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Total Synthesis of (−)-Martinellic Acid via Radical Addition−Cyclization−Elimination Reaction

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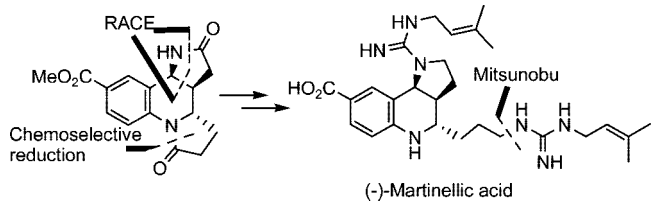
Received December 17, 2007



The asymmetric total synthesis of martinellic acid, the first pyrrolo[3,2-*c*]quinoline alkaloid found in nature, is described. Three key steps in our synthesis of (−)-martinellic acid are the Bu_3SnH-promoted radical addition−cyclization−elimination (RACE) reaction of an oxime ether with an α,β-unsaturated ester to generate the pyrrolo[3,2-*c*]quinoline core, a chemoselective lactam carbonyl reduction, and guanidinylation under Mitsunobu reaction conditions. The key radical cyclization has also been investigated by using SmI_2. (−)-Martinellic acid was synthesized from commercially available methyl 4-bromo-3-methylbenzoate in fewer steps than previous syntheses and in an improved overall yield.

The martinella alkaloids were isolated in 1995 by Merck Research Laboratories from the root bark of the tropical plant *Martinella iquitosensis* and were found to be a new class of pyrroloquinoline alkaloid (Figure 1).[1] The structures involving relative configurations were firmly established by the spectral data but the absolute configurations were not determined.[1] The plant extracts have been used as an eye medication in over 13 different ethnolinguistic groups from eight South American countries.[2] These alkaloids were found to possess antibacterial activity as well as affinity for adrenergic, muscarinic, and bradykinin receptors. Furthermore, these are the first examples of nonpeptidic compounds to be identified as bradykinin receptor antagonists.

Over the past decade, considerable effort has been devoted to the synthesis of the martinella alkaloids.[3−11] The pyrrolo[3,2-*c*]quinoline core of the martinella alkaloids has been prepared by several synthetic routes including the imino Diels−Alder reaction of 2-pyrroline and an *N*-arylimine,[6] the inter- and intramolecular 1,3-dipolar cycloadditions of azomethine ylides to olefins,[7] Heck reactions under palladium catalysis,[8] intramolecular radical cyclizations between aryl iodides and pyrroles,[9] Fischer-type cycloaddition,[10] and others.[11]

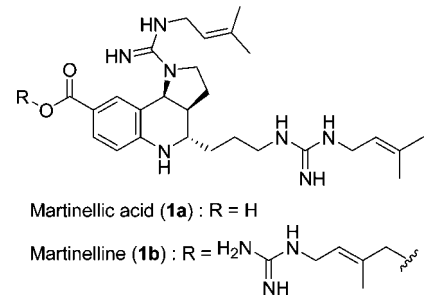


FIGURE 1. Martinellic acid (**1a**) and martinelline (**1b**).

The first asymmetric total synthesis of martinellic acid (**1a**) was reported by the group of Ma,[5d,e] who employed a CuI-catalyzed coupling reaction of a β-amino ester with 1,4-diiodobenzene and a guanylation of a secondary amine under mild conditions as the key steps. In 2007, Iwabuchi reported syntheses of both enantiomers of martinellic acid (**1a**) and martinelline (**1b**)

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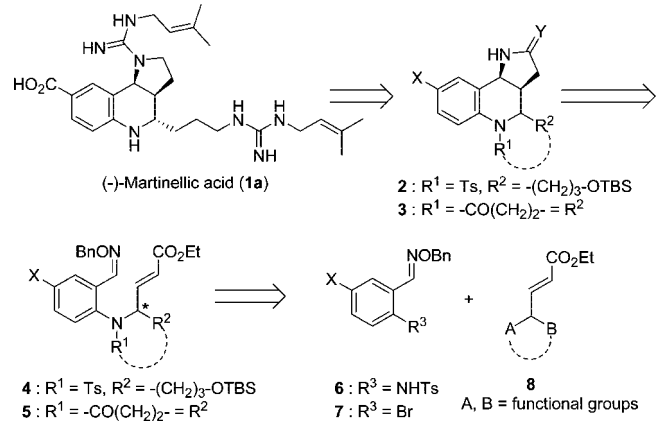
10.1021/jo800560p CCC: $40.75
Published on Web 05/13/2008

employing a tandem Mukaiyama−Mannich reaction/aminal cyclization as a key step.[5f] Interestingly, all the synthetic samples of the natural product exhibit optical rotation values that are different from that reported for the isolated natural product. More recently, Lovely has reported the asymmetric synthesis of (−)-martinellic acid (**1a**) using an intramolecular [3 + 2]azomethine ylide−alkene cyclization as a key reaction. Again, the optical rotation of the final product was ambiguous.[5g]

As part of our studies on the stannyl radical addition−cyclization reactions of imine derivatives,[12] we have recently developed the radical addition−cyclization−elimination (RACE) reactions of oxime ethers with α,β-unsaturated esters.[12m] In this article, we describe in detail an asymmetric total synthesis of martinellic acid (**1a**) based on the RACE reaction of a chiral oxime ether **5b**.[4f]

SCHEME 1



Results and Discussion

Our retrosynthetic analysis of (−)-martinellic acid (**1a**) is outlined in Scheme 1. We envisaged that martinellic acid (**1a**) could be derived from pyrroloquinolines **2** and **3** by introduction of the guanidine moiety and hydrolysis of an ester group. We proposed that the intermediates **2** and **3** would be produced by diastereoselective RACE reactions of oxime ethers **4** and **5**, in which the diastereroselectivity of the reactions would be controlled by the stereocenter bearing the R^2 group. The oxime ethers **4** and **5** would be prepared by reaction of either **6**[12m] or **7** with the unsaturated esters **8**.

The oxime ether **4** bearing an alkyl chain at the allylic position was chosen for preliminary studies on the proposed RACE reaction (Scheme 2). Benzyl alcohol **9** was prepared from commercially available methyl anthranilate according to the reported procedure.[13] Oxidation of benzyl alcohol **9** with use of MnO_2 followed by treatment of the resulting aldehyde with benzyloxyamine hydrochloride in the presence of sodium acetate gave oxime ether **6**.[12m] The Wittig reaction of 2,3-dihydroxypyran **10**[14] with (carbethoxymethylene)triphenylphosphorane, followed by protection of the diol intermediate with TBSCl provided monoalcohol **11** in 60% yield for 2 steps. The Mitsunobu reaction of sulfonamide **6** with alcohol **11** proceeded smoothly under standard conditions[15] to provide *N*-allyl sulfonamide **4** in 49% yield.

We next investigated the RACE reaction of **4** under standard conditions (Scheme 3). Treatment of oxime ether **4** with Bu_3SnH and AIBN in refluxing benzene gave pyrroloquinolines **2a−c** in a 15:11:1 ratio. In all cases, the *N*-benzyloxy group was lost during the cyclization.[12m] Isomers **2a−c** were readily separated by column chromatography.[16] Unfortunately, the cyclization

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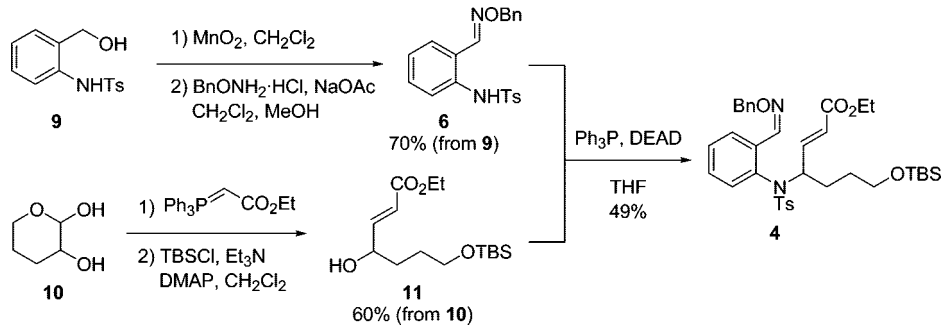
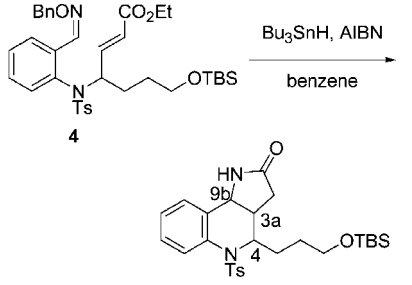
SCHEME 2



SCHEME 3



proceeded with low diastereoselectivity and the desired diastereomer **2b** was isolated as a minor product.

We next turned our attention to the RACE reaction of oxime ethers **5a**,**b** bearing a 2-pyrrolidone moiety (Schemes 4 and 5). Initially, treatment of the commercially available 2-bromobenzaldehyde **13a** with benzyloxyamine hydrochloride in the presence of sodium acetate gave oxime ether **7a**. Palladium-catalyzed cross-coupling[17,18a,b] of bromobenzene **7a** with L-pyroglutamic acid ethyl ester[19] gave anilide **14a** in 99% yield. This coupling reaction proceeded in moderate yield when copper iodide was used instead of the palladium catalyst.[18c] The ester group in **14a** was reduced to the corresponding alcohol followed by Swern oxidation to give the aldehyde. The resulting aldehyde was treated with (carbethoxymethylene)triphenylphosphorane to give the α,*β*-unsaturated ester **5a** in 87% yield for 3 steps.

Under standard stannyl radical reaction conditions, the RACE reaction of **5a** proceeded smoothly to provide dipyrroloquinolines **3aA**−**aD** (17:6:5:3), amino ester **15a**, and *N*-benzyloxydipyrroloquinoline **16a**. A major product of the reaction was the desired 3a*S*,3b*S*,11b*S*-dipyrroloquinoline **3aA** (33%). On the basis of the promising preliminary results, we next investigated the RACE reaction of oxime ether **5b** bearing an ester group on the benzene ring (Schemes 4 and 5). The preparation of the requisite oxime ether **5b** began with commercially available methyl 4-bromo-3-methylbenzoate **12**. Benzylic bromination of **12** provided the benzyl dibromide in quantitative yield. The benzyl dibromide was then treated with $AgNO_3$ in acetone and H_2O to give aldehyde **13b**, which was converted to **5b** by using a similar route to that described for the preparation of **5a**. We next carried out the RACE reaction of **5b**, which proceeded smoothly to give the desired 3a*S*,3b*S*,11b*S*-dipyrroloquinoline **3bA** as a major product (29%) and its stereoisomers **3bB**−**bD** in 45% combined yield (**3bA**:**3bB**:**3bC**:**3bD** = 7:2:1:1). Although side products were obtained in addition to the desired products **3aA** and **3bA**, the RACE reaction of both **5a** and **5b** allowed the desired products **3aA** and **3bA** to be isolated easily as colorless crystalline solids from the reaction mixture after the radical cyclization.

The radical cyclization of **5b** was also investigated with use of SmI_2[20] as an alternative to Bu_3SnH. While oxime−carbonyl cyclizations with SmI_2 are well-precedented in target synthesis,[12c,d,h,21] oxime−alkene cyclizations have received little attention.[22] Treatment of **5b** with SmI_2 in THF with *t*-BuOH as a proton source gave a 4:1 diastereoisomeric mixture of **3bA**:**3bB** in addition to minor byproduct. **3bA** was isolated in 41% yield. Thus, the cyclization with SmI_2 gives an improved yield of **3bA** (41%) when compared to the Sn-mediated reaction (29%).

The stereochemistry of the products **3aA** and **3bA** was established by X-ray crystallography and that of **2b** was determined by the transformations shown in Scheme 6. Detosylation of **2b** with magnesium in the presence of ammonium chloride gave **17** that was identical with the sample derived from **3aA** (Scheme 6). The relative stereochemistry of the isomers **2a** and **2c** was deduced from comparison of their ^{1}H NMR spectra and NOE data with those of **2b**.

The structure of the isomers **3aB**−**aD** and **3bB**−**bD** was deduced from comparison of ^{1}H NMR spectra and NOE data with those of **3aA** and **3bA**.

Our explanation of the stereoselectivity of the Sn-mediated RACE reactions is shown in Scheme 7. In the (α-stannylamino)benzyl radical, formed by the addition of stannyl radical to oxime ether **4**, $A^{1,3}$-strain gives rise to the prefered conformations **A** and **B**, of which *anti*-transition structure **A** is favored

(16) In addition to **2a**−**c**, bicyclic amino ester (3%) was obtained by column chromatography and characterized as shown in the Supporting Information.

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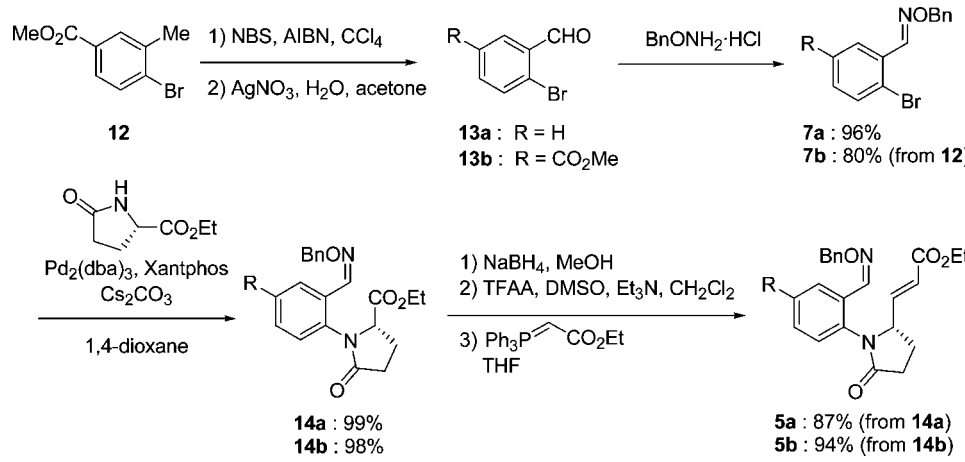
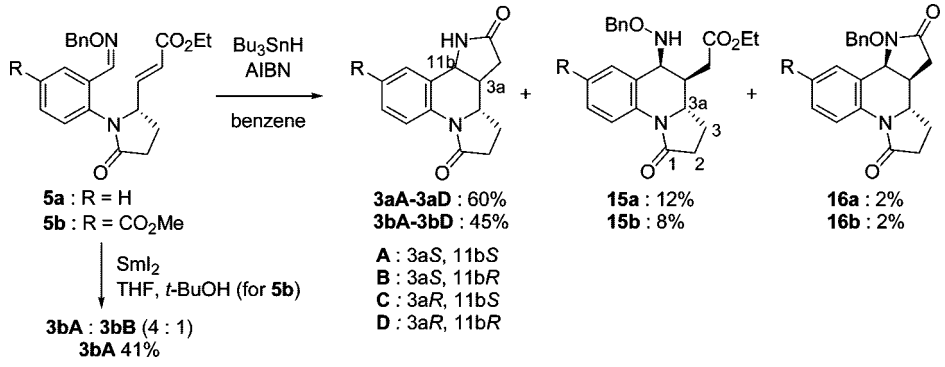
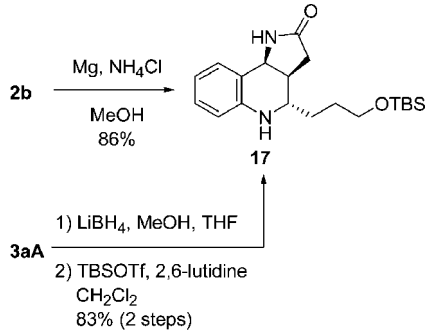
SCHEME 4



SCHEME 5



SCHEME 6



over **B**, which involves unfavorable interactions between the ester and alkoxyaminostannane. Prefered transition structure **A** leads to the formation of **2a**. Cyclic oxime ethers **5a**,**b** give **3aA** or **3bA** as major products via prefered *syn*-transition structure **C** as the corresponding *anti*-transition structure **D** is disfavored due to steric repulsion between the alkoxyaminostannane and pyrrolidone moiety. This interaction overrides the usual *anti*-selectivity of the RACE cyclization (Scheme 7).

While the mechanism of the SmI_2-mediated RACE reaction for a benzaldehyde-derived oxime ether is unclear,[22] it is reasonable to invoke the cyclization of an α-aza radical complexed to samarium(III) (Scheme 8).

We next investigated systematic study on the selective reduction both of *tert*-*N*-aryllactam in the C-ring of **3bA** to amino alcohol and of *sec*-NH-lactam in the A ring to cyclic amine without reduction of the ester group (Scheme 9). Treatment of **3bA** with borane reagents such as 9-BBN, BMS (borane dimethyl sulfide complex), and disiamylborane gave only a complex mixture. It is known that the selective reduction of lactams to cyclic amines proceeds smoothly even in the presence of an ester moiety. However, it seems hard to prepare the corresponding amino alcohol by the selective reduction of lactams carrying an ester group.

Soai[23] has reported that upon treatment with $LiBH_4$ in the presence of MeOH in THF, primary and tertiary amides gave the corresponding primary amines and two products of secondary amines and alcohols, respectively, in which the latter two products would be formed as the result of carbon−nitrogen bond cleavage of the hemiaminal intermediate. His group has also reported that reduction of the secondary amides was not observed under the same reaction conditions but esters also were easily reduced by using $LiBH_4$ and MeOH in Et_2O. Thus, in our case, the secondary lactam in the A-ring is not expected to be reduced but the lactam carbonyl in the C-ring and ester carbonyl groups would be reduced under the Soai reaction conditions. However, we expected that the lactam carbonyl group in the C-ring would be more activated by the ester group in the para position to undergo C-ring opening due to higher reactivity of the lactam carbonyl than that of the ester group. Thus, we did a systematic study on the selective reduction of dipyrroloquinoline **3bA** bearing both ester and two types of *N*-substituted lactam carbonyl groups (Scheme 10; Table 1).

Treatment of dipyrroloquinoline **3bA** with $LiBH_4$ in THF in the presence of MeOH at room temperature gave the benzyl alcohol **20** (67%) as a major product in addition to the desired amino alcohol **19** (30%) (entry 1). We found that the reaction

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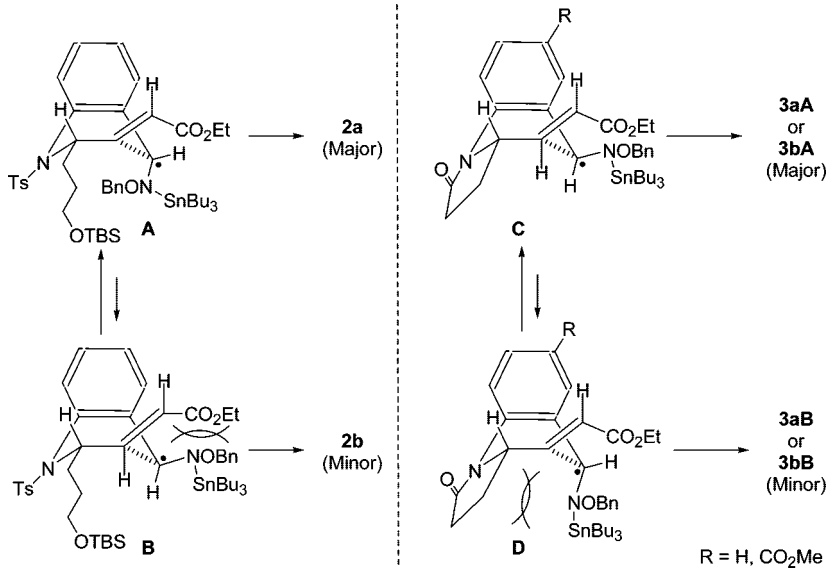
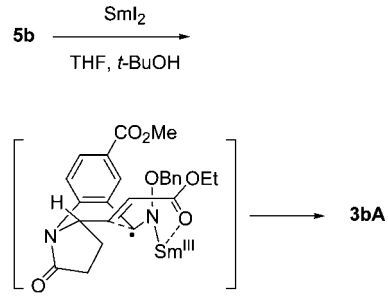
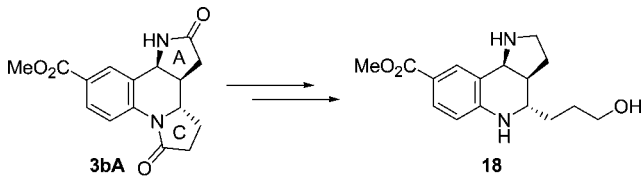
SCHEME 7



SCHEME 8



SCHEME 9



temperature plays a critical role in the formation of the desired product **19**, which was obtained in 76% yield at 66 °C (entry 2). Unfortunately, further higher temperature (90 °C) decreased the yield of **19** (entry 3).

Thus, we succeeded in the reductive ring opening reaction of the *N*-arylpyrrolidinone part in **3bA** with $LiBH_4$−MeOH−THF at 66 °C, which provided selectively desired amino alcohol **19** without the reduction of an ester group.

Finally, again the selective reduction of NH-lactam in the A-ring of **19** with BH_3·THF gave the desired cyclic amine **18** (Scheme 11).

The amino alcohol **18** was converted into the trifluoroacetamide **22a**[5d,e] and tri-Troc compound **21** under standard conditions. To convert **21** into alcohol **22b**, we examined selective deprotection of the carbonate moiety (Scheme 11; Table 2). The treatment of **21** with K_2CO_3 (5 equiv) in MeOH gave methyl carbamate **23** (entry 2) while only **21** was recovered under the acidic conditions (entry 1). The selective deprotection of the carbonate group proceeded smoothly in the presence of K_2CO_3 (1.5 equiv) in MeOH:H_2O (20:1) to give the desired product

SCHEME 10

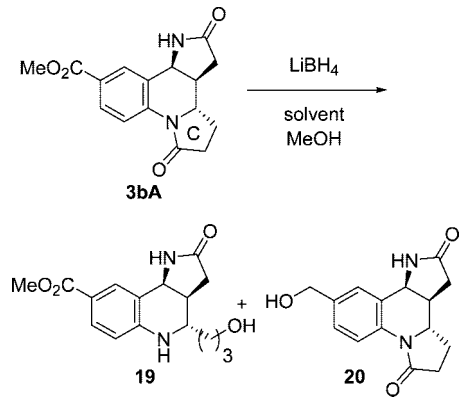


TABLE 1. Chemoselective Reduction of 3bA

			yield (%)[a]	
entry	solvent	temp (°C)	**19**	**20**
1	THF	rt	30	67
2	THF	66	76	17
3	diglyme	90	25	19

[a] Isolated yields.

22b in good yield without formation of the methyl carbamate **23** (entry 3).

As methods for the introduction of the guanidine moiety typically proceed in moderate yield and require multistep sequences,[5c–g] we explored a shorter route involving a Mitsunobu reaction.

In our preliminary study, we used tetrahydroquinolines **24a**−**c** as substrates to evaluate our proposed method for introduction of the guanidine group (Scheme 12; Table 3). The amino group of **24a**, prepared by the reduction of 3,3a,4,5-tetrahydropyrrolo[1,2-*c*]quinolin-1-one[24] with $LiBH_4$, was protected by the treatment with trifluoroacetic anhydride (TFAA) or 2,2,2-trichloroethoxycarbonyl chloride (TrocCl) to give **24b** and **24c**, respectively. Our first

(24) (a) Kocián, O.; Ferles, M. *Collect. Czech. Chem. Commun.* **1978**, *43*, 1413–1430. (b) Baumgarten, H. E.; Beckerbauer, R.; Debrunner, M. R. *J. Org. Chem.* **1961**, *26*, 1539–1546.

SCHEME 11

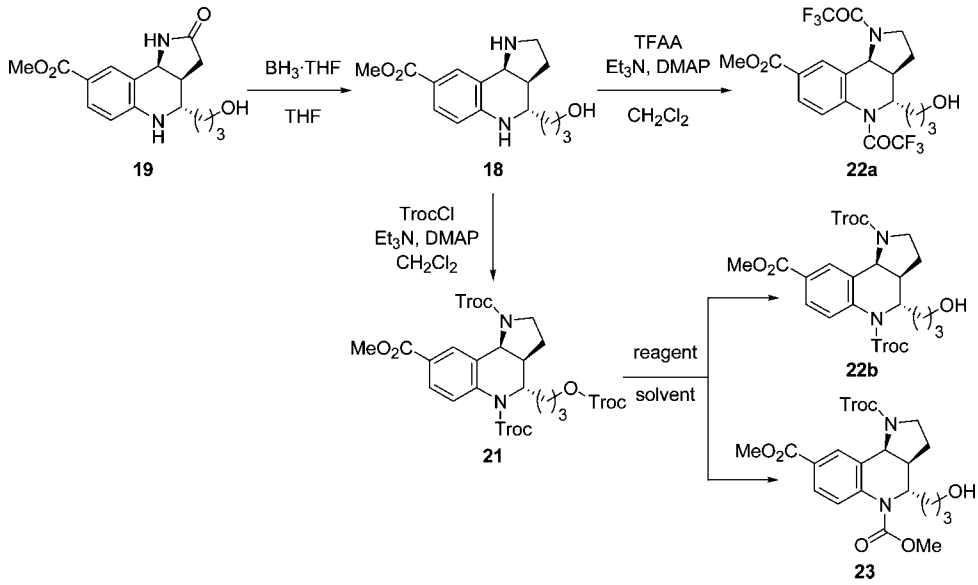


TABLE 2. Selective Deprotection of Troc Carbonate of 21

			yield (%)[a]		
entry	reagent	solvent	**22b**	**23**	**21**
1	TFA (1 equiv)	MeOH			quant.
2	K_2CO_3 (5 equiv)	MeOH		67	
3	K_2CO_3 (1.5 equiv)	MeOH, H_2O	87		

[a] Isolated yields.

attempt of direct preparation of **27a** from **24a** via the route involving the Mitsunobu reaction using *N*,*N*′-bis(*tert*-butoxycarbonyl)-*N*″-prenylguanidine **25a**[25] as a nucleophile was unsuccessful and only undesired **28**[26] was obtained in 68% yield as a result of intramolecular reaction (entry 1). Under the same reaction conditions, **24b** gave the complex mixture (entry 2).

Kim has reported Mitsunobu reactions using isothiourea as a nucleophile.[27] According to his procedure, treatment of **24b** with isothiourea **25b**, DEAD, and Ph_3P in THF at room temperature gave **26b** in 88% yield (entry 3). The subsequent reaction of **26b** with prenylamine[28] proceeded at room temperature to afford *N*-Boc-protected guanidine **27b** in 93% yield. In the case of the Mitsunobu reaction employing DIAD, a similar chemical yield (92%) was obtained (entry 4). Furthermore, we tested the Mitsunobu reaction of *N*-Troc tetrahydroquinoline **24c** and obtained **26c** in moderate yield (entries 5 and 6). **26c** was also treated with prenylamine to afford *N*-Boc-protected guanidine **27c** in 83% yield (Scheme 12). Quinoline compounds, such as **27b** and **27c**, containing a guanidine group are known to exhibit bradykinin antagonist activity as well as activity with the α-adrenergic, histaminergic, and muscarinic receptors.[29]

On the basis of the preliminary results from our model studies, we investigated the use of the Mitsunobu reaction for the introduction of the guanidine moiety to alcohol **22a** bearing two trifluoroacetyl groups (Scheme 13). Trifluoroacetamide **22a** was first subjected to the Mitsunobu reaction with use of isothiourea **25b**, DIAD, and Ph_3P. Unfortunately, the desired product **29a** was formed in only moderate yield (44%) and *N*-deprotected aniline **30a** was also isolated in 17% yield (Scheme 13). The attempted introduction of a guanidine group to aniline **30a** was unsuccessful and starting material was recovered in 61% yield.

The synthesis of (−)-martinellic acid was completed as shown in Scheme 14. The addition−elimination reaction of isothiourea **29a** with prenylamine[28] proceeded to afford the *N*-Boc guanidine **31a** in addition to **31′a**. To install the second guanidine moiety at the N(1)-position, treatment of a mixture of **31a** and **31′a** with K_2CO_3 followed by isothiourea **32**,[5] in the presence of $HgCl_2$, gave bisguanidine **33a** in excellent yield. The spectral data of **33a** were identical with those of an authentic sample reported in the literature.[5c–g] Removal of one Boc group would appear to occur during treatment with K_2CO_3.[5a] Finally, hydrolysis of the methyl ester and removal of the two Boc groups of **33a**, followed by HPLC purification (C18 silica gel, H_2O−MeOH−CF_3CO_2H) gave (−)-martinellic acid (**1a**) as its bistrifluoroacetate salt in 56% yield for 2 steps. The low yield (44%) observed in conversion of **22a** into **29a** led us to investigate an improved synthesis of (−)-martinellic acid using **22b**, bearing Troc protection as a substrate for the introduction of a guanidino group. The Mitsunobu reaction of *N*-Troc carbamate **22b** proceeded smoothly to give the desired product **29b** in 96% yield (Scheme 13). The isothiourea **29b** was then converted to **33b** by treatment with prenylamine,[28] deprotection of the Troc group, and introduction of the guanidino group (Scheme 14). Finally, **33b** was subjected to hydrolysis and deprotection to give (−)-martinellic acid (**1a**).

Ma, Iwabuchi, and Lovely have shown that the transformation of alcohols **22** to the desired product **33a**, bearing two guanidino groups, proceeded in 28−50% yields over 5 steps.[5c–g] In contrast, our synthesis of **33b** was achieved in 4 steps and in 62% overall yield from **22b**.

Synthetic martinellic acid (**1a**) was shown to be identical with natural martinellic acid by direct comparison of their ^1H and ^{13}C NMR spectra provided by Drs. Sheo Bux Singh and Steven

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(26) Omar-Amrani, R.; Thomas, A.; Brenner, E.; Schneider, R.; Fort, Y. *Org. Lett.* **2003**, *5*, 2311–2314.

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(28) Jordis, U.; Grohmann, F.; Küenburg, B. *Org. Prep. Proced. Int.* **1997**, *29*, 549–560.

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SCHEME 12

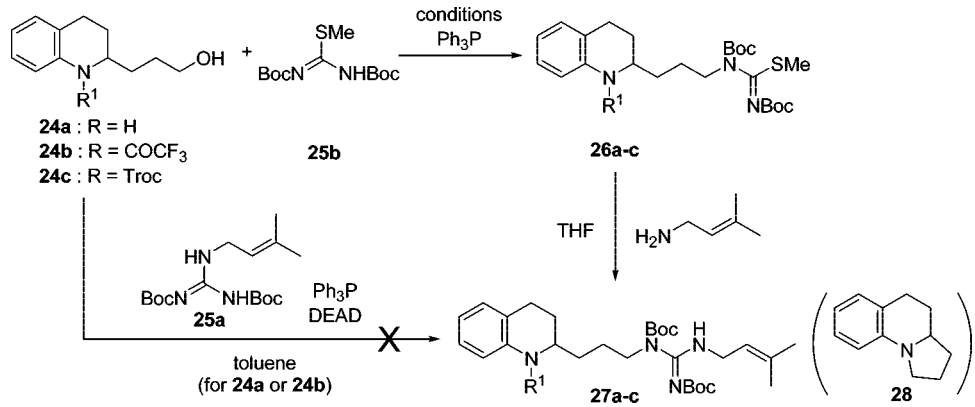


TABLE 3. Introduction of Guanidine Moiety by Using a Mitsunobu Reaction[a]

entry	substrate	nucleophile	conditions	yield (%)[b]
1	**24a**	**25a**	DEAD, toluene	–[c]
2	**24b**	**25a**	DEAD, toluene	–[d]
3	**24b**	**25b**	DEAD, THF	88
4	**24b**	**25b**	DIAD, THF	92
5	**24c**	**25b**	DEAD, THF	61
6	**24c**	**25b**	DIAD, THF	66

[a] Reaction conditions: nucleophile (1.0 equiv), azodicarboxylate (1.5 equiv), Ph_3P (1.5 equiv) in solvent at room temperature. [b] Isolated yields. [c] Intramolecular cyclization product **28** was isolated in 68% yield. [d] Complex mixture was observed. DEAD = diethyl azodicarboxylate. DIAD = diisopropyl azodicarboxylate.

M. Pitzenberger of Merck Research Laboratories.[30] However, there is again a discrepancy between the optical rotation of the alkaloid isolated from natural sources and our synthetic sample. The optical rotation of our synthetic martinellic acid bistrifluoroacetate was $[\alpha]^{23}_D$ −164.8 (*c* 0.33, MeOH), while $[\alpha]_D$ −8.5 (*c* 0.01, MeOH) was reported for the natural product.[1] Recently, Dr. Sheo Bux Singh, director and head of the Merck group, has informed us that the natural product may have been nearly racemic in his private communication. Our synthetic sample and Prof. Iwabuchi's sample exhibited almost identical optical rotations.[5f] Thus, both Iwabuchi's synthesis of both enantiomers of martinellic acid and our synthesis of (−)-martinellic acid determined unambiguously the absolute structure as 3a*S*,4*S*,9b*S*-configuration.

Conclusion

The total synthesis of (−)-martinellic acid has been accomplished by the preparation of the chiral dipyrroloquinoline intermediate **3bA**. The three key steps in our approach are a Bu_3SnH-promoted radical addition−cyclization−elimination reaction of oxime ether **5b**, chemoselective reduction of **3bA**, and a new method for the introduction of the guanidine moiety with use of the Mitsunobu reaction. An alternative radical cyclization with SmI_2 has also been evaluated in our approach. Our synthetic route involves 18 steps making it the shortest of the syntheses to date. Our synthetic strategy will allow improved access to a variety of pyrroloquinoline structures in the future.

Experimental Section

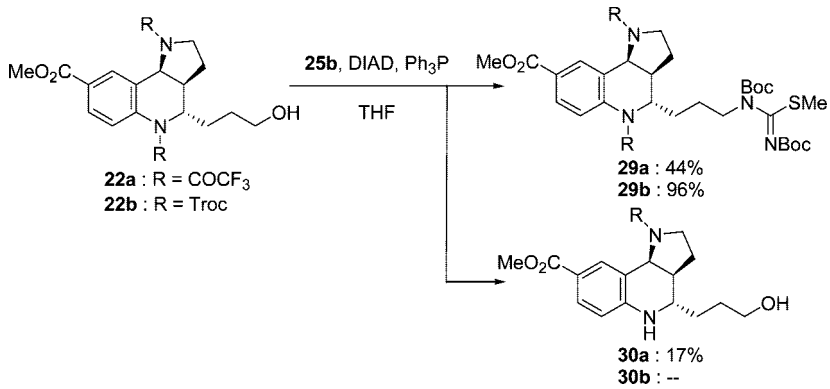
Methyl (*E*)-4-Bromo-3-[(phenylmethoxyimino)methyl]benzoate (7b). A solution of a mixture of methyl 4-bromo-3-methylbenzoate (**12**) (10 g, 43.7 mmol), NBS (23.3g, 131.1 mmol), and AIBN (717.6 mg, 4.37 mmol) in CCl_4 (437 mL) was refluxed with stirring under a nitrogen atmosphere. After 1.5 h, AIBN (358.8 mg, 2.19 mmol) was added. After the mixture was stirred at reflux for a further 5 h, AIBN (717.6 mg, 4.37 mmol) was added. After the solution was refluxed for 6 h, AIBN (359.6 mg, 2.19 mmol) was added and the mixture was refluxed for 1 h. Then the reaction mixture was filtered to remove the resulting succinimide. The filtrate was washed with water, dried over Na_2SO_4, and concentrated at reduced pressure. The residue was recrystallized from *n*-hexane to afford benzyl dibromide (16.9 g, quant.) as pale-yellow crystals.

Methyl 4-Bromo-3-(dibromomethyl)benzoate. Mp 82−83 °C (hexane). IR ν_{max} cm^{-1} 1725. ^1H NMR (200 MHz) δ 8.66 (1H, d, J = 2.0 Hz), 7.82 (1H, dd, J = 8.5, 2.0 Hz), 7.59 (1H, d, J = 8.5 Hz), 7.08 (1H, s), 3.96 (3H, s). ^{13}C NMR (50 MHz) δ 165.5, 140.9, 132.9, 132.2, 131.6, 130.8, 124.8, 52.6, 38.7. HRMS *m*/*z* calcd for $C_9H_7Br_3O_2$ (M^+) 383.7996, found 383.8002. Anal. Calcd for $C_9H_7Br_3O_2$: C, 27.94; H, 1.82. Found: C, 27.94; H, 1.95. To a solution of benzyl dibromide (10 g, 25.8 mmol) in acetone (308 mL) and H_2O (62 mL) was added $AgNO_3$ (8.77 g, 51.6 mmol) at room temperature. After being stirred at reflux under a nitrogen atmosphere for 1.5 h, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated at reduced pressure and extracted with $CHCl_3$. The organic phase was washed with brine, dried with $MgSO_4$, and concentrated at reduced pressure to afford crude **13b**. To a solution of crude **13b** in pyridine (246 mL) was added $BnONH_2 \cdot HCl$ (4.53 g, 28.4 mmol) at room temperature. After being stirred at room temperature under a nitrogen atmosphere overnight, the reaction mixture was extracted with Et_2O and 2 M HCl. The organic phase was washed with brine, dried with $MgSO_4$, and concentrated at reduced pressure. The residue was recrystallized from AcOEt to afford **7b** (7.19 g, 80%) as colorless crystals. Mp 58−60 °C (AcOEt). IR ν_{max} cm^{-1} 1723. ^1H NMR (300 MHz) δ 8.52 (1H, s), 8.51 (1H, d, J = 2.0 Hz), 7.85 (1H, dd, J = 8.5, 2.0 Hz), 7.63 (1H, d, J = 8.5 Hz), 7.46−7.30 (5H, m), 5.27 (2H, s), 3.93 (3H, s). ^{13}C NMR (50 MHz) δ 166.0, 147.5, 137.0, 133.4, 132.0, 131.4, 129.7, 128.6, 128.55, 128.49, 128.2, 77.1, 52.4. HRMS *m*/*z* calcd for $C_{16}H_{14}BrNO_3$ (M^+) 347.0157, found 347.0159. Anal. Calcd for $C_{16}H_{14}BrNO_3$: C, 55.19; H, 4.05; N, 4.02. Found: C, 55.44; H, 3.97; N, 4.03.

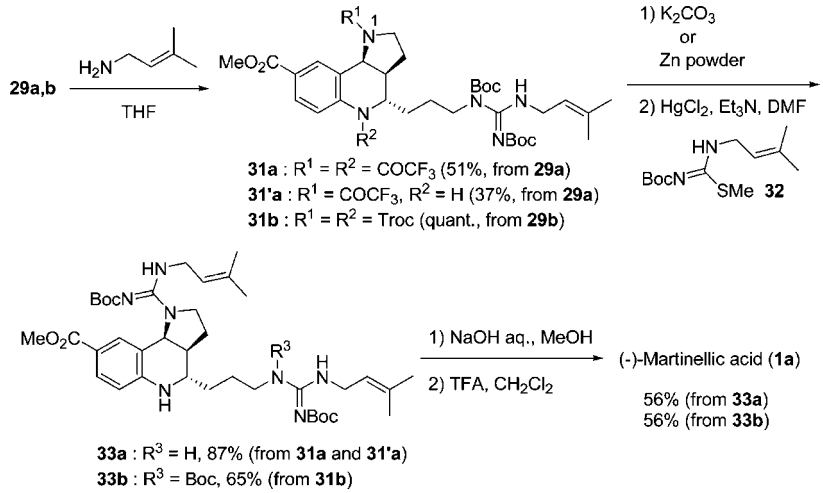
(*S*)-1-[4-(Methoxycarbony)-2-[(*E*)-(phenylmethoxyimino)methyl]phenyl]-5-oxoproline Ethyl Ester (14b): In the Presence of Palladium Catalyst. To **7b** (1.8 g, 5.16 mmol), L-pyroglutamic acid ethyl ester[19] (971.3 mg, 6.18 mmol), $Pd_2(dba)_3$ (247.2 mg, 0.27 mmol), Xantphos (52.1 mg, 0.09 mmol), and Cs_2CO_3 (2.39 g, 7.32 mmol) was added 1,4-dioxane (5.16 mL) through the septum under an Ar atmosphere at room temperature. After being stirred at 100 °C for 8 h, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated at reduced pressure. The residue was purified by FCC (hexane/AcOEt 1:1) to afford **14b** (2.15 g, 98%) as colorless crystals. Mp 101−104 °C (AcOEt). IR

(30) The natural martinellic acid NMR is used with permission of Merck & Co., Inc., Whitehouse Station, NJ, USA.

SCHEME 13



SCHEME 14



ν_{max} cm^{-1} 1721. ^{1}H NMR (300 MHz) δ 8.46 (1H, d, J = 2.0 Hz), 8.20 (1H, s), 8.04 (1H, dd, J = 8.5, 2.0 Hz), 7.43−7.32 (6H, m), 5.24 (2H, s), 4.59−4.55 (1H, m), 4.14−4.03 (2H, m), 3.93 (3H, s), 2.71−2.61 (1H, m), 2.53−2.40 (2H, m), 2.23−2.12 (1H, m), 1.16 (3H, t, J = 7.0 Hz). ^{13}C NMR (50 MHz) δ 173.8, 170.2, 164.9, 144.9, 138.5, 136.2, 130.2, 129.03, 128.98, 128.8, 127.5, 127.2, 127.1, 127.0, 75.6, 61.6, 60.8, 51.4, 28.7, 22.6, 13.0. HRMS *m/z* calcd for $C_{23}H_{24}N_2O_6$ (M^+) 424.1633, found 424.1647. Anal. Calcd for $C_{23}H_{24}N_2O_6$: C, 65.08; H, 5.70; N, 6.60. Found: C, 65.18; H, 5.63; N, 6.65. $[\alpha]^{28}_D$ −9.06 (*c* 1.035, $CHCl_3$).

In the Presence of Copper Catalyst. To **7b** (1.35 g, 3.89 mmol), L-pyroglutamic acid ethyl ester[19] (757.5 mg, 4.82 mmol), CuI (38.1 mg, 0.20 mmol), *N*,*N*′-dimethylethylenediamine (0.04 mL, 0.4 mmol), and K_2CO_3 (1.11 g, 8.04 mmol) was added 1,4-dioxane (2.0 mL) through the septum under an Ar atmosphere at room temperature. After being stirred at 130 °C for 5 h, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated at reduced pressure. The residue was purified by FCC (hexane/AcOEt 1:1) to afford **14b** (1.01 g, 61%).

Methyl 4-[(5*S*)-5-[(*E*)-3-Ethoxy-3-oxo-1-propenyl]-2-oxo-1-pyrrolidinyl]-3-[(1*E*)-(phenylmethoxyimino)methyl]benzoate (5b). To a solution of **14b** (199.5 mg, 0.47 mmol) in MeOH (7.0 mL) was added $NaBH_4$ (106.7 mg, 2.82 mmol) under a nitrogen atmosphere at room temperature. After being stirred for 40 min, the reaction mixture was diluted with 2 M HCl at 0 °C and extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated at reduced pressure. The residue was purified by FCC (AcOEt) to afford alcohol (179.7 mg, quant.) as a colorless oil.

Methyl 4-[(5*S*)-5-(Hydroxymethyl)-2-oxo-1-pyrrolidinyl]-3-[(*E*)-(phenylmethoxyimino)methyl]benzoate. IR ν_{max} cm^{-1} 3375, 1723. ^{1}H NMR (300 MHz) δ 8.26 (1H, d, J = 2 Hz), 8.22 (1H, s), 8.04 (1H, dd, J = 8.5, 2 Hz), 7.41−7.25 (6H, m), 5.17 (1H, d, J = 11.0 Hz), 5.16 (1H, d, J = 11.0 Hz), 4.17 (1H, br s), 3.93 (3H, s), 3.59 (1H, dd, J = 12.0, 3.0 Hz), 3.42 (1H, dd, J = 12.0, 3.0 Hz), 2.41 (2H, t, J = 8.0 Hz), 2.27−2.06 (2H, m). ^{13}C NMR (75 MHz) δ 174.7, 165.7, 146.9, 139.1, 137.0, 131.3, 131.0, 130.0, 129.4, 128.4, 128.1, 128.0, 127.1, 76.3, 62.2, 62.1, 52.4, 31.1, 20.8. HRMS *m/z* calcd for $C_{21}H_{22}N_2O_5$ (M^+) 382.1528, found 382.1530. $[\alpha]^{27}_D$ +23.2 (*c* 1.35, $CHCl_3$). To a solution of DMSO (2.75 mL, 38.8 mmol) in CH_2Cl_2 (60 mL) was added dropwise a solution of TFAA (2.69 mL, 19.4 mmol) in CH_2Cl_2 (30 mL) under a nitrogen atmosphere at −65 °C. After being stirred at −65 °C for 20 min, a solution of the above-mentioned alcohol (4.93 g, 12.9 mmol) in CH_2Cl_2 (30 mL) was added dropwise. After being stirred at −65 °C for 3.5 h, the reaction mixture was warmed briefly to −30 °C (10 min) and cooled to −65 °C. Et_3N (5.22 mL, 37.5 mmol) was added dropwise at this temperature and the reaction mixture was stirred at −65 °C for 30 min and warmed to room temperature. The reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated at reduced pressure to give the crude aldehyde. To a solution of the crude aldehyde in THF (258 mL) was added (carbethoxymethylene)triphenylphosphorane (6.76 g, 19.4 mmol) under a nitrogen atmosphere at room temperature. After being stirred overnight, the reaction mixture was diluted with H_2O and extracted with Et_2O. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated at reduced pressure. The residue was purified by FCC (hexane/AcOEt 1:1) to afford **5b** (5.46 g, 94%) as a colorless oil. IR ν_{max} cm^{-1} 1720. ^{1}H NMR (300 MHz) δ 8.42 (1H, d, J = 2.0 Hz), 8.14 (1H, s), 8.02 (1H, dd, J = 8.5, 2.0 Hz), 7.44−7.30 (5H, m), 7.16 (1H, d, J = 8.5 Hz), 6.66 (1H, dd, J = 15.5, 8.5 Hz), 5.74 (1H, dd, J = 15.5, 0.5 Hz), 5.24 (2H, s), 4.57 (1H, br q, J = 8.0 Hz), 4.12 (2H, q, J = 7.0 Hz), 3.92 (3H, s), 2.62−2.28 (3H, m), 1.98−1.86 (1H, m), 1.24 (3H, t, J = 7.0

Hz). ^{13}C NMR (50 MHz) δ 174.4, 165.7, 165.1, 145.6, 144.8, 139.1, 137.1, 131.0, 130.0, 129.8, 129.7, 128.4, 128.1, 128.0, 124.3, 76.5, 61.6, 60.6, 52.3, 30.2, 25.8, 14.0. HRMS *m*/*z* calcd for $C_{25}H_{26}N_2O_6$ (M^+) 450.1789, found 450.1789. $[\alpha]^{28}_D$ −3.17 (*c* 1.105, $CHCl_3$).

Radical Cyclization of 5b with Bu_3SnH and AIBN. To a boiling solution of **5b** (604.4 mg, 1.34 mmol) in benzene (7.0 mL) was added a solution of Bu_3SnH (0.72 mL, 2.68 mmol) and AIBN (44.3 mg, 0.27 mmol) in benzene (6.4 mL) by syringe pump for 10 min under a nitrogen atmosphere. After being stirred at reflux for 3.0 h, a solution of Bu_3SnH (0.72 mL, 2.68 mmol) and AIBN (44.3 mg, 0.27 mmol) in benzene (6.4 mL) was added by syringe pump for 10 min. After being stirred at reflux for 1.5 h, the reaction mixture was cooled to room temperature and then stirred at room temperature overnight to precipitate **3bA**. The reaction mixture was filtered through a glass filter to give **3bA** as colorless crystals (100.6 mg, 25%). The filtrate was extracted with hexane/MeCN. The MeCN phase was concentrated at reduced pressure to give the residue, which was purified by FCC (hexane/AcOEt 1:1) to afford **3bA** (16 mg, 4%; total 29%), **3bB** (32.2 mg, 8%), **3bC** (16 mg, 4%), **3bD** (16 mg, 4%), **15b** (48.5 mg, 8%), and **16b** (10.1 mg, 2%).

Methyl (3a*S*,3b*S*,11b*S*)-1,3a,3b,4,5,11b-Hexahydro-2,6-dioxo-3*H*-dipyrrolo[1,2-*a*:3′,2′-*c*]quinoline-10-carboxylate (3bA). Colorless crystals. Mp 165−168 °C (acetone, MeOH). IR ν_{max} cm^{-1} 3428, 1702. ^{1}H NMR (500 MHz) δ 8.65 (1H, d, J = 8.5 Hz), 8.02 (1H, dd, J = 8.5, 2.0 Hz), 7.96 (1H, d, J = 2.0 Hz), 5.84 (1H, br s), 4.84 (1H, d, J = 5.5 Hz), 3.91 (3H, s), 3.75 (1H, td, J = 11.0, 7.5 Hz), 2.80 (1H, dd, J = 17.0, 7.5 Hz), 2.72−2.57 (2H, m), 2.54−2.43 (2H, m), 2.23 (1H, d, J = 17.0 Hz), 1.81−1.73 (1H, m). ^{13}C NMR (125 MHz) δ 174.6, 173.8, 166.2, 139.8, 131.1, 130.7, 125.7, 123.5, 119.6, 55.8, 53.2, 52.3, 40.3, 34.0, 31.4, 23.1. HRMS *m*/*z* calcd for $C_{16}H_{16}N_2O_4$ (M^+) 300.1109, foun: 300.1128. Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.85; H, 5.25; N, 9.25. $[\alpha]^{28}_D$ +100.7 (*c* 0.235, $CHCl_3$).

Methyl (3a*S*,3b*S*,11b*R*)-1,3a,3b,4,5,11b-Hexahydro-2,6-dioxo-3*H*-dipyrrolo[1,2-*a*:3′,2′-*c*]quinoline-10-carboxylate (3bB). Colorless crystals. Mp 227−230 °C (acetone, MeOH). IR ν_{max} cm^{-1} 3426, 1711. ^{1}H NMR (500 MHz) δ 8.97 (1H, d, J = 8.5 Hz), 7.97 (1H, dd, J = 8.5, 2.0 Hz), 7.78 (1H, br s), 6.76 (1H, br s), 4.51 (1H, d, J = 10.5 Hz), 4.21 (1H, td, J = 11.0, 5.5 Hz), 3.92 (3H, s), 2.73−2.57 (3H, m), 2.36−2.20 (3H, m), 1.90−1.80 (1H, m). ^{13}C NMR (125 MHz) δ 177.0, 174.7, 166.4, 139.5, 130.4, 124.9, 124.7, 124.0, 118.1, 62.6, 57.7, 52.2, 43.6, 34.0, 32.9, 25.5. HRMS *m*/*z* calcd for $C_{16}H_{16}N_2O_4$ (M^+) 300.1109, found 300.1108. Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.80; H, 5.45; N, 9.13. NOE was observed between 3b-H (δ 4.21) and 11b-H (δ 4.51) in NOESY spectroscopy. The coupling constant of 10.5 Hz was observed between 3a-H and 11b-H.

Methyl (3a*R*,3b*S*,11b*S*)-1,3a,3b,4,5,11b-Hexahydro-2,6-dioxo-3*H*-dipyrrolo[1,2-*a*:3′,2′-*c*]quinoline-10-carboxylate (3bC). Colorless crystals. Mp 105−109 °C (acetone, MeOH). IR ν_{max} cm^{-1} 3424, 1704. ^{1}H NMR (500 MHz) δ 8.06 (1H, dd, J = 8.0, 2.0 Hz), 7.88 (1H, br s), 7.79 (1H, d, J = 8.0 Hz), 6.70 (1H, br s), 4.22−4.17 (1H, ddd, J = 11.5, 7.5, 4.5 Hz), 4.14 (1H, d, J = 10.5 Hz), 3.93 (3H, s), 2.74−2.67 (1H, m), 2.59−2.46 (4H, m), 2.21−2.16 (1H, m), 2.08−2.01 (1H, m). ^{13}C NMR (125 MHz) δ 177.0, 173.7, 166.5, 137.4, 132.8, 129.4, 126.9, 124.0, 122.6, 56.4, 53.5, 52.4, 45.8, 32.6, 32.1, 24.2. HRMS *m*/*z* calcd for $C_{16}H_{16}N_2O_4$ (M^+) 300.1109, found 300.1104. Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.95; H, 5.48; N, 9.19. NOE was observed between 4-H (δ 2.08−2.01) and 11b-H (δ 4.14) in NOESY spectroscopy. The coupling constant of 10.5 Hz was observed between 3a-H and 11b-H.

Methyl (3a*R*,3b*S*,11b*R*)-1,3a,3b,4,5,11b-Hexahydro-2,6-dioxo-3*H*-dipyrrolo[1,2-*a*:3′,2′-*c*]quinoline-10-carboxylate (3bD). Colorless crystals. Mp 231−234 °C (acetone, MeOH). IR ν_{max} cm^{-1} 3428, 1704. ^{1}H NMR (500 MHz) δ 8.65 (1H, d, J = 8.0 Hz), 7.89 (1H, dd, J = 8.0, 2.0 Hz), 7.83 (1H, d, J = 2.0 Hz), 6.64 (1H, br s), 4.86 (1H, d, J = 8.0 Hz), 4.17 (1H, td, J = 7.5, 3.0 Hz), 3.89 (3H, s), 3.22−3.15 (1H, m), 2.70−2.57 (2H, m), 2.38−2.25 (3H, m), 1.87−1.78 (1H, m). ^{13}C NMR (125 MHz) δ 175.7, 174.0, 166.1, 139.0, 130.6, 129.9, 126.4, 126.2, 119.0, 56.9, 53.0, 52.2, 38.9, 31.6, 28.7, 21.8. HRMS *m*/*z* calcd for $C_{16}H_{16}N_2O_4$ (M^+) 300.1109, found 300.1111. NOE was observed between 3b-H (δ 4.17) and 11b-H (δ 4.86) in NOESY spectroscopy. The coupling constant of 8.0 Hz was observed between 3a-H and 11b-H.

Ethyl (3a*S*,4*S*,5*S*)-3,3a,4,5-Tetrahydro-7-methoxycarbonyl-1-oxo-5-[(phenylmethoxy)-amino]-1*H*-pyrrolo[1,2-*a*]quinoline-4-acetate (15b). A pale-yellow oil. IR ν_{max} cm^{-1} 3261, 1718. ^{1}H NMR (500 MHz) δ 8.90 (1H, d, J = 9.0 Hz), 8.04 (1H, d, J = 2.0 Hz), 7.94 (1H, dd, J = 9.0, 2.0 Hz), 7.34−7.24 (5H, m), 5.48 (1H, d, J = 3.5 Hz), 4.62 (1H, d, J = 11.5 Hz), 4.54 (1H, d, J = 11.5 Hz), 4.32 (1H, br t, J = 3.0 Hz), 4.20−4.06 (3H, m), 3.89 (3H, s), 2.71 (1H, dd, J = 16.5, 10.0 Hz), 2.64−2.48 (3H, m), 2.34−2.20 (2H, m), 1.76−1.66 (1H, m), 1.24 (3H, t, J = 7.0 Hz). ^{13}C NMR (125 MHz) δ 174.3, 171.1, 166.4, 140.6, 136.9, 132.1, 130.4, 128.5, 128.4, 128.0, 124.8, 123.9, 117.8, 75.9, 60.7, 58.3, 57.0, 52.0, 39.1, 32.5, 32.2, 24.6, 14.2. HRMS *m*/*z* calcd for $C_{25}H_{28}N_2O_6$ (M^+) 452.1945, found 452.1929. The absolute configuration of 15b was determined by leading to the formation of 16b by the reaction with *p*-TsOH·H_2O.

Methyl (3a*S*,3b*S*,11b*S*)-2,3,3a,3b,4,5,6,11b-Octahydro-2,6-dioxo-1-(phenylmethoxy)-1*H*-dipyrrolo[1,2-*a*:3′,2′-*c*]quinoline-10-carboxylate (16b). Colorless crystals. Mp 230−233 °C (AcOEt). IR ν_{max} cm^{-1} 1711. ^{1}H NMR (300 MHz) δ 8.72 (1H, d, J = 8.5 Hz), 8.23 (1H, d, J = 2.0 Hz), 8.07 (1H, dd, J = 8.5, 2.0 Hz), 7.30−7.18 (5H, m), 4.92 (1H, d, J = 9.5 Hz), 4.64 (1H, d, J = 5.5 Hz), 4.54 (1H, d, J = 9.5 Hz), 3.93 (3H, s), 3.68 (1H, td, J = 10.0, 8.5 Hz), 2.75−2.52 (3H, m), 2.50−2.25 (2H, m), 2.29 (1H, br d, J = 17.5 Hz), 1.82−1.65 (1H, m). ^{13}C NMR (125 MHz) δ 173.7, 170.6, 166.2, 140.1, 134.0, 133.7, 131.3, 130.0, 128.9, 128.3, 125.3, 120.4, 119.1, 78.4, 56.8, 56.4, 52.2, 34.4, 31.5, 30.7, 23.5. HRMS *m*/*z* calcd for $C_{23}H_{22}N_2O_5$ (M^+) 406.1527, found 406.1526. Anal. Calcd for $C_{23}H_{22}N_2O_5 \cdot {}^1/_2H_2O$: C, 66.50; H, 5.58; N, 6.74. Found: C, 66.90; H, 5.45; N, 6.64. NOE was observed between 3-H (δ 2.29) and 3b-H (δ 3.68) in NOESY spectroscopy. The coupling constant of 5.5 Hz was observed between 3a-H and 11b-H.

Sammarium-Mediated Reaction of 5b. To a stirred solution of SmI_2 (0.1 M in THF, 17.2 mL, 1.72 mmol) at 0 °C was added *t*-BuOH (4.0 mL) and the resulting solution was stirred for 10 min. A solution of oxime ether **5b** (155 mg, 0.34 mmol) in THF (3.0 mL) was then added and the resulting solution was stirred at 0 °C for 3 h. The reaction was quenched by opening to the air, followed by the addition of saturated $NaHCO_3$. The aqueous layer was separated and extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give the crude product mixture containing **3bA** and **3bB** (4:1 by ^{1}H NMR). Purification by column chromatography (silica gel, EtOAc/MeOH/NEt_3 89:10:1) gave **3bA** (42 mg, 41%).

Chemoselective Reduction of 3bA. (a) Table 1, Entry 1. To a solution of **3bA** (9 mg, 0.03 mmol) in THF (3 mL) and MeOH (0.3 mL) was added $LiBH_4$ (0.6 mg, 0.03 mmol) under a nitrogen atmosphere at room temperature. More $LiBH_4$ (0.6 mg, 0.03 mmol) was added to the solution every 24 h. After being stirred at room temperature for 7 days, the reaction mixture was acidified with 1 M HCl at 0 °C and basified with 10% NaOH at 0 °C. The mixture was extracted with $CHCl_3$. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated at reduced pressure. The residue was purified by PTLC ($CHCl_3$/MeOH 10:1) to afford **19** (2.7 mg, 30%) and **20** (5.5 mg, 67%).

(b) Table 1, Entry 2. To a boiling solution of **3bA** (99.1 mg, 0.33 mmol) in THF (6 mL) and MeOH (0.6 mL) was added $LiBH_4$ (21.6 mg, 0.99 mmol) under a nitrogen atmosphere. After being stirred at reflux for 15 min, $LiBH_4$ (21.6 mg, 0.99 mmol) was added. After being stirred at reflux for 10 min, the reaction mixture was acidified with 1 M HCl at 0 °C and basified with 10% NaOH at 0 °C. The mixture was extracted with $CHCl_3$. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated at reduced

pressure. The residue was purified by FCC ($CHCl_3$/MeOH 10:1) to afford **19** (76.3 mg, 76%) and **20** (15.3 mg, 17%).

(c) Table 1, Entry 3. To a solution of **3bA** (20.4 mg, 0.068 mmol) in Diglyme (1.5 mL) and MeOH (0.1 mL) was added $LiBH_4$ (1.5 mg, 0.068 mmol) at 90 °C under a nitrogen atmosphere. After being stirred at 90 °C for 1.5 h, $LiBH_4$ (1.5 mg, 0.068 mmol) was added. After being stirred at 90 °C for 4 h, $LiBH_4$ (1.5 mg, 0.068 mmol) was added. After being stirred at 90 °C for 1 h, the reaction mixture was acidified with 1 M HCl at 0 °C and basified with 10% NaOH at 0 °C. The mixture was extracted with $CHCl_3$. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated at reduced pressure. The residue was purified by PTLC ($CHCl_3$/MeOH 10:1) to afford **19** (5.2 mg, 25%) and **20** (3.5 mg, 19%).

Methyl (3a*S*,3b*S*,11b*S*)-2,3,3a,4,5,9b-Hexahydro-4-(3-hydroxypropyl)-2-oxo-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylate (19). Colorless crystals. Mp 170−175 °C (benzene, MeOH). IR ν_{max} cm^{-1} 3341, 1695, 1683. ^1H NMR (500 MHz, d_6-DMSO) δ 8.22 (1H, br s), 7.77 (1H, d, J = 1.5 Hz), 7.55 (1H, dd, J = 8.5, 1.5 Hz), 6.67 (1H, d, J = 8.5 Hz), 6.64 (1H, br s), 4.56 (1H, d, J = 7.0 Hz), 4.43 (1H, t, J = 5.0 Hz), 3.74 (3H, s), 3.39 (2H, br q, J = 5.5 Hz), 3.00−2.98 (1H, m), 2.46−2.38 (1H, m), 2.35 (1H, dd, J = 16.5, 8.5 Hz), 2.02 (1H, dd, J = 16.5, 6.0 Hz), 1.64−1.52 (2H, m), 1.52−1.38 (2H, m). ^{13}C NMR (125 MHz, d_6-DMSO) δ 175.4, 166.2, 148.6, 132.4, 129.5, 119.2, 116.3, 113.8, 60.7, 51.2, 50.6, 50.2, 37.1, 34.2, 29.5, 28.5. HRMS *m*/*z* calcd for $C_{16}H_{20}N_2O_4$ (M^+) 304.1422, found 304.1427. Anal. Calcd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.20. Found: C, 62.94; H, 6.43; N, 9.21. $[\alpha]^{29}_D$ −19.4 (*c* 0.785, MeOH).

(3a*S*,3b*S*,11b*S*)-1,3a,3b,4,5,11b-Hexahydro-2,6-dioxo-10-hydroxymethyl-3*H*-dipyrrolo[1,2-*a*:3′,2′-*c*]quinoline (20). Colorless crystals. Mp >260 °C (MeOH). IR ν_{max} (KBr) cm^{-1} 3445, 3377, 3211, 1709, 1684, 1661. ^1H NMR (500 MHz, CD_3OD) δ 8.36 (1H, d, J = 8.5 Hz), 7.39 (1H, br s), 7.31 (1H, dd, J = 8.5, 1.5 Hz), 4.84 (1H, d, J = 6.0 Hz), 4.58 (2H, s), 3.67 (1H, tt, J = 7.5, 7.5 Hz), 2.82 (1H, dd, J = 17, 8.0 Hz), 2.70−2.62 (1H, m), 2.60−2.50 (2H, m), 2.50−2.40 (1H, m), 2.17 (1H, d, J = 17.0 Hz), 1.84−1.74 (1H, m). ^{13}C NMR (125 MHz, CD_3OD) δ 178.3, 176.0, 139.0, 135.9, 129.8, 128.4, 126.0, 120.8, 64.6, 57.8 55.0, 41.5, 35.1, 32.2, 23.6. HRMS *m*/*z* calcd for $C_{15}H_{16}N_2O_3$ (M^+) 272.1160, found 272.1160.

Methyl (3a*S*,3b*S*,9b*S*)-1,5-Bis(trifluoroacetyl)-2,3,3a,4,5,9b-hexahydro-4-(3-hydroxypropyl)-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylate (22a). To a solution of **19** (10 mg, 0.033 mmol) in THF (2 mL) was added slowly BH_3·THF (1 M in THF, 0.165 mL, 0.165 mmol) under an Ar atmosphere at room temperature. After being stirred for 10 min, the reaction mixture was heated to reflux. After being stirred at reflux for 1.5 h, 6 M HCl (1.0 mL) was added at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was basified with 10% NaOH and extracted with $CHCl_3$. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated at reduced pressure to afford crude **18**. To a solution of crude **18** in CH_2Cl_2 (2 mL) was added Et_3N (0.02 mL, 0.116 mmol), DMAP (0.4 mg, 0.003 mmol), and TFAA (0.02 mL, 0.116 mmol) under a nitrogen atmosphere at room temperature. After being stirred at room temperature overnight, saturated $NaHCO_3$ (0.5 mL) was added at 0 °C. After being stirred at 0 °C for 0.5 h, the reaction mixture was extracted with $CHCl_3$. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated at reduced pressure. The residue was purified by FCC (AcOEt/hexane 1:1) to afford **22a**[5d,e] (12.6 mg, 79%) as a colorless oil. IR ν_{max} (neat) cm^{-1} 3526, 1695. ^1H NMR (500 MHz) δ 8.43 (1H, d, J = 1.5 Hz), 8.02 (1H, dd, J = 8.5, 1.5 Hz), 7.40 (1H, br s), 5.36 (1H, br s), 4.74 (1H, br s), 3.92 (4H, br s), 3.64−3.50 (3H, m), 2.74−2.68 (1H, m), 2.34−2.24 (1H, m), 2.18−2.08 (1H, m), 1.66−1.48 (4H, m). ^{13}C NMR (125 MHz) δ 165.8, 157.1 (q, *C*OCF$_3$), 137.8, 133.6, 130.4, 129.9, 125.3, 116.5 (q, CO*C*F$_3$), 116.2 (q, CO*C*F$_3$), 61.9, 58.6, 57.7, 52.4, 46.0, 30.8, 30.1, 29.7, 28.6. HRMS *m*/*z* calcd for $C_{20}H_{20}F_6N_2O_5$ (M^+) 482.1275, found 482.1273. $[\alpha]^{16}_D$ +64.0 (*c* 0.99, $CHCl_3$) [lit. $[\alpha]^{20}_D$ +65.1 (*c* 0.97, $CHCl_3$)].[5d,e] The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances.

Methyl (3a*S*,3b*S*,9b*S*)-1,5-Bis(2,2,2-trichloroethoxycarbonyl)-4-[3-(2,2,2-trichloroethoxycarbonyloxy)propyl]-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylate (21). To a solution of **19** (240.4 mg, 0.79 mmol) in THF (20 mL) was added slowly BH_3·THF (0.9 M in THF, 4.4 mL, 3.95 mmol) under an Ar atmosphere at room temperature. After being stirred for 20 min, the reaction mixture was heated to reflux. After being stirred at reflux for 1.5 h, 6 M HCl (4.0 mL) was added at 0 °C. After being stirred at room temperature for 2.5 h, the reaction mixture was basified with 10% NaOH and extracted with $CHCl_3$. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated at reduced pressure to afford crude **18**. To a solution of crude **18** in CH_2Cl_2 (10 mL) were added pyridine (0.22 mL, 2.8 mmol), DMAP (48.9 mg, 0.4 mmol), and 2,2,2-trichloroethyl chloroformate (0.39 mL, 2.8 mmol) under a nitrogen atmosphere at room temperature. After being stirred at room temperature overnight, the reaction mixture was diluted with saturated NH_4Cl. The mixture was extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated at reduced pressure. The residue was purified by FCC (AcOEt/hexane 1:3) to afford **21** (522.5 mg, 81%) as a white solid. IR ν_{max} cm^{-1} 2956, 1761, 1739, 1714. ^1H NMR (300 MHz) δ 8.54 ($^2/_3$H, s), 8.42 ($^1/_3$H, s), 7.93 (1H, d, J = 8.5 Hz), 7.73 (1H, d, J = 8.5 Hz), 5.28 (1H, d, J = 8.0 Hz), 5.05 (1H, d, J = 12.0 Hz), 4.90−4.70 (6H, m), 4.30−4.10 (2H, m), 3.88 (3H, s), 3.80−3.60 (1H, m), 3.60−3.48 ($^2/_3$H, m), 2.80−2.58 (1H, m), 2.32−2.12 (1H, m), 2.0−1.5 (5H, m). ^{13}C NMR (125 MHz) δ 166.3, 154.8, 153.8, 153.3, 138.1, 137.5, 132.4, 132.0, 129.6, 129.4, 128.7, 127.3, 124.6, 95.7, 95.0, 94.3, 75.4, 75.0, 68.1, 56.1, 55.6, 54.8, 52.2, 52.1, 45.7, 45.4, 41.7, 28.8, 28.4, 27.9, 25.4. HRMS *m*/*z* calcd for $C_{25}H_{25}Cl_9N_2O_9$ (M^+) 811.8755, found 811.8766. $[\alpha]21_D$ −18.5 (*c* 1.245, $CHCl_3$). The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances.

General Procedure for Selective Deprotection of Troc Carbonate of 21 [Table 2]. To a solution of **21** in solvent (0.01 mmol/mL) (MeOH:H_2O = 20:1) was added TFA or K_2CO_3 at room temperature. After being stirred overnight, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated at reduced pressure. The residue was purified by PTLC to afford **22b**, **23**, or **21** in yields shown in Table 2.

Methyl (3a*S*,3b*S*,9b*S*)-1,5-Bis(2,2,2-trichloroethoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-4-(3-hydroxypropyl)-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylate (22b). A colorless oil. IR ν_{max} (neat) cm^{-1} 3509, 2953, 1715. ^1H NMR (300 MHz) δ 8.54 ($^2/_3$H, s), 8.42 ($^1/_3$H, s), 7.93 (1H, d, J = 8.5 Hz), 7.74 (1H, d, J = 8.5 Hz), 5.28 (1H, d, J = 8.0 Hz), 5.06 (1H, d, J = 11.5 Hz), 4.86 (1H, br s), 4.83 (1H, s), 4.76 (1H, s), 4.72 (1H, s), 3.88 (3H, s), 3.80−3.44 ($^7/_2$H, m), 3.44−3.30 ($^1/_2$H, m), 2.74−2.58 (1H, m), 2.28−2.10 (1H, m), 2.00−1.80 (1H, m), 1.80−1.30 (4H, m). ^{13}C NMR (75 MHz) δ 166.4, 154.8, 153.3, 137.8, 132.3, 132.0, 129.3, 128.8, 127.1, 124.5, 95.7, 95.0, 77.2, 75.4, 75.0, 62.0, 55.9, 54.8, 52.1, 45.4, 41.7, 29.7, 29.2, 29.1, 28.7, 27.9. HRMS *m*/*z* calcd for $C_{22}H_{24}Cl_6N_2O_7$ (M^+) 637.9713, found 637.9725. $[\alpha]^{25}_D$ −17.9 (*c* 1.015, $CHCl_3$). The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances.

Methyl (3a*S*,3b*S*,9b*S*)-1-(2,2,2-Trichloroethoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-4-(3-hydroxypropyl)-5-methoxycarbonyl-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylate (23). A colorless oil. IR ν_{max} (neat) cm^{-1} 3501, 1723, 1695. ^1H NMR (300 MHz) δ 8.51 ($^2/_3$H, s, 9-H), 8.40 ($^1/_3$H, s, 9-H), 7.89 (1H, d, J = 8.5 Hz, 7-H), 7.62 (1H, d, J = 8.5 Hz, 6-H), 5.27 (1H, d, J = 8 Hz, 9b-H), 4.87 ($^2/_5$H, s, Troc), 4.83 ($^3/_5$H, s, Troc), 4.72−4.62 (1H, m, 4-H), 3.87 (3H, s, CO_2Me), 3.83 (3H, s, H_3COCON), 3.80−3.46 ($^7/_2$H, m, 2-H$_1$, 3′-H$_2$), 3.42−3.28 ($^1/_2$H, m, 2-H$_1$), 2.70−2.54 (1H, m, 3a-H), 2.24−2.10 (1H, m, 3-H$_1$), 1.92−1.48 (5H, m, 3-H$_1$, 1′-H$_2$, 2′-H$_2$). ^{13}C NMR (75 MHz) δ 166.4, 155.7, 154.7, 138.5, 132.2,

129.1, 128.3, 126.3, 124.5, 124.3, 95.7, 77.2, 74.9, 62.0, 55.6, 55.2, 54.8, 53.4, 52.0, 45.6, 45.4, 41.5, 30.8, 29.0, 28.6, 27.6. HRMS *m*/*z* calcd for $C_{21}H_{25}Cl_3N_2O_7$ (M^+) 522.0726, found 522.0755. $[\alpha]^{26}_D$ −38.8 (*c* 1.07, $CHCl_3$). The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances.

Mitsunobu Reaction of 22a. To a solution of **22a** (48.2 mg, 0.10 mmol) in THF (1.0 mL) were added **25b** (87.1 mg, 0.3 mmol), Ph_3P (39.3 mg, 0.15 mmol), and DIAD (2.2 M in toluene, 0.07 mL, 0.15 mmol) under an Ar atmosphere at room temperature. After being stirred for 1.0 h, the reaction mixture was concentrated at reduced pressure. The residue was purified by FCC (AcOEt/hexane 1:2) to afford **29a** (33.2 mg, 44%) and **30a** (6.6 mg, 17%).

Methyl (3a*S*,3b*S*,9b*S*)-4-{3-[*N*-(*tert*-Butoxycarbonyl)-*N*-[(*tert*-butoxycarbonylimino)(methylthio)methyl]amino]propyl}-1,5-bis(trifluoroacetyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylate (29a). A colorless oil. IR ν_{max} (neat) cm^{-1} 1695. ^1H NMR (300 MHz) δ 8.43 (1H, d, J = 1.0 Hz), 8.03 (1H, dd, J = 8.0, 1.0 Hz), 7.40 (1H, br s), 5.33 (1H, br s), 4.71 (1H, br s), 3.93 (4H, br s), 3.60−3.48 (1H, m), 3.44 (2H, br t, J = 7.0 Hz), 2.74−2.64 (1H, m), 2.35 (4H, br s), 2.14 (1H br s), 1.65 (4H, m), 1.49 (9H, s), 1.43 (9H, s). ^{13}C NMR (125 MHz) δ 165.8, 162.3, 157.8, 156.8 (q, *C*OCF_3), 151.8, 137.7, 133.5, 130.4, 129.6, 125.4, 116.3 (q, CO*C*F_3), 116.0 (q, CO*C*F_3), 82.5, 82.0, 58.3, 52.4, 47.6, 46.0, 30.4, 29.7, 28.00, 27.96, 24.9, 15.5. HRMS *m*/*z* calcd for $C_{32}H_{40}F_6N_4O_8S$ (M^+) 754.2468, found 754.2497. $[\alpha]^{21}_D$ +27.9 (*c* 1.51, $CHCl_3$). The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances.

Methyl (3a*S*,3b*S*,9b*S*)-1-Trifluoroacetyl-2,3,3a,4,5,9b-hexahydro-4-(3-hydroxypropyl)-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylate (30a). A colorless oil. IR ν_{max} (neat) cm^{-1} 3627, 3441, 1687. ^1H NMR (300 MHz) δ 7.98 (1H, s), 7.73 (1H, d, J = 8.5 Hz), 6.47 (1H, d, J = 8.5 Hz), 5.56 (1H, d, J = 7.0 Hz), 3.83 (3H, s), 3.80−3.60 (4H, m), 3.45−3.30 (1H, m), 2.40 (1H, br q, J = 9.0 Hz), 2.13 (1H, br q, J = 6.5 Hz), 1.80−1.50 (5H, m). ^{13}C NMR (125 MHz) δ 167.0, 157.2 (q, *C*OCF_3), 145.6, 132.0, 130.8, 119.6, 117.2, 116.6 (q, CO*C*F_3), 114.0, 62.6, 54.1, 51.7, 51.2, 44.6, 39.8, 32.7, 29.7, 29.1, 27.5. HRMS *m*/*z* calcd for $C_{18}H_{21}F_3N_2O_4$ (M^+) 386.1452, found 386.1433.

Methyl (3a*S*,3b*S*,9b*S*)-4-{3-[*N*-(*tert*-Butoxycarbonyl)-*N*-[(*tert*-butoxycarbonylimino)(methylthio)methyl]amino]propyl}-1,5-bis(2,2,2-trichloroethoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylate (29b). According to the procedure given for the Mitsunobu reaction of **22a**, reaction of **22b** (34.6 mg, 0.054 mmol) with **25b** (47.0 mg, 0.162 mmol), Ph_3P (21.2 mg, 0.081 mmol), and DIAD (2.2 M in toluene, 0.04 mL, 0.081 mmol) gave **29b** (47.4 mg, 96%) as a colorless oil. IR ν_{max} (neat) cm^{-1} 2981, 1715, 1615. ^1H NMR (300 MHz) δ 8.54 ($^2/_3$H, s), 8.42 ($^1/_3$H, s), 7.93 (1H, d, J = 8.5 Hz), 7.77 (1H, d, J = 8.5 Hz), 5.27 (1H, d, J = 8.0 Hz), 5.12−4.90 (1H, m), 4.86 (1H, br s), 4.83 (1H, s), 4.77 (1H, s), 4.73 (1H, s), 3.88 (3H, s), 3.80−3.30 (2H, m), 3.47 (2H, t, J = 7.0 Hz), 2.72−2.56 (1H, m), 2.33 (3H, s), 2.26−2.10 (1H, m), 2.00−1.80 (1H, m), 1.82−1.60 (4H, m), 1.48 (9H, s), 1.42 (9H, s). ^{13}C NMR (75 MHz) δ 166.3, 162.5, 157.7, 154.7, 153.2, 151.8, 137.8, 132.3, 131.9, 129.3, 128.8, 127.0, 124.6, 95.7, 95.0, 82.3, 81.9, 77.2, 75.4, 75.0, 55.6, 54.8, 52.1, 47.9, 45.4, 41.6, 29.6, 29.4, 29.2, 28.00, 27.96, 27.85, 25.5, 21.9, 21.7, 15.6. SIMS calcd for $C_{34}H_{45}Cl_6N_4O_{10}S$ (M + H) 911.0984, found 911.0978. $[\alpha]^{26}_D$ −22.6 (*c* 0.55, $CHCl_3$). The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances.

Guanylation Reaction of 29a. To a solution of **29a** (113.2 mg, 0.15 mmol) in THF (3.0 mL) was added 3-methyl-2-buten-1-amine[28] (127.7 mg, 1.50 mmol) at room temperature. After being stirred for 5.0 h, the reaction mixture was concentrated at reduced pressure. The residue was purified by PTLC (Et_2O) to afford **31a** (60.6 mg, 51%) and **31′a** (38.6 mg, 37%).

Methyl (3a*S*,3b*S*,9b*S*)-4-{3-[1,2-Di(*tert*-butoxycarbonyl)-3-(3-methylbut-2-enyl)guanidino]propyl}-1,5-bis(trifluoroacetyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylate (31a). A colorless oil. IR ν_{max} (neat) cm^{-1} 1694. ^1H NMR (300 MHz) δ 8.43 (1H, d, J = 1.5 Hz), 8.04 (1H, dd, J = 7.0, 1.5 Hz), 7.42 (1H, br s), 5.31 (1H, br s), 5.18 (1H, br t, J = 7.0 Hz), 4.71 (1H, br s), 3.93 (3H, s), 4.00−3.84 (1H, m), 3.71 (2H, d, J = 6.5 Hz), 3.65−3.40 (3H, m), 2.80−2.62 (1H, m), 2.22−2.40 (1H, m), 2.24−2.04 (1H, m), 1.75 (3H, s), 1.66 (3H, s), 1.49 (9H, s), 1.45 (9H, s), 1.80−1.40 (4H, m). ^{13}C NMR (75 MHz) δ 165.7, 156.8 (q, *C*OCF_3), 137.8, 133.5, 130.4, 129.6, 125.3, 118.5, 116.1 (q, CO*C*F_3), 82.6, 79.3, 77.2, 52.3, 46.5, 45.9, 41.7, 28.2, 28.1, 25.6, 25.0, 17.9. SIMS calcd for $C_{36}H_{48}F_6N_5O_8$ (M + H) 792.3404, found 792.3415. $[\alpha]^{29}_D$ +20.4 (*c* 0.93, $CHCl_3$). The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances.

Methyl (3a*S*,3b*S*,9b*S*)-4-{3-[1,2-Di(*tert*-butoxycarbonyl)-3-(3-methylbut-2-enyl)guanidino]propyl}-1-trifluoroacetyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylate (31′a). A colorless oil. IR ν_{max} (neat) cm^{-1} 3366, 1705. ^1H NMR (300 MHz) δ 9.38 (1H, br s), 7.96 (1H, s), 7.71 (1H, dd, J = 8.5, 1.5 Hz), 6.61 (1H, d, J = 8.5 Hz), 5.88−5.72 (1H, m), 5.55 (1H, d, J = 7.0 Hz), 5.23 (1H, br t, J = 6.0 Hz), 3.82 (3H, s), 3.90−3.60 (3H, m), 3.60−3.36 (3H, m), 2.35 (1H, br q, J = 9.0 Hz), 2.14 (2H, br q, J = 9.0 Hz), 1.75 (3H, s), 1.67 (3H, s), 1.50 (9H, s), 1.49 (9H, s), 1.90−1.30 (4H, m). ^{13}C NMR (75 MHz) δ 167.1, 157.2 (q, *C*OCF_3), 146.0, 137.9, 131.9, 130.6, 118.8, 118.6, 116.6, 116.4 (q, CO*C*F_3), 114.1, 83.0, 79.4, 77.2, 54.1, 51.5, 49.5, 46.1, 44.6, 42.0, 39.8, 31.8, 28.2, 28.1, 27.5, 25.6, 24.8, 18.0. SIMS calcd for $C_{34}H_{49}F_3N_5O_7$ (M + H) 696.3581, found 696.3571. $[\alpha]^{29}_D$ −294.23 (*c* 0.52, $CHCl_3$). The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances.

Methyl (3a*S*,4*S*,9b*S*)-1-[*N*′-(*tert*-Butoxycarbonyl)-*N*-(3-methylbut-2-enyl)carbamimidoyl]-4-{3-[2-(*tert*-butoxycarbonyl)-3-(3-methylbut-2-enyl)guanidino]propyl}-2,3,3a4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylate (33a). To a solution of **31a**:**31′a** (1.6:1, 89.8 mg, 0.119 mmol) in MeOH (3.0 mL) was added K_2CO_3 (98.7 mg, 0.714 mmol) under a nitrogen atmosphere at room temperature. After being stirred at room temperature overnight, K_2CO_3 (49.3 mg, 0.357 mmol) was added. After being stirred at room temperature for 8 h, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated at reduced pressure to afford crude amine. To a solution of the crude amine in DMF (3.0 mL) were added isothiourea **32**[5] (36.9 mg, 0.143 mmol) and Et_3N (0.05 mL, 0.357 mmol) under a nitrogen atmosphere at room temperature. After being stirred at room temperature for 10 min, $HgCl_2$ (38.8 mg, 0.143 mmol) was added. After being stirred at room temperature for 2 h, the reaction mixture was diluted with H_2O and extracted with Et_2O. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated at reduced pressure. The residue was purified by PTLC ($CHCl_3$/MeOH 10:1) to afford **33a**[5d−g] (73.5 mg, 87%) as a white foam. IR ν_{max} (neat) cm^{-1} 3294, 2977, 1696, 1608. ^1H NMR (300 MHz) δ 7.98 (1H, s), 7.65 (1H, d, J = 8.5 Hz), 7.07 (1H, br s), 6.60 (1H, d, J = 8.5 Hz), 5.72 (1H, d, J = 7.0 Hz), 5.38−5.24 (1H, m), 5.24−5.12 (1H, m), 3.95−3.60 (4H, m), 3.81 (3H, s), 3.50−3.20 (4H, m), 3.25−3.05 (1H, m), 2.40−2.20 (1H, m), 2.15−1.90 (2H, m), 1.73 (3H, s), 1.72 (3H, s), 1.67 (3H, s), 1.65 (3H, s), 1.52 (9H, s), 1.49 (9H, s), 1.80−1.40 (4H, m). ^{13}C NMR (75 MHz) δ 167.4, 163.9, 161.9, 161.4, 160.1, 146.5, 137.0, 131.7, 130.0, 120.3, 119.5, 118.2, 117.7, 113.7, 78.0, 77.6, 77.2, 53.3, 51.3, 50.5, 46.7, 42.5, 40.0, 39.42, 39.36, 31.9, 28.44, 28.38, 28.0, 27.9, 26.5, 25.6, 17.9. SIMS calcd for $C_{38}H_{60}N_7O_6$ (M + H) 710.4602, found 710.4594. $[\alpha]^{25}_D$ −179.2 (*c* 1.20, $CHCl_3$) [lit. $[\alpha]^{28}_D$ −179.1 (*c* 0.80, $CHCl_3$),[5f] $[\alpha]^{20}_D$ −94.2 (*c* 0.28, $CHCl_3$),[5d,e] $[\alpha]_D$ −95.2 (*c* 0.58, $CHCl_3$)[5g]].

(−)-Martinellic Acid (1a). To a solution of **33a** (51.1 mg, 0.072 mmol) in MeOH (8.0 mL) was added 0.2 M NaOH (2.76 mL) under a nitrogen atmosphere at room temperature. After being stirred at reflux for 14 h, the reaction mixture was diluted with saturated NH_4Cl and extracted with $CHCl_3$. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated at reduced pressure

to afford crude acid. To a solution of the crude acid in CH_2Cl_2 (5.0 mL) was added TFA (0.07 mL) under a nitrogen atmosphere at room temperature. After being stirred at room temperature for 24 h, further TFA (0.035 mL) was added. After being stirred at room temperature for 24 h, the reaction mixture was concentrated at reduced pressure. The residue was purified by preparative HPLC through a COSMOSIL 5C18-PAQ (20 × 250 mm) eluting with 80:20 H_2O/MeOH (with 0.1% TFA) to 60:40 H_2O/MeOH (with 0.1% TFA) as a gradient over 80 min and with a flow rate of 5 mL/min. The detector was set to 330 nm and the major fraction had a retention time of 67.6 min. This fraction was concentrated at reduced pressure to afford **1a** (27.8 mg, 56%) as a white powder. IR ν_{max} (neat) cm^{-1} 3318, 3198, 1659, 1610. ^1H NMR (500 MHz, d_6-DMSO) δ 7.73 (1H, br s), 7.67 (1H, br s), 7.63 (1H, br s), 7.53 (1H, dd, J = 8.5, 1.5 Hz), 7.45 (2H, br s), 7.36 (2H, br s), 7.03 (1H, br d, J = 3.0 Hz), 6.56 (1H, d, J = 8.5 Hz), 5.32−5.26 (1H, m), 5.23 (1H, d, J = 6.5 Hz), 5.18−5.12 (1H, m), 3.96−3.90 (1H, m), 3.88−3.80 (1H, m), 3.71 (2H, br t, J = 5.5 Hz), 3.40−3.30 (2H, m), 3.30−3.22 (1H, m), 3.18−3.06 (2H, m), 2.46−2.38 (1H, m), 2.10−2.02 (1H, m), 1.73 (3H, s), 1.69 (3H, s), 1.68 (3H, s), 1.63 (3H, s), 1.70−1.50 (3H, m), 1.42−1.36 (2H, m). ^{13}C NMR (125 MHz, d_6-DMSO) δ 167.2, 155.4, 154.3, 146.3, 136.0, 135.6, 130.4, 130.0, 119.6, 119.2, 117.1, 115.7, 113.3, 53.0, 49.2, 45.8, 40.7, 39.9*, 39.4*, 39.0*, 33.4, 26.3, 25.4, 25.30, 25.28, 17.9, 17.8. (3 peaks observed at 39.9, 39.4, and 39.0 by Witherup and coworkers[1] could not be unequivocally assigned as they were underneath the DMSO peak, but these 3 peaks could be detected in the DEPT data we carried out on synthetic **1a**). MS (SIMS, 3-nitrobenzyl alcohol) m/z 722 (100, [M − H + 2CF_3CO_2H]), 608 (75, [M − H + CF_3CO_2H]), 494 (6, [M − H]). HRMS (SIMS, 3-nitrobenzyl alcohol) calcd for $C_{27}H_{40}N_7O_2$ (M − H, free guanidine) 494.3241, found 494.3267. $[\alpha]^{23}_D$ −164.8 (c 0.33, MeOH) [lit. natural $[\alpha]_D$ −8.5 (c 0.01, MeOH),[1] $[\alpha]^{29}_D$ −164.3 (c 0.14, MeOH),[5f] $[\alpha]^{20}_D$ −122.7 (c 0.31, MeOH)[5d,e]].

Methyl (3a*S*,3b*S*,9b*S*)-4-{3-[1,2-Di(*tert*-butoxycarbonyl)-3-(3-methylbut-2-enyl)guanidino]propyl}-1,5-bis(2,2,2-trichloroethoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylate (31b). According to the procedure given for the guanylation reaction of **29a**, reaction of **29b** (51.1 mg, 0.056 mmol) with 3-methyl-2-buten-1-amine[28] (71.5 mg, 0.84 mmol) gave **31b** (53.2 mg, quant.) as a colorless oil. IR ν_{max} (neat) cm^{-1} 3423, 2980, 1715, 1643, 1615. ^1H NMR (300 MHz) δ 9.31 (1H, s), 8.53 ($^2/_3$H, s), 8.42 ($^1/_3$H, s), 7.92 (1H, d, J = 8.5 Hz), 7.75 (1H, d, J = 8.5 Hz), 5.30−5.20 (1H, m), 5.20−5.10 (1H, m), 5.10−5.00 (1H, m), 4.90−4.68 (4H, m), 3.88 (3H, s), 3.80−3.30 (7H, m), 2.72−2.54 (1H, m), 2.26−2.10 (1H, m), 2.00−1.80 (1H, m), 1.75 (3H, s), 1.65 (3H, s), 1.49 (9H, s), 1.43 (9H, s), 1.70−1.40 (4H, m). ^{13}C NMR (75 MHz) δ 166.3, 154.7, 153.2, 137.8, 132.3, 131.9, 129.4, 128.7, 127.1, 124.4, 118.6, 95.7, 95.1, 82.5, 79.3, 77.2, 75.3, 75.0, 55.6, 54.7, 53.8, 52.1, 46.8, 45.7, 45.4, 41.7, 29.7, 29.5, 28.2, 28.1, 27.9, 25.7, 25.6, 18.0. SIMS calcd for $C_{38}H_{51}Cl_6N_5O_{10}$ (M + H) 948.1842, found 948.1827. $[\alpha]^{25}_D$ −32.3 (c 0.51, $CHCl_3$). The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances.

Methyl (3a*S*,4*S*,9b*S*)-1-[*N*′-(*tert*-Butoxycarbonyl)-*N*-(3-methylbut-2-enyl)carbamimidoyl]-4-{3-[1,2-di(*tert*-butoxycarbonyl)-3-(3-methylbut-2-enyl)guanidino]propyl}-2,3,3a4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylate (33b). To a solution of **31b** (38.0 mg, 0.04 mmol) in THF (3.0 mL) were added Zn powder (10.5 mg, 0.16 mmol) and saturated NH_4Cl (0.3 mL) under a nitrogen atmosphere at room temperature and the resulting mixture was stirred at room temperature. Zn powder (50.0 mg, 0.76 mmol) was added every 1 h during 6 h. After being stirred at room temperature for 6 h, the reaction mixture was filteted through a pad of Celite and filtrate was diluted with 10% NaOH and extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated at reduced pressure to afford crude amine. To a solution of the crude amine in DMF (2.0 mL) were added isothiourea **32**[5] (12.4 mg, 0.048 mmol) and Et_3N (0.02 mL, 0.12 mmol) under a nitrogen atmosphere at room temperature. After the mixtue was stirred at room temperature for 10 min, $HgCl_2$ (13.0 mg, 0.048 mmol) was added. After being stirred at room temperature for 2 h, the reaction mixture was diluted with H_2O and extracted with Et_2O. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated at reduced pressure. The residue was purified by PTLC (AcOEt) to afford **33b** (21.1 mg, 65%) as a sticky oil. IR ν_{max} (neat) cm^{-1} 3310, 2977, 2932, 1709, 1609. ^1H NMR (500 MHz) δ 7.99 (1H, d, J = 2.0 Hz), 7.66 (1H, dd, J = 9.0, 2.0 Hz), 6.54 (1H, d, J = 9.0 Hz), 5.70 (1H, d, J = 7.5 Hz), 5.54−5.48 (1H, br s), 5.27 (1H, br t, J = 7.0 Hz), 5.22 (1H, br t, J = 7.0 Hz), 3.87 (1H, dd, J = 14.0, 7.5 Hz), 3.82−3.76 (1H, m), 3.80 (3H, s), 3.76−3.70 (2H, m), 3.70−3.60 (1H, m), 3.54−3.44 (1H, m), 3.44−3.30 (3H, m), 2.36−2.28 (1H, m), 2.10−1.80 (2H. m), 1.74 (3H, s), 1.70 (3H, s), 1.66 (3H, s), 1.64 (3H, s), 1.80−1.60 (4H, m), 1.51 (9H, s), 1.49 (9H, s), 1.47 (9H, s). ^{13}C NMR (125 MHz) δ 167.4, 162.1, 161.7, 146.2, 137.8, 137.0, 131.9, 130.0, 120.4, 118.7, 118.5, 118.3, 113.7, 82.8, 79.3, 77.5, 53.2, 51.4, 50.0, 46.7, 42.5, 41.9, 39.7, 32.2, 30.3, 29.7, 28.5, 28.2, 28.1, 28.0, 25.61, 25.58, 24.9, 18.0, 17.97. SIMS calcd for $C_{43}H_{67}N_7O_8$ (M + H) 810.5125, found 810.5121. $[\alpha]^{28}_D$ −125.9 (c 0.52, $CHCl_3$).

(−)-Martinellic Acid (1a). According to the procedure given for hydrolysis and deprotection of **33a**, **33b** (33.2 mg, 0.041 mmol) was converted into **1a** (15.8 mg, 56%).

Acknowledgement. We are grateful to acknowledge the research Grants-in-Aid for Scientific Research (B) (to T.N.) and (C) (to O.M.) from the Japan Society for the Promotion of Science (JSPS) and Scientific Research on Priority Areas (A) (to T.N.) from the Ministry of Education, Culture, Sports, and Technology. We also acknowledge a research grant from the Science Research Promotion Fund of the Japan Private School Promotion Foundation. We particularly thank Drs. Sheo Bux Singh, Steven M. Pitzenberger, and Nobuyoshi Yasuda of Merck Research Laboratories for providing ^1H NMR and ^{13}C NMR spectra of natural martinellic acid and their helpful suggestions.

Supporting Information Available: Experimental procedures, compound characterizations except for the Experimental Section, copies of ^1H NMR and ^{13}C NMR spectra for selected compounds and natural martinellic acid, copies of MASS for **5b** and **20**, X-ray crystallographic data, and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800560P