Natural Products

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Enantioselective Total Synthesis of (−)-Martinellic Acid

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Abstract: *An enantioselective total synthesis of martinellic acid is described. The pyrroloquinoline alkaloid core is efficiently prepared from a quinoline, employing a method which relies on a newly developed Cu-catalyzed enantioselective alkynylation using the chiral imidazole-based biaryl P,N ligand StackPhos to establish the absolute stereochemistry. The remaining carbon atoms are then installed by means of a diastereoselective Pd-catalyzed decarboxylative allylation and the synthesis is completed after straightforward functional-group manipulation. This new synthetic method enables the most concise enantioselective synthesis of this important class of molecules to date.*

The pyrroloquinoline alkaloids (−)-martinellic acid **1** and (+)-martinelline **2** were isolated by a group at Merck[1] who were studying the root bark extracts of *Martinella iquitoensis* used by South American indigenous peoples for treating eye infirmities such as conjunctivitis (Figure 1).[2–4] Witherup,

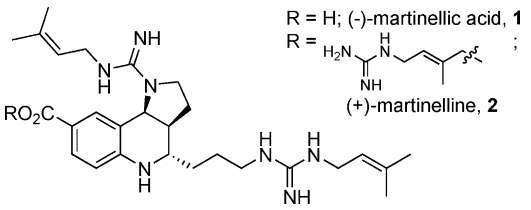
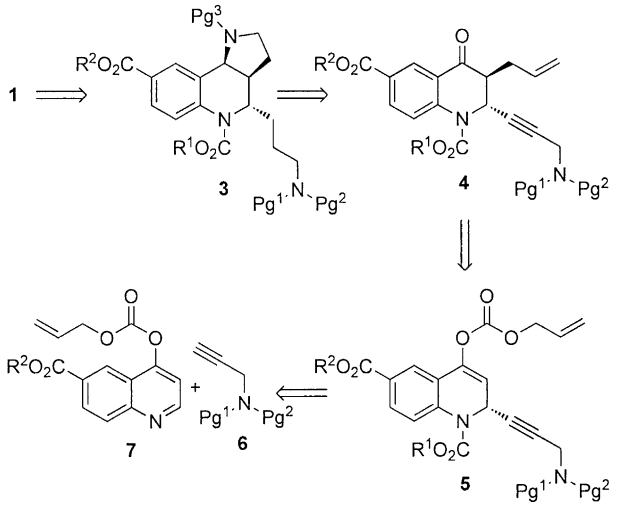


Figure 1. *Martinella* alkaloids.

Varga, and co-workers determined the *Martinella* alkaloid structures **1** and **2**, which are composed of a pyrroloquinoline core structure that was previously unknown in natural products chemistry.[1] These compounds were found to possess a variety of different biological activities. They were the first reported nonpeptide bradykinin receptor antagonists (μM), exhibit anti-α-adrenic activity (nM), and are moderately effective antibiotics against both Gram-positive and Gram-negative bacteria.[1]

The *martinella* alkaloids have attracted significant continued attention from the synthetic community, likely because of the combination of interesting biological activity and unique structural features. These efforts initially centered on methods to prepare the novel pyrroloquinoline core[5] and the first total synthesis was reported by Ma et al. in 2001.[6] Additional syntheses of the natural products in both racemic[7] and nonracemic[8] form continue to appear.[9] Batey and Powell reported an elegant nine-step synthesis of (±)-martinelline, but described their structures as "deceptively simple".[7b] However, if synthetic efficiency is assessed in terms of the step count, enantioselective synthesis has proven considerably more difficult. Although there are only three stereogenic centers, the most recent synthesis was reported by Davies et al. in 2013 and required 20 steps.[8d] This step count is common among the enantioselective syntheses reported to date and the relatively high number is indicative of the inherent synthetic challenges embedded in what speciously appear to be relatively simple structures. Considering previous approaches, we felt that a direct route to these alkaloids from the corresponding quinoline would be advantageous; however, our strategy would necessitate the development of new synthetic method (see below). Herein we report a concise total synthesis of martinellic acid **1** that relies on a new enantioselective Cu-catalyzed alkynylation using the imidazole-based biaryl ligand StackPhos[10] to establish the absolute stereochemistry in the early stages of the synthesis.

Our initial retrosynthetic analysis required the efficient generation of ketone **4**, which we believed would be rapidly and easily converted into martinellic acid by standard synthetic methods, thus streamlining the synthesis. As such, introduction of the prenyl-substituted guanidines would occur at a late stage leading back to the differentially protected *martinella* core structure **3** (Scheme 1). It seemed prudent to design a synthesis that could differentiate the three nitrogen atoms and the carboxylate for ease in substituting these positions to probe biological activity. The pyrrolidine ring of



Scheme 1. Retrosynthetic analysis. Pg = protecting group.

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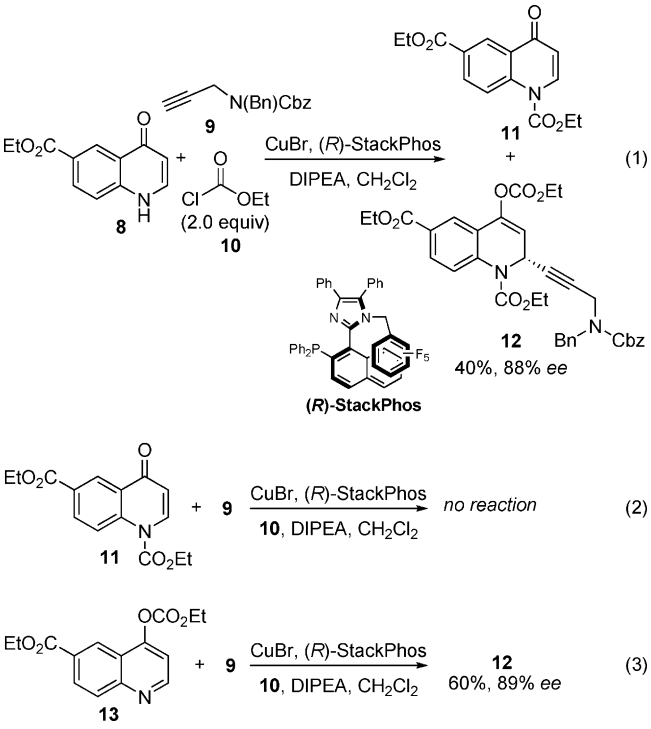
the core would be derived from a double reductive amination of a dicarbonyl compound that should be available from the α-allyl ketone **4**. The 1,2-*trans* stereochemistry required here should be readily accessible by a variety of ketone α-allylation methods, and a diastereoselective Pd-catalyzed decarboxylative allylation[11] leads back to the allylic carbonate **5**. Further simplification of **5** to the corresponding quinoline **7** and alkyne **6** was postulated to be a good disconnection, however, at the outset no such enantioselective alkynylation reaction was known[12] and it was unclear if an allylic carbonate would be compatible.

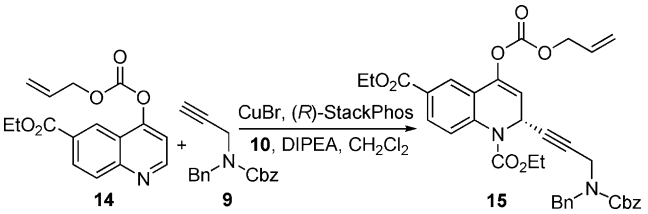
As part of a program directed at using the imidazole-based chiral biaryl ligand StackPhos, we recently developed a highly enantioselective Cu-catalyzed dearomative quinoline alkynylation reaction similar to what would be needed here.[13] The method focused on using simple quinolines, and it was unknown what effect the 4-OR substituents, specifically a 4-allyl carbonate, would have on both the reactivity and selectivity. However, we felt that if the product could be formed, the allylic carbonate should survive the mild reaction conditions. Furthermore, it seemed possible to form the carbonate in situ by reaction of excess chloroformate with a quinolone, which would be an exceptionally convenient starting material. To probe this hypothesis, the study commenced with preliminary experiments on a simplified system using 2 equivalents of ethyl chloroformate (**10**), quinolone **8**, and alkyne **9** [Scheme 2; Eq. (1)]. Under catalytic conditions with (*R*)-StackPhos (5.5 mol%), CuBr (5 mol%), and DIPEA (*N*,*N*-diisopropylethylamine), the desired product **12** was isolated in 40% yield and 88% *ee* along with carbamate **11**. While these results were quite encouraging, substantial efforts to minimize the formation of **11** and favor **12** were unsuccessful. Further studies demonstrated that, once formed, carbamate **11** does not undergo further reaction [Scheme 2, Eq. (2)], but that, once formed, carbonate **13** is a viable substrate for the formation of **12** [Scheme 2, Eq. (3)]. Interestingly, this suggested that the outcome was governed by the partitioning between **11** and **13** in the first acylation step and also demonstrated that a C4-carbonate-substituted quinoline could be a suitable substrate. Further optimization with respect to both yield and selectivity would be needed, but more importantly it was unclear if the allylic carbonate would be stable under the reaction conditions, or if there might be *O* to *N* crossover by acyl transfer.

To this end, the allylic carbonate **14** was prepared in three steps from benzocaine, an inexpensive and convenient starting material that is available in large quantities. The reaction between **14** and the *N*-protected propargyl amine **9**, which had been demonstrated to work in the initial experiments, was optimized with the StackPhos/CuBr conditions (Table 1). Fortunately, under these conditions, minimal amounts of acyl transfer products were detected and the allylic carbonate persisted to form the desired product **15** in all cases. As a starting point, the reaction (employing 2 equivalents of **9** and 2 equivalents of **10**) was conducted at 0 °C with 0.1 M of **14** (Table 1, entry 1). These conditions afforded **15** in 86% *ee* and the reaction progressed to 95% conversion after 15 h. Lowering the temperature predictably decreased the conversion but the selectivity was improved to 89% *ee* (entry 2).



Scheme 2. Initial enantioselective alkynylation experiments. Conditions [Eq. (1)]: CuBr (5 mol%), (*R*)-StackPhos (5.5 mol%), DIPEA (2.8 equiv). Conditions [Eqs. (2, 3)]: **9** (2 equiv), **10** (1 equiv), CuBr (5 mol%), (*R*)-StackPhos (5.5 mol%), DIPEA (1.4 equiv). Bn = benzyl.

Table 1: Optimization of the Cu-catalyzed alkynylation.



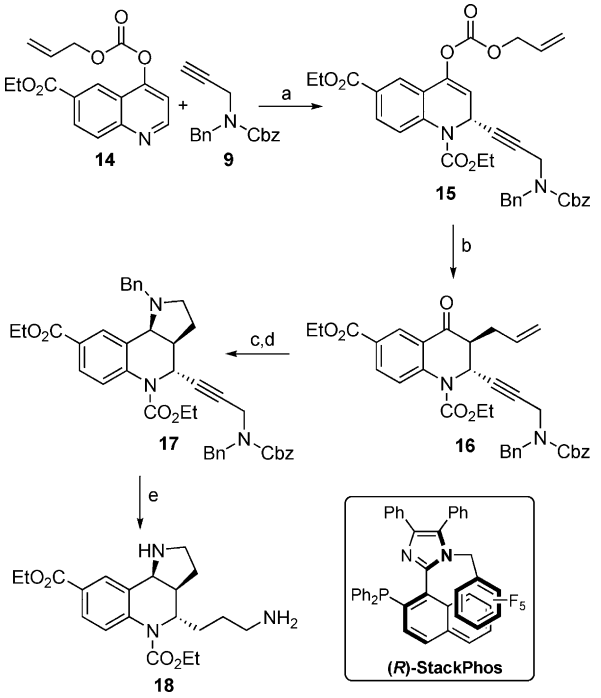
entry[a]	**14** [M]	Temperature	Time	conversion [%][b]	*ee* [%][c]
1	0.1	0 °C	15 h	95	86
2	0.1	−25 °C	80 h	50	89
3	0.2	−25 °C	42 h	60	89
4	0.4	−25 °C	48 h	70[d]	91
5	0.8	−25 °C	24 h	30	87

[a] Conditions: **9** (2 equiv), **10** (2 equiv), CuBr (5 mol%), (*R*)-StackPhos (5.5 mol%), DIPEA (2.8 equiv). [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by HPLC with a chiral stationary phase. [d] Yield of isolated product.

Increasing the concentration of **14** first to 0.2 M (entry 3) and then 0.4 M (entry 4) restored reactivity and the product was isolated in an acceptable 70% yield in 91% *ee* under these conditions. Interestingly, further increasing the concentration (entry 5) did not appear to significantly benefit the reaction. Carbamate **15** appeared to be a good starting material as it was readily available, but more importantly provided four different carbonyl groups (ester, carbonate, carbamate, Cbz;

Cbz = benzyloxycarbonyl) that could all be selectively manipulated in distinct ways.

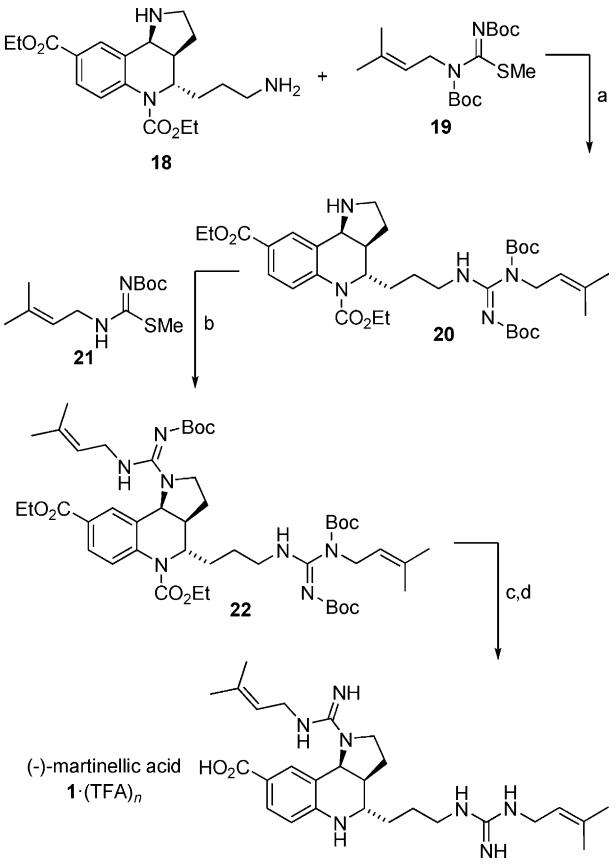
With the development of a reliable synthetic method for **15**, the reaction was scaled up to provide sufficient material to move forward. It was found that on larger scales the catalyst loading could be reduced to 2.0 mol% without negatively impacting the yield or *ee* value, although a prolonged reaction time was required (Scheme 3). Under these conditions, **15** was



Scheme 3. Synthesis of the pyrroloquinoline core structure. a) EtOC(O)Cl (2.0 equiv), CuBr (2.0 mol%), StackPhos (2.2 mol%), DIPEA (2.8 equiv), CH_2Cl_2, −30°C, 90 h, 73%, 91% *ee*; b) $[Pd(PPh_3)_4]$ (2.5 mol%), THF, RT, 3 h, 80%, d.r. ≥ 25:1; c) O_3, CH_2Cl_2, −78°C, 10 min; DMS −78°C to RT, 18 h, 66%; d) $BnNH_2$·HCl, $NaCNBH_3$, MeOH, RT, 18 h, 72%; e) $Pd(OH)_2$, H_2, EtOAc, MeOH, 50 psi, RT, 18 h, 82%. DMS = dimethylsulfide.

prepared in 73% yield and 91% *ee*. This set the stage for the decarboxylative allylation step. Although Stoltz et al. and others have reported many syntheses that rely on enantioselective decarboxylative allylation to set the absolute stereochemistry, diastereoselective reactions are much less frequently encountered in total synthesis.[14] Treatment of **15** with $[Pd(PPh_3)_4]$ (2.5 mol%) smoothly provided the α-allyl ketone **16** in 80% yield with a ≥25:1 ratio of diastereomers, favoring the desired *trans* isomer. The olefin of the allyl group was then selectively cleaved under ozonolysis conditions to provide a 1,4-diacarbonyl compound that was subsequently transformed into the pyrrolidine **17** in 72% yield by a double reductive amination using benzyl amine and sodium cyanoborohydride.[15] Under hydrogenation conditions, the alkyne was reduced to an alkane and the three nitrogen protecting groups cleaved in 82% yield to reveal the *martinella* alkaloid core structure **18**.

To complete the synthesis of martinellic acid **1**, introduction of the guanidine side-chains, deprotection of the nitrogen, and saponification of the ester remained. With the ester and carbamate in place in **18**, the primary and secondary amines should have differential reactivity that could be exploited for sequential introduction of the side-chains to form compounds that may prove useful to probe biological activity. Gratifyingly, it was found that the primary amine could be selectively functionalized in 66% yield with the bis-Boc reagent **19** (Scheme 4; Boc = *tert*-butoxycarbonyl).[7b]



Scheme 4. Completion of the synthesis. a) Et_3N, CH_3CN, RT, 14 h, 66%; b) $HgCl_2$, Et_3N, DMF, RT, 3 h, 74%; c) 1 N NaOH, MeOH, 65°C, 16 h, 87%; d) TFA, anisole, CH_2Cl_2, RT, 18 h, 70%. DMF = dimethylformamide; TFA = trifluoroacetic acid.

Using the more reactive mono-Boc reagent **21**,[7b] the remaining secondary amine in **20** could then be guanidinylated to form **22** in 74% yield. Deprotection of the carbamate and saponification of the ester proceeded in 87% yield, completing a formal synthesis of martinelline.[7b] Finally, deprotection of the Boc groups[6] yielded martinellic acid **1** as the trifluoroacetic acid (TFA) salt. The spectroscopic characterization of this compound completely matched previously reported spectral data.[6–8] The observed optical rotation verified that we had prepared the correct enantiomer of the natural product, (−)-martinellic acid **1**.[16]

In conclusion, we have reported a catalytic enantioselective total synthesis of (−)-martinellic acid that proceeds in twelve steps from benzocaine and employs a new strategy to

assemble the *martinella* alkaloid core. Key steps include an enantioselective Cu-catalyzed alkyne addition to an allyl carbonate substituted quinolone, followed by diastereoselective decarboxylative allylation, and a double reductive amination to set both the absolute and relative stereochemistry. This route is the most concise enantioselective synthesis of (−)-martinellic acid to date and highlights the power of the new catalytic enantioselective alkyne addition method using StackPhos as the ligand.

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