, $CDCl_3$) δ 171.9, 170.8, 149.3, 148.8, 134.5, 133.3, 128.6, 128.3, 121.5, 119.6, 119.0, 108.7, 108.2, 91.4, 89.4, 76.7, 69.5, 62.3, 60.2, 56.3, 50.6, 50.4, 42.7, 38.6, 35.5, 34.1, 20.7, 18.3; FTIR (NaCl, thin film): 3518, 3447, 3049, 3010, 2953, 2937, 2894, 2794, 1670, 1610, 1481, 1448, 1425, 1391, 1349, 1312, 1299, 1274, 1209, 1194, 1167, 1123, 1091, 1064, 1039, 1021, 1001, 975, 940, 909, 893, 862, 832, 804, 789, 780, 752, 746, 718 cm^{-1}; HRMS (MM) calc'd for $C_{29}H_{33}N_4O_4$ $[M+H]^+$ 501.2496, found 501.2508.

Preparation of mono-mesylate A-5

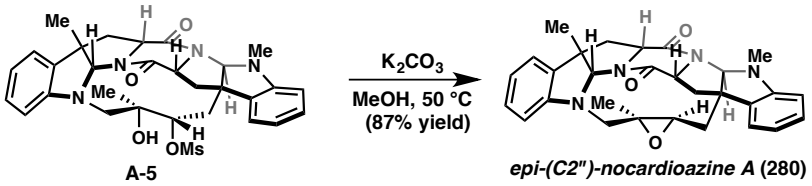


279 **A-5**

To a flame-dried 0.5-dram vial was added diol **279** (6.9 mg, 0.014 mmol, 1.0 equiv) and THF (0.2 mL). The reaction flask was cooled to 0 °C. Mesyl chloride (MsCl, 5.5 μL, 0.069 mmol, 5.0 equiv) was added into the reaction solution, followed by Et_3N (11.5 μL, 0.083 mmol, 6.0 equiv). After 40 minutes, the reaction was quenched with saturated $NaHCO_3$ (4 mL). The mixture was extracted with EtOAc (3 x 4 mL). Combined organic layers were washed with brine (8 mL), dried over Na_2SO_4, filtered, and concentrated down to give a yellow liquid. Preparative TLC chromatography (60% EtOAc in hexanes) afforded mono-mesylate **A-5** as a white solid (5.8 mg, 0.10 mmol, 75% yield). $[\alpha]_D^{25}$ = +67° (*c* = 0.45, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (td, *J* = 7.7, 1.2 Hz, 1H), 7.14 (td, *J* = 7.9, 1.3 Hz, 1H), 7.07 (ddd, *J* = 8.8, 7.4, 1.3 Hz, 2H), 7.00 (d, *J* = 7.9 Hz, 1H), 6.85 (td, *J* = 7.4, 1.0 Hz, 1H), 6.79 (td, *J* = 7.5, 1.0 Hz, 1H), 6.53 (d, *J* = 7.8 Hz, 1H), 5.83 (s, 1H), 5.62 (s, 1H), 4.61 (dd, *J* = 10.2, 8.0 Hz, 1H), 4.58 (d, *J* = 10.7 Hz, 1H), 4.46 (d, *J* = 8.5 Hz, 1H), 3.52 (d, *J* = 15.5 Hz, 1H), 3.33 (d, *J* = 15.5 Hz,

1H), 2.96 (s, 3H), 2.94 (d, *J* = 12.7 Hz, 1H), 2.83 (dd, *J* = 13.4, 10.2 Hz, 1H), 2.74 (s, 3H), 2.53 (dd, *J* = 12.7, 8.6 Hz, 1H), 2.49 (dd, *J* = 16.8, 10.8 Hz, 1H), 2.40 (s, 1H), 2.30 (dd, *J* = 13.4, 7.9 Hz, 1H), 2.13 (d, *J* = 16.8 Hz, 1H), 1.48 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 171.7, 149.5, 149.2, 133.3, 132.7, 128.7, 128.6, 121.5, 121.3, 120.0, 118.8, 109.8, 108.4, 90.7, 89.7, 83.5, 76.6, 62.1, 60.5, 57.9, 50.5, 50.3, 42.8, 38.9, 38.6, 34.1, 33.1, 20.6, 18.8; FTIR (NaCl, thin film): 3541, 3390, 3024, 2954, 2925, 2855, 2798, 1694, 1674, 1610, 1482, 1447, 1427, 1379, 1347, 1337, 1301, 1273, 1198, 1171, 1124, 1091, 1062, 1028, 1000, 974, 957, 944, 933, 916, 895, 851, 835, 806, 781, 752 cm^{-1}; HRMS (MM) calc'd for $C_{30}H_{35}N_4O_6S$ $[M+H]^+$ 579.2272, found 579.2278.

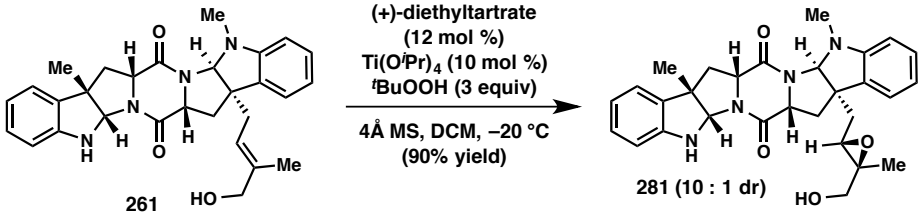
Preparation of *epi*-(C2")-nocardioazine A (280)



To a flame-dried 1-dram vial was added mono-mesylate **A-5** (4.0 mg, 0.007 mmol, 1.0 equiv) and K_2CO_3 (12.6 mg, 0.091 mmol, 13.0 equiv). Methanol (0.9 mL) was added at last. The vial was sealed using a Teflon cap and heated to 50 °C for 90 minutes. The reaction was cooled to room temperature and quenched with saturated $NaHCO_3$ (4 mL). The mixture was extracted with EtOAc (3 x 4 mL). Combined organic layers were washed with brine (8 mL), dried over Na_2SO_4, filtered, and concentrated down to give a white liquid. Flash chromatography (10% to 50% EtOAc in hexanes) afforded *epi*-(C2")-nocardioazine A (**280**) as a white solid, which was contaminated with an unknown side product as a 10 : 1 mixture detected by ^{1}H NMR, (corrected yield: 2.9 mg, 0.0060 mmol, 87% yield). $[\alpha]_D^{25}$ = +36° (*c* = 0.33, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (td, *J* =

7.7, 1.3 Hz, 1H), 7.10 (td, *J* = 7.7, 1.2 Hz, 1H), 7.11 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.06 (dd, *J* = 7.3, 1.3 Hz, 1H), 6.79 (td, *J* = 7.5, 1.0 Hz, 1H), 6.66 (td, *J* = 7.4, 0.9 Hz, 1H), 6.53 (d, *J* = 7.8 Hz, 1H), 6.49 (d, *J* = 7.8 Hz, 1H), 5.75 (s, 1H), 5.73 (s, 1H), 4.51 (dd, *J* = 10.6, 7.6 Hz, 1H), 4.40 (d, *J* = 8.6 Hz, 1H), 3.59 (d, *J* = 15.6 Hz, 1H), 3.37 (d, *J* = 15.7 Hz, 1H), 2.95 (s, 3H), 2.91 (d, *J* = 12.6 Hz, 1H), 2.83 (dd, *J* = 11.6, 3.7 Hz, 1H), 2.77 (dd, *J* = 13.2, 10.7 Hz, 1H), 2.66 (dd, *J* = 16.0, 3.7 Hz, 1H), 2.45 (dd, *J* = 12.7, 8.7 Hz, 1H), 2.25 (dd, *J* = 13.1, 7.6 Hz, 1H), 2.00 (dd, *J* = 16.0, 11.6 Hz, 1H), 1.45 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 171.4, 149.7, 147.1, 132.9, 132.1, 128.8, 128.3, 121.7, 121.5, 118.3, 116.9, 108.0, 105.7, 92.9, 86.8, 64.2, 62.2, 61.7, 60.0, 52.0, 50.7, 45.0, 42.1, 39.5, 33.9, 30.3, 26.1, 19.5; FTIR (NaCl, thin film): 3051, 3009, 2956, 2927, 2893, 2869, 2821, 2791, 1692, 1671, 1610, 1484, 1467, 1452, 1440, 1425, 1382, 1353, 1301, 1282, 1266, 1235, 1214, 1197, 1172, 1158, 1144, 1123, 1115, 1093, 1073, 1055, 1048, 1035, 1020, 991, 973, 958, 945, 924, 892, 881, 859, 847, 830, 801, 792, 780, 751, 742 cm^{-1}; HRMS (MM) calc'd for $C_{29}H_{31}N_4O_3$ $[M+H]^+$ 483.2391, found 483.2387.

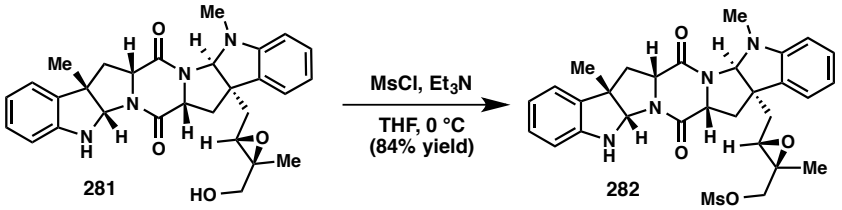
Preparation of epoxide 281



To a flame-dried 10 mL flask was added $Ti(O^iPr)_4$ (3.7 μL, 0.012 mmol, 10 mol %), activated 4Å molecular sieves and DCM (2 mL). The reaction flask was cooled to –20 °C (crushed ice mixed with NaCl at about 3 : 1 ratio). (+)-Diethyl-tartrate (2.5 μL, 0.015 mmol, 12 mol %) was added. After stirring for 5 minutes, allylic alcohol **261** (60 mg, 0.124 mmol, 1.0 equiv) was added as a DCM solution (0.5 mL). After 30 minutes,

^{t}BuOOH (5.0-6.0 M decane solution, 68 μL, 0.371 mmol, 3.0 equiv) was added. In 105 minutes, the flask was warmed to 0 °C using an ice water bath. The reaction was quenched with freshly prepared and ice-cold $FeSO_4$/citric acid solution (0.66 g $FeSO_4$, 0.22 g citric acid monohydrate, 2 mL distilled water). The mixture was extracted with Et_2O (5 x 5 mL). Combined organic layers were cooled to 0 °C and then treated with precooled 30% NaOH (w/v) in saturated NaCl solution (prepared using 10 g NaOH, 1.7 g NaCl, 30 ml distilled water). The mixture was stirred vigorously for 1 hour. Then two layers were separated and the aqueous layer was extracted with Et_2O (2 x 30 mL). Combined organic layers were dried over $MgSO_4$, filtered, and concentrated down to give a colorless oil. Flash chromatography (20% to 95% EtOAc in hexanes) afforded epoxy alcohol **281** (10 : 1 mixture of epoxide diastereomers by ^{1}H NMR), as a white foam (56.5 mg, 0.113 mmol, 90% yield). $[\alpha]_D^{25}$ = +74° (*c* = 0.26, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (td, *J* = 7.6, 1.2 Hz, 1H), 7.07 (app dd, *J* = 8.0, 6.9 Hz, 3H), 6.79 – 6.74 (m, 1H), 6.72 (td, *J* = 7.5, 1.0 Hz, 1H), 6.57 (dt, *J* = 7.5, 1.0 Hz, 1H), 6.40 (d, *J* = 7.8 Hz, 1H), 5.59 (s, 1H), 5.34 (s, 1H), 5.28 (s, 1H), 4.44 (ddd, *J* = 9.9, 8.1, 1.9 Hz, 1H), 4.14 (ddd, *J* = 10.8, 6.3, 1.9 Hz, 1H), 3.41 (d, *J* = 12.2 Hz, 1H), 3.30 (d, *J* = 12.3 Hz, 1H), 3.04 (s, 3H), 2.83 – 2.71 (m, 2H), 2.42 – 2.34 (m, 2H), 2.31 (dd, *J* = 12.8, 10.9 Hz, 1H), 2.11 (dd, *J* = 14.4, 4.9 Hz, 1H), 1.87 (dd, *J* = 14.4, 7.0 Hz, 1H), 1.46 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 165.7, 150.8, 147.0, 133.3, 130.2, 129.3, 128.4, 122.8, 122.3, 119.2, 118.1, 109.4, 106.2, 84.5, 83.7, 65.3, 60.2, 59.8, 59.2, 56.6, 53.1, 51.2, 41.0, 40.9, 37.1, 33.5, 23.3, 14.3; FTIR (NaCl, thin film): 3354, 3052, 3006, 2956, 2928, 2870, 1668, 1608, 1486, 1471, 1418, 1339, 1302, 1253, 1197, 1161, 1092, 1036, 1001, 978, 894, 748 cm^{-1}; HRMS (MM) calc'd for $C_{29}H_{33}N_4O_4$ $[M+H]^+$ 501.2496, found 501.2500.

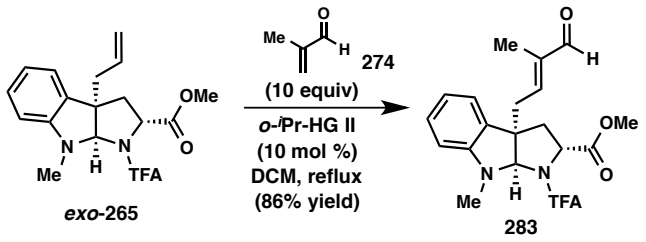
Preparation of mesylate 282



To a half-a-dram vial was added alcohol **281** (7 mg, 0.014 mmol, 1.0 equiv), which was co-evaporated with benzene (0.4 mL) and dried in vacuo. Under N_2, alcohol **281** was dissolved in THF (0.1 mL) and cooled to 0 °C, when MsCl (1.2 μL, 0.015 mmol, 1.1 equiv) and Et_3N (3.9 μL, 0.028 mmol, 2.0 equiv) were added in sequence as a freshly prepared THF stock solution. The reaction mixture was allowed to stir at 0 °C for 40 minutes before filtering through a Kimwipe plug and concentrating down to give a colorless oil. Flash chromatography (5% to 70% EtOAc in hexanes) afforded epoxy mesylate **282**, as a colorless oil (6.8 mg, 0.012 mmol, 84% yield). $[\alpha]_D^{25}$ = +74° (*c* = 0.735, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (td, *J* = 7.7, 1.3 Hz, 1H), 7.12 – 7.04 (m, 3H), 6.78 (td, *J* = 7.6, 1.1 Hz, 1H), 6.75 (td, *J* = 7.4, 0.9 Hz, 1H), 6.59 (d, *J* = 7.5 Hz, 1H), 6.41 (d, *J* = 7.8 Hz, 1H), 5.59 (s, 1H), 5.35 (s, 1H), 4.46 (td, *J* = 8.9, 1.8 Hz, 1H), 4.16 (ddd, *J* = 10.2, 5.9, 1.5 Hz, 1H), 4.02 (d, *J* = 11.5 Hz, 1H), 3.84 (d, *J* = 11.5 Hz, 1H), 3.04 (s, 3H), 2.95 (s, 3H), 2.78 (dd, *J* = 12.7, 6.2 Hz, 1H), 2.65 (dd, *J* = 7.2, 4.7 Hz, 1H), 2.38 (d, *J* = 8.9 Hz, 2H), 2.28 (dd, *J* = 12.8, 11.0 Hz, 1H), 2.16 (dd, *J* = 14.4, 4.8 Hz, 1H), 1.86 (dd, *J* = 14.4, 7.2 Hz, 1H), 1.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 165.8, 150.9, 147.0, 133.3, 129.7, 129.5, 128.5, 122.8, 122.4, 119.3, 118.2, 109.3, 106.3, 84.2, 83.7, 73.3, 59.8, 59.2, 57.6, 57.5, 53.0, 51.3, 41.3, 41.0, 37.7, 36.9, 33.4, 23.3, 14.1; FTIR (NaCl, thin film): 3364, 3011, 2958, 2932, 1668, 1608, 1486, 1471, 1445, 1418,

1354, 1300, 1253, 1197, 1175, 1092, 1018, 978, 961, 896, 817, 750, 667, 644 cm^{-1}; HRMS (MM) calc'd for $C_{30}H_{35}N_4O_6S$ $[M+H]^+$ 579.2272, found 579.2287.

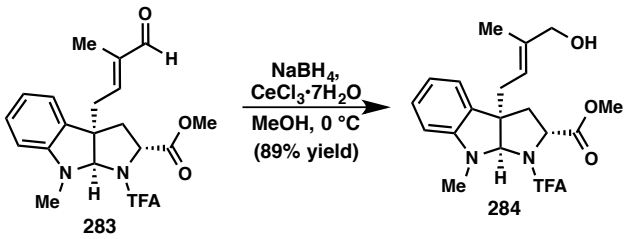
Preparation of aldehyde 283



To a 50 mL flame-dried flask was added 3-allyl pyrroloindoline **265** (1.0 g, 2.7 mmol, 1.0 equiv) and DCM (20 mL), followed by methacrolein (95%, 2.36 mL, 27.1 mmol, 10 equiv). *ortho*-^{i}Pr-Hoveyda-Grubbs II catalyst (170 mg, 0.27 mmol, 10 mol %) was added as a DCM solution (4 mL) at last. The flask was equipped with a condenser and heated to 40 °C for 3 days. The reaction was then quenched with ethyl vinyl ether (1.5 mL) and filtered through a silica gel plug, eluting with EtOAc. The filtrate was concentrated down to give a brown oil. Flash chromatography (5% to 35% EtOAc in hexanes) afforded aldehyde **283** as a light brown thick oil (951 mg, 2.32 mmol, 86% yield). $[\alpha]_D^{25}$ = +106° (*c* = 1.27, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 2.0:1 mixture of rotamers; the major rotamer is denoted by *, minor rotamer denoted by §) δ 9.26 (s, 1H§), 9.20 (s, 1H*), 7.14 (t, *J* = 7.6 Hz, 1H*, 1H§), 7.03 (d, *J* = 7.4 Hz, 1H*, 1H§), 6.79 (s, 1H§), 6.73 (t, *J* = 7.4 Hz, 1H*), 6.60 – 6.51 (m, 1H§), 6.48 (d, *J* = 8.0 Hz, 1H*), 6.33 – 6.17 (m, 1H§), 6.13 (t, *J* = 7.0 Hz, 1H*), 5.55 (s, 1H*), 5.38 (s, 1H§), 4.66 (d, *J* = 7.5 Hz, 1H*), 4.38 (s, 1H§), 3.77 (s, 3H*), 3.71 (s, 3H§), 3.01 (s, 3H*), 2.83 (s, 3H§), 2.74 (d, *J* = 7.7 Hz, 2H*, 2H§), 2.69 (d, *J* = 10.2 Hz, 1H*), 2.57 (s, 1H§), 2.44 (d, *J* = 13.0 Hz, 1H*), 2.18 (s, 1H§), 1.66 (s, 3H*, 3H§); ^{13}C NMR (126 MHz, $CDCl_3$) δ

194.3*§, 172.4*, 170.2§, 158.6* (q, *J* = 37.3 Hz), 157.1§ (q, *J* = 39.4 Hz), 149.7*, 149.5§, 147.4*, 147.2§, 141.5*§, 130.9*, 130.5§, 129.3§, 129.1*, 121.7*§, 119.9§, 118.9*, 115.7* (q, *J* = 288.7 Hz), 109.5§, 108.1*, 90.1*, 88.9§, 60.5§, 59.4*, 56.8§, 53.1*, 52.9*, 52.3§, 42.4*, 39.1§, 36.2*, 35.5*, 34.6§, 34.2§, 9.2*§; FTIR (NaCl, thin film): 3421, 3052, 3026, 2955, 2827, 2717, 1751, 1688, 1609, 1490, 1437, 1358, 1302, 1204, 1155, 1061, 1021, 985, 932, 873, 850, 794, 754 cm^{-1}; HRMS (MM) calc'd for $C_{20}H_{22}F_3N_2O_4$ $[M+H]^+$ 411.1526, found 411.1531.

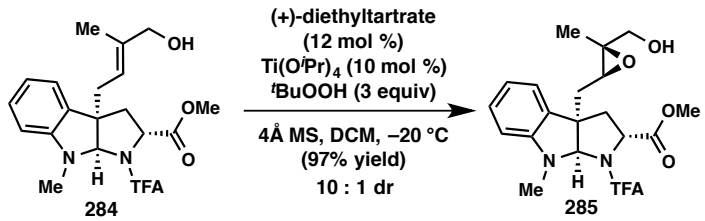
Preparation of allylic alcohol 284



To a 100 mL flask was added aldehyde **283** (636 mg, 1.55 mmol, 1.0 equiv) and methanol (31 mL). Then, cerium chloride heptahydrate (693 mg, 1.86 mmol, 1.2 equiv) was dissolved in methanol (2.5 mL), while $NaBH_4$ (59 mg, 1.55 mmol, 1.0 equiv) was mixed with methanol (1.2 mL). The reaction was cooled to 0 °C. The pre-generated methanol solution of cerium chloride was added into the reaction flask, quickly followed by the slow addition of $NaBH_4$ methanol solution. After reacting at 0 °C for 15 minutes, the reaction was quenched with saturated ammonium chloride solution (70 mL), followed by EtOAc (50 mL). The mixture was separated and aqueous layer was extracted with EtOAc (3 x 50 mL). Combined organic layers were washed with brine (120 mL), dried over Na_2SO_4, filtered, and concentrated down to give a grey oil. Flash chromatography (5% to 60% EtOAc in hexanes) afforded allylic alcohol **284** as a light brown thick oil

(567 mg, 1.37 mmol, 89% yield). $[\alpha]_D^{25}$ = +88° (*c* = 1.16, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 1.6:1 mixture of rotamers; the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.11 (t, *J* = 7.6 Hz, 1H*, 1H§), 7.01 (d, *J* = 7.5 Hz, 1H*, 1H§), 6.80 – 6.76 (m, 1H§), 6.71 (t, *J* = 7.4 Hz, 1H*), 6.53 (d, *J* = 7.9 Hz, 1H§), 6.46 (d, *J* = 7.9 Hz, 1H*), 5.52 (s, 1H*), 5.37 (s, 1H§), 5.25 (t, *J* = 7.2 Hz, 1H§), 5.13 (t, *J* = 7.4 Hz, 1H*), 4.63 (d, *J* = 7.5 Hz, 1H*), 4.30 (t, *J* = 8.0 Hz, 1H§), 3.85 (s, 2H§), 3.83 (s, 2H*), 3.77 (s, 3H*), 3.69 (s, 3H§), 3.02 (s, 3H*), 2.85 (s, 3H§), 2.61 (dd, *J* = 13.6, 9.3 Hz, 2H*, 2H§), 2.53 – 2.44 (m, 1H*), 2.41 (d, *J* = 3.9 Hz, 2H§), 2.39 (d, *J* = 6.8 Hz, 2H*), 2.17 – 2.09 (m, 1H§), 1.55 (s, 3H*, 3H§); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5*, 170.6§, 158.7* (q, $J_{C\text{-}F}$ = 37.0 Hz), 157.4§ (q, $J_{C\text{-}F}$ = 38.1 Hz), 149.9§, 149.8*, 138.6*§, 132.3*, 132.1§, 128.8§, 128.6*, 121.9§, 121.8*, 119.9§, 119.1*, 118.6*§, 115.8* (q, $J_{C\text{-}F}$ = 288.5 Hz), 115.7§ (app d, $J_{C\text{-}F}$ = 286.6 Hz), 109.8§, 108.0*, 90.2*, 89.0§, 67.6*§, 60.5§, 59.4*, 57.6§, 53.5*, 52.8*, 52.3§, 41.9*, 38.4§, 36.4*, 35.3§, 34.3*, 34.1§, 13.6*§; FTIR (NaCl, thin film): 3421, 3052, 2954, 2921, 2875, 1749, 1690, 1608, 1490, 1437, 1356, 1301, 1203, 1155, 1062, 1021, 994, 931, 852, 794, 746, 727 cm^{-1}; HRMS (MM) calc'd for $C_{20}H_{24}F_3N_2O_4$ $[M+H]^+$ 413.1683, found 413.1690.

Preparation of epoxy alcohol 285

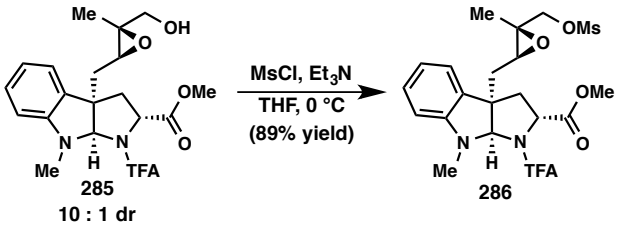


To a flame-dried 50 mL flask was added $Ti(O^iPr)_4$ (31 μL, 0.105 mmol, 10 mol %), activated 4Å molecular sieves, and DCM (18 mL). The reaction flask was cooled to –

20 °C (crushed ice mixed with NaCl at about 3 : 1 ratio). (+)-Diethyl-tartrate (21.5 μL, 0.126 mmol, 12 mol %) was added. After stirring for 5 minutes, allylic alcohol **284** (432 mg, 1.05 mmol, 1.0 equiv) was added as a DCM solution (2 mL). After 30 minutes, ^{t}BuOOH (5.0-6.0 M decane solution, 0.57 mL, 3.14 mmol, 3.0 equiv) was added. In 90 minutes, the flask was warmed to 0 °C using an ice water bath. The reaction was quenched with freshly prepared $FeSO_4$/citric acid solution (4 g $FeSO_4$, 0.66 g citric acid monohydrate, 12 mL distilled water). The mixture was extracted with Et_2O (4 x 20 mL). Combined organic layers were cooled to 0 °C and then treated with precooled 30% NaOH (w/v) in saturated NaCl solution (prepared using 30 g NaOH, 5 g NaCl, 90 ml distilled water). The mixture was stirred vigorously for 1 hour. Then two layers were separated and the aqueous layer was extracted with Et_2O (2 x 80 mL). Combined organic layers were dried over $MgSO_4$, filtered, and concentrated down to give a colorless oil. Flash chromatography (10% to 70% EtOAc in hexanes) afforded epoxy alcohol **285** (10 : 1 mixture of epoxide diastereomers by ^{1}H NMR), as a white foam (434 mg, 1.01 mmol, 97% yield). $[\alpha]_D^{25}$ = +104° (*c* = 0.87, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 1.7 : 1 mixture of rotamers; the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.17 (td, *J* = 7.7, 1.2 Hz, 1H*, 1H§), 7.03 (d, *J* = 7.3 Hz, 1H*, 1H§), 6.80 (d, *J* = 8.4 Hz, 1H§), 6.77 (d, *J* = 7.2 Hz, 1H*), 6.56 (d, *J* = 8.4 Hz, 1H§), 6.52 (d, *J* = 8.7 Hz, 1H*), 5.89 (s, 1H*), 5.82 (s, 1H§), 4.70 – 4.53 (m, 1H*), 4.33 (t, *J* = 8.1 Hz, 1H§), 3.77 (s, 3H*), 3.73 (s, 3H§), 3.55 – 3.43 (m, 1H*, 1H§), 3.42 – 3.26 (m, 1H*, 1H§), 3.12 (s, 3H*), 2.91 (s, 3H§), 2.85 – 2.78 (m, 1H§), 2.78 – 2.65 (m, 2H*), 2.61 – 2.50 (m, 1H§), 2.41 (dd, *J* = 13.4, 4.7 Hz, 1H§), 2.22 (d, *J* = 14.7 Hz, 1H§), 2.12 (d, *J* = 12.5 Hz, 1H*), 2.02 – 1.86 (m, 2H*), 1.78 (dd, *J* = 15.4, 8.6 Hz, 1H§), 1.23 (s, 3H§), 1.15 (s, 3H*); ^{13}C

NMR (126 MHz, $CDCl_3$) δ 172.4*, 170.6§, 158.6* (q, $J_{C\text{-}F}$ = 37.1 Hz), 157.6§ (q, $J_{C\text{-}F}$ = 37.9 Hz), 150.2*§, 131.4*, 130.7§, 129.2*§, 122.0*§, 119.9§, 188.8*, 115.9* (q, $J_{C\text{-}F}$ = 288.3 Hz), 109.5§, 108.3*, 90.1*, 88.8§, 65.0*§, 60.9§, 60.23*, 60.15*, 59.1*, 56.4*, 56.3§, 52.9*§, 52.6*§, 42.9*, 40.4§, 36.8*, 35.7*, 34.9§, 34.8§, 14.3*§; FTIR (NaCl, thin film): 3462, 3004, 2955, 1751, 1691, 1609, 1490, 1437, 1358, 1302, 1203, 1159, 1103, 1063, 1034, 985, 928, 848, 754 cm^{-1}; HRMS (MM) calc'd for $C_{20}H_{24}F_3N_2O_5$ $[M+H]^+$ 429.1632, found 429.1643.

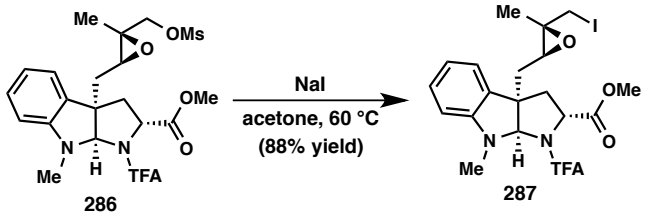
Preparation of epoxy mesylate 286



To a flame-dried 25 mL flask was added epoxy alcohol **285** (284 mg, 0.66 mmol, 1.0 equiv) and DCM (6.6 mL). The reaction flask was cooled to 0 °C. Methanesulfonyl chloride (MsCl, 57 μL, 0.73 mmol, 1.1 equiv) was added, followed by Et_3N (185 μL, 1.33 mmol, 2.0 equiv). After stirring for 1 hour, the reaction was quenched with saturated $NaHCO_3$ solution (15 mL). The aqueous layer was extracted with EtOAc (4 x 15 mL). Combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated down to give a colorless oil. Flash chromatography (5% to 60% EtOAc in hexanes) afforded epoxy mesylate **286** as a white foam (296 mg, 0.58 mmol, 89% yield; resulting epoxy mesylate diastereomers from previous step were readily separated at this stage). $[\alpha]_D^{25}$ = +89° (*c* = 0.85, $CHCl_3$); ^1H (500 MHz, $CDCl_3$; compound exists as a 1.7 : 1 mixture of rotamers; the major rotamer is denoted by *, minor rotamer denoted

by [§]) δ 7.17 (t, *J* = 7.8 Hz, 1H*, 1H[§]), 7.04 (d, *J* = 7.3 Hz, 1H*, 1H[§]), 6.87 – 6.71 (m, 1H*, 1H[§]), 6.65 – 6.47 (m, 1H*, 1H[§]), 5.87 (s, 1H*), 5.79 (s, 1H[§]), 4.60 (s, 1H*), 4.33 (s, 1H[§]), 4.08 (d, *J* = 14.0 Hz, 1H[§]), 4.04 (d, *J* = 11.1 Hz, 1H*), 3.89 (s, 1H[§]), 3.85 (d, *J* = 10.6 Hz, 1H*), 3.76 (s, 3H*), 3.73 (s, 3H[§]), 3.10 (s, 3H*), 2.94 (s, 3H*, 3H[§]), 2.88 (s, 3H[§]), 2.72 (dt, *J* = 18.8, 9.4 Hz, 1H*, 1H[§]), 2.68 – 2.60 (m, 1H*), 2.55 (dd, *J* = 13.2, 8.1 Hz, 1H[§]), 2.39 (dd, *J* = 13.4, 4.6 Hz, 1H*), 2.28 (d, *J* = 14.6 Hz, 1H[§]), 2.16 (d, *J* = 14.7 Hz, 1H*), 2.13 – 2.06 (m, 1H[§]), 1.95 (t, *J* = 11.7 Hz, 1H[§]), 1.76 (dt, *J* = 15.0, 5.7 Hz, 1H*), 1.34 (s, 3H[§]), 1.25 (s, 3H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4*, 170.4[§], 158.5* (q, $J_{C\text{-}F}$ = 37.3 Hz), 157.4[§] (q, $J_{C\text{-}F}$ = 36.8 Hz), 150.1*[§], 130.9*, 130.1[§], 129.3*[§], 121.9*[§], 119.7[§], 118.8*, 115.8[§] (q, $J_{C\text{-}F}$ = 288.7 Hz), 109.3[§], 108.2*, 90.0*, 88.6[§], 73.2[§], 73.1*, 60.2[§], 59.0*, 57.4*[§], 57.4*, 56.2[§], 52.9*[§], 52.4*[§], 42.9*, 40.3[§], 37.4*[§], 36.7*, 35.3*, 34.5[§], 34.1[§], 14.0*[§]; FTIR (NaCl, thin film): 3028, 2956, 1747, 1693, 1608, 1489, 1439, 1360, 1303, 1203, 1175, 1160, 1106, 1063, 1022, 982, 962, 897, 846, 817, 755 cm^{-1}; HRMS (MM) calc'd for $C_{21}H_{26}F_3N_2O_7S$ $[M+H]^+$ 507.1407, found 507.1411.

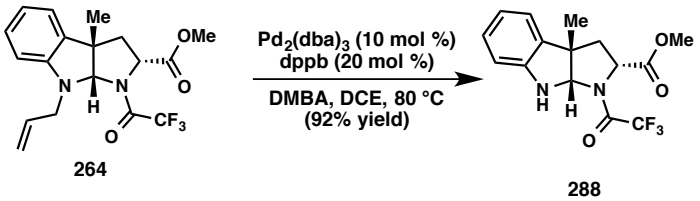
Preparation of epoxy iodide 287



To a 10 mL flame-dried flask equipped with a condenser was added epoxy mesylate **286** (146 mg, 0.288 mmol, 1.0 equiv) and sodium iodide (432 mg, 2.88 mmol, 10.0 equiv). Acetone (2.8 mL) was then added and the reaction was heated to 60 °C, resulting in a yellow clear solution gradually turning blurry. After 90 minutes, the reaction was cooled to room temperature and the mixture was quenched with saturated

NH_4Cl solution (10 mL) and extracted with EtOAc (3 x 10 mL). Combined organic layers were washed with saturated $NaHCO_3$ solution (50 mL) and brine (50 mL). It was dried over Na_2SO_4, filtered and concentrated down to give an oil. Flash chromatography (1% to 25% EtOAc in hexanes) afforded epoxy iodide **287**, as white foam (136 mg, 0.253 mmol, 88% yield). $[\alpha]_D^{25}$ = +110° (*c* = 0.545, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 1.7 : 1 mixture of rotamers the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.20 (t, *J* = 7.7 Hz, 1H*, 1H§), 7.06 (d, *J* = 7.2 Hz, 1H*, 1H§), 6.88 – 6.76 (m, 1H*, 1H§), 6.61 – 6.49 (m, 1H*, 1H§), 5.88 (s, 1H*), 5.78 (s, 1H§), 4.62 (s, 1H*), 4.35 (s, 1H§), 3.79 (s, 3H*), 3.76 (s, 3H§), 3.14 (s, 3H*), 3.10 – 3.03 (m, 3H§), 2.93 (d, *J* = 10.7 Hz, 2H*, 2H§), 2.79 – 2.62 (m, 1H*, 1H§), 2.62 – 2.53 (m, 1H§), 2.49 – 2.40 (m, 1H*), 2.35 – 2.21 (m, 1H§), 2.15 (d, *J* = 15.1 Hz, 1H*), 2.02 – 1.87 (m, 1H§), 1.73 (dd, *J* = 14.6, 8.1 Hz, 1H*), 1.45 (s, 3H§), 1.37 (s, 3H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4*, 170.5§, 158.6* (q, $J_{C\text{-}F}$ = 36.2, 35.4 Hz), 150.2*§, 131.3*, 130.5§, 129.3*§, 122.0*§, 119.9§, 118.9*, 115.9* (q, $J_{C\text{-}F}$ = 288.9 Hz), 109.5§, 108.5*, 90.1*, 88.7§, 62.5*, 60.3§, 59.2*§, 56.3§, 53.0*, 52.6§, 52.4*, 43.0*, 40.5§, 36.9*, 36.4*, 35.2§, 34.7§, 16.4*§, 13.1*§; FTIR (NaCl, thin film): 3444, 3054, 3022, 3005, 2956, 1747, 1699, 1608, 1489, 1435, 1386, 1360, 1303, 1203, 1158, 1023, 986, 929, 853, 809, 755 cm^{-1}; HRMS (MM) calc'd for $C_{20}H_{23}F_3N_2O_4I$ $[M+H]^+$ 539.0649, found 539.0633.

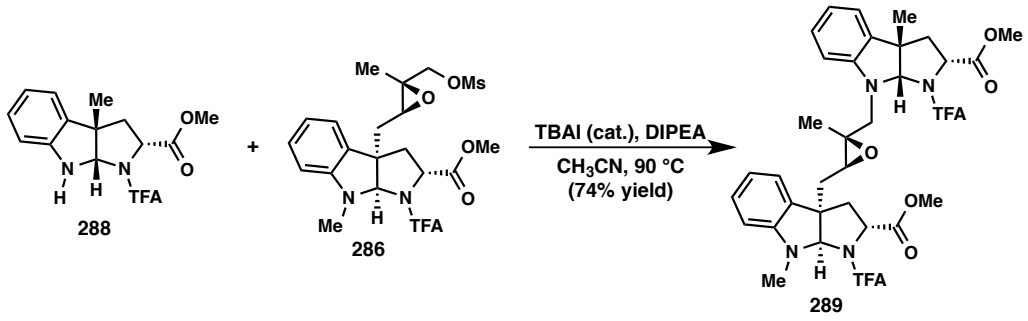
Preparation of amine 288



To a 25 mL flame-dried screw-cap Schlenk flask was added *N*-allyl pyrroloindoline **264** (500 mg, 1.36 mmol, 1.0 equiv) and dimethylbibarturic acid (636 mg, 4.07 mmol, 3.0 equiv). The Schlenk flask was then evacuated and backfilled with argon three times. The solids were then dissolved in dry DCE (3.8 mL). In the meantime, in a 1-dram vial, $Pd_2(dba)_3$ (62 mg, 0.068 mmol, 5 mol %) and 1,4-bis(diphenylphosphino)butane (dppb, 58 mg, 0.135 mmol, 10 mol %) were mixed in DCE (1.6 mL) and the mixture was allowed to stir at room temperature for 1 hour; then the resulting solution was added into Schlenk flask. The reaction was heated to 80 °C. After 4 days, the reaction was cooled to room temperature and quenched with saturated Na_2CO_3 aqueous solution (40 mL). The mixture was extracted with EtOAc (3 x 40 mL). Combined organic layers were washed with brine (100 mL). It was dried over Na_2SO_4, filtered and concentrated down to give a brown oil. Flash chromatography (1% to 20% EtOAc in hexanes) afforded amine **288**, which was contaminated with phosphine oxide formed from the dppb ligand. The mixture was then subjected to preparative reverse phase HPLC (t = 0 – 14 min, 65% to 75% CH_3CN in H_2O; t = 14 – 15 min, 75% to 95% CH_3CN in H_2O; t = 15 – 17 min, 95% to 100% CH_3CN in H_2O; t = 17 – 17.5 min, 100% to 65% CH_3CN in H_2O; t = 17.5 – 25 min, 65% CH_3CN in H_2O; t_R = 16.5 – 20.0 min), to give pure product **43** as a yellow oil (408 mg, 1.24 mmol, 92% yield). $[\alpha]_D^{25}$ = –228° (c = 0.93, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 3.4 : 1 mixture of rotamers; the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.08 – 7.01 (m, 1H*, 2H§), 7.00 (ddd, J = 7.4, 1.3, 0.6 Hz, 1H*), 6.75 (td, J = 7.4, 0.9 Hz, 1H§), 6.70 (td, J = 7.5, 0.9 Hz, 1H*), 6.61 – 6.58 (m, 1H§), 6.58 (dt, J = 7.9, 0.7 Hz, 1H*), 5.45 (tt, J = 1.9, 1.1 Hz, 1H§), 5.34 (s, 1H*), 5.21 (br s, 1H§), 4.91 (dd, J = 8.7, 2.3 Hz, 1H§), 4.74

(ddd, J = 8.9, 1.9, 1.0 Hz, 1H*), 3.24 (s, 3H[§]), 3.12 (s, 3H*), 2.86 (d, J = 13.2 Hz, 1H*), 2.70 (dd, J = 13.0, 2.3 Hz, 1H[§]), 2.50 (dd, J = 13.2, 8.5 Hz, 1H*), 2.33 (dd, J = 13.0, 8.7 Hz, 1H[§]), 1.46 (s, 3H[§]), 1.42 (s, 3H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0*, 169.5[§], 156.8* (q, $J_{C\text{-}F}$ = 37.3 Hz), 155.9[§] (q, $J_{C\text{-}F}$ = 37.5 Hz), 148.8*, 147.6[§], 131.3[§], 131.0*, 128.9*[§], 122.8*, 122.7[§], 119.4[§], 119.0*, 116.2[§] (q, $J_{C\text{-}F}$ = 287.4 Hz), 115.8* (q, $J_{C\text{-}F}$ = 288.0 Hz), 108.9[§], 108.8*, 84.6*, 83.2[§], 60.7[§], 60.1* (q, $J_{C\text{-}F}$ = 3.2 Hz), 54.4[§], 52.4*, 52.2[§], 50.7*, 41.9*, 40.2[§], 24.4[§], 24.2*; FTIR (NaCl, thin film): 3401, 3055, 2957, 2929, 2871, 2121, 1738, 1687, 1612, 1521, 1485, 1470, 1455, 1408, 1354, 1334, 1315, 1302, 1260, 1204, 1148, 1104, 1065, 1034, 1018, 1000, 977, 939, 904, 865, 837, 748, 718 cm^{-1}; HRMS (MM) calc'd for $C_{15}H_{16}F_3N_2O_3$ $[M+H]^+$ 329.1108, found 329.1113.

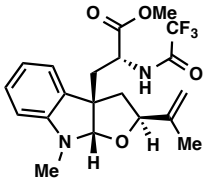
Preparation of bis(pyrroloindoline) 289



To a 0.5-dram vial was added amine **288** (76 mg, 0.23 mmol, 3.0 equiv), which was then co-evaporated with benzene (2 x 1 mL). Epoxy mesylate **286** (39 mg, 0.08 mmol, 1.0 equiv) was added as a solid, followed by tetra-*n*-butylammonium iodide (TBAI, 5.7 mg, 0.015 mmol, 0.2 equiv), and acetonitrile (90 μL). DIPEA (20 μL, 0.12 mmol, 1.5 equiv) was added at last. The vial was sealed using a Teflon cap and heated to 90 °C for 5 days. It was then cooled to room temperature and quenched with saturated $NaHCO_3$ aqueous solution (2 mL). The mixture was extracted with EtOAc (5 x 2 mL).

Combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated down to give a yellow liquid. Flash chromatography (1% to 28% EtOAc in hexanes) afforded bis(pyrroloindoline) **289** as a light yellow oil (41.9 mg, 0.057 mmol, 74% yield). Starting material **288** can be recovered. $[\alpha]_D^{25} = -21°$ ($c = 0.61$, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3CN; *half of proton peaks* in compound exist as a 1.6 : 1 mixture of rotamers; the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.15 (td, J = 7.7, 1.2 Hz, 1H*, 1H§), 7.11 – 7.00 (m, 1H*, 1H§, 1H), 6.92 (dd, J = 7.3, 1.2 Hz, 1H), 6.83 (t, J = 8.1 Hz, 1H§), 6.78 (t, J = 7.3 Hz, 1H*), 6.66 (t, J = 7.4 Hz, 1H), 6.56 – 6.48 (m, 1H*, 1H§), 6.47 (d, J = 8.1 Hz, 1H), 5.90 (s, 1H*), 5.79 (s, 1H§), 5.37 (s, 1H), 4.70 (d, J = 8.2 Hz, 1H), 4.64 – 4.55 (m, 1H*), 4.29 (t, J = 8.2 Hz, 1H§), 3.75 (s, 3H*), 3.73 (s, 3H§), 3.59 – 3.35 (m, 2H*, 2H§), 3.13 (s, 3H), 3.05 (s, 3H*), 2.81 (s, 3H§), 2.78 (d, J = 13.0 Hz, 1H), 2.73 (dd, J = 13.8, 9.4 Hz, 1H§), 2.67 – 2.59 (m, 1H*), 2.42 (dd, J = 13.5, 4.4 Hz, 1H*), 2.31 (dd, J = 13.0, 8.4 Hz, 1H), 2.33 – 2.27 (m, 1H§), 2.21 (d, J = 14.3 Hz, 1H*), 2.17 – 2.10 (m, 1H§), 1.87 (dt, J = 16.5, 6.3 Hz, 1H§), 1.76 – 1.60 (m, 1H*), 1.30 (s, 3H§), 1.25 (s, 3H*, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3*, 170.6§, 169.6, 158.5* (q, $J_{C\text{-}F}$ = 37.4 Hz), 157.8§ (app d, $J_{C\text{-}F}$ = 41.7 Hz), 156.9 (q, $J_{C\text{-}F}$ = 36.8 Hz), 150.8§, 150.5*, 149.5, 131.7*, 131.4, 131.0§, 129.3§, 129.1*, 128.9*§, 122.3*§, 122.0, 120.1§, 118.8*, 118.3, 116.1 (q, $J_{C\text{-}F}$ = 288.5 Hz), 116.0* (q, $J_{C\text{-}F}$ = 288.6 Hz), 115.8§ (q, $J_{C\text{-}F}$ = 286.1 Hz), 110.0§, 108.5*, 107.3, 90.2*, 88.9, 88.8§, 60.2§, 60.0*, 60.0, 59.8§, 59.5*, 59.1*§, 57.6*, 56.8§, 52.9*, 52.8*, 52.5§, 52.4, 52.1§, 50.6, 42.9*, 42.4, 40.1§, 37.0*, 36.2*, 35.8§, 35.7§, 25.8, 15.5§, 15.4*; FTIR (NaCl, thin film): 2956, 2927, 1750, 1694, 1608, 1491, 1436, 1357, 1341, 1302, 1255, 1206, 1155, 1105, 1065, 1034, 998,

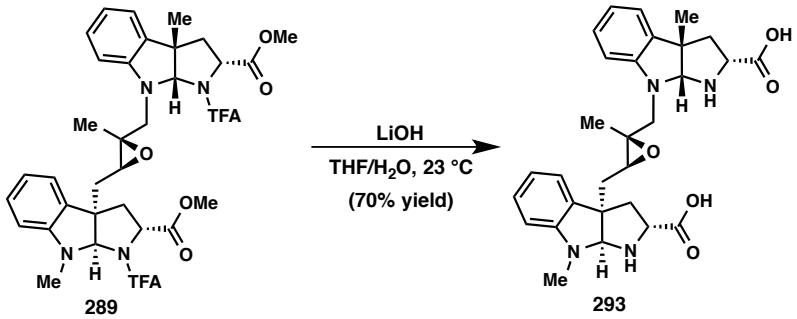
944, 861, 845, 845, 747 cm^{-1}; HRMS (MM) calc'd for $C_{35}H_{37}F_6N_4O_7$ $[M+H]^+$ 739.2561, found 739.2570.



290

When epoxy iodide **287** was used instead of epoxy mesylate, a 42% yield of rearranged product **290** was isolated. $[\alpha]_D^{25} = -122°$ (*c* = 0.475, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (td, *J* = 7.6, 1.3 Hz, 1H), 7.03 (ddd, *J* = 7.3, 1.3, 0.5 Hz, 1H), 6.75 (td, *J* = 7.4, 1.0 Hz, 1H), 6.60 (d, *J* = 8.3 Hz, 1H), 6.43 (d, *J* = 7.9 Hz, 1H), 5.23 (s, 1H), 4.94 (dt, *J* = 1.9, 1.0 Hz, 1H), 4.86 – 4.74 (m, 1H), 4.33 (td, *J* = 8.1, 4.8 Hz, 1H), 3.99 (dd, *J* = 11.1, 4.4 Hz, 1H), 3.64 (s, 3H), 2.89 (s, 3H), 2.65 (dd, *J* = 14.7, 4.9 Hz, 1H), 2.37 – 2.19 (m, 2H), 1.91 (dd, *J* = 11.8, 11.1 Hz, 1H), 1.68 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 156.3 (q, $J_{C\text{-}F}$ = 37.6 Hz), 151.4, 143.3, 129.7, 129.4, 123.0, 118.0, 115.5 (q, $J_{C\text{-}F}$ = 287.9 Hz), 111.8, 106.2, 101.7, 80.7, 55.3, 52.9, 50.9, 46.1, 39.2, 30.4, 17.9; FTIR (NaCl, thin film): 3307, 2953, 2924, 2853, 1747, 1713, 1608, 1557, 1495, 1442, 1290, 1262, 1208, 1179, 1033, 1021, 997, 959, 900, 743 cm^{-1}; HRMS (MM) calc'd for $C_{20}H_{24}F_3N_2O_4$ $[M+H]^+$ 413.1683, found 413.1690.

Preparation of bis(amino acid) 293

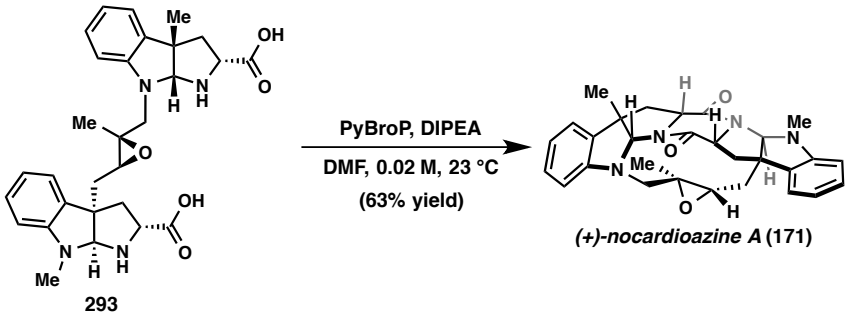


289 **293**

A solution of lithium hydroxide (7.4 mg, 0.31 mmol, 5.0 equiv) in distilled water (200 μL) was added dropwise to a solution of bis(pyrroloindoline) **289** (45.7 mg, 0.062

mmol, 1.0 equiv) in THF (350 μL) and distilled water (150 μL). After stirring at room temperature for 6 hours, the reaction was quenched with 1M HCl until pH reached 7 (210 μL). The resulting solution was concentrated down using rotavap to get rid of THF, and then put under high vacuum to give a yellow oil. It was dissolved in methanol and subjected to reverse phase preparative HPLC (10% to 60% CH_3CN in H_2O over 12 min, t_R = 6.8 – 8.0 min), giving bis(amino acid) **293** as a white solid (22.3 mg, 0.043 mmol, 70% yield). $[\alpha]_D^{25}$ = +59° (*c* = 0.59, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 7.20 – 7.15 (m, 2H), 7.11 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.09 (td, *J* = 8.0, 1.5 Hz, 1H), 6.79 (td, *J* = 7.4, 0.8 Hz, 1H), 6.77 (td, *J* = 7.5, 0.8 Hz, 1H), 6.55 (dd, *J* = 8.2, 0.9 Hz, 1H), 6.21 (d, *J* = 7.9 Hz, 1H), 5.21 (s, 1H), 4.88 (s, 1H), 4.10 (dd, *J* = 8.6, 3.2 Hz, 1H), 3.67 (d, *J* = 16.2 Hz, 1H), 3.62 (d, *J* = 16.2 Hz, 1H), 3.51 (dd, *J* = 12.3, 5.9 Hz, 1H), 3.35 (dd, *J* = 8.2, 3.6 Hz, 1H), 2.90 (s, 3H), 2.85 (dd, *J* = 13.5, 3.2 Hz, 1H), 2.64 (t, *J* = 12.7 Hz, 1H), 2.52 (dd, *J* = 13.0, 5.9 Hz, 1H), 2.46 (dd, *J* = 13.5, 8.6 Hz, 1H), 2.19 (dd, *J* = 15.1, 3.7 Hz, 1H), 2.06 (dd, *J* = 15.1, 8.2 Hz, 1H), 1.38 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 174.3, 173.5, 151.2, 149.7, 134.3, 133.7, 130.3, 130.0, 124.1, 124.0, 121.0, 120.0, 107.8, 107.6, 93.4, 88.2, 62.2, 61.7, 61.3, 57.8, 57.7, 54.5, 54.4, 42.5, 42.4, 36.7, 33.1, 26.4, 15.6; FTIR (NaCl, thin film): 3049, 2957, 2930, 2603, 1631, 1607, 1490, 1462,1451, 1402, 1383, 1350, 1308, 1275, 1213, 1187, 1129, 1106, 1043, 1026, 921, 860, 741 cm^{-1}; HRMS (MM) calc'd for $C_{29}H_{35}N_4O_5$ $[M+H]^+$ 519.2602, found 519.2615.

Preparation of (+)-nocardioazine A (171)



To a 0.5-dram vial was added bis(amino acid) **293** (2.9 mg, 0.006 mmol, 1.0 equiv). It was co-evaporated with benzene (1 mL). DMF (280 μL) was added into the vial. At 0 °C, DIPEA (4.5 μL, 0.026 mmol, 4.6 equiv) was added, followed by bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP, 10.4 mg, 0.022 mmol, 4.0 equiv). After 5 minutes, the reaction was allowed to stir at room temperature. After 24 hours, the reaction was quenched with saturated $NaHCO_3$ solution (1 mL). The aqueous layer was extracted with EtOAc (5 x 1 mL). Combined organic layers were washed with brine (3 mL), dried over Na_2SO_4, filtered and concentrated down to give a light yellow oil. Flash chromatography (5% to 40% EtOAc in hexanes) afforded (+)-nocardioazine A (**171**) as a white solid (1.7 mg, 0.0035 mmol, 63% yield). $[\alpha]_D^{25}$ = +45° (*c* = 0.50, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (td, *J* = 7.7, 1.3 Hz, 1H), 7.16 (td, *J* = 7.7, 1.3 Hz, 1H), 7.10 (td, *J* = 7.5, 1.0 Hz, 2H), 6.79 (td, *J* = 7.5, 0.9 Hz, 1H), 6.74 (td, *J* = 7.4, 0.9 Hz, 1H), 6.49 (t, *J* = 7.3 Hz, 2H), 5.66 (s, 1H), 5.40 (s, 1H), 4.55 – 4.49 (m, 2H), 3.73 (d, *J* = 15.3 Hz, 1H), 3.33 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.28 (dd, *J* = 14.2, 1.8 Hz, 1H), 2.93 (s, 3H), 2.80 (dd, *J* = 15.0, 3.4 Hz, 1H), 2.76 (d, *J* = 15.4 Hz, 1H), 2.62 (dd, *J* = 13.7, 9.2 Hz, 1H), 2.40 (dd, *J* = 14.3, 11.2 Hz, 1H), 2.31 (dd, *J* = 13.7, 8.8 Hz, 1H), 1.53 (dd, *J* = 14.9, 10.7 Hz, 1H), 1.52 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$)

δ 169.8, 169.0, 149.0, 147.2, 133.7, 133.3, 128.9, 128.7, 121.7, 121.3, 118.7, 118.0, 107.6, 105.5, 91.6, 88.2, 62.7, 61.8, 61.6, 59.3, 53.4, 51.2, 51.1, 40.2, 36.5, 35.0, 34.3, 20.1, 14.2; FTIR (NaCl, thin film): 3051, 3011, 2956, 2923, 2871, 2821, 2793, 1681, 1608, 1483, 1453, 1428, 1390, 1359, 1345, 1303, 1278, 1245, 1216, 1190, 1158, 1146, 1119, 1095, 1068, 1053, 1038, 1024, 1001, 981, 966, 920, 909, 890, 874, 841, 829, 810, 788, 750, 703 cm^{-1}; HRMS (MM) calc'd for $C_{29}H_{31}N_4O_3$ $[M+H]^+$ 483.2391, found 483.2409.

Table 3.5. *Comparison of ^1H NMR data for natural vs. synthetic (+)-nocardioazine A (**171**)*

Raju et al. Report,[3] Natural (+)-nocardioazine A ^1H NMR, 600 MHz, $CDCl_3$	This Work, Synthetic (+)-nocardioazine A ^1H NMR, 500 MHz, $CDCl_3$
δ 7.16 (ddd, *J* = 7.7, 7.5, 1.2 Hz, 1H)	δ 7.18 (td, *J* = 7.7, 1.3 Hz, 1H)
7.14 (ddd, *J* = 7.7, 7.7, 1.2 Hz, 1H)	7.16 (td, *J* = 7.7, 1.3 Hz, 1H)
7.09 (dd, *J* = 7.6, 1.2 Hz, 1H)	7.10 (td, *J* = 7.5, 1.0 Hz, 2H)
7.07 (dd, *J* = 7.4, 1.1 Hz, 1H)	–
6.76 (ddd, *J* = 7.6, 7.5, 0.8 Hz, 1H)	6.79 (td, *J* = 7.5, 0.9 Hz, 1H)
6.73 (ddd, *J* = 7.7, 7.4, 0.7 Hz, 1H)	6.74 (td, *J* = 7.4, 0.9 Hz, 1H)
6.48 (dd, *J* = 7.7, 0.8 Hz, 1H)	6.49 (t, *J* = 7.3 Hz, 2H)
6.47 (dd, *J* = 7.7, 0.7 Hz, 1H)	–
5.64 (s, 1H)	5.66 (s, 1H)
5.38 (s, 1H)	5.40 (s, 1H)
4.50 (m, 1H)	4.55 – 4.49 (m, 2H)
4.49 (m, 1H)	–
3.72 (d, *J* = 15.5 Hz, 1H)	3.73 (d, *J* = 15.3 Hz, 1H)
3.30 (dd, *J* = 11.0, 3.7 Hz, 1H)	3.33 (dd, *J* = 11.0, 3.5 Hz, 1H)
3.26 (dd, *J* = 14.4, 1.6 Hz, 1H)	3.28 (dd, *J* = 14.2, 1.8 Hz, 1H)
2.91 (s, 3H)	2.93 (s, 3H)
2.79 (dd, *J* = 11.0, 3.7 Hz, 1H)	2.80 (dd, *J* = 15.0, 3.4 Hz, 1H)
2.74 (d, *J* = 15.5 Hz, 1H)	2.76 (d, *J* = 15.4 Hz, 1H)
2.60 (dd, *J* = 13.7, 9.1 Hz, 1H)	2.62 (dd, *J* = 13.7, 9.2 Hz, 1H)
2.38 (dd, *J* = 14.4, 11.0 Hz, 1H)	2.40 (dd, *J* = 14.3, 11.2 Hz, 1H)
2.30 (dd, *J* = 13.7, 8.7 Hz, 1H)	2.31 (dd, *J* = 13.7, 8.8 Hz, 1H)
1.51 (obscured, 1H)	1.53 (dd, *J* = 14.9, 10.7 Hz, 1H)
1.50 (s, 3H)	1.52 (s, 3H)
1.10 (s, 3H)	1.12 (s, 3H)

Table 3.6. *Comparison of ^{13}C NMR data for natural vs. synthetic (+)-nocardioazine A (**171**)*

Raju et al. Report,[3] Natural (+)-nocardioazine A ^{13}C NMR, 150 MHz, $CDCl_3$	This Work, Synthetic (+)-nocardioazine A ^{13}C NMR, 126 MHz, $CDCl_3$	Chemical Shift Difference, Δδ
δ 169.6	δ 169.8	0.2
168.8	169.0	0.2
148.8	149.0	0.2
146.9	147.2	0.3
133.6	133.7	0.1
133.0	133.3	0.3
128.8	128.9	0.1
128.4	128.7	0.3
121.5	121.7	0.2
121.1	121.3	0.2
118.4	118.7	0.3
117.8	118.0	0.2
107.4	107.6	0.2
105.4	105.5	0.1
91.5	91.6	0.1
88.0	88.2	0.2
62.4	62.7	0.3
61.7	61.8	0.1
61.4	61.6	0.2
59.2	59.3	0.1
53.3	53.4	0.1
51.0	51.2	0.2
50.9	51.1	0.2
40.1	40.2	0.1
36.4	36.5	0.1
34.9	35.0	0.1
34.2	34.3	0.1
19.9	20.1	0.2
14.1	14.2	0.1

3.6 NOTES AND REFERENCES

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