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AN ASYMMETRIC TOTAL SYNTHESIS OF MARTINELLIC ACID

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Abstract – We describe an asymmetric total synthesis of the pyrrolo[3,2-*c*]quinoline natural product martinelllic acid starting from pyrroglutamic acid. A convergent strategy involving a Pd-catalyzed aryl amination reaction of a chiral, non-racemic pyrrolidine derivative incorporates the C2-chiral center which controls the remaining two stereocenters. Elaboration of this adduct through a Grieco-elimination sets the stage for a diastereoselective intramolecular [3+2] azomethine ylide-alkene cycloaddition and the construction of the remaining two chiral centers. Elaboration of the cycloadduct and incorporation the prenyl guanidine units delivered martinelllic acid after removal of the protecting groups.

INTRODUCTION

Martinelline (**1**) and martinelllic acid (**2**) are a pair of guanidine-containing pyrrolo[3,2-*c*]quinolines which were isolated from the South American plant *Martinella iquitosensis* by a group at Merck and described in 1995 (Figure 1).¹ These relatively simple alkaloids have attracted a remarkable amount of attention from the synthetic community with various total syntheses and approaches being reported in the literature.²⁻¹² While these molecules display biological activity, indeed they have been reported to be used for the treatment of conjunctivitis by several indigenous tribes in the region where the plant is found and the Merck group reported that these molecules were bradykinin receptor antagonists, these activities are relatively modest. However, as synthetic targets, the presence of three contiguous stereocenters around a relatively simple heterocyclic core render them tractable targets and offer opportunities to develop strategies to the core heterocycle that may have broader applications in medicinal chemistry contexts. Indeed, our own entry into this area was driven by these very considerations.

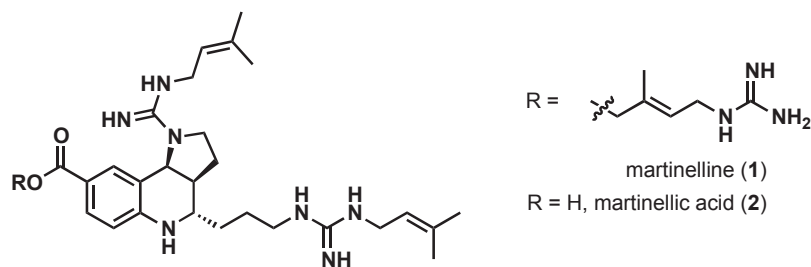


Figure 1

Our analysis of the structural features of this molecule, like many other groups, centered on the late-stage introduction of the guanidino moieties and thus the problem comes down to the construction of the pyrroloquinoline core **3** (Figure 2). Very early on in our synthetic studies, we focused on the utility of a [3+2] cycloaddition to construct the pyrrolidine ring and in particular the utility of a non-stabilized azomethine ylide.¹³⁻¹⁴ These early studies resulted in the construction of the core **5** and subsequently the development of methods for the introduction of the three-carbon C2-sidechain **5**→**4** via iminium ion chemistry (Figure 2).¹⁵⁻¹⁷ However, our ultimate goal was to develop an asymmetric synthesis of this alkaloid. In a general sense, our approach represented by **5**→**4**→**3**→**2/1** could have been tailored to an asymmetric version if conditions could have been developed to render the cycloaddition enantioselective, i.e., the formation of (+)- or (-)-**5**. However, in order to improve the overall convergency, we wished to pursue an approach in which the cycloaddition precursor **7** contained all of the contiguous carbon framework with the exception of the one carbon atom that would derive from glycine in the form of the azomethine ylide. The requisite precursor would then derive from an aryl amination with the amine originating from *S*-glutamic acid.

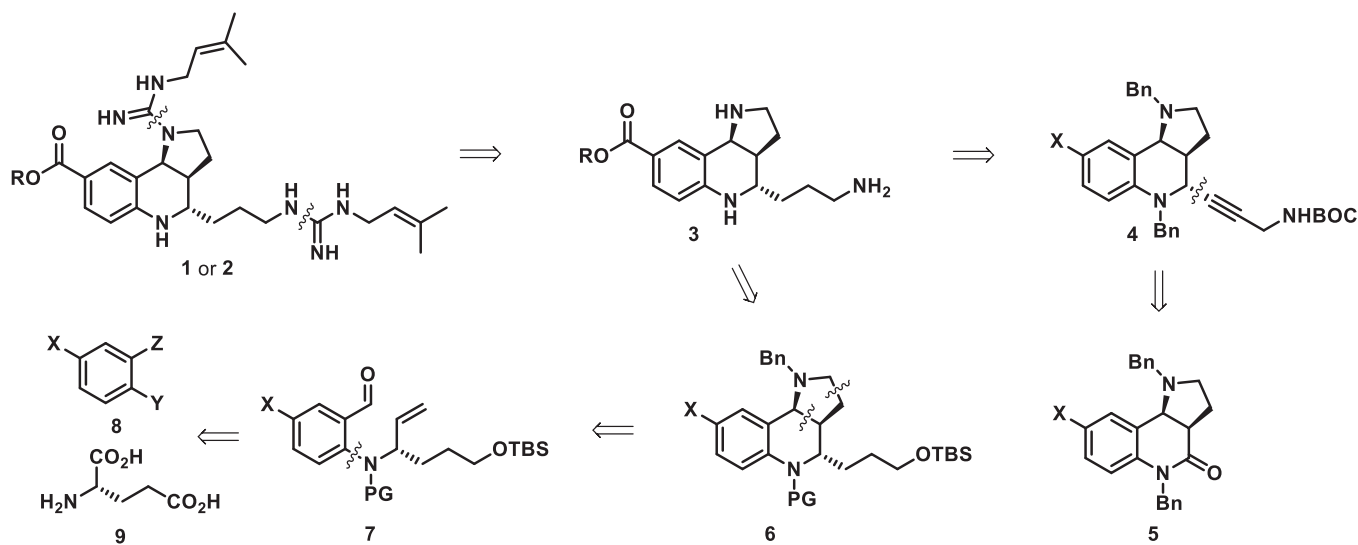
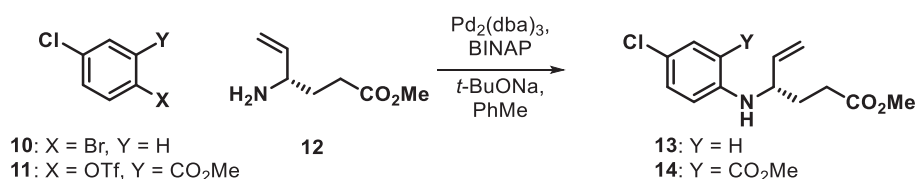


Figure 2. Retrosynthetic analyses of martinelline and martinelic acid

RESULTS AND DISCUSSION

Initial attempts to execute this strategy were made with the known allyl amine **12** which can be prepared in five steps from glutamic acid. However, our attempts to couple **12** with either an aryl bromide or triflate were unsuccessful (Scheme 1), although it is important to note that these experiments were conducted at a time when options in terms of potential catalysts for the Buchwald-Hartwig aryl amination were quite limited and at least in our labs this type of system has not been revisited as more substrate-tolerant catalysts have been described. There were a number of potential reasons why this reaction may have failed, including the possibility that under the reaction conditions an intramolecular reaction between the amino group and the ester leading to the formation of a pyrroglutamate derivative. Although we did not demonstrate the formation of such products, this line of thought suggested an alternative approach to us involving a pyrroglutamate derivative wherein the three carbon sidechain would be internally protected and due to the cyclic nature of the amino group (as an amide) it would be potentially less sterically encumbered. Accordingly, our retrosynthetic analysis was modified to accommodate this new strategy.¹⁸ Snider and coworkers have similarly explored a [3+2] azomethine ylide-alkene cycloaddition sequence *en route* to a total synthesis of (±)-martinellic acid via an



Scheme 1. Preliminary aryl amination experiments

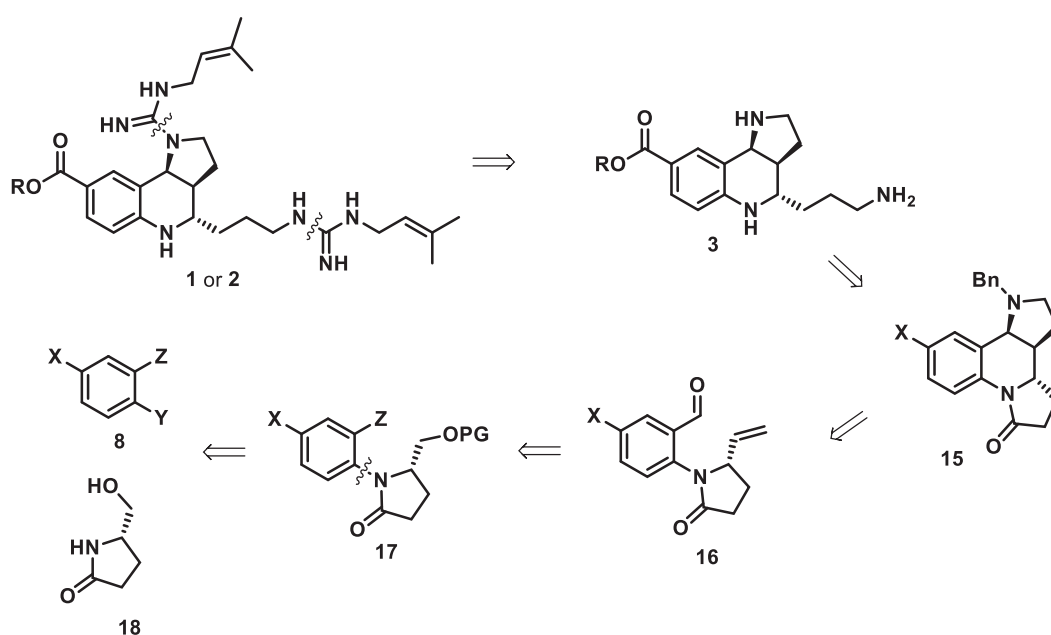
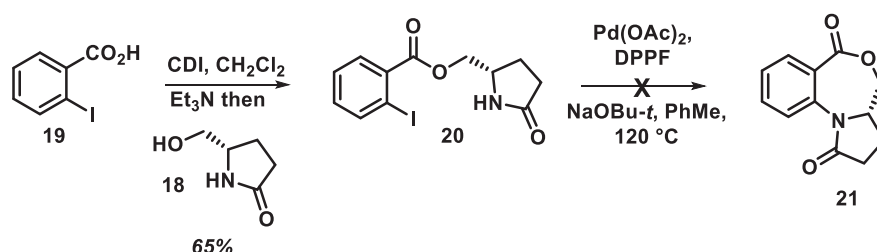


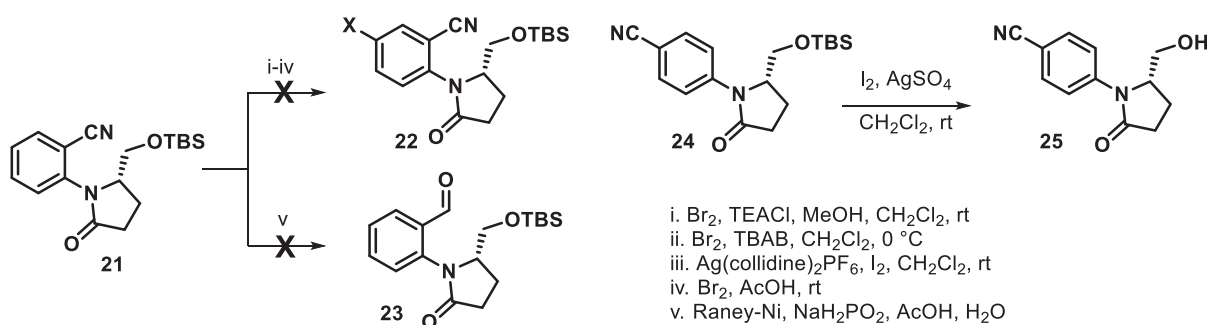
Figure 3. Modified retrosynthetic approach to the *Martinella* alkaloids

intermediate almost identical to **16**.¹⁹⁻²⁰ In their approach, the vinylpyrrolidinone was constructed through a homo conjugate addition/lactamization to an activated cyclopropane (cf. Scheme 11),¹⁹⁻²⁰ whereas our own approach relies on a completely different strategy for the construction of **16** and it is enantioselective.



Scheme 2. Attempted intramolecular aryl amidation

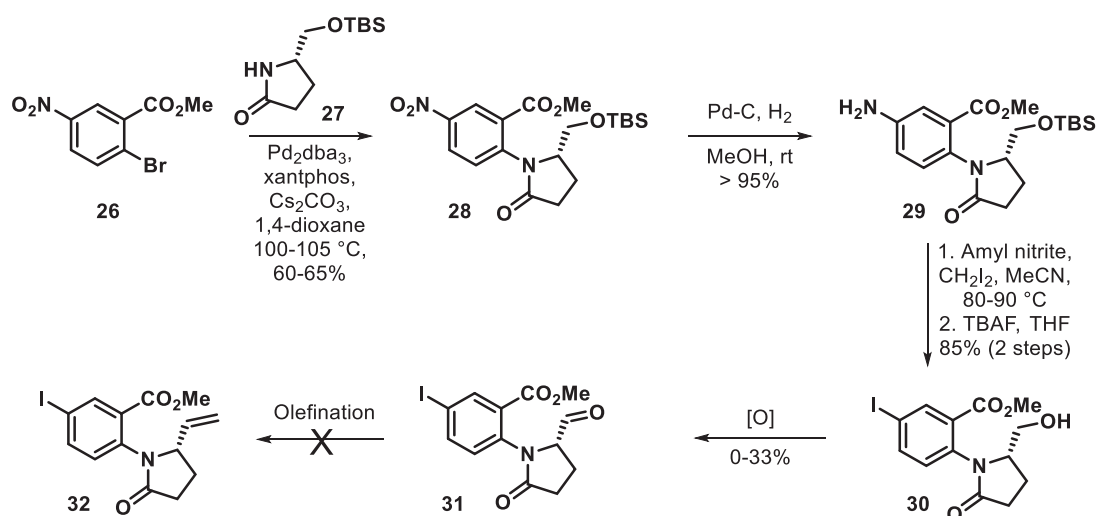
In an initial experiment, we attempted to execute an intramolecular version of the aryl amidation reaction through cyclization of ester **20**; the ester was prepared via the intermediacy of the mixed anhydride and the corresponding alcohol **18** (Scheme 2). Unfortunately, this chemistry failed to deliver the corresponding coupled product, presumably as a result of the ring size. At this point, we turned our attention to the intermolecular variant based on a report from Shakespeare for the aryl amidation of lactams²¹ and subsequently the modified conditions of Buchwald²² allowed us to prepare a series of *N*-arylated pyrroglutamate derivatives, chemistry that has been reported previously.²³⁻²⁴ Initial attempts to elaborate some of these substrates, in particular the nitrile-containing derivatives, through halogenation or semi-reduction were unsuccessful (Scheme 3).



Scheme 3. Attempted elaboration of the nitrile-containing derivatives

Given the lack of success at introducing the third substituent on the aromatic ring, we were faced with the proposition of carrying this from the beginning of the sequence. We had learned in the course of our cross-coupling studies an *ortho* substituent, unless small, was not well tolerated and that electron deficient arenes were the most efficient in this chemistry. This did not leave a great deal of choice in potential

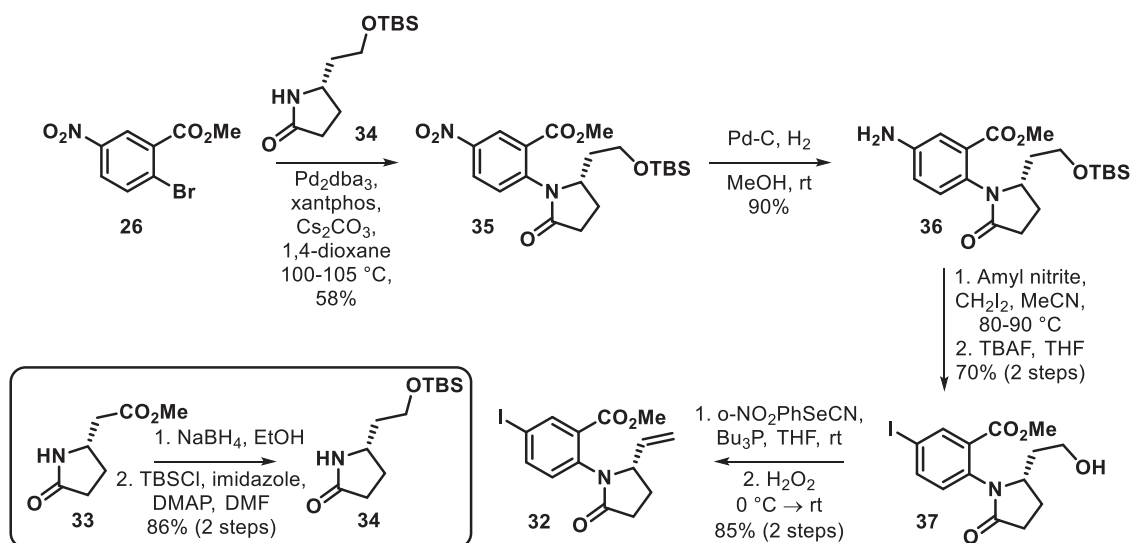
partners and thus we opted to use methyl 2-bromo-5-nitrobenzoate (**26**) as a substrate. Initial attempts to perform the cross-coupling reaction under standard conditions of 2.5 mol% Pd₂dba₃ and 7.5 mol% of xantphos were encouraging in that 30-35% of the cross-coupled product **28** was obtained (Scheme 4). Synthetically useful yields of 60-65% could be obtained through the use of the double quantities of the catalyst; on a 10 mmol scale 60% yields could be routinely realized. With the coupling product in hand, we were now positioned to elaborate the core prior to evaluating the cycloaddition chemistry. Reduction of the nitro group through catalytic hydrogenation proceeded uneventfully to deliver aniline **29**, which upon diazotization with *n*-amyl nitrite in the presence of diiodomethane²⁵ provided the corresponding aryl iodide along with varying amounts of the desilylated product. This mixture was directly treated with TBAF to provide the alcohol **30** (Scheme 4). At this point, our plans called for the conversion of the alcohol **30** into the corresponding aldehyde **31** and then olefination. A significant number of oxidation reactions were attempted to perform the initial transformation, and while there was some formation of the aldehyde 11-33% with activated DMSO oxidations or the DMP, this was clearly not optimal. Further, attempts to convert this limited material into alkene **32** failed.



Scheme 4. First generation approach to **32** ([O] = i. TPAP, NMO, 4 Å ms, CH₂Cl₂, 11%; ii. PCC, CH₂Cl₂, rt, 0%; iii. DCC, pyridine, TFA, DMSO, PhH, rt, 33%; iv. Dess-Martin periodinane (DMP), CH₂Cl₂, rt, 30%; v. IBX, DMSO, rt, 25%; vi. trichlorocyanuric acid, DMSO – 30 °C then Et₃N; vii. TEMPO, NaOCl, NaBr, PhMe, EtOAc, water, rt, 0%.

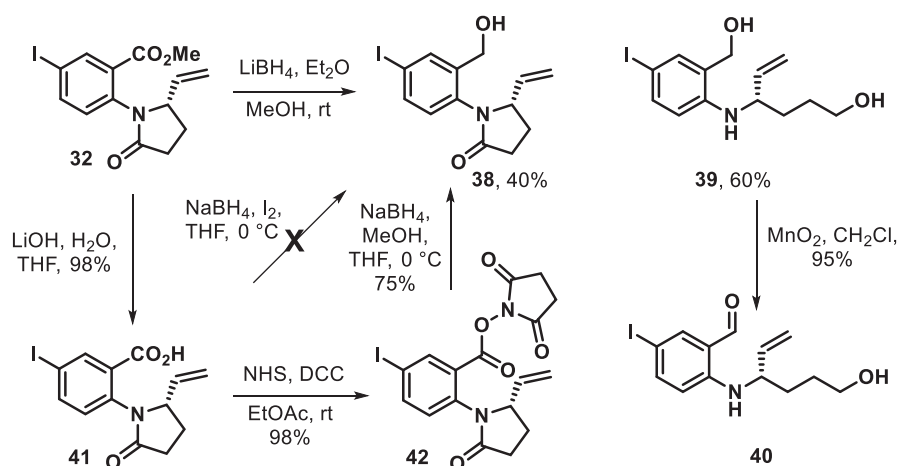
Given our inability to elaborate the alcohol, a minor adjustment to the sequence was necessary such that the homologation was performed prior to the cross-coupling event. In order to accomplish this, pyrrolidinone **34** was prepared via the corresponding known ester through reduction and silylation (Scheme 5 inset).²⁶ Gratifyingly, the aryl amination leading to the formation of **35** occurred in essentially identical yield to the lower homolog and could be performed on a 20 mmol scale (Scheme 5). Under these conditions, the unreacted lactam could be recovered in approximately 35% yield.

Subjecting the coupled product to hydrogenation delivered the corresponding aniline derivative **36**, which upon diazotization and subsequent desilylation produced the alcohol **37**. At this point, our plan was to convert primary alcohol into the corresponding selenide and oxidative elimination would provide the olefin. Attempts to accomplish this by exposure to *N*-(phenylselenenyl)phthalimide were unsuccessful, but use of *o*-nitrophenyl selenocyanate afforded the selenide which upon treatment with aqueous hydrogen peroxide underwent oxidation-elimination to provide the required alkene **32**.²⁷



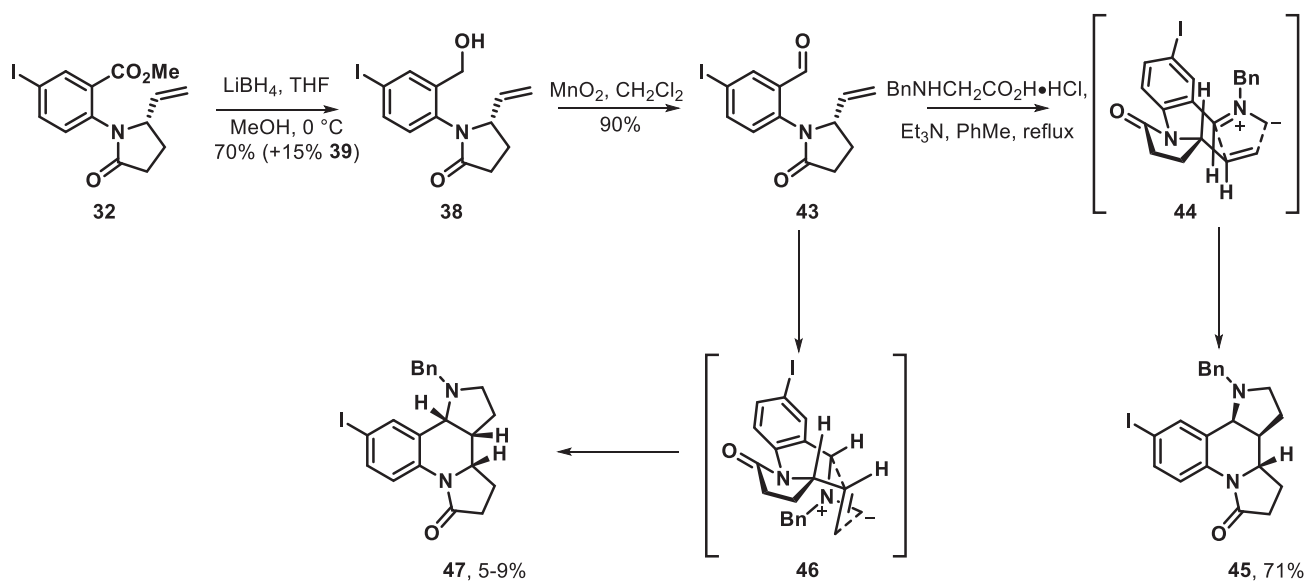
Scheme 5. Second generation approach to **32**

In order to proceed with the synthesis of the martinelline core, one last functional group transformation was necessary, that is, the conversion of the methyl ester to the aldehyde. Experience in model systems suggested that this would be best accomplished by reduction to the alcohol and then re-oxidation. An initial attempt to accomplish this chemistry was made with LiBH_4 and while the required alcohol **38** was obtained, the major product **39** was derived from reduction of the ester and reductive ring-opening of the lactam (Scheme 6). Attempts to engage the benzaldehyde **40** derived from **38** by MnO_2 oxidation in cycloaddition or to protect the aniline nitrogen were unsuccessful and so it was necessary to find a way to optimize the preparation of **38**. Hydrolysis of the methyl ester to the corresponding acid **41** was readily accomplished but the resulting acid did not undergo direct reduction with for example with *in situ* generated borane. Activation of the acid as the mixed anhydride **42** with *N*-hydroxysuccinimide provided an intermediate that underwent reduction to the required alcohol **38** on exposure to NaBH_4 . While this sequence provided sufficient material to establish the viability of later steps, subsequently we were able to identify conditions that allowed the direct acquisition of **38** from **32** through the use of LiBH_4 but maintaining a reaction temperature of $0\text{ }^\circ\text{C}$ over a 20 – 24 h period, although even under these conditions, some reductive cleavage of the lactam to produce **39** was observed.

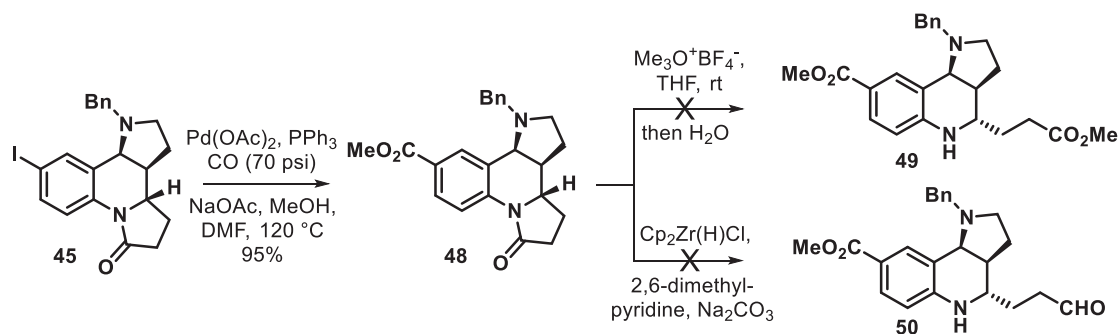


Scheme 6. Chemoselective reduction of the methyl ester

Oxidation of the benzylic alcohol was readily achieved through treatment with activated MnO_2 or IBX giving rise to the corresponding benzaldehyde (Scheme 7). Exposure of **43** to *N*-benzylglycine·HCl in the presence of triethylamine in toluene at reflux results in the *in situ* formation of the non-stabilized azomethine ylide, which undergoes rapid [3+2] cycloaddition leading to the formation of two cycloaddition products **45** and **47** in a 6-10:1 ratio. Chromatographic separation of the two adducts delivers the required cycloadduct **45** in 71% yield along with the minor diastereomer **47**. X-Ray crystallographic analysis of the major cycloadduct clearly reveals that it possesses the appropriate stereochemistry for application to the *Martinella* framework. Analysis of the two putative transition states **44** and **46** suggests that the major product derives from **44** which minimizes the non-bonded interactions whereas the minor product derives from **46** in which there appear to be non-bonded interactions between the terminal olefin methylene and the lactam ring.

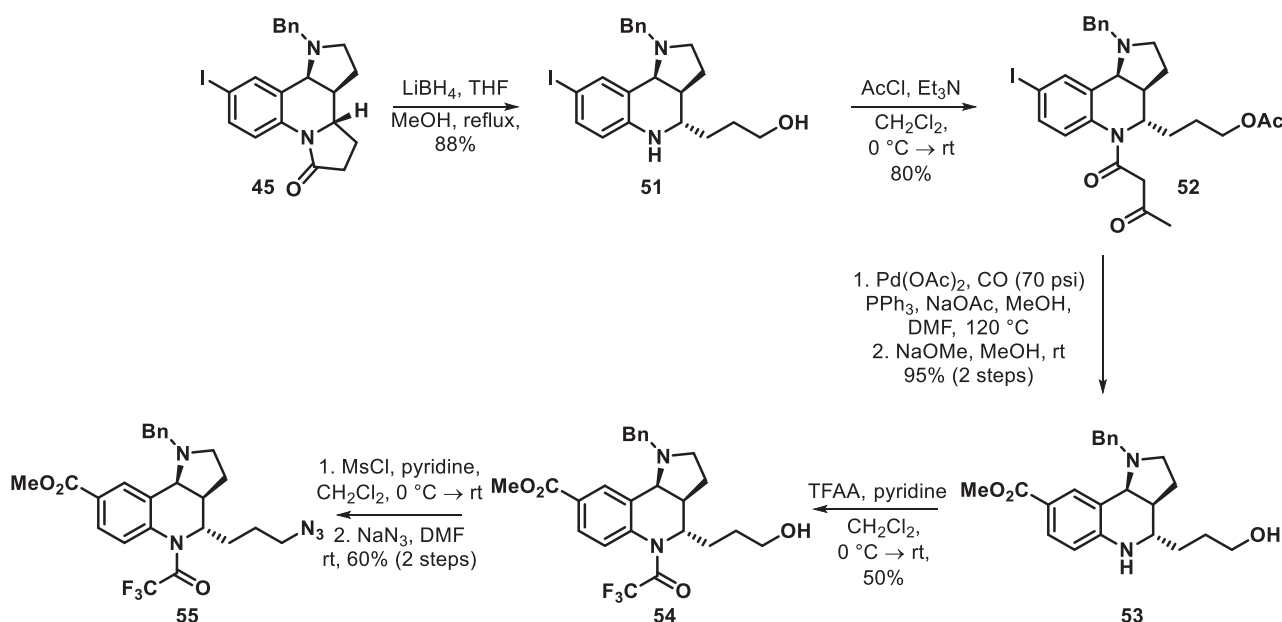


Scheme 7. Construction of the complete heterocyclic core of the *Martinella* alkaloids



Scheme 8. First generation attempts to elaborate the core

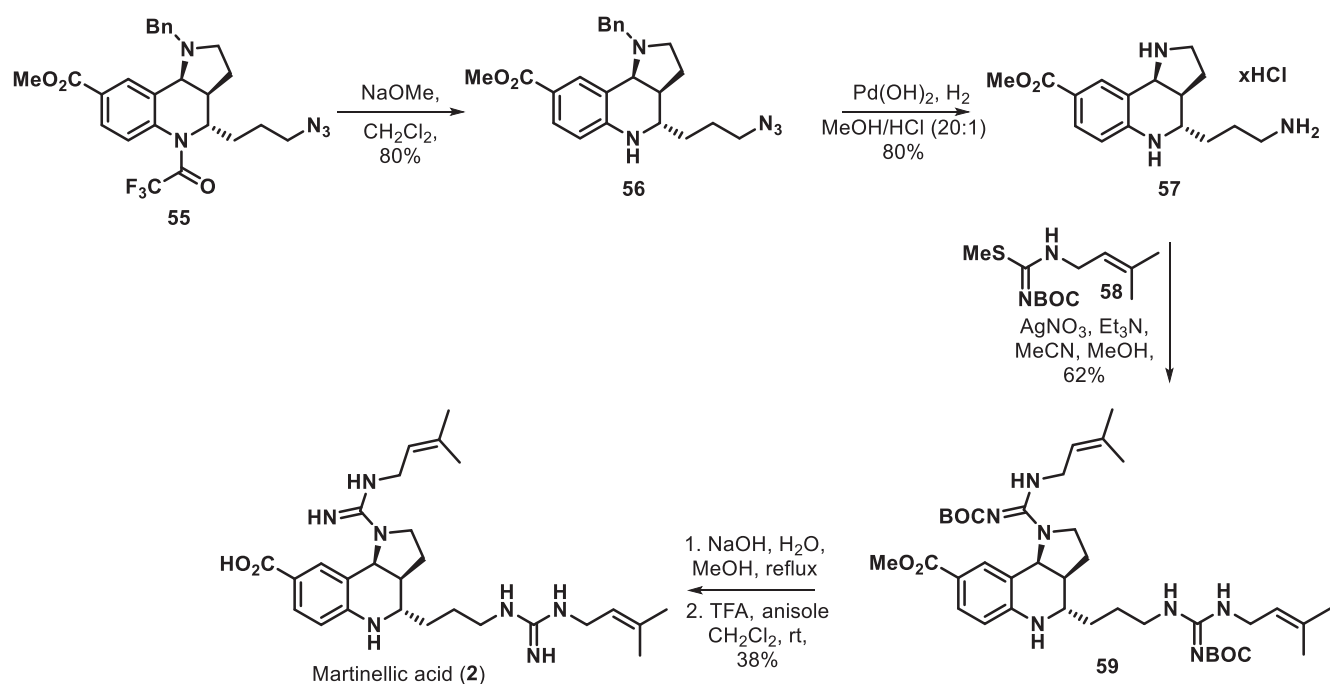
With quantities of the key cycloadduct **45** in hand, we were now in a position to investigate elaboration to the natural product target. Carbonylation of the aryl iodide proceeded uneventfully using conditions previously developed in our group for carboxymethylation of pyrroloquinolines to produce **48** (Scheme 8). Unfortunately, our efforts elaborate the lactam were unsuccessful, for example attempts to prepare and hydrolyze the imidate or cleave the lactam reductively with Schwartz reagent failed to produce the desired compounds **49** and **50**. It is worth noting that Naito and coworkers were able to cleave the lactam reductively in a related substrate after we completed our synthesis. At this point we decided to adapt the sequence reported by Snider and coworkers for elaborating a related (bromide rather than iodide), but racemic, cycloadduct.



Scheme 9. Elaboration of core

Reductive cleavage of the lactam in **45** was accomplished through treatment with LiBH_4 in a mixture of refluxing THF and methanol and was quite slow, requiring four days for complete reaction, but provided

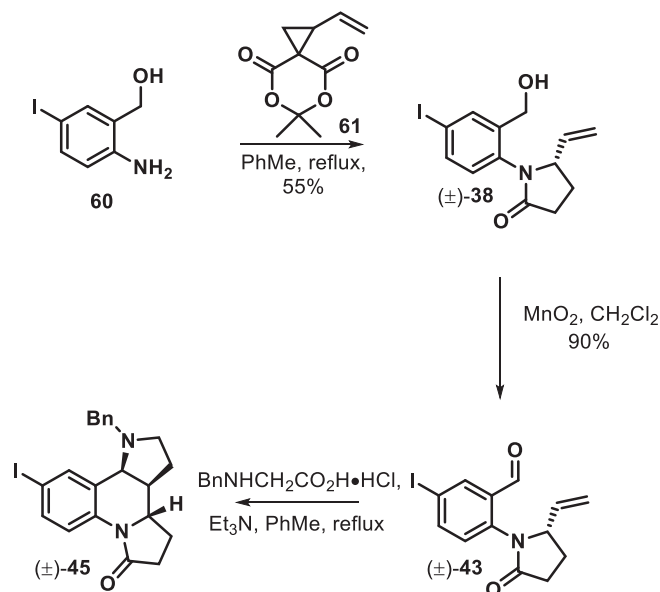
the amino alcohol **51** in excellent yield (Scheme 9). Protection of the alcohol and quinoline nitrogen as the acetate was planned, but rather than a simple acetamide, the β -dicarbonyl **52** was formed. Fortunately this was suitable for the carbonylation reaction which proceeded according to plan, although it was accompanied by some methanolysis of the acetate and so the crude reaction mixture was treated with NaOMe to complete the removal of the protecting groups to afford **53**. Protection of the quinoline nitrogen as the trifluoroacetamide allowed activation of the primary alcohol as the mesylate and azide displacement then delivered **55** (Scheme 9).



Scheme 10. Completion of the synthesis

The final stages of the synthesis were relatively straightforward involving amide methanolysis followed by reduction of the azide to the corresponding amine and reductive debenylation; these latter two transformations were performed simultaneously on exposing **56** to hydrogen in the presence of Pearlman's catalyst to afford **57** (Scheme 10). **57** (or very closely related analog) has been a late stage intermediate in all total syntheses reported to date. Introduction of the two guanidine moieties was performed using Ma's procedure involving the silver mediated addition of isothiourrea **58**, although for good yields in this transformation we used longer reaction times. Saponification of the methyl ester and deprotection of the BOC moieties with TFA gave martinelliac in 38% yield for the two steps. The thus obtained material was identical spectroscopically to both the naturally occurring material and synthetic versions. However, the specific rotation for our synthetic material $[\alpha]_D^{20}$ -28.8 (*c* 0.32, MeOH) was different from both the natural material $[\alpha]_D^{20}$ -8.5 (*c* 0.01, MeOH) and synthetic materials

($[\alpha]_D^{20}$ -118 (*c* 0.3, MeOH);⁶ $[\alpha]_D^{20}$ -112.7 (*c* 0.31, MeOH);²⁸ $[\alpha]_D^{29}$ -164.3 (*c* 0.14, MeOH);²⁹ -164.8 (*c* 0.33, MeOH)).³ Our initial reaction to this observation was that our material was scalemic. On analyzing the synthetic sequence, there is only one transformation where racemization can occur reasonably after the cross-coupling chemistry,³⁰ and that is in the cycloaddition step. Racemization of the vinyl pyrrolidinone would lead to racemic product, whereas racemization after this step would require inversion of multiple stereocenters and therefore is unlikely.



Scheme 11. Preparation of racemic cycloaddition precursor and cycloadduct

In order to address this possibility the stereochemical homogeneity of both the cycloaddition precursor **43** and cycloadduct **45** had to be established and therefore we prepared the corresponding racemic materials. Rather than repeat our chemistry, acquisition of the requisite racemic compounds was accomplished through repetition of Snider's chemistry except with the iodoaniline derivative.²⁰ Reaction of aniline **60** with the vinylcyclopropane derivative **61** leads directly to the racemic benzyl alcohol derivative **(±)-38** (Scheme 11). Oxidation with MnO₂ provides **(±)-43** and cycloaddition in the presence of *N*-benzylglycine hydrochloride delivers the corresponding racemic cycloadduct **(±)-45**. In our earlier studies we had used ¹H NMR spectroscopy and Pirkle's reagent **62**³¹⁻³⁴ as a chiral solvating agent to establish the stereochemical homogeneity in the cross-coupling reactions.²³⁻²⁴ We again resorted to this approach in the present context; typically two equivalents of **62** were added to a chloroform solution of the racemic and non-racemic precursors and cycloadducts (Figure 4). These experiments show clearly that racemization does not occur at any stage prior to or during cycloaddition and thus it is reasonable to conclude that the samples of synthetic martinellidic acid prepared in the course of these studies are close to enantiomerically pure. It is not clear why different specific rotations were obtained for synthetic

samples both in a general sense and in comparison to the natural sample. In all cases, the sign of the rotation is the same but the magnitude varies; these are highly polar molecules and it is conceivable that varying amounts of TFA used as part of the eluent during the final purification is leading to this variance or in our case the presence of impurities. It is also worth noting that **59** (Scheme 10), which is identical to Ma's intermediate, had an identical specific rotation and was comparable to those obtained in other asymmetric syntheses.

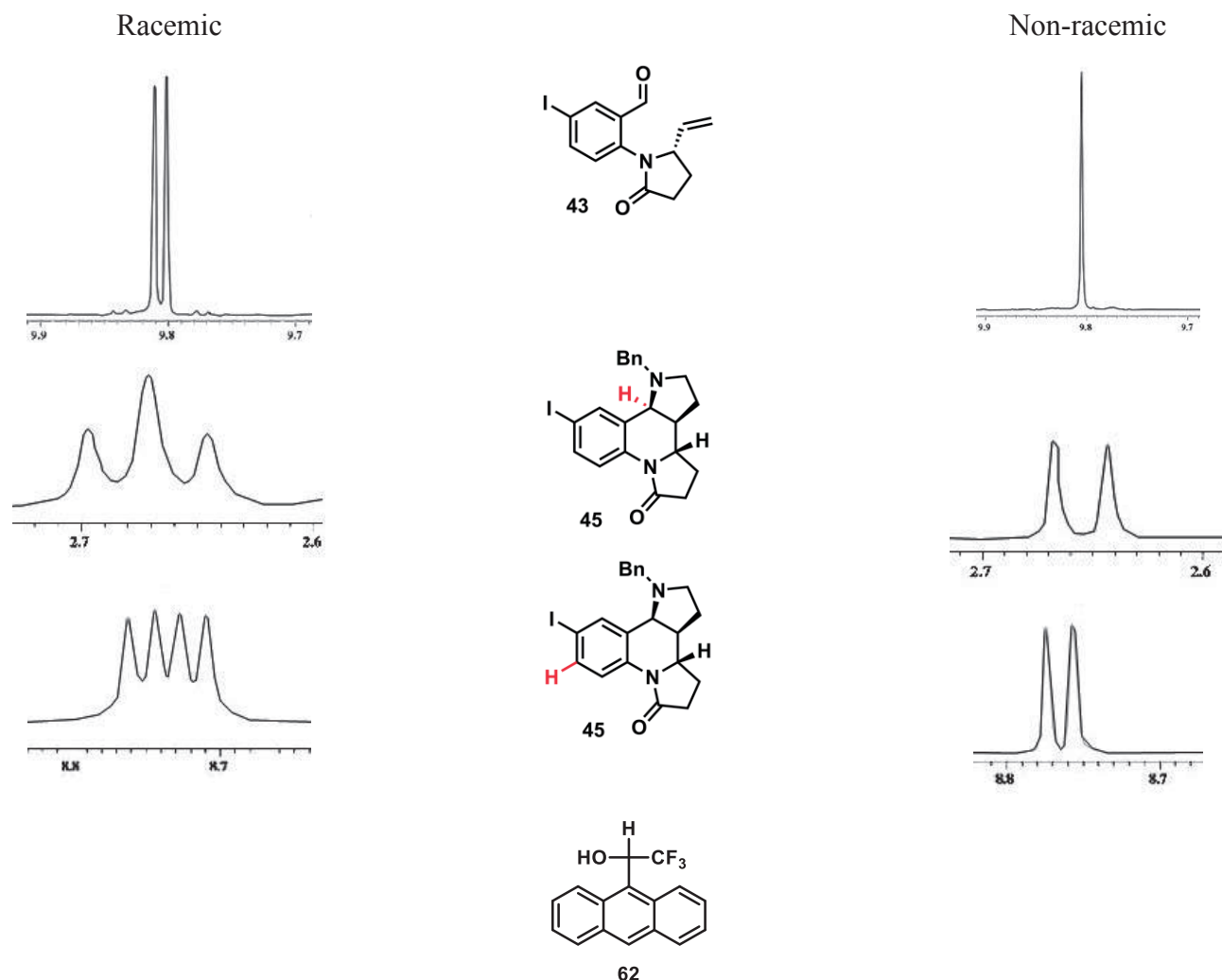


Figure 4. Analysis ^1H NMR spectroscopy of enantiomeric composition of racemic (left) and non-racemic substrates (right) in the presence of two equivalents of Pirkle's reagent (**62**) in CDCl_3 .

In summary, we have developed an asymmetric total synthesis of the pyrrolo[3,2-*c*]quinoline natural product martinellie acid from pyrroglutamic acid. Key steps in the synthetic sequence include a Pd-catalyzed aryl amination reaction for introduction of substituted pyrrolidinones; an intramolecular [3+2] cycloaddition of a non-stabilized azomethine ylide with an alkene. We also demonstrate the utility

of Pirkle's reagent for establishing the enantiomeric purity of a number of complex synthetic intermediates.

EXPERIMENTAL

General procedures: All reagents were purchased from commercial suppliers and were used as received unless otherwise noted. Solvents were dried by distillation over appropriate drying agents: tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone ketyl; benzene and dichloromethane were distilled over calcium hydride or purified using Pure Solv SPS-400-5 solvent purification system. ^1H and ^{13}C NMR (δ in ppm) spectra were recorded in CDCl_3 (unless otherwise noted) at 500 and 125.8 MHz, respectively; using a JEOL Eclipse+ 500 spectrometer unless otherwise noted using residual CHCl_3 as reference (^1H NMR and carbon absorption of CDCl_3 for ^{13}C NMR). Infrared spectra were recorded either as neat films or as KBr pellets using a Bruker Vector 22 spectrometer. Electron impact mass spectra (EI-MS) were obtained with a Finnigan MAT-70 or electrospray mass spectra (ESI-MS) on a Bear Instruments Kodiak spectrometer. Elemental analyses were performed using a Perkin-Elmer 2400 CHN analyzer. Optical rotation was measured on a Perkin-Elmer 241MC polarimeter ($c = \text{g}/100 \text{ mL}$) and the observed value was an average of 2-3 runs. The solvent used for optical rotation is CHCl_3 unless otherwise noted. High resolution mass spectra (HR-MS) were obtained from Dr. Powell's lab in University of Florida, Gainesville, Florida or from HT labs Inc, San Diego, CA.

Methyl-2'-pyrrolidinone 2-iodobenzoic acid (20). CDI (195 mg, 1.2 mmol) was added to a solution of 2-iodobenzoic acid (248 mg, 1.0 mmol) in THF (15 mL) and the resulting mixture stirred at room temperature for 2 h. Lactam **18** (138 mg, 1.2 mmol) and $\text{NaO}i\text{Bu}$ (115 mg, 1.2 mmol) was added and the resulting mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with EtOAc (30 mL), washed with water (2 x 30 mL), sat. brine (30 mL) and then dried (MgSO_4). The organic solution was concentrated and the residue recrystallized from CH_2Cl_2 to afford ester **20** as a colorless solid (218 mg, 63%). mp 86-87 °C. ^1H NMR: δ 7.98 (dd, $J = 7.7, 1.0$ Hz, 1H), 7.80 (dd, $J = 7.8, 1.1$ Hz, 1H), 7.41 (ddd, $J = 15.3, 7.6, 1.1$ Hz, 1H), 4.10-4.05 (m, 1H), 2.45-2.29 (m, 3H), 1.96-1.89 (m, 1H); ^{13}C NMR: δ 178.0, 166.2, 141.3, 134.6, 133.0, 131.2, 128.0, 93.9, 68.1, 52.7, 29.5, 23.2. FT-IR (KBr, cm^{-1}) 3188, 3089, 1731, 1688, 1245, 746; EIMS (m/z): 345.0 (12, M^+), 203.1 (100). Anal. Calcd for $\text{C}_{12}\text{H}_{12}\text{INO}_3$: C, 41.76, H, 3.50; N, 4.06. Found: C, 41.51; H, 3.23; N, 3.93.

Methyl 5-nitro-2-[(5S)-5-[(*tert*-butyl)dimethylsilyloxy]]-2-oxo-1-pyrrolidinyl]benzoate (28). A 10 mL Schlenk tube containing lactam **27** (0.278 g, 1.2 mmol), Cs_2CO_3 (0.456 g, 1.4 mmol), xantphos (88 mg, 0.15 mmol), and $\text{Pd}_2(\text{dba})_3$ (46 mg, 0.05 mmol) was alternately evacuated and backfilled with nitrogen. Dioxane (1.0 mL) and methyl 5-nitro-2-bromobenzoate (**26**) (0.26 g, 1.0 mmol) were introduced and then resulting mixture was heated at 105 °C for 10 h. The mixture was cooled, diluted with CH_2Cl_2 and then

filtered through a pad of Celite. After concentration, the residue was purified by flash chromatography (SiO₂, 1:1 hexane/EtOAc) to give pale orange crystals of the *N*-arylpyrrolidinone **28** (0.27 g, 66%). mp 76-78 °C. $[\alpha]_D^{20}$ 0.00 (*c* 0.66); ¹H NMR δ = 8.77 (d, *J* = 2.7 Hz, 1H), 8.36 (dd, *J* = 8.7, 2.7 Hz, 1H), 7.51 (d, *J* = 8.7 Hz, 1H), 4.28 (m, 1H), 3.91 (s, 3H), 3.66 (dd, *J* = 11.0, 4.6 Hz, 1H), 3.61 (dd, *J* = 11.0, 4.1 Hz, 1H), 2.61 (m, 1H), 2.51 (m, 1H), 2.35 (m, 1H), 2.03 (m, 1H), 0.78 (s, 9H), -0.059 (s, 3H) -0.06 (s, 3H); ¹³C NMR δ = 175.7, 164.4, 145.9, 143.8, 129.9, 129.6, 127.1, 126.6, 64.3, 62.8, 52.9, 30.9, 25.7, 21.9, 18.1, -5.6; FT-IR (KBr, cm⁻¹): 2918, 1773, 1762, 1347, 749. ESI-MS (*m/z*): 431 (M+Na⁺, 100), 409 (M+H⁺, 37), 377 (23). Anal. Calcd for C₁₉H₂₈N₂O₆Si: C, 55.86; H, 6.91; N, 6.86. Found: C, 55.70; H, 7.05; N, 7.05.

Methyl 5-amino-2-[(5*S*)-5-[(*tert*-butyl)dimethylsilyloxy]-2-oxo-1-pyrrolidinyl]benzoate (29). In a 25 mL round bottom flask were placed the *N*-arylpyrrolidinone **28** (0.27 g, 0.66 mmol), and 10% palladium on charcoal (27 mg). The flask was alternatively evacuated and backfilled with hydrogen. MeOH (4.0 mL) was introduced and the mixture was stirred at room temperature under a balloon of hydrogen gas (1 atm) for 16 h. The mixture was filtered through a Celite pad. After concentration, the residue was purified by flash chromatography (SiO₂, 1:4 hexane/EtOAc) to give pale yellow crystals of the amine **29** (0.24 g, 97%). mp 137-139 °C. $[\alpha]_D^{20}$ -37.3 (*c* 0.85); ¹H NMR δ = 7.26 (d, *J* = 2.7 Hz, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 6.79 (dd, *J* = 8.2, 2.7 Hz, 1H), 3.97 (m, 1H), 3.81 (s, 3H), 3.57 (dd, *J* = 10.5, 4.1 Hz, 1H), 3.50 (dd, *J* = 10.5, 2.7 Hz, 1H), 2.56 (m, 1H), 2.44 (m, 1H), 2.26 (m, 1H), 2.05 (m, 1H), 0.86 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ¹³C NMR δ = 176.7, 165.9, 146.1, 128.9, 128.1, 119.1, 117.5, 63.2, 62.7, 52.2, 30.9, 25.9, 21.9, 18.2, -5.4, -5.5; FT-IR (KBr, cm⁻¹): 3457, 3355, 2953, 2856, 1719, 1670, 1328, 1233, 837, 775. ESI-MS (*m/z*): 401 (M+Na⁺, 90), 379 (M+H⁺, 100), 347 (59). Anal. Calcd for C₁₉H₃₀N₂O₄Si: C, 60.29; H, 7.99; N, 7.40. Found: C, 59.98; H, 8.22; N, 7.54.

Methyl 5-iodo-2-[(5*S*)-5-{hydroxymethy}-2-oxo-1-pyrrolidinyl]benzoate (30). The amine **29** (0.20 g, 0.54 mmol) was taken up in MeCN (1.8 mL) and CH₂I₂ (0.20 mL, 2.48 mmol) and *n*-pentyl nitrite (0.52 mL) were added. The solution was purged with nitrogen for 15 min and heated to 85-90 °C for 22 h under nitrogen. The reaction mixture was cooled to room temperature followed by the addition of TBAF solution (1.0 M, 0.54 mL, 0.54 mmol) in THF. The resulting mixture was stirred at room temperature for 7 h, quenched with water, and extracted with EtOAc. The organic phase was washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo to give a dark orange oil. The crude product was purified by flash chromatography (SiO₂, 0.5:9.5 MeOH/EtOAc) to give pale yellow crystals of **30** (0.16 g, 81%). mp 142-144 °C. $[\alpha]_D^{20}$ -149.1 (*c* 0.61). ¹H NMR δ = 8.11 (d, *J* = 1.8 Hz, 1H), 7.85 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 4.31 (m, 1H), 3.90 (s, 3H), 3.75 (dt, *J* = 12.8, 2.3 Hz, 2H), 3.46 (td, *J* = 12.1, 1.8 Hz, 2H), 2.68 (m, 1H), 2.49 (m, 1H), 2.31 (m, 2H); ¹³C NMR δ = 175.0, 167.3, 141.6, 139.1, 135.6, 131.2, 127.1, 91.1, 62.7, 53.5, 31.9, 20.6; FT-IR

(KBr, cm^{-1}): 3466, 3066, 2966, 2883, 2118, 1700, 1667, 832, 781, 561. ESI-MS (m/z): 398 ($\text{M}+\text{Na}^+$, 56), 376 ($\text{M}+\text{H}^+$, 16), 344 (100). Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{INO}_4$: C, 41.62; H, 3.76; N, 3.73. Found: C, 41.90; H, 4.08; N, 3.67.

Methyl (S)-5-oxo-2-pyrrolidineacetate (33). The nitrile³⁵ (8.50 g, 68.0 mmol) was dissolved in MeOH (68 mL). Sulfuric acid (13.8 mL) was added slowly to the nitrile solution. Then the reaction mixture was heated at reflux for 96 h. The reaction mixture was cooled in an ice bath followed by addition of cold water (13.8 mL) and neutralized with solid K_2CO_3 with small portions of sat. aq. K_2CO_3 added to maintain a thick solution. Once the pH reached 7.0 the neutralized reaction mixture was filtered and extracted with CH_2Cl_2 (3 x 300 mL). The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. The dried organic layer was concentrated to provide **33** (5.90 g, 55%) as a colorless oil which was used directly in the next step. ^1H NMR δ = 6.41 (br, 1H), 4.01-3.97(m, 1H), 3.69 (s, 3H), 2.60-2.56 (dd, J = 16.7, 4.0 Hz, 1H), 2.50-2.44 (dd, J = 16.7, 9.2 Hz, 1H) 2.35-2.29 (m, 3H), 1.74-1.68 (m, 1H); ^{13}C NMR δ = 177.8, 171.8, 52.0, 51.7, 50.5, 40.9, 30.8, 29.7, 26.8.

(5S)-5-(tert-Butyldimethylsilyloxyethyl)-2-pyrrolidinone (34). Sodium borohydride (3.50 g, 92.0 mmol) was added portionwise to a solution of the ester **33** (5.90 g, 37.0 mmol) in dry EtOH (200 mL) at room temperature. After 50 h, acetone (10 mL) was added and the solution stirred for another 0.5 h. The mixture was acidified using concentrated hydrochloric acid with cooling, not permitting the pH to fall below 3.5. The solvent was evaporated and the residue was purified by flash chromatography (SiO_2 , 4:1 EtOAc/MeOH) to give (4.40 g, 92%) of the desired alcohol as a clear oil. $[\alpha]_D^{20}$ +32.7 (c 0.33 MeOH). ^1H NMR (D_2O) δ = 3.84-3.80 (quint, 6.9 Hz, 1H), 3.68-3.65 (t, J = 6.4 Hz, 2H), 2.40-2.35 (ddd, 7.3, 2.8 Hz, 2H), 2.34-2.26 (m, 1H), 1.84-1.70 (m, 3H); ^{13}C NMR δ = 181.5, 58.7, 52.7, 37.7, 29.9, 26.4; FT-IR (neat, cm^{-1}): 3270, 2937, 1676. HR-MS: Calcd. for $\text{C}_6\text{H}_{11}\text{NO}_2\text{Na}$ (m/z): 152.0682 [$\text{M}+\text{Na}$]⁺, found 152.0685. TBSCl (7.80 g, 51.8 mmol) was added portionwise to a stirred solution of the above alcohol (4.40 g, 34.0 mmol), DMAP (1.98 g, 8.18 mmol) and imidazole (4.70 g, 74.0 mmol) in DMF (22.8 mL). The mixture was stirred for 16 h at which point of EtOAc (100 mL) was added. The solution was washed with water and brine, dried with Na_2SO_4 and evaporated. The product was purified via flash column chromatography (SiO_2 , 100% EtOAc) to give (7.60 g, 92%) of the desired product as a white solid. $[\alpha]_D^{20}$ +26.2 (c 1.1). ^1H NMR δ = 6.43 (br, 1H), 3.72-3.70 (m, 3H), 2.27-2.20 (m, 3H), 1.67-1.64 (m, 3H), 0.82 (s, 9H), -0.01 (s, 6H); ^{13}C NMR δ = 171.9, 61.5, 53.6, 39.2, 30.1, 28.0, 26.0, 25.0, 18.3, -5.3, -5.4; FT-IR (KBr, cm^{-1}): 3104, 1731, 1604, 1348, 1251. HR-MS: Calcd for $\text{C}_{12}\text{H}_{26}\text{NO}_2\text{Si}$ (m/z): 244.1727 [$\text{M}+\text{H}$]⁺, found 244.1723.

Methyl 5-nitro-2-[(5S)-5-[(tert-butyl)dimethylsilyloxyethyl]-2-oxo-1-pyrrolidinyl]benzoate (35). A 10 mL Schlenk tube containing lactam **34** (2.92 g, 12.0 mmol), Cs_2CO_3 (4.56 g, 14.0 mmol), xantphos (0.88 g, 1.5 mmol), and $\text{Pd}_2(\text{dba})_3$ (0.46 g, 0.5 mmol) was alternately evacuated and backfilled with

nitrogen. Dioxane (10 mL) and methyl 5-nitro-2-bromobenzoate (**26**) (2.60 g, 10.0 mmol) were introduced and then resulting mixture was heated at 105 °C for 10 h. The mixture was cooled, diluted with CH₂Cl₂ and then filtered through a pad of Celite. After concentration, the residue was purified by flash chromatography (SiO₂, 1:1 hexane/EtOAc) to give the *N*-arylpyrrolidinone **35** (2.11 g, 55%) as a pale orange oil; unreacted lactam (1.0 g, 35%) was recovered. $[\alpha]_D^{20}$ 0.00. ¹H NMR δ = 8.72 (d, *J* = 2.8 Hz, 1H), 8.36 (dd, *J* = 8.7, 2.8 Hz, 1H), 7.36 (d, *J* = 8.7 Hz, 1H), 4.48 (m, 1H), 3.90 (s, 3H), 3.64-3.60 (m, 2H), 2.58-2.53 (m, 2H), 2.47-2.43 (m, 1H), 1.99-1.97 (m, 1H), 1.91-1.89 (m, 1H), 1.71-1.65 (m, 1H), 0.86 (s, 9H), -0.01 (s, 3H), -0.02 (s, 3H); ¹³C NMR δ = 174.9, 164.9, 145.3, 142.6, 129.9, 127.1, 126.9, 126.4, 59.2, 58.4, 52.9, 36.9, 31.0, 25.9, 25.3, 18.3, -5.4; FT-IR (neat, cm⁻¹): 2951, 1733, 1528, 1343, 1102, 836. HR-MS: Calcd for C₂₀H₃₂N₂O₆Si (*m/z*): 423.1946, [M+H]⁺, found 423.1945.

Methyl 5-amino-2-[(5*S*)-5-[(*tert*-butyl)dimethylsilyloxyethyl]-2-oxo-1-pyrrolidinyl]benzoate (36**).**

In a 25 mL round bottom flask were placed **35** (2.11 g, 5.40 mmol) and 10% palladium on charcoal (0.21 g). The flask was alternatively evacuated and backfilled with hydrogen. MeOH (40 mL) was introduced and the mixture was stirred at room temperature under a balloon of hydrogen gas (1 atm) for 24 h. The mixture was filtered through a Celite pad. After concentration, the residue was purified by flash chromatography (SiO₂, 100% EtOAc) to give pale yellow crystals of the amine (1.74 g, 89%). mp 100-102 °C. $[\alpha]_D^{20}$ -39.3 (*c* 0.65). ¹H NMR δ = 7.26 (d, *J* = 2.8 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 1H), 6.80 (dd, *J* = 8.7, 2.8 Hz, 1H), 4.11-4.09 (m, 1H), 3.82 (s, 3H), 3.58-3.57 (m, 2H), 2.51-2.48 (m, 2H), 2.38-2.34 (m, 1H), 1.87-1.83 (m, 2H), 1.61-1.56 (m, 1H), 0.84 (s, 9H), -0.01 (s, 3H), -0.03 (s, 3H); ¹³C NMR δ = 175.8, 166.1, 145.9, 129.1, 127.9, 118.9, 117.5 (2C), 59.9, 59.8, 52.3, 37.2, 30.9, 25.9, 18.2, -5.4, -5.5; FT-IR (neat cm⁻¹): 3451, 3376, 2955, 1721, 1667, 1508, 1446, 1243, 1094. HR-MS Calcd for C₂₀H₃₂N₂O₄Si (*m/z*): 415.2024, [M+H]⁺, found 415.2012. Anal. Calcd for C₂₀H₃₂N₂O₄Si: C, 61.19; H, 8.22; N, 7.14. Found: C, 60.79; H, 7.87; N, 7.20.

Methyl 5-iodo-2-[(5*S*)-5-(hydroxyethyl)-2-oxo-1-pyrrolidinyl]benzoate (37**).** Amine **36** (1.65 g, 4.15 mmol) was taken up in MeCN (29 mL). CH₂I₂ (3.20 mL, 2.48 mmol) and *n*-pentyl nitrite (7.7 mL) were added. The solution was purged with nitrogen for 15 min and heated to 85-90 °C for 22 h under nitrogen. The reaction mixture is cooled to room temperature followed by addition of 1.0 M TBAF (10 mL) in THF. The reaction was stirred at room temperature for 7 h, quenched with water, and extracted with EtOAc. The organic phase was washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo to give dark orange oil. The crude product was purified by flash chromatography (SiO₂, 0.5:9.5 methanol/EtOAc) to give pale yellow crystals (1.11 g, 68%) of **37**. mp 135-137 °C. $[\alpha]_D^{20}$ -67.3 (*c* 0.81). ¹H NMR δ = 8.22 (d, *J* = 2.3 Hz, 1H), 7.84 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 4.32-4.29 (m, 1H), 3.84 (s, 3H), 3.63-3.58 (m, 2H), 2.52-2.45 (m, 2H), 2.41-2.38

(m, 1H), 1.93-1.87 (m, 2H), 1.74-1.69 (m, 1H); ^{13}C NMR δ = 175.2, 165.2, 141.6, 140.0, 136.9, 130.5, 129.3, 91.6, 58.9, 58.4, 52.7, 36.4, 30.9, 25.3; FT-IR (neat cm^{-1}): 3466, 2945, 1730, 1664, 1580, 1480, 1438. EIMS (m/z): 389 (M^+ , 68), 357 (53), 344 (100), 312 (84), 243 (39). Anal. Calcd for $\text{C}_{14}\text{H}_{16}\text{INO}_4$: C, 43.21; H, 4.14; N, 3.60. Found: C, 43.47; H, 4.10; N, 3.54.

Methyl 5-iodo-2-[(5*S*)-5-(ethenyl)-2-oxo-1-pyrrolidinyl]benzoate (32). Alcohol **37** (1.1 g, 2.8 mmol) and *o*-nitrophenyl selenocyanate (1.2 g, 5.4 mmol) were taken up in THF (8.5 mL). PBu_3 (2.4 mL, 9.5 mmol) was added dropwise by syringe. TLC showed no starting material after 1 h, at which point the reaction mixture was cooled to 0 °C and 30% H_2O_2 (1.5 mL, ca. 5.0 equiv.) was added dropwise. TLC showed no change for 5 min at 0 °C and so an additional portion of 30% H_2O_2 (1.5 mL, ca. 5.0 equiv.) was added and the reaction was stirred at room temperature for 7 h. EtOAc was added and the organic layer was washed with saturated sodium hydrogen carbonate. The aqueous phase was then extracted twice with EtOAc. The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate followed by concentration. The crude product was purified via flash column chromatography (SiO_2 , 100% EtOAc) to give **32** (0.89 g, 85%) as a pale yellow solid. mp 99-101 °C. $[\alpha]_D^{20}$ +12.7 (*c* 0.65). ^1H NMR δ = 8.23 (d, J = 1.8 Hz, 1H), 7.81 (dd, J = 8.7, 2.3 Hz, 1H), 6.85 (d, J = 8.7 Hz, 1H), 5.80-5.76 (m, 1H), 5.13-5.07 (dd, J = 17.0, 4.5 Hz, 2H), 4.52 (q, J = 8.7 Hz, 1H), 3.86 (s, 3H), 2.56-2.52 (m, 2H), 2.47-2.42 (m, 1H), 1.98-1.94 (m, 1H); ^{13}C NMR δ = 175.4, 164.9, 141.4, 140, 137.7, 137.2, 130.4, 118.9, 91.8, 64.7, 52.6, 30.9, 26.7; FT-IR (KBr cm^{-1}): 3065, 2947, 1729, 1695, 1581, 1556, 1481, 1456. ESI-MS (m/z): 394 ($\text{M}+\text{Na}^+$, 84), 372 ($\text{M}+\text{H}^+$, 13), 340 (100). Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{INO}_3$: C, 45.30; H, 3.80; N, 3.77. Found: C, 45.29; H, 3.69; N, 3.70.

(5*S*)-5-Ethenyl-1-[4-iodo-2-(hydroxymethyl)phenyl]-2-pyrrolidinone (38) via *N*-hydroxysuccinimide.

Methyl ester **32** (0.70 g, 1.88 mmol) was dissolved in THF (4.5 mL) followed by addition of an aqueous solution of 1 M LiOH (7.0 mL). The reaction mixture was stirred for 16 h at room temperature, then the reaction mixture was quenched with water and the aqueous layer was extracted with EtOAc (3 x 20 mL). The aqueous layer was then acidified with 1 N HCl until the pH reached 7.0. The acidified solution was extracted with EtOAc (3 x 30 mL), dried over anhydrous sodium sulfate and concentrated to give **41** (1.00 g, 99%) as a pale yellow oil which was used in the next step. ^1H NMR δ = 8.29 (d, J = 1.8 Hz, 1H), 7.82 (dd, J = 8.7, 1.8 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 5.81-5.78 (m, 1H), 5.09 (dd, J = 17.0, 4.5 Hz, 2H), 4.53 (q, J = 7.8 Hz, 1H), 2.64 (t, J = 9.2 Hz, 2H), 2.01-1.94 (m, 1H); ^{13}C NMR δ = 177.2, 167, 141.7, 140.5, 137.4, 136.9, 130.4, 119.3, 65.4, 31.0, 26.7; FT-IR (neat, cm^{-1}): 3000, 2918, 2850, 1708, 1649, 1481, 1415.

Acid **41** (1.00 g, 2.90 mmol) was dissolved in EtOAc (13.3 mL) and cooled in an ice-bath. *N*-Hydroxysuccinimide (0.40 g, 3.48 mmol) was added followed by addition of DCC (0.71 g, 3.44 mmol). The reaction mixture was stirred at 0 °C for 10-15 min and at room temperature for 12 h. After 12 h the

white precipitate was filtered through Celite and washed with EtOAc (100 mL). The combined organic extracts were washed with saturated sodium hydrogen carbonate (2 x 30 mL) followed by saturated sodium chloride (2 x 30 mL). The organic solution was dried and concentrated to give a yellow oil (1.21 g, 95%). To a stirred solution of **42** (1.21 g, 2.76 mmol) in THF (5.5 mL) was added NaBH₄ (0.13 g, 3.43 mmol) at 0 °C. After 5 min EtOH (1.5 mL) was added to the reaction mixture and then stirred for 11 h at room temperature. The reaction mixture was then quenched by addition of saturated ammonium chloride and diluted with water. The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organic extract was dried over sodium sulfate and concentrated to give yellow oil (SiO₂, 4:1 EtOAc/hexane) to give (0.69 g, 73%) of the product as colorless oil.

(5S)-5-Ethenyl-1-[4-iodo-2-(hydroxymethyl)phenyl]-2-pyrrolidinone (38) via direct reduction.

N-Arylpyrrolidinone **32** (0.62 g, 1.70 mmol) was dissolved in dry THF (6.2 mL). This solution was purged with nitrogen and cooled in an ice-bath to 0 °C followed by addition of anhydrous MeOH (0.1 mL, 1.5 mmol). LiBH₄ (1.0 mL, 2 M in THF) was added to this mixture dropwise and the resulting mixture is stirred at 0 °C. The reaction was closely monitored by TLC (3:2 EtOAc/CH₂Cl₂) and another portion LiBH₄ (1.0 mL) was added after 16 h. After 20 h from the start of the reaction, it was quenched by the addition of saturated ammonium chloride (20 mL) and the resultant solution was extracted with EtOAc (3 x 50 mL). The organic extracts were washed once with saturated sodium chloride, dried over anhydrous sodium sulfate and concentrated. The resulting yellow oil was purified via flash column chromatography (SiO₂, 4:1 EtOAc/hexane) to give **38** (0.43 g, 70%) of the product as colorless oil. $[\alpha]_D^{20} +32.6$ (*c* 0.30). ¹H NMR δ = 7.87 (d, *J* = 1.8 Hz, 1H), 7.63 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 5.62-5.55 (m, 1H), 5.08 (dd, *J* = 17.9, 10.5 Hz, 2H), 4.51-4.46 (m, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 4.31 (d, *J* = 12.0 Hz, 1H), 2.65-2.57 (m, 2H), 2.48-2.44 (m, 1H), 2.01-1.97 (m, 1H); ¹³C NMR 176.2, 140.9, 139.9, 137.8, 136.5, 135.1, 119.6, 93.5, 65.1, 61.2, 30.9, 26.6; FT-IR (neat cm⁻¹) 3389, 2981, 1683, 1559, 1405. ESI-MS (*m/z*): 366 (M+Na⁺, 100), 326 (M+H⁺, 50), 268 (12), 214 (13). Anal. Calcd for C₁₃H₁₄INO₂: C, 45.5; H, 4.11; N, 4.08. Found: C, 45.62; H, 4.36; N, 4.10.

The byproduct (**39**) (87 mg, 15%) was isolated as yellow oil. $[\alpha]_D^{20} +0.12$ (*c* 1.0). ¹H NMR δ = 7.41-7.39 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.30 (d, *J* = 2.3 Hz, 1H), 6.40 (d, *J* = 8.7 Hz, 1H), 5.75-5.7 (dq, *J* = 10.5, 6.0 Hz, 1H), 5.19 (d, *J* = 17.0 Hz, 1H), 5.12 (d, *J* = 10.5 Hz, 1H), 4.57 (d, *J* = 3.7 Hz, 2H), 3.82-3.80 (m, 1H), 3.65-3.63 (dd, *J* = 6.0, 5.5 Hz, 2H), 1.75-1.65 (m, 4H); ¹³C NMR δ = 146.6, 139.4, 137.9, 137.4, 126.7, 115.4, 114.1, 64.2, 62.6, 55.4, 32.1, 29.1; FT-IR (neat cm⁻¹) 3376, 2938, 1575, 1504, 1405. HR-MS: Calcd for C₁₃H₁₉INO₂ (*m/z*): 348.0455 (M+H⁺), found 348.0447.

5-Iodo-2-[(2S)-vinyl-5-hydroxy-1-butylamino]benzaldehyde (40). Diol **39** (80 mg, 0.23 mmol) was dissolved in CH₂Cl₂ (2.5 mL) and 85% activated MnO₂ (129 mg, 1.26 mmol, 5.5 equiv.) was added to this

solution. The slurry was stirred at room temperature for 24 h at which point another portion of MnO₂ (129 mg, 1.26 mmol, 5.5 eq) was added. The reaction mixture was stirred for another 24 h, followed by filtration through Celite. The Celite pad was washed with MeOH and the filtrate was concentrated. The crude was purified by flash column chromatography (SiO₂, 4:1 EtOAc/hexane) to give **40** (79 mg, 90%) as a yellow oil. $[\alpha]_D^{20} +59.3$ (*c* 1.2). ¹H NMR δ = 9.70 (s, 1H), 8.4 (brd, 1H), 7.70 (d, *J* = 2.3 Hz, 1H), 7.53 (dd, *J* = 9.2, 2.3 Hz, 1H), 6.48 (d, *J* = 9.2 Hz, 1H), 5.76-5.71 (dq, *J* = 10.5, 6.0 Hz, 1H), 5.18 (td, *J* = 11.0, 1.4 Hz, 1H), 5.15 (td, *J* = 4.5, 1.4, 0.90 Hz, 1H), 3.97-3.95 (m, 1H), 3.69-3.67 (dd, *J* = 6.4 Hz, 2H), 1.79-1.66 (m, 4H); ¹³C NMR δ = 193.0, 149.5, 144.5, 143.7, 138.2, 120.7, 115.9, 114.6, 62.5, 55.0, 31.7, 28.9; FT-IR (neat, cm⁻¹) 3371, 2941, 1655, 1571, 1503, 1428. HR-MS: Calcd for C₁₃H₁₇INO₂ (*m/z*): 346.0298 [M+H]⁺, found 346.0294.

(5S)-5-Ethenyl-1-[4-iodo-2-formylphenyl]-2-pyrrolidinol (43). A slurry of the alcohol **38** (0.44 g, 1.28 mmol) and 70% activated MnO₂ (0.86 g 5.4 equiv.) in CH₂Cl₂ (12.0 mL) was stirred at 25 °C under N₂ for 24 h. Another portion of MnO₂ (0.86 g, 5.4 mmol) was added and the reaction mixture was allowed to stir for another 24 h. The solution was filtered through Celite, which was washed with MeOH (2 x 20 mL) and the combined filtrates were concentrated. The crude product was purified via flash column chromatography (SiO₂, 4:1 EtOAc/hexane) to give **43** (0.39 g, 90%) as a colorless oil. $[\alpha]_D^{20} -53.0$ (*c* 0.41). ¹H NMR δ = 9.83 (s, 1H), 8.21 (d, *J* = 1.8 Hz, 1H), 7.90 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.9 (d, *J* = 8.3 Hz, 1H), 5.67-5.64 (m, 1H), 5.18 (d, *J* = 16.9, 1H) 5.12 (d, *J* = 10.0 Hz, 1H), 5.70-4.60 (m, 1H), 2.65-2.62 (m, 2H), 2.52-2.48 (m, 1H), 2.02-1.98 (m, 1H); ¹³C NMR δ = 187.9, 175.4, 143.1, 138.9, 138.4, 136.7, 133.5, 128.3, 119.7, 92.4, 64.3, 30.8, 26.6; FT-IR (neat cm⁻¹): 2872, 1701, 1581, 1477, 1397. ESI-MS (*m/z*): 364 (M+Na⁺, 100), 342 (M+H⁺, 72), 314 (37), 248 (35), 187 (11). Anal. Calcd for C₁₃H₁₂INO₂: C, 45.77; H, 3.55; N, 4.11. Found: C, 45.54; H, 3.78; N, 4.11.

(3a*S*,3b*S*,11b*S*)-10-Iodo-1,2,3,3a,4,5,11b-octahydro-1-(phenylmethyl)-6*H*-dipyrrolo[1,2-*a*:3',2'-*c*]-quinolin-6-one (45). Compound **43** (0.24 g, 0.70 mmol) and *N*-benzylglycine hydrochloride (0.25 g, 1.26 mmol, 1.8 equiv.) was dried under the pump for 15 min and then purged with nitrogen. Dry toluene (23 mL) was added followed by addition of Et₃N (0.27 mL, 2.1 mmol, 3 equiv.). The reaction mixture was heated in oil bath at 120 °C for 23 h. After completion of the reaction the toluene was removed by evaporation and the resulting green solid was partitioned between water and EtOAc. The aqueous layer was extracted three times with EtOAc and the combined organic extracts were washed with saturated sodium chloride, dried over anhydrous sodium sulfate and concentrated. The crude brown solid was purified via flash column chromatography (SiO₂, 1:1 EtOAc/hexane) and the resulting solid was recrystallized (3:2 EtOAc/CH₂Cl₂) to provide **45** (0.22 g, 71%) of as an off white crystalline solid. mp 191-193 °C. $[\alpha]_D^{20} -80.9$ (*c* 0.44). ¹H NMR δ = 8.62 (d, *J* = 9.2 Hz, 1H), 7.61-7.59 (dd, *J* = 9.2, 2.0 Hz,

1H), 7.56 (d, $J = 2.0$ Hz, 1H), 7.25-7.21 (m, 5H), 4.28 (d, $J = 12.4$ Hz, 1H), 4.05 (ddd, $J = 17.0, 9.6, 8.0$ Hz, 1H), 3.16 (d, $J = 3.7$ Hz, 1H), 3.12 (d, $J = 12.4$ Hz, 1H), 2.92 (ddd, $J = 9.7, 7.0, 3.7$ Hz, 1H), 2.65-2.59 (m, 1H), 2.56-2.52 (m, 1H), 2.36-2.34 (m, 1H), 2.22-2.17 (m, 1H), 2.06-2.0 (m, 1H), 1.69-1.57 (m, 3H); ^{13}C NMR $\delta = 174.2, 140.2, 139.6, 137.4, 136.9, 128.4$ (2C), 128.3, 127, 126.7 (2C), 121, 85.9, 64, 58.2, 57.2, 51.3, 41.5, 32.3, 24.1, 23.8; FT-IR (KBr, cm^{-1}): 2928, 2785, 1693, 1481, 1367. ESI-MS (m/z): 467 ($\text{M}+\text{Na}^+$, 100), 445 ($\text{M}+\text{H}^+$, 89), 366 (53), 338 (66), 301 (14), 288 (13), 274 (8). Anal. Calcd for $\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}$: C, 56.77; H, 4.76; N, 6.30. Found: C, 56.60; H, 4.80; N, 6.42.

The diastereomer **47** (28 mg, 5%) was isolated. $[\alpha]_D^{20} -64.2$ (c 0.33). ^1H NMR $\delta = 8.18$ (d, $J = 8.9$ Hz, 1H), 7.61 (d, $J = 2.0$ Hz, 1H), 7.51-7.48 (dd, $J = 8.9, 2.0$ Hz, 1H), 7.37-7.28 (m, 5H), 4.11-4.09 (ddd, $J = 7.7, 3.1$ Hz, 1H); 4.00 (d, $J = 8.3$ Hz, 1H), 3.96 (d, $J = 12.8$ Hz, 1H), 3.74 (d, $J = 12.8$ Hz, 1H), 2.84-2.82 (m, 2H), 2.61-2.54 (m, 3H), 2.23-2.19 (m, 1H), 1.98-1.93 (m, 1H), 1.91-1.85 (m, 1H), 1.65-1.61 (m, 1H); ^{13}C NMR $\delta = 173.7, 139.4, 138.6, 129.0, 128.6, 127.4, 121.1, 88.1, 62.5, 60.5, 57.8, 51.9, 41.1, 32.0, 23.7, 22.1$.

(3aS,4S,9bS)-8-Iodo-2,3,3a,4,5,9b-hexahydro-1-(phenylmethyl)-1H-pyrrolo[3,2-c]quinoline-4-propanol (51). The pyrroloquinoline **45** (0.18 g, 0.41 mmol) was dissolved in dry THF (150 mL) followed by addition of MeOH (0.03 mL, 2 equiv.). The solution was degassed with nitrogen and a solution of LiBH_4 (0.19 mL, 2 M in THF) was added dropwise. The reaction mixture was heated in an oil bath at 85-90 °C for 2 days. Additional LiBH_4 (0.19 mL, 2 M in THF) and MeOH (0.03 mL) were added to the refluxing solution every 24 h. After 4 days the reaction mixture was cooled in an ice bath and acidified to pH 4-5 with 1 N hydrochloric acid followed by neutralization with 2 N NaOH. The THF was removed under vacuum. The resulting mixture was dissolved in water and extracted three times with EtOAc. The combined organic solutions were washed with saturated sodium chloride, dried over anhydrous sodium sulfate and concentrated in vacuo. The brown oil was purified via flash column chromatography (SiO_2 , 3:2 EtOAc/hexane) to give **51** (0.15 g, 85%) as an off white solid. mp 39-41 °C. $[\alpha]_D^{20} -84.7$ (c 0.53). ^1H NMR $\delta = 7.36$ (s, 1H), 7.30 (d, $J = 8.3$ Hz, 1H), 7.29-7.18 (m, 5H), 6.38 (d, $J = 8.3$ Hz, 1H) 4.28 (d, $J = 12.0$ Hz, 1H), 3.70 (d, $J = 6.4$, Hz, 1H), 3.69 (d, $J = 5.5$ Hz, 1H) 3.22 (t, $J = 8.0$ Hz, 1H), 3.14 (d, $J = 12.0$ Hz, 2H), 2.87 (td, $J = 9.0, 3.2$ Hz, 1H), 2.18-2.08 (m, 1H), 2.02-1.89 (m, 2H), 1.77-1.66 (m, 3H), 1.61-1.55 (m, 1H), 1.52-1.47 (m, 1H); ^{13}C NMR $\delta = 144.6, 140.0, 136.9, 128.7, 128.2, 126.9, 116.5, 63.6, 62.9, 57.8, 52.5, 51.5, 39.2, 29.9, 28.6, 25.8$; FT-IR (neat cm^{-1}): 3337, 3025, 2932, 2784, 1595, 1490. HR-MS: Calcd for $\text{C}_{21}\text{H}_{26}\text{IN}_2\text{O}$ (m/z): 449.1084 [$\text{M}+\text{H}$] $^+$, found 449.1070.

(3aS,4S,9bS)-8-Iodo-2,3,3a,4,5,9b-hexahydro-5-(3-oxobutanoyl)-1-(phenylmethyl)-1H-pyrrolo[3,2-c]quinoline-4-propyl acetate (52). Amino alcohol **51** (83 mg, 0.19 mmol) was dissolved in CH_2Cl_2 (20 mL) and cooled in an ice bath (0 °C). Et_3N (0.52 mL, 3.8 mmol, 20 equiv.) was added followed by dropwise addition of acetyl chloride (0.13 mL, 1.9 mmol, 10 equiv.). The resulting yellow solution was

stirred at 0 °C for 5 min and then at room temperature for 5 h under nitrogen. After 5 h the reaction mixture was diluted with CH₂Cl₂ (20 mL) and washed with saturated sodium hydrogen carbonate (15 mL), the organic layer was dried over anhydrous sodium sulfate and Et₃N was removed by azeotropic distillation with CH₂Cl₂. The brown oil was purified via flash column chromatography (SiO₂, 1:1 EtOAc/hexane) to give **52** (0.13 g, 75%) (3:2 keto/enol mixture) as a yellow semi solid. ¹H NMR δ = 7.65-7.63 (dd, *J* = 8.3, 1.8 Hz, 0.6H), 7.62-7.60 (dd, *J* = 8.3, 1.8 Hz, 0.4H), 7.55 (d, *J* = 1.8 Hz, 0.6H), 7.5 (d, *J* = 1.8 Hz, 0.4H), 7.22-7.17 (m, 3H), 7.13 (d, *J* = 7.3 Hz, 1H), 7.08 (d, *J* = 7.3 Hz, 1H), 6.97 (d, *J* = 8.3 Hz, 0.4H), 6.90 (d, *J* = 8.3 Hz, 0.6H), 5.26 (s, 0.4H), 4.93-4.91 (dd, *J* = 11.0, 4.6 Hz, 0.6H), 4.9 (brd, *J* = 11.0 Hz, 0.4H), 3.94-3.89 (m, 3H), 3.63 (d, *J* = 15.5 Hz, 0.6H), 3.58 (d, *J* = 15.5 Hz, 0.6H), 2.90-2.84 (m, 1H), 2.56-2.50 (m, 1H), 2.45 (d, *J* = 11.0 Hz, 0.4H), 2.30 (d, *J* = 11.0 Hz, 0.4H), 2.22 (s, 0.6 x 3H), 2.19-2.13 (m, 0.4 x 3H), 2.04-1.99 (m, 1H), 1.96 (s, 0.6 x 3H), 1.94 (s, 0.4 x 3H), 1.86-1.81 (m, 1H), 1.57-1.54 (m, 1H), 1.47-1.46 (m, 1H), 1.28-1.25 (m, 1H), 1.04-0.96 (m, 1H); ¹³C NMR δ = 203, 175, 171.7, 171.1, 166.9, 139.4, 139.1, 137.5, 128.3, 128.2, 128.1, 128.0, 91.0, 89.9, 89.2, 64.2, 63.8, 57.7, 57.6, 52.9, 50.3, 46.6, 46.5, 31.0, 30.5, 29.8, 25.3, 25.2, 21.0. FT-IR (neat cm⁻¹) 2961, 1733, 1643, 1484.

Methyl (3a*S*,4*S*,9b*S*)-2,3,3a,4,5,9b-hexahydro-5-(3-oxobutanoyl)-1-(phenylmethyl)-1*H*-pyrrolo-[3,2-*c*]quinoline-8-carboxylate (53). A slurry of NaOAc (106 mg 1.29 mmol), Ph₃P (47.0 mg 0.18 mmol), **52** (248 mg 0.43 mmol) and Pd(OAc)₂ (27 mg, 0.12 mmol) in dry MeOH (2.5 mL) and DMF (2.5 mL) was placed in a pressure vessel. The vessel was purged with nitrogen for 10 min and then with CO. The reaction mixture was stirred under CO (75 psi) at 120 °C. After 24 h the reaction mixture was filtered through Celite and washed with MeOH. The filtrate was evaporated and the residue was taken up in CH₂Cl₂ (22 mL) and 0.5 M NaOMe (0.94 mL) and stirred overnight at room temperature. After the reaction was complete it was diluted with CH₂Cl₂ and washed twice with saturated sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and concentrated. The crude was purified via flash column chromatography (SiO₂, gradient elution 100% CHCl₃ – 99:1 CHCl₃/MeOH) to give **53** (156 mg, 96%) as a yellow solid. mp 42-44 °C. [α]_D²⁰ -132.7 (*c* 0.49). ¹H NMR δ = 7.8 (d, *J* = 1.8 Hz, 1H), 7.75 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.24-7.23 (m, 4H), 7.21-7.17 (m, 1H), 6.53 (d, *J* = 8.7 Hz, 1H), 4.8 (brs, 1H) 4.31 (d, *J* = 12.4 Hz, 1H), 3.83 (s, 3H), 3.75-3.69 (m, 2H), 3.31-3.28 (t, *J* = 16.5, 8.5 Hz), 3.2 (brd, *J* = 3.7 Hz, 1H), 3.14 (d, *J* = 12.4 Hz, 1H), 2.92-2.88 (td, *J* = 10.5, 3.2 Hz, 1H), 2.22-2.12 (m, 1H), 1.91-1.79 (m, 3H), 1.75-1.68 (m, 3H), 1.58-1.47 (m, 2H); ¹³C NMR δ = 167.5, 149.2, 139.9, 134.3, 130.6, 128.6, 128.1, 126.8, 117.8, 116.9, 113.2, 64.0, 62.8, 57.5, 52.4, 51.6, 51.4, 38.8, 29.7, 28.6, 25.8; FT-IR (neat cm⁻¹) 3369, 2947, 1698, 1613, 1521, 1436. HR-MS: Calcd for C₂₃H₂₈N₂O₃ (*m/z*): 381.2173 [M+H]⁺, found 381.2163.

Methyl (3a*S*,4*S*,9b*S*)-2,3,3a,4,5,9b-hexahydro-5-(3-oxobutanoyl)-1-(phenylmethyl)-5-(trifluoroacetyl)-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylate (55). TFAA (0.52 mL, 3.7 mmol, 10 equiv.) was added dropwise to a solution of **54** (139 mg, 0.37 mmol) and pyridine (0.8 mL, 3.7 mmol, 10 equiv.) in dry CH₂Cl₂ (13.0 mL) at 0 °C. The solution was allowed to stir for an additional 30 min at 0 °C and then at room temperature for 12 h, becoming dark brown. Dry MeOH (13.0 mL) was added to the solution, which was stirred for 30 min. The solution was concentrated by blowing nitrogen through the flask. The solution was diluted with CH₂Cl₂ (40 mL) and washed with saturated sodium hydrogen carbonate solution (10 mL). The organic solution was separated and dried over saturated sodium sulfate and concentrated to obtain the crude material as brown oil. The crude was purified via flash column chromatography (SiO₂, gradient elution 100% CHCl₃ – 99:1 CHCl₃/MeOH) to give **54** (87 mg, 50%) as a yellow oil. ¹H NMR δ = 8.34 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 2.7 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.21-7.15 (m, 6), 3.95 (s, 3H), 3.82-3.85 (m, 2H), 3.51 (m, 1H), 3.36 (d, *J* = 10 Hz, 1H), 3.05 (d, *J* = 10 Hz, 1H), 2.87 (dd, *J* = 8.4, 7.5 Hz, 1H), 2.56 (m, 1H), 2.21 (m, 1H), 1.95 (m, 1H), 1.78 (m, 1H), 1.51 (m, 1H), 1.43-1.37 (m, 3H), 1.0 (m, 1H); HR-MS: Calcd for C₂₅H₂₇F₃N₂O₄ (*m/z*): 477.1996, [M+H⁺], Found 477.1990.

Methyl (3a*S*,4*S*,9b*S*)-4-(3-azidopropyl)-2,3,3a,4,5,9b-hexahydro-1-(phenylmethyl)-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylate (56). MsCl (0.07 mL, 0.91 mmol, 10 equiv.) was added dropwise to a stirred solution containing of **54** (46 mg, 0.09 mmol) and pyridine (0.15 mL, 1.42 mmol, 15 equiv.) in dry CH₂Cl₂ (47 mL) at 0 °C under nitrogen. The solution was stirred at 0 °C for 10 min and 24 h at room temperature. The solution was diluted with CH₂Cl₂ (80 mL) and washed with water (4 x 20 mL) and brine (2 x 20 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to obtain 52 mg of the crude mesylate as a colorless oil. The crude mesylate was dissolved in DMF (2 mL) and sodium azide (58 mg, 0.9 mmol, 10 equiv.) was added to the solution. The solution was stirred at room temperature for 36 h. The solution was diluted with CH₂Cl₂ (20 mL) and washed with water (4 x 6 mL) and saturated sodium chloride (4 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to obtain 26 mg of the crude trifluoroacetamide azide as an oil. The crude trifluoroacetamide azide was dissolved in dry CH₂Cl₂ (10 mL) and NaOMe (0.31 mL, 0.5 M in MeOH) was added. The solution was stirred for 1 h, diluted with CH₂Cl₂ (10 mL) and washed with saturated sodium chloride (4 mL). The aqueous layer was extracted with CH₂Cl₂ (2 x 10 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated. The crude was purified by flash column chromatography (SiO₂ gradient elution 100% CHCl₃ – 99:1 CHCl₃/MeOH) to give **56** (20.0 mg, 51%) as a yellow oil. [α]_D²⁰ -134.8 (*c* 0.66). ¹H NMR δ = 7.81 (s, 1H), 7.76 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.24-7.16 (m, 5H), 6.56 (d, *J* = 8.7 Hz, 1H), 4.55 (s, 1H), 4.3 (brd, *J* = 12.5 Hz, 1H), 3.84 (s, 3H), 3.37 (t, *J* = 6.4 Hz, 2H), 3.33 (t, *J* = 8.7 Hz, 1H), 3.21 (brd, *J* = 4.6 Hz, 1H), 3.13 (d, *J* = 12.5 Hz, 1H), 2.90 (td, *J* = 8.9, 2.8 Hz, 1H),

2.16-2.12 (m, 1H), 2.04-1.98 (m, 1H), 1.96-1.88 (m, 1H), 1.80-1.66 (m, 3H), 1.62-1.50 (m, 3H), 1.57-1.52; ^{13}C NMR δ = 167.4, 148.9, 134.3, 130.6, 128.6, 128.1, 126.8, 117.4, 113.3, 68.1, 63.9, 57.4, 53.5, 52.1, 51.6, 51.3, 38.5, 30.3, 25.7; FT-IR (neat cm^{-1}): 2957, 2095, 1704, 1610, 1517, 1437. HR-MS: Calcd for $\text{C}_{38}\text{H}_{28}\text{N}_5\text{O}_2$ (m/z): 406.2236, $[\text{M}+\text{H}^+]$, found 406.2238.

Methyl (3aS, 4S, 9bS)-4-(3-aminopropyl)-2,3,3a,4,5,9b-hexahydro-1-(phenylmethyl)-1H-pyrrolo-[3,2-c]quinoline-8-carboxylate hydrochloride salt (57). A slurry containing of 20% $\text{Pd}(\text{OH})_2$ (116 mg) on carbon and **56** (39.0 mg) in of 20:1 MeOH/HCl (20 mL) was stirred under a balloon of H_2 gas (1 atm) for 3 h. The solution was filtered through Celite and washed with MeOH (2 x 100 mL). The combined filtrates were concentrated to give 38 mg of crude oil. The oil was dried by azeotropic distillation with MeOH to give **57** (25 mg, 89%) as a yellow oil. ^1H NMR (CD_3OD): δ = 8.00 (s, 1H), 7.71 (s, 1H), 6.86 (s, 1H), 4.7 (s, 1H), 3.8 (s, 3H), 3.2 (s, 1H), 3.1 (s, 2H), 3.05 (s, 2H), 2.48-2.27 (m, 1H), 2.02 (s, 3H), 1.97 (s, 1H), 1.29 (m, 1H); ^{13}C NMR: δ = 167.1, 149.8, 132.7, 131.4, 117.9, 114.5, 112, 49.6, 48.6, 48.3, 48.1, 47.9, 47.8, 47.6, 47.4, 47.3, 38.2, 29.2, 22.7.

Methyl martinellate (59). A solution of AgNO_3 (60 mg, 0.35 mmol) in MeCN (0.5 mL) was added dropwise over 0.5 h to a solution containing **57** (20 mg, 0.07 mmol), **58** (64 mg, 0.25 mmol), and Et_3N (0.08 mL, 0.6 mmol) in a mixture of MeCN (2 mL) and MeOH (1 mL). After the reaction mixture was stirred 16 h at 40 °C in the dark, it was filtered and the filtrate concentrated to dryness. The residue was dissolved in CHCl_3 and washed with water once. The aqueous layer was extracted with CHCl_3 twice and the combined organic layer was dried and concentrated. The residue was purified by flash column chromatography (SiO_2 , 9:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to give **59** (13.0 mg, 38%) of the product as yellow oil. $[\alpha]_D^{20}$ -95.2 (c 0.58). ^1H NMR δ = 7.95 (s, 1H), 7.66 (d, J = 8.0 Hz, 1H), 6.60 (d, J = 8.0 Hz, 1H), 5.29-5.23 (m, 1H), 5.21-5.20 (m, 2H), 3.89 (dd, J = 8.0 Hz, 1H), 3.79 (s, 3H), 3.77-3.74 (m, 2H), 3.43-3.34 (m, 6H), 3.20-3.10 (m, 1H), 2.40-2.32 (m, 1H), 2.08-2.04 (m, 2H), 1.72 (s, 3H), 1.70 (s, 3H), 1.69 (s, 3H), 1.67 (s, 3H), 1.69-1.66 (m, 2H), 1.51 (s, 9H), 1.47 (s, 9H), 1.47-1.40 (m, 4H); ^{13}C NMR δ = 167.4, 162.2, 159.7, 159.5, 146.5, 137.5, 137.4, 137.2, 131.7, 130.2, 120.2, 119.5, 118.1, 113.9, 82, 78, 53.8, 51.5, 50.6, 46.9, 43.6, 43.1, 42.6, 39.7, 39.5, 32.0, 30.1, 29.8, 29.5, 28.5, 28.1, 27.9, 26.5, 25.7, 18.1, 14.2, 13.9, 13.3. HR-MS: Calcd for $\text{C}_{38}\text{H}_{60}\text{N}_7\text{O}_6$ (m/z): 710.4600 ($\text{M}+\text{H}^+$), found 710.4609.

Martinellie acid (2). NaOH (0.15 M, 0.5 mL) was added to a solution of **59** (10 mg, 0.01 mmol) in MeOH (1.5 mL) and water (0.5 mL). The reaction mixture was refluxed for 10 h and then neutralized with 0.1 N HCl cautiously. MeOH was removed under reduced pressure and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were dried and concentrated. The residue was purified by column chromatography (SiO_2 , 9:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to give 6 mg of the corresponding acid, which was confirmed by NMR spectroscopy. This acid was dissolved in 1 mL of CH_2Cl_2 before 0.03 mL of anisole and 0.05 mL

of anhydrous trifluoroacetic acid were added. The mixture was stirred at room temperature for 14 h and then concentrated. The residue was purified by using Baker Bond (C₁₈) 40 μm Prep LC packing (Gradient elution 100% H₂O to 100% MeOH in 20% increments with 0.05% TFA in MeOH) to yield 4.6 mg (38%) of martinelllic acid. $[\alpha]_D^{20}$ -25.0 (*c* 2.0, MeOH), -28.8 (*c* 0.32, MeOH), ¹H NMR (CD₃OD) δ = 7.83 (s, 1H), 7.65 (dd, *J* = 1.8, 8.7 Hz, 1H), 6.57 (d, *J* = 8.7 Hz, 1H), 5.38 (t, *J* = 6.5 Hz, 1H), 5.3 (d, *J* = 6.5 Hz, 1H), 5.23 (t, *J* = 6.5 Hz, 1H), 3.98 (d, *J* = 6.5 Hz, 1H), 3.93 (d, *J* = 6.5 Hz, 1H), 3.77 (d, *J* = 6.5 Hz, 2H), 3.48-3.46 (m, 3H), 3.22 (m, 1H), 3.19 (m, 1H), 2.55-2.53 (m, 1H), 2.19-2.16 (m, 1H), 1.79 (s, 3H), 1.75 (s, 6H), 1.74-1.71 (m, 2H), 1.70 (s, 3H), 1.67-1.58 (m, 2H), 1.55-1.52 (m, 1H).

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