

Asymmetric Synthesis of (–)-Martinelllic Acid

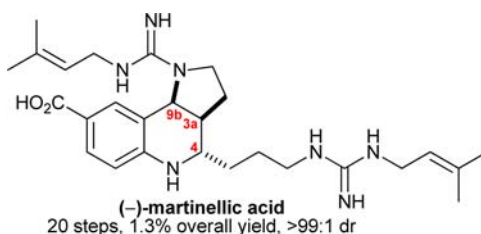
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ABSTRACT



A high-yielding total asymmetric synthesis of (–)-martinelllic acid is reported. The conjugate addition of lithium (*R*)-*N*-allyl-*N*-(α -methyl-4-methoxybenzyl)amide to *tert*-butyl (*E*)-3-[2'-(*N,N*-diallylamino)-5'-bromophenyl]propenoate and alkylation of the resultant β -amino ester have been used as the key steps to install the C(9b) and C(3a) stereogenic centers, respectively, and a highly diastereoselective Wittig reaction/intramolecular Michael addition was then used to create the C(4) stereogenic center within this tricyclic molecular architecture.

A variety of extracts from Amazonian *Martinella* plants are used by local tribes to treat inflammation of the eye¹ and are said to cure conjunctivitis caused by infection from microorganisms such as Gram-positive and Gram-negative bacteria.² In 1995, Witherup isolated (–)-martinelllic acid **1** and (+)-martinelline **2** from the species *Martinella iqui-toensis* and showed them to be responsible for this effect.³

The interesting medicinal properties of **1** and **2** combined with their unique fused pyrroloquinoline structure have spurred research into the synthesis of this tricyclic molecular architecture,⁴ as well as numerous analogues,⁵ with several

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total^{6,7} and formal^{8,9} syntheses of **1** and **2** having been reported to date (Figure 1).¹⁰

As part of our ongoing research program concerning the conjugate addition of enantiopure lithium amides,¹¹ and in particular the application of this methodology to the total asymmetric synthesis of natural products,¹² we envisaged that the conjugate addition of lithium (*R*)-*N*-allyl-*N*-(α -methyl-4-methoxybenzyl)amide **6** to *tert*-butyl (*E*)-3-[2'-(*N,N*-diallylamino)-5'-bromophenyl]propenoate **5** could be used as the key stereodefining step in the total synthesis of the tricyclic core within (–)-martinellic acid **1**. Herein we report our investigations within this area, which culminate in the total asymmetric synthesis of (–)-martinellic acid **1**.

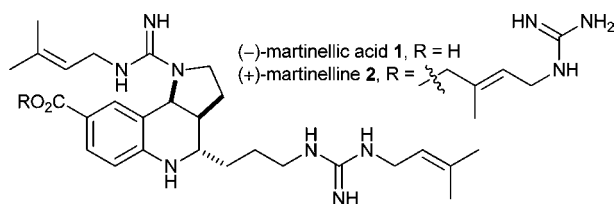
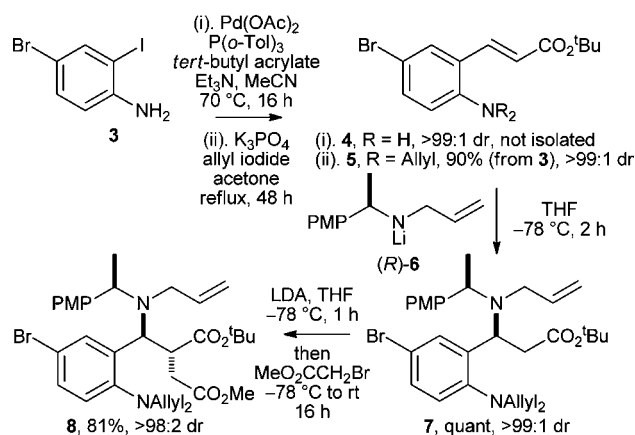


Figure 1. (–)-Martinellic acid **1** and (+)-martinelline **2**.

α,β -Unsaturated ester **5** was prepared from Heck coupling of 2-iodo-4-bromoaniline **3** with *tert*-butyl acrylate to give **4**, which was bis-*N*-allyl protected upon treatment with excess allyl iodide and K₃PO₄ in acetone at reflux to give **5** in 90% yield (from **3**) and >99:1 dr. Conjugate addition of lithium amide (*R*)-**6** to α,β -unsaturated ester **5** gave the corresponding β -amino ester **7** in quantitative

yield and >99:1 dr. The configuration of the newly formed C(3)-stereogenic center within **7** was assigned by reference to our well established transition state mnemonic for this class of reactions.¹³ Subsequent deprotonation of **7** with LDA followed by the addition of methyl bromoacetate gave **8** in 81% isolated yield and >98:2 dr (Scheme 1); the stereochemical outcome of this reaction was initially assigned by reference to analogous alkylations,^{11,14} and the absolute configuration within **8** was later confirmed unambiguously by single crystal X-ray diffraction analysis of a derivative.

Scheme 1



Treatment of **8** with Pd(PPh₃)₄ and *N,N*-dimethylbarbituric acid (DMBA) proceeded to give **9**, then treatment of **9** with 10 mol % PhCO₂H in PhMe at reflux for 16 h gave complete conversion to tricycle **10**. Attempted isolation of **10** gave poor mass return, although it was found that treatment of **10** with Boc₂O gave **11** in 49% yield (from **8**) after the three step procedure (Scheme 2). The relative configuration within **11** was unambiguously established by single crystal X-ray diffraction analysis (Figure 2),¹⁵ with the absolute (3*aR*,9*bS*, α *R*)-configuration within **11** being assigned from the known configuration of the α -methyl-4-methoxybenzyl fragment. Furthermore, the determination of a Flack *x* parameter¹⁶ of 0.011(8) for the crystal structure of **11** allowed its absolute configuration to be confirmed. This analysis also secured the assigned absolute configurations within intermediates **7**–**10**.

Chemoselective reduction of **11** with LiAl(O*t*Bu)₃H proceeded cleanly to give a single diastereoisomeric hemiaminal **12** [of unknown configuration at C(4)] in quantitative yield, without any detectable reduction of the amide functionality

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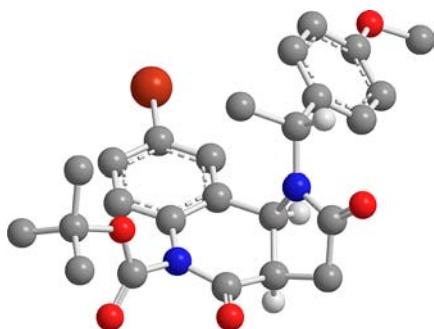
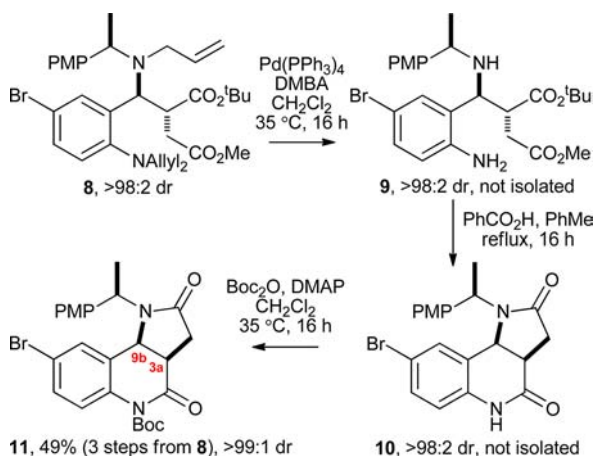
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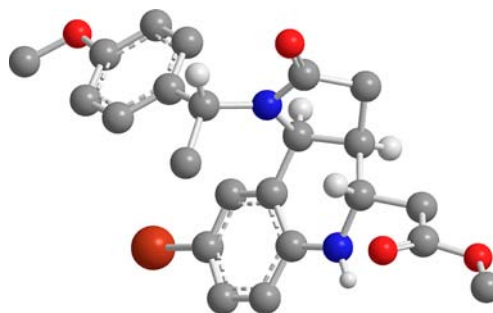
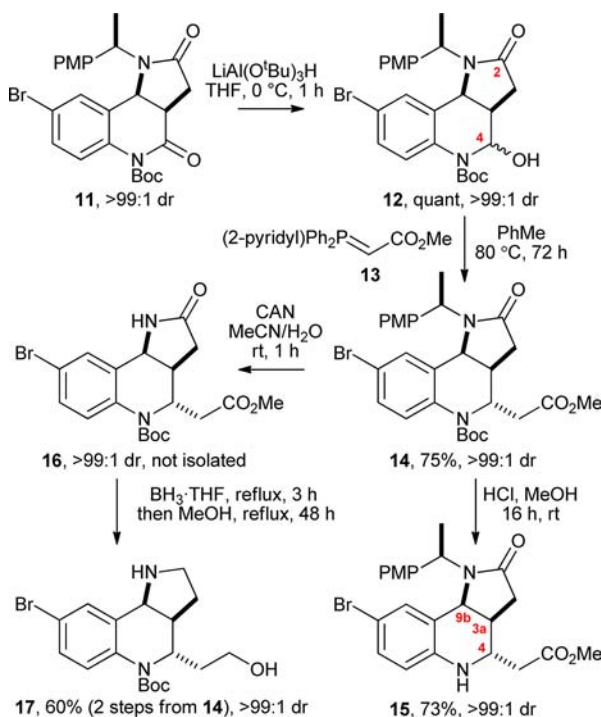
Scheme 2

Figure 2. X-ray crystal structure of **11** (selected H atoms are omitted for clarity).

at C(2). Treatment of **12** with ylid **13** in PhMe at 80 °C for 3 days installed the final stereogenic center required for the synthesis of (–)-martinellic acid **1** and gave **14** as a single diastereoisomer in 75% isolated yield. *N*-Boc deprotection of **14** upon treatment with HCl in MeOH then gave **15** in 73% isolated yield. The relative configuration within **15** was unambiguously established by single crystal X-ray diffraction analysis (Figure 3),¹⁵ and the absolute (3*a**S*,4*S*,9*b**S*, α *R*)-configuration within **15** was assigned by reference to the known configuration of the α -methyl-4-methoxybenzyl fragment; the determination of a Flack χ parameter¹⁶ of 0.014(9) for the crystal structure of **15** allowed this assignment to be confirmed. Attempted *N*(1)-deprotection of **15** was not successful due to difficulties in the isolation of the product. However, *N*(1)-deprotection of **14** upon treatment with CAN gave **16**, then reduction of **16** with BH₃ proceeded to give amine **17** (after decomplexation of BH₃ upon heating a solution of the intermediate complex in MeOH at reflux); in this case **17** was isolated in 60% overall yield (from **14**) and > 99:1 dr after chromatographic purification (Scheme 3).

N-Boc protection of the N(1) atom within **17** upon treatment with Boc₂O, followed by *O*-tosylation of **18** gave

Scheme 3

Figure 3. X-ray crystal structure of **15** (selected H atoms are omitted for clarity).

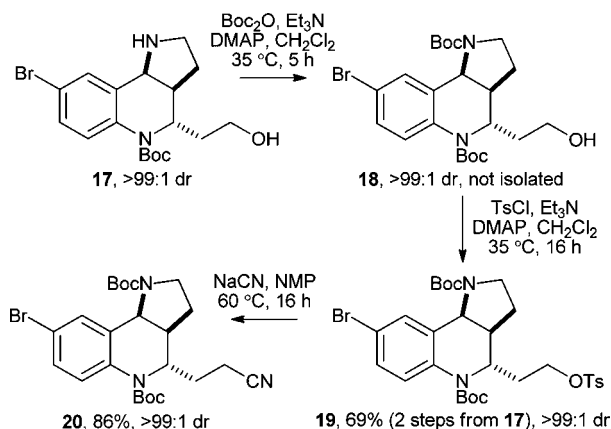
19 in 69% yield (from **17**), then treatment of **19** with NaCN in *N*-methyl-2-pyrrolidinone (NMP) gave **20** in 86% yield and > 99:1 dr (Scheme 4).

Carbonylation¹⁷ of **20** upon treatment with CO (1 atm), Pd(OAc)₂, Xantphos and Et₃N in MeOH at 70 °C for 48 h gave **21** in 69% yield. Subsequent reduction of the nitrile group¹⁸ within **21** upon treatment with NiCl₂·H₂O, NaBH₄ and Boc₂O in MeOH at 0 °C gave **22** in 91% yield. Deprotection of the three *N*-Boc groups within **22** upon treatment with methanolic HCl gave “Ma’s intermediate”^{6a} **23** in quantitative yield and > 99:1 dr, completing a formal

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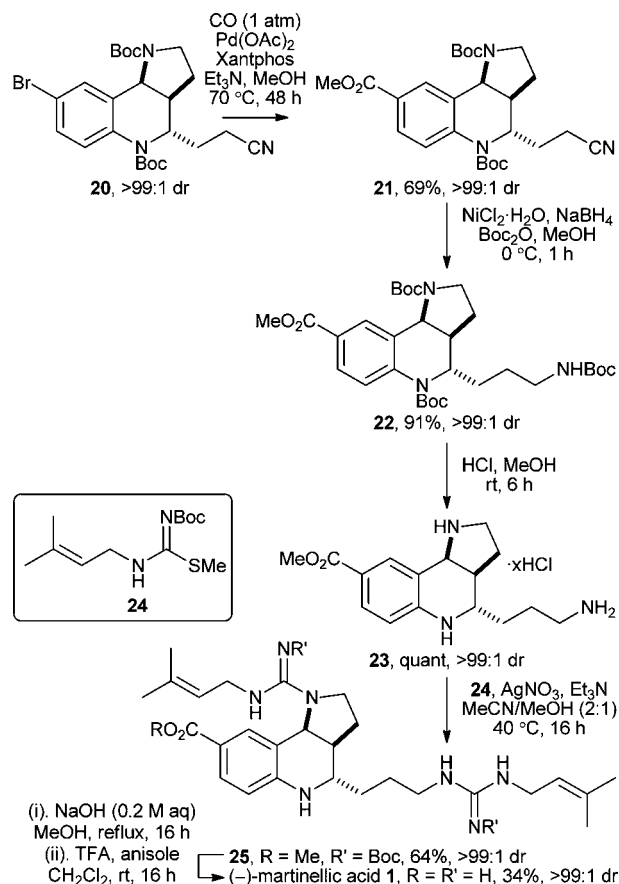
Scheme 4



synthesis of (–)-martinellic acid **1** {in 6.0% yield over 17 steps from commercially available starting materials; $[\alpha]_D^{20} -48.7$ (c 0.3 in MeOH); lit.^{6a} $[\alpha]_D^{20} -49.9$ (c 1.25 in MeOH)}. Finally, **23** was converted into (–)-martinellic acid **1** according to a literature procedure:^{6a} in our hands, application of this protocol gave **1**·TFA in 22% yield. The spectroscopic data for this sample of (–)-martinellic acid **1**, including its specific rotation $\{[\alpha]_D^{20} -118$ (c 0.3 in MeOH); lit.³ for sample isolated from natural source $[\alpha]_D -8.5$ (c 0.01 in MeOH); lit.^{6a} $[\alpha]_D^{20} -112.7$ (c 0.31 in MeOH); lit.^{6b} $[\alpha]_D^{29} -164.3$ (c 0.14 in MeOH); lit.^{6c} $[\alpha]_D^{23} -164.8$ (c 0.33 in MeOH)}}, were consistent with literature data (Scheme 5).

In conclusion, the diastereoselective conjugate addition of lithium (*R*)-*N*-allyl-*N*-(α -methyl-4-methoxybenzyl)-amide to *tert*-butyl (*E*)-3-[2'-(*N,N*-diallylamino)-5'-bromophenyl]-propenoate and alkylation of the resultant β -amino ester have been used as the key steps to install correct stereochemistry for the C(9b) and C(3a) stereogenic centers within (–)-martinellic acid, respectively. A diastereoselective Wittig reaction/intramolecular Michael addition was then used to create the final C(4) stereogenic center. After further elaboration, (–)-martinellic acid was isolated as its trifluoroacetate salt in 20 steps and 1.3% overall yield from commercially available starting materials.

Scheme 5



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Supporting Information Available. Experimental procedures, characterization data, copies of ¹H and ¹³C NMR spectra, and crystallographic information files (for structures CCDC 926034 and 926035). This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.