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Total Synthesis of (±)-Martinellic Acid

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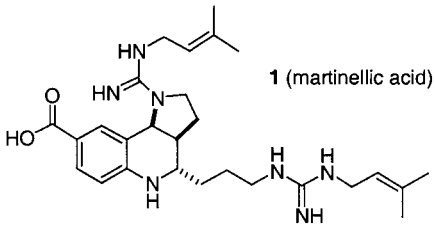
ABSTRACT



A 14-step synthesis of martinellic acid (1) that proceeds in 3% overall yield has been completed using the reaction of aniline 11 with Meldrum's acid-activated vinylcyclopropane 4 to give vinyl pyrrolidinone 12, condensation of aldehyde 13 with *N*-benzylglycine to form an azomethine ylide that cyclizes to give 14, selective reduction of 14 to amino alcohol 16 with $LiBH_4$ and MeOH, and guanidine formation by reaction of a cyanamide with 3-methyl-2-buten-1-amine in hexafluoro-2-propanol at 120 °C as key steps.

Martinellic acid (**1**) and martinelline (**2**), isolated from an organic extract of *Martinella iquitosensis* roots by Witherup and co-workers in 1995, are novel non-peptide antagonists for the bradykinin (BK) B_1 and B_2 receptors (Figure 1).[1]

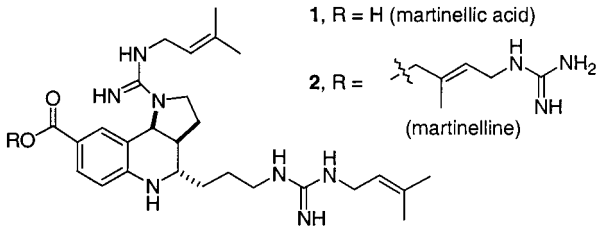


Figure 1. Structures of martinellic acid and martinelline.

These alkaloids contain the unusual pyrroloquinoline ring system, previously unobserved in natural products, and multiple guanidine side chains. Their unusual structure and biological activity have made them the subject of intense synthetic interest,[2] recently culminating in the first synthesis of (−)-martinellic acid.[3]

We reported an efficient synthesis of the triamine core **9** lacking the carboxylic acid using an azomethine ylide [3 + 2] dipolar cycloaddition to form the pyrroloquinoline ring system (see Scheme 1).[4] Reaction of aniline **3** with Danishefsky's Meldrum's acid-activated vinylcyclopropane **4**[5] in toluene at 65 °C for 2 d affords 56% of the

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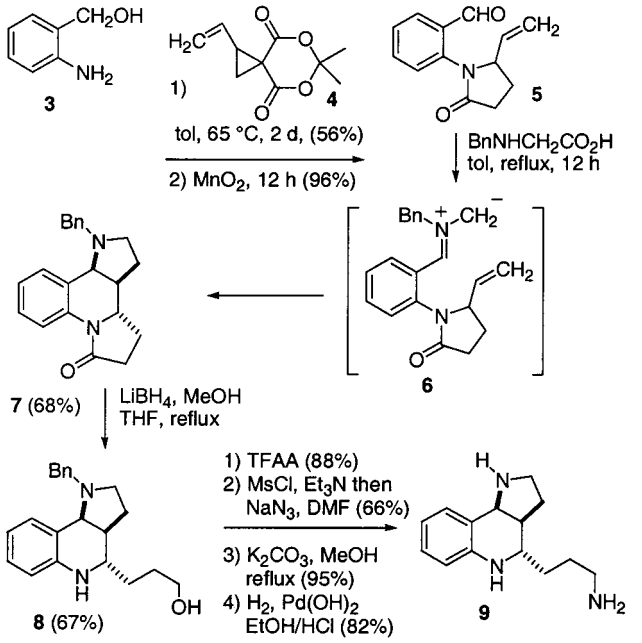
Scheme 1. Synthesis of Model Triamine **9**



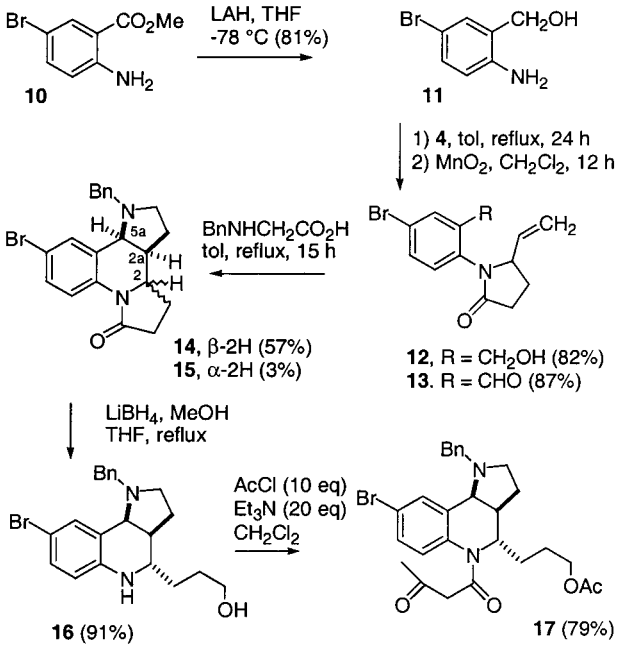
vinylpyrrolidinone in a one-pot sequence involving addition of the aniline to the allylic cyclopropane carbon, cyclization to form the pyrrolidinone with loss of acetone, and decarboxylation. Oxidation of the benzylic alcohol with MnO_2 gives 96% of aldehyde **5**. Condensation of **5** with *N*-benzylglycine provides the iminium salt which decarboxylates to give azomethine ylide **6**, which cyclizes to yield 68% of the desired cis, anti adduct **7** and only 7% of the undesired cis, syn adduct.[6]

Reduction of the pyrrolidinone of **7** to form amino alcohol **8** was complicated by the formation of substantial amounts of the pyrrolidine with most reducing reagents. Optimal results were obtained with $LiBH_4$ and MeOH in THF,[7] which affords 67% of **8** and only 4% of the pyrrolidine. Protection of the aniline of **8** as the trifluoroacetamide, mesylation and immediate displacement of the mesylate with sodium azide, cleavage of the trifluoroacetamide, and hydrogenolysis affords triamine **9** in eight steps and 11% overall yield.

To synthesize the fully functionalized triamine ester **22** (see Scheme 3) using the sequence developed for the synthesis of **9**, we needed to introduce a carboxylic acid onto the benzene ring. Since an ester is not compatible with the reduction of the pyrrolidinone, we decided to introduce it by carbonylation of an aryl bromide after the reduction.

Despite reports to the contrary,[8] reduction of methyl 4-bromoanthranilate (**10**) or the corresponding acid to give alcohol **11** was accompanied by formation of various amounts of difficulty separable alcohol **3** resulting from reductive cleavage of the aryl bromide. The best results were obtained by addition of a solution of ester **10** to LAH in THF at −78 °C and slow warming to 25 °C, which gives a 33:1 mixture of **11** and **3** from which aniline alcohol **11** can be isolated in 81% yield (see Scheme 2).

Scheme 2. Synthesis of Acetoacetamide **17**



Refluxing a solution of **11** and **4** in toluene for 1 d affords vinyl pyrrolidinone alcohol **12** in 82% yield. The reaction proceeds more efficiently at reflux than at the lower temperature (65 °C) used in the synthesis of **5**. MnO_2 oxidation of benzylic alcohol **12** gives aldehyde **13** in 87% yield. Reaction of *N*-benzylglycine and aldehyde **13** in toluene at reflux for 12−24 h provides a 10:1 mixture of cis, anti and cis, syn fused tetracyclic lactams, **14** and **15**, respectively. Flash chromatography affords 57% of the desired product **14** and 3% of the undesired adduct **15**.

The relative stereochemistry of cis, anti fused tetracyclic lactam **14** was assigned by analysis of the coupling constants. The coupling constant between H_{5a} and H_{2a} is 4.3 Hz, which is consistent only with a cis ring fusion. The coupling constant between H_{2a} and H_2 is 9.8 Hz, which is consistent with vicinal trans pseudoaxial hydrogens. The ^1H NMR spectrum and the coupling constants of **14** correspond closely to those of model **7**, whose structure was confirmed by X-ray crystallographic structural analysis.[4] The 8.0 Hz coupling constant between H_{2a} and H_{5a} and the 3.1 Hz coupling constant between H_2 and H_{2a} are consistent with those calculated for cis, syn adduct **15** by MM2. An NOE between H_2 at δ 4.11 and H_{5a} at δ 4.02 confirmed the stereochemistry of **15**.

Reductive cleavage of the pyrrolidinone without cleavage of the bromide is also problematic. The best results are obtained by addition of $LiBH_4$ and MeOH to a dilute solution

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(3 mM)[9] of **14** in THF at reflux, with periodic addition of more $LiBH_4$ and MeOH over several days to give 91% of the desired amino alcohol **16**, 2% recovered **14a**, and no **8** or pyrrolidine.[7,10] The absence of the pyrrolidine is probably due to the electron-withdrawing effect of the bromine group, which favors cleavage of the tetrahedral intermediate to the aldehyde and retards formation of the imine that is the pyrrolidine precursor.

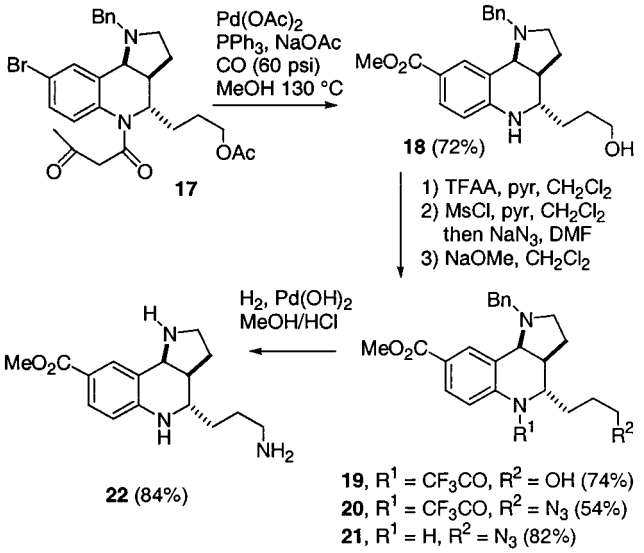
p-Bromoaniline was used to optimize methoxycarbonylation conditions. Reaction of *p*-bromoacetanilide, $Pd(OAc)_2$ (4%), PPh_3 (16%), CO (60 psi), and NaOAc (5 equiv) in MeOH at 120−130 °C for 24 h gives 80% of the desired methyl ester. A similar reaction of *p*-bromotrifluoroacetanilide affords 95% of *p*-bromoaniline and <1% of the desired methyl ester, indicating that the trifluoroacetamide is not stable to carbonylation conditions. *p*-Bromoaniline is also not methoxycarbonylated under these conditions. We therefore attempted to acetylate amino alcohol **16**.

Reaction of **16** with AcCl (3 equiv) and Et_3N (5 equiv) in CH_2Cl_2 only acetylates the alcohol. However, reaction of **16**, AcCl (10 equiv), and Et_3N (20 equiv) in CH_2Cl_2 affords 79% of acetoxy acetoacetamide **17** as a mixture of keto and enol tautomers. The structure of **17** was verified by acetoacetylation of the acetate of **16** with diketene in CH_2Cl_2, which yields the identical material in lower yield. Reaction of AcCl and Et_3N is known to give diketene, and products of addition of diketene have occasionally been isolated from reactions with AcCl and Et_3N.[11] The aniline nitrogen of **16** is very hindered and does not react with acetyl chloride but is acylated with the unhindered diketene. This result is similar to the observation that the side chain of taxol can be introduced more easily by acylation with a β-lactam than an acid chloride.[12]

Reaction of **17**, $Pd(OAc)_2$ (10%), PPh_3 (40%), CO (60 psi), and NaOAc (5 equiv) in dry MeOH at 120−130 °C for 3 d provides a 3:1 mixture of amino alcohol **18** and the corresponding acetate. Hydrolysis of the acetate is completed by heating the crude mixture and 5 equiv of NaOAc in dry MeOH at 120 °C for 24 h to give amino alcohol **18** in 72% yield (see Scheme 3). Conversion of the bromide of **17** to a methyl ester makes the aniline a better leaving group, so NaOAc cleaves the acetoacetamide under the reaction conditions after carbonylation.

Reaction of amino alcohol **18**, TFAA, and Et_3N in CH_2Cl_2 as in the protection of **8** provides trifluoroacetamide **19** in low yield presumably due to ester hydrolysis catalyzed by Et_3N. Reaction of **18**, 10 equiv of TFAA, and 20 equiv of the weaker base pyridine in CH_2Cl_2 for 12 h yields 74% of trifluoroacetamide alcohol **19** after hydrolysis of the trifluoroacetate ester during workup. Treatment of **19** with

Scheme 3. Synthesis of Triamine Ester **22**



MsCl and pyridine in CH_2Cl_2 affords the crude mesylate, which is treated with 10 equiv of NaN_3 in dry DMF to give 54% of crude trifluoroacetamide azide **20**. Hydrolysis of trifluoroacetamide **20** with NaOMe in dry CH_2Cl_2 provides pure aniline **21** in 44% yield from **19**. Hydrogenation and hydrogenolysis of **21** over $Pd(OH)_2$ under H_2 (1 atm) in 20:1 MeOH/concentrated HCl gives 84% of the hydrochloride salt of **22** that is 90−95% pure.[13] The synthesis of fully functionalized tricyclic triamine **22** was accomplished in 11 steps in 5% overall yield from methyl 2-amino-5-bromobenzoate (**10**).

Introduction of the guanidine onto the hindered secondary amine of **22** is difficult, and the standard methods fail. In his synthesis of martinellic acid, Ma developed a novel $AgNO_3$-catalyzed reaction with *N*-(Boc)-*N*-(3-methyl-2-butenyl)-*S*-methylisothiourea.[3] We recently reported a general new method for the preparation of hindered guanidines.[14] Treatment of a hindered amine with cyanogen bromide and $NaHCO_3$ in EtOH gives the cyanamide in virtually quantitative yield. Reaction with a second amine in the polar, nonnucleophilic solvent hexafluoro-2-propanol in a sealed tube at 90−120 °C forms the guanidine in >80% yield.

This sequence works well on triamine **22**. Reaction with $NaHCO_3$ (25 equiv) and cyanogen bromide (2.2 equiv) in MeOH for 1 h at 0 °C yields bis cyanamide **23** quantitatively (see Scheme 4). As expected the hindered aniline does not react. Heating **23** (2×10^{-2} M) and 3-methyl-2-buten-1-amine[15] (2 equiv) in hexafluoro-2-propanol at 120 °C for 32 h provides crude methyl martinellate (**24**). Hydrolysis of the methyl ester cannot be carried out under acidic conditions since the prenyl double bonds are reactive.[14] Hydrolysis in

(9) Both **8** and the pyrrolidine are formed at higher concentrations.

(10) Reduction with $LiNH_2BH_3$ was less effective: Myers, A. G.; Yang, B. H.; Kopecky D. J. *Tetrahedron Lett.* **1996**, *37*, 3623−3626.

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(13) The free triamino ester is unstable and readily forms polymeric amides. This compound is best stored and characterized as the hydrochloride salt.

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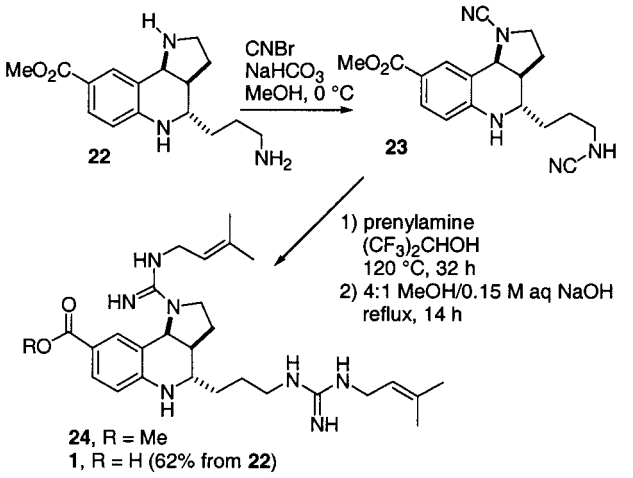
(15) Jordis, U.; Grohmann, F.; Küenburg, B. *Org. Prep. Proced. Int.* **1997**, *29*, 549−560.

Scheme 4. Introduction of the Guanidines of **1**



4:1 MeOH/0.15 M aqueous NaOH at reflux for 14 h and neutralization with 1% TFA in MeOH affords crude martinellic acid (**1**) as the bis trifluoroacetate salt. Reverse phase chromatography eluting with water to MeOH in 20% increments removes the sodium trifluoroacetate and organic impurities. Elution with 0.05% TFA in MeOH affords pure martinellic acid (**1**) in 62% yield for the three-step sequence from **22** with ^{1}H and ^{13}C NMR spectral data in DMSO-d_6 identical to those reported.[1]

In conclusion, we have developed a 14-step synthesis of martinellic acid that proceeds in 3% overall yield. Key steps include the reaction of aniline **11** with Meldrum's acid-activated vinylcyclopropane **4** to give vinyl pyrrolidinone **12**, condensation of aldehyde **13** with *N*-benzylglycine to form an azomethine ylide that cyclizes to give **14**, selective reduction of **14** to amino alcohol **16** with $LiBH_4$ and MeOH, and guanidine introduction by formation of the cyanamide and reaction with 3-methyl-2-buten-1-amine in hexafluoro-2-propanol at 120 °C.

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Supporting Information Available: Full experimental procedures for the conversion of **10** to martinellic acid (**1**). This material is available free of charge via the Internet at http://pubs.acs.org.

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