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Asymmetric Synthesis of (−)-Martinellic Acid

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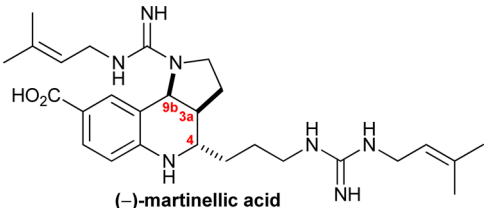
ABSTRACT



(−)-martinellic acid
20 steps, 1.3% overall yield, >99:1 dr

A high-yielding total asymmetric synthesis of (−)-martinellic 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 eye[1] and are said to cure conjunctivitis caused by infection from microorganisms such as Gram-positive and Gram-negative bacteria.[2] In 1995, Witherup isolated (−)-martinellic acid **1** and (+)-martinelline **2** from the species *Martinella iquitoensis* 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**.

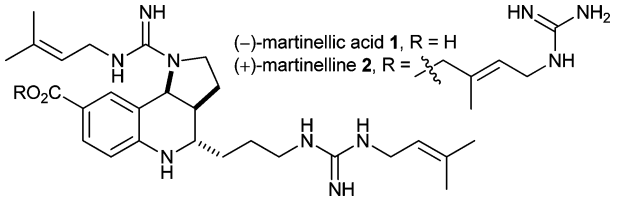
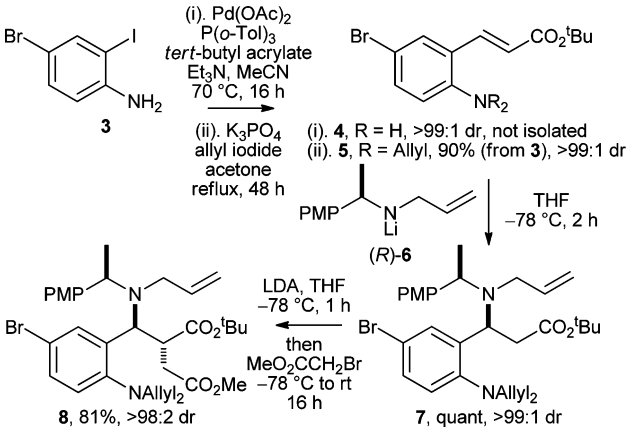


Figure 1. (−)-Martinellic acid **1** and (+)-martinelline **2**.

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 K_3PO_4 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 $Pd(PPh_3)_4$ and *N*,*N*-dimethylbarbituric acid (DMBA) proceeded to give **9**, then treatment of **9** with 10 mol % $PhCO_2H$ 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 Boc_2O 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 (3a*R*,9b*S*,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* parameter[16] 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 $LiAl(O^tBu)_3H$ 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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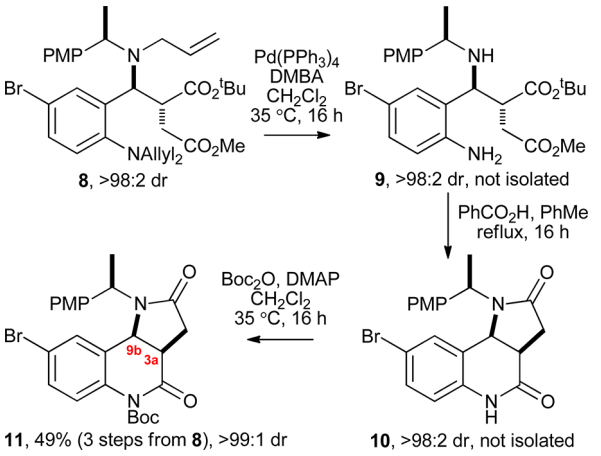
Scheme 2



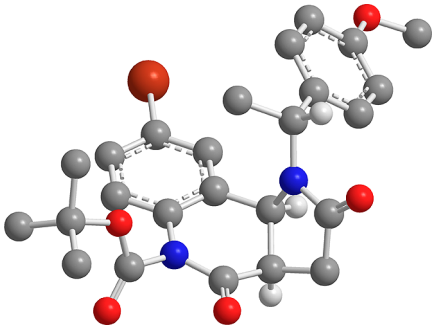
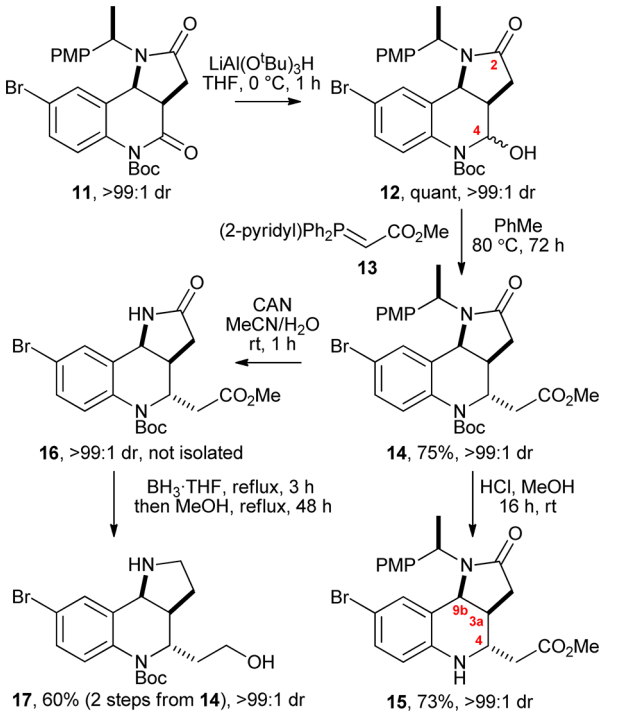


Figure 2. X-ray crystal structure of **11** (selected H atoms are omitted for clarity).

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 (3a*S*,4*S*,9b*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 *x* parameter[16] 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 BH_3 proceeded to give amine **17** (after decomplexation of BH_3 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 Boc_2O, followed by *O*-tosylation of **18** gave

Scheme 3



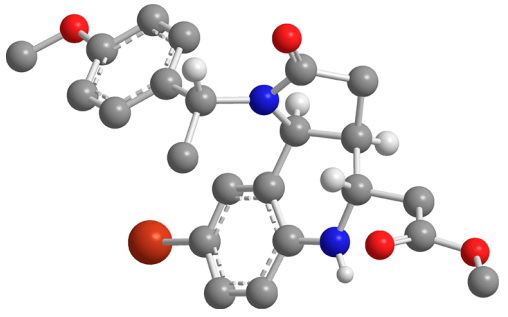


Figure 3. X-ray crystal structure of **15** (selected H atoms are omitted for clarity).

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).

Carbonylation[17] of **20** upon treatment with CO (1 atm), $Pd(OAc)_2$, Xantphos and Et_3N in MeOH at 70 °C for 48 h gave **21** in 69% yield. Subsequent reduction of the nitrile group[18] within **21** upon treatment with $NiCl_2 \cdot H_2O$, $NaBH_4$ and Boc_2O 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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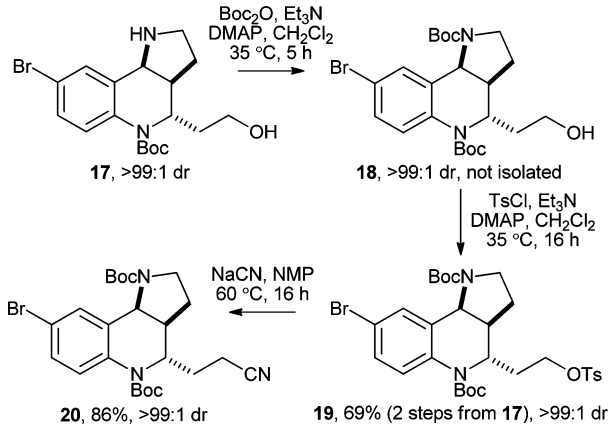
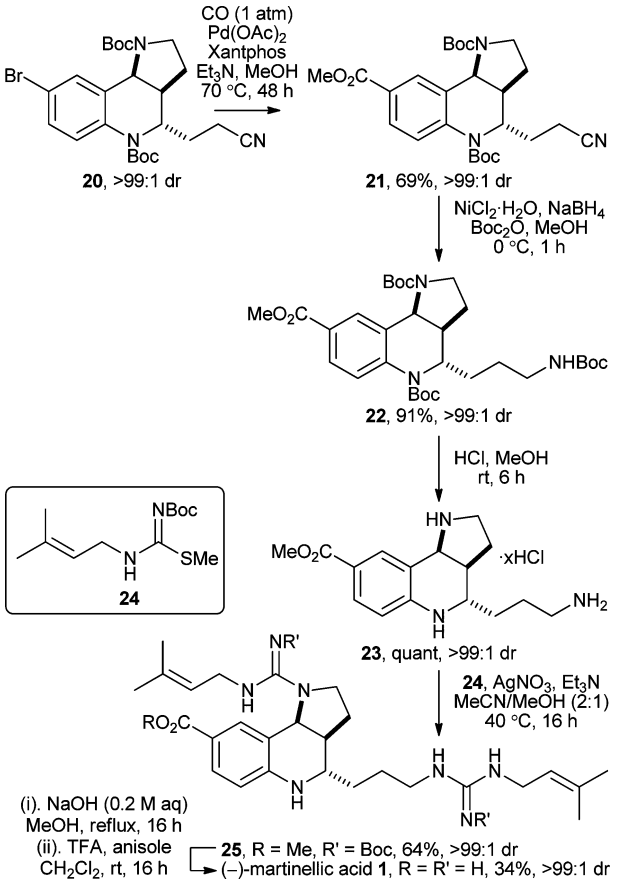
Scheme 4



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 ^{1}H and ^{13}C 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.