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Synthesis of the Tricyclic Triamine Core of Martinelline and Martinellic Acid

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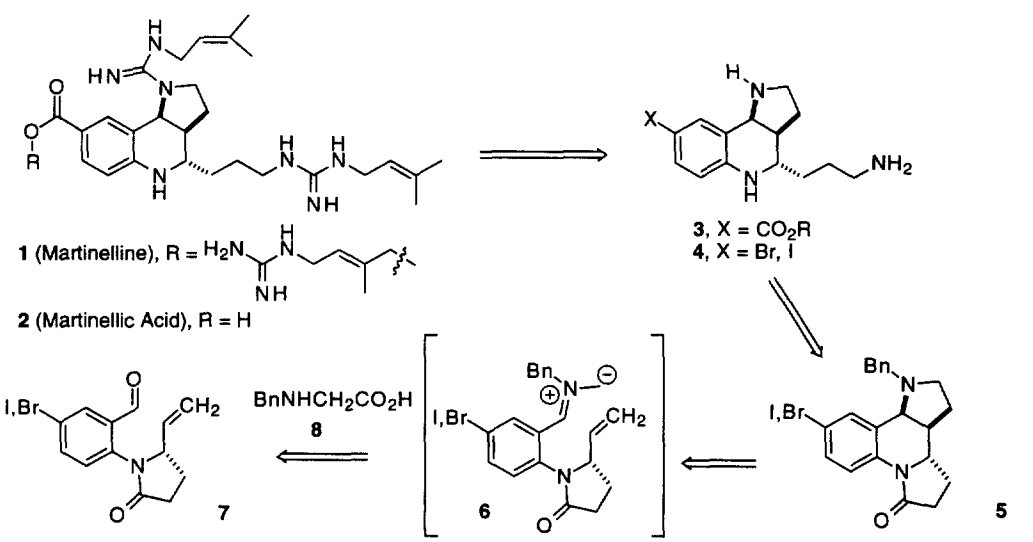
Abstract: The tricyclic triamine core **27** of martinellic acid (**2**) has been prepared stereospecifically in eight steps from 2-hydroxymethylaniline in 11% overall yield. The key steps are the addition of 2-hydroxymethylaniline to vinylcyclopropane **14** to prepare cycloaddition precursor **19** in only two steps and an intramolecular [3+2] azomethine ylide cycloaddition reaction to produce tetracycle **20** with >9:1 diastereoselectivity.

Keywords: alkaloids, cycloadditions, azides, cyclopropanes

Martinelline (**1**) and martinellic acid (**2**) were isolated by Witherup, Varga and coworkers at Merck Research Laboratories from the roots of the tropical plant *Martinella iquitosensis*.[1] These alkaloids are the first naturally occurring nonpeptide bradykinin B_1 and B_2 receptor antagonists and the first naturally occurring pyrrolo[3,2-*c*]quinoline tricycles. It is therefore not surprising that these compounds have been the object of intense synthetic effort.[2-5]



We envisioned that martinelline and martinellic acid should be accessible from triamine carboxylate **3**, which could be prepared by palladium-catalyzed carbonylation of bromide or iodide **4**. The aniline and primary amine of **4** should be available by reductive ring opening of the pyrrolidinone ring of tetracycle **5**, followed by functional group interchange. The key step in our scheme is the intramolecular [3+2] cycloaddition[6] of azomethine ylide alkene **6**,

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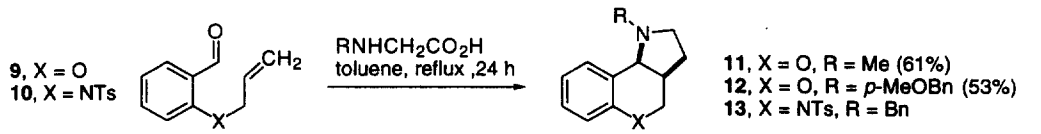
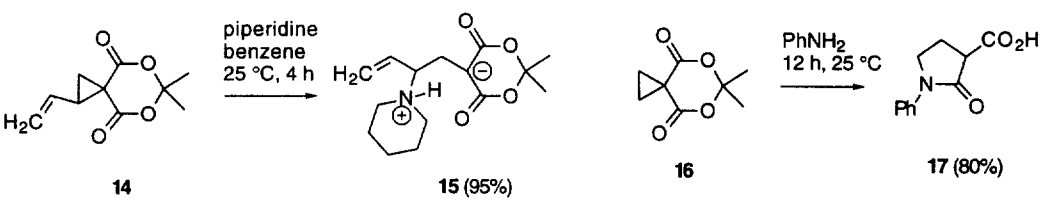
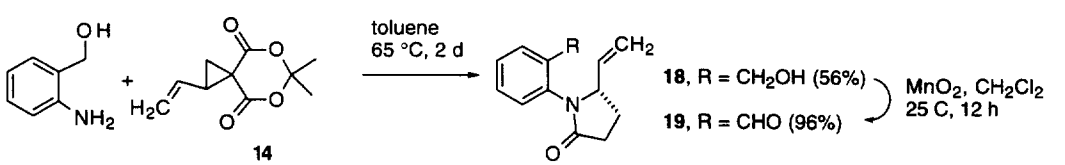
which should give predominantly the cis,anti-tetracycle **5** containing all the stereocenters of **1** and **2**. Condensation of benzaldehyde **7** with *N*-benzylglycine (**8**) will generate azomethine ylide **6** by formation of the iminium salt and decarboxylation.

This azomethine [3 + 2] cycloaddition is well-precedented in simpler systems. Confalone reported that condensation of *o*-allyloxybenzaldehyde (**9**) with *N*-methylglycine TMS ester in toluene at reflux afforded 61% of **11**.[7] Kanemasa and Tsuge reported a similar sequence with *p*-methoxybenzylglycine leading to 53% of **12**.[8] While our work was in progress, Lovely reported an analogous cycloaddition with allylsulfonamide **10** leading to **13** as a martinellic acid model study.[4]



The synthesis of 5-ethenyl-1-arylpyrrolidinones such as **7** and **19** proved to be surprisingly challenging. For instance, a variety of routes from *N*-arylsuccinimides were unsuccessful. Eventually, we concluded that homoconjugate addition of a substituted aniline to the electrophilic vinylcyclopropane **14** developed by Danishefsky[9] should provide a one-step synthesis of the required 5-ethenyl-1-arylpyrrolidinone. Danishefsky found that addition of piperidine to vinylcyclopropane **14** occurred on the cyclopropane at the substituted carbon to give 95% of betaine **15**.[9c] Furthermore, addition of aniline to electrophilic cyclopropane **16** at 25 °C resulted in homoconjugate addition followed by attack of the substituted aniline on the Meldrum's acid to give 80% of pyrrolidinone carboxylic acid **17**.[9d,f]

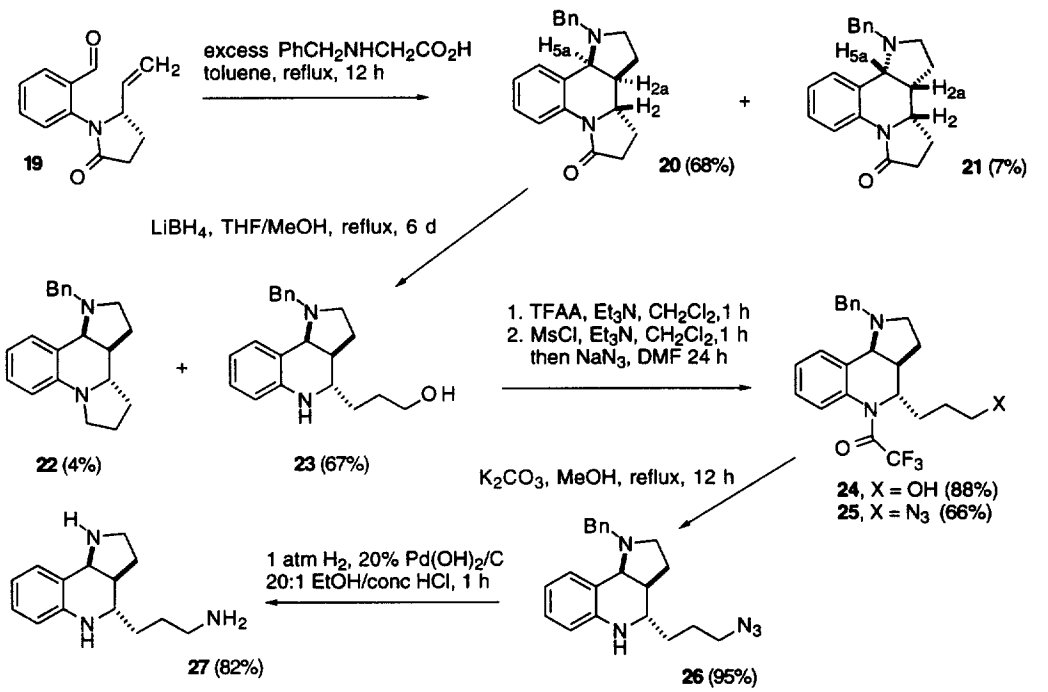




In a model study lacking the halide on the aromatic ring, we were delighted to find that reaction of 2-hydroxymethylaniline with **14**[10] in toluene at 65 °C for 2 d afforded 56% of the desired 5-ethenyl-1-arylpyrrolidinone **18**. Homoconjugate addition to **14** occurred at the desired position as in the synthesis of **15**, the secondary aniline cyclized to form the pyrrolidinone carboxylic acid as in the synthesis of **17**, and decarboxylation proceeded spontaneously at the higher temperature needed for the addition of a hindered aniline to **14**.

Oxidation of **18** with activated MnO_2 in CH_2Cl_2 at 25 °C provided 96% of the required cycloaddition precursor pyrrolidinone aldehyde **19**.

Condensation of excess *N*-benzylglycine with aldehyde **19** provided 75% of a readily separable ≈9:1 mixture of cis-anti- and cis-syn-tetracycles **20** and **21**, respectively. The stereochemistry of the desired, major product **20** was determined by analysis of the coupling constants between the methine hydrogens. $J_{2a,5a}$ = 4.0 Hz established that the ring fusion is cis. $J_{2,2a}$ = 9.8 Hz indicated that these hydrogens are trans and diaxial on the six-membered ring. This stereochemical assignment was confirmed by X-ray structure determination.[12] The coupling constants in the minor isomer, $J_{2a,5a}$ = 8.3 Hz, and $J_{2,2a}$ = 3.4 Hz, are consistent only with those predicted for the cis,syn-isomer **21** by MM2 calculations.



As expected, reduction of pyrrolidinone **20** inevitably provided pyrrolidine **22** in addition to the desired product, amino alcohol **23**. Reduction with Dibal-H gave only pyrrolidine **22**, while use of LAH afforded a 1:1 mixture of **22** and **23**. Excellent selectivity was eventually obtained by reduction with $LiBH_4$ in 20:1 THF/MeOH[13] at reflux for several d, which gave 67% of amino alcohol **23** and only 4% of pyrrolidine **22**.

The secondary nitrogen of **23** was protected with TFAA and Et_3N to give 88% of trifluoroacetamide **24**. Reaction of alcohol **24** with MsCl and Et_3N gave the crude mesylate, which was immediately treated with NaN_3 in DMF for 24 h at 25 °C to yield 66% of azide **25**. If the aniline was not protected, the amino mesylate cyclized to give pyrrolidine **22**. With the azide in place, the trifluoroacetamide of **25** was hydrolyzed with K_2CO_3 in MeOH at reflux to give 95% of amino azide **26**. The model study was completed by hydrogenation (1 atm) over 20% $Pd(OH)_2/C$ in 20:1 EtOH/conc HCl which reduced the azide to the primary

amine and cleaved the benzyl protecting group to yield 82% of triamine **27**.[14] Although **27** was very polar, it could be purified by flash chromatography on silica gel using 3:1 EtOH/conc NH_4OH as the eluent.[15]

In conclusion, we have developed a stereospecific eight-step route from 2-hydroxymethylaniline to the tricyclic triamine core **27** of martinellic acid (**2**) in 11% overall yield using the addition of 2-hydroxymethylaniline to vinylcyclopropane **14** to construct cycloaddition precursor **19** in only two steps and an intramolecular [3+2] azomethine ylide cycloaddition reaction to produce tetracycle **20** with >9:1 diastereoselectivity. We are now addressing the preparation of the benzoic acid functionality present in **3** by starting with halo aldehyde **7** and the introduction of prenyl guanidines onto the more reactive aliphatic amines of **3** needed to complete a synthesis of martinellic acid.

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