Total Synthesis of Isoroquefortine C

Bruno M. Schiavi, David J. Richard, and Madeleine M. Joullié*

Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323

mjoullie@sas.upenn.edu

Received June 27, 2001

A short and efficient total synthesis of isoroquefortine C, the 3,12-(*Z*)-isomer of roquefortine C, from L-tryptophan methyl ester hydrochloride and 4(5)-(hydroxy)methylimidazole hydrochloride is described.

Introduction

Roquefortine C (**1**) was first isolated by two independent groups from *Penicillium roqueforti* Thom strain along with several other indole compounds (roquefortines A and B).[1−4] Since its initial discovery, roquefortine C (**1**) has been found in a number of other *P. roqueforti* cultures,[5,6] as well as in penicillium strains isolated from a variety of food products.[7−10]

Isoroquefortine C (**2**), which has not been isolated from nature, is the 3,12-double bond isomer of roquefortine C (**1**). This compound has been obtained with complete conversion from the natural product under photochemical conditions (Figure 1).[11]

During a study designed to establish the stereochemistry of the histidine double bond, Vleggaar and Wessels[8] assigned the name isoroquefortine to the photoproduct of roquefortine C. To avoid possible confusion with isomers of other roquefortines and to establish a clear relationship between the two isomers, we have decided to add C to this original name.

The existence of isoroquefortine C (**2**) was not noted until 1979 when the configuration of the 3,12-double bond of roquefortine became the focus of attention.[8,11] The (*E*)-configuration of the 3,12-double bond in the dehydrohistidine side chain was established by comparison of spectral properties of the two isomers,[11] and also by ^{13}C experiments.[8] The absolute configuration of roquefortine C (**1**) was later determined by degradation and NOE ^1H NMR experiments (Scheme 1).[12]

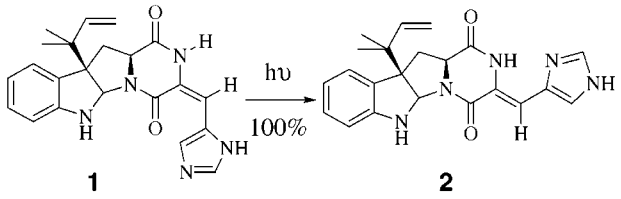
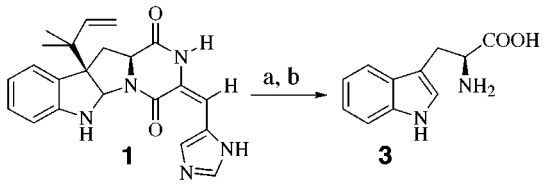


Figure 1. Photoisomerization of roquefortine C (**1**) to isoroquefortine C (**2**).

Scheme 1[a]



[a] Reagents and conditions: (a) 1 N HCl/MeOH, Δ; (b) 4 N $MeSO_3H$, 115 °C.

Roquefortine C is found in the blue vein of Roquefort and other blue cheeses and has also been detected in other sources such as feed grain. Neurotoxic properties were reported by Wagener et al. (paralytic activities),[9] and Scott et al.[3] estimated the 50% lethal dose in mice to be 15−20 mg/kg after intraperitoneal injection. Clinical symptoms observed in cows included extensive paralysis, which did not respond to calcium treatment. The disease symptoms disappeared as soon as the cows were no longer fed moldy grain. The same symptoms were observed in a human study and were linked to the presence of roquefortine C in a contaminated commercial beer.[13] However, these results could not be reproduced. Arnold and co-workers were unable to duplicate the previously detected activity and found the lethal dose to be 10 times larger than reported.[14] The inconsistency of these observations may be due either to the presence of an impurity or to the presence or absence of isoroquefortine. Both roquefortine C (**1**) and isoroquefortine C (**2**) may be recrystallized from methanol and therefore may not be separated by this method. Isoroquefortine C is the more stable isomer, possibly because of the presence of a

(1) Ohmomo, S.; Sato, T.; Utagawa, T.; Abe, M. *Agric. Biol. Chem.* **1975**, *39*, 1333−1334.
(2) Scott, P. M.; Kennedy, B. P. C. *J. Agric. Food Chem.* **1976**, *24*, 865−868.
(3) Scott, P. M.; Merrien, M.-A.; Polonsky, J. *Experientia* **1976**, *32*, 140−141.
(4) Ohmomo, S.; Utagawa, S.; Abe, M. *Agric. Biol. Chem.* **1977**, *41*, 2097−2098.
(5) Scott, P. M.; Kennedy, B. P. C.; Harwig, J.; Blanchfield, B. *Appl. Environ. Microbiol.* **1977**, *33*, 249−253.
(6) Engel, G.; Teuber, M. *Eur. J. Appl. Microbiol. Biotechnol.* **1978**, *6*, 107−111.
(7) Leistner, L.; Eckardt, C. *Fleischwirtschaft* **1979**, *59*, 1892−1896.
(8) Vleggaar, R.; Wessels, P. L. *J. Chem. Soc., Chem. Commun.* **1980**, 160−162.
(9) Wagener, R. E.; Davis, N. D.; Diener, U. L. *Appl. Environ. Microbiol.* **1980**, *39*, 882−887.
(10) Ohmomo, S.; Ohashi, T.; Abe, M. *Agric. Biol. Chem.* **1980**, *44*, 1929−1930.
(11) Scott, P. M.; Polonsky, J.; Merrien, M. A. *J. Agric. Food. Chem.* **1979**, *27*, 201−202.
(12) Yamaguchi, T.; Nozawa, K.; Nakajima, S.; Kawai, K.; Udagawa, S. *Proc. Jpn. Assoc. Mycotoxicol.* **1991**, *34*, 29−32.
(13) Cole, R. J.; Dorner, J. W.; Cox, R. H.; Raymond, L. W. *J. Agric. Food Chem.* **1983**, *31*, 655−657.
(14) Arnold, D. L.; Scott, P. M.; McGuire, P. F.; Hartwig, J.; Nera, E. A. *Food Cosmet. Toxicol.* **1978**, *16*, 369−371.

10.1021/jo0106593 CCC: $22.00
Published on Web 10/26/2001

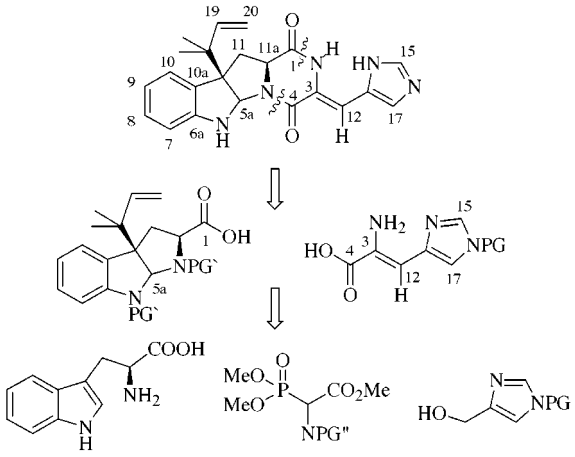


Figure 2. Retrosynthetic analysis of isoroquefortine (**2**).

hydrogen bond between the NH of the diketopiperazine and the sp^2 nitrogen of the imidazole. As the biological activity of this indole alkaloid has not yet been investigated, isoroquefortine C is worthy of synthetic investigation in its own right.

In an attempt to clarify the biological activity profile of these compounds, as well as to develop methods for the stereoselective synthesis of both (*E*)- and (*Z*)-dehydrohistidine residues, we have undertaken the synthesis of both isomers. We now disclose a short and efficient total synthesis of isoroquefortine C (**2**).

Results and Discussion

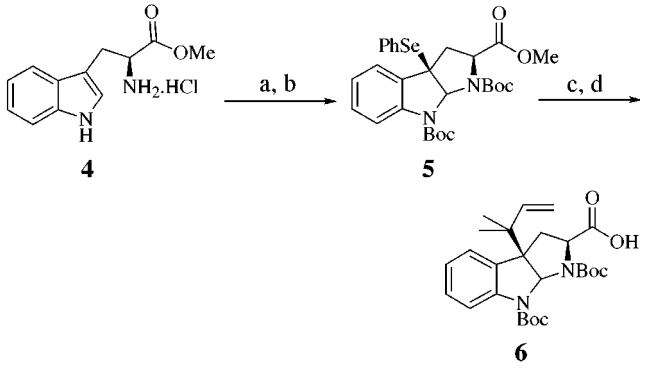
The retrosynthesis of isoroquefortine (Figure 2) begins with disconnection of the two amide bonds of the diketopiperazine to provide a reverse-prenyl hexahydropyrroloindole and a (*Z*)-dehydrohistidine moiety. The former intermediate may be prepared from tryptophan, while the latter compound may obtained by condensation of glycine ester derivatives with imidazole carboxaldehyde derivatives.

The synthesis of the reverse prenylated hexadihydropyrrolo[2,3-*b*]indole moiety **6** was accomplished according to the procedure of Mardsen et al.,[15] starting from L-tryptophan methyl ester hydrochloride **4** (Scheme 2). Following protection of both the α- and side chain amino groups of ester **4**, selenylation-induced ring closure with *N*-phenylselenophthalimide (NPSP)[16] provided the tricyclic compound **5**. Displacement of the phenylselenide was achieved by treatment with tributyl(3-methyl-2-butenyl)stannane.[17] Saponification of the ester group provided the desired carboxylic acid **6** (Scheme 2).

The *N*-acyl-2-(dialkyloxyphosphinyl)glycine ester derivatives **9**−**11** were easily prepared from glyoxylic acid **7** in three, four, and five steps, respectively, following the procedure of Schmidt et al. (Scheme 3).[18]

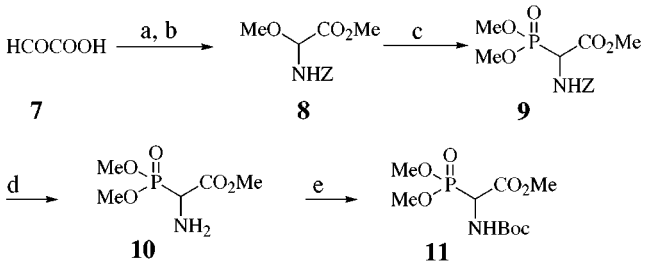
The imidazole moiety was produced from alcohol **12** via a protection/Dess−Martin oxidation sequence[19,20] (Scheme 4). Both the trityl (Tr)[21] and *o*-nitrobenzyl group (ONB)[22] were employed. These derivatives, which are

Scheme 2[a]



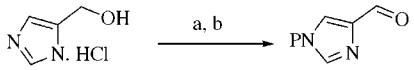
[a] Reagents and conditions: (a) $(Boc)_2$, NaOH, Bu_4NHSO_4, CH_2Cl_2, 91%; (b) NPSP, PPTS, CH_2Cl_2, 78%; (c) MeOTf, tributyl(3-methyl-2-butenyl)stannane, 2,6-di-*tert*-butyl-4-methylpyridine, −10 °C−Δ, 69%; (d) LiOH, THF/MeOH, quantitative.

Scheme 3[a]



[a] Reagents and conditions: (a) benzyl carbamate, 56%; (b) $MeOH/H^+$, 88%; (c) PCl_3, $P(OMe)_3$, 85%; (d) H_2 Pd/C 5%, quantitative; (e) Boc_2O, 95%.

Scheme 4[a]



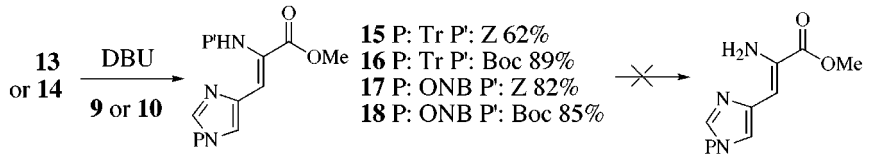
[a] Reagents and conditions: (a) P=Tr: TrCl, TEA, DMF 94% or P=ONB: Na_2CO_3,ONBCl, DMF, 69%; (b) Dess−Martin 89−99%.

labile under relatively mild conditions (dilute TFA or Hg lamp), appeared to be compatible with the acid-sensitive target compound.

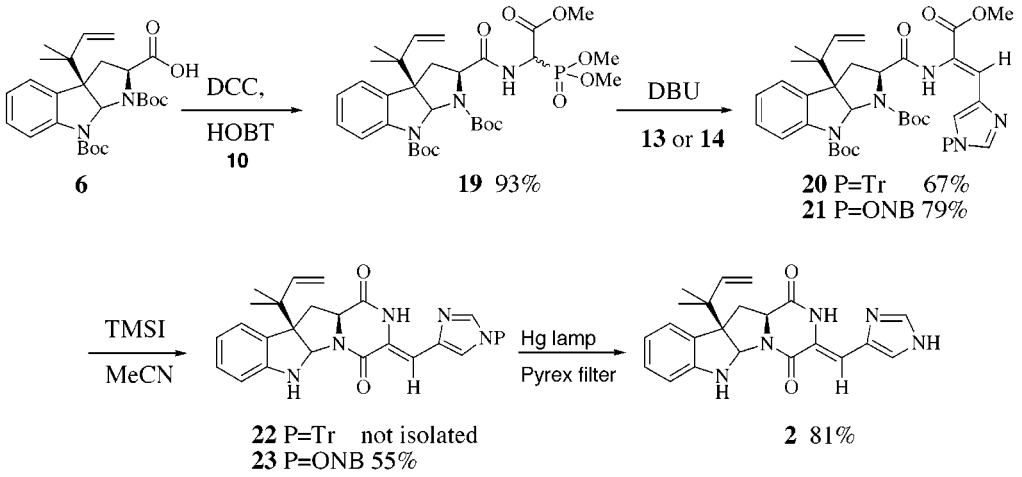
The three main building blocks described above were readily prepared in large scale. The next challenge was the isolation of dehydrohistidine derivatives to allow for coupling with indole moiety **6**. The Wittig−Horner reaction between glycine ester derivatives **9** and **11** and aldehydes **13** and **14** provided the desired protected (*Z*)-dehydrohistidines (**15** to **18**).[23,24] However, the selective deprotection of the amine was unsuccessful. Results varied between degradation of the starting material or

(15) Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143−11144.
(16) Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *Tetrahedron* **1985**, *41*, 4835−4841.
(17) Engler, T. A.; Reddy, J. P.; Combrink, K. D.; Vander Velde, D. *J. Org. Chem.* **1990**, *55*, 1248−1254.
(18) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53−60.
(19) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.
(20) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
(21) Dinsmore, C. J.; Williams, T. M.; O'Neill, T. J.; Liu, D.; Rands, E.; Culberson, J. C.; Lobell, R. B.; Koblan, K. S.; Kohl, N. E.; Gibbs, J. B.; Oliff, A. I. *Bioorg. Med. Chem. Lett.* **1999**, *23*, 3301−3306.
(22) Antonini, I. C., G.; Franchetti, P.; Grifantini, M.; Martelli, S. *Synthesis* **1983**, 47−49.
(23) Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. *Synthesis* **1992**, 487−489.
(24) Oba, M.; Ueno, R.; Fukuoka, M.; Kainosho, M.; Nishiyama, K. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1603−1609.

Scheme 5



Scheme 6



isolation of the fully deprotected compound, which proved extremely unstable and not suitable for further reaction (Scheme 5).

To overcome this problem, an alternative coupling strategy was investigated (Scheme 6). The acid **6** was first coupled with the free amine **10** in the presence of DCC and HOBT to give the glycine ester derivative **19** as a mixture of diastereomers in excellent yield (93%). Aldehydes **13** and **14** were condensed with phosphonate **19** in the presence of DBU to give linear compounds **20** and **21** in 67% and 79% yield, respectively.

Product **21** possessed unusual characteristics in its ^{1}H NMR spectrum. The proton resonances corresponding to positions 12 and 17 (see Figure 2) were not observed initially. Low-temperature spectra exhibited poor resolution and indicated the presence of a number of rotamers. High-temperature experiments, however, led to the appearance of H_{12} and H_{17} as two broad signals, with chemical shifts similar to those of the corresponding H_{12} and H_{17} of compound **20**.

Formation of the fourth ring was envisioned as a two-step sequence: deprotection of *tert*-butoxycarbonyl groups, followed by cyclization under classical basic conditions in a manner analogous to our previously reported synthesis of roquefortine D.[25] Unfortunately, the use of trifluoroacetic acid in dichloromethane led only to degradation of starting material. Use of other acidic conditions proved equally unsuccessful. Attempts were then made to activate the ester and trap the free amine intermediate in a one-step reaction. Use of TMSCl/PhOH,[26] TMSOTf/2,6-lutidine,[27] or $ZnBr_2$[28] led to the recovery of starting material. However, we were gratified to discover that use of TMSI (prepared from hexamethyldisilane/I_2) in acetonitrile afforded compound **23** with an *o*-nitrobenzyl-protected imidazole in 55% yield. Attempts to carry out the same reaction with a trityl-protected imidazole failed. The intermediate was observed on TLC, but isolation was unsuccessful presumably due to its instability during the workup sequence. It is interesting to note that only one intermediate was observed during the course of this reaction, the tetracyclic compound protected on the indole nitrogen. Deprotection was completed by treatment of this intermediate with silica. A similar deprotection of aromatic amino-Boc groups in the presence of silica has been reported.[29]

Indole-containing compounds related to carboxylic acid **6** have been known to exhibit interesting NMR properties.[15] The aromatic proton in position 7 (see Figure 2) generally appears either as a broad or weak signal. Compounds **19**−**21** showed similar spectral characteristics. However, after formation of the fourth ring, the four protons were clearly visible in the expected aromatic range. It is believed that this behavior is the result of a change in hybridization of one or more atoms in the polycyclic compound.

As a final step, the imidazole was successfully deprotected using photochemical conditions (mercury lamp irradiation) to yield isoroquefortine C in good yield. The chemical shift of the H_{12} proton was found at 6.67 ppm in contrast with the 6.35 ppm value reported for the same proton in roquefortine C (**1**).[11] Chemical shifts for C_{12}, C_{17}, and C_3, which are different from those exhibited by **1**, were found at the following positions: 137.85 ppm for C_3 (122.30 for **1**), 117.65−105.45 ppm for C_{12}−C_{17} (110.90−134.30 ppm for **1**), in agreement with previously reported values.[8]

Conclusion

Isoroquefortine C (**2**) was synthesized for the first time in eight linear steps from L-tryptophan methyl ester

(25) Chen, W. C.; Joullié, M. M. *Tetrahedron Lett.* **1998**, *39*, 8401−8404.

(26) Keiser Sr, E.; Picart, F.; Kubiak, T.; Tam, J. P.; Merrifield, R. B. *J. Org. Chem* **1993**, *58*, 5167.

(27) Xiao, D.; East, S. P.; Joullié, M. M. *Tetrahedron Lett.* **1998**, *39*, 9631−9632.

(28) Nigam, S. C.; Mann, A.; Taddei, M.; Wermuth, C. G. *Synth. Commun.* **1989**, *19*, 3139−3142.

(29) Apelqvist, T.; Wensbo, D. *Tetrahedron Lett.* **1996**, *37*, 1471−1472.

hydrochloride in an overall yield of 16%. The three fragments (**6**, **9** or **11**, **3** or **4**) necessary to perform this synthesis were easily prepared in large scale, allowing for preparation of quantities of isoroquefortine C (**2**) suitable for biological testing.

Experimental Section

General Methods. Reactions requiring air-sensitive manipulations were conducted under an argon atmosphere. Methylene chloride was distilled from calcium hydride, and tetrahydrofuran, diethyl ether, and hexane were distilled from sodium/benzophenone. Analytical TLC was performed on 0.25 mm E. Merck silica gel 60 F_{254} plates. Merck silica gel (60, particle size 0.040−0.063 mm) was used for flash column chromatography. NMR spectra were recorded on Bruker AMX-500 spectrometers and calibrated by using residual undeuterated solvent as an internal reference. Chemical shifts (δ) were measured in parts per million, and coupling constants (J values) are in hertz (Hz). Infrared spectra (IR) were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on a Micromass AutoSpec spectrometer using electron impact (EI). Optical rotations were recorded on a Perkin-Elmer model 341 polarimeter at the sodium D line.

Products **4**−**6** were prepared following the procedure of Mardsen et al.[15] Products **7**−**11** were prepared following the procedure of Schmidt et al.[18]

1-Trityl-1*H*-imidazole-4-carbaldehyde 13 and 1-(2-Nitrobenzyl)-1*H*-imidazole-4-carbaldehyde 14. Protection of 4(5)-hydroxymethylimidazole **12** was done according to the procedure of Dinsmore et al.[21] for the trityl group and Antonin et al.[22] for the *o*-nitrobenzyl group. The oxidation step was reported with manganese dioxide in dioxane with 80−95% yield[30,31] for compound **13** and 24−48% yield for **14**.[22] Yields were improved to 99% for **13** and 89% for **14** using the Dess−Martin reagent.[19,20] The physical data for all compounds were identical to those reported in the literature.

General Procedure for the Horner−Wadsworth−Emmons Reaction. The phosphonate (1 equiv) was dissolved in CH_2Cl_2 (1 mL/0.05 mmol) and placed in an ice bath at 0 °C. The solution was treated with DBU (2 equiv) and stirred at the same temperature for 10 min. The aldehyde (1.6 equiv) in CH_2Cl_2 (0.1 mmol/mL) was then added to the solution. The mixture was allowed to warm to room temperature and was stirred overnight. The yellow solution was then washed with 1 N HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield a yellow foam. Flash chromatography, eluting with ether for tryptophan derivatives and 1% methanol/CH_2Cl_2 for dehydrohistidine derivatives, yielded the products as a white foam.

2-Benzyloxycarbonylamino-3-(1-trityl-1*H*-imidazol-4-yl)acrylic Acid Methyl Ester 15. $C_{34}H_{29}N_3O_4$. White solid. R_f: 0.65 (5/95 MeOH/CH_2Cl_2). IR ($CHCl_3$): 1724, 1652, 1542, 750−700 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.71 (s, 1H, NH), 7.51 (s, 1H, H_{15}), 7.40−7.30 (m, 14H, Tr + Z), 7.16−7.13 (m, 6H, Tr), 6.93 (s, 1H, H_{17}), 6.51 (s, 1H, H_{12}), 5.18 (s, 2H, Z), 3.80 (CH_3 ester). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.10 (C=O ester), 154.50 (C=O carbamate), 142.30 (Tr), 139.35 (C_{17}), 137.10 (Z), 136.70 (C_{13}), 130.10 (Tr), 128.80 (Z), 128.70 (Tr), 128.65 (Tr), 128.60 (Z), 128.40 (Z), 127.65 (C_3), 123.35 (C_{17}), 112.70 (C_{12}), 76.20 (Tr), 67.60 (Z), 52.60 (CH_3 ester). HRMS (EI): m/z calcd for $C_{34}H_{30}N_3O_4$ and $C_{34}H_{29}N_3O_4Na$ 544.2236 and 566.2055, found 544.2251 and 566.2076. Product **15** was isolated in 62% yield (401 mg).

2-*tert*-Butoxycarbonylamino-3-(1-trityl-1*H*-imidazol-4-yl)acrylic Acid Methyl Ester 16. $C_{31}H_{31}N_3O_4$. White solid. R_f: 0.6 (5/95 MeOH/CH_2Cl_2). IR ($CHCl_3$): 1721, 1650, 1446, 748−701 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.33 (s, 1H, NH), 7.49 (s, 1H, H_{15}), 7.35 (m, 9H, Tr), 7.14 (m, 6H, Tr), 6.88 (s, 1H, H_{17}), 6.38 (s, 1H, H_{12}), 3.81 (s, 3H, CH_3 ester), 1.47 (s, 9H, Boc). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.55 (C=O ester), 153.70 (C=O carbamate), 142.40 (Tr), 139.30 (C_{15}), 137.40 (C_{13}), 130.15 (Tr), 128.70 (Tr), 128.60 (Tr), 127.95 (C_3), 123.05 (C_{17}), 111.50 (C_{12}), 80.80 (Boc), 75.70 (Tr), 52.50 (CH_3 ester), 28.60 (Boc). HRMS (EI): m/z calcd for $C_{31}H_{32}N_3O_4$ and $C_{31}H_{31}N_3O_4Na$ 509.2315 and 532.2212, found 510.2377 and 532.2204. Product **16** was isolated in 89% yield (80 mg).

3-(1-(*o*-Nitrobenzyl)-1*H*-imidazol-4-yl)-2-benzyloxycarbonylaminoacrylic Acid Methyl Ester 17. $C_{22}H_{20}N_4O_6$. White solid. R_f: 0.25 (5/95 MeOH/CH_2Cl_2). IR ($CHCl_3$): 1721, 1649, 1527, 1223, 860−750 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.58 (s, 1H, NH), 8.17 (dd, J = 1, 8 Hz, ONB), 7.64 (m, 1H, ONB), 7.62 (s, 1H, H_{17}), 7.58 (m, 1H, ONB), 7.50−7.30 (m, 5H, Z), 7.05 (s, 1H, H_{15}), 6.90 (dd, J = 1, 8 Hz, ONB), 6.57 (s, 1H, H_{12}), 5.54 (s, 2H, ONB), 5.18 (s, 2H, Z), 3.80 (s, 3H, CH_3 ester). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.10 (C=O ester), 154.50 (C=O carbamate), 147.60 (ONB), 138.85 (Z), 138.30 (C_{15}), 136.65 (C_{13}), 134.90 (ONB), 132.20 (ONB), 129.95 (ONB), 129.43 (ONB), 128.85 (ONB), 128.60 (Z), 128.50 (Z), 127.90 (Z), 126.00 (C_3), 121.15 (C_{17}), 112.65 (C_{12}), 67.65 (Z), 52.70 (CH_3 ester), 48.65 (ONB). HRMS (EI): m/z calcd for $C_{22}H_{20}N_4O_6Na$ 459.1280, found 459.1272. Product **17** was isolated in 82% yield (75 mg).

3-(1-(*o*-Nitrobenzyl)-1*H*-imidazol-4-yl)-2-*tert*-butoxycarbonylaminoacrylic Acid Methyl Ester 18. $C_{19}H_{22}N_4O_6$. White solid. R_f: 0.15 (5/95 MeOH/CH_2Cl_2). IR ($CHCl_3$): 1714, 1640, 1529, 755−729 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.24 (d, J = 8 Hz, 1H, ONB), 7.66 (s, 1H, H_{15}), 7.60 (m, 1H, ONB), 7.53 (m, 1H, ONB), 6.88 (s, 1H, H_{17}), 6.71 (d, J = 8 Hz, 1H, ONB), 6.21 (s, 1H, H_{12}), 5.69 (s, 2H, ONB), 3.77 (s, 3H, CH_3 ester), 1.47 (s, 9H, Boc). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.60 (C=O ester), 152.75 (C=O carbamate), 147.20 (ONB), 140.25 (C_{15}), 136.20 (C_{13}), 134.30 (ONB), 132.40 (ONB), 129.60 (ONB), 128.45 (ONB), 127.95 (C_3), 126.00 (C_{17}), 115.80 (C_{12}), 81.75 (Boc), 53.00 (CH_3 ester), 46.55 (ONB), 28.60 (Boc). HRMS (EI): m/z calcd for $C_{19}H_{23}N_4O_6$ 403.1617, found 403.1622. Product **18** was isolated in 85% yield (65 mg).

3a-(1,1-Dimethylallyl)-2-[1-methoxycarbonyl-2-(1-trityl-1*H*-imidazol-4-yl)vinylcarbamoyl]-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-1,8-dicarboxylic Acid Di-*tert*-butyl Ester 20. $C_{52}H_{57}N_5O_7$. White solid. R_f: 0.4 (95/5 CH_2Cl_2/MeOH). IR ($CHCl_3$): 2976, 1715, 1708 cm^{-1}. $[\alpha]^{20}_D$: −43 (c 0.9, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.52 (s, 1H, H_{17}), 7.38−7.32 (m, 9H, Tr), 7.24 (t, J = 7.7 Hz, 1H, Ph), 7.17 (d, J = 7.4 Hz, 1H, Ph), 7.12 (m, 5H, trityl), 7.04 (t, J = 8 Hz, 1H, Ph), 6.88 (s, 1H, H_{15}), 6.34 (s, 1H, H_{5a}), 6.23 (s, 1H, H_{12}), 5.85 (dd, J = 10.8, 17.3 Hz, 1H, H_{19}), 4.96 (m, 2H, H_{20}), 3.83 (m, 1H, H_{11a}), 3.80 (s, 3H, CH_3 ester), 2.49 (dd, J = 7, 12.8 Hz, 1H, H_{11}), 2.45 (dd, J = 9.9, 12.8 Hz, 1H, H_{11}), 1.51 (s. 9H, Boc), 1.26 (s, 9H, Boc), 1.01 (s, 3H, H_{22}), 0.94 (s, 3H, H_{21}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.95 (C_4), 159.85 (C_1), 152.30 (Boc), 143.45 (C_{19}), 142.95 (C_{6a}), 141.95 (Tr), 138.95 (C_{15}), 136.50 (C_3), 133.50 (C_{10a}), 129.75 (Tr), 128.45 (C_8), 128.35 (Tr) 128.25 (Tr), 127.40 (C_{13}), 124.75 (C_{10}), 122.75 (C_9), 122.50 (C_{17}) 114.00 (C_{20}), 111.10 (C_{12}), 81.45 (Boc), 81.05 (Boc), 79.25 (C_{5a}), 75.75 (Tr), 61.80 (C_{11a}), 60.90 (C_{10a}), 52.10 (MeO), 40.45 (C_{18}), 35.70 (C_{11}), 28.35 (Boc), 28.05 (Boc), 23.05 (C_{21}), 22.35 (C_{22}). HRMS (EI): m/z calcd for $C_{52}H_{58}N_5O_7$ 864.4336, found 864.4344. Product **20** was isolated in 67% yield.

2-[2-(1-(*o*-Nitrobenzyl-1*H*-imidazol-4-yl)-1-methoxycarbonylvinylcarbamoyl]-3a-(1,1-dimethylallyl)-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-1,8-dicarboxylic Acid Di-*tert*-butyl Ester 21. $C_{40}H_{48}N_6O_9$. White solid. R_f: 0.4 (95/5 CH_2Cl_2/MeOH). IR ($CHCl_3$): 1712, 1529, 1344, 1154 cm^{-1}. $[\alpha]^{20}_D$ −46 (c 0.85, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.14 (dd, J = 1.3, 8.1 Hz, 1H, ONB), 7.65 (s, 1H, H_{15}), 7.60 (dt, J = 1.3, 8.1 Hz, 1H, ONB), 7.51 (m, 1H, ONB), 7.25 (m, 1H, Ph), 7.21 (m, 1H, Ph), 7.14 (s, br, 1H, H_{17}), 7.05 (dt, J = 1, 7.5 Hz, 1H,), 6.96 (d, J = 7.8 Hz, 1H, ONB), 6.51 (s, br, 1H, H_{12}), 6.29 (s, 1H, H_{5a}), 5.88 (dd, J = 10.8, 17.3 Hz, 1H, H_{20}), 5.55 (s, 2H, ONB), 5.01 (dd, J = 1, 10.8 Hz, 1H, H_{19}), 4.98 (dd, J = 1, 17.3 Hz, 1H, H_{19}), 3.85 (dd, J = 7.2, 9.6 Hz, 1H, H_{11a}), 3.80 (s, 3H,

(30) Hunt, J. T.; Lee, V. G.; Leftheris, K.; Seizinger, B.; Carboni, J.; Mabus, J.; Ricca, N. Y.; Veeraswamy, M. *J. Med. Chem.* **1996**, *39*, 353−358.

(31) Lee, K. J.; Joo, K. C.; Kim, E. J.; Lee, M.; Kim, D. H. *Bioorg. Med. Chem.* **1997**, *5*, 1989−1998.

CH_3 ester), 2.53 (dd, J = 7.1, 12.9 Hz, 1H, H_{11}), 2.48 (dd, J = 9.7, 12.9 Hz, 1H, H_{11}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.20 (C_3), 166.10 (C_1), 152.65 (Boc), 147.50 (ONB), 143.60 (C_{19}), 143.15 (C_{6a}), 138.60 (C_2), 138.15 (C_{15}), 134.80 (ONB), 134.30 (C_{10a}), 132.20 (ONB), 129.80 (C_8), 129.40 (ONB), 128.70 (C_9), 125.85 (ONB), 125.80 (C_{13}), 125.15 (C_{10}), 123.30 (ONB), 121.15 (C_{17}), 118.30 (C_1), 114.35 (C_{20}), 110.90 (C_{12}), 81.55−80.85 (Boc), 79.50 (C_{5a}), 62.10 (C_{10b}), 61.40 (C_{11a}), 52.60 (CH_3 ester), 48.50 (ONB), 40.70 (C_{18}), 35.85 (C_{11}), 28.65−28.30 (Boc), 23.30−22.60 (C_{21}−C_{22}). HRMS (EI): m/z calcd for $C_{40}H_{48}N_6O_9Na$ 779.3380, found 779.3383. Product **21** was isolated in 79% yield (298 mg).

2-[[(Dimethoxyphosphoryl)methoxycarbonylmethyl]-carbamoyl]-3a-(1,1-dimethylallyl)-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-1,8-dicarboxylic Acid Di-*tert*-butyl Ester 19. To a solution of **6** (320 mg, 0.68 mmol) in dichloromethane (20 mL) were added DCC (182 mg, 0.88 mmol), HOBT (110 mg, 0.81 mmol), and **10** (270 mg, 1.36 mmol). The mixture was stirred at room temperature for 12 h and diluted with ether (50 mL). The DCU was removed by filtration and the organic layer washed with 1 N HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield a light yellow foam. Flash chromatography, eluting with 1% methanol/CH_2Cl_2, yielded the product as a white foam (410 mg, 93%). $C_{31}H_{46}N_3O_{10}P$. R_f: 0.5 (95/5 CH_2Cl_2/MeOH). IR ($CHCl_3$): 2976, 1749, 1714 cm^{-1}. $[\alpha]^{20}_D$ −36 (c 0.45, EtOH). 1H NMR (500 MHz, $CDCl_3$) δ: 7.27 (t, J = 7.7 Hz, 1H, Ph), 7.20 (d, J = 7.5 Hz, 1H, Ph), 7.09 (t, J = 7.5 Hz, 1H, Ph), 6.47 (d, J = 8.9 Hz, 1H, NH), 6.18 (d, J = 7 Hz, H_{5a}), 5.89−5.93 (m, 1H, H_{19}), 5.20−5.27 (m, 1H, H_3), 5.10 (dd, J = 7.6, 10.8 Hz, H_{20}), 5.03 (dd, J = 3.6, 17.3 Hz, H_{20}), 3.75−3.90 (m, 4H, H_{11a}+CH_3 ester), 2.43−2.48 (m, 1H, H_{11}), 2.31−2.38 (m, 1H, H_{11}), 1.58 (s, 9H, Boc), 1.45 (s, 9H, Boc), 1.07−1.06−0.99−0.98 (4s, 4*3H, CH_3 prenyl). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.20−171.90 (C═O ester), 167.25−167.20 (C═O amide), 152.75 (C═O carbamate), 143.60−143.55 (C_{19}), 143.20 (C_{6a}), 134.00 (C_{10a}), 128.90 (C_{10}), 125.20 (C_9), 123.75 (C_8), 118.62 (br; C_7), 114.75 (C_{20}), 81.90−81.60 (Boc), 79.60−79.40 (C_{5a}), 66.20 (C_{10b}), 61.60−61.50 (C_{11a}), 54.65−54.60−54.55−54.50 ($POCH_3$), 54.30−54.25−54.20−54.15 ($POCH_3$), 53.65−53.60 (CH_3 ester), 50.80−50.70−49.60−49.55 (C_3), 40.70−40.75 (C_{18}), 35.60−35.45 (C_{11}), 28.80−28.65−28.60 (Boc), 23.35−23.30−22.55 (CH_3 prenyl). HRMS (EI): m/z calcd for $C_{31}H_{46}N_3O_{10}NaP$ 674.2816, found 674.2827. Product **19** was isolated in 67% yield (415 mg).

3-(3-(*o*-Nitrobenzyl)-3*H*-imidazol-4-ylmethylene)-10b-(1,1-dimethylallyl)-2,3,6,10b,11,11a-hexahydro-5a*H*-pyrazino[1′,2′:1,5]pyrrolo[2,3-*b*]indole-1,4-dione 23. The TMSI solution was prepared by dissolving freshly sublimed iodine (5 equiv) in CH_2Cl_2 (1 mL/70 mg) under a nitrogen atmosphere and adding hexamethyldisilane (7.5 equiv). The solution was heated at 70 °C (bath temperature) until disappearance of the purple color gave way to a pale yellow solution. The solution was allowed to warm to room temperature under a nitrogen atmosphere and was used immediately. The protected linear compound (1 equiv) was dissolved in freshly distilled acetonitrile (0.023 mmol/mL), cooled in an ice bath under a nitrogen atmosphere, and treated with the TMSI solution. The mixture was then stirred for 45 min at 0 °C or until the TLC showed the disappearance of starting material. The reaction was warmed to room temperature and quenched with saturated $NaHCO_3$ (0.04 mmol/mL). The organic layer was dried over $MgSO_4$ and filtered. The organic layer was treated with silica and stirred at room temperature overnight, and solvent was then removed by filtration. The silica was washed with a 10% methanol/CH_2Cl_2 solution. The organic layers were distilled under reduced pressure, and the residue was then recrystallized from methanol to give the cyclic compound. Product **23** was isolated in 55% yield (45 mg). $C_{29}H_{28}N_6O_4$. White solid. R_f: 0.8 (95/5 CH_2Cl_2/MeOH). IR ($CHCl_3$): 1731, 1688, 1630 cm^{-1}. $[\alpha]^{20}_D$ −307 (c 0.7, EtOH). 1H NMR (500 MHz, $CDCl_3$) δ: 11.46 (s, br, NH), 8.20 (dd, J = 1, 8.2 Hz, 1H, H_{26}), 7.66 (m, 1H, H_{27}), 7.64 (s, 1H, H_{15}), 7.57 (m, 1H, H_{28}), 7.19 (d, J = 7.4 Hz, H_{10}), 7.12 (m, 1H, H_9), 7.08 (s, 1H, H_{17}), 6.92 (d, J = 7.7 Hz, 1H, H_{29}), 6.78 (pseudo t, J = 7 Hz, 1H, H_8), 6.68 (s, 1H, H_{12}), 6.61 (d, J = 7.8 Hz, 1H, H_7), 6.02 (dd, J = 10.8, 17.4 Hz, 1H, H_{19}), 5.69 (s, 1H, H_{5a}), 5.59 (s, 2H, H_{23}), 5.15 (dd, J = 1, 11 Hz, H_{20}), 5.12 (dd, J = 1, 17.4 Hz, 1H, H_{20}), 5.00 (s, br, NH), 4.14 (dd, J = 5.8, 11.5 Hz, H_{11a}), 2.63 (dd, J = 5.8, 12.3 Hz, 1H, H_{11}), 2.50 (pseudo t, J = 11.9 Hz, 1H, H_{11}), 1.18 (s, 3H, H_{21}), 1.08 (s, 3H, H_{22}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.80 (C_1), 158.60 (C_4), 150.85 (C_{6a}), 147.60 (C_{24}), 144 (C_{19}), 139.20 (C_{29}), 138.35 (C_{15}), 134.90 (C_{17}), 130.00 (C_{28}), 129.35 (C_{27}), 129.30 (C_{26}), 129.25 (C_8), 127.60 (C_{10a}), 126.05 (C_{13}), 125.60 (C_{10}), 121.10 (C_3), 119.10 (C_9), 114.85 (C_{20}), 109.30 (C_{12}), 104.65 (C_7), 78.40 (C_{5a}), 62.00 (C_{10b}), 59.50 (C_{11a}), 48.70 (C_{23}), 41.35 (C_{18}), 37.65 (C_{11}), 23.4 (C_{21}), 22.90 (C_{22}). HRMS (EI): m/z calcd for $C_{29}H_{28}N_6O_4Na$ 547.2069, found 547.2091.

Isoroquefortine C or 10b-(1,1-Dimethylallyl)-3-(3*H*-imidazol-4-ylmethylene)-2,3,6,10b,11,11a-hexahydro-5a*H*-pyrazino[1′,2′:1,5]pyrrolo[2,3-*b*]indole-1,4-dione 2. A solution of **23** (20 mg) in 1,4-dioxane (40 mL) was placed in a quartz immersion cell. A stream of nitrogen was introduced into the solution while it was irradiated with a mercury vapor lamp with a Pyrex filter (450-W). The photolysis was complete after 1.5 h. The solvent was then removed under reduced pressure and the residue was recrystallized from methanol to give **2** in 81% yield (12 mg). $C_{22}H_{23}N_5O_2$. White solid. R_f: 0.1 (90/10 CH_2Cl_2/MeOH + ammonia vapors). IR ($CHCl_3$): 1680, 1630 cm^{-1} (lit.[11] IR 1676, 1627 cm^{-1}). $[\alpha]^{20}_D$ −390 (c 0.05, $CHCl_3$) (lit.[11] $[\alpha]_D$ −409 (c 0.071, $CHCl_3$)). 1H NMR (500 MHz, $CDCl_3$) δ: 11.66 (s, br, 1H, NH), 10.03 (s, br, 1H, NH), 7.68 (s, br, 1H, H_{15}), 7.18 (m, 1H, H_{10}), 7.10 (t, J = 7.5 Hz, 1H, H_9), 7.08 (s, 1H, H_{17}), 6.76 (t, J = 7.5 Hz, 1H, H_8), 6.71 (s, 1H, H_{12}), 6.59 (d, J = 7.8 Hz, 1H, H_7), 6.00 (dd, J = 10.8, 17.3 Hz, 1H, H_{19}), 5.67 (s, 1H, H_{5a}), 5.11 (m, 2H, H_{20}), 4.97 (s, br, 1H, NH), 4.12 (dd, J = 5.6, 11.6 Hz, 1H, H_{11a}), 2.60 (dd, J = 6, 12.2 Hz, 1H, H_{11}), 2.49 (m, 1H, H_{11}), 1.15−1.04 (H_{21}−H_{22}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.00 (C_1), 158.85 (C_4), 150.75 (C_{6a}), 144.00 (C_{19}), 137.85 (C_3), 135.65 (C_{15}), 129.35 (C_8), 129.25 (C_{10a}), 127.00 (C_{13}), 125.65 (C_{10}), 119.25 (C_9), 117.65 (C_{17}), 114.90 (C_{20}), 109.35 (C_7), 105.45 (C_{12}), 78.40 (C_{5a}), 62.00 (C_{10b}), 59.50 (C_{11a}), 41.35 (C_{18}), 37.65 (C_{11}), 23.00−22.50 (C_{21}−C_{22}). HRMS (EI): m/z calcd for $C_{22}H_{24}N_5O_2$ 390.1930, found 390.1956.

Acknowledgment. We gratefully acknowledge the NSF (CHE 99-01449) and the University of Pennsylvania for financial support.

Supporting Information Available: 1H NMR and ^{13}C NMR of compounds **15**−**21**, **23**, and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0106593