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Formal total synthesis of (±)-martinellic acid

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Abstract—A concise formal total synthesis of the pyrrolo[3,2-*c*]quinoline containing natural product, martinellic acid, has been achieved from a pyrroloquinol-2-one through addition of a copper acetylide to an iminium ion. Global deprotection and alkyne reduction then provides the tricyclic triamine, which can be converted to martinelline and martinellic acid.

The *Martinella* alkaloids (Fig. 1, **1** and **2**),[1] which were isolated from the root bark extracts of the South American medicinal plant, *Martinella iquitosensis*, have captured the attention of a number of synthetic groups.[2] The novel heterocyclic core coupled with the ability of these molecules to function as antagonists of the bradykinin receptors render these alkaloids attractive targets for total synthesis.[3] As such, several imaginative strategies have evolved for the construction of the pyrrolo[3,2-*c*]quinoline core, resulting in four distinct total syntheses,[4] and two formal total syntheses.[5] Our own efforts toward these natural products have relied on the application of azomethine ylide chemistry for the assembly of the heterocyclic core.[6] Based on these efforts, two related but strategically distinct approaches have been developed in our laboratories. The culmination of one of these studies is the subject of this communication.

Our early feasibility studies toward these natural products led to an efficient approach to C2-truncated models,[6a,b] which subsequently evolved into the preparation of 2-quinolone derivatives (e.g., **4**; PG = Bn).[6c] These latter heterocycles appeared to be ideally suited for elaboration into the natural products and congeners, provided that appropriate conditions could be developed for activation of the carbonyl bearing carbon (C2) to nucleophilic addition so that the three-carbon side chain (corresponding to C10–C12) could be introduced. It was envisioned that this could be achieved through the in situ formation of an iminium ion and subsequent nucleophilic addition (e.g., allylsilane, Fig. 1, **4** → **3**). The results of this investigation are described in this letter (Fig. 1).

Our first goal was the development of an efficient method for the conversion of the lactam into the methoxy aminal, which was expected to serve as an iminium ion precursor. After some experimentation with various reducing agents, it was found that the lactam **4** could be reduced to the aminal **6** with DIBAL-H,[7] which in turn was converted into the corresponding methoxy derivative **7** simply by treating **6** in a 4:1 mixture of methanol and chloroform at reflux (Scheme 1).[8] Although the majority of α-methoxyamine derivatives in the literature that have been converted into iminium ions containing an *N*-acyl group or other electron-withdrawing group,[9] there was sufficient precedent for the use of *N*-alkyliminium ions for us to evaluate **7** in nucleophilic addition reactions.[10] On exposure of **7** to allylsilane in the presence of $TiCl_4$,[11] a diastereoselective allyl addition reaction occurred to provide two major products. The required three-carbon addition product was isolated in 30% yield (*exo*:*endo* = 7:1), after removal of the minor diastereomer, and the elimination product **11** (ca. 50%). That the major diastereomer had the correct relative stereochemistry for use in the total synthesis was established through a NOESY experiment. Attempts to improve the efficiency of this transformation by using other Lewis acids were not successful, in fact only $TiCl_4$ led to the incorporation of the allyl group. Other Lewis acids that were investigated either led to no reaction or to the formation of the elimination products **11** and **12**. This low efficiency was compounded in attempts to hydroborate the allylated product **9**, which although the corresponding alcohol **10** was obtained, the yield was disappointingly low.

Keywords: Alkaloid; Guanidine; Copper acetylide; Heterocycle.
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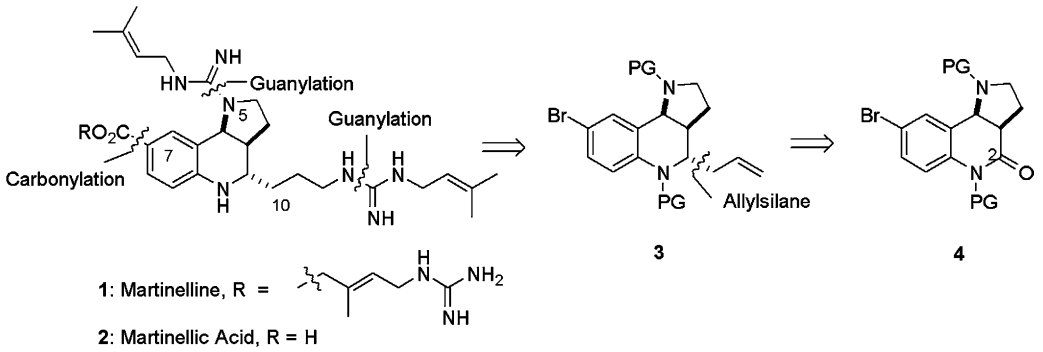
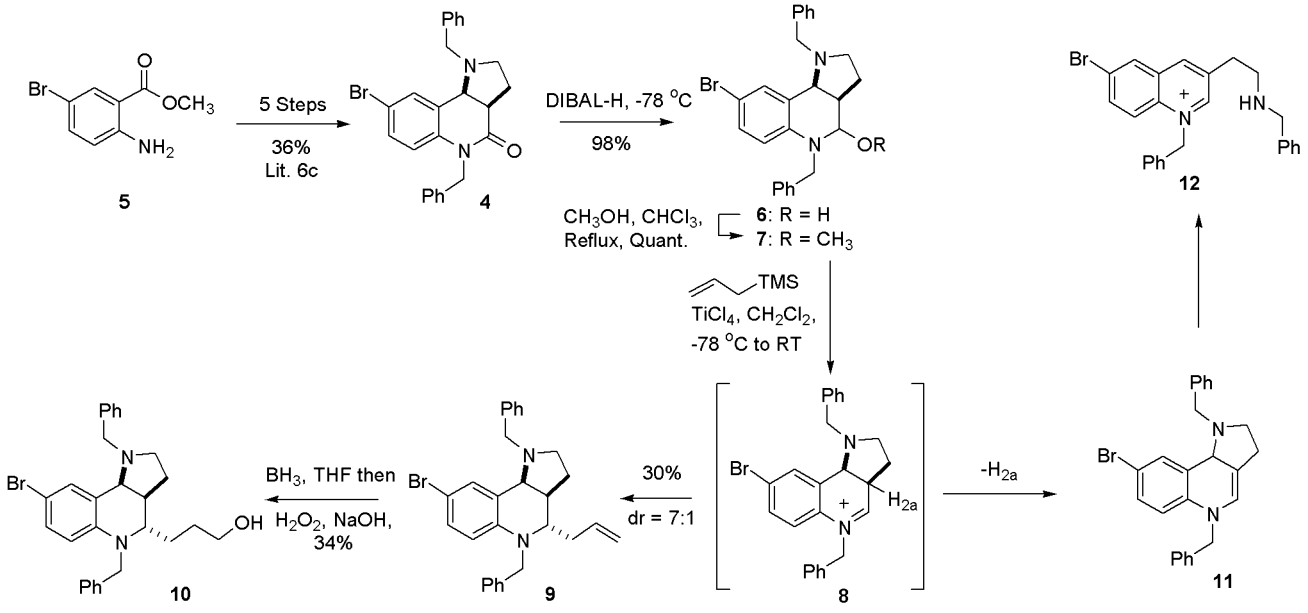
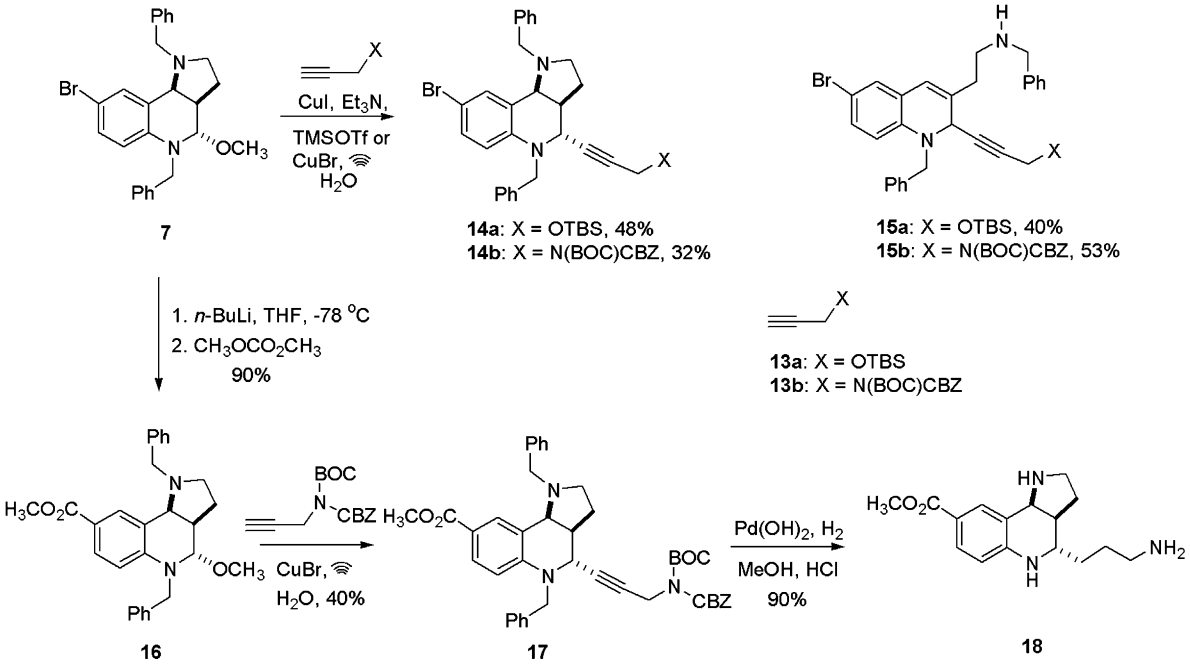


Figure 1. Retrosynthesis of the *Martinella* alkaloids.

However, when taken as a whole, these initial experiments suggested that the iminium ion **8** was formed, but that the allylsilane was not sufficiently nucleophilic, allowing the unproductive side reactions (Scheme 1, **8** → **11** → **12**) to occur to a dominant level and thus we considered some alternative three-carbon nucleophiles.[12] In order to circumvent these fragmentation issues it appeared that a more reactive three-carbon nucleophile was required, and thus metal acetylides were evaluated.[13] Initial experiments with copper acetylides promoted by Lewis acids (e.g., TMSOTf) were encouraging in that the three-carbon side chain was incorporated with reasonable efficiencies (70%), but these reactions were compromised by fragmentation of the pyrrole ring (Scheme 2, **7** → **15**), reminiscent of the side products observed in the addition of allylsilane in the presence of Lewis acids.[14] Evaluation of other metal acetylides indicated that they were less effective and so our attention returned to the copper based reactions.[15] Recently, Li and co-workers have demonstrated that copper acetylides (prepared in situ from CuBr and terminal acetylenes) add to *N*-acyl iminium ions derived from α-methoxyamines under aqueous conditions with sonication without the need to add Lewis acids or other promoters to facilitate the formation of the iminium ion.[16] Presumably, the HBr produced in the course of the reaction between the CuBr and the acetylene ionizes the α-methoxyamine. We were delighted to find that these conditions were reasonably effective in promoting addition to the iminium ion and the required adduct (**14a**, 48%) and the fragmentation product (**15a**, 40%) were formed in almost equimolar amounts (Scheme 2).[17] Some optimization was attempted by increasing the stoichiometry of the acetylide employed, but this was found to have little effect on the ratio of adduct to fragmentation product, or the overall yield. Part of the attractiveness of this general approach was that it should be feasible to use a propargyl amine derivative as the nucleophilic component, and indeed it was determined that the protected propargyl amine **13b** would add to **7** under these sonication conditions, although the ratio of addition to fragmentation decreased to 0.6:1 (^{1}H NMR analysis of the crude reaction mixture). Subsequent isolation of the two adducts provided **14b** in 32% and **15b** in 53% yield, respectively. However, rather than pursue extensive optimization on this substrate, it



Scheme 1.



Scheme 2.

was decided to introduce the carboxymethyl moiety, and then evaluate this as a substrate. It was hoped that by rendering the aromatic ring more electron deficient, the substrate would be more susceptible to nucleophilic attack and thus be less prone to fragmentation. In our previous studies a Pd-catalyzed carbonylation reaction had been employed to accomplish this,[6] but this was not viewed as a practical solution to this transformation with this more electron rich substrate. It was found that a classical lithium–bromine exchange, followed by reaction with dimethyl carbonate provided an expedient solution to this transformation, affording the ester in 90% yield (Scheme 2). The carbonylated product **16** was subjected to the alkynylation reaction with the protected propargyl amine derivative, again with sonication under aqueous conditions. We were delighted to observe that addition of the acetylide occurred, providing a single alkylated pyrroloquinoline **17** in 40% yield.[18] The material balance was a small (<5%) quantity of unreacted starting material plus 40% of the fragmentation product. The stereochemical outcome of these acetylide addition reactions of **16** are critical to the application of these adducts to the total synthesis of the *Martinella* alkaloids. Coupling constants between H2 and H2a are not diagnostic due to the similarity (ca. 2 Hz) found between *cis* and *trans* isomers of related systems. Fortunately, NOESY experiments were diagnostic (key NOE's are indicated in Fig. 2) and provided confirmation that the relative configuration matches that found in the target alkaloids. Reduction of the alkyne along with global deprotection of the benzyl groups, the Cbz moiety and the Boc group was accomplished using $Pd(OH)_2$ in the presence of HCl, providing the tricyclic triamine in 90% yield. This material has served as a late-stage intermediate in all of the published total syntheses of both martinelline and martinellic acid.[4,19]

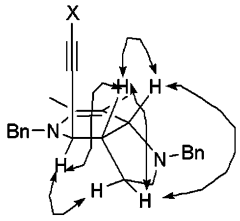


Figure 2. Key NOE interactions derived from NOESY experiments for assignment of relative stereochemistry of acetylide adducts.

In summary, a concise formal total synthesis of the tricyclic triamine core of martinelline and martinellic acid has been described, which relies on a stereoselective addition of a highly functionalized copper acetylide to an in situ generated iminium ion to construct the C2–C10 bond. A sequence of 10 linear steps provides the fully elaborated core in an overall yield of 11% from the bromoanthranilate derivative **5**. No chromatography of intermediates from the initial quinolone **4** until the acetylide adduct **17** is required.[20] The design of the synthetic approach is such that significant flexibility can be envisioned in the potential electrophilic (**7** → **16**) or nucleophilic partners (**16** → **17**), and thus this synthetic approach should serve as an efficient entry for extended SAR studies. Currently, efforts to improve the efficiency of the acetylide addition step are underway, and will be reported in a full manuscript on this and related studies.

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References and notes

1. Witherup, K. M.; Ransom, R. W.; Graham, A. C.; Bernard, A. M.; Salvatore, M. J.; Lumma, W. C.; Anderson, P. S.; Pitzenberger, S. M.; Varga, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 6682.
2. For a recent review of approaches to pyrrolo[3,2-*c*]quinolines, including the *Martinella* alkaloids see: Nyerges, M. *Heterocycles* **2004**, *63*, 1685; For other contributions in this area see: (a) Makino, K.; Hara, O.; Takiguchi, Y.; Katano, T.; Asakawa, Y.; Hatano, K.; Hamada, Y. *Tetrahedron Lett.* **2003**, *44*, 8925; (b) Hara, O.; Sugimoto, K.; Makino, K.; Hamada, Y. *Synlett* **2004**, 1625; (c) Hara, O.; Sugimoto, K.; Hamada, Y. *Tetrahedron* **2004**, *60*, 9381.
3. Bock, M. G.; Longmore, J. *Curr. Opin. Chem. Biol.* **2000**, *4*, 401.
4. (a) Ma, D.; Xia, C.; Jiang, J.; Zhang, X. *J. Org. Lett.* **2001**, *3*, 2189; (b) Xia, C.; Heng, L.; Ma, D. *Tetrahedron Lett.* **2002**, *43*, 9405; (c) Ma, D.; Xia, C.; Jiang, J.; Zhang, J.; Tang, W. *J. Org. Chem.* **2003**, *68*, 442; (d) Snider, B. B.; Ahn, Y.; O'Hare, S. M. *Org. Lett.* **2001**, *3*, 4217; (e) Powell, D. A.; Batey, R. A. *Org. Lett.* **2002**, *4*, 2913.
5. (a) Hadden, M.; Nieuwenhuyzen, M.; Potts, D.; Stevenson, P. J.; Thompson, N. *Tetrahedron* **2001**, *57*, 5615; (b) Takeda, Y.; Nakabayashi, T.; Shirai, A.; Fukumoto, D.; Kiguchi, T.; Naito, T. *Tetrahedron Lett.* **2004**, *45*, 3481.
6. (a) Lovely, C. J.; Mahmud, H. *Tetrahedron Lett.* **1999**, *40*, 2079; (b) Mahmud, H.; Lovely, C. J.; Dias, H. V. R. *Tetrahedron* **2001**, *57*, 4095; (c) He, Y.; Mahmud, H.; Wayland, B. R.; Dias, H. V. R.; Lovely, C. J. *Tetrahedron Lett.* **2002**, *43*, 1171; See also: Martin, S. F.; Cheavens, T. H. *Tetrahedron Lett.* **1989**, *30*, 7017; For intermolecular variants see: Nyerges, M.; Fejes, I.; Töke, L. *Synthesis* **2002**, 1823.
7. For examples of the formation of iminium ions from lactams by DIBAL reduction: (a) Overman, L. E.; Lesuisse, D.; Hashimoto, M. *J. Am. Chem. Soc.* **1983**, *105*, 5373; (b) Ahn, K. H.; Lee, S. J. *Tetrahedron Lett.* **1992**, *33*, 507.
8. Presumably, the trace amounts of HCl in commercial chloroform are sufficient to catalyze the exchange reaction.
9. (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817; (b) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367; (c) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431; See also: (d) Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K.; Kanzawa, T.; Tsuda, K. J. *Org. Chem.* **1984**, *49*, 3711; (e) Luker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 8131; (f) Kinderman, S. S.; VanMaarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Synthesis* **2004**, 1413.
10. See Ref. 6, also: Ramsden, N. G.; Fleet, G. W. J.; Namgoong, S. K. *J. Chem. Soc., Perkin Trans. 2* **1991**.
11. For a recent example of allylsilane addition to *N*-acyliminium ions: Kiewel, K.; Tallant, M.; Sulikowski, G. A. *Tetrahedron Lett.* **2001**, *42*, 6621.
12. For example, cyanide, in the form of TMSCN added very smoothly to either **6** or **7** to provide a single α-cyanoamine. A complete description of these studies will be reported in a full manuscript on this chemistry.
13. Wei, C.; Li, Z.; Li, C.-J. *Synlett* **2004**, 1472, and references cited therein.
14. Presumably fragmentation proceeds addition, which occurs via the quinolinium ion **12**. For the addition of metal acetylides to quinolinium ions see: (a) Porco, J. A.; Schoenen, F. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 7410; (b) Rezgui, F.; Mangeney, P.; Alexakis, A. *Tetrahedron Lett.* **1999**, *40*, 6241.
15. The use of Grignards, organolithiums, zinc acetylides, and silver acetylides was unsuccessful.
16. Zhang, J.; Wei, C.; Li, C.-J. *Tetrahedron Lett.* **2002**, *43*, 5731.
17. It should be noted that the hydroxy aminal can be employed as a substrate in the reaction with the copper acetylide with comparable efficiency.
18. Compound **15** (100 mg, 0.22 mmol) and *N*-Boc-*N*-Cbz-propargylamine (190 mg, 0.66 mmol) were mixed efficiently in a test tube. Then CuBr (97 mg, 0.66 mmol) was added followed by addition of water (3 mL) and mixed by efficient magnetic stirring. The reaction mixture was sonicated (Fischer Scientific FS20H) for 3 h under N_2 protection and in a darkened fume hood. After cooling to room temperature (the bath temperature increases to ca. 40–45 °C during the course of the reaction), the reaction mixture was partitioned between CH_2Cl_2 and 10% aqueous NH_3 solution. The organic layer was separated and further washed with 10% NH_3 solution, H_2O, brine, dried (Na_2SO_4), and concentrated. The crude oil was purified by column chromatography (gradient elution with hexanes–EtOAc, 6:1 → 1:1) to provide **16** (63 mg, 40%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.78 (d, J = 2.0 Hz, 1H), 7.74 (dd, J = 8.8, 2.0 Hz, 1H), 7.37–7.26 (m, 8H), 7.25–7.18 (m, 7H), 6.67 (d, J = 8.8 Hz, 1H), 5.18 (s, 2H), 4.93 (d, J = 16.9 Hz, 1H), 4.69 (d, J = 16.9 Hz, 1H), 4.37 (d, J = 1.5 Hz, 2H), 4.28 (dt, J = 8.8, 1.5 Hz, 1H), 4.21 (d, J = 13.0 Hz, 1H), 3.83 (s, 3H), 3.36 (d, J = 5.1 Hz, 1H), 3.20 (d, J = 13.0 Hz, 1H), 2.89 (ddd, J = 9.0, 9.0, 3.7 Hz, 1H), 2.45 (m, 1H), 2.19 (ddd, J = 9.8, 9.5, 7.1 Hz, 1H), 2.04 (m, 1H), 1.78 (m, 1H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.3, 153.0, 151.1, 149.0, 140.0, 137.8, 135.4, 133.6, 130.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 127.1, 127.0, 126.8, 120.4, 117.9, 112.6, 83.6, 81.6, 80.6, 68.7, 63.0, 57.0, 53.0, 52.3, 51.7, 50.8, 41.5, 36.4, 28.0, 27.1; FT-IR (neat, cm^{-1}): 3062, 3006, 3030, 2979, 2945, 2796, 1794, 1756, 1711, 1610, 1509.
19. We have prepared this material independently via an alternative route and found that the spectroscopic data agrees in all respects.
20. In fact, only two chromatographic purifications are necessary from **5** → **4**.