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First Total Synthesis of Martinellic Acid, a Naturally Occurring Bradykinin Receptor Antagonist

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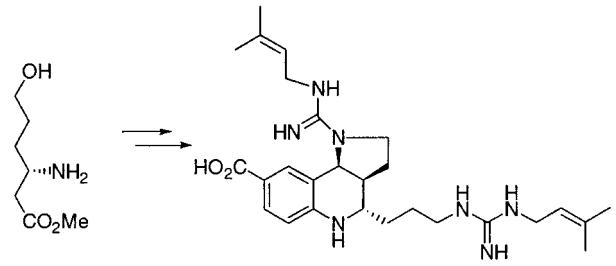
ABSTRACT



The first total synthesis of martinellic acid, a naturally occurring bradykinin receptor antagonist, via a CuI-catalyzed coupling reaction of *β*-amino ester 6 with 1,4-diiodobenzene and a guanylation reaction of secondary amine 3 under mild conditions as key steps, is described.

Martinellic acid **1** and martinelline **2** (Figure 1) are two alkaloids isolated by Merck Research Laboratories from an organic extract of *Martinella iquitosensis* roots.[1] The *Martinella* has been used as an eye medication in over 13 different ethnolinguistic groups from eight South American countries. The presence of alkaloids **1** and **2** in *Martinella* could partially be used to explain its therapeutic properties.[1] Through biological evaluation it has been found that both compounds possess potent antagonist activity toward bradykinin (BK) B1 and B2 receptors. These are the first examples of nonpeptide natural products to be identified as BK receptor antagonists. In addition, both alkaloids contain a pyrroloquinoline ring system, which has not been discovered in natural products before. The unique structure and interesting biological activity of these compounds have stimulated intense synthetic studies.[2−12] In the past three years, several

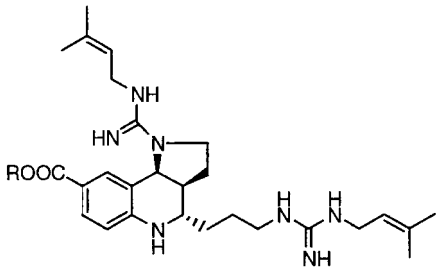


Figure 1. Structures of martinellic acid and martinelline

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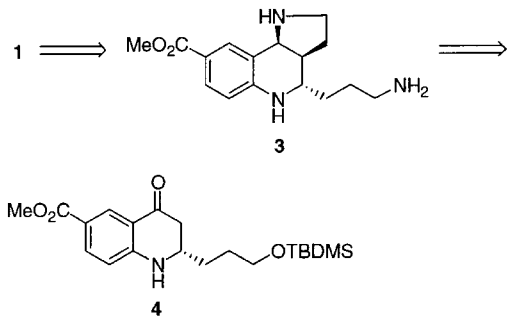
groups have reported their efforts to synthesize the tricyclic core of these natural products.[2−12] But the total synthesis of these natural products has not been accomplished yet. Herein we wish to report the first total synthesis of **1**.

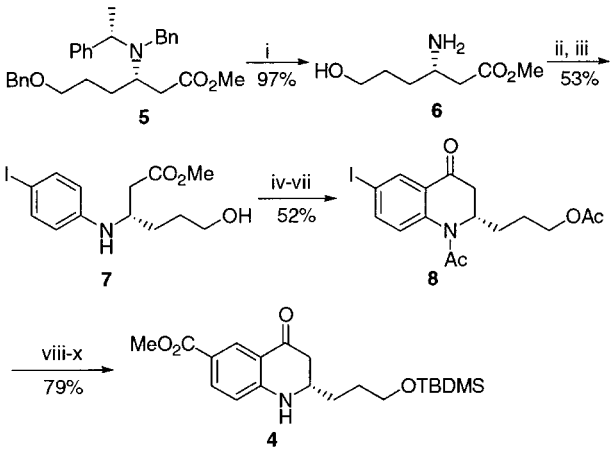
Our retrosynthetic analysis for **1** is shown in Scheme 1. Obviously, this compound could be synthesized with tricyclic

Scheme 1



triamine **3** as a key intermediate because the guanylation of an amine is the most popular method for introducing the guanidine moiety.[13] We envisaged that the pyrrolidine ring of **3** could be constructed by alkylation and subsequent reductive amination[14] of 2-substituted 4-oxoquinoline **4**. The synthesis of **4** is outlined in Scheme 2, which relied on a

Scheme 2[a]



[a] Reagents and conditions: (i) Pd/C, H_2, HCl, MeOH; then Pd/C, H_2, MeOH; (ii) 1,4-diiodobenzene, CuI, K_2CO_3, DMF, H_2O, 100 °C; (iii) $SOCl_2$/MeOH; (iv) Ac_2O, 100 °C; (v) aqueous NaOH, MeOH; (vi) Ac_2O, 80 °C; (vii) oxalyl chloride, CH_2Cl_2, then $AlCl_3$; (viii) $Pd(OAc)_2$, dppp, CO, MeOH, Et_3N, DMF, 80 °C; (ix) HCl, MeOH; (x) TBDMSCl, DMAP, Et_3N, CH_2Cl_2.

strategy to build the desired *N*-aryl β-amino acid skeleton by a cuprous ion catalyzed coupling reaction of aryl iodide with β-amino ester. First, deprotection of *N*,*N*-disubstituted β-amino ester **5**[15,16] afforded β-amino ester **6**, which was coupled with 1,4-diiodobenzene catalyzed by CuI at 100 °C in DMF to provide *N*-aryl β-amino acid. This acid was esterified with $SOCl_2$/MeOH to afford **7** in 53% overall yield. It was notable that this coupling reaction worked at lower temperature than that required by a typical Ullmann aryl amination reaction , which implied that, similar to α-amino acids, the structure of β-amino acid also had an accelerating effect for Ullmann type aryl amination reaction.[17] Next, the *N*-aryl β-amino ester **7** was converted into 4-oxoquinoline **8** in four steps: (1) protection of the amino and hydroxy groups of **7** with acetic anhydride at 100 °C; (2) hydrolysis of the ester and acetate moieties with aqueous NaOH in methanol; (3) reprotection of free hydroxy group with acetic anhydride; (4) conversion of the acid to the acyl chloride and subsequent intramolecular acylation mediated by $AlCl_3$. Finally, a Pd-catalyzed carbonylation reaction of aryl iodide **8** followed by protecting group switch gave **4**.

The alkylation of **4** was carried out at −40 °C using $TfOCH_2CH_2Br$ as a coupling agent (Scheme 3). The coupling product was unstable and directly converted into the azide. Treatment of this azide with Ph_3P/H_2O provided the cyclic imine **9** ($[\alpha]^{20}_D = -68.9$ ($c = 0.5$ in $CHCl_3$)). Reduction of the imine **9** with $NaBH_4$ in methanol at −40 °C followed by protection of two amino groups with trifluoroacetic anhydride afforded the amide **10** and its 4-epimer in a ratio of 2.8/1. Their stereochemistry was established by NOESY experiment and further confirmed by X-ray structure analysis of tetracyclic compound **11**, which was obtained as a side product by deprotection of **10** with TBAF/HOAc and subsequent cyclization under the assistance of $MsCl/Et_3N$. Without affecting the *N*-trifluoroacetyl group, cleavage of the silyl ether in **10** was achieved under catalysis of TFA in THF. The alcohol generated was then converted into azide **12** through mesylate. Reduction of the azide moiety of **12** with triphenylphosphine and water followed by deprotection with HCl/MeOH gave tricyclic triamine **3** as a hydrochloride salt.

The introduction of guanidine moiety into **3** was a challenging task in this total synthesis because there are only a few reports on the formation of dialkyl guanidine by guanylation of a sterically hindered secondary amine.[13a−c] Initially, we tried the known methods[13a−c] to guanylate the

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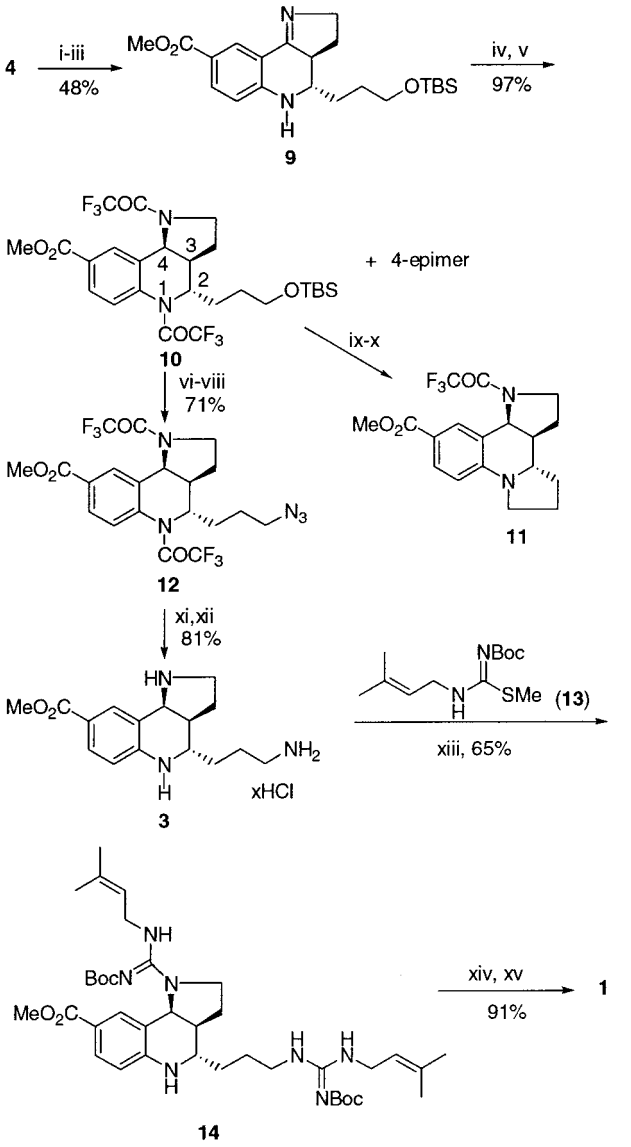
(17) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459. The detailed studies for the CuI-catalyzed coupling reaction of aryl halides with β-amino esters will be published elsewhere.

Scheme 3[a]



[a] Reagents and conditions: (i) LiHMDS, then $BrCH_2CH_2OTf$, THF, −40 °C; (ii) NaN_3, DMF, rt; (iii) Ph_3P, H_2O, THF, rt; (iv) $NaBH_4$, MeOH, −40 °C to rt; (v) $(CF_3CO)_2O$, DMAP, Et_3N, CH_2Cl_2; (vi) TFA, THF, rt; (vii) MsCl, Et_3N, CH_2Cl_2; (viii) NaN_3, DMF, rt; (ix) TBAF, HOAc, THF, rt; (x) MsCl, Et_3N, CH_2Cl_2; (xi) Ph_3P, H_2O, THF, rt; (xii) HCl, MeOH; (xiii) **13**, $AgNO_3$, Et_3N, MeOH, MeCN, rt; (xiv) aqueous NaOH, MeOH, rt; (xv) 5% TFA, anisole, THF, rt.

triamine **3** but failed mainly because **3** was unstable at higher reaction temperature. Through some model studies, we developed a mild reaction condition which was suitable for transformation of this triamine into the desired guanylation product.[18] Thus, treatment of **3** with *N*-(*tert*-butoxycarbonyl)-*N*′-(3-methyl-2-butenyl)-*S*-methylisothiourea **13** at room temperature with the assistance of $AgNO_3$[13i] afforded the product **14** in 65% yield.[19] This success was found to rely on using more reactive *N*-Boc-protected isothiourea as a reagent and sliver nitrate as a promoter.[20] Hydrolysis of the ester moiety in **14** with 1 N NaOH and then treatment with 5% TFA in methylene chloride using anisole as a carbocation scavenger[21] furnished **1** as a TFA salt, with all analytic data identical with those reported except for specific rotation (lit.[1] $[\alpha]^{20}_D = -9$ ($c = 0.01$ in MeOH); observed $[\alpha]^{20}_D = -122.7$ ($c = 0.31$ in MeOH)). Although the reason for this difference is not clear, one possible explanation is that either the natural martinellic acid may be partially racemic or too dilute a solution was used when Merck chemists measured its specific rotation.

In conclusion, we have developed a stereocontrolled route for the total synthesis of martinellic acid in 25 linear steps from the β-amino ester **5** with 2.5% overall yield. Two key steps in this synthesis are the CuI-catalyzed coupling reaction of an enantiopure β-amino ester with 1,4-diiodobenzene and guanylation of a secondary amine under mild conditions. Further conversion of the present intermediate into martinelline, as well as SAR studies of martinelline analogues, are under investigation.

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Supporting Information Available: Experimental procedures and characterizations for compounds **1** and **4**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The detailed studies for this guanylation reaction condition will be published elsewhere.

(19) **Synthetic procedure for 14:** To a solution of **3** (62 mg, 0.16 mmol), **13** (200 mg, 0.78 mmol), and Et_3N (0.26 mL, 1.87 mmol) in 2 mL of MeCN and 1 mL of MeOH was added a solution of $AgNO_3$ (185 mg, 1.09 mmol) in 0.5 mL of MeCN over 30 min. After the reaction mixture was stirred overnight in dark, the precipitate was filtered off and the filtrate was concentrated to dryness. The residue was partitioned between water and chloroform. The organic layer was separated, and the aqueous layer was extracted with chloroform. The combined organic layers were dried over Na_2SO_4 and concentrated to dryness. The residue was purified by flash chromatography, eluting with 30/1 chloroform/methanol to give 68 mg (65%) of **14**. $[\alpha]^{20}_D$ −94.2 (*c* 0.28, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.67 (d, $J = 8.4$ Hz, 1H), 6.62 (m, 1H), 5.71 (m, 1H), 5.29 (m, 1H), 5.20 (m, 1H), 3.81 (s, 3H), 3.75 (m, 1H), 3.40−3.32 (m, 6H), 3.12 (m, 1H), 2.34−2.27 (m, 3H), 2.06 (m, 2H), 1.73 (s, 3H), 1.72 (s, 3H), 1.67 (s, 3H), 1.66 (s, 3H), 1.59−1.45 (m, 4H), 1.52 (s, 9H), 1.49 (s, 9H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 167.4, 163.8, 160.1, 159.8, 146.5, 142.2, 137.1, 131.7, 130.0, 120.3, 119.6, 118.2, 113.8, 112.8, 78.1, 53.4, 51.4, 50.6, 46.7, 46.4, 42.7, 42.5, 42.0, 40.1, 39.5, 39.4, 38.0, 37.0, 29.6, 28.5, 28.4, 28.0, 27.9, 25.6, 22.1, 17.9, 14.0, 13.2; ESIMS *m/z* 733 ($M + Na^+$), 711 ($M + H^+$), 610 ($M^+ - Boc$); HRMS found *m/z* 710.4600 ($M + H^+$), $C_{38}H_{59}N_7O_6$ requires 710.4605.

(20) Both Ag(I) and Hg(II) were known to be able to activate the elimination of the sulfur fragment when isothiourea was reacted with an amine. See refs 13g and 13j.

(21) Masui, Y.; Chino, N.; Sakakibara, S. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 464. It was found that complicated products formed without addition of anisole or when the TFA concentration was over 5%.