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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. © 1999 Elsevier Science Ltd. All rights reserved.

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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] cycloaddition⁶ of azomethine ylide alkene 6,

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 Danishefsky⁹ 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 $\approx 9:1$ 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 LiBH₄ in 20:1 THF/MeOH¹³ 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 NaN₃ 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 K₂CO₃ 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 NH₄OH 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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