JOC Article

Aromatic Nucleophilic Substitution or CuI-Catalyzed Coupling Route to Martinellic Acid

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Received July 1, 2002

Condensation of β-amino ester **8b** with triflate **7** gives *N*-aryl amino ester **11**, which is converted into 2-substituted 4-oxoquinoline **4** using an intramolecular Dieckmann reaction as the key step. CuI-mediated coupling of β-amino ester **8a** with 1,4-diiodobenzene followed by an intramolecular acylation and Pd-catalyzed carbonylation provide another manner to **4**. Alkylation of **4** and subsequent reductive amination deliver the cyclic imine **14**, which is transformed into triamine **3** by ordinary operations. Guanylation of **3** under mild condition followed by deprotection results in the synthesis of martinellic acid **1**.

Introduction

Martinellic acid **1** and martinelline **2** are two alkaloids that were isolated from an organic extract of *Martinella iquitosensis* roots in Merck Research Laboratories.[1] Both compounds contain a pyrroloquinoline ring system, which had not been discovered in natural products before. More interestingly, further biological tests revealed that among these two alkaloids, especially martinelline has potent antagonist activity to some G-protein coupled receptors such as bradykinin (BK) B1 and B2, α1-adrenergic, and muscarinic receptors.[1] These are the first examples for nonpeptide natural products to be identified as BK receptor antagonists. This character could partially be used to explain the therapeutic properties of the *Martinella* as an eye medication in over 13 different ethnolinguistic groups from eight South American countries. The unique structure and interesting biological activity of these compounds have stimulated intense synthetic studies.[2−11] In a previous communication,[11] we reported the first total synthesis of martinellic acid. Herein we wish to detail our efforts on the development of two routes to the core structure of **1** and **2**, as well as the discovery of a mild reaction condition for guanylation of hindered secondary amines and its application in the synthesis of martinellic acid.

Our synthetic strategy for martinellic acid is outlined in Scheme 1, in which this compound could be synthesized by a guanylation reaction of the tricyclic triamine **3** with a suitable guanylation reagent. The pyrrolidine ring of **3** could be assembled by alkylation and subsequent reductive amination from 2-substituted 4-oxoquinoline **4**. Two methods would allow us to construct the skeleton of **4** from enantiopure β-amino ester **8**. One was using an aromatic nucleophilic substitution reaction of **8** with the triflate **7** to provide the triester **6** and the subsequent intramolecular Dieckmann reaction. Another one was through a CuI-catalyzed coupling reaction of **8** with 1,4-diiodobenzene to afford *N*-aryl β-amino ester **5** and the subsequent intramolecular acylation.

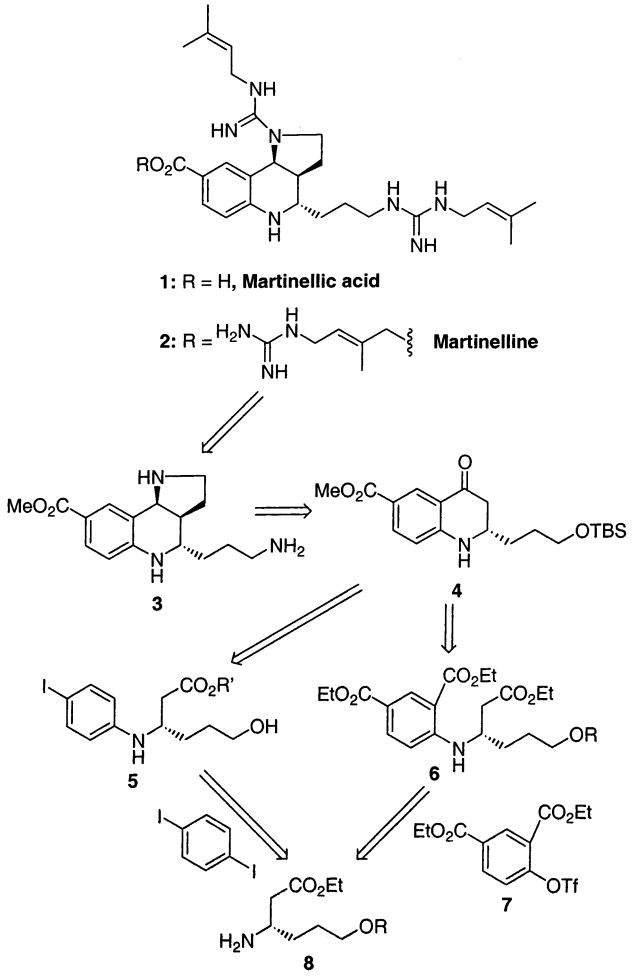
Results and Discussions

Synthesis of 2-Substituted 4-Oxoquinoline 4. The aromatic nucleophilic substitution protocol for synthesizing **4** is illustrated in Scheme 2. We started the synthesis from protected β-amino ester **9**,[12] which was prepared from 1,4-butandiol in four steps according to Davies's procedure.[13] After hydrogenation over Pd/C, free β-amino ester **8a** was obtained. At this time we planned to build *N*-aryl β-amino ester **11** via an aromatic nucleophilic substitution reaction of **8a** with the triflate **7**, which was prepared by treating 4-hydroxyisophthalic acid diethyl ester **10** with trifluoromethanesulfonic anhydride. Although there was no report regarding this kind of

(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) Gurjar, M. K.; Pal, S.; Rao, A. V. R. *Heterocycles* **1997**, *45*, 231.
(3) Ho, T. C. T.; Jones, K. *Tetrahedron* **1997**, *53*, 8287.
(4) Kim, S. S.; Cheon, H. G.; Kang, S. K.; Yum, E. K.; Choi, J. K. *Heterocycles* **1998**, *48*, 221.
(5) (a) Hadden, M.; Stevenson, P. J. *Tetrahedron Lett.* **1999**, *40*, 1215. (b) Hadden, M.; Nieuwenhuyzen, M.; Osborne, D.; Stevenson, P. J.; Thompson, N.; *Tetrahedron Lett.* **2001**, *42*, 6417. (c) Hadden, M.; Nieuwenhuyzen, M.; Potts, D.; Stevenson, P. J.; Thompson, N.; *Tetrahedron* **2001**, *57*, 5615.
(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.
(7) (a) Snider, B. B.; Ahn, Y.; Foxman, B. M. *Tetrahedron Lett.* **1999**, *40*, 3339. (b) Snider, B. B.; O'Hare, S. M. *Tetrahedron Lett.* **2001**, *42*, 2455. (c) Snider, B. B.; Ahn, Y.; O'Hare, S. M. *Org. Lett.* **2001**, *3*, 4217.
(8) (a) Batey, R. A.; Simoncic, P. D.; Lin, D.; Smyj, R. P.; Lough, A. J. *Chem. Commun.* **1999**, 651. (b) Batey, R. A.; Powell, D. A. *Chem. Commun.* **2001**, 2362.
(9) Frank, K. E.; Aubé, J. *J. Org. Chem.* **2000**, *65*, 655.
(10) Nieman, J. A.; Ennis, M. D. *Org. Lett.* **2000**, *2*, 1395.
(11) Ma, D.; Xia, C.; Jiang, J.; Zhang, J. *Org. Lett.* **2001**, *3*, 2189.
(12) Ma, D.; Zhang, J. *Tetrahedron Lett.* **1998**, *39*, 9067.
(13) Davies, S. G.; Ichihara, O.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1141.

10.1021/jo026125z CCC: $25.00
Published on Web 11/28/2002

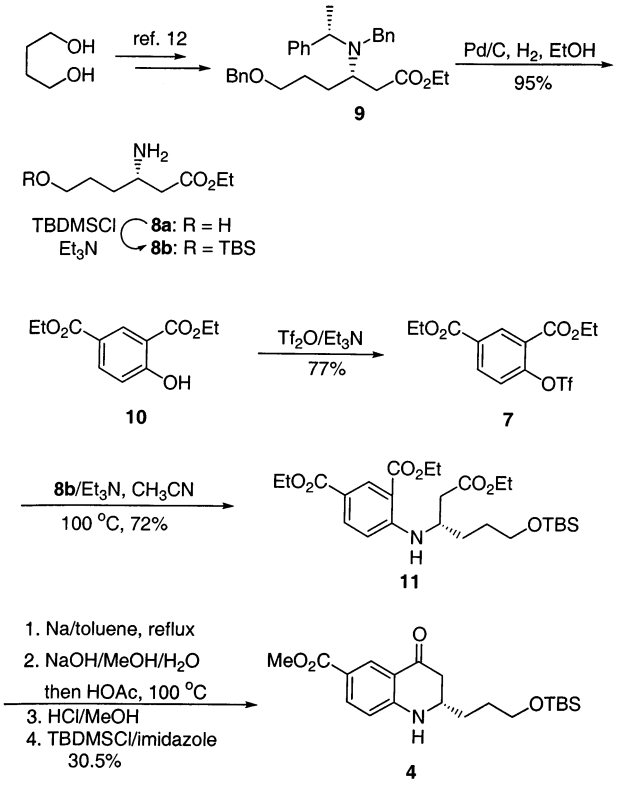
SCHEME 1



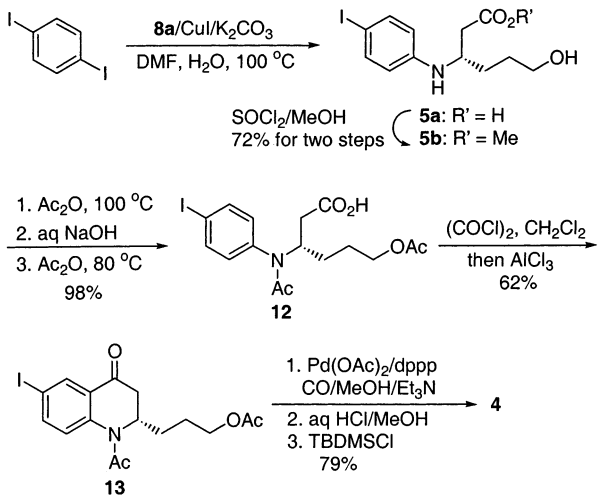
reaction, the result of Kotsuki and co-workers gave insight that our idea might work.[14] As expected, the reaction of **8a** with **7** under the action of triethylamine in refluxing acetonitrile provided the coupling product **11**. However, the yield was quite low (less than 30%) mainly because of decomposition of the triflate **7** to the phenol **10** mediated by the free hydroxy group of **8a**. Therefore, we decided to solve the problem by protecting the hydroxy group of **8a**. Thus, treatment of **8a** with *tert*-butyldimethylsilyl chloride and triethylamine produced **8b**. The coupling reaction of **8b** with the triflate **7** in acetonitrile at 100 °C worked well to afford the substitution product **11** in 72% yield. Next, triester **11** was transformed into 4-oxoquinoline **4** by the following four steps: (1) Dieckmann reaction of **11** in refluxing toluene under the action of sodium; (2) decarboxylation of the generated keto ester by hydrolysis with 2 N NaOH, followed by acidification; (3) esterification of the free acid with methanolic hydrogen chloride; and (4) reprotection of the hydroxy group with TBDMS group. The overall yield was about 30%.

Although the above route to the 2-substituted 4-oxoquinoline **4** worked, a drawback was that the Dieckmann reaction and subsequent decarboxylation steps gave low yield. This problem might result from the fact that the

SCHEME 2



SCHEME 3



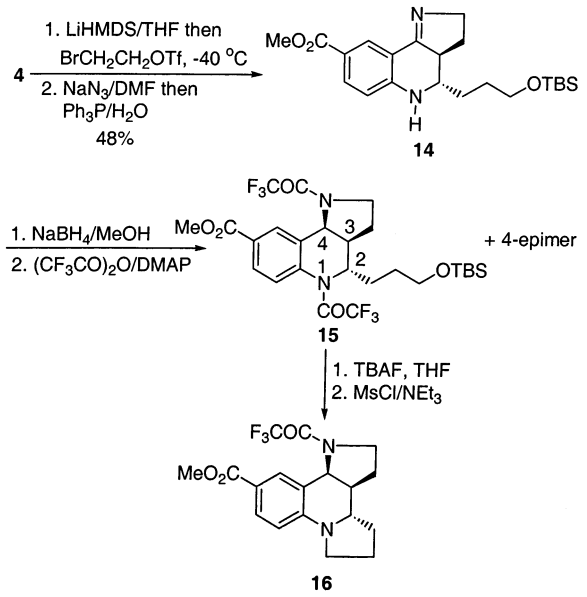
4-oxoquinoline moiety was unstable under the present reaction conditions. Thus, an alternate route was explored.

The second method for construction of **4** is demonstrated in Scheme 3, which relied on a strategy to build the desired *N*-aryl *β*-amino acid skeleton by cuprous ion-catalyzed coupling of aryl iodide and *β*-amino ester under relatively mild condition discovered by our group.[15] Thus, heating of a mixture of the amino ester **8a**, 1,4-diiodobenzene, CuI, and K_2CO_3 in DMF at 100 °C for 24 h provided the *N*-aryl *β*-amino acid **5a**, which was esterified with $SOCl_2$/MeOH to afford **5b** in 72% overall yield. After

(14) Kotsuki, H.; Kobayashi, S.; Suenaga, H.; Nishizawa, Y. *Synthesis* **1990**, 1145.

(15) (a) Ma, D.; Xia, C. *Org. Lett.* **2001**, *3*, 2583. (b) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459.

SCHEME 4



indirect acylation of the acid **5a** under the action of PPA failed, we decided to run the intramolecular acylation in a stepwise manner. Thus, protection of both the amino and hydroxyl groups was the first task. Initially, direct treatment of the amino acid **5a** with acetic anhydride or acetic chloride was attempted. However, it was observed that only the *O*-protection occurred under various conditions. After many experiments, we found if a mixture of the amino ester **5b** and acetic anhydride was heated at 100 °C, the desired *N*- and *O*-diprotected product could be obtained. Hydrolysis of the ester moiety of this protected product with aqueous NaOH in methanol followed by reprotection of free hydroxy group with acetyl anhydride provided the acid **12**. Treatment of **12** with oxalyl chloride produced the corresponding acyl chloride, which was subjected to an intramolecular acylation mediated by $AlCl_3$ to afford the ketone **13**. Finally, a Pd-catalyzed carbonylation reaction of aryl iodide **13** followed by protecting group switch gave **4** in 79% overall yield. Although this route contained some undesired protection and deprotection steps due to the failure of direct acylation of **5a**, the stability of the intermediates under the reaction conditions presented here and the convenient operation allowed us to synthesize enough **4** for further conversions.

Synthesis of the Triamine 3. With the intermediate **4** in hand, we tried alkylation and reductive amination methods[16] to set up the pyrrolidine ring of martinellic acid. The alkylation of **4** was carried out at −40 °C by using $TfOCH_2CH_2Br$ as the coupling agent. The generated bromide was found to be unstable and was therefore directly converted into the corresponding azide by treatment with sodium azide in DMF. Reduction of this azide with triphenylphosphine and water produced the free amine, which attacked spontaneously the ketone moiety to provide the cyclic imine **14**. After the imine **14** was reduced with sodium borohydride in methanol at −40 °C, the amine generated was protected with trifluoroacetic anhydride to give the amide **15** 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 a tetracyclic compound **16**, which was obtained as a side product by deprotection of **15** with TBAF/HOAc and subsequent cyclization under the assistance of mesyl chloride and triethylamine. The bad stereoselectivity of the reduction step prompt us to try other reducing reagents such as L-selectctide and sodium cyanoborohydride. However, the selectivity was not improved, although many experiments were performed (Scheme 4 and Figure 1).

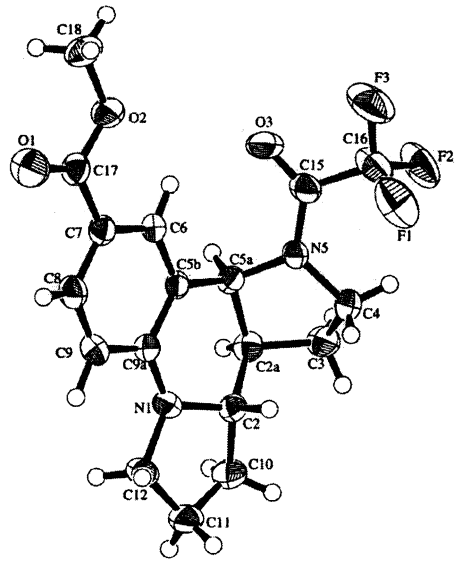
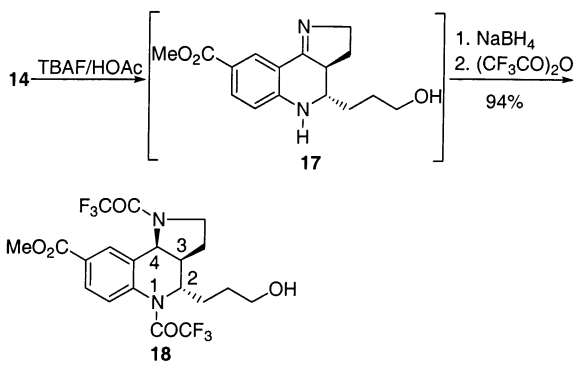


FIGURE 1. X-ray structure of **16**.

SCHEME 5

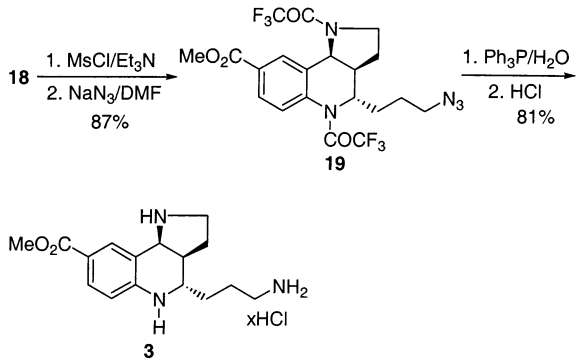


After careful analysis, we felt that if we removed the silyl group of **14**, the free hydroxyl group would probably chelate with borohydride, thereby eliminating the attack from the outside and giving better selectivity. Thus, cleavage of silyl ether in **14** with TBAF/HOAc in THF provided the alcohol **17**. As expected, the reduction of **17** with sodium borohydride followed by protection with trifluoroacetic anhydride delivered **18** as a sole product in 94% yield (Scheme 5).

The alcohol **18** was then converted into the azide **19** through its mesylate in 85% overall yield. Reduction of the azide moiety of **19** with triphenylphosphine and water followed by deprotection with aqueous hydrochloride in methanol gave tricyclic triamine **3** as its hydrochloride salt (Scheme 6).

(16) (a) Sha, C.-K.; Chiu, R.-T.; Yang, C.-F.; Yao, N.-T.; Tseng, W.-H.; Liao, F.-L.; Wang, S.-L. *J. Am. Chem. Soc.* **1997**, *119*, 4130. (b) Hanessian, S.; Raghavan, S.; *Bioorg. Med. Chem. Lett.* **1994**, *4*. 1697.

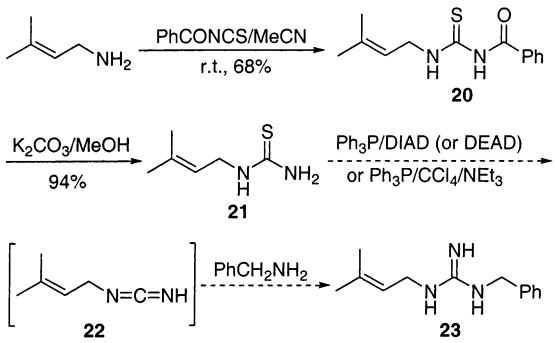
SCHEME 6



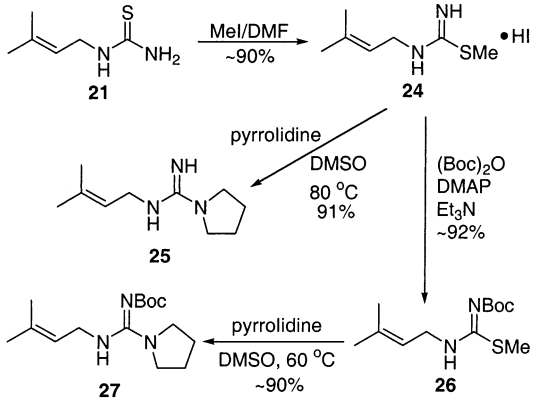
Model Studies for Guanylation of the Sterically Hindered Secondary Amine under the Mild Reaction Condition. Literature survey[17] indicated that there are few reports on the formation of dialkyl guanidine by guanylation of a sterically hindered secondary amine,[17a–c] which implied that introduction of the guanidine moiety onto the secondary amine of **3** was a challenging task in the total synthesis of martinellic acid. To solve this problem several model studies were undertaken. Initially, we tried to prepare a carbodiimide **22**, because this kind of intermediate was proven to react with hindered secondary amines easily to afford the corresponding guanidines.[18] Accordingly, treatment of prenylamine with phenylcarbonyl isothiocyanate in acetonitrile at room temperature provided the compound **20**, which was deprotected with potassium carbonate in methanol to give the thiourea **21**. Desulfidryzation of **21** with Ph_3P/DIAD (or $Ph_3P/CCl_4/Et_3N$[19]) was expected to deliver carbodiimide **22**, which could be trapped with benzylamine to produce guanidine **23**.[18] However, no desired product was isolated, mainly because the carbodiimide **22** might be too unstable or even not form under the present conditions (Scheme 7).

Inspired by a report of Flygare and co-workers,[17b] we turned our attention to employ methyl isothiourea hydroiodide salt **24** as our guanylation agent, which was prepared by the methylation of the thiourea **21** with iodomethane. In a model study, reaction of **24** with pyrrolidine in DMSO at 80 °C under the assistance of triethylamine gave guanidine **25** in 91% yield. However, when this reagent was reacted with the triamine **3** under the same condition, no guanidine formation but decomposition of the triamine **3** was observed. At this stage we decided to increase the reactivity of the methyl isothiourea **24** by introducing an electrodeficient group on to its nitrogen. Thus, treatment of **24** with di-*tert*-butyl dicarbonate assisted by triethylamine gave *N*-(*tert*-butoxycarbonyl)-*N*′-(3-methyl-2-butenyl)-*S*-methylisothiourea **26**. The subsequent reaction of **26** with pyrrolidine worked at 60 °C to afford the *N*-Boc-protected guanidine **27** in good yield. Unfortunately, when this reagent was applied to the triamine **3** under the same conditions, except for adding triethylamine as the HCl trapping agent, we still did not isolate any guanylation product (Scheme 8).

SCHEME 7



SCHEME 8



In the synthesis of a monosubstituted guanidine by the reaction of a methylisothiourea intermediate with NH_3, Burgess and co-workers used $AgNO_3$ to promote the leaving of methanethiol during the guanylation reaction.[17i] Stimulated by their report, we did a model study by reacting **26** with a hindered 2-substituted pyrrolidine **28** under the action of $AgNO_3$. As expected, this reaction completed at room temperature to produce the displacement product **29** in excellent yield. Fortunately, application of this reaction to the triamine **3** worked at 40 °C to provide the desired coupling product **30** in 20% yield. It was found that the low yield mainly resulted from the poor solubility of **3** in acetonitrile. This problem was solved by using a mixture of acetonitrile and methanol as the solvent to give improved yield (65%) (Scheme 9).

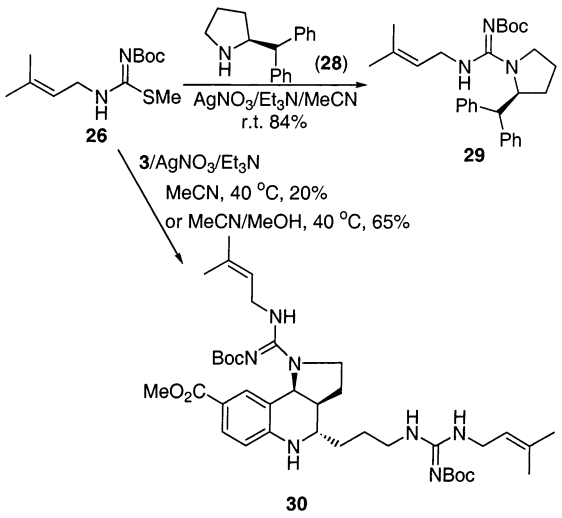
To demonstrate the usage of the present method to synthesize *N*,*N*,*N*′-trisubstituted guanidines from the hindered secondary amines, we did some experiments to react *N*-Boc-protected *S*-methylisothiourea **31** with various amines. As shown in Table 1, all hindered secondary amines were suitable for this reaction to provide the corresponding displacement product in excellent yield. This reaction might go through a carbodiimide mechanism that is illustrated in Scheme 10, because the secondary amine derived *N*-Boc-protected *S*-methylisothiourea **41** could not react with benzylamine to provide guanylation product **42**.

(17) (a) Dodd, D. S.; Wallace, O. B. *Tetrahedron Lett.* **1998**, *39*, 5701. (b) Kearney, P. C.; Fernandez, M.; Flygare, J. A. *Tetrahedron Lett.* **1998**, *39*, 2663. (c) Levallet, C.; Lerpiniere, J.; Ko, S. Y. *Tetrahedron* **1997**, *53*, 5291. (d) Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 3804. (e) Barvian, M. R.; Showalter, H. D. H.; Doherty, A. M. *Tetrahedron Lett.* **1997**, *38*, 6799. (f) Yong, Y. F.; Kowalski, J. A.; Lipton, M. A. *J. Org. Chem.* **1997**, *62*, 1540. (g) Ramadas, K.; Srinivasan, N. *Tetrahedron Lett.* **1995**, *36*, 2841. (h) Drake, B.; Patek, M.; Lebl, M. *Synthesis*, **1994**, 579. (i) Burgess, K.; Lim, D.; Ho, K. K.; Ke, C. Y. *J. Org. Chem.* **1994**, *59*, 2179.

(18) Chinchilla, R.; Nájera, C.; Sánchez-Aulló, P. *Tetrahedron: Asymmetry*, **1994**, *5*, 1393.

(19) Appel, R.; Kleinstück, R.; Zehn, K. D. *Chem. Ber.* **1971**, *104*, 1335.

SCHEME 9



Synthesis of Martinellic Acid. With the compound **30** in hand, we finished the total synthesis of martinellic acid by the following conversions: (1) hydrolysis of the ester moiety in **30** with aqueous NaOH in methanol at reflux and (2) treatment with 5% TFA in methylene chloride using anisole as a carbocation scavenger[20] furnished **1** as its TFA salt. All analytic data of the synthetic compound were identical with those reported except for rotation ($[\alpha]^{20}_D$ −122.7 (*c* 0.31, MeOH); lit.[1] $[\alpha]^{20}_D$ −9 (*c* 0.01, 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 a too dilute solution was used when Merck chemists measured the rotation (Scheme 11).

In conclusion, we have developed two stereocontrolled routes for synthesizing the core structure of martinellic acid and martinelline and a protocol to convert this core structure to martinellic acid. In addition, the mild condition presented here for forming protected guanidines from sterically hindered secondary amine would be of benefit for preparing the related compounds. Further conversion of the present intermediate into martinelline as well as the SAR studies of martinelline analogues are under investigation in our laboratory.

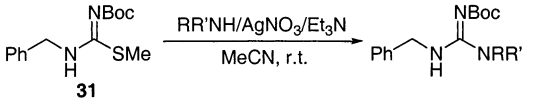
Experimental Section

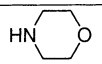
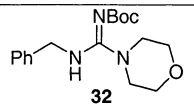
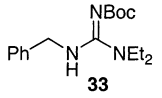
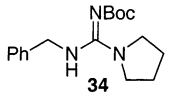
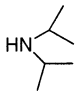
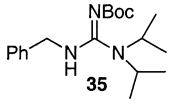
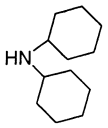
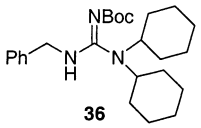
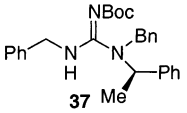
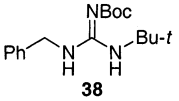
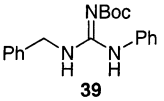
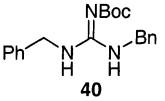
General Procedures. Analytically pure toluene, DMSO, and DMF were used directly without further purification. CH_2Cl_2 was distilled from CaH_2, and THF was distilled from a deep blue ketyl prior to use. All other solvents were reagent grade quality and used as received. Na_2SO_4 was used as the drying agent in all workup procedures. Column chromatography was performed over silica gel (300−400 mesh). All reactions were run in flame-dried glassware under nitrogen atmosphere unless stated otherwise.

Ethyl (3*S*)-Amino-6-hydroxyhexanoate 8a. To a solution of **9** (100 g, 0.22 mol) in 600 mL of ethanol were added concentrated HCl (22 mL, 0.26 mol), 30 mL of water, and 5 g of 10% Pd/C. After the reaction mixture was stirred under hydrogen (50 atm) at 50 °C for 6 h, Pd/C was filtrated off and the filtrate was neutralized to pH = 8 with $NaHCO_3$. To this solution another 5 g of 10% Pd/C was added. The resultant suspension solution was stirred under the above hydrogenation conditions for 8 h. After Pd/C was filtered off, the filtrate was evaporated under reduced pressure to give 38 g of **8a** in 98% yield. $[\alpha]^{20}_D$ +45.2 (*c* 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) dδ 6.65 (m, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.59−3.71 (m, 3H), 2.95 (dd, *J* = 17.1, 6.8 Hz, 1H), 2.76 (dd, *J* = 17.1, 5.9 Hz, 1H), 1.96 (m, 1H), 1.83 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H); EI-MS *m*/*z* 176 ($M^+ + H^+$), 116, 101, 86; HRMS found *m*/*z* 175.123 (M^+), $C_8H_{17}NO_3$ requires 175.121.

(20) 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 with TFA of more than 5% concentration.

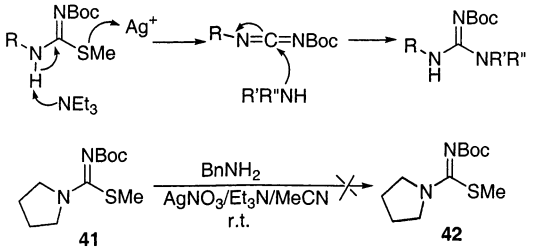
TABLE 1. Guanylation Reaction of 31 with Various Amines[a]



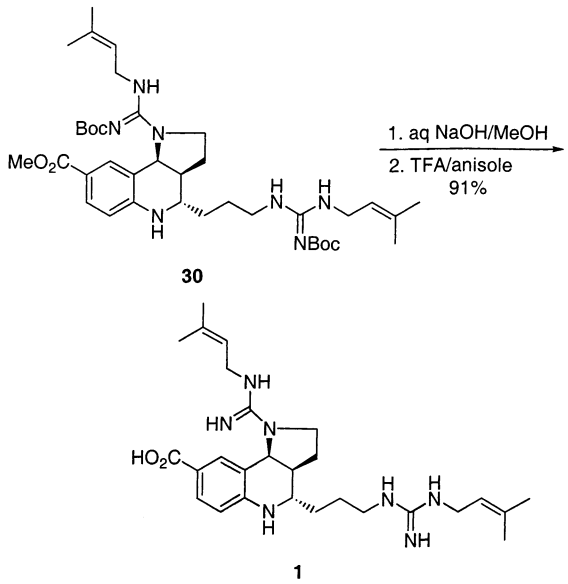
entry	amine	product	yield (%)
1		 **32**	99
2	Et_2NH	 **33**	98
3		 **34**	98
4		 **35**	96
5		 **36**	91
6		 **37**	93
7	*t*-$BuNH_2$	 **38**	93
8	$PhNH_2$	 **39**	88
9	$BnNH_2$	 **40**	98

[a] **Reaction condition: 31** (1.2 mmol), amine (1 mmol), triethylamine (2 mmol), and $AgNO_3$ (1.5 mmol) in MeCN (5 mL).

SCHEME 10



SCHEME 11



Ethyl (3*S*)-Amino-6-(*tert*-butyldimethylsilanyoxy)hexanoate 8b. To a solution of **8a** (11 g, 62.9 mmol) and Et_3N (16 mL, 76 mmol) in 200 mL of anhydrous CH_2Cl_2 at 0 °C was added a solution of TBSCl (11.4 g, 75.4 mmol) in 40 mL of anhydrous CH_2Cl_2. The reaction mixture was allowed to warm to room temperature and then stirred overnight. The solution was diluted with 200 mL of CH_2Cl_2 and then washed with water and brine. The organic layer was dried and concentrated. The residue was purified by column chromatography eluting with 2/1 ethyl acetate/*n*-hexane to give 17.5 g (80%) of **8b**: ^{1}H NMR (300 MHz, $CDCl_3$) dδ 4.18 (q, J = 7.2 Hz, 2H), 3.59 (t, J = 7.1 Hz, 2H), 3.10 (m, 1H), 2.31 (m, 2H), 1.50−1.11 (m, 7H), 0.85 (s, 9H), 0.00 (s, 6H).

4-(Trifluoromethanesulfonyloxy)isophthalic Acid Diethyl Ester 7. To a solution of **10** (10.82 g, 45.5 mmol) and Et_3N (12.7 g, 90.6 mmol) in 100 mL of anhydrous CH_2Cl_2 at −15 °C was added a solution of Tf_2O (9.18 mL, 54.5 mmol) in 15 mL of CH_2Cl_2. The reaction mixture was stirred for 0.5 h before 100 mL of CH_2Cl_2 was added. The resultant solution was washed with 20 mL of saturated $NaHCO_3$ and 20 mL of brine. The organic layer was dried and concentrated. The residue was purified by column chromatography eluting with 1/5 ethyl acetate/*n*-hexane to give 13 g (77%) of **7**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (d, J = 2.2 Hz, 1H), 8.28 (dd, J = 8.7, 2.1 Hz, 1H), 7.38 (d, J = 8.6 Hz, 1H), 4.45 (m, 4H), 1.42 (m, 6H).

(2′*S*)-4-[5′-(*tert*-Butyldimethylsilanyloxy)-1′-ethoxycarbonylpent-2′-yl]aminoisophthalic Acid Diethyl Ester 11. A solution of **7** (3.50 g, 9.45 mmol), **8b** (2.78 g, 9.62 mmol), and Et_3N (1.6 mL, 11.4 mmol) in 4 mL of anhydrous MeCN was heated at 100 °C in a sealed tube under nitrogen atmosphere for 12 h. The cooled solution was diluted with 100 mL of ethyl acetate before it was washed with water and brine. The organic layer was dried and concentrated. The residue was purified by column chromatography eluting with 1/8 ethyl acetate/*n*-hexane to give 3.49 g (72%) of **11**: $[\alpha]^{20}_D$ +4.2 (*c* 0.6, $CHCl_3$); IR (KBr) 1763, 1712, 1686 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (d, J = 2.1 Hz, 1H), 8.39 (br s, 1H), 7.97 (dd, J = 9.1, 2.1 Hz, 1H), 6.79 (d, J = 9.1 Hz, 1H), 4.35 (dd, J = 14.2, 7.1 Hz, 4H), 4.13 (m, 2H), 4.08 (m, 1H), 3.62 (t, J = 6.1 Hz, 2H), 2.60 (m, 2H), 1.70 (m, 4H), 1.40 (m, 6H), 1.23 (t, J = 7.0 Hz, 3H), 0.91 (s, 9H), 0.30 (s, 6H); EI-MS *m*/*z* 509 (M^+), 464, 422, 364, 290, 318; HRMS found *m*/*z* 509.281 (M^+); $C_{26}H_{43}NO_7Si$ requires 509.281.

(2*S*)-2-(3-*tert*-Butyldimethylsilyloxypropyl)-4-oxo-1,2,3,4-tetrahydroquinoline-6-carboxylic Acid Methyl Ester 4. To a suspension of Na (700 mg, 30.4 mmol) in 80 mL of refluxing anhydrous toluene under nitrogen atmosphere was added a solution of **11** (3.06 g, 6.0 mmol) in 20 mL of anhydrous toluene in 30 min. The reaction mixture was stirred for 1.5 h before it was cooled to room temperature. To this solution was added 5 mL of HOAc with caution to quench the reaction. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried, and concentrated to give a yellow solid. This crude product and NaOH (0.72 g, 18 mmol) were dissolved in 20 mL of water and 60 mL of methanol. The resulting mixture was stirred at 50 °C for 4 h before 20 mL of HOAc was added at 0 °C. After the mixture was heated at 80 °C for 2 h, the solvent was removed under reduced pressure and the residue was dissolved with 50 mL of ethyl acetate. The organic layer was separated and washed with water and brine, respectively. After it was dried, the solution was concentrated and the residue was treated with 60 mL of methanolic hydrogen chloride overnight at room temperature. The resultant solution was concentrated and the residue was partitioned between saturated Na_2CO_3 and ethyl acetate. The organic layer was dried and concentrated to give 497 mg of the corresponding methyl ester.

A solution of the above ester (405 mg, 1.54 mmol), imidazole (200 mg, 2.94 mmol), and TBSCl (300 mg, 2.01 mmol) in 10 mL of anhydrous DMF was stirred at room temperature overnight. The resultant mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, and dried. The solution was concentrated and the residue was purified by column chromatography eluting with 1/6 ethyl acetate/*n*-hexane to give 490 mg (30% overall yield) of **4**: $[\alpha]^{20}_D$ −120.5 (*c* 1.0, $CHCl_3$); IR (KBr) 3344, 1713, 1666 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 2.1 Hz, 1H), 7.94 (dd, J = 8.7, 2.1 Hz, 1H), 6.66 (d, J = 8.7 Hz, 1H), 5.70 (br s, 1H), 3.86 (s, 3H), 3.70 (t, J = 5.3 Hz, 2H), 2.74 (dd, J = 16.0, 4.1 Hz, 1H), 2.53 (dd, J = 16.0, 11.6 Hz, 1H), 1.70 (m, 4H), 0.90 (s, 9H), 0.06 (s, 6H); EI-MS *m*/*z* 377 (M^+), 346, 320, 246, 228, 204; HRMS found *m*/*z* 377.205 (M^+), $C_{20}H_{31}NO_4Si$ requires 377.202.

Methyl (3*S*)-6-Hydroxyl-3-(4′-iodophenylamino)hexanoate 5b. To a solution of amino ester **8a** (9.66 g, 45.7 mmol), 1,4-diiodobenze (18.00 g, 54.8 mmol), and potassium carbonate (18.95 g, 137 mmol) in 100 mL of DMF and 0.5 mL of water was added CuI (0.87 g, 4.6 mmol). The resultant mixture was heated at 100 °C under nitrogen atmosphere for 2 days. The solvent was removed under reduced pressure and the residue was diluted with 100 mL of $CHCl_3$. After the resultant solution was acidified to pH = 5 with 1 N HCl, the organic layer was separated and the aqueous layer was extracted with $CHCl_3$ in three portions. The combined organic layers were washed with brine, dried, and concentrated to dryness to give the crude amino acid **5a**.

To a solution of the above crude acid in 200 mL of methanol was added $SOCl_2$ (4.75 mL, 55 mmol) in a dropwise manner at 0 °C. The mixture was stirred overnight at room temperature. After the methanol was evaporated, 50 mL of saturated $NaHCO_3$ was employed to neutralize the residue. The resultant mixture was extracted with ethyl acetate in three portions. The combined organic layers were washed with brine, dried, and concentrated. The residue was purified by column chromatography eluting with 1/1 ethyl acetate/petroleum ether to afford 11.9 g (72% yield for two steps) of **5b**: $[\alpha]^{20}_D$ −20.4 (*c* 1.0, $CHCl_3$); IR (KBr) 3388, 1727, 1590 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 7.0 Hz, 2H), 6.41 (d, J = 7.0 Hz, 2H), 3.72 (m, 1H), 3.64 (s, 3H), 2.50 (m, 2H), 1.75−1.59 (m, 4H); EI-MS *m*/*z* 363 (M^+), 304, 290, 237, 178, 104; HRMS calcd for $C_{13}H_{18}INO_3$ (M^+) 363.0331, found 363.0323.

(3*S*)-6-Acetoxy-3-[*N*-(4′-iodophenyl)acetamido]hexanoic Acid 12. A solution of **5b** (15.5 g, 42.7 mmol) in 200 mL of acetic anhydride was heated to 100 °C for 2 h. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography eluting with 2/1 petroleum ether/ethyl acetate to give 17.5 g of the corresponding amide.

To a solution of the above amide (17.5 g, 39.1 mmol) in 200 mL of MeOH and 100 mL of water was added NaOH (6.4 g, 160 mmol). After the mixture was stirred for 20 h, the reaction was quenched by adding concentrated HCl. The MeOH was removed under reduced pressure and the aqueous layer was extracted with $CHCl_3$ three times. The combined organic layers were dried and concentrated. The residue was purified by column chromatography eluting with 1/1 ethyl acetate/petroleum ether (containing 2% acetic acid) to give 14.7 g of alcohol.

The above alcohol (14.7 g, 37.6 mmol) was dissolved in 150 mL of Ac_2O before it was heated with stirring at 80 °C for 2 h. After the solution was concentrated in vacuo, the residue was dissolved in 100 mL of 1,4-dioxane and 50 mL of water and stirred at 50 °C for 0.5 h. The solvent was evaporated under reduced pressure and the residue was diluted with 150 mL of $CHCl_3$. The resultant solution was washed with brine, dried, and concentrated. The residue was purified by column chromatography eluting with 2/1 ethyl acetate/*n*-hexane to give 15.5 g (84% yield for three steps) of **12**: $[\alpha]^{20}_D$ −3.7 (*c* 0.84, $CHCl_3$); IR (KBr) 3445, 1727, 1633 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 8.5 Hz, 2H), 7.00 (br s, 2H), 5.22 (m, 1H), 4.06 (t, J = 6.4 Hz, 2H), 3.39 (br s, 1H), 2.43 (d, J = 6.6 Hz, 2H), 2.05 (s, 3H), 1.79 (s, 3H), 1.77−1.72 (m, 2H), 1.57−1.45 (m, 2H); EI-MS *m*/*z* 433 (M^+), 391, 331, 290, 261, 245, 219.

(2*S*)-2-(3-Acetoxypropyl)-1-acetyl-6-iodo-4-oxo-1,2,3,4-tetrahydroquinoline 13. To an ice-cooled suspension of **12** (10.0 g, 23 mmol) and 0.05 mL of DMF in 100 mL of dry CH_2Cl_2 was added oxalyl chloride (3 mL, 34.6 mmol) in 10 min. The mixture was stirred for another 10 min at 0 °C and then 1 h at room temperature. After the solvent was evaporated to dryness, another 100 mL of dry CH_2Cl_2 was added. To this stirring solution was added $AlCl_3$ (9.8 g, 73.6 mmol) in several portions at 0 °C. The resultant reaction mixture was stirred for 12 h at room temperature and then cautiously quenched into a rapidly stirred mixture of 200 g of ice and 100 mL of $CHCl_3$. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried, and concentrated. The residue was purified by column chromatography eluting with 1/2 ethyl acetate/*n*-hexane to give 5.9 g (62%) of **13**. $[\alpha]^{20}_D$ +203.0 (*c* 1.1, $CHCl_3$); IR (KBr) 3448, 1736, 1664 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, J = 1.9 Hz, 1H), 7.86 (dd, J = 8.5, 1.9 Hz, 1H), 7.10 (br s, 1H), 5.18 (br s, 1H), 3.97 (t, J = 5.5 Hz, 2H), 3.01 (dd, J = 18.1, 5.8 Hz, 1H), 2.65 (d, J = 18.0 Hz, 1H), 2.33 (s, 3H), 1.96 (s, 3H), 1.76−1.54 (m, 4H); EIMS *m*/*z* 415 (M^+), 373, 272; HRMS found *m*/*z* 415.0298 (M^+), $C_{16}H_{18}INO_4$ requires 415.0281.

An Alternative Route to 4. To a solution of **13** (5 g, 12 mmol) in 50 mL of DMF and 2 mL of MeOH were added Et_3N (3.3 mL, 24 mmol), dppp (247 mg, 0.6 mmol), and $Pd(OAc)_2$ (135 mg, 0.6 mmol). The resulting suspension was purged with CO and stirred at 80 °C in a CO atmosphere (balloon pressure). After 12 h of stirring, the DMF was evaporated in vacuo and 100 mL of $CHCl_3$ was added to dissolve the residue. The solution was washed with water, dried, and concentrated in vacuo. The residue was purified by flash column chromatography eluting with 1/2 ethyl acetate/petroleum ether to give 3.86 g of the corresponding methyl ester.

The above methyl ester (3.86 g, 11.1 mmol) was dissolved in 30 mL of methanolic hydrogen chloride and 3 mL of water. The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure, and the residue was neutralized by saturated $NaHCO_3$ and then extracted with $CHCl_3$. The combined organic layers were dried and concentrated in vacuo. Purification of the residue by column chromatography eluting with ethyl acetate gave 2.60 g of the amino alcohol.

To a solution of the above amino alcohol (2.6 g, 9.9 mmol), Et_3N (1.93 mL, 13.8 mmol), and a catalytic amount of DMAP in 30 mL of CH_2Cl_2 at room temperature was added a solution of *tert*-butyldimethylsilyl chloride (1.64 g, 10.9 mmol) in 2 mL of CH_2Cl_2. The reaction mixture was stirred at room temperature for 6 h and then diluted with 30 mL of water. After the aqueous phase was extracted with CH_2Cl_2, the combined extracts were washed with brine and dried. Purification of the residue by flash column chromatography eluting with 1/6 ethyl acetate/*n*-hexane gave 3.6 g of **4** (79% yield for three steps) as a straw-yellow solid: $[\alpha]^{20}_D$ −120.5 (*c* 1.0, $CHCl_3$); IR (KBr) 3344, 1713, 1666 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 2.1 Hz, 1H), 7.93 (dd, J = 8.7, 2.1 Hz, 1H), 6.64 (d, J = 8.7 Hz, 1H), 5.19 (br s, 1H), 3.87 (s, 3H), 3.69 (t, J = 5.3 Hz, 2H), 2.73 (dd, J = 16.1, 4.1 Hz, 1H), 2.53 (dd, J = 16.1, 11.6 Hz, 1H), 1.26−1.75 (m, 4H), 0.92 (s, 9H), 0.08 (s, 6H); EI-MS *m*/*z* 377 (M^+), 346, 320, 246, 228, 204; HRMS found *m*/*z* 377.2049 (M^+), $C_{20}H_{31}NO_4Si$ requires 377.2022.

(3a*S*,4*S*)-4-(3-*tert*-Butyldimethylsilyloxypropyl)-3,3a,4,5-tetrahydro-2*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylic Acid Methyl Ester 14. To a solution of **4** (1.0 g, 2.65 mmol) in 2.5 mL of anhydrous THF at −78 °C was slowly added a 1.0 M solution of lithium hexamethyldisilazide (5.6 mL, 5.6 mmol) in THF. The reaction mixture was allowed to warm to −40 °C over a 0.5 h period, and then treated with $BrCH_2CH_2OTf$ (1.59 g, 5.83 mmol) at −40 °C. The mixture was stirred for 1 h at this temperature, quenched with saturated NH_4Cl, and diluted with EtOAc. The aqueous layer was separated and extracted with EtOAc. The combined organic layers were washed with brine, dried, and concentrated in vacuo. Purification of the residue by column chromatography eluting with 1/8 ethyl acetate/*n*-hexane produced crude alkylation product.

To a solution of the above crude product in 10 mL of DMF was added sodium azide (345 mg, 5.3 mmol). This slurry was stirred for 10 h under nitrogen atmosphere before the solvent was evaporated in vacuo. After 5 mL of water was added to dissolve the residue, extraction with ethyl acetate was carried out. The combined extracts were dried over Na_2SO_4 and concentrated in vacuo to provide the corresponding azide.

A solution of the above azide, PPh_3 (0.94 g, 3.6 mmol), and water (0.2 mL) in 10 mL of THF was stirred at ambient temperature for 14 h. The reaction mixture was concentrated to dryness under reduced pressure. The residue was purified by column chromatography eluting with 1/8 ethyl acetate/*n*-hexane to produce 512 mg (48% yield for three steps) of **14**: $[\alpha]^{20}_D$ −68.9 (*c* 0.50, $CHCl_3$); IR (KBr) 3231, 1702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, J = 1.8 Hz, 1H), 7.86 (dd, J = 8.7, 2.0 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 4.90 (br s, 1H), 4.19 (m, 1H), 3.93 (s, 3H), 3.82 (m, 1H), 3.76 (m, 2H), 3.20 (m, 1H), 2.81 (m, 1H), 2.27 (m, 1H), 1.82 (m, 1H), 1.74−1.62 (m, 4H); EI-MS *m*/*z* 402 (M^+), 345, 269, 242, 229; HRMS found *m*/*z* 402.2311 (M^+), $C_{22}H_{34}N_2O_3Si$ requires 402.2339.

(1a*S*,3a*S*,4*S*)-2-(3-*tert*-Butyldimethylsilyloxypropyl)-1,5-bis(trifluoroacetyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylic Acid Methyl Ester 15. A solution of **14** (232 mg, 0.58 mmol) in 5 mL of MeOH at −40 °C was treated with $NaBH_4$ (87 mg, 2.3 mmol). The reaction mixture was allowed to warm to room temperature for a 2 h period. The solvent was removed under reduced pressure before 5 mL of water was added to dissolve the residue and then extracted with $CHCl_3$. The extracts were dried and concentrated to dryness. The residue, Et_3N (0.28 mL, 2.03 mmol), and a catalytic amount of DMAP were dissolved in 5 mL of anhydrous CH_2Cl_2. To this stirring solution was added a solution of $(CF_3CO)_2O$ (0.25 mL, 1.74 mmol) in 1 mL of CH_2Cl_2. After the reaction mixture was stirred for 2 h at room temperature, it was diluted with 10 mL of CH_2Cl_2 and 10 mL of water. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to dryness. The residue was purified by column chromatography eluting with 1/8 ethyl acetate/petroleum ether to give 245 mg of **15** as a colorless oil and 89 mg of its 4-epimer. **15**: $[\alpha]^{20}_D$ +19.5 (*c* 0.74, $CHCl_3$); IR (KBr) 1726, 1692, 1440 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, J = 1.4 Hz, 1H), 8.05 (dd, J = 8.3, 1.5 Hz,

1H), 7.43 (br s, 1H), 5.39 (br s, 1H), 4.72 (br s, 1H), 3.95 (s, 3H), 3.53 (m, 2H), 2.74 (m, 1H), 2.33 (m, 1H), 2.13 (m, 1H), 1.64−1.41 (m, 6H), 0.83 (s, 9H), 0.02 (s, 6H); ESI-MS *m*/*z* 1216 ($2M^+ + Na^+$), 597 ($M^+ + H^+$), 565 ($M^+ - OMe$); EI-MS *m*/*z* 581 ($M^+ - Me$), 518, 450, 423, 395; HRMS found *m*/*z* 581.1918 ($M^+ - Me$), $C_{25}H_{31}F_6N_2O_5Si$ requires 581.1907. 4-Epimer of **15**: $[\alpha]^{20}_D$ +310.3 (*c* 0.59, $CHCl_3$); IR (KBr) 1698, 1618 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (dd, J = 8.3, 1.9 Hz, 1H), 7.62 (s, 1H), 7.35 (d, J = 8.1 Hz), 4.58 (m, 1H), 4.37 (d, J = 11.8 Hz, 1H), 4.24 (t, J = 9.2 Hz, 1H), 3.93 (s, 3H), 3.77 (m, 1H), 3.61 (m, 2H), 2.25 (m, 1H), 1.97 (m, 1H), 1.80−1.71 (m, 3H), 1.56−1.48 (m, 2H), 0.86 (s, 9H), 0.02 (s, 6H); ESI *m*/*z* 1216 ($2M^+ + Na^+$), 597 ($M^+ + H^+$), 565 ($M^+ - OMe$); EI-MS *m*/*z* 581 ($M^+ - Me$), 518, 450, 423, 395; HRMS found *m*/*z* 596.2150 (M^+), $C_{26}H_{34}F_6N_2O_5Si$ requires 596.2141.

(1a*S*,3a*S*,4*S*)-1-Trifluoroacetyl-2,3,3a,3b,4,5,6,11b-octahydro-1*H*-dipyrrolo[1,2-*a*,3′,2′-*c*]quinoline-10-carboxylic Acid Methyl Ester 16. To a solution of **15** (14 mg, 0.023 mmol) in 1 mL of THF were added TBAF (12 mg, 0.046 mmol) and HOAc (2 μL). The mixture was stirred for 2 h and then partitioned between CH_2Cl_2 and water. The aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried and concentrated to dryness. The residue, Et_3N (7 μL, 0.05 mmol), and a catalytic amount of DMAP were dissolved in 1 mL of CH_2Cl_2. After MsCl (3 μL, 0.039 mmol) was added by syringe, the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was partitioned between CH_2Cl_2 and water. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried and concentrated to dryness. The residue was purified by column chromatography eluting with 1/2 ethyl acetate/*n*-hexane to produce 7 mg (83%) of **16**: $[\alpha]^{20}_D$ −29.4 (*c* 0.94, $CHCl_3$); IR (KBr) 1705, 1685, 1604 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.86 (d, J = 8.6 Hz, 1H), 6.49 (d, J = 8.6 Hz, 1H), 5.06 (d, J = 5.5 Hz, 1H), 3.89 (m, 1H), 3.84 (s, 3H), 3.64 (m, 1H), 3.45 (m, 2H), 3.01 (m, 1H), 2.29 (m, 1H), 2.21−2.10 (m, 2H), 1.97 (m, 2H), 1.63 (m, 2H). EI-MS *m*/*z* 368 (M^+), 339, 308, 271, 228; HRMS found *m*/*z* 368.1334 (M^+), $C_{18}H_{19}F_3N_2O_3$ requires 368.1348.

(1a*S*,3a*S*,4*S*)-4-(3-Hydroxypropyl)-1,5-bis(trifluoroacetyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylic Acid Methyl Ester 18. A solution of **14** (300 mg, 0.70 mmol) in 10 mL of THF was treated with TBAF (275 mg, 1.05 mmol) and HOAc (90 μL, 1.6 mmol) for 6 h. After 30 mL of ethyl acetate was added to dilute the reaction mixture, it was washed with water and brine. The organic layer was dried and concentrated. The residue was dissolved in 10 mL of THF and 0.5 mL of HOAc before $NaBH_4$ (79 mg, 2.1 mmol) was added at 0 °C. The suspension was stirred for 4 h. The solvent was removed under reduced pressure and the residue was dissolved with 20 mL of $CHCl_3$. The organic layer was washed with water and brine, dried, and concentrated. The residue was dissolved in 10 mL of anhydrous CH_2Cl_2, and then Et_3N (0.49 mL, 3.5 mmol), a catalytic amount of DMAP, and $(CF_3CO)_2O$ (0.35 mL, 2.45 mmol) were added. After the resulting mixture was stirred at room temperature overnight, 20 mL of CH_2Cl_2 was added to dilute the reaction mixture. The organic layer was washed with water and brine, dried, and concentrated. The residue was purified by column chromatography eluting with 2/1 ethyl acetate/*n*-hexane to give 317 mg of **18** in 94% yield for three steps: $[\alpha]^{20}_D$ +65.1 (*c* 0.97, $CHCl_3$); IR (KBr) 3126, 1691, 1613 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.04 (d, J = 7.7 Hz, 1H), 7.41 (br s, 1H), 5.38 (br s, 1H), 4.78 (br s, 1H), 3.96 (s, 3H), 3.62 (m, 2H), 2.76 (m, 1H), 2.36 (m, 1H), 2.16 (m, 1H), 1.74 (m, 2H), 1.47 (m, 4H); EIMS *m*/*z* 482 (M^+), 450, 423, 395, 284; HRMS found *m*/*z* 482.1267 (M^+), $C_{20}H_{20}F_6N_2O_5$ requires 482.1277.

(1a*S*,3a*S*,4*S*)-4-(3-Azidopropyl)-1,5-bis(trifluoroacetyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylic Acid Methyl Ester 19. A solution of **18** (164 mg, 0.35 mmol), Et_3N (78 μL, 0.56 mmol), and a catalytic amount of DMAP in 5 mL of CH_2Cl_2 was treated with MsCl (36 μL, 0.46 mmol) via syringe and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was partitioned between CH_2Cl_2 and water. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried and concentrated. The residue was purified by column chromatography eluting with 3/2 ethyl acetate/*n*-hexane to produce 185 mg of the corresponding mesylate.

To a solution of the above mesylate (164 mg, 0.30 mmol) in 5 mL of DMF was added sodium azide (60 mg, 0.90 mmol). This slurry was stirred for 10 h under nitrogen atmosphere before the solvent was evaporated in vacuo. The residue was partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined extracts were dried and concentrated to dryness. The residue was purified by column chromatography eluting with 1/1 ethyl acetate/*n*-hexane to give 134 mg (88%) of **19**: $[\alpha]^{20}_D$ +41.0 (*c* 0.95, $CHCl_3$); IR (KBr) 2101, 1725, 1693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, J = 1.6 Hz, 1H), 8.06 (dd, J = 8.4, 1.7 Hz, 1H), 7.33 (br s, 1H), 5.34 (br s, 1H), 4.73 (br s, 1H), 3.91 (s, 3H), 3.56 (m, 1H), 3.24 (t, J = 5.9 Hz, 2H), 2.68 (m, 1H), 2.33 (m, 1H), 2.13 (m, 1H), 1.69−1.47 (m, 5H); EI-MS *m*/*z* 507 (M^+), 476, 382, 365; HRMS found *m*/*z* 507.1342 (M^+), $C_{20}H_{19}F_6N_2SO_7$ requires 507.1341.

(1a*S*,3a*S*,4*S*)-4-(3-Aminopropyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylic Acid Methyl Ester 3. A solution of **19** (134 mg, 0.26 mmol), PPh_3 (208 mg, 0.79 mmol), and water (0.1 mL) in 2 mL of THF was stirred at ambient temperature for 14 h. The reaction mixture was concentrated to dryness under reduced pressure. The residue was treated with 5 mL of methanolic hydrogen chloride and 1 mL of water overnight. The solvent was removed under reduced pressure and 5 mL of water was added to dissolve the residue. The aqueous phase was extracted with EtOAc twice. The organic extracts were discarded, and the aqueous layer was concentrated to dryness in vacuo to produce 76 mg of **3** in 81% yield as its hydrochloride salt: $[\alpha]^{20}_D$ −49.9 (*c* 1.25, CH_3OH); IR (KBr) 3420, 1618, 1509 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 8.03 (d, 1.5 Hz, 1H), 7.76 (dd, J = 8.6, 1. 3 Hz, 1H), 6.88 (d, J = 8.7 Hz, 1H), 4.69 (d, J = 3.8 Hz, 1H), 3.84 (s, 3H), 3.41 (m, 2H), 3.13 (m, 1H), 3.04 (m, 2H), 2.45 (m, 2H), 2.18 (m, 1H), 1.92−1.74 (m, 4H); EI-MS *m*/*z* 289 (M^+), 259 ($M^+ - CH_2NH_2$), 245, 228, 214; HRMS found *m*/*z* 259.1437 ($M^+ - CH_2NH_2$), $C_{15}H_{19}N_2O_2$ requires 259.1447.

1-Benzoyl-3-(3′-methylbut-2′-enyl)thiourea 20. To a suspension of KSCN (6.16 g, 63.4 mmol) in 50 mL of anhydrous acetone was added slowly benzoyl chloride (7.36 mL, 63.4 mmol). After the mixture was stirred at room temperature for 1 h, the resultant precipitant was filtered off and the filtrate was concentrated to dryness. The residue was dissolved with 50 mL of anhydrous MeCN and then a solution of 3-methylbut-2-enylamine (5.4 g, 63.4 mmol) in 10 mL of anhydrous MeCN was added. The resultant solution was stirred overnight before the solvent was removed under reduced pressure. The residue was purified by column chromatography eluting with 2/1 ethyl acetate/*n*-hexane to give 10.7 g (68%) of **20**: IR (KBr) 3222, 1665, 1535 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.57 (br s, 1H), 9.00 (br s, 1H), 7.85−7.82 (m, 2H), 7.44−7.49 (m, 3H), 5.36 (t, J = 8.1 Hz, 1H), 4.27 (m, 2H), 1.78 (s, 3H), 1.74 (s, 3H); EI-MS *m*/*z* 248 (M^+), 234, 213, 205, 122, 105, 84, 77; HRMS found *m*/*z* 248.1022 (M^+), $C_{13}H_{16}N_2OS$ requires 248.0983.

1-(*tert*-Butoxycarbonyl)-3-(3′-methylbut-2′-enyl)-2-methylisothiourea 26. To a solution of **20** (6.04 g, 24.3 mmol) in 20 mL of methanol was added K_2CO_3 (6.36 g, 46 mmol) and the resulting mixture was stirred at room temperature for 6 h. The solvent was removed in vacuo and then 50 mL of $CHCl_3$ was added to dissolve the residue. The resultant solution was washed with water and brine and dried. After removal of the solvent, the residue was chromatographed eluting with 30/1 chloroform/methanol to give 3.3 g of **21** in 94% yield: IR (KBr) 3426, 3235, 3184, 1627 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.49 (br s, 1H), 5.96 (br s, 2H), 5.24 (t, J = 6.5 Hz, 1H), 3.76

(m, 2H), 1.76 (s, 3H), 1.70 (s, 3H); EI-MS *m/z* 144 (M^+), 129, 120, 111, 101, 68, 41; HRMS found *m/z* 144.0721 (M^+), $C_6H_{12}N_2S$ requires 144.0721.

A solution of **21** (3.3 g, 22.9 mmol) and CH_3I (2.85 mL, 45.8 mmol) in 20 mL of anhydrous DMF was stirred at room temperature overnight. The solvent was removed in vacuo to give 6 g of a crude of **24**.

To a solution of above crude product, Et_3N (6.73 mL, 48.3 mmol), and catalytic DMAP in 20 mL of anhydrous CH_2Cl_2 was added $(Boc)_2O$ (5.52 g, 25.3 mmol). After the mixture was stirred at room temperature for 4 h, it was washed by water and brine. The organic layer was dried and concentrated. The residue was purified by column chromatography eluting with 30/1 chloroform/methanol to give 5.27 g of **26** in 89% yield for two steps: IR (KBr) 3244, 1637 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.64 (br s, 1H), 5.23 (t, J = 7.0 Hz, 1H), 3.88 (m, 2H), 2.47 (s, 3H), 1.74 (s, 3H), 1.68 (s, 3H), 1.50 (s, 9H); EI-MS *m/z* 259 ($M^+ + H^+$), 203, 185, 169, 159, 137, 117, 69, 57, 41; HRMS found *m/z* 258.1429 (M^+), $C_{12}H_{22}N_2SO_2$ requires 258.1402.

(2′*S*)-*N*^{1}-Benzyl-*N*^{2}-(tert-butoxycarbonyl)-1′-[2′-(diphenylmethyl)pyrrolidine]carboxamidine 29. To a solution of **26** (23 mg, 0.089 mmol), **28** (23 mg, 0.097 mmol), and Et_3N (14 μL, 0.10 mmol) in 2 mL of anhydrous MeCN was added a solution of $AgNO_3$ (16 mg, 0.094 mmol) in 0.5 mL of MeCN in 30 min. After the mixture was stirred overnight in the dark, the resultant precipitate was filtered off and the filtrate was concentrated to dryness. The residue was dissolved in 10 mL of $CHCl_3$ and then washed with water and brine. The organic layer was dried and concentrated. The residue was purified by column chromatography eluting with 20/1 chloroform/methanol to give 33 mg (84%) of **29**: IR (KBr) 3275, 1633, 1581 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.14 (m, 10H), 5.31 (m, 1H), 5.03 (t, J = 8.1 Hz, 1H), 4.16 (d, J = 8.4 Hz, 2H), 3.60 (m, 1H), 3.37 (m, 2H), 2.08 (m, 2H), 1.77 (m, 2H), 1.61 (s, 3H), 1.54 (s, 3H), 1.47 (s, 9H); EI-MS *m/z* 447 (M^+), 390, 373, 346, 236, 224, 206, 165, 138, 70; HRMS found *m/z* 447.2894 (M^+), $C_{28}H_{37}N_3O_2$ requires 447.2886.

Compound 30. To a solution of **3** (62 mg, 0.16 mmol), **26** (200 mg, 0.78 mmol), and Et_3N (0.26 mL, 1.87 mmol) in MeCN (2 mL) and MeOH (1 mL) was added dropwise a solution of $AgNO_3$ (185 mg, 1.09 mmol) in 0.5 mL of MeCN over a 0.5 h period. After the reaction mixture was stirred overnight in the dark, it was filtered 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 extracts were dried and concentrated. The residue was purified by column chromatography eluting with 30/1 chloroform/methanol to give 68 mg (65%) of **30**: $[\alpha]^{20}_D$ −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.

Martinellic Acid 1. To a solution of **30** (21 mg, 0.03 mmol) in MeOH (3 mL) and water (1 mL) was added NaOH (6 ng, 0.15 mmol). The suspension was refluxed for 10 h and then neutralized with 0.1 N HCl cautiously. MeOH was removed under reduced pressure and the aqueous was extracted with $CHCl_3$. The combined organic layers were dried and concentrated. The residue was purified by column chromatography eluting with 5/1 chloroform/methanol to give 19 mg of the corresponding acid. This acid was dissolved in 2 mL of anhydrous CH_2Cl_2 before 0.05 mL of anisole and 0.1 mL of anhydrous trifluoroacetic acid were added. The mixture was stirred at room temperature for 14 h and then concentrated. The residue was purified by reversed phase column chromatography (C18 silica gel) eluting with 8/1 to 2/1 water/methanol to give 15 mg of **1** in 65% yield as its trifluoroacetic salt: $[\alpha]^{20}_D$ −122.7 (*c* 0.31, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.55 (d, J = 8.5 Hz, 1H), 6.59 (d, J = 8.5 Hz, 1H), 5.34 (t, J = 6.6 Hz, 1H), 5.31 (d, J = 6.5 Hz, 1H), 5.18 (t, J = 6.8 Hz, 1H), 3.97 (dd, J = 15.3, 6.5 Hz, 1H), 3.87 (dd, J = 15.3, 6.3 Hz, 1H), 3.74 (d, J = 6.6 Hz, 2H), 3.39 (m, 2H), 3.28(m, 1H), 3.14 (m, 2H), 2.45 (m, 1H), 2.08(m, 1H), 1.74 (s, 3H), 1.70 (s, 3H), 1.69 (s, 3H), 1.64 (s, 3H),1.69−1.63 (m, 2H), 1.56−1.45 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 167.2, 155.5, 154.3, 146.4, 136.1, 135.7, 130.5, 130.1, 119.6, 119.2, 117.1, 115.8, 113.3, 53.1, 49.1, 45.7, 40.7, 39.7, 39.2, 38.8, 33.4, 26.3, 25.5, 25.4, 25.2, 18.0, 17.9; ESI-MS *m/z* 724 ($M^+ + H^+ + 2CF_3COOH$), 610 ($M^+ + H^+ + CF_3COOH$), 496 ($M^+ + H^+$), 428.

3-Benzyl-1-(*tert*-butyloxycarbonyl)-2-methylisothiourea 31. Following the procedure for synthesizing **26** from 3-methyl-but-2-enylamine, compound **31** was prepared from benzylamine in 89% yield: IR (KBr) 3238, 1721, 1647 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.2 (br s, 1H), 7.35 (m, 5H), 4.52 (d, J = 5.7 Hz, 2H), 2.48 (s, 3H), 1.51 (s, 9H); EI-MS *m/z* 280 (M^+), 252, 224, 209, 158, 91; HRMS found *m/z* 280.1216 (M^+), $C_{14}H_{20}N_2O_2S$ requires 280.1246.

General Procedure of $AgNO_3$-Promoted Guanylation from 31. To a solution of compound **31** (1.0 mmol), amine (1.0 mmol), and Et_3N (2.0 mmol) in 5 mL of anhydrous MeCN was added a solution of $AgNO_3$ (1.5 mmol) in 1 mL of MeCN over 30 min. After the mixture was stirred for 4 h in the dark, the resultant precipitate was filtered and the filtrate was concentrated to dryness. The residue was dissolved by 10 mL of $CHCl_3$ and then washed with water and brine. After the solution was dried and concentrated, the residue was purified by column chromatography eluting with 10/1 to 30/1 chloroform/methanol to give the corresponding guanylation product.

***N*^{1}-Benzyl-*N*^{2}-(tert-butoxycarbonyl)-4′-morpholinecarboxanidine 32:** 99% yield; IR (KBr) 3183, 3090, 1662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.9 (br s, 1H), 7.30 (m, 5H), 4.39 (s, 2H), 3.69 (d, J = 4.8 Hz, 4H), 3.39 (d, J = 4.9 Hz, 4H), 1.50 (s, 9H); EI-MS *m/z* 319 (M^+), 264, 247, 219, 188, 158, 133, 106, 91; HRMS found *m/z* 264.1356 ($M^+ - Bu^t + H^+$), $C_{13}H_{18}N_3O_3$ requires 264.1348.

1-Benzyl-2-(*tert*-butoxycarbonyl)-3,3-diethylguanidine 33: 98% yield; IR (KBr) 3174, 3030, 1663 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5H), 6.80 (br s, 1H), 4.39 (s, 2H), 3.67 (q, J = 7.1 Hz, 4H), 1.51 (s, 9H), 1.15 (t, J = 7.2 Hz, 6H); EI-MS *m/z* 305 (M^+), 249, 232, 205, 176, 106, 91; HRMS found *m/z* 249.1491 ($M^+ - Bu^t + H^+$), $C_{13}H_{19}N_3O_2$ requires 249.1477.

***N*^{1}-Benzyl-*N*^{2}-(tert-butoxycarbonyl)-1′-pyrrolidinecarboxamidine 34:** 98% yield; IR (KBr) 3200, 3088, 1647 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5H), 6.95 (br s, 1H), 4.45 (s, 2H), 3.42 (m, 4H), 1.87 (m, 4H), 1.50 (s, 9H); EI-MS *m/z* 303 (M^+), 247, 230, 146, 106, 91, 70, 57; HRMS found *m/z* 303.1901 (M^+), $C_{17}H_{25}N_3O_2$ requires 303.1947.

1-Benzyl-2-(*tert*-butoxycarbonyl)-3,3-diisopropylguanidine 35: 96% yield; IR (KBr) 3271, 1616 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (m, 5H), 5.00 (br s, 1H), 4.42 (s, 2H), 4.11 (m, 2H), 1.55 (s, 9H), 1.28 (d, J = 6.3 Hz, 12H); EI-MS *m/z* 333 (M^+), 290, 260, 234, 190, 106, 100, 91, 57; HRMS found *m/z* 333.2413 (M^+), $C_{19}H_{31}N_3O_2$ requires 333.2416.

1-Benzyl-2-(*tert*-butoxycarbonyl)-3,3-dicyclohexylguanidine 36: 91% yield; IR (KBr) 3298, 1644 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5H), 5.20 (br s, 1H), 4.37 (s, 2H), 3.51 (m, 2H), 1.76 (m, 8H), 1.62 (m, 6H), 1.51 (s, 9H), 1.27 (m, 4H), 0.98 (m, 2H); EI-MS *m/z* 413 (M^+), 340, 274, 219, 182, 138, 91, 57; HRMS found *m/z* 413.3023 (M^+), $C_{25}H_{39}N_3O_2$ requires 413.3042.

(1′*R*)-1,3-Dibenzyl-2-(*tert*-butoxycarbonyl)-3-(1′-phenylethyl)guanidine 37: 93% yield; IR (KBr) 3235, 3089, 1641 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.13 (m, 13H), 6.83 (m, 2H), 5.88 (q, J = 7.1 Hz, 1H), 5.40 (br s, 1H), 4.31 (s, 2H),

4.21 (m, 2H), 1.62 (d, $J = 7.5$ Hz, 3H), 1.53 (s, 9H); EI-MS *m*/*z* 443 (M^+), 369, 340, 295, 277, 264, 196, 120, 106, 91, 57; HRMS found *m*/*z* 387.1976 ($M^+ - Bu^t + H^+$), $C_{24}H_{25}N_3O_2$ requires 387.1947.

1-Benzyl-2-(*tert*-butoxycarbonyl)-3-tert-butylguanidine 38: 93% yield; IR (KBr) 3336, 3109, 1612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5H), 4.56 (s, 2H), 1.51 (s, 9H), 1.36 (s, 9H); EI-MS *m*/*z* 305 (M^+), 249, 232, 219, 205, 193, 173, 148, 106, 91, 57; HRMS found *m*/*z* 305.2116 (M^+), $C_{17}H_{27}N_3O_2$ requires 305.2103.

1-Benzyl-2-(*tert*-butoxycarbonyl)-3-phenylguanidine 39: 88% yield; IR (KBr) 3350, 1643 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.76 (br s, 1H), 7.30 (m, 10H), 5.02 (br s, 1H), 4.61 (s, 2H), 1.55 (s, 9H); EI-MS *m*/*z* 325 (M^+), 280, 263, 219, 207, 131, 77, 65, 59; HRMS found *m*/*z* 325.1839 (M^+), $C_{19}H_{23}N_3O_2$ requires 325.1796.

1,3-Dibenzyl-2-(*tert*-butoxycarbonyl)guanidine 40: 98% yield. IR (KBr) 3339, 3287, 3001, 1591 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.17 (m, 10H), 4.44 (m, 4H), 1.53 (s, 9H); EI-MS *m*/*z* 339 (M^+), 283, 266, 239, 222, 192, 174, 148, 106, 91; HRMS found *m*/*z* 339.1914 (M^+), $C_{20}H_{25}N_3O_2$ requires 339.1947.

Acknowledgment. The authors are grateful to the Chinese Academy of Sciences, National Natural Science Foundation of China (grants 29725205 and 20132030) and Qiu Shi Science & Technologies Foundation for financial support. We thank Dr. K. M. Witherup of Merck research laboratories for providing NMR spectra of natural martinelline.

Supporting Information Available: ^1H NMR spectra of compounds **1**, **3**, **4**, **11**, **14**, **15**, **18**, and **30**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026125Z