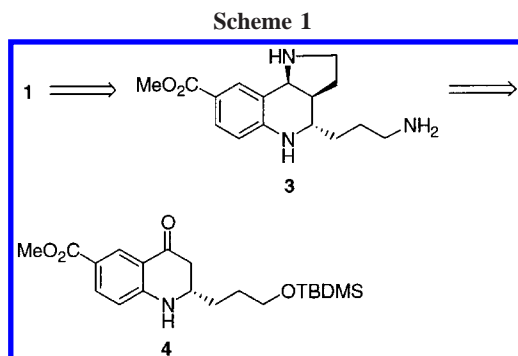
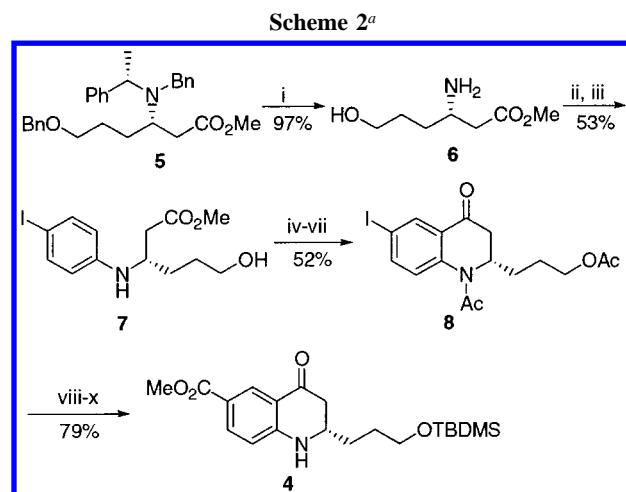


groups have reported their efforts to synthesize the tricyclic core of these natural products.^{2–12} But the total synthesis of these natural products has not been accomplished yet. Herein we wish to report the first total synthesis of **1**.

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



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 amination¹⁴ of 2-substituted 4-oxoquinoline **4**. The synthesis of **4** is outlined in Scheme 2, which relied on a



^a Reagents and conditions: (i) Pd/C, H₂, HCl, MeOH; then Pd/C, H₂, MeOH; (ii) 1,4-diiodobenzene, CuI, K₂CO₃, DMF, H₂O, 100 °C; (iii) SOCl₂/MeOH; (iv) Ac₂O, 100 °C; (v) aqueous NaOH, MeOH; (vi) Ac₂O, 80 °C; (vii) oxalyl chloride, CH₂Cl₂, then AlCl₃; (viii) Pd(OAc)₂, dppp, CO, MeOH, Et₃N, DMF, 80 °C; (ix) HCl, MeOH; (x) TBDMSCl, DMAP, Et₃N, CH₂Cl₂.

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 SOCl₂/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) re-protection of free hydroxy group with acetic anhydride; (4) conversion of the acid to the acyl chloride and subsequent intramolecular acylation mediated by AlCl₃. 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 TfOCH₂CH₂Br as a coupling agent (Scheme 3). The coupling product was unstable and directly converted into the azide. Treatment of this azide with Ph₃P/H₂O provided the cyclic imine **9** ([α]_D²⁰ = –68.9 (*c* = 0.5 in CHCl₃)). Reduction of the imine **9** with NaBH₄ 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/Et₃N. 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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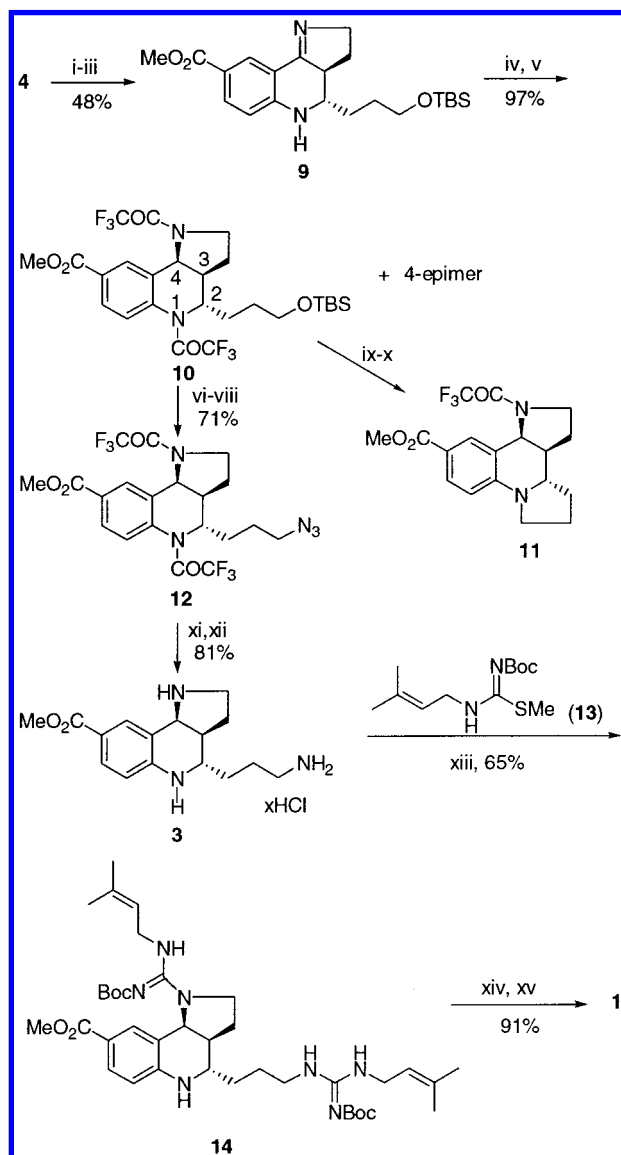
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Scheme 3^a

^a Reagents and conditions: (i) LiHMDS, then BrCH₂CH₂OTf, THF, -40 °C; (ii) NaN₃, DMF, rt; (iii) Ph₃P, H₂O, THF, rt; (iv) NaBH₄, MeOH, -40 °C to rt; (v) (CF₃CO)₂O, DMAP, Et₃N, CH₂Cl₂; (vi) TFA, THF, rt; (vii) MsCl, Et₃N, CH₂Cl₂; (viii) NaN₃, DMF, rt; (ix) TBAF, HOAc, THF, rt; (x) MsCl, Et₃N, CH₂Cl₂; (xi) Ph₃P, H₂O, THF, rt; (xii) HCl, MeOH; (xiii) **13**, AgNO₃, Et₃N, 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*-methylisothiurea **13** at room temperature with the assistance of AgNO₃¹³ⁱ afforded the product

14 in 65% yield.¹⁹ This success was found to rely on using more reactive *N*-Boc-protected isothiurea as a reagent and silver 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 scavenger²¹ furnished **1** as a TFA salt, with all analytic data identical with those reported except for specific rotation (lit.¹ [α]_D²⁰ = -9 (c = 0.01 in MeOH); observed [α]_D²⁰ = -122.7 (c = 0.31 in MeOH)). Although the reason for this difference is not clear, one possible explanation is that either the natural martinelline 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 martinelline 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 Et₃N (0.26 mL, 1.87 mmol) in 2 mL of MeCN and 1 mL of MeOH was added a solution of AgNO₃ (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 Na₂SO₄ and concentrated to dryness. The residue was purified by flash chromatography, eluting with 30/1 chloroform/methanol to give 68 mg (65%) of **14**. [α]_D²⁰ -94.2 (c 0.28, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (150.9 MHz, CDCl₃) 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⁺), C₃₈H₅₉N₇O₆ requires 710.4605.

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

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