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An Approach to the Pyrroloquinoline Core of Martinelline and Martinellic Acid

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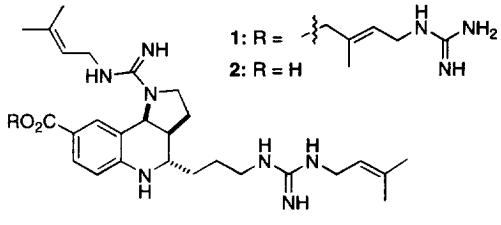
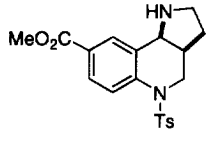
Abstract: An expedient method for the assembly of the pyrroloquinoline skeleton found in the martinelline alkaloids using a [3+2] cycloaddition of an azomethine ylide and an alkene has been developed.

Martinelline **1** and martinellic acid **2** were recently isolated from the roots of the South American plant, *Martinella iquitosensis*, and have been shown to possess antagonistic behavior towards bradykinin receptors (B_1 and B_2).[1] Bradykinin, a nonapeptide, is involved in a number of physiological processes and therefore selective agonists and antagonists of its receptors may prove useful therapeutically and/or as biochemical probes.[2,3] These natural products are the first naturally occurring examples of the pyrrolo[3,2-*c*]quinoline skeleton to have been discovered and are members of a select set of non-peptidic bradykinin receptor antagonists.[4-8] The majority of bradykinin receptor antagonists reported to date are peptidic, therefore non-peptide compounds have significant potential as novel leads.[4-8] Moreover, the compact nature of the pyrrolo[3,2-*c*]quinoline structure coupled with several sites for the introduction of diversity provides an ideal opportunity for its exploitation as a combinatorial scaffold.[9] The novel structure and the unique biological activity of these natural products has encouraged us to





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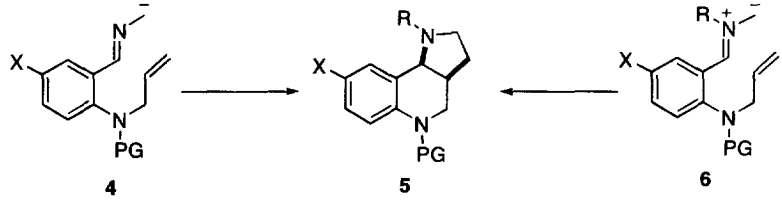
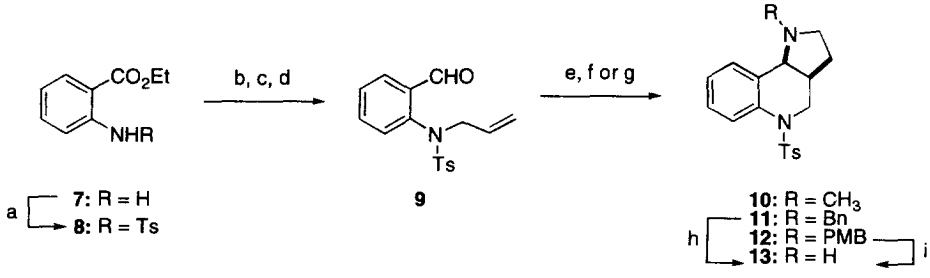
develop a short and flexible total synthesis of martinelline and martinellic acid.[10-13] Herein we outline an approach, in a model system, to the *cis* pyrroloquinoline core **3** of the natural product.



In considering possible synthetic schemes to these natural products, we determined that an intramolecular cycloaddition afforded the most concise approach. Of all the various possibilities, an intramolecular [3+2] cycloaddition appeared to be the most flexible in terms of a total synthesis and eventual analog synthesis. We considered two possibilities for this approach, employing either an azaallyl anion-alkene cycloaddition (**4**→**5**) or an azomethine ylide-alkene cycloaddition (**6**→**5**).[14,15] Herein, we describe the latter, utilizing the *in situ* formation of an azomethine ylide *via* the decarboxylative-condensation of *N*-alkylglycine derivative with an aldehyde.[14,16]

Scheme 1

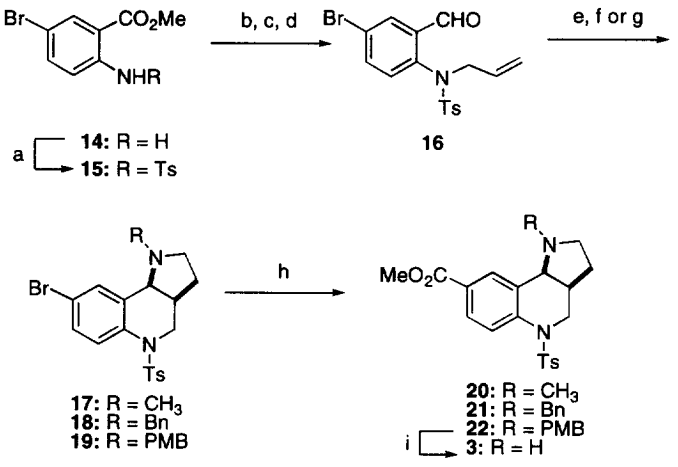


Reagents and conditions: a. TsCl, Et_3N, CH_2Cl_2, RT, 79%; b. K_2CO_3, allyl bromide, acetone, RT, 93%; c. $LiAlH_4$, THF, 0 °C, 89%; d. DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -60 °C, 75% or MnO_2-C, CH_2Cl_2, 80%; e. $CH_3HNCH_2CO_2H$, DMF, Et_3N, reflux; f. $BnHNCH_2CO_2H$.HCl, Et_3N, DMF, reflux, 75%; g. $PMBHNCH_2CO_2H$.HCl, Et_3N, DMF, reflux, 88%; h. Pd-C, H_2, MeOH, **11**→**13** 59%, **12**→**13** 50%.

Our synthetic studies commenced with the tosylation of ethyl anthranilate under standard conditions. The resulting sulfonamide **8** was treated with allyl bromide to afford the alkylated sulfonamide.[17] Reduction of the ester with LAH and Swern oxidation of the resulting alcohol gave the key aldehyde **9**. Oxidation of the alcohol to aldehyde **9** could also be achieved using carbon-supported MnO_2 in comparable yield. Heating a mixture of sarcosine (*N*-methylglycine), aldehyde **9**, and Et_3N in DMF at reflux gave rise to a new compound **10**.[14,16] ^{1}H- and ^{13}C-NMR spectroscopy indicated that the new compound was indeed the desired *N*-methyl pyrroloquinoline **10**. This was subsequently confirmed by X-ray crystallographic analysis. When this reaction was repeated utilizing *N*-benzylglycine and N-*p*-methoxybenzylglycine, the *N*-benzyl and *N*-*p*-methoxybenzyl pyrroloquinolines **11** and **12** were obtained respectively.[18] Both the *N*-benzyl- and *N*-*p*-methoxybenzyl group could be removed

by hydrogenolysis with Pd-C/H_2. However, attempts to remove the *p*-methoxybenzyl group oxidatively (DDQ, CAN) were unsuccessful.

Scheme 2



Reagents and conditions: a. TsCl, Et_3N, CH_2Cl_2, RT, 89%; b. K_2CO_3, allyl bromide, acetone, RT, 94%; c. $LiAlH_4$, THF, 0 °C, 68%; d. DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -60 °C, 73% or MnO_2-C, CH_2Cl_2, 55%; e. $CH_3HNCH_2CO_2H$, DMF, Et_3N, reflux, 70%; f. $BnHNCH_2CO_2H$.HCl, Et_3N, DMF, reflux, 81%; g. $PMBHNCH_2CO_2H$.HCl, Et_3N, DMF, reflux, 83%; h. $Pd(OAc)_2$, MeOH, DMF, NaOAc, 60 psi CO, 100 °C, **17**→**20** 94%; **18**→**21** 81%; **19**→**22** 92%; i. $Pd(OH)_2$-C, EtOH, HCl, H_2, RT, 86%.

With a successful synthesis of the tricyclic core of the natural product developed, we wished to evaluate this approach with an aromatic derivative that contained a functional group suitable for conversion into the ester group present in the natural product. In addition to serving this role, this group would ideally function as a site for the introduction of diversity. A halide appeared to meet these needs as it would participate in transition metal-mediated processes such as the Heck, Stille, and Suzuki reactions. Commercially available methyl 5-bromo-2-aminobenzoate was tosylated and allylated.[17] Reduction of the ester with LAH and oxidation of the resulting alcohol under Swern conditions afforded aldehyde **16**. Subsequent treatment of the aldehyde with sarcosine, *N*-benzylglycine and *N*-*p*-methoxybenzylglycine gave the respective *N*-alkyl 8-bromopyrroloquinoline in moderate to good yield. With the bromopyrroloquinolines in hand, it was anticipated that it would be a straightforward matter to convert them into the methyl ester *via* halogen-lithium exchange, treatment of the resulting organolithium with CO_2 and then Fischer esterification with acidic methanol. In the event this route proved problematic, however, it was found that the methyl esters could be prepared efficiently via palladium-catalyzed carbonylation of **17-19**, affording **20-22** respectively in excellent yield. Removal of the *N*-*p*-methoxybenzyl protecting group on the pyrrole nitrogen was achieved by catalytic hydrogenation with Pearlman's catalyst, affording **3** in a satisfactory 86% yield.[19]

We are currently investigating the application of this method of pyrroloquinoline ring construction in the enantiospecific synthesis of martinelline, our efforts to this end will be reported in due course.

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18. *N*-*p*-methoxybenzylglycine.HCl was prepared in 33% yield by the $NaBH_4$ mediated reductive amination of *p*-methoxybenzaldehyde with glycine and precipitation of the product with concentrated HCl.
19. **8-Methoxycarbonyl-5-(*p*-toluenesulfonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 3:** ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08 (d, *J* = 2.3 Hz, 1H), 7.88 (ddd, *J* = 8.6, 2.3, 0.5 Hz, 1H), 7.78 (d, *J* = 8.7 Hz, 1H), 7.53 (m, 2H), 7.21 (m, 2H), 4.24 (dd, *J* = 13.8, 5.4 Hz, 1H), 3.88 (s, 3H), 3.63 (d, *J* = 7.3 Hz, Bn H, 1H), 3.00 (ddd, *J* = 11.2, 8.0, 4.1 Hz, 1H), 2.90 (dd, *J* = 13.8, 12.1 Hz, 1H), 2.80 (ddd, *J* = 11.2, 7.9, 7.9 Hz, 1H), 2.38 (s, 3H), 2.16 (m, 1H), 2.05 (dddd, *J* = 12.6, 8.3, 8.3, 3.9 Hz, 1H), 1.89 (br s, 1H), 1.41 (dddd, *J* = 12.0, 8.0, 8.0, 4.0 Hz, 1H); ^{13}C NMR (125.9 MHz, $CDCl_3$): 166.5 (C=O), 144.1, 140.7, 137.2, 131.8, 131.0, 129.9, 128.7, 127.0, 126.7, 123.7, 57.1, 52.2, 48.1, 45.3, 35.3, 30.6, 21.6.