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Total synthesis of (−)-martinellic acid

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Abstract—An enantioselective formal total synthesis of the pyrrolo[3,2-*c*]quinoline natural product martinellic acid has been achieved. The key steps involve a Pd-catalyzed aryl amidation reaction of a pyrroglutamate derivative, an intramolecular [3+2] azomethine ylide–alkene cycloaddition and a reductive ring opening reaction.
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The *Martinella* alkaloids (Fig. 1, **1** and **2**), which were isolated from the root bark extracts of the South American medicinal plant,[1] *Martinella iquitosensis*, have captured the attention of a number of synthetic groups.[2–18] The novel heterocyclic core of these molecules coupled with the ability of these molecules to function as antagonists of bradykinin render these alkaloids attractive targets for total synthesis.[2] As such, several imaginative strategies have evolved for the construction of the pyrrolo[3,2-*c*]quinoline core,[2–18] resulting in five total syntheses,[8c,9c,12,18] and three formal total synthesis.[6d,7e,16b] Of these syntheses, five lead to racemic material, whereas only three approaches are enantioselective.

Our own efforts towards these natural products have relied on the application of azomethine ylide chemistry for the assembly of the heterocyclic core and have resulted in the development of two related, but strategically different, approaches.[7] One of these approaches is depicted retrosynthetically in Figure. 1. Strategically, this approach involves the incorporation of the three-carbon containing side chain at the outset of the synthesis through an aryl-amidation reaction with a chiral, non-racemic lactam.[19] Transformation of the protected alcohol into an olefin and conversion of the ester moiety to an aldehyde then sets the stage for an intramolecular [3+2] azomethine ylide–olefin cyclization via **4** to

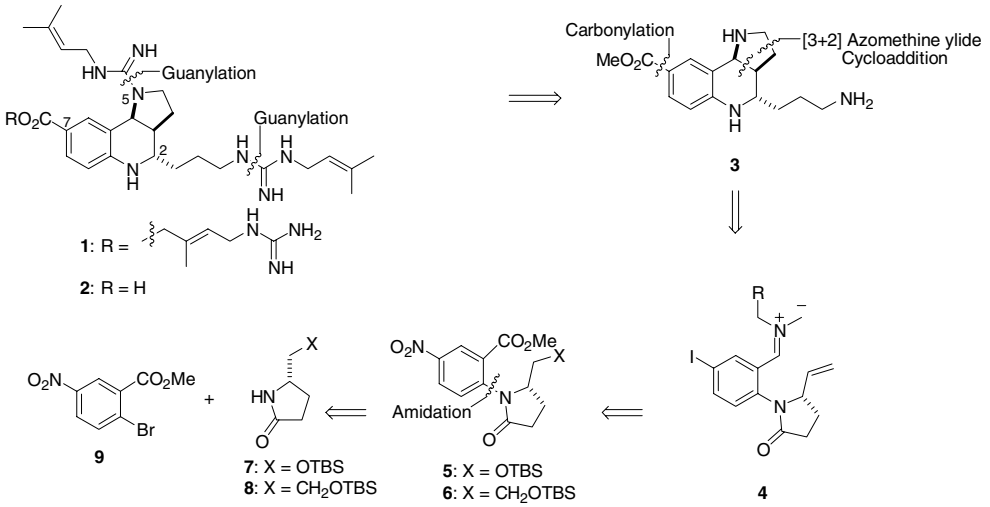

Figure 1. Retrosynthetic analysis of the *Martinella* alkaloids.

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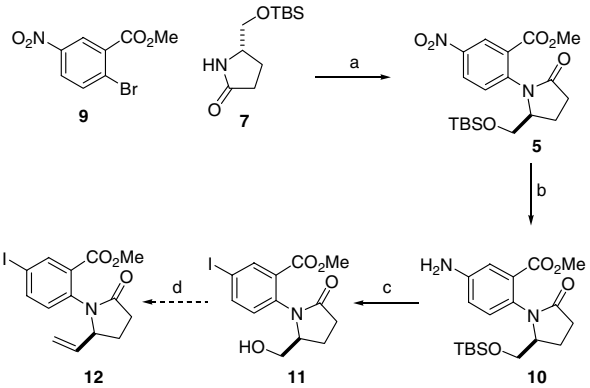
provide a tetracyclic intermediate which contains all but one of the carbon skeleton.[20] Further elaboration of this adduct by reported procedures should then provide the natural products. This series of disconnections permits this use of pyroglutamate-derived lactam **7** (or **8**) as both the source of the C2 side chain carbons and asymmetry.

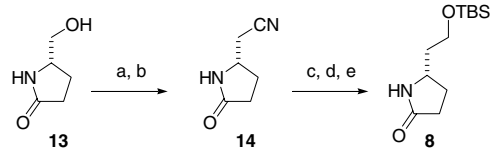
Our first generation approach involved the cross-coupling of aryl bromide **9** and the pyroglutamate derived lactam **7**[22] in 68% yield (Scheme 1).[23] Reduction of the nitro group (Pd/H_2) provided amine **10**, which was converted into the iodide through diazotization (n-$C_5H_{11}ONO$) and treatment with CH_2I_2.[24] Some desilylation occurred during this process and so the deprotection was completed through the addition of TBAF to provide **11**. It was our intent to convert the resulting alcohol into the corresponding olefin **12** via the aldehyde. However, despite extensive experimentation, we were unable to obtain either the aldehyde or alkene from **11** in useful yields for us to proceed with the synthesis. Smith and co-workers had encountered similar difficulties in their attempts to oxidize an *N*-vinyl derivative related **12**.[25] Interestingly, Naito and co-workers successfully obtained the olefin from a related alcohol through a Moffat oxidation and Wittig reaction with a stablized ylide.[16b] However, rather than engage in an extensive trial and error search for a suitable oxidant, it was decided to modify the approach and perform the homologation prior to cross-coupling of the lactam.

Our studies commenced with the preparation of the homologated silyl ether **8** (Scheme 2). This was achieved through application of procedures reported by Lhommet and co-workers.[26] The commercially available alcohol **13** was tosylated and then reacted with cyanide anion to provide the corresponding nitrile **14**. Hydrolysis of the nitrile in the presence of methanol gave the methyl ester which was readily reduced to the corresponding alcohol with $NaBH_4$ and was protected as silyl ether **8**.[27] Amide **8** was subjected to a Pd-catalyzed cross-coupling reaction with the activated trisubstituted aryl bromide **9** (Scheme 3).[23] This adduct was then elaborated in an essentially identical fashion to **5**. Reduction of the nitro group was readily achieved with Pd/H_2 to give amine **15**, which was subjected to diazotization ($C_5H_{11}ONO$) in the presence of CH_2I_2 to give aryl iodide **16**.[24] As with the lower homolog **10**, some desilylation occurred and so this was completed by the addition of TBAF. At this point the primary alcohol was dehydrated by conversion into the aryl selenide and treatment with H_2O_2 to afford the terminal olefin.[28]

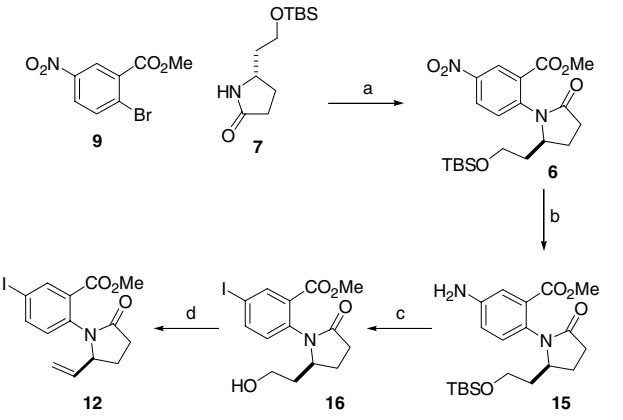
Manipulation of the oxidation level of the aryl methyl ester was achieved by reduction with $LiBH_4$ at 0 °C, which occurred to provide the benzyl alcohol predominantly (Scheme 4). A small quantity of reductive cleavage of the lactam to the amino alcohol (ca. 15%) was observed. Oxidation of the benzyl alcohol to the corresponding benzaldehyde derivative **17** could be achieved with MnO_2 in good yield. At this point our approach merges with Snider's reported synthesis of **2**,[8c] although our substrate is optically active and contains a 7-iodo substituent rather than a bromide. With the unsaturated benzaldehyde derivative in hand it was treated with *N*-benzylglycine.HCl, forming the corresponding azomethine ylide **4** in situ (Fig. 1, R = Ph), which underwent cycloaddition with the pendant olefin to provide the key tetracycle **18** in 65% yield, in addition a small amount (9%) of the diastereomer epimeric at C2a and C5a was obtained.[29,30] Reductive ring opening of the lactam with $LiBH_4$ gave amino alcohol **19**, which was converted into the tricyclic triamine in an essentially analogous fashion to that described by Snider et al.[8] Acylation of the aniline nitrogen and the alcohol provided **20**, which was carbonylated according to the conditions previously identified in our group to afford the corresponding methyl ester.[20b] Partial deacylation



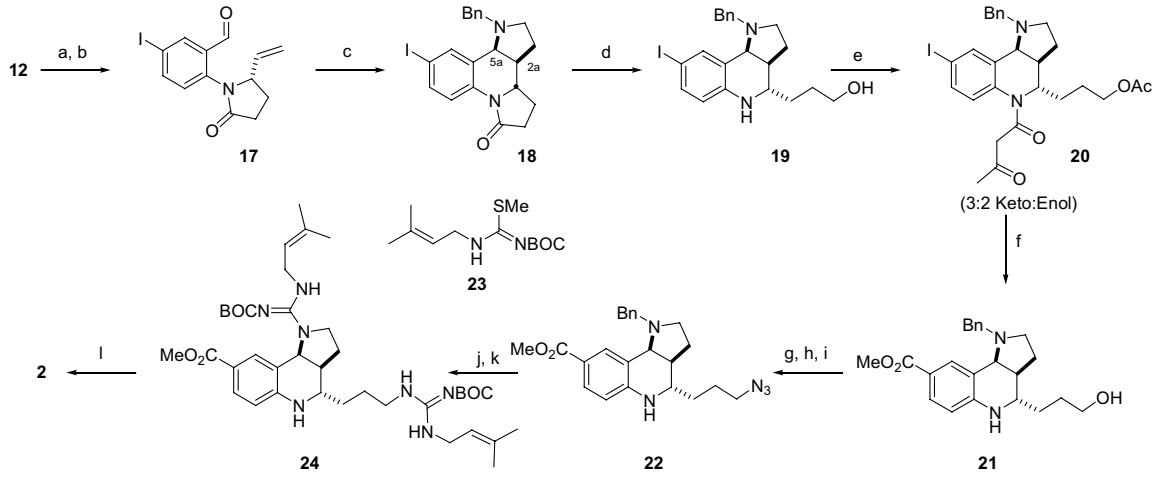
Scheme 1. Reagents and conditions: (a) Pd_2dba_3, xantphos, Cs_2CO_3, dioxane, 68%; (b) Pd/C, H_2, EtOH, 97%; (c) (i) n-$C_5H_{11}ONO$, CH_2I_2; (ii) TBAF, THF, 75–80%; (d) (i) various oxidants;[21] (ii) olefination.



Scheme 2. Reagents and conditions: (a) TsCl, Et_3N, CH_2Cl_2, 75%; (b) NaCN, DMSO, 95%; (c) H_2SO_4, H_2O, MeOH, 55%; (d) $NaBH_4$, MeOH, 90%; (e) TBSCl, imidazole, DMF, 95%.



Scheme 3. Reagents and conditions: (a) Pd_2dba_3, xantphos, Cs_2CO_3, dioxane, 61%; (b) Pd/C, H_2, EtOH, 90%; (c) (i) n-$C_5H_{11}ONO$, CH_2I_2; (ii) TBAF, THF, 70%; (d) (i) o-$NO_2C_6H_4SeCN$, PBu_3, THF; (ii) H_2O_2, 85%.



Scheme 4. Reagents and conditions (a) $LiBH_4$, MeOH, 0 °C, 80%; (b) MnO_2, CH_2Cl_2, 90%; (c) $BnHNCH_2CO_2H{\cdot}HCl$, PhH, Et_3N, reflux, 65% (+9% C2a,C5a epimer); (d) $LiBH_4$, MeOH, THF, reflux, 88%; (e) Ac_2O, Et_3N, CH_2Cl_2, 80%; (f) (i) $Pd(OAc)_2$, NaOAc, DMF, MeOH, CO (60 psi); (ii) NaOMe, MeOH, 96%; (g) TFAA, pyridine, CH_2Cl_2, 55%; (h) (i) MsCl, Et_3N, CH_2Cl_2; (ii) NaN_3, 60% (two steps); (i) NaOMe, MeOH, 80%; (j) $Pd(OH)_2$, H_2, MeOH, HCl, 95%; (k) **23**, $AgNO_3$, 62%; (l) Lit.[12]

occurred during this reaction which was taken to completion through exposure to NaOMe to afford **21**, which corresponds to a racemic intermediate in the Snider synthesis. Treatment with trifluoroacetic anhydride protects the quinoline nitrogen, prior to activation of the alcohol with mesyl chloride and reaction with sodium azide providing the corresponding azide **22**. Catalytic hydrogenation converted the azide to the amine and simultaneously leads to cleavage of the *N*-benzyl group, providing tricyclic triamine **3** as the HCl salt.[8c] Guanylation according to Ma's protocol with **23**[31] and $AgNO_3$ gave **24**, which is the same intermediate as both the Ma and Iwabuchi syntheses. It should be noted that our own material exhibited an optical rotation essentially identical to that obtained by the Ma group, but substantially different from the Iwabuchi group. Both the Ma and Iwabuchi groups have converted this material into **2**, and therefore the synthesis of **24** constitutes a formal total synthesis of **2**.[32]

In summary, a concise and formal enantiospecific total synthesis of martinellic acid has been described, which relies on a Pd-catalyzed aryl amidation reaction of non-racemic lactams and an intramolecular azomethine ylide/alkene cycloaddition. Preparation and analysis of racemic intermediates suggest that the key cycloaddition proceeds without racemization.

Acknowledgements

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29. Data for **17**: mp = 191–193 °C. $[\alpha]_D$ −80.9 (*c* 0.44, $CHCl_3$). ^1H NMR $\delta = 8.62$ (d, $J = 9.2$ Hz, 1H), 7.61–7.59 (dd, $J = 9.2$, 2.0 Hz, 1H), 7.56 (d, $J = 2.0$ Hz, 1H), 7.25–7.21 (m, 5H), 4.28 (d, $J = 12.4$ Hz, 1H), 4.05 (ddd, $J = 17.0$, 9.6, 8.0 Hz, 1H), 3.16 (d, $J = 3.7$ Hz, 1H), 3.12 (d, $J = 12.4$ Hz, 1H), 2.92 (ddd, $J = 9.7$, 7.0, 3.7 Hz, 1H), 2.65–2.59 (m, 1H), 2.56–2.52 (m, 1H), 2.36–2.34 (m, 1H), 2.22–2.17 (m, 1H), 2.06–2.0 (m, 1H), 1.69–1.57 (m, 3H); ^{13}C NMR $\delta = 174.2$, 140.2, 139.6, 137.4, 136.9, 128.4 (2C), 128.3, 127, 126.7 (2C), 121, 85.9, 64, 58.2, 57.2, 51.3, 41.5, 32.3, 24.1, 23.8; FT-IR (KBr, cm^{-1}): 2928, 2785, 1693, 1481, 1367. ESI-MS (*m*/*z*): 467 ($M+Na^+$, 100), 445 ($M+H^+$, 89), 366 (53), 338 (66), 301 (14), 288 (13), 274 (8). Anal. Calcd for $C_{21}H_{21}IN_2O$: C, 56.77; H, 4.76; N, 6.30. Found: C, 56.60; H, 4.80; N, 6.42.
30. We have demonstrated independently that racemization does not occur during the cycloaddition through the preparation of racemic **17** and **18** using the approach reported by Snider et al.[8c] starting from the corresponding iodoanthranilate derivative. Then the ^1H NMR spectra of (±)-**17** and (±)-**18** were recorded in the presence of 2 equiv of (*R*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (Pirkle's chiral solvating agent),[33] wherein non-equivalence of several signals was observed. On the other hand, when (−)-**17** and (−)-**18** were employed under otherwise identical conditions, only single absorptions were observed for the same signals. These experiments unequivocally demonstrate that both the cycloaddition precursors and adducts are single enantiomers, and by extrapolation so are subsequent intermediates.
31. We would like to thank Dr. Hossen Mahmud for assistance in the preparation of **23**. See Ref. 12c.
32. Data for **24**: $[\alpha]_D$ −95.2 (*c* 0.58, $CHCl_3$) lit. −94.2 (*c* 0.28, $CHCl_3$);[12] −179.1 (*c* 0.80, $CHCl_3$).[18] ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.95$ (s, 1H), 7.66 (d, $J = 8.0$ Hz, 1H), 6.60 (d, $J = 8.0$ Hz, 1H), 5.29–5.23 (m, 1H), 5.21–5.20 (m, 2H), 3.89 (m, 1H), 3.79 (s, 3H), 3.77–3.74 (m, 2H), 3.43–3.34 (m, 6H), 3.20–3.10 (m, 1H), 2.40–2.32 (m, 1H), 2.08–2.04 (m, 2H), 1.72 (s, 3H), 1.70 (s, 3H), 1.69 (s, 3H), 1.67 (s, 3H), 1.69–1.66 (m, 2H), 1.51 (s, 9H), 1.47 (s, 9H), 1.47–1.40 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 167.4$, 162.2, 159.7, 159.5, 146.5, 137.5, 137.4, 137.2, 131.7, 130.2, 120.2, 119.5, 118.1, 113.9, 82.0, 78.0, 53.8, 51.5, 50.6, 46.9, 43.6, 43.1, 42.6, 39.7, 39.5, 32.0, 30.1, 29.8, 29.5, 28.5, 28.1, 27.9, 26.5, 25.7, 18.1, 14.2, 13.9, 13.3. HR-MS: calcd for $C_{38}H_{60}N_7O_6$ (*m*/*z*): 710.4600 ($M+H^+$). Found: 710.4609.
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