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Total Synthesis of (−)-Fumiquinazolines A, B, C, E, H, and I. Approaches to the Synthesis of Fiscalin A

Barry B. Snider* and Hongbo Zeng

Department of Chemistry, MS015, Brandeis University, Waltham, Massachusetts 02454-9110

snider@brandeis.edu

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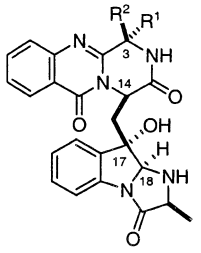
The first syntheses of (−)-fumiquinazolines A, B, and I, which proceed in 14 steps from protected tryptophan, anthranilic acid, leucine, and alanine in 7% overall yield, are described. Tricycle **30** was formed by a palladium-catalyzed cyclization. Oxidation of **30a** with saccharine-derived oxaziridine **21** for fumiquinazolines A and B and oxidation of **30b** with dimethyldioxirane for fumiquinazoline I selectively formed the appropriate imidazoindolone stereoisomers. Application of the Ganesan−Mazurkiewicz cyclization completed the syntheses. Efficient 14-step syntheses of (−)-fumiquinazolines C (**7**) and E (**3**) and a 15-step synthesis of (−)-fumiquinazoline H (**8**) using FmocNHCH(CH_2SePh)CO_2H as a dehydroalanine precursor that spontaneously eliminated benzeneselenol without oxidation under the cyclization conditions are also reported. Model **86** for fiscalins A with the H and OH anti to each other has been prepared, but the procedure that worked for the model failed with the fully functionalized side chain.

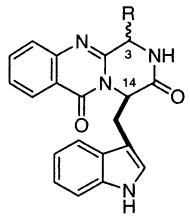
Introduction

Numata and co-workers recently isolated the moderately cytotoxic fumiquinazolines A (**1**), B (**2**), C (**7**), E (**3**), F (**4**), and G (**5**) from a strain of *Aspergillus fumigatus* found in the gastrointestinal tract of the fish *Pseudolabrus japonicus*.[1] Belofsky, Köck, and co-workers isolated the antifungal fumiquinazolines H (**8**) and I (**9**) from a fungus *Acremonium* sp. isolated from the surface of the Caribbean tunicate *Ecteinascidia turbinata*.[2] A Sterling Winthrop group isolated fiscalins A (**10**), B (**6**), and C (**11**), which inhibit substance P binding, from the broth extracts of the fungus *Neosartorya fischeri*.[3]

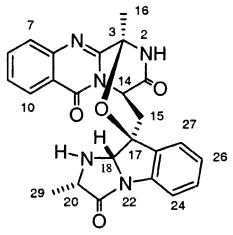
The simplest members of this family, fumiquinazolines F (**4**) and G (**5**) and fiscalin B (**6**), are tripeptide alkaloids formed from a tryptophan, anthranilic acid, and alanine or valine. In fumiquinazolines A (**1**) and B (**2**) the indole nitrogen has been coupled to an alanine and oxidative cyclization has occurred to form an additional ring. Fumiquinazoline I (**9**) is analogous to fumiquinazoline A (**1**) except that the indole nitrogen has been coupled to a leucine and oxidative cyclization has occurred with the opposite stereochemistry at both C-17 and C-18 on the indole ring. The relationship between fiscalins A (**10**) and B (**6**) is the same as that between fumiquinazolines A (**1**) and F (**4**) with the important exception that oxidative cyclization has occurred with the opposite stereochem-



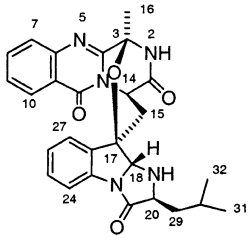
1, R^1 = Me, R^2= H (fumiquinazoline A)
2, R^1 = H, R^2= Me (fumiquinazoline B)
3, R^1 = Me, R^2 = OMe (fumiquinazoline E)



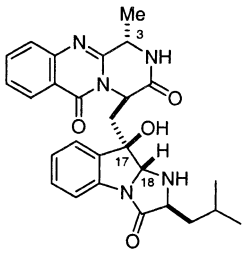
4, R = α-Me (fumiquinazoline F)
5, R = β-Me (fumiquinazoline G)
6, R = α-*i*-Pr (fiscalin B)



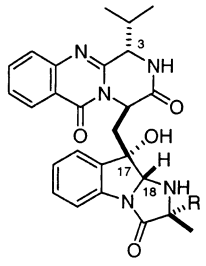
7 (fumiquinazoline C)



8 (fumiquinazoline H)



9 (fumiquinazoline I)



10, R = H (fiscalin A)
11, R = Me (fiscalin C)

* Address correspondence to this author. Fax 781-736-2516.

(1) (a) Numata, A.; Takahashi, C.; Matsushita, T.; Miyamoto, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Inoue, M.; Ohishi, H.; Shingu, T. *Tetrahedron Lett.* **1992**, *33*, 1621−1624. (b) Takahashi, C.; Matsushita, T.; Doi, M.; Minoura, K.; Shingu, T.; Kumeda, Y.; Numata, A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2345−2353.

(2) Belofsky, G. N.; Anguera, M.; Jensen, P. R.; Fenical, W.; Köck, M. *Chem. Eur. J.* **2000**, *6*, 1355−1360.

(3) Wong, S.-M.; Musza, L. L.; Kydd, G. C.; Kullnig, R.; Gillum A. M.; Cooper, R. *J. Antibiot.* **1993**, *46*, 545−553.

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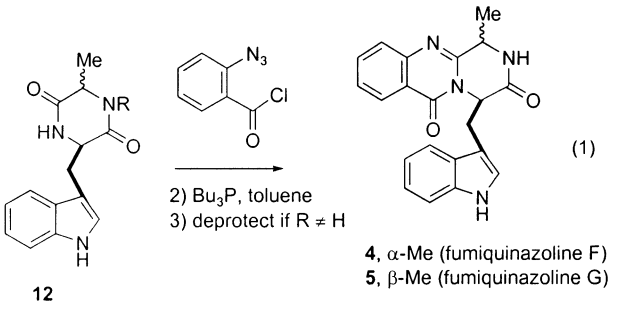
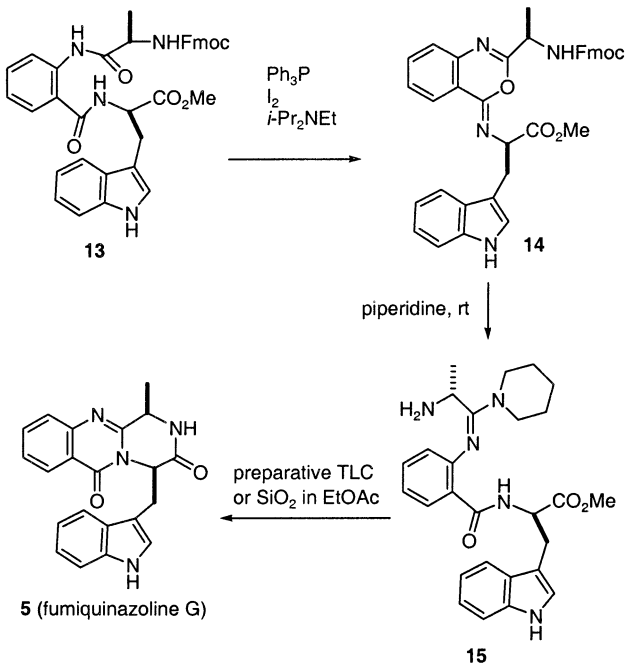
istry at C-18. Oxidation at C-3 in fumiquinazolines A (**1**) or B (**2**) will give a cation that will react with MeOH to give fumiquinazoline E (**3**), cyclize with the tertiary alcohol to give fumiquinazoline C (**7**), or cyclize with the secondary amine to give fumiquinazoline D (**73**). Similarly, oxidation at C-3 in fumiquinazoline I (**9**) and cyclization with the tertiary alcohol will give fumiquinazoline H (**8**).

These compounds consist of two polycyclic halves connected by a methylene group. Therefore one needs to develop procedures to construct each half and to design sequences such that the procedures used to synthesize the top half are compatible with the bottom half and vice versa. Not surprisingly, procedures for the top half were initially developed for the simplest members of this family, fumiquinazolines F (**4**) and G (**5**). We reported syntheses of fumiquinazoline G (**5**) using the Eguchi aza-Wittig protocol with 2-azidobenzoyl chloride on a monoprotected diketopiperazine **12** using either R = 2,4-dimethoxybenzyl[4] or 2-nitrobenzyl (eq 1).[5] Avendaño and

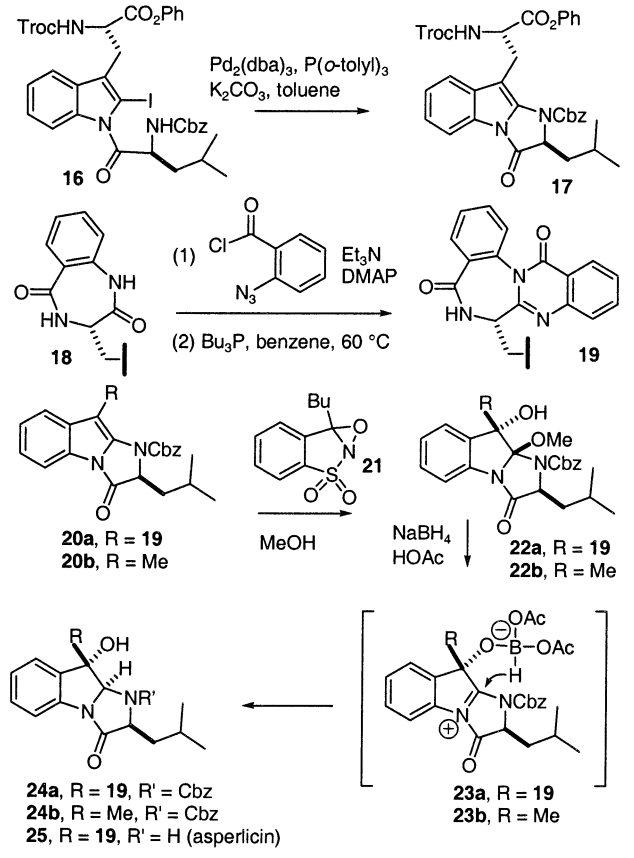


Söllhuber prepared both fumiquinazolines F and G in 30−40% yield without protection (**12**, R = H).[6] Wang and Ganesan reported a remarkably simple dehydrative cyclization of tripeptide **13** leading to fumiquinazoline G, and also prepared fumiquinazolines F and fiscalin B.[7] We showed that this sequence is much more complicated than expected (Scheme 1).[8] The initial cyclization gave iminobenzoxazine **14** as reported earlier by Mazurkiewicz.[9] Deprotection of the Fmoc group with piperidine also opened the ring to give amidine **15**, which cyclized on silica gel or heating to give the quinazolinone. Once the quinazolinone has formed the amino ester cyclized to complete the synthesis of fumiquinazoline G (**5**). Hart and Magomedov have shown that this transformation can also be carried out with $LiAl(Me)_3SPh$.[10]We developed a procedure to prepare the bottom half of the more complex members of this family and used it in the synthesis of the potent cholecystokinin antagonist asperlicin (**25**) (Scheme 2).[11] Buchwald's palladium-catalyzed cyclization of iodoindole carbamate **16** formed the novel imidazoin-

SCHEME 1



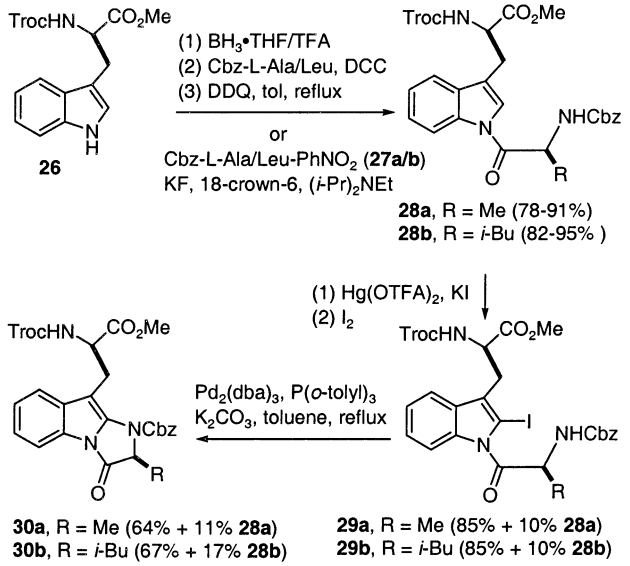
SCHEME 2



dolone **17**. Cleavage of the Troc group, coupling with anthranilic acid, and cyclization provided **18**. Selective acylation with the Eguchi reagent on the more acidic anilide nitrogen formed the quinazolinone ring of **19**.

(4) He, F.; Snider, B. B. *Synlett* **1997**, 483−484.
(5) Snider, B. B.; Busuyek, M. V. *Tetrahedron* **2001**, *57*, 3301−3307.
(6) Hernández, F.; Lumetzberger, A.; Avendaño, C.; Söllhuber, M. *Synlett* **2001**, 1387−1389.
(7) (a) Wang, H.; Ganesan, A. *J. Org. Chem.* **1998**, *63*, 2432−2433. (b) Wang, H.; Ganesan, A. *J. Org. Chem.* **2000**, *65*, 1022−1030.
(8) He, F.; Snider, B. B. *J. Org. Chem.* **1999**, *64*, 1397−1399.
(9) Mazurkiewicz, R. *Monatsh. Chem.* **1989**, *120*, 973−980.
(10) (a) Hart, D. J.; Magomedov, N. A. *Tetrahedron Lett.* **1999**, *40*, 5429−5432. (b) Freed, J. D.; Hart, D. J.; Magomedov, N. A. *J. Org. Chem.* **2001**, *66*, 839−852. (c) Hart, D. J.; Magomedov, N. A. *J. Am. Chem. Soc.* **2001**, *123*, 5892−5899.
(11) He, F.; Foxman B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1998**, *120*, 6417−6418.

SCHEME 3



Epoxidation of **20a** with Davis' saccharine-derived oxaziridine **21** in MeOH afforded the methoxy alcohol **22a**. Directed reduction of **22a** with $NaBH(OAc)_3$ proceeded through **23a** in which the hydride was delivered from the same face as the OH group to give an 11:1 mixture of Cbz-asperlicin (**24a**) and the diastereomer with both the H and OH up. Hydrogenolysis completed the synthesis of asperlicin (**25**).

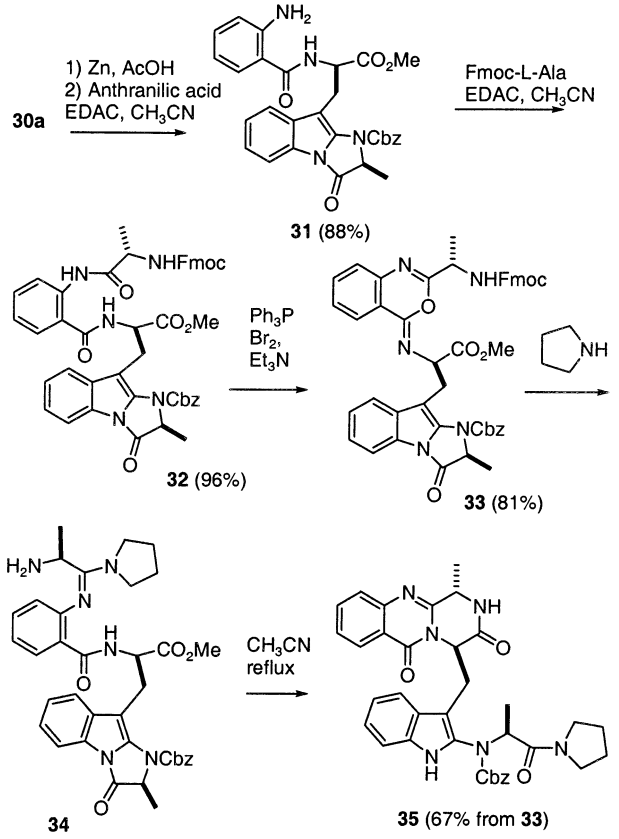
The relative stereochemistry of the H and OH groups is controlled by the reduction. The stereochemistry of the OH group is controlled by the epoxidation. In model studies with **20b**, we found that epoxidation with oxaziridine **21** occurred mainly (70−80%) from the bottom face, that there was little selectivity with *m*-CPBA, and that epoxidation with dimethyldioxirane occurred with modest selectivity from the top face.[11]

We thought that combining our route for the preparation of the bottom half and using the Mazurkiewicz−Ganesan cyclization for the top half should provide an attractive route to the more complex fumiquinazolines and fiscalins.[12]

Results and Discussion

Fumiquinazolines A and B. Our initial approach was to construct dipeptide **32** with a fully functionalized bottom half and to elaborate it to fumiquinazolines A and B via iminobenzoxazine **33**. Reaction of D-tryptophan methyl ester with Troc chloride and $NaHCO_3$ in a mixture of Et_2O and H_2O gave Troc-tryptophan methyl ester (**26**) quantitatively (Scheme 3).[13] Reduction of **26** with BH_3·THF in TFA,[14] acylation of the indoline with Cbz-L-Ala, and oxidation with 2,3-dichloro-5,6-dicyanoquinone (DDQ)[15] afforded 78% of *N*-acylindole **28a** in three steps. More recently, we found that **28a** can be prepared in a single step in 91% yield by reaction of **26** with *N*-Cbz-L-alanine nitrophenyl ester (**27a**), KF, 18-crown-6, and $(i\text{-Pr})_2NEt$ in CH_3CN.[16] Mercuration[17] of **28a** with $Hg(OTFA)_2$, and then KI work up, followed by treatment with iodine provided 85% of iodoindole **29a** and 10% of starting material **28a**. Subjection of iodoindole **29a** to the Buchwald palladium-catalyzed condensation[18] gave the desired imidazoindolone **30a** in 64% yield and 11% of the reduction product **28a**, which was recycled.

SCHEME 4



Deprotection of the Troc group of **30a** with Zn in AcOH provided the free amine, which was coupled with anthranilic acid and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDAC) in CH_3CN to yield 88% of aniline **31** (Scheme 4). Coupling of **31** with Fmoc-L-alanine and EDAC in CH_3CN afforded 96% of diamide **32**. Treatment of **32** with Ph_3P, Br_2, and Et_3N in CH_2Cl_2 at room temperature for 5 min provided 81% of iminobenzoxazine **33**. Treatment of **33** with 2 equiv of pyrrolidine, which forms an amidine more readily than piperidine, in EtOAc at 25 °C for 5 min gave crude amidine **34** with an intact bottom portion. Heating **34** in CH_3CN for 2 h led to the formation of the desired top half. However, the pyrrolidine released from the isomerization of the amidine to the quinazolinone cleaved the reactive acyl indole bond affording **35** in 67% yield from iminobenzoxazine **33**. Heating amidine **34** in CH_3CN

(12) For preliminary communications on portions of this work see: (a) Snider, B. B.; Zeng, H. *Org. Lett.* **2000**, *2*, 4103−4106. (b) Snider, B. B.; Zeng, H. *Org. Lett.* **2002**, *4*, 1087−1090.

(13) Vedejs, E.; Wang, J. *Org. Lett.* **2000**, *2*, 1031−1032.

(14) Maryanoff, B. E.; McComsey, D. F.; Nortey, S. O. *J. Org. Chem.* **1981**, *46*, 355−360.

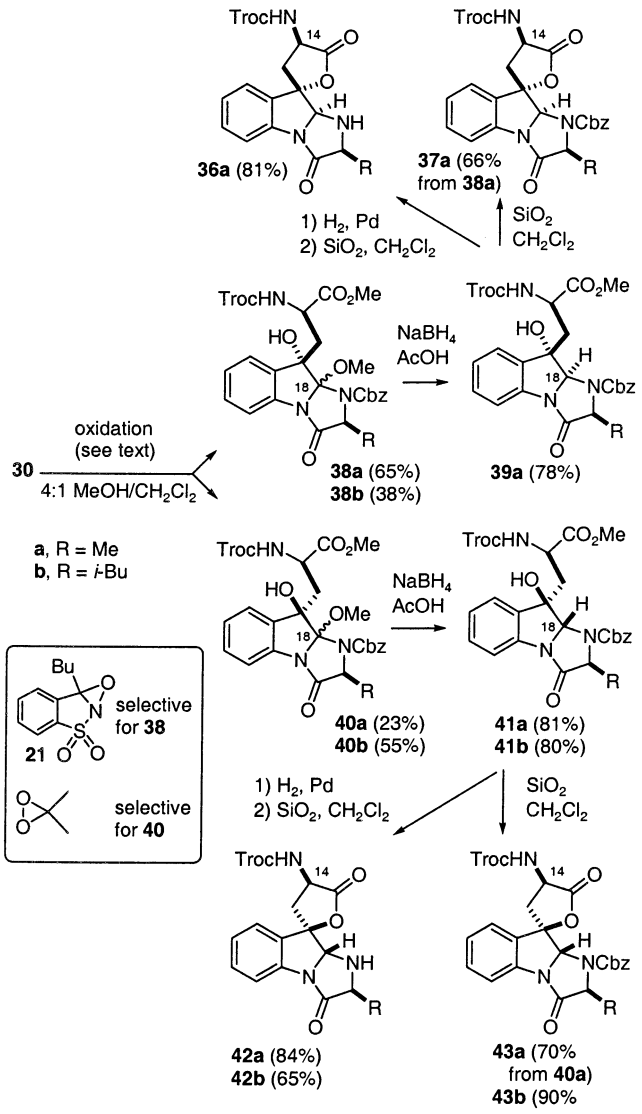
(15) Preobrazhenskaya, M. N. *Russ. Chem. Rev.* **1967**, *36*, 753−771.

(16) (a) Nakagawa, M.; Taniguchi, M.; Sodeoka, M.; Ito, M.; Yamaguchi, K.; Hino, T. *J. Am. Chem. Soc.* **1983**, *105*, 3709−3710. (b) Nakagawa, M.; Ito, M.; Hasegawa, Y.; Akashi, S.; Hino, T. *Tetrahedron Lett.* **1984**, *25*, 3865−3868. (c) Nakagawa, M.; Sodeoka, M.; Yamaguchi, K.; Hino, T. *Chem. Pharm. Bull.* **1984**, *32*, 1373−1384.

(17) Mingoia, Q. *Gazz. Chim. Ital.* **1930**, *60*, 509−515.

(18) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525−7546.

SCHEME 5



containing 1% AcOH to protonate the liberated pyrrolidine still gave **35**, but in lower yield. This suggests that the acyl indole would also be cleaved with piperidine.

Since the acyl indole did not survive the preparation of the quinazolinone, we decided to carry out the epoxidation−reduction sequence before the dehydrative cyclization and rearrangement that forms the quinazolinone. Epoxidation of **30a** with oxaziridine **21**[19] in 4:1 MeOH/CH_2Cl_2 at room temperature yielded a readily separable mixture of 65% of **38a** with an α-hydroxy group and 23% of **40a** with a *β*-hydroxy group (Scheme 5). Both compounds are mixtures of diastereomers at C-18. The 3:1 selectivity for **38a** is similar to that observed with model **20b** and much lower than the 11:1 selectivity obtained with **20a** with a complete top half. Reduction of **38a** with freshly prepared $NaBH(OAc)_3$ in acetic acid at room temperature for 2 h provided 78% of **39a** with an α-hydrogen at C-18 by intramolecular delivery of hydride as shown in **23**.[20] The tertiary hydroxy group was protected as the lactone by stirring the crude product with silica gel in CH_2Cl_2 for 12 h to give **37a** (66% from **38a**). A similar sequence converted **40a** to **43a** in 70% yield. Mild conditions are necessary since the lactone is easily epimerized at C-14.[21]

Because of slow rotation about the C−N bond in the Cbz protecting group, it was not possible to confirm the stereochemistry of lactones **37a** and **43a** spectroscopically. Hydrogenolysis of the Cbz group of these lactones also reduced the benzylic lactone. Fortunately, hydrogenolysis of the Cbz group of alcohol **39a** gave the free amine alcohol, which lactonized upon stirring with silica gel in CH_2Cl_2 to give the lactone amine **36a** in 81% yield from **39a**. A similar sequence converted **40a** to **42a** in 84% yield. 2-D NOE studies confirmed the stereochemical assignments of **36a** and **42a**. We tried unsuccessfully to improve the selectivity by using chiral oxidants with model **20b**. Davis' camphor-derived oxaziridines were too hindered to react. Lower yields of products were obtained with Shi's fructose-derived dioxirane. Sharpless asymmetric dihydroxylation failed to give the diol.

Elaboration of lactone **37a** to fumiquinazolines A (**1**) and B (**2**) now proceeded easily (Scheme 6). Reductive removal of the Troc group with Zn in AcOH afforded the amine, which was coupled with anthranilic acid and EDAC in CH_3CN to yield 85% of aniline **44**. A second coupling with Fmoc-L-alanine gave diamide **45a** in 89% yield. Dehydrative cyclization of **45a** with PPh_3, Br_2, and Et_3N in CH_2Cl_2 at 25 °C provided 76% of iminobenzoxazine **46a**. Although I_2 is much easier to handle than Br_2, longer reaction times were required with I_2, so that more Fmoc cleavage occurred with either Et_3N or *i*-Pr_2NEt as the base. Reaction of **46a** with 10 equiv of piperidine in EtOAc at 25 °C for 10 min gave crude amidine amine **47a**, which was refluxed in CH_3CN for 2 h to afford Cbz-fumiquinazoline A (**48a**) in 65% yield. The readily separable isomer **49a** at C-14 was also obtained in 19% yield. The lactone is easily epimerized[21] at C-14 by the liberated piperidine prior to the last step in the sequence, which forms the piperazine. Heating amidine **47a** at lower temperatures proceeded with less epimerization, but gave a lower yield of **48a**. Later, during the preparation of fumiquinazolines C and E, we found that adding 1% acetic acid to the CH_3CN decreased the epimerization at C-14 from 15−20% to 5−10%.

Hydrogenolysis of **48a** afforded 90% of fumiquinazoline A (**1**) with spectral data, melting point, and optical rotation identical with those reported for the natural product.[1] Hydrogenolysis of **49a** gave 86% of **50a** with spectral data identical with those reported for a base-catalyzed rearrangement product of fumiquinazolines A and B.[22]

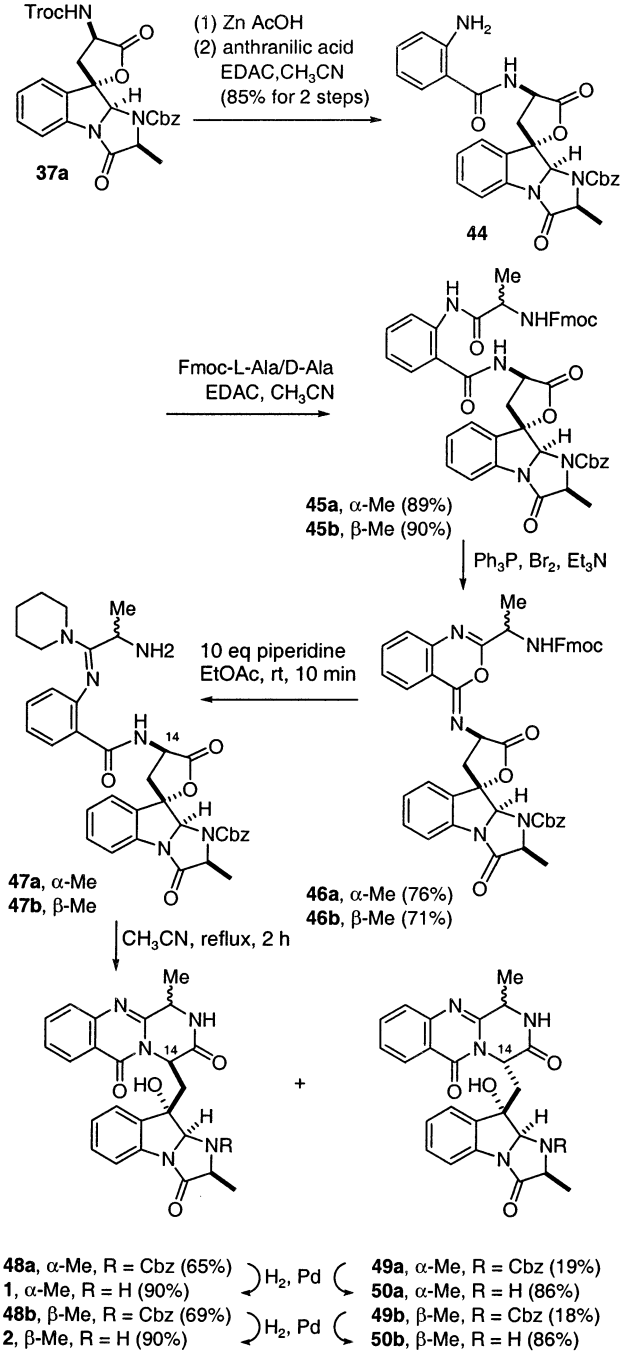
A similar sequence coupling aniline **44** with Fmoc-D-alanine afforded 90% of **45b**. Dehydrative cyclization gave 71% of iminobenzoxazine **46b**, which was rearranged via amidine **47b** to give 69% of Cbz-fumiquinazoline B (**48b**) and 18% of the C-14 epimer **49b**. Hydrogenolysis of **48b** afforded 90% of fumiquinazoline B (**2**)

(19) (a) Davis, F. A.; Sheppard, A. C. *Tetrahedron Lett.* **1988**, *29*, 4365−4368. (b) Davis, F. A.; Towson, J. C.; Vashi, D. B.; ThimmaReddy, R.; McCauley, J. P., Jr.; Harakal, M. E.; Gosciniak, D. G. *J. Org. Chem.* **1990**, *55*, 1254−1261.

(20) (a) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273−276. (b) Hoveyda, A.; Evans, D. A.; Fu, G. *Chem. Rev.* **1993**, *93*, 3, 1307−1368.

(21) (a) Michl, K. *Liebigs Ann. Chem.* **1981**, 33−39. (b) Büchi, G.; DeShong, P.; Katsumura, S.; Sugimura, Y. *J. Am. Chem. Soc.* **1979**, *101*, 5084−5086.

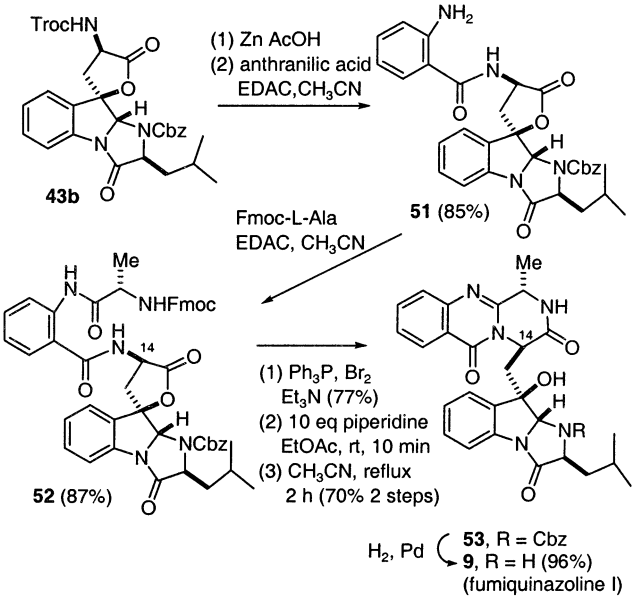
SCHEME 6



with spectral data, melting point, and optical rotation identical with those reported for the natural product.[1] The proton NMR spectrum of fumiquinazoline B is concentration dependent. The spectrum of a 0.08 M solution in $CDCl_3$ matches that reported,[1] while the spectrum of a 0.01 M solution is shifted by as much as 0.1 ppm. Hydrogenolysis of **49b** gave 86% of **50b** with spectral data identical with those reported for a base-catalyzed rearrangement product of fumiquinazolines A and B.[22]

Fumiquinazoline I. Fumiquinazoline I (**9**) differs from fumiquinazoline A (**1**) in two respects. The substituent on the imidazoindolone ring is an isobutyl group from L-leucine as in asperlicin, rather than a methyl substituent from L-alanine. More significantly, the hydrogen and hydroxyl substituents on the indoline ring are cis to the alkyl substituent on the imidazoindolone ring, rather than trans as in fumiquinazoline A. Fortunately, our survey of oxidants found that oxidation of **20** or **30** with dimethyldioxirane (DMDO) favored oxidation from the same face as the alkyl group with modest selectivity.[11]

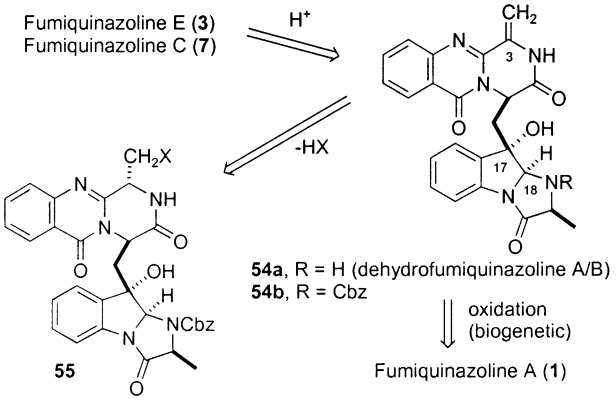
SCHEME 7



Conversion of **26** to **28b** proceeded in 82% yield by the three-step sequence or in 95% in a single step staring with Cbz-L-leucine *p*-nitrophenyl ester (Scheme 3). Iodination and palladium-catalyzed cyclization afforded **30b** in the yields indicated. Epoxidation of **30b** with DMDO in 15:4:1 acetone/MeOH/CH_2Cl_2 at −78 °C gave 55% of the desired methoxy alcohol **40b** with the hydroxy group cis to the isobutyl group and only 38% of methoxy alcohol **38a**, which was the major product with the saccharine-derived oxaziridine **21** (Scheme 5). Reduction of **40b** with $NaBH(OAc)_3$ in AcOH provided **41b** (80%), which lactonized with silica gel in CH_2Cl_2 to afford **43b** (90%).Diamide **52** was prepared from **43b** analogously to **45a** in the yields indicated in Scheme 7. Dehydrative cyclization of

(22) The spectral data for **50a** correspond exactly to those reported for compound 6 in ref 1, where this compound was assigned as the C-14 epimer of fumiquinazoline B, not A. The spectral data for **50b** correspond to those reported for compound 5 in ref 2, where this compound was assigned as the C-14 epimer of fumiquinazoline A, not B. From both mechanistic and spectroscopic considerations discussed below, the stereochemistry of 5 and 6 must be switched in this reference. Treatment of either fumiquinazolines A (**1**) or B (**2**) with base afforded a mixture of **1**, **2**, **50a**, and **50b**; epimerization occurred at both C-14 and C-3. Treatment of **1** with acid gave a mixture of only **1** and **2;** epimerization occurred only at C-3. In our experiment, **47a** gave rise to only **1** and **50a**, indicating that epimerization occurred only at C-14. This assignment is supported by analysis of coupling constants. The piperazine ring exists in a boat conformation with an axial-like R group at C-14 to avoid $A^{1,3}$ strain with the carbonyl group. In fumiquinazoline A (**1**), the methyl group at C-3, which is trans to R, is equatorial-like. Therefore, there is a 81° torsion angle between the axial-like H-3 and N−H (PCMODEL 7.5), which is consistent with the observed 0.3-Hz coupling constant. In fumiquinazoline B (**2**), the methyl group, which is cis to R, is axial-like. Therefore there is a 46° torsion angle between the equatorial H-3 and N−H, which is consistent with the observed 4.9-Hz coupling constant. The coupling constant reported for 5 in ref 1 is 0.3 Hz, which indicates that the substituents are trans not cis and that this compound actually has structure 6 (**50b**). The coupling constant reported for 6 in ref 1 is 4.2 Hz, which indicates that the substituents are cis not trans and that this compound actually has structure 5 (**50a**).

SCHEME 8

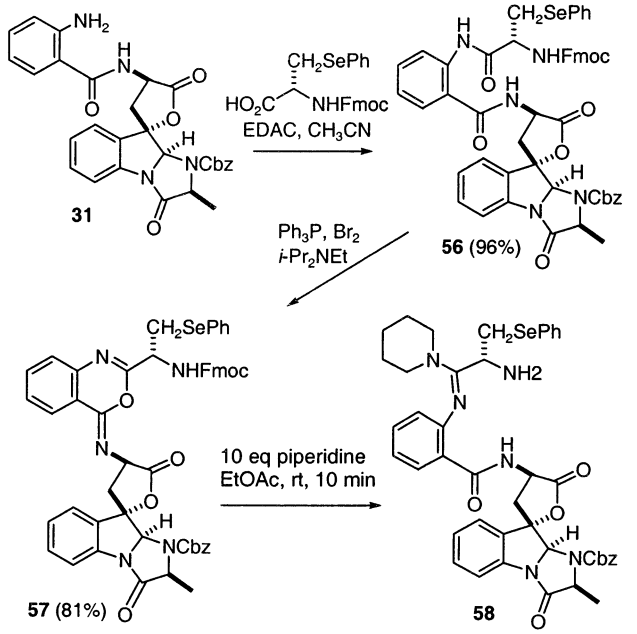


52 with Ph_3P, Br_2, and Et_3N in CH_2Cl_2 afforded 77% of the iminobenzoxazine. Deprotection of the Fmoc group and ring opening of the iminobenzoxazine with piperidine gave the amidine, which was refluxed in CH_3CN to afford 70% of Cbz-fumiquinazoline I (**53**) and 10% of the impure C-14 epimer corresponding to **49a**. Hydrogenolysis of **53** afforded 96% of fumiquinazoline I (**9**) with spectral data identical with those reported.[2] The melting point for synthetic fumiquinazoline I, 169−171 °C, is much higher than that reported for the natural product, 116−120 °C. Similarly, the optical rotation $[\alpha]_D$ for synthetic fumiquinazoline I, −222, is larger than that for the natural product, −138, suggesting that the natural product is contaminated with minor impurities.

Fumiquinazolines C and E. Fumiquinazolines C (**7**), E (**3**), and H (**8**) present an additional challenge since they are more highly oxidized with a methoxy group at C-3 in fumiquinazoline E, and a seven-membered ring formed between C-3 and the oxygen on C-17 in fumiquinazolines C and H. Fumiquinazolines C and E are probably biosynthesized by oxidation of fumiquinazoline A (**1**) or B (**2**) to form dehydrofumiquinazoline A/B (**54a**) (Scheme 8). Protonation and cyclization of **54a** will give fumiquinazoline C (**7**), while protonation and reaction of **54a** with MeOH will give fumiquinazoline E (**3**). This reaction can also be accomplished chemically. Oxidation of fumiquinazoline G (**5**) with one batch of excess activated MnO_2 for several days gave 80% of dehydrofumiquinazoline F/G.[4] However, this reaction could not be repeated with other batches of activated MnO_2. Wang and Sim recently reported the oxidation of the C-3 position of the related fused quinazolinone verrucine B in DMSO-d_6 during storage to introduce an alcohol at C-3 in low yield.[23,24]

Our scheme can be easily modified in the later steps by using FmocNHCH(CH_2X)CO_2H instead of Fmoc-alanine to prepare **55**, in which X is any group that can be eliminated to give Cbz-dehydrofumiquinazoline A/B (**54b**). A variety of dehydroalanine precursors have been developed including *O*-acetylserine,[25] *O*-tosylserine,[26] and *S*-methylcysteine,[27] which has been used by Hart and

SCHEME 9



Magomedov for the syntheses of dehydrofumiquinazoline F/G and alantrypinone.[10] Oxidation of *ent*-16-methylthiofumiquinazoline G with *m*-CPBA provided a 3:2 mixture of diastereomeric sulfoxides, which underwent elimination upon refluxing in benzene in the presence of Ph_3P for 18 h.[10]

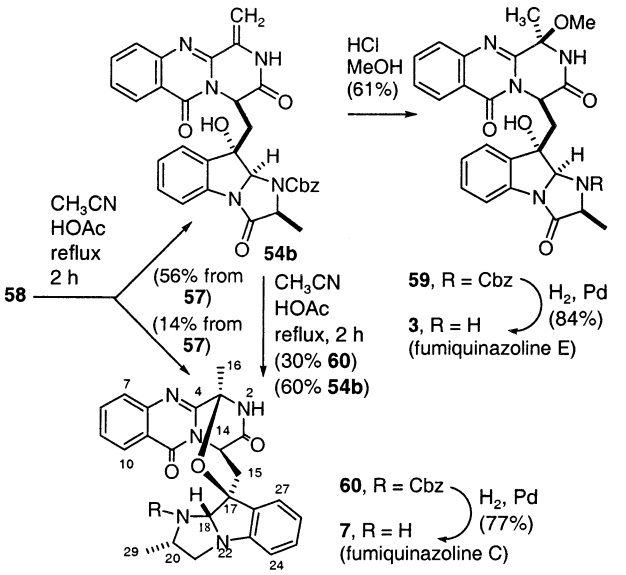
More recently, van der Donk developed Fmoc-L-NHCH(CH_2SePh)CO_2H as a dehydroalanine precursor.[28] Oxidation of a $PhSeCH_2$-containing peptide with $NaIO_4$ in aqueous THF at 25 °C gave the selenoxide, which underwent facile elimination of PhSeOH to give a dehydroalanine-containing peptide in high yield. This method was particularly appealing because these conditions are so mild.

Reaction of **31** with Fmoc-L-NHCH(CH_2SePh)CO_2H and EDAC in CH_3CN afforded 96% of diamide **56** (Scheme 9). Dehydrative cyclization of **56** with Ph_3P, Br_2 and *i*-Pr_2NEt provided 81% of iminobenzoxazine **57**. Treatment of **57** with 5 equiv of piperidine in EtOAc at 25 °C for 10 min cleaved the Fmoc group and opened the iminobenzoxazine to give amidine **58**, which still contained the phenylselenyl group.

Refluxing **58** in CH_3CN containing 5 equiv of acetic acid[29] for 2 h gave 56% of Cbz-dehydrofumiquinazoline A/B (**54b**) containing 6% of the inseparable C-14 epimer and 14% of Cbz-fumiquinazoline C (**60**) (Scheme 10).

(23) Wang, H.; Sim, M. M. *J. Nat. Prod.* **2001**, *64*, 1497−1501.
(24) Attempted oxidation of **48a** or **48b** with either MnO_2 or DDQ was unsuccessful.
(25) Chai, C. L. L.; King, A. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1173−1182.
(26) Kwon, O. S.; Park, S. H.; Yun, B.-S.; Pyun, Y. R.; Kim, C.-J. *J. Antibiot.* **2000**, *53*, 954−958.
(27) (a) Miao, Z.; Tam, J. P. *Org. Lett.* **2000**, *2*, 3711−3713. (b) Burrage, S. A.; Raynham, T.; Bradley, M. *Tetrahedron Lett.* **1998**, *39*, 2831−2834.
(28) (a) Okeley, N. M.; Zhu, Y.; van der Donk, W. A. *Org. Lett.* **2000**, *2*, 3603−3606. (b) Gieselman, M. D.; Xie, L.; van der Donk, W. A. *Org. Lett.* **2001**, *3*, 1331−1334.
(29) Model studies in a simpler system in which the bottom side chain was benzyl (from phenylalanine) established that in the absence of acetic acid the piperidine adds conjugatively to the dehydrofumiquinazoline to give about 10% of the product with the $C_5H_{10}NCH_2$ group at C-3 trans to the benzyl group at C-14. Addition of acetic acid both suppresses this reaction and minimizes epimerization at C-14. Cyclization to give **60** occurs even without the acetic acid. Refluxing amidine **58** in CH_3CN without acetic acid for 2 h yields **54b** in 33% yield with 15% of the C-14 epimer, 7% of **60**, and 4% of the cyclic ether from the C-14 epimer.

SCHEME 10

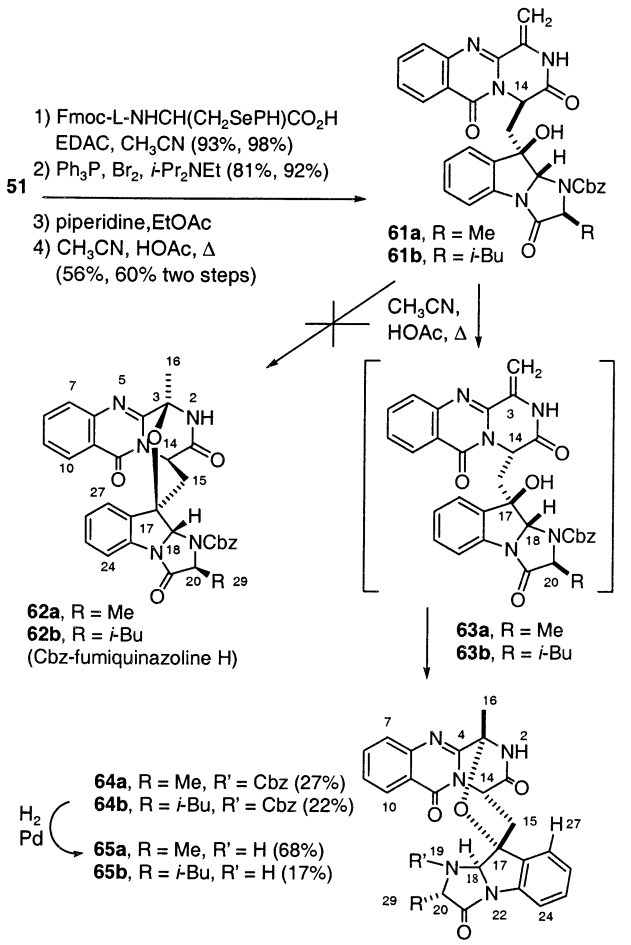


Under these reaction conditions, amidine **58** underwent four sequential reactions. The amidine amide cyclized to form the quinazolinone by losing one molecule of piperidine. The amine lactone reacted to give the piperazine. At this point, benzeneselenol was eliminated to give **54b** without the need for oxidation to the selenoxide, although we cannot exclude the possibility of adventitious oxidation during the reaction. Finally, the double bond of **54b** was protonated to give a cation that reacted with the OH group at C-17 to form the seven-membered ether ring of Cbz-fumiquinazoline C (**60**). Further heating of **54b** in 100:1 CH_3CN/HOAc at reflux for 2 h afforded 30% of **60** and 60% of recovered **54b**, which could be recycled. Slow decomposition occurred on longer heating, so that reaction for 12 h consumed all **54b** but gave only 40−50% of **60**.

We briefly examined the use of Fmoc-*S*-methylcysteine to prepare **54b**. Reaction with **31**, dehydrative cyclization, ring opening with piperidine, and heating in CH_3CN gave only 12% of Cbz-dehydrofumiquinazoline A/B (**54b**) and 23% of the *S*-methyl precursor. Isomerization of the iminobenzoxazine using (Me_3AlSPh)Li as described by Hart gave only 12% of the *S*-methyl precursor.[10] The low yields in this sequence appear to be due to interference with the complex bottom half since we can repeat Hart's synthesis of dehydrofumiquinazoline F/G from Fmoc-*S*-methylcysteine using either piperidine or (Me_3AlSPh)Li to catalyze the rearrangement of the iminobenzoxazine.

Protonation of the double bond of **54b** with 0.2 M HCl in MeOH at 25 °C provided 61% of Cbz-fumiquinazoline E (**59**). Hydrogenolysis of **59** with Pd/C under 1 atm of H_2 for 30 min proceeded cleanly giving 84% of (−)-fumiquinazoline E (**3**) with spectral data, melting point, and optical rotation identical with those reported for the natural product.[1,30] Deprotection of the Cbz group of **60** with Pd/C required 4 atm of H_2 for 30 h to afford 77% of (−)-fumiquinazoline C (**7**) with spectral data, melting point, and optical rotation identical with those reported for the natural product.[1] The additional ring of **60** forces the Cbz group into a more hindered environment than the Cbz group of **59** so that hydrogenation requires longer times and higher pressures.

SCHEME 11



Fumiquinazoline H. Fumiquinazoline H (**8**) is the oxidatively cyclized product biosynthesized from fumiquinazoline I (**9**). It should be possible to prepare fumiquinazoline H (**8**) from fumiquinazoline I intermediate **51** using the same series of reactions used to convert fumiquinazoline A/B intermediate **31** to fumiquinazoline C (**7**). However, the hydrogen and hydroxyl substituents on the indoline ring in fumiquinazolines H and I are cis to the alkyl substituent on the imidazoindolone ring, rather than trans as in fumiquinazoline A. Therefore, on formation of the seven-member ring ether, the indoline is over the quinazolinone in fumiquinazoline H (**8**), while the imidazoline ring is over the quinazolinone ring in fumiquinazoline C (**7**). MM2 calculations with conformational searching indicate that the fumiquinazoline H ring system is more strained than fumiquinazoline C by about 2 kcal/mol.

Coupling aniline **51** with Fmoc-L-$NHCH(CH_2SePh)CO_2H$ using EDAC in CH_3CN gave 98% of the diamide (Scheme 11). Dehydrative cyclization provided 92% of the iminobenzoxazine, which was treated with 10 equiv of piperidine to give the crude amidine. Heating the crude

(30) We unambiguously confirmed the stereochemistry of fumiquinazoline E by NOE correlations between OMe and H-15a and OMe and H-15b. In fumiquinazoline E, the methoxy group and the C(14)−C(15) bond are cis and both axial-like on the six-membered piperazine ring which is in the boat conformation.[22] Presumably the selective formation of **59** from **54b** is a result of axial-like addition of methanol to the intermediate cation.

amidine in CH_3CN with 2 equiv of AcOH gave 60% of Cbz-dehydrofumiquinazoline I (**61b**). 17,18-Bisepi-Cbz-dehydrofumiquinazoline A/B (**61a**) was prepared by an analogous series of reactions from **43a**.

To our surprise, cyclization of **61b** by heating in 25:1 CH_3CN/HOAc was slow. After heating for 12 h, we obtained 22% of **64b**, 33% of recovered **61b** containing some C-14 epimer **63b**, and no Cbz-fumiquinazoline H (**62b**). Epimerization of **61b** at C-14 formed **63b**, which has the same relative stereochemistry as Cbz-dehydrofumiquinazoline A/B (**54b**) except at C-20. As expected, **63b** cyclized under the acidic conditions to form **64b**, which has the fumiquinazoline C ring system. Similar results were obtained in the cyclization of **61a**.

The stereochemistry of the cyclic ethers was determined by 2-D NOE studies. For fumiquinazoline C (**7**), Cbz-fumiquinazoline C (**60**), **64**, and **65**, there are NOE correlations between H-2 and H-27. In **60** and **64**, the Cbz methylene hydrogens are shifted upfield to δ 4.40−4.25 as a result of shielding by the quinazolinone ring. NOE correlations between H-2 and both H-18 and H-19 were observed for fumiquinazoline H (**8**).

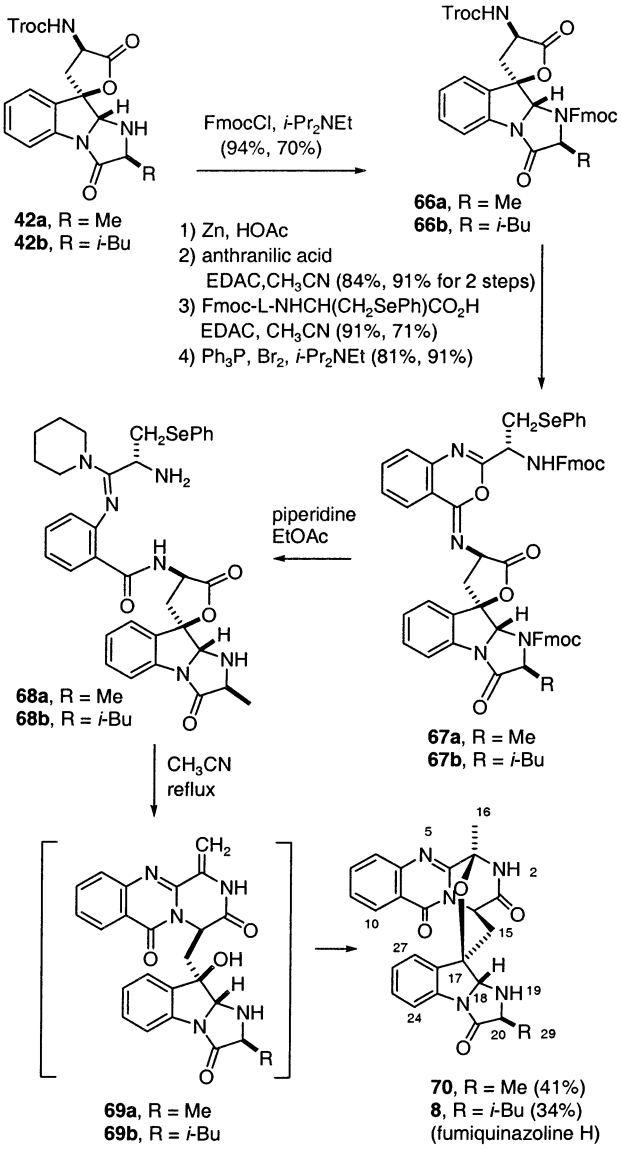
As in Cbz-fumiquinazoline C (**60**), the Cbz groups of **64a** and **64b** are forced into hindered environments. Hydrogenolysis of **64a** under 4 atm of H_2 for 24 h gave 68% of **65a**. The isobutyl group of **64b** made the Cbz group even more hindered so that hydrogenolysis under 4 atm of H_2 for 24 h yielded only 17% of **65b**.

These experiments indicated that the additional steric hindrance of the fumiquinazoline H ring system prevented the cyclization of **61a** and **61b** to give **62a** and **62b**. Facile epimerization at C-14[1] led to intermediate **63**, which cyclized readily to give **64** with the fumiquinazoline C ring system. MM2 calculations indicated that Cbz-fumiquinazoline H (**62b**) is also 2 kcal/mol more strained than Cbz-fumiquinazoline C (**60**). Even though the Cbz group does not appear to affect the relative stability, examination of models indicated that it severely hinders the approach of the hydroxy group to a cation at C-3 to form the fumiquinazoline H ring system. Finally, the isobutyl group of **64b** retarded hydrogenolysis, suggesting that even if we could obtain Cbz-fumiquinazoline H, deprotection would be difficult.

Nature does cyclize dehydrofumiquinazoline I (**69b**) to fumiquinazoline H (**8**). Therefore, we decided to adapt our route to prepare unprotected dehydrofumiquinazoline I (**69b**), with the expectation that it would cyclize to fumiquinazoline H (**8**) (Scheme 12). The Cbz group of **61** cannot be cleaved in the presence of the double bond. We therefore decided to replace the Cbz group with an Fmoc group, which will be cleaved without an additional step during rearrangement of the iminobenzoxazine. We had already developed a route to unprotected tetracyclic lactones **36** and **42** as compounds suitable for NOE studies on the stereochemistry of the Cbz-lactones **37** and **43**.

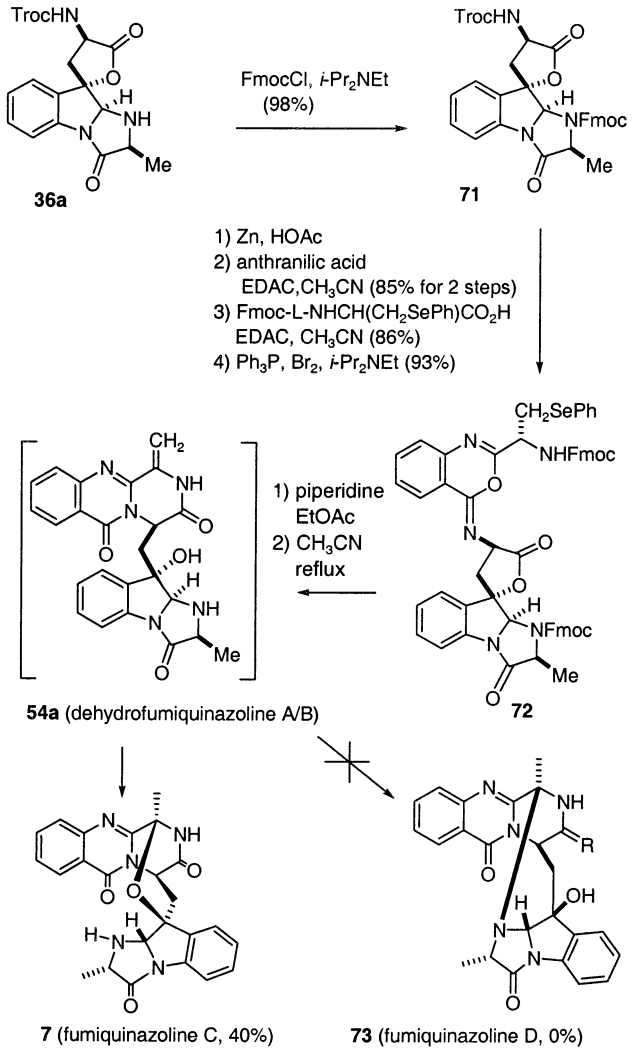
Hydrogenolysis of **41b** with Pd/C under 1 atm of H_2 for 30 min followed by lactonization with silica gel in CH_2Cl_2 gave 65% of **42b**. Reaction of **42b** with 5 equiv of FmocCl and *i*-Pr_2NEt for 24 h afforded 70% of **66b** and 25% of recovered **42b**. Acylation of the secondary amine of **42b** is hindered by the bulky isobutyl group. The yields of **42a** (84%) and **66a** (94%) in the methyl series are much higher. Reductive removal of the Troc group with Zn in

SCHEME 12



acetic acid gave the free amine, which was coupled with anthranilic acid and EDAC to afford 91% of the aniline, which was coupled with Fmoc-L-NHCH(CH_2SePh)CO_2H to give the diamide in 71% yield. Dehydrative cyclization with Ph_3P, Br_2, and *i*-Pr_2NEt yielded 71% of the desired iminobenzoxazine **67b**. Treatment of **67b** with 10 equiv of piperidine in EtOAc for 10 min cleaved both Fmoc groups and opened the iminobenzoxazine to give the crude amidine **68b**. Heating crude **68b** in CH_3CN at reflux for 1 h effected ring closure of the amidine to the quinazolinone, formation of the piperazine ring, and elimination of benzeneselenol to give the dehydrofumiquinazoline I analogue (**69b**). In the absence of the bulky Cbz group, cyclization proceeded spontaneously to give 34% of fumiquinazoline H (**8**) with spectral data, melting point, and optical rotation identical with those reported for the natural product.[1] The conversion of **67b** to **8** involved seven distinct chemical steps! Conversion of **66a** to **70** proceeded analogously in the yields indicated. Adding acetic acid to the refluxing solution of **68b** in CH_3CN, which is desirable in all the other amidine cyclizations, prevented the formation of fumiquinazoline

SCHEME 13

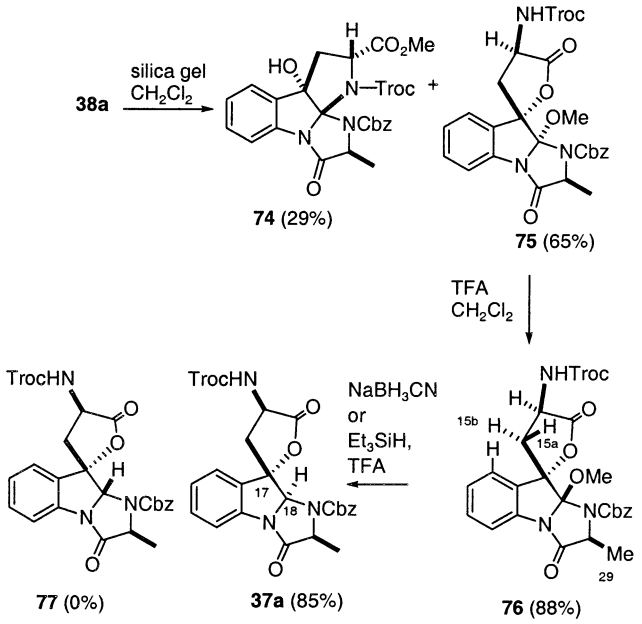


H (**8**) and gave a complex mixture of products. Presumably the secondary amine is protonated, making it hard to form the cation at C-3 needed for formation of the cyclic ether.

Fumiquinazoline D (**73**),[1] which has a bridge from the imidazolinone nitrogen to C-3, is now the only unsynthesized member of this family. We were not optimistic about preparing it by cyclization of its biogenetic precursor dehydrofumiquinazoline A/B (**54a**) since this would require the preparation of a cation at C-3 by protonation of the double bond without protonation of the amine. Nevertheless, we investigated this cyclization since the requisite iminobenzoxazine **72** can be prepared easily from **36a** analogously to the preparation of **67**. Treatment of iminobenzoxazine **72** with 10 equiv of piperidine in EtOAc for 10 min and then heating the resulting amidine at reflux in CH_3CN for 1.5 h afforded **54a**, which cyclized to give 40% of fumiquinazoline C (**7**) and no fumiquinazoline D (**73**) (Scheme 13).

Approaches to Fiscalin A. Fiscalin A (**10**)[3] and fumiquinazoline A (**1**)[1] have very similar structures, differing only in the substituent on the top of the piperazine ring and more significantly in the stereochemistry of the hydrogen on C-18, which is trans to the hydroxyl group on C-17 of the indoline ring in fiscalin A, rather than cis

SCHEME 14



as in fumiquinazoline A. We envisioned that fiscalin A could be prepared by reduction of **38a** from the opposite face to give **77** rather than fumiquinazoline A intermediate **37a**.

Treatment of **38a** with silica gel in CH_2Cl_2 for 24 h at room temperature gave the α-methoxy lactone **75** in 65% yield and the more polar triamide derivative **74** in 29% yield (Scheme 14). Treatment of **75** with TFA in CH_2Cl_2 gave 88% of the apparently more stable *β*-methoxy lactone **76** and 8% of the analogous alcohol. The structure of **76** was confirmed by NOEs between the methoxy group and both H-29 and H-15a. Reduction of **76** with either $NaBH_3CN$ at pH 3 or Et_3SiH[31] and TFA gave **37a** and none of the desired product **77**. Both isomerization of **75** to **76** and reduction of **76** to **37a** occur through a common cation intermediate formed by loss of methanol. Apparently kinetically controlled addition of hydride occurs from the α-face, while reversible addition of methanol eventually gives the more stable isomer **76** with a *β*-methoxy group.

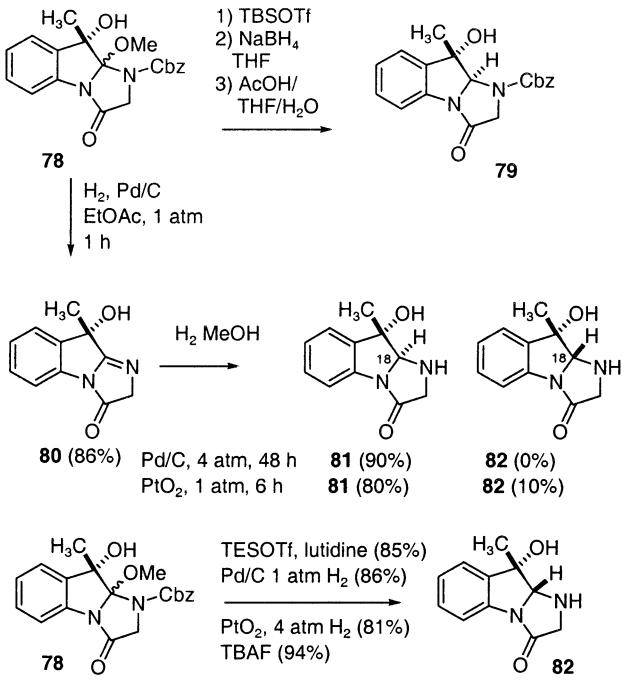
In his synthesis of tryptoquivaline G, Büchi reported that reduction of a substrate related to **76** gave a 1:1 mixture of stereoisomers.[21b] However, Büchi's substrate had the nitrogen on the opposite face of the lactone and already fully elaborated into a quinazolinone. In our case, the TrocNH group may block delivery of the hydride from the top face. We therefore tried to use the nitrogen to direct the reduction from the top face via an amine borane complex.[32] Reductive cleavage of the Troc group of **76** gave the free amine, which was treated with borane−THF to give the borane amine complex.[33] Unfortunately no reduction occurred. Use of chlorodimethylsilane was also unsuccessful. A variety of other ap-

(31) Sternbach, D. D.; Jamison, W. C. L. *Tetrahedron Lett.* **1981**, *22*, 3331−3334.

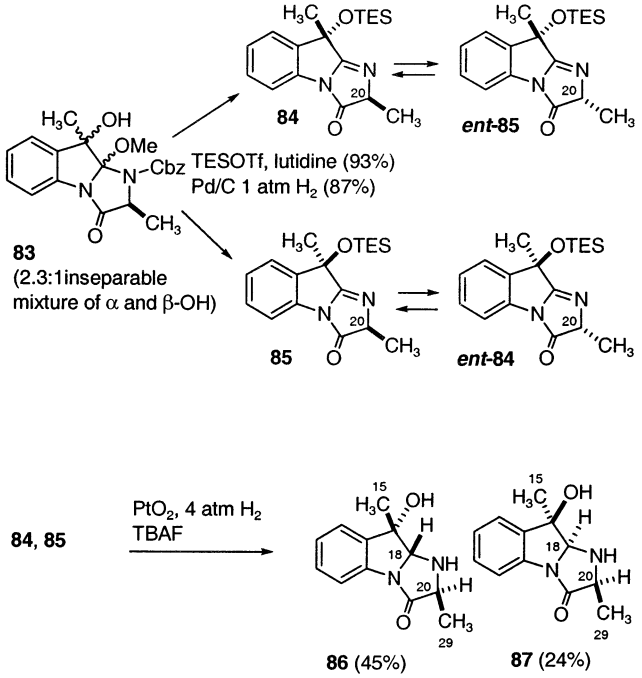
(32) (a) Hutchins, R. O.; Learn, K.; Nazer, B.; Pytlewski, D.; Pelter, A. *Org. Prep. Proc.* **1984**, *16*, 335−371. (b) Berger, J. G.; Teller, S. R.; Adams, C. D.; Guggenberger, L. J. *Tetrahedron Lett.* **1975**, 1807−1810.

(33) (a) Tamao, K.; Nakagawa, Y.; Ito, Y. *J. Org. Chem.* **1990**, *55*, 3438−3439. (b) Tamao, K.; Nakagawa, Y.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 218−221.

SCHEME 15



SCHEME 16



proaches were unsuccessful so we decided to examine reduction in a simple model system.

Model **78** was prepared from glycine and 3-methylindole analogously to **22b** (Scheme 15).[11] To prevent attack from the bottom face, the alcohol was protected with TBS triflate to give the TBS silyl ether, which was treated with $NaBH_4$ in THF to give the crude reduction product. To facilitate analysis, the TBS group was deprotected to give only the undesired stereoisomer **79** in 81% yield and none of the desired diastereomer with a β-hydrogen. Treatment of **78** with Et_3SiH[31] and TFA gave only **79** after deprotection. Apparently, the directed reduction by $NaBH(OAc)_3$ proceeding through **23** is not critical for the formation of **37a** or **79** with the hydrogen and hydroxy groups cis. This isomer is formed from all successful reductions that we examined.

We then decided to remove the Cbz group and explore the reduction of the free secondary amine. Hydrogenolytic removal of the Cbz group of **78** with Pd/C (1 atm of H_2, 2 h) gave the unstable amine, which lost methanol to afford imine **80** in 86% yield. More vigorous hydrogenation of **80** with Pd/C (4 atm of H_2, 48 h) in MeOH afforded 90% of reduction product **81** and none of the desired isomer **82**. Hydrogenation of **80** with PtO_2 under 1 atm of hydrogen in MeOH for 6 h afforded 80% of **81** and 10% of **82**.[34] There is an NOE between H-18 and the methyl group in **82**, but not **81**. Although the yield of **82** was still unacceptable, its formation as even a minor component was encouraging.

We hoped that protecting the hydroxy group of **80** with a bulky group might improve the facial selectivity for **82**. Since it was hard to form the TBS silyl ether, we treated **78** with 3 equiv of TES triflate and 5 equiv of 2,6-lutidine in CH_2Cl_2 for 24 h to give 85% of the TES ether and 10% of recovered **78**. Hydrogenolysis of the TES ether with Pd/C in MeOH gave 86% of the TES protected imine. Hydrogenation (81%) of the TES protected imine with PtO_2 in MeOH (1 atm of H_2, 4 h) and deprotection (94%) of the TES group with TBAF in THF afforded the desired product **82** and no **81**.

We now turned to the more complete model **83** that was prepared as an inseparable 2.3:1 mixture of α- and β-alcohols.[11] Treatment of **83** with TES triflate and 2,6-lutidine gave 93% of an inseparable 2.3:1 mixture of silyl ethers (Scheme 16). Hydrogenation of the mixture with Pd/C (1 atm of H_2, 1 h) gave 87% of a 2.1:1 mixture of imines **84** and **85**. Epimerization of **84** to give *ent*-**85** and **85** to give *ent*-**84** is very facile since the enol tautomer is an aromatic hydroxy imidazole.[35] On standing in air, **84** and **85** undergo oxidation to give a mixture of isomers with both hydroxy and methyl groups on C-20.[36] It was therefore crucial to rapidly hydrogenate the mixture of **84** and **85** with excess catalyst. Hydrogenation over 0.8 equiv of PtO_2 (1 atm of H_2, 2 h) gave, after cleavage of the TES ethers with TBAF, 45% of **86** with fiscalin A stereochemistry and 25% of **87**, which is formed from the minor diastereomer of **83**. The structures were established by NOE correlations between H-15 and H-18 and H-18 and H-29 in **86**, and between H-15 and H-18 and H-18 and H-20 in **87**. The platinum-catalyzed hydrogenation occurred exclusively from the face opposite to the triethylsilyloxy group. Although this method is not ideal because of the facile epimerization of imines **84** and **85**, it appeared to provide a route to fiscalin A.

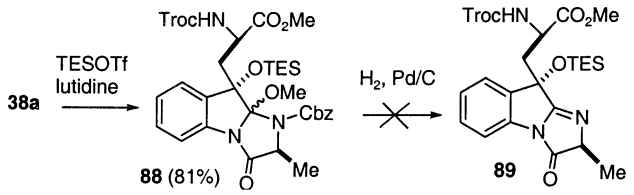
Treatment of **38a** with TES triflate and 2,6-lutidine gave 81% of the triethylsilyl ether **88** as a 65:16 mixture of β- and α-methoxy isomers (Scheme 17). Unfortunately, hydrogenolytic removal of the Cbz group of **88** with Pd/C in EtOAc or MeOH gave a complex mixture of products

(34) Griot, R. G. U.S. Patent 3609140, 1971; *Chem. Abstr.* **1971**, *75*, 151845d.

(35) Hofmann, K. *Imidazole and its Derivatives, Part 1*; Interscience: New York, 1953; pp 93−99.

(36) Campagna, F.; Carotti, A.; Casini, G. *J. Heterocycl. Chem.* **1990**, *27*, 1973−1977.

SCHEME 17



that did not appear to contain the desired imine **89**. We suspect that the TrocNH group on the side chain is participating in this reaction as in the formation of **74** from **38a**. Therefore, while we have developed a route to **86** with the appropriate stereochemistry for fiscalin A, we have been unable to apply it to a substrate suitably functionalized for elaboration to the quinazolinone ring system.

Conclusion

We have completed the first syntheses of (−)-fumiquinazolines A, B, and I, which proceed in 14 steps from protected tryptophan, anthranilic acid, leucine, and alanine in 7% overall yield making this family of compounds and a wide variety of analogues readily available. Oxidation of **30a** with saccharine-derived oxaziridine (**21**) for fumiquinazolines A and B and oxidation of **30b** with dimethyldioxirane for fumiquinazoline I selectively formed the appropriate imidazoindolone stereoisomers. We have also completed efficient 14-step syntheses of (−)-fumiquinazolines C (**7**) and E (**3**) and a 15-step synthesis of (−)-fumiquinazoline H (**8**) using FmocNHCH(CH_2SePh)-CO_2H as a dehydroalanine precursor that spontaneously eliminated benzeneselenol without oxidation under the cyclization conditions. We have successfully prepared model **86** for fiscalins A with the H and OH anti to each other, but the procedure that worked for the model failed with the fully functionalized side chain.

Experimental Section

General. NMR spectra were recorded in $CDCl_3$ at 400 MHz. Chemical shifts are reported in δ, coupling constants are reported in Hz, and IR data are reported in cm^{-1}.

***N*$_\alpha$-2,2,2-Trichloroethoxycarbonyl-D-tryptophan Methyl Ester (26).** To a mixture of $NaHCO_3$ (0.84 g, 10 mmol) and 10% aqueous $NaHCO_3$ solution (10 mL) and ether (10 mL) at 0 °C was added D-tryptophan methyl ester hydrochloride (2.55 g, 10 mmol) in several portions over 10 min. A solution of 2,2,2-trichloroethyl chloroformate (2.12 g, 10 mmol) in 10 mL of ether was then added dropwise over 1 h. The reaction mixture was stirred at room temperature for 4 h, and the ether layer was separated. The aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography of the residue on silica (ether) gave 3.78 g (96%) of pure **26** as a white foamy solid: mp 48−54 °C; $[\alpha]_D$ −38.9 (*c* 0.36, $CHCl_3$); ^{1}H NMR 8.10 (br s, 1, NH), 7.55 (d, 1, J = 8.0), 7.36 (d, 1, J = 8.0), 7.20 (dd, 1, J = 8.0, 7.3), 7.13 (dd, 1, J = 8.0 7.3), 7.10 (d, 1, J = 2.4), 5.56 (br d, 1, J = 7.9, NH), 4.80 (d, 1, J = 12.2), 4.75 (dt, 1, J = 7.9, 5.5), 4.65 (d, 1, J = 12.2), 3.70 (s, 3), 3.35 (d, 2, J = 5.5); ^{13}C NMR 171.8, 153.9, 136.1, 127.4, 122.9, 122.3, 119.8, 118.6, 111.2, 109.6, 95.4, 74.6, 54.7, 52.5, 27.9; IR (KBr) 3405 (br, NH), 1735, 1726.

***N*$_{in}$-L-Cbz-alanyl-*N*$_\alpha$-2,2,2-trichloroethoxycarbonyl-D-tryptophan Methyl Ester (28a).** BH_3·THF in THF (1 M, 17 mmol) was added dropwise to a solution of indole **26** (3.33 g, 8.4 mmol) in trifluoroacetic acid (17 mL) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h and concentrated under reduced pressure. The residue was dissolved in EtOAc (50 mL), which was washed with saturated $NaHCO_3$, dried (Na_2SO_4), and evaporated to give 2.99 g (90%) of the foamy indoline.

DCC (1.57 g, 7.6 mmol) was added to a solution of *N*-Cbz-L-alanine (1.70 g, 7.6 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 5 min, and a solution of crude indoline in CH_2Cl_2 (5 mL) was added. The resulting mixture was stirred at room temperature for 20 min. The insoluble byproduct was filtered off and the filtrate was evaporated at reduced pressure to give the amide as a colorless oil. The oil was dissolved in toluene (25 mL) and DDQ (1.36 g, 6.0 mmol) was added. The resulting black-red mixture was heated at 110 °C for 1 h, and additional DDQ (0.68 g, 3.0 mmol) was added. The mixture was stirred at 110 °C for 1 h and cooled and filtered. The filtrate was washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated to give a black-red oil. Flash chromatography on silica gel (50:1 CH_2Cl_2/EtOAc) gave 3.53 g (78%) of **28a** as a foamy solid.

Alternatively, **28a** can be prepared as following. To a solution of **26** (1.32 g, 3.35 mmol) in CH_3CN (8 mL) was added *p*-nitrophenyl *N*-Cbz-L-alanine (**27a**) (1.73 g, 5.0 mmol), 18-crown-6 (0.884 g, 3.35 mmol), anhydrous KF (0.39 g, 6.7 mmol), and (*i*-Pr)$_2$NEt (0.59 mL, 3.35 mmol). The reaction mixture was sonicated for 30 min and then stirred at room temperature for 24 h. The reaction mixture was diluted with EtOAc (50 mL) and filtered through a pad of Celite, which was washed with EtOAc. The combined EtOAc solution was concentrated under reduced pressure. Flash chromatography on silica gel (5:1 hexane/EtOAc) gave 1.82 g of **28a** (91%) as a white solid: mp 63−67 °C; $[\alpha]_D$ −54.0 (*c* 0.53, $CHCl_3$); ^{1}H NMR 8.43 (d, 1, J = 8.0), 7.52 (d, 1, J = 8.0), 7.43−7.32 (m, 7), 7.32 (td, 1, J = 8.0, 1.0), 5.70 (br d, 1, J = 7.4, NH), 5.65 (br d, 1, J = 7.9, NH), 5.16 (d, 1, J = 12.2), 5.12 (d, 1, J = 12.2), 5.12 (q, 1, J = 6.7), 4.80 (d, 1, J = 12.2), 4.79−4.72 (m, 1), 4.67 (d, 1, J = 12.2), 3.74 (s, 3), 3.33 (dd, 1, J = 15.3, 6.1), 3.26 (dd, 1, J = 15.3, 5.5), 1.55 (d, 3, J = 6.7); ^{13}C NMR 171.3, 170.9, 155.5, 153.8, 136.1, 136.0, 130.4, 128.5 (2 C), 128.2 (2 C), 128.1, 125.9, 124.3, 122.4, 118.8, 117.8, 116.9, 95.2, 74.6, 67.1, 53.9, 52.8, 49.4, 27.9, 19.6; IR (KBr) 3347 (br, NH), 1720, 1701; HRMS (FAB, DCM/NBA) calcd for $C_{26}H_{26}Cl_3N_3O_7Na^+$ (MNa^+) 620.0734, found 620.0714.

***N*$_{in}$-L-Cbz-leucyl-*N*$_\alpha$-2,2,2-trichloroethoxycarbonyl-D-tryptophan Methyl Ester (28b).** Reduction of indole **26** (3.33 g, 8.4 mmol) as described above gave 2.93 g (92%) of the foamy solid indoline.

DCC (1.55 g, 7.5 mmol) was added to a solution of *N*-Cbz-L-leucine (1.99 g, 7.5 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 5 min, and a solution of crude indoline in CH_2Cl_2 (5 mL) was added. The resulting mixture was stirred at room temperature for 20 min. The insoluble byproduct was filtered off and the filtrate was evaporated at reduced pressure to give the amide as a colorless oil. The oil was dissolved in toluene (25 mL) and DDQ (1.36 g, 6.0 mmol) was added. The resulting black-red mixture was heated at 110 °C for 1 h and additional DDQ (0.68 g, 3.0 mmol) was added. The mixture was stirred at 110 °C for 1 h, cooled, and filtered. The filtrate was washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated to give a black-red oil. Flash chromatography on silica gel (50:1 CH_2Cl_2/EtOAc) gave 3.64 g (77%) of **28b** as a foamy solid.

Alternatively **28b** can be prepared as follows. To a solution of **26** (1.60 g, 4.0 mmol) in CH_3CN (10 mL) was added *p*-nitrophenyl *N*-Cbz-leucine (**27b**) (2.31 g, 6.0 mmol), 18-crown-6 (1.06 g, 4.0 mmol), anhydrous KF (0.46 g, 8.0 mmol), and (*i*-Pr)$_2$NEt (0.70 mL, 4.0 mmol). The reaction mixture was sonicated for 30 min and then stirred at room temperature for 60 h. The reaction mixture was diluted with EtOAc and filtered through a pad of Celite, which was washed with EtOAc. The combined EtOAc solution was concentrated under reduced pressure. Flash chromatography on silica gel (9:1

hexane/EtOAc) gave 2.47 g of **28b** (95%) as a white solid: mp 63−66 °C; $[\alpha]_D$ −52.0 (*c* 0.22, $CHCl_3$); ^{1}H NMR 8.43 (d, 1, *J* = 8.0), 7.53 (d, 1, *J* = 8.0), 7.43 (s, 1), 7.41−7.28 (m, 7), 5.66 (br d, 1, *J* = 7.9, NH), 5.48 (br d, 1, *J* = 9.2, NH), 5.15 (d, 1, *J* = 12.2), 5.13 (m, 1), 5.10 (d, 1, *J* = 12.2), 4.80 (m, 1), 4.74 (br s, 2), 3.74 (s, 3), 3.33 (dd, 1, *J* = 15.1, 6.3), 3.28 (dd, 1, *J* = 15.1, 5.5), 1.80 (m, 1), 1.69 (m, 2), 1.08 (d, 3, *J* = 6.7), 0.94 (d, 3, *J* = 6.7); ^{13}C NMR 171.3, 171.2, 156.1, 153.9, 136.03, 135.95, 130.4, 128.5 (2 C), 128.2, 128.0 (2 C), 125.8, 124.2, 122.5, 118.8, 117.7, 116.9, 95.2, 74.6, 67.2, 54.0, 52.7, 52.0, 42.5, 27.8, 24.8, 23.1, 21.8; IR (KBr) 3336 (br, NH), 1720, 1702; HRMS (FAB, DCM/NBA) calcd for $C_{29}H_{32}Cl_3N_3O_7Na^+$ (MNa^+) 662.1204, found 662.1178.

***N*$_{in}$-L-Cbz-alanyl-2-*N*$_\alpha$-2,2,2-trichloroethoxycarbonyl-2-iodo-D-tryptophan Methyl Ester (29a).** To a solution of **28a** (1.20 g, 2.0 mmol) in dry CH_2Cl_2 (15 mL) was added Hg(OTFA)$_2$ (1.10 g, 2.6 mmol). The solution was stirred at room temperature for 20 min, washed with aqueous saturated KI solution, dried (Na_2SO_4), filtered, and treated with iodine (760 mg, 3.0 mmol) in one portion. The resulting mixture was stirred at room temperature for 3 h. The red precipitate was filtered off and the filtrate was washed with aqueous $Na_2S_2O_3$, dried (Na_2SO_4), and evaporated to give a yellow oil. Flash chromatography on silica gel (100:1 CH_2Cl_2/EtOAc) gave 115 mg (10%) of recovered **28a** preceded by 1.23 g (85%) of iodoindole **29a** as a light yellow solid: mp 67−70 °C; $[\alpha]_D$ −18.5 (*c* 0.45, $CHCl_3$); ^{1}H NMR 8.01 (d, 1, *J* = 7.9), 7.59 (dd, 1, *J* = 7.9, 1.0), 7.40−7.25 (m, 7), 5.85 (dq, 1, *J* = 7.9, 6.7), 5.70 (br d, 1, *J* = 7.9, NH), 5.68 (br d, 1, *J* = 6.7, NH), 5.18 (d, 1, *J* = 12.2), 5.14 (d, 1, *J* = 12.2), 4.75 (q, 1, *J* = 6.7), 4.71 (d, 1, *J* = 11.6), 4.64 (d, 1, *J* = 11.6), 3.64 (s, 3), 3.33 (dd, 1, *J* = 14.4, 6.7), 3.26 (dd, 1, *J* = 14.4, 6.7), 1.40 (d, 3, *J* = 6.7); ^{13}C NMR 174.1, 171.3, 155.7, 153.7, 138.3, 136.1, 129.6, 128.6 (2 C), 128.2 (2 C), 128.1, 126.2, 125.4, 123.6, 118.5, 114.3, 95.2, 79.6, 74.6, 67.1, 53.7, 52.9, 52.4, 31.36, 19.0; IR (KBr) 3358 (br, NH), 1725; HRMS (FAB, DCM/NBA) calcd for $C_{26}H_{25}Cl_3IN_3O_7Na^+$ (MNa^+) 745.9701, found 745.9698.

***N*$_{in}$-L-Cbz-leucyl-2-*N*$_\alpha$-2,2,2-trichloroethoxycarbonyl-2-iodo-D-tryptophan Methyl Ester (29b).** To a solution of **28b** (1.92 g, 3.0 mmol) in dry CH_2Cl_2 (20 mL) was added Hg(OTFA)$_2$ (1.67 g, 3.9 mmol). The solution was stirred at room temperature for 20 min, washed with aqueous saturated KI solution, dried (Na_2SO_4), filtered, and treated with iodine (1.27 g, 5.0 mmol) in one portion. The resulting mixture was stirred at room temperature for 3 h. The red precipitate was filtered off and the filtrate was washed with aqueous $Na_2S_2O_3$, dried (Na_2SO_4), and evaporated to give a yellow oil. Flash chromatography on silica gel (100:1 CH_2Cl_2/EtOAc) gave 192 mg (10%) of recovered **28b** preceded by 1.95 g (85%) of iodoindole **29b** as a light yellow solid: mp 64−69 °C; $[\alpha]_D$ −13.2 (*c* 0.20, $CHCl_3$); ^{1}H NMR 8.05 (d, 1, *J* = 7.9), 7.57 (d, 1, *J* = 7.9), 7.40−7.22 (m, 7), 5.87 (m, 1), 5.79 (br d, 1, *J* = 8.5, NH), 5.64 (br d, 1, *J* = 9.2, NH), 5.18 (d, 1, *J* = 12.2), 5.15 (d, 1, *J* = 12.2), 4.76 (m, 1), 4.71 (d, 1, *J* = 11.6), 4.65 (d, 1, *J* = 11.6), 3.66 (s, 3), 3.33 (dd, 1, *J* = 14.4, 6.7), 3.26 (dd, 1, *J* = 14.4, 6.7), 1.79−1.65 (m, 1), 1.57−1.47 (m, 1), 1.47−1.37 (m, 1), 0.94 (d, 3, *J* = 6.7), 0.81 (d, 3, *J* = 6.7); ^{13}C NMR 174.7, 171.3, 156.2, 153.7, 138.2, 136.0, 129.5, 128.5 (2 C), 128.2, 128.0 (2 C), 125.8, 125.2, 123.4, 118.4, 113.9, 95.1, 79.7, 74.5, 67.1, 55.3, 53.6, 52.8, 42.1, 31.2, 24.9, 22.9, 21.6; IR (KBr) 3365 (br, NH), 1720; HRMS (FAB, DCM/NBA) calcd for $C_{29}H_{31}Cl_3N_3O_7Na^+$ (MNa^+) 788.0170, found 788.0190.

Methyl (α*R*,2*S*)-2,3-Dihydro-2-methyl-3-oxo-1-[(phenylmethoxy)carbonyl]-α-[[(2,2,2-trichloroethoxy)carbonyl]amino]-1*H*-imidazo(1,2-*a*)indole-9-propanoate (30a). To a solution of **29a** (725 mg, 1.0 mmol) in dry toluene (5 mL) was added $Pd_2(dba)_3$ (46 mg, 0.05 mmol, 0.05 equiv), P(*o*-tolyl)$_3$ (61 mg, 0.2 mmol, 0.2 equiv), and finely ground anhydrous K_2CO_3 (414 mg, 3.0 mmol, 3 equiv). The mixture was vigorously stirred and heated under N_2 at 105 °C for 1 h. Additional $Pd_2(dba)_3$ (46 mg, 0.05 mmol, 0.05 equiv) and P(*o*-tolyl)$_3$ (61 mg, 0.2 mmol, 0.2 equiv) were added and the mixture was heated at 105 °C for an additional hour. The solution was cooled and filtered, and the filtrate was evaporated at reduced pressure to give a red oil. Flash chromatography on silica gel (CH_2Cl_2) gave 80 mg (11%) of the deiodinated indole **28a** preceded by 382 mg (64%) of **30a** as a light yellow solid: mp 53−57 °C; $[\alpha]_D$ −20.4 (*c* 0.42, $CHCl_3$); ^{1}H NMR 7.89 (d, 1, *J* = 8.0), 7.52 (d, 1, *J* = 8.0), 7.37−7.46 (m, 5), 7.33 (td, 1, *J* = 8.0, 1.0), 7.27 (td, 1, *J* = 8.0, 1.0), 5.38 (d, 1, *J* = 12.8), 5.33 (d, 1, *J* = 12.8), 4.77 (q, 1, *J* = 6.7), 4.70 (d, 1, *J* = 12.2), 4.57 (d, 1, *J* = 12.2), 4.69−4.43 (m, 1), 3.80−3.59 (m, 1), 3.70 (s, 3), 3.43−3.26 (m, 1), 1.67 (d, 3, *J* = 6.7); ^{13}C NMR 171.9, 165.6, 154.1, 151.3, 136.4, 134.7, 129.0 (2 C), 128.9 (2 C), 128.6, 126.9, 125.1, 123.7, 118.6, 118.5, 113.2, 95.40, 95.37, 74.5, 69.0, 62.6, 54.3, 52.4, 26.4, 17.4; IR (KBr) 3352, 1730 (br), 1630. Anal. Calcd for $C_{26}H_{24}Cl_3N_3O_7$: C, 52.32; H, 4.05; N, 7.04. Found: C, 51.81; H, 3.90; N, 6.79.

Methyl (α*R*,2*S*)-2,3-Dihydro-2-(2-methylpropyl)-3-oxo-1-[(phenylmethoxy)carbonyl]-α-[[(2,2,2-trichloroethoxy)carbonyl]amino]-1*H*-imidazo(1,2-*a*)indole-9-propanoate (30b). To a solution of **29b** (767 mg, 1.0 mmol) in dry toluene (5 mL) was added $Pd_2(dba)_3$ (46 mg, 0.05 mmol, 0.05 equiv), P(*o*-tolyl)$_3$ (61 mg, 0.2 mmol, 0.2 equiv), and finely ground anhydrous K_2CO_3 (414 mg, 3.0 mmol, 3 equiv). The mixture was vigorously stirred and heated under N_2 at 105 °C for 1 h. Additional $Pd_2(dba)_3$ (46 mg, 0.05 mmol, 0.05 equiv) and P(*o*-tolyl)$_3$ (61 mg, 0.2 mmol, 0.2 equiv) were added and the mixture was heated at 105 °C for an additional hour. The solution was cooled and filtered, and the filtrate was evaporated at reduced pressure to give a deep-red oil. Flash chromatography on silica gel (3:1 CH_2Cl_2/hexane) gave 130 mg (17%) of the deiodinated indole **28b** preceded by 428 mg (67%) of **30b** as a light yellow solid: mp 57−60 °C; $[\alpha]_D$ −9.7 (*c* 0.20, $CHCl_3$); ^{1}H NMR 7.89 (d, 1, *J* = 8.0), 7.52 (d, 1, *J* = 8.0), 7.46−7.37 (m, 5), 7.32 (t, 1, *J* = 8.0), 7.26 (t, 1, *J* = 8.0), 6.17 (br, 1, NH), 5.40 (d, 1, *J* = 12.8), 5.29 (d, 1, *J* = 12.8), 4.75 (m, 1), 4.63 (s, 2), 4.52 (qd, 1, *J* = 6.7, 4.3), 3.75−3.59 (m, 1), 3.70 (s, 3), 3.36−3.26 (m, 1), 2.01−1.82 (m, 3), 0.82 (d, 3, *J* = 6.7), 0.80 (d, 3, *J* = 6.7); ^{13}C NMR 171.9, 165.4, 154.2, 151.4, 136.7, 134.7, 135.5, 129.0, 128.9 (2 C), 128.8 (2 C), 126.9, 125.0, 123.6, 118.5, 113.2, 95.3 (2 C), 74.5, 69.1, 62.6, 54.4, 52.4, 39.9, 26.3, 23.9, 23.3, 21.9; IR (KBr) 3354, 1735 (br), 1630. Anal. Calcd for $C_{29}H_{30}Cl_3N_3O_7$: C, 54.52; H, 4.73; N, 6.58. Found: C, 54.66; H, 4.63; N, 6.37.

Methyl (α*R*,2*S*,9*S*)- and (α*R*,2*S*,9*R*)-2,3,9,9a-Tetrahydro-9-hydroxy-9a-methoxy-2-methyl-3-oxo-1-[(phenylmethoxy)carbonyl]-α-[[(2,2,2-trichloroethoxy)carbonyl]amino]-1*H*-imidazo(1,2-*a*)indole-9-propanoate (38a and 40a). To a solution of **30a** (382 mg, 0.64 mmol) in 4:1 MeOH/CH_2Cl_2 (5 mL) was added 7b-butyl-7b*H*-oxazirino[2,3-*b*][1,2]-benzisothiazole 3,3-dioxide (**21**) (230 mg, 0.96 mmol, 1.5 equiv). The resulting mixture was stirred at room temperature for 12 h. After removal of the solvent under reduced pressure, the mixture was purified by flash chromatography on silica gel (30:1 CH_2Cl_2/EtOAc) to give 95 mg (23%) of **40a** as a white solid followed by 268 mg (65%) of **38a** as a white solid.

Data for **38a**: mp 81−84 °C; ^{1}H NMR 7.51 (d, 1, *J* = 7.9), 7.49−7.35 (m, 6), 7.34 (t, 1, *J* = 7.9), 7.25−7.17 (m, 1), 5.88−5.79 (br, 1, NH), 5.39−5.15 (m, 2), 4.73 (d, 1, *J* = 12.2), 4.78−4.61 (m, 1), 4.67 (d, 1, *J* = 12.2), 4.53 (q, 1, *J* = 6.7), 3.62−3.48 (br, 3), 3.21−3.07 (br, 3), 2.52−2.32 (br, 1), 2.00−1.86 (br, 1), 1.67−1.56 (br, 3); ^{13}C NMR 171.7, 166.6 (br), 153.8, 152.8 (br), 137.0 (br), 135.0, 133.6, 129.7, 128.7 (3 C), 128.5 (2 C), 126.2, 125.4, 116.5, 95.2, 81.3 (br), 74.6, 68.6, 60.7 (br), 52.4, 51.1, 49.4, 37.8, 17.6, 16.7; IR (KBr) 3346, 1728, 1610.

Data for **40a**: mp 79−85 °C; ^{1}H NMR 7.53−7.31 (m, 8), 7.26−7.19 (m, 1), 6.53 (br, 1, NH), 5.75 (br, 1), 5.31 (d, 1, *J* = 12.8), 5.26 (d, 1, *J* = 12.8), 4.81 (br s, 2), 4.53 (m, 1), 3.97 (m, 1), 3.64 (s), 3.60 (s), 3.31 (br s, 3), 1.77 (br, d, *J* = 6.7), 1.72 (br d, *J* = 6.7); IR (KBr) 3453, 1735.

Tetracyclic Lactone 37a. To 2 mL of acetic acid in an ice water bath was added $NaBH_4$ (470 mg, 12.4 mmol) in several portions. The $NaBH_4$ solution in acetic acid was warmed to

25 °C and added to a solution of **38a** (260 mg, 0.41 mmol) in acetic acid (2 mL). The resulting mixture was stirred at 25 °C for 3 h. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with water, saturated $NaHCO_3$ solution, and brine, dried (Na_2SO_4), and evaporated to give a crude mixture of **39a** and lactone **37a** (233 mg). Silica gel (EM 9385, silica gel 60, 230−400 mesh, 3.0 g) was added to a solution of this mixture in CH_2Cl_2 (5 mL). The suspension was stirred at room temperature for 12 h and filtered. The filtrate was evaporated under reduced pressure to give a residue that was purified by flash chromatography on silica gel (50:1 CH_2Cl_2/EtOAc) to give 158 mg (66%) of **37a** as a white solid: mp 113−115 °C; $[\alpha]_D$ +18.4 (*c* 0.54, $CHCl_3$); ^{1}H NMR (1:1 mixture of rotamers) 7.60 (d, 1, *J* = 7.9), 7.55−7.35 (m, 6), 7.34−7.22 (m, 2), 5.96 (br s, 1), 5.69 (br, 1, NH), 5.44−5.16 (br, 2), 5.10−4.18 (m, 4), 2.74−2.05 (m, 2), 7.55 (br d, 3, *J* = 6.7); ^{13}C NMR (two rotamers, most peaks are broad, partial) 169.3, 156.0, 154.5, 131.5 (sharp), 130.1, 129.2 (sharp), 128.6 (sharp), 127.2 (sharp), 124.2, 117.1, 95.3, 84.2, 82.2, 75.2 (sharp), 69.2, 68.4, 59.4, 50.2, 36.2, 18.6, 18.3 (two quaternary carbons were not observed); IR (KBr) 3397 (br), 1800, 1734, 1608. Anal. Calcd for $C_{25}H_{22}Cl_3N_3O_7$: C, 51.52; H, 3.80; N, 7.21. Found: C, 51.53; H, 3.73, N, 7.03.

Tetracyclic Lactone 43a. To 1 mL of acetic acid in an ice water bath was added $NaBH_4$ (120 mg, 3.0 mmol) in several portions. The $NaBH_4$ solution in acetic acid was warmed to 25 °C and added to a solution of **40a** (64 mg, 0.10 mmol) in acetic acid (1 mL). The resulting mixture was stirred at 25 °C for 3 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with water, saturated $NaHCO_3$ solution, and brine, dried (Na_2SO_4), and evaporated to give crude **41a** (58 mg). To a solution of crude **41a** in CH_2Cl_2 (2 mL) was added silica gel (EM 9385, silica gel 60, 230−400 mesh, 800 mg). The suspension was stirred at room temperature for 24 h. The silica gel was filtered off and the filtrate was evaporated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (50:1 CH_2Cl_2/EtOAc) to give 41 mg (70%) of **43a** as a white solid: mp 172−175 °C; $[\alpha]_D$ +67.4 (*c* 0.52, $CHCl_3$); ^{1}H NMR (5:1 mixture of rotamers) 7.77 (d, 1, *J* = 8.0), 7.51 (d, 1, *J* = 8.0), 7.46−7.35 (m, 5), 7.28 (t, 2, *J* = 8.0), 5.95 (s, 1), 5.66 (br d, 1, *J* = 6.7, NH), 5.26 (d, 1, *J* = 12.2), 5.21 (d, 1, *J* = 12.2), 4.80 (d, 1, *J* = 12.2), 4.71 (d, 1, *J* = 12.2), 4.45 (q, 1, *J* = 6.7), 4.52−4.02 (m, 1), 2.81 (dd, 1, *J* = 13.7, 10.8), 2.26 (dd, 1, *J* = 13.7, 9.0), 1.63 (br d, 3, *J* = 6.7); ^{1}H NMR (minor rotamer, partial) 7.68 (d, 1, *J* = 7.9), 7.47 (d, 1, *J* = 7.9), 5.91 (s, 1), 5.60 (br d, 1, *J* = 6.1, NH), 5.30 (d, 1, *J* = 12.2), 5.16 (d, 1, *J* = 12.2), 4.61 (br, 1), 4.51−4.42 (br, 1), 3.93−3.81 (m, 1), 3.00−2.86 (m,1), 2.39−2.28 (m, 1), 1.59 (br d, 3, *J* = 6.7); ^{13}C NMR (major rotamer) 173.5, 169.1, 154.4, 153.8, 136.0, 135.7, 135.4, 130.8, 128.8 (2 C), 128.6, 128.4 (2 C), 127.3, 125.6, 116.2, 95.0, 89.5, 83.3, 74.8, 68.5, 59.7, 51.7, 35.1, 11.0; ^{13}C NMR (minor rotamer, partial) 129.6, 129.0, 125.1, 116.6, 89.9, 60.2, 51.3, 34.8, 16.6; IR (KBr) 3344, 1796, 1727, 1710, 1678, 1606.

Tetracyclic Lactone 36a. To a solution of **39a** (190 mg, 0.31 mmol) in methanol (5 mL) was added Pd (5%) on carbon (50 mg). The suspension was stirred at room temperature under H_2 for 30 min. The catalyst was filtered off and the filtrate was evaporated under reduced pressure to give the crude amine. To a solution of the crude amine in CH_2Cl_2 (10 mL) was added silica gel (EM 9385, silica gel 60, 230−400 mesh, 5 g). The mixture was stirred at room temperature for 12 h. Flash chromatography on silica gel (10:1 CH_2Cl_2/EtOAc) gave 110 mg (81%) of tetracyclic lactone **36a** as a white solid: mp 202−203 °C; $[\alpha]_D$ −177.2 (*c* 0.32, $CHCl_3$); ^{1}H NMR 7.61 (d, 1, *J* = 7.9, H-24), 7.42 (t, 1, *J* = 7.9, H-26), 7.26 (d, 1, *J* = 7.9, H-27), 7.21 (t, 1, *J* = 7.9, H-25), 5.87 (br d, 1, *J* = 6.7, NH, H-13), 5.70 (s, 1, H-18), 4.82 (d, 1, *J* = 12.2), 4.73 (d, 1, *J* = 12.2), 4.68 (ddd, 1, *J* = 10.0, 9.1, 6.7, H-14), 4.28 (q, 1, *J* = 6.7, H-20), 3.23 (dd, 1, *J* = 13.9, 9.1, H-15b), 2.86 (br s, 1, NH, H-19), 2.48 (dd, 1, *J* = 13.9, 10.0, H-15a), 1.34 (d, 3, *J* = 6.7, H-29); ^{13}C NMR 174.4, 172.6, 155.3, 138.7, 135.1, 132.0, 126.8, 124.8, 117.0, 96.1, 91.8, 82.7, 75.8, 59.7, 51. 7, 35.7, 19.4; a ROESY experiment showed cross-peaks between H-27 and H-14, H-27 and H-15a, H-13 and H-15b, H-13 and H-14, H-14 and H-15a, H-19 and H-15b, H-18 and H-19, H-18 and H-20, H-20 and H-29; IR (KBr) 3346 (br, NH), 1787, 1723, 1678, 1607.

Tetracyclic Lactone 42a. To a solution of **41a** (180 mg, 0.29 mmol) in methanol (2 mL) was added Pd (5%) on carbon (40 mg). The suspension was stirred at room temperature under H_2 (1 atm) for 30 min. The catalyst was filtered off and the filtrate was evaporated under reduced pressure to give the crude amine. To a solution of the crude amine in CH_2Cl_2 (10 mL) was added silica gel (EM 9385, silica gel 60, 230−400 mesh, 5 g). The mixture was stirred at room temperature for 12 h. The silica gel was filtered off and the filtrate was evaporated under reduced pressure. Flash chromatography on silica gel (5:1 CH_2Cl_2/EtOAc) gave 108 mg (84%) of tetracyclic lactone **42a** as a white solid: mp 139−141 °C; $[\alpha]_D$ −33.7 (*c* 0.32, $CHCl_3$); ^{1}H NMR 7.55 (dd, 1, *J* = 8.2, 1.2, H-24), 7.45−7.39 (m, 2, H-26, H-27), 7.26 (t, 1, *J* = 8.2, H-25), 5.72 (d, 1, *J* = 7.9, NH, H-13), 5.59 (br d, 1, *J* = 7.3, H-18), 4.78 (d, 1, *J* = 12.2), 4.75 (d, 1, *J* = 12.2), 4.72 (ddd, 1, *J* = 12.4, 8.6, 7.9, H-14), 4.05−3.96 (m, 1, H-20), 3.17 (dd, 1, *J* = 12.8, 8.6, H-15a), 2.22 (dd, 1, *J* = 12.8, 12.4, H-15b), 2.19 (br, 1, NH, H-19), 1.56 (d, 3, *J* = 6.8, H-29); ^{13}C NMR 174.9, 174.3, 155.1, 138.7, 134.5, 132.0, 127.5, 125.6, 117.4, 96.2, 92.0, 85.2, 75.8, 61.1, 52.0, 37.3, 20.6; a ROESY experiment showed cross-peaks between H-27 and H-13, H-27 and H-15b, H-13 and H-15b, H-14 and H-15a, H-18 and H-29, H-29 and H-20; IR (KBr) 3346, 1795, 1708, 1608.

Aniline 44. To a solution of **37a** (177 mg, 0.3 mmol) in acetic acid (3.0 mL) was added zinc dust (600 mg). The mixture was stirred at room temperature for 30 min. The zinc dust was filtered off and the filtrate was concentrated. The residue was dissolved in EtOAc, which was washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated under reduced pressure to give the crude amine.

To a mixture of the crude amine and EDAC (127 mg, 0.66 mmol) in MeCN (1 mL) was added anthranilic acid (82 mg, 0.6 mmol) in several portions over 60 min at room temperature with stirring. The reaction mixture was stirred for an additional 20 min, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, which was washed with water and saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated. Flash chromatography on silica gel (10:1 CH_2Cl_2/EtOAc) gave 134 mg (85%) of aniline **44** as a white solid: mp 115−118 °C; $[\alpha]_D$ +76.2 (*c* 0.32, $CHCl_3$); ^{1}H NMR 7.60 (d, 1, *J* = 7.9), 7.45 (td, 2, *J* = 7.9, 1.2), 7.42−7.20 (m, 8), 7.10 (br, 1, NH), 6.70 (d, 1, *J* = 8.0), 6.73−6.62 (m, 1), 5.90 (br, 1), 5.56 (br, 2, NH), 5.48−5.20 (br, 2), 5.08 (d, 1, *J* = 11.6), 4.58 (br, 1), 2.75 (br, 1), 2.45 (br, 1), 1.52 (br d, 3, *J* = 6.7); ^{13}C NMR 172.0, 169.0 (br, 2 C), 154.4, 149.1, 133.1, 131.1, 130.7, 128.8 (br, 3 C), 128.5 (2 C), 128.3 (br), 127.6 (br), 127.2, 127.0, 124.3 (br), 117.4, 116.6, 116.1 (br, 2 C), 89.9 (br), 84.2 (br), 68.7 (br), 59.0 (br), 48.4 (br), 36.5 (br), 17.6 (br); IR (KBr) 3361, 1795, 1726, 1642, 1612.

Diamide 45a. To a solution of **44** (105 mg, 0.2 mmol) and EDAC (84 mg, 0.44 mmol) in MeCN (1 mL) was added *N*-Fmoc-L-alanine (124 mg, 0.40 mmol). The resulting mixture was stirred at room temperature for 1.5 h and concentrated. The residue was dissolved in CH_2Cl_2, which was washed with water and saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated. Flash chromatography on silica gel gave 147 mg (89%) of **45a** as a white solid: mp 139−142 °C; $[\alpha]_D$ +59.0 (*c* 0.34, $CHCl_3$); ^{1}H NMR 11.55 (br, 1, NH), 8.64 (br d, 1, *J* = 7.9), 7.77−7.67 (m, 2), 7.67−7.53 (m, 4), 7.57−7.47 (m, 1), 7.47−7.13 (m, 13), 7.09 (br, 1, NH), 5.91 (br s, 1), 5.52 (br d, 1, *J* = 7.1, NH), 5.40−5.15 (m, 2), 5.06 (d, 1, *J* = 11.7), 4.54 (br, 1), 4.52−4.32 (br, 2), 4.36−4.13 (m, 2), 2.69−2.50 (br, 1), 2.47−2.24 (br, 1), 1.53 (br d, 3, *J* = 6.7), 1.51 (br d, 3, *J* = 6.7); ^{13}C NMR 173.5 (br), 171.2, 168.8, 168.6, 155.8, 144.0, 143.7 (2 C), 141.2 (2 C), 139.7 (br), 137.0, 133.5, 131.2, 129.0 (2 C), 128.8 (3 C), 128.0

(br), 127.7, 127.7, 127.1 (2 C), 127.08, 126.8 (br), 125.2, 125.1 (br), 124.7 (br), 124.3 (br), 123.1, 121.6, 120.0 (2 C), 119.0, 116.4 (br), 89.9, 84.2 (br), 68.8 (br), 67.1, 58.9 (br), 51.8, 48.3 (br), 47.2, 36.0, 19.0, 18.3 (br); IR (KBr) 3344 (br), 1796, 1725, 1692, 1657, 1603. Anal. Calcd for $C_{47}H_{41}N_5O_9 \cdot H_2O$: C, 67.39; H, 5.14; N, 8.36. Found: C, 67.82; H, 4.99, N, 8.27.

Diamide 45b. To a solution of **44** (184 mg, 0.35 mmol) and EDAC (147 mg, 0.77 mmol) in MeCN (2 mL) was added *N*-Fmoc-D-alanine (218 mg, 0.70 mmol). The resulting mixture was stirred at room temperature for 1.5 h and concentrated. The residue was dissolved in CH_2Cl_2, washed with water and saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated. Flash chromatography on silica gel gave 258 mg (90%) of **45b** as a white solid: mp 138−142 °C; $[\alpha]_D$ +52.6 (*c* 0.43, $CHCl_3$); ^{1}H NMR (6:1 mixture of rotamers) 11.71 (br, 1, NH), 8.65 (br d, 1, *J* = 8.0), 7.83−7.64 (m, 3), 7.63−7.44 (m, 4), 7.44−7.32 (m, 4), 7.32−7.14 (m, 8), 7.13−6.97 (m, 2), 5.83 (s, 1), 5.59 (br s, 1), 5.27−5.11 (m, 2), 5.09−4.96 (m, 1), 4.59 (br, 1), 4.54−4.37 (m, 1), 4.28−4.18 (m, 2), 4.18−4.06 (br, 1), 2.25 (br, 2), 1.53 (br, 3), 1.44 (br, 3); ^{1}H NMR (minor rotamer, partial) 11.08 (s, 1), 6.16 (br, 1), 5.40 (br, 1), 2.46 (br, 2); ^{13}C NMR (two rotamers) 173.5 (br), 171.2, 168.7 (br), 168.5, 155.9 (br), 144.3 (br, 2 C), 143.4, 141.1, 139.6 (br), 136.9 (br), 133.6, 133.3, 131.1, 128.9 (2 C), 128.8 (3 C), 128.0, 127.7 (2 C), 127.1, 127.0, 126.9, 126.8, 125.5, 125.1 (2 C), 124.3, 123.1, 121.7, 119.93, 119.86, 119.3, 116.3 (br), 89.8, 84.2, 68.8, 67.2, 58.9, 52.0, 48.1, 47.2, 35.6, 18.8, 18.2; IR (KBr) 3329 (br), 1796, 1726, 1692, 1656, 1603. Anal. Calcd for $C_{47}H_{41}N_5O_9$: C, 68.85; H, 5.04; N, 8.54. Found: C, 68.26; H, 5.08; N, 8.27.

Iminobenzoxazine 46a. To a solution of Ph_3P (78 mg, 0.3 mmol, 2.0 equiv) in dry CH_2Cl_2 (5 mL) was added a Br_2 solution in CH_2Cl_2 (1.0 M, 0.29 mmol, 1.95 equiv) under N_2. The resulting solution was stirred at room temperature for 15 min, and Et_3N (0.10 mL, 3 equiv) and **45a** (123 mg, 0.15 mmol) were added. The resulting mixture was stirred at room temperature for 15 min and concentrated. The dark residue was shaken with anhydrous benzene (5 mL) and the triethylamine hydrobromide was filtered off. The filtrate was concentrated to give a dark red residue. Flash chromatography on silica gel (20:1 CH_2Cl_2/EtOAc) gave 91 mg (76%) of **46a** as a light red solid: mp 138−140 °C; $[\alpha]_D$ +82.5 (*c* 0.34, $CHCl_3$); ^{1}H NMR 8.13 (d, 1, *J* = 8.0), 7.78−7.72 (m, 2), 7.68−7.53 (m, 4), 7.48−7.35 (m, 8), 7.35−7.23 (m, 6), 6.02 (s, 1), 5.73 (d, 1, *J* = 8.5, NH), 5.38 (br d, 1, *J* = 11.6), 5.31 (dd, 1, *J* = 9.7, 8.5), 4.95 (br d, 1, *J* = 11.6), 4.71 (dq, 1, *J* = 8.5, 6.7), 4.64 (q, 1, *J* = 6.7), 4.46−4.34 (m, 2), 4.23 (t, 1, *J* = 6.7), 2.85 (dd, 1, *J* = 13.0, 8.5), 2.42 (dd, 1, *J* = 13.0, 9.7), 1.63 (br d, 3, *J* = 6.7), 1.62 (br d, 3, *J* = 6.7); ^{13}C NMR 173.3, 169.3, 159.4, 155.6, 154.4, 150.1, 143.9, 143.7, 141.24, 141.15, 136.5, 135.4, 134.7, 133.9, 130.8, 129.0 (br), 128.8, 128.5 (3 C), 128.4 (2 C), 127.7 (2 C), 127.0 (2 C), 126.9, 126.39, 126.36, 125.0 (2 C), 123.7, 120.0 (br, 2 C), 118.8, 116.9, 89.9, 82.9, 68.2, 67.0, 59.3, 53.6, 49.0, 47.1, 37.0, 19.4, 18.0 (br); IR (KBr) 3344 (br), 1795, 1725, 1677, 1641, 1606; HRMS (CI) calcd for $C_{47}H_{40}N_5O_8^+$ (MH^+) 802.2877, found 802.2838.

Iminobenzoxazine 46b ($C_{47}H_{39}N_5O_8$). To a solution of Ph_3P (130 mg, 0.5 mmol, 2.0 equiv) in dry CH_2Cl_2 (5 mL) was added a Br_2 solution in CH_2Cl_2 (1.0 M, 0.49 mmol, 1.95 equiv) under N_2. The resulting solution was stirred at room temperature for 10 min, and Et_3N (0.16 mL, 3 equiv) and **45b** (205 mg, 0.25 mmol) were added. The resulting mixture was stirred at room temperature for 15 min and concentrated. The dark residue was shaken with anhydrous benzene (5 mL) and the triethylamine hydrobromide was filtered off. The filtrate was concentrated to give a dark red residue. Flash chromatography on silica gel (20:1 CH_2Cl_2/EtOAc) gave 142 mg (71%) of **46b** as a light red solid: mp 141−143 °C; $[\alpha]_D$ +71.3 (*c* 0.33, $CHCl_3$); ^{1}H NMR 8.14 (dd, 1, *J* = 7.9, 1.2), 7.76 (d, 2, *J* = 7.9), 7.49−7.58 (m, 5), 7.35−7.49 (m, 7), 7.22−7.35 (m, 6), 6.02 (s, 1), 5.51 (d, 1, *J* = 7.9, NH), 5.46−5.30 (br, 1), 5.36 (dd, 1, *J* = 9.2, 8.7), 5.08−4.91 (br, 1), 4.77 (dq, 1, *J* = 7.9, 6.7), 4.63 (q, 1, *J* = 6.7), 4.50−4.36 (m, 2), 4.26 (t, 1, *J* = 6.7), 2.83 (dd, 1, *J* = 13.4, 9.2), 2.45 (dd, 1, *J* = 13.4, 8.7), 1.58 (d, 3, *J* = 6.7), 1.57 (d, 3, *J* = 6.7); ^{13}C NMR 173.3, 169.4, 159.0, 155.8, 154.4, 150.3, 144.0, 143.7, 141.3, 141.2, 136.5, 135.5, 134.8, 133.9, 130.8, 129.1 (br), 128.6 (br, 3 C), 128.5 (2 C), 128.4, 127.7 (br, 2 C), 127.0 (br, 3 C), 126.5, 126.4, 125.2, 125.0, 124.0, 120.0 (2 C), 118.8, 117.0, 89.6, 82.9, 68.3, 67.1, 59.4, 53.7, 48.7, 47.2, 36.9, 18.7, 18.0; IR (KBr) 3309 (br), 1794, 1725, 1676, 1655, 1607; HRMS (CI) calcd for $C_{47}H_{40}N_5O_8^+$ (MH^+) 802.2877, found 802.2855.

***N*-19-Cbz-fumiquinazoline A (48a) and C-14 Epimer 49a.** To a solution of **46a** (80 mg, 0.10 mmol) in dry EtOAc (0.5 mL) was added dry piperidine (0.10 mL, 10 equiv). The resulting mixture was stirred at room temperature for 10 min and concentrated under reduced pressure to give crude amidine **47a**, which was dissolved in dry MeCN (4 mL). The solution was refluxed for 2 h, cooled, and concentrated to give a light red residue. Flash chromatography on silica gel (2:1 CH_2Cl_2/EtOAc) gave 38 mg (65%) of **48a** as a white solid followed by 11 mg (19%) of **49a** as a white solid.

Data for **48a**: mp 156−160 °C; $[\alpha]_D$ −221.6 (*c* 0.36, $CHCl_3$); ^{1}H NMR 8.17 (d, 1, *J* = 7.9), 8.06 (br d, 1, *J* = 7.9), 7.76 (ddd, 1, *J* = 7.9, 7.9, 1.1), 7.69 (d, 1, *J* = 7.9), 7.60 (d, 1, *J* = 7.9), 7.47 (ddd, 1, *J* = 7.9, 7.9, 1.2), 7.42 (dd, 1, *J* = 7.9, 1.2), 7.36 (br m, 5), 7.32 (ddd, 1, *J* = 7.9, 7.9, 1.2), 6.81 (br, 1, NH), 5.78 (s, 1), 5.72 (dd, 1, *J* = 10.7, 8.0), 5.36−5.18 (m, 2), 5.24 (s, 1, OH), 4.64−4.46 (m, 2), 2.29 (dd, 1, *J* = 13.7, 10.7), 1.90 (br dd, 1, *J* = 13.7, 8.0), 1.74 (br d, 3, *J* = 6.7), 1.45 (d, 3, *J* = 6.7); ^{13}C NMR 170.0 (br), 167.9, 160.1, 155.8 (br), 150.9, 146.8, 136.2, 135.8, 135.6, 134.8, 130.1, 128.6 (3 C), 128.5 (2 C), 128.2, 127.50, 127.46, 127.1, 126.4, 120.1, 116.4, 87.2, 80.1, 68.3, 59.7, 51.9, 49.2, 36.7, 18.2, 17.3; IR (KBr) 3261 (br), 1721, 1690, 1607, 1603; HRMS (FAB, DCM/NBA) calcd for $C_{32}H_{29}N_5O_6Na^+$ (MNa^+) 602.2016, found 602.1994.

Data for **49a**: mp 159−163 °C; $[\alpha]_D$ +135.0 (*c* 0.11, $CHCl_3$); ^{1}H NMR 8.24 (dd, 1, *J* = 7.8, 1.2), 7.85 (t, 1, *J* = 7.8), 7.78−7.67 (m, 1), 7.71 (d, 1, *J* = 7.8), 7.54 (t, 1, *J* = 7.8), 7.49 (d, 1, *J* = 7.8), 7.42−7.22 (m, 6), 7.20−7.06 (m, 1), 6.67 (br, 1, NH), 5.82 (br s, 1), 5.64 (t, 1, *J* = 4.9), 5.29 (s, 1, OH), 5.28 (d, 1, *J* = 12.2), 5.12 (br d, 1, *J* = 12.2), 4.70 (qd, 1, *J* = 6.7, 4.2), 4.59 (q, 1, *J* = 6.7), 2.30 (br d, 2, *J* = 4.9), 1.63 (br d, 3, *J* = 6.7), 1.53 (d, 3, *J* = 6.7); ^{13}C NMR 167.7, 161.7, 150.7, 147.1, 136.8, 135.5, 135.4, 135.3 (br), 129.7, 128.6 (2 C), 128.5, 128.4 (2 C), 127.6 (br), 127.1, 126.9 (br, 2 C), 125.8 (br), 120.0, 116.1, 87.2, 79.8, 68.1, 59.8, 52.4, 51.1, 41.0, 24.5, 18.0 (two quaternary C were not observed); IR (KBr) 3370 (br), 1720, 1691, 1604, 1657.

***N*-19-Cbz-fumiquinazoline B (48b) and C-14 Epimer 49b ($C_{32}H_{29}N_5O_6$).** To a solution of **46b** (120 mg, 0.15 mmol) in dry EtOAc (0.6 mL) was added dry piperidine (0.14 mL, 10 equiv). The resulting mixture was stirred at room temperature for 10 min and concentrated under reduced pressure to give crude amidine **47b**, which was dissolved in dry MeCN (5 mL). The solution was refluxed for 2 h, cooled, and concentrated to give a light red residue. Flash chromatography on silica gel (5:2 CH_2Cl_2/EtOAc) gave 60 mg (69%) of **48b** as white solid preceded by 16 mg (18%) of **50b** as a white solid.

Data for **48b**: mp 152−156 °C; $[\alpha]_D$ +226.7 (*c* 0.24, $CHCl_3$); ^{1}H NMR 8.13 (d, 1, *J* = 8.0), 8.04 (br d, 1, *J* = 7.3), 7.75 (ddd, 1, *J* = 8.2, 7.0, 1.0), 7.63 (d, 1, *J* = 7.9), 7.61 (d, 1, *J* = 7.9), 7.39−7.47 (m, 4), 7.29−7.38 (m, 4), 6.69, (br s, 1, NH), 5.85 (s, 1), 5.57 (dd, 1, *J* = 11.0, 3.0), 5.29 (d, 1, *J* = 11.2), 5.25 (s, 1, OH), 5.22 (d, 1, *J* = 11.2), 4.73 (m, 1), 4.55 (q, 1, *J* = 6.7), 2.26 (dd, 1, *J* = 13.4, 11.0), 2.08 (dd, 1, *J* = 13.4, 3.0), 1.61 (br d, 3, *J* = 6.7), 1.44 (d, 3, *J* = 6.7); ^{13}C NMR 170.1, 168.2, 159.9, 155.4, 150.9, 146.9, 136.2 (2 C), 135.6, 134.9, 130.0, 128.6 (2 C), 128.4, 128.1 (2 C), 127.3, 127.1, 126.8, 126.4, 126.2, 119.9, 116.5, 88.3, 81.1, 69.0, 60.6, 53.6, 52.2, 39.4, 25.8, 19.4; IR (KBr) 3344 (br), 2919, 1723, 1710, 1691, 1678, 1641, 1606; HRMS (FAB, DCM/NBA) calcd for $C_{32}H_{29}N_5O_6Na^+$ (MNa^+) 602.2016, found 602.2012.

Data for **50b**: mp 163−169 °C; $[\alpha]_D$ +51.7 (*c* 0.40, $CHCl_3$); ^{1}H NMR 8.22 (br d, 1, *J* = 8.0), 7.81 (t, 1, *J* = 8.0), 7.73 (d, 1, *J* = 8.0), 7.72−7.62 (br, 1), 7.51 (t, 1, *J* = 8.0), 7.49 (d, 1, *J* = 8.0), 7.44−7.21 (m, 6), 7.10−6.90 (br, 1), 6.30 (br s, 1, NH),

5.76 (dd, 1, J = 5.5, 4.9), 5.73 (s, 1), 5.27 (d, 1, J = 11.6), 5.19 (d, 1, J = 11.6), 4.70 (br, 1), 4.58 (q, 1, J = 6.7), 4.42 (br, 1, OH), 2.35 (dd, 1, J = 14.0, 5.5), 2.23 (dd, 1, J = 14.0, 4.9), 1.75 (d, 3, J = 6.7), 1.57 (d, 3, J = 6.7); ^{13}C NMR 150.9, 146.7, 136.6, 135.5, 135.3, 134.9, 129.8, 128.6 (3 C), 128.4 (2 C), 127.5 (2 C), 127.0, 126.2, 125.4, 120.3, 116.2, 87.0, 79.8, 68.4, 59.8, 52.4, 49.4, 40.0, 18.0, 17.8 (four quaternary C were not observed); IR (KBr) 3368 (br), 1721, 1687, 1604.

Fumiquinazoline A (1). To a solution of **48a** (23 mg, 0.040 mmol) in MeOH (2 mL) was added 5% Pd/C (10 mg). The suspension was stirred at room temperature under H_2 for 30 min. The catalyst was filtered off and the filtrate was evaporated to give crude **1**. Flash chromatography on silica gel (1:1 CH_2Cl_2/EtOAc) gave 16 mg (90%) of pure fumiquinazoline A (**1**) as a light yellow solid: mp 178−183 °C (lit.[1] mp 178−182 °C); $[\alpha]_D$ −225.4 (c 0.36, $CHCl_3$) {lit.[1] $[\alpha]_D$ −225.4 (c 0.47, $CHCl_3$)}; λ_{max} (EtOH) nm (log ϵ) 208 (4.58), 226 (4.47), 234 (4.42), 256 (4.17), 264 (4.13), 278 (3.97), 306 (3.39), 318 (3.24); ^{1}H NMR 8.23 (dd, 1, J = 7.9, 1.1), 7.75 (ddd, 1, J = 8.2, 7.0, 1.1), 7.67 (d, 1, J = 8.2), 7.61 (d, 1, J = 7.5), 7.52 (d, 1, J = 7.3), 7.49 (ddd, 1, J = 7.9, 7.0, 1.1), 7.31 (td, 1, J = 7.5, 1.1), 7.16 (td, 1, J = 7.5, 1.1), 6.31 (br s, 1, NH), 5.97 (ddd, 1, J = 10.8, 6.1, 0.9), 5.49 (br d, 1, J = 4.8), 4.88 (q, 1, J = 6.7), 4.82 (s, 1, OH), 4.22 (qd, 1, J = 6.7, 6.1), 2.72 (br dd, 1, J = 6.1, 4.8, NH), 2.51 (dd, 1, J = 13.7, 10.8), 2.28 (dd, 1, J = 13.7, 6.1), 1.79 (d, 3, J = 6.7), 1.35 (d, 3, J = 6.7); ^{13}C NMR 172.2, 170.2, 160.4, 150.6, 146.8, 138.5, 136.2, 134.8, 129.8, 127.5, 127.6, 126.8, 125.6, 124.8, 120.2, 115.0, 86.3, 80.1, 59.0, 53.0, 49.2, 36.8, 18.6, 16.9; IR (KBr) 3347 (br), 1686 (br), 1607. The spectral data are identical with those previously reported.[1]

***epi*-Fumiquinazoline A (50a).** To a solution of **49a** (11 mg, 0.019 mmol) in MeOH (1 mL) was added 5% Pd/C (5 mg). The suspension was stirred at room temperature under H_2 for 30 min. The catalyst was filtered off and the filtrate was evaporated to give crude **50a**. Flash chromatography on silica gel (3:2 EtOAc/CH_2Cl_2) gave 7.3 mg (86%) of pure **50a** as a light yellow solid: mp 248−252 °C; λ_{max} (EtOH) nm (log ϵ) 208 (4.68), 228 (4.58), 234 (4.56), 256 (4.27), 268 (4.27), 280 (4.12), 308 (3.67), 320 (3.57); ^{1}H NMR 8.29 (dd, 1, J = 7.8, 1.0), 7.81 (td, 1, J = 7.8, 1.2), 7.68 (d, 1, J = 7.8), 7.55 (d, 1, J = 7.8), 7.53 (t, 1, J = 7.8), 7.43 (d, 1, J = 7.8), 7.31 (td, 1, J = 7.8, 1.0), 7.13 (td, 1, J = 7.8, 1.0), 6.61 (br s, 1, NH), 6.02 (t, 1, J = 6.8), 5.52 (br d, 1, J = 6.8), 5.18 (s, 1, OH), 4.78 (qd, 1, J = 7.0, 4.2), 4.08 (qd, 1, J = 6.8, 6.8), 2.89 (t, 1, J = 6.8), 2.71 (dd, 1, J = 14.8, 6.8), 2.18 (dd, 1, J = 14.8, 6.8), 1.83 (d, 3, J = 7.0), 1.33 (d, 3, J = 6.8); IR (KBr) 3344 (br), 1703, 1678, 1603.

Fumiquinazoline B (2). To a solution of **48b** (46 mg, 0.080 mmol) in MeOH (2 mL) was added 5% Pd/C (15 mg). The suspension was stirred at room temperature under H_2 for 30 min. The catalyst was filtered off and the filtrate was evaporated to give crude **12**. Flash chromatography on silica gel (2:3 CH_2Cl_2/EtOAc) gave 32 mg (90%) of pure fumiquinazoline B (**2**) as a light yellow solid: mp 174−178 °C (lit.[1] mp 174−176 °C); $[\alpha]_D$ −179.6 (c 0.50, $CHCl_3$) {lit.[1] $[\alpha]_D$ −196.6 (c 0.38, $CHCl_3$)}; λ_{max} (EtOH) nm (log ϵ) 208 (4.74), 228 (4.63), 234 (4.59), 256 (4.30), 268 (4.19), 278 (3.97), 306 (3.39), 318 (3.24); ^{1}H NMR (0.08 M) 8.20 (dd, 1, J = 7.9, 1.0), 7.74 (ddd, 1, J = 7.9, 7.0, 1.0), 7.62 (dd, 1, J = 7.6, 1.2), 7.57 (dd, 1, J = 7.9, 1.0), 7.52 (dd, 1, J = 7.6, 1.2), 7.46 (ddd, 1, J = 7.9, 7.0, 1.0), 7.31 (td, 1, J = 7.6, 1.2), 7.25 (br s, 1, NH), 7.17 (td, 1, J = 7.6, 1.2), 5.79 (dd, 1, J = 11.4, 4.9), 5.45 (s, 1, OH), 5.42 (br s, 1), 4.72 (qd, 1, J = 7.2, 4.9), 4.15 (q, 1, J = 6.7), 2.72 (br s, 1, NH), 2.61 (dd, 1, J = 13.3, 11.4), 2.48 (dd, 1, J = 13.3, 4.9), 1.83 (d, 3, J = 7.2), 1.29 (d, 1, J = 6.7); ^{1}H NMR (0.01 M) 8.26 (dd, 1, J = 7.9, 1.2), 7.77 (ddd, 1, J = 7.9, 7.0, 1.2), 7.66 (d, 1, J = 7.6), 7.62 (d, 1, J = 7.9), 7.55 (d, 1, J = 7.6), 7.49 (dd, 1, J = 7.9, 7.0), 7.33 (td, 1, J = 7.6, 1.2), 7.19 (td, 1, J = 7.6,1.2), 6.48 (br s, 1, NH), 5.84 (dd, 1, J = 11.4, 4.9), 5.47 (dd, 1, J = 5.5, 1.8), 5.25 (s, 1, OH), 4.78 (qd, 1, J = 7.2, 4.9), 4.19 (qd, 1, J = 6.7, 6.7), 2.62 (dd, 1, J = 13.3, 11.4), 2.61 (br d, 1, J = 6.7, NH), 2.51 (dd, 1, J = 13.3, 4.9), 1.87 (d, 3, J = 7.2), 1.33 (d, 1, J = 6.7); ^{13}C NMR (0.08 M) 170.6, 170.5, 160.3, 150.7, 147.0, 138.6, 136.5, 134.9, 129.7, 127.2, 126.8 (2 C), 125.5, 125.0, 120.0, 114.8, 86.4, 80.2, 59.0, 52.7, 52.0, 38.9, 24.8, 18.1; IR (KBr) 3345 (br), 1672, 1603. The spectral data are identical with those previously reported.[1]

***epi*-Fumiquinazoline B (50b).** To a solution of **49b** (15 mg, 0.025 mmol) in MeOH (1 mL) was added 5% Pd/C (5 mg). The suspension was stirred at room temperature under H_2 for 30 min. The catalyst was filtered off and the filtrate was evaporated to give crude **50b**. Flash chromatography on silica gel (1:1 EtOAc/CH_2Cl_2) gave 9.5 mg (86%) of pure **50b** as a light yellow solid: mp 175−178 °C; $[\alpha]_D$ +215.0 (c 0.42,$CHCl_3$); λ_{max} (EtOH) nm (log ϵ) 206 (4.84), 226 (4.72), 234 (4.67), 256 (4.38), 266 (4.33), 276 (4.20), 306 (3.67), 318 (3.55); ^{1}H NMR 8.31 (dd, 1, J = 7.9, 1.2), 7.83 (td, 1, J = 7.9, 1.2), 7.75 (d, 1, J = 7.9), 7.56 (td, 1, J = 7.9, 1.2), 7.51 (d, 2, J = 7.8), 7.30 (t, 1, J = 7.8), 7.15 (td, 1, J = 7.8, 1.2), 6.60 (br s, 1, NH), 5.91 (dd, 1, J = 9.8, 5.0), 5.41 (br s, 1), 5.41 (s, 1, OH), 4.81 (q, 1, J = 6.7), 3.97 (q, 1, J = 6.1), 2.67 (dd, 1, J = 14.7, 9.8), 2.22 (br s, 1, NH), 2.14 (dd, 1, J = 14.7, 5.0), 1.78 (d, 3, J = 6.7), 1.19 (d, 1, J = 6.1); ^{13}C NMR 170.4, 169.9, 162.2, 151.2, 147.0, 139.0, 136.0, 135.4, 129.8, 127.8, 127.8, 126.9, 135.6, 124.4, 119.8, 115.0, 85.9, 80.8, 59.0, 53.3, 49.2, 38.0, 18.0, 16.9; IR (KBr) 3338 (br), 1690 (br), 1606.

Alcohol 41b. To a solution of **30b** (956 mg, 1.50 mmol) in 4:1 MeOH/CH_2Cl_2 (5 mL) was added dimethyldioxirane (0.1 M in acetone, 15 mL, 15 mmol) at −78 °C. The resulting mixture was stirred at −78 °C for 5 min. After removal of the solvent under reduced pressure, the mixture was purified by flash chromatography on silica gel (50:1 CH_2Cl_2/EtOAc) to give 391 mg (38%) of **38b** as a white solid followed by 566 mg (55%) of **40b** as a white solid.

To 5 mL of acetic acid in an ice water bath was added $NaBH_4$ (460 mg, 24 mmol) in several portions. The $NaBH_4$ solution in acetic acid was warmed to 25 °C and added to a solution of **40b** (566 mg, 0.82 mmol) in acetic acid (5 mL). The resulting mixture was stirred at 25 °C for 3 h, then diluted with CH_2Cl_2 (15 mL) and washed with water, saturated $NaHCO_3$ solution, and brine, dried (Na_2SO_4), and evaporated to give a crude mixture of **41b** and **43b**. Flash chromatography on silica (100:1 CH_2Cl_2/EtOAc) gave 45 mg (9%) of **43b** as a white solid followed by 408 mg (76%) of **41b** as a white solid: mp 79−81 °C; $[\alpha]_D$ +78.4 (c 0.22, $CHCl_3$); ^{1}H NMR (6:1 mixture of rotamers, major rotamer), 7.52 (d, 1, J = 8.0), 7.46 (d, 1, J = 8.0), 7.43−7.35 (m, 6), 7.23 (t, 1, J = 8.0), 6.43 (br d, 1, J = 4.9, NH), 5.70 (s, 1), 5.34 (d, 1, J = 12.2), 5.20 (d, 1, J = 12.2), 4.81 (d, 1, J = 12.2), 4.74 (d, 1, J = 12.2), 4.47 (m, 1), 4.47 (s, 1, OH), 4.47−4.42 (m, 1), 3.66 (s, 3), 1.99−1.78 (m, 5), 0.92 (d, 3, J = 6.7), 0.85 (d, 3, J = 6.7); ^{1}H NMR (minor rotamer, partial) 7.59 (d, 1, J = 8.0), 6.27 (br, 1, NH), 5.66 (s, 1), 5.61 (d, 1, J = 11.6), 4.99 (d, 1, J = 11.6), 4.54 (m, 1), 3.63 (s, 3), 1.05 (d, 3, J = 6.7), 0.99 (d, 1, J = 6.7); ^{13}C NMR (major rotamer) 171.9, 167.0, 155.1, 154.0, 135.4, 134.9, 134.6, 130.3, 128.9, 128.8 (2 C), 128.6 (2 C), 126.6, 125.3, 117.0, 95.5, 86.6, 81.7, 74.6, 68.7, 62.8, 52.5, 51.1, 40.0, 34.3, 24.1, 23.5, 22.1; ^{13}C NMR (minor rotamer, partial) 131.3, 129.7,129.6, 38.8; IR (KBr) 3386, 1734 (br), 1609.

Tetracyclic Lactone 43b. To a solution of **41b** (328 mg, 0.50 mmol) in CH_2Cl_2 (10 mL) was added silica gel (EM 9385, silica gel 60, 230−400 mesh, 3.5 g). The suspension was stirred at room temperature for 5 d. The silica gel was filtered off and the filtrate was evaporated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (50:1 CH_2Cl_2/EtOAc) to give 55 mg (17%) of recovered **41b**, which could be recycled, preceded by 223 mg (71%) of **43b** as a white solid: mp 237−238 °C; $[\alpha]_D$ +79.8 (c 0.24, $CHCl_3$); ^{1}H NMR (5:1 mixture of rotamers, major rotamer) 7.75 (d, 1, J = 8.0), 7.49 (d, 1, J = 8.0), 7.42−7.33 (m, 5), 7.25 (t, 2, J = 8.0), 5.91 (s, 1), 5.56 (br d, 1, J = 6.7, NH), 5.26 (d, 1, J = 12.2), 5.15 (d, 1, J = 12.2), 4.77 (d, 1, J = 12.2), 4.68 (d, 1, J = 12.2), 4.40 (m, 1), 4.10 (m, 1), 2.79 (dd, 1, J = 14.0, 10.4), 2.23 (dd, 1, J = 14.0, 9.4), 1.95−1.72 (m, 3), 0.90 (br d, 3, J = 6.7), 0.83 (d, 1, J = 6.7); ^{1}H NMR (minor rotamer, partial) 7.67 (d, 1, J

= 7.9), 7.45 (d, 1, J = 7.9), 5.51 (br d, 1, J = 6.1, NH), 5.30 (d, 1, J = 12.2), 5.10 (d, 1, J = 12.2), 4.47 (m, 1), 3.90−3.79 (m, 1), 2.90−2.78 (m, 1), 2.36−2.27 (m, 1), 2.10−1.93 (m, 3), 0.96 (br d, 3, J = 6.7); ^{13}C NMR (major rotamer) 173.5, 168.8, 154.2, 153.8, 136.0, 135.7, 135.4, 130.8, 128.8 (3 C),128.7 (2 C), 127.2, 125.6, 116.2, 95.0, 89.6, 83.6, 74.8, 68.4, 62.3, 51.8, 40.0, 35.2, 24.1, 23.5, 22.0; ^{13}C NMR (minor rotamer, partial) 129.6, 129.1, 127.4, 125.1, 116.7, 89.9, 63.0, 51.4, 37.9, 22.3; IR (KBr) 3333, 1797, 1728, 1710, 1678, 1608. Anal. Calcd for $C_{28}H_{28}Cl_3N_3O_7$: C, 53.82; H, 4.52; N, 6.72. Found: C, 54.06; H, 4.50; N, 6.52.

Aniline 51. To a solution of **43b** (200 mg, 0.32 mmol) in acetic acid (3.0 mL) was added zinc dust (600 mg). The mixture was stirred at room temperature for 30 min. The zinc dust was filtered off and the filtrate was concentrated. The residue was dissolved in EtOAc (10 mL), which was washed with saturated $NaHCO_3$ solution and brine, dried (Na_2SO_4), and evaporated under reduced pressure to give the crude amine.

To a mixture of the crude amine and EDAC (150 mg, 0.76 mmol) in MeCN (2 mL) was added anthranilic acid (102 mg, 0.74 mmol) in several portions over 60 min at room temperature with stirring. The reaction mixture was stirred for an additional 20 min, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL), which was washed with water and saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated. Flash chromatography on silica gel (50:1 CH_2Cl_2/EtOAc) gave 154 mg (85%) of aniline **51** as a white solid: mp 191−194 °C; $[\alpha]_D$ +176.6 (c 0.24, $CHCl_3$); ^{1}H NMR (5:1 mixture of rotamers) 8.00 (d, 1, J = 7.9), 7.49 (d, 1, J = 8.0), 7.45−7.36 (m, 5), 7.37 (td, 1, J = 8.0, 1.0), 7.29 (d, 1, J = 8.0), 7.25 (t, 1, J = 8.0), 7.17 (t, J = 8.0), 6.74 (d, 1, J = 6.7, NH), 6.66−6.56 (m, 2), 5.95 (br, 1), 5.57 (br, 2, NH), 5.27 (d, 1, J = 12.2), 5.18 (d, 1, J = 12.2), 4.48−4.00 (m, 1), 4.16 (m, 1), 2.74 (dd, 1, J = 14.0, 10.4), 2.29 (dd, 1, J = 14.0, 9.1), 2.01−1.73 (m, 3), 0.93 (br d, 3, J = 6.7), 0.85 (br d, 3, J = 6.7); ^{1}H NMR (minor rotamer, partial) 7.91 (d, 1, J = 8.0), 7.45 (d, 1, J = 8.0), 6.78 (d, 1, J = 6.7, NH), 6.63−6.52 (m, 2), 5.93 (s, 1), 5.35 (d, 1, J = 12.2), 5.07 (d, 1, J = 12.2), 4.39 (m, 1), 3.98 (m, 1), 2.83 (dd, 1, J = 13.4, 9.8), 2.50−2.40 (m, 1), 2.14−1.96 (m, 3), 0.98 (d, 3, J = 6.7); ^{13}C NMR (major rotamer) 174.6, 168.95, 168.90, 154.1, 149.2, 136.0, 135.6, 132.9, 130.6, 129.5, 128.70 (2 C), 128.68 (2 C), 128.5, 127.4, 127.2, 126.1, 117.4, 116. 5, 116.1, 113.8, 89.7, 83.7, 68.3, 62.2, 51.3, 39.9, 35.1, 24.1, 23.5, 22.0; ^{13}C NMR (minor rotamer, partial) 174.1, 165.9, 128.9, 125.7, 113.8, 90.1, 64.0, 51.0, 37.9, 35.6, 24.2, 22.3; IR (KBr) 3460 (br, NH), 3358 (br, NH), 1788, 1702, 1642, 1610.

Diamide 52. To a solution of aniline **51** (125 mg, 0.22 mmol) and EDAC (93 mg, 0.48 mmol) in MeCN (2 mL) was added *N*-Fmoc-L-alanine (150 mg, 0.48 mmol). The resulting mixture was stirred at room temperature for 1.5 h and concentrated. The residue was dissolved in CH_2Cl_2 (10 mL), which was washed with water and saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated. Flash chromatography on silica gel (20:1 CH_2Cl_2/EtOAc) gave 165 mg (87%) of **52** as a white solid: mp 141−143 °C; $[\alpha]_D$ +145.3 (c 0.22, $CHCl_3$); ^{1}H NMR (10:1 mixture of rotamers, major rotamer) 11.25 (br s, 1, NH), 8.38 (br d, 1, J = 7.9), 8.01 (d, 1, J = 8.0), 7.72 (d, 2, J = 8.0), 7.70−7.61 (m, 2), 7.53−7.43 (m, 3), 7.42−7.30 (m, 8), 7.30−7.17 (m, 3), 7.03 (t, 1, J = 8.0), 5.91 (br s, 1), 5.79 (br d, 1, J = 7.1, NH), 5.23 (d, 1, J = 12.2), 5.17 (d, 1, J = 12.2), 4.46 (m, 1), 4.43−4.26 (m, 4), 4.18 (dd, 1, J = 11.7, 9.4), 2.73 (dd, 1, J = 13.8, 11.7), 2.25 (dd, 1, J = 13.8, 9.4), 1.95−1.72 (m, 3), 1.51 (br d, 3, J = 6.7), 0.91 (br d, 3, J = 6.7), 0.83 (br d, 3, J = 6.7); ^{1}H NMR (minor rotamer, partial) 11.07 (br s, 1, NH), 8.42 (br d, 1, J = 7.9), 7.89 (d, 1, J = 8.0), 5.84 (br s, 1), 5.74 (br d, 1, J = 7.1, NH), 5.35 (d, 1, J = 12.2), 4.99 (d, 1, J = 12.2), 4.09 (m, 3), 4.02 (m, 1), 2.87 (m, 1), 2.03 (m, 1), 1.37 (br, 3), 0.95 (br d, 3, J = 6.7), 0.81 (br d, 3, J = 6.7); ^{13}C NMR (major rotamer) 175.0, 171.0, 168.85, 168.79, 155.9, 154.2, 144.0, 143.6 (2 C), 141.2 (2 C), 139.0, 136.1, 135.7, 135.4, 133.2, 130.9, 128.8 (2 C), 128.6 (3 C), 127.6 (2 C), 127.0 (2 C), 126.8, 125.9, 125.3, 125.1 (2 C), 123.3, 121.7, 119.9 (2 C), 116.2, 90.2, 83.6, 68.3, 67.1, 62.2, 51.7 (2 C), 47.0, 40.0, 34.7, 24.1, 23.5, 22.0, 19.0; ^{13}C NMR (minor rotamer, partial) 171.2, 139.3, 135.0, 133.4, 131.2, 129.5, 119.2, 91.7, 84.2, 24.5; IR (KBr) 3347 (br), 1794, 1707, 1647, 1602. Anal. Calcd for $C_{50}H_{47}N_5O_9$: C, 69.67; H, 5.50; N, 8.12. Found: C, 69.44; H, 5.41; N, 7.92.

Iminobenzoxazine from 52. To a solution of Ph_3P (78 mg, 0.3 mmol, 2.0 equiv) in dry CH_2Cl_2 (5 mL) was added a Br_2 solution in CH_2Cl_2 (1.0 M, 0.29 mmol, 1.95 equiv) under N_2. The resulting solution was stirred at room temperature for 15 min, and Et_3N (0.10 mL, 3 equiv) and **52** (130 mg, 0.15 mmol) were added. The resulting mixture was stirred at room temperature for 15 min and concentrated. The residue was shaken with anhydrous benzene (5 mL) and the triethylamine hydrobromide was filtered off. The filtrate was concentrated to give a light brown residue. Flash chromatography on silica gel (30:1 CH_2Cl_2/EtOAc) gave 98 mg (77%) of the iminobenzoxazine as a light-yellow solid: mp 129−131 °C; $[\alpha]_D$ +86.9 (c 0.17, $CHCl_3$); ^{1}H NMR (3:1 mixture of rotamers, major rotamer) 8.13 (d, 1, J = 8.0), 7.78−7.72 (m, 2), 7.68−7.56 (m, 3), 7.56−7.48 (m, 2), 7.48−7.23 (m, 13), 6.03 (s, 1), 5.76 (d, 1, J = 8.5, NH), 5.40 (br d, 1, J = 12.2), 5.21 (d, 1, J = 12.2), 5.02 (dd, 1, J = 9.2, 7.9), 4.66−4.53 (m, 2), 4.44−4.31 (m, 2), 4.27−4.16 (m, 1), 2.99 (dd, 1, J = 13.8, 9.2), 2.22 (dd, 1, J = 13.8, 7.9), 2.16−1.75 (m, 3), 1.62 (br d, 3, J = 6.7), 0.93 (br d, 3, J = 6.7), 0.83 (br d, 3, J = 6.7); ^{1}H NMR (minor rotamer, partial) 7.93 (d, 1, J = 8.0), 7.78 (d, 2, J = 8.0), 5.98 (s, 1), 5.86 (d, 1, J = 8.5, NH), 5.45 (d, 1, J = 12.2), 5.30 (m, 1), 4.50 (m, 1), 4.19 (m, 1), 2.90 (m, 1), 2.12 (m, 1), 2.16−1.75 (m, 3), 1.58 (br d, 3, J = 6.7), 0.98 (br d, 3, J = 6.7), 0.85 (br d, 3, J = 6.7); ^{13}C NMR (major rotamer) 174.4, 169.0, 159.4, 155.7, 154.2, 149.7, 143.8 (2 C), 141.3 (2 C), 136.1, 135.2, 133.8, 130.7, 129.2, 128.8, 128.5 (2 C), 128.5 (2 C), 127.9, 127.7 (2 C), 127.1, 127.0 (2 C), 126.4, 126.2, 125.9, 125.4, 125.2 (2 C), 124.9, 119.9 (2 C), 119.0, 116.2, 90.2, 83.6, 68.2, 67.0, 55.4, 49.1, 47.1, 40.0, 38.0, 24.1, 23.5, 22.0, 19.4; ^{13}C NMR (minor rotamer, partial) 144.0, 143.2, 141.2 (2 C), 134.0, 120.0 (2 C), 119.0, 118.4, 115.0, 89.9, 83.1, 72.2, 68.0, 62.9, 54.8, 49.4, 46.7, 37.5, 22.3, 19.2; IR (KBr) 3413 (br), 1793, 1725, 1717, 1676, 1654, 1607; HRMS (CI) calcd for $C_{50}H_{46}N_5O_8^+$ (MH^+) 844.3346, found 844.3378.

***N*-19-Cbz-fumiquinazoline I (53).** To a solution of the iminobenzoxazine (84 mg, 0.10 mmol) in dry EtOAc (0.5 mL) was added dry piperidine (0.1 mL, 10 equiv). The resulting mixture was stirred at room temperature for 10 min, and concentrated under reduced pressure to the give crude amidine, which was dissolved in dry MeCN (4 mL). The solution was refluxed for 2 h, cooled, and concentrated to give a light red residue. Flash chromatography on silica gel (5:1 CH_2Cl_2/EtOAc) gave 43 mg (70%) of **53** as a white solid: mp 161−162 °C; $[\alpha]_D$ −21.8 (c 0.25, $CHCl_3$); ^{1}H NMR (3:1 mixture of rotamers, major rotamer) 8.20 (d, 1, J = 7.9), 7.75 (t, 2, J = 7.9), 7.69 (d, 1, J = 7.9), 7.48 (d, 1, J = 7.9), 7.47 (d, 1, J = 7.9), 7.43−7.32 (m, 6), 7.03 (t, 1, J = 7.9), 6.71 (s, 1, NH), 5.74 (s, 1), 5.59 (dd, 1, J = 7.7, 5.5), 5.24 (s, 2), 4.59 (q, 1, J = 6.7), 4.53 (m, 1), 4.30 (s, 1, OH), 2.29 (dd, 1, J = 14.6, 7.7), 2.20 (dd, 1, J = 14.6, 5.5), 2.16−2.05 (m, 1), 2.00−1.79 (m, 2), 1.68 (br d, 3, J = 6.7), 0.93 (d, 3, J = 6.7), 0.85 (d, 3, J = 6.7); ^{1}H NMR (minor rotamer, partial) 8.26 (d, 1, J = 7.9), 7.82 (t, 1, J = 7.9), 7.74 (t, 1, J = 7.9), 7.18 (t, 1, J = 7.9), 7.14 (t, 1, J = 7.9), 6.65 (s, 1, NH), 5.85 (s, 1), 5.22 (d, 1, J = 12.2), 5.09 (d, 1, J = 12.2), 4.64 (br, 1), 4.35 (s, 1, OH), 1.70 (br d, 3, J = 6.7), 1.02 (d, 3, J = 6.7), 0.90 (d, 3, J = 6.7); ^{13}C NMR (major rotamer) 169.2, 167.3, 160.8, 154.9, 151.2, 146.7, 136.5, 135.5, 135.2, 134.6, 129.8, 128.7 (2 C), 128.6 (3 C), 127.32, 127.26, 127.1, 126.2, 125.4, 120.4, 116.5, 86.7, 81.0, 68.3, 62.9, 52.3, 49.4, 39.9, 35.5, 24.2, 23.6, 22.1, 17.9; ^{13}C NMR (minor rotamer, partial) 168.8, 168.2, 161.3, 152.5, 150.5, 146.8, 137.1, 135.0, 130.1, 128.7, 128.5, 127.9, 127.8, 127.6, 127.5, 126.4, 120.1, 116.7, 86.4, 81.2, 68.0, 63.0, 52.3, 49.1, 38.3, 37.1, 22.3, 17.2; IR (KBr) 3460 (br), 3285 (br), 1701, 1686, 1654, 1607. Anal. Calcd for $C_{35}H_{35}N_5O_6 \cdot H_2O$: 65.72; H, 5.79; N, 10.95. Found: C, 65.48; H, 5.52; N, 10.71.

Fumiquinazoline I (9). To a solution of **53** (29 mg, 0.047 mmol) in MeOH (2 mL) was added 5% Pd/C (15 mg). The

suspension was stirred at room temperature under H_2 for 30 min. The catalyst was filtered off and the filtrate was evaporated to give crude **9**. Flash chromatography on silica gel (2.5:1 CH_2Cl_2/EtOAc) gave 22 mg (96%) of pure fumiquinazoline I (**9**) as a light yellow solid: mp 169−171 °C (lit.[17] 116−120 °C); $[\alpha]_D$ −222.4 (*c* 0.10, $CHCl_3$) {lit.[17] $[\alpha]_D$ −138 (*c* 0.10, $CHCl_3$)}; λ_{max} (MeOH) nm (log ϵ) 208 (4.90), 224 (4.80), 230 (4.78), 255 (4.47), 266 (4.39), 277 (4.28), 304 (3.79), 318 (3.47); ^{1}H NMR 8.32 (dd, 1, *J* = 7.9, 1.2), 7.83 (td, 1, *J* = 7.9, 1.2), 7.74 (d, 1, *J* = 7.9), 7.56 (td, 1, *J* = 7.9, 1.2), 7.55 (d, 1, *J* = 7.3), 7.45 (d, 1, *J* = 7.3), 7.30 (td, 1, *J* = 7.9, 1.2), 7.19 (br s, 1 NH), 7.18 (td, 1, *J* = 7.9, 1.2), 5.82 (dd, 1, *J* = 9.8, 3.7), 5.64 (s, 1, OH), 5.44 (d, 1, *J* = 6.4), 4.76 (q, 1, *J* = 6.7), 3.59 (br, 1), 2.59 (dd, 1, *J* = 14.6, 9.8), 2.14 (dd, 1, *J* = 14.6, 3.6), 1.77 (d, 3, *J* = 6.7), 1.58 (br, 1, NH), 1.57−1.48 (m, 1), 1.42−1.33 (m, 1), 1.03−0.85 (m, 1), 0.75 (d, 3, *J* = 6.7), 0.71 (d, 3, *J* = 6.7); ^{1}H NMR (d_6-acetone) 8.23 (dd, 1, *J* = 7.9, 1.2), 7.87 (td, 1, *J* = 7.9, 1.2), 7.77 (s, 1, NH), 7.73 (d, 1, *J* = 7.9), 7.56 (t, 1, *J* = 7.9), 7.55 (d, 1, *J* = 7.3), 7.36 (d, 1, *J* = 7.3), 7.28 (td, 1, *J* = 7.6, 1.2), 7.15 (td, 1, *J* = 7.3, 1.2), 5.74 (dd, 1, *J* = 9.8, 4.4), 5.69 (s, 1, OH), 5.39 (d, 1, *J* = 7.3), 5.11 (q, 1, *J* = 6.7), 3.59 (br m, 1), 2.73 (dd, 1, *J* = 14.7, 9.8), 2.63 (br, 1, NH), 2.13 (dd, 1, *J* = 14.7, 4.4), 1.74 (d, 3, *J* = 6.7), 1.48−1.35 (m, 2), 1.25−1.13 (m, 1), 0.78 (d, 3, *J* = 6.7), 0.77 (d, 3, *J* = 6.7); ^{13}C NMR (d_6-acetone) 174.1, 170.0, 163.0, 153.6, 148.2, 140.3, 138.5, 135.5, 129.9, 128.3, 127.9, 127.5, 125.9, 125.5, 121.2, 115.9, 88.8, 81.8, 63.0, 54.2, 49.7, 42.3, 38.5, 25.6, 23.5, 21.6, 16.9; IR (KBr) 3347 (br), 1696 (br), 1607, 1651. The spectral data are identical with those previously reported.[2]

Diamide (56). To a solution of **31** (480 mg, 0.91 mmol) and EDAC (280 mg, 1.46 mmol, 1.6 equiv) in MeCN (3 mL) was added *N*-Fmoc-phenylselenyl-L-alanine (636 mg, 1.36 mmol, 1.5 equiv). The resulting mixture was stirred at room temperature for 1 h and concentrated. The residue was dissolved in CH_2Cl_2 (10 mL), which was washed with water and saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel gave 850 mg (96%) of **56** as a white solid: mp 139−141 °C; $[\alpha]_D$ +124.6 (*c* 0.50 in $CHCl_3$); ^{1}H NMR 11.75 (br, 1, NH), 8.51 (br d, 1, *J* = 7.9), 7.77−7.65 (m, 2), 7.65−7.50 (m, 4), 7.50−7.40 (m, 1), 7.40−7.10 (m, 18), 7.06 (br, 1, NH), 5.87 (br s, 1), 5.82 (br d, 1, *J* = 7.1, NH), 5.30−5.15 (m, 2), 5.06 (d, 1, *J* = 11.7), 4.66 (br, 1), 4.52 (br, 1), 4.40 (br, 1), 4.30−4.10 (m, 2), 3.44 (br, 2), 2.49 (dd, 1, *J* = 14.4, 11.4), 2.32 (dd, 1, *J* = 14.4, 6.7), 1.48 (br, 3); ^{13}C NMR 174.6 (br), 168.7, 168.6, 168.5, 156.0, 155.7, 143.9, 143.6 (2 C), 141.1 (2 C), 139.4 (br), 137.0, 133.5 (4 C), 131.1, 130.6, 129.1 (2 C), 128.9, 128.8 (3 C), 128.0 (br), 127.67, 127.64, 127.4, 127.0, 126.9, 126.6 (br), 125.2 (2 C), 124.7, 124.3 (br), 123.1, 121.6, 119.9 (2 C), 118.8, 116.3 (br), 89.8, 84.2 (br), 68.7 (br), 67.3, 58.9 (br), 55.9, 48.2 (br), 47.1, 35.8, 30.3, 18.3 (br); IR (KBr) 3424 (br), 1794, 1721, 1685, 1657, 1603. Anal. Calcd for $C_{53}H_{45}N_5O_9Se$: C, 65.29; H, 4.65; N, 7.18. Found: C, 65.19; H, 4.74; N, 6.91.

Iminobenzoxazine (57). To a solution of Ph_3P (450 mg, 1.72 mmol, 2 equiv) in dry CH_2Cl_2 (10 mL) was added a Br_2 solution in CH_2Cl_2 (1.0 M, 1.68 mmol, 1.95 equiv) under N_2. The resulting solution was stirred at room temperature for 5 min, and (*i*-Pr)$_2$NEt (0.58 mL, 4 equiv) and 820 mg (0.84 mmol) of **56** were added. The resulting mixture was stirred at room temperature for 5 min and quenched with saturated $NaHCO_3$, washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography on silica gel (20:1 CH_2Cl_2/EtOAc) gave 653 mg (81%) of **57** as a light-yellow solid: mp 125−127 °C; $[\alpha]_D$ +88.7 (*c* 0.50 in $CHCl_3$); ^{1}H NMR 8.03 (d, 1, *J* = 8.0), 7.79−7.73 (m, 2), 7.68−7.53 (m, 7), 7.48−7.23 (m, 14), 7.12−7.02 (m, 2), 6.02 (br, 2, NH and H-18), 5.44−5.34 (m, 1), 5.13 (dd, 1, *J* = 10.0, 9.0), 5.01−4.85 (m, 2), 4.63 (q, 1, *J* = 6.7), 4.36 (d, 2, *J* = 6.7), 4.22 (t, 1, *J* = 6.7), 3.53 (dd, 1, *J* = 13.0, 4.9), 3.46 (dd, 1, *J* = 13.0, 5.8), 2.79 (dd, 1, *J* = 13.1, 9.0), 2.42 (dd, 1, *J* = 13.1, 10.0), 1.60 (br d, 3, *J* = 6.7); ^{13}C NMR 173.3, 169.3, 167.2, 156.8, 155.6, 154.3, 149.7, 143.7, 143.6, 141.3, 140.8, 136.5, 135.5, 134.7, 133.9, 133.8, 133.4 (3 C), 130.8, 129.1 (2 C), 128.6 (2 C), 128.5, 127.7 (2 C), 127.3, 127.04 (2 C), 127.01 (2 C), 126.9, 126.6, 126.2, 125.1 (2 C), 123.7, 120.0 (br, 2 C), 118.7, 117.0, 89.8, 82.9, 68.2, 67.3, 59.4, 53.6, 52.9, 47.0, 36.9, 30.8, 16.9 (br); IR (KBr) 3420 (br), 1790, 1728, 1681, 1652, 1608. Anal. Calcd for $C_{53}H_{43}N_5O_8Se$: C, 66.52; H, 4.53; N, 7.32. Found: C, 66.24; H, 4.82; N, 7.10.

***N*-19-Cbz-dehydrofumiquinazoline A (54b) and *N*-19-Cbz-fumiquinazoline C (60).** To a solution of **57** (550 mg, 0.57 mmol) in dry EtOAc (1.0 mL) was added dry piperidine (0.2 mL, 4 equiv). The resulting mixture was stirred at room temperature for 10 min, diluted with hexane (3 mL), and concentrated under reduced pressure to give the crude amidine **58** as yellow solid, which was dissolved in dry MeCN (4 mL). AcOH (0.1 mL) was added and the solution was refluxed for 1.5 h, cooled, and concentrated to give a light-red residue. Flash chromatography on silica gel (5:1 CH_2Cl_2/EtOAc) gave 48 mg (14%) of **60** as a white solid followed by 185 mg (56%) of a 8:1 mixture of **54b** and the C-14 epimer as a yellow solid.

Data for **54b** were determined from the mixture: ^{1}H NMR 9.10, (br, 1, NH), 8.15 (d, 1, *J* = 7.9), 7.92 (br d, 1, *J* = 7.9), 7.76 (ddd, 1, *J* = 7.9, 7.9, 1.1), 7.69 (d, 1, *J* = 7.9), 7.57 (d, 1, *J* = 7.9), 7.45 (ddd, 1, *J* = 7.9, 7.9, 1.2), 7.40 (ddd, 1, *J* = 7.9, 7.9, 1.2), 7.39−7.29 (m, 5), 7.28 (ddd, 1, *J* = 7.9, 7.9, 1.2), 6.04 (d, 1, *J* = 1.9), 5.72 (s, 1), 5.65 (dd, 1, *J* = 9.8, 3.7), 5.17 (br, 2), 4.49 (q, 1, *J* = 6.7), 4.41 (d, 1, *J* = 1.9), 4.20 (s, 1, OH), 2.24 (dd, 1, *J* = 13.7, 9.8), 1.94 (br dd, 1, *J* = 13.7, 3.7), 1.39 (d, 3, *J* = 6.7); ^{13}C NMR 167.7 (br), 167.1, 159.8, 155.8 (br), 146.9, 144.5, 136.2, 135.9, 135.4, 134.9, 133.5, 130.1, 128.7 (3 C), 128.5 (2 C), 128.1, 127.7, 127.6, 127.1, 126.3, 120.3, 116.4, 103.2, 87.3, 80.1, 68.3, 59.7, 51.6, 38.8, 18.1; IR (KBr) 3261 (br), 1793, 1723, 1686, 1609, 1585, 1563, 1512; HRMS (FAB, DCM/NBA) calcd for $C_{32}H_{27}N_5O_6Na^+$ (MNa^+) 600.1859, found 600.1884.

***N*-19-Cbz-fumiquinazoline C (60).** To a solution of **54b** (58 mg, 0.10 mmol) in MeCN (1 mL) was added AcOH (0.01 mL). The solution was refluxed for 2 h, cooled, and concentrated. Flash chromatography on silica gel (5:1 CH_2Cl_2/EtOAc) gave 35 mg (60%) of **54b** as white solid preceded by 17 mg (30%) of **60** as a white solid: mp 168−170 °C; $[\alpha]_D$ −15.8 (*c* 0.50 in $CHCl_3$); ^{1}H NMR 8.27 (d, 1, *J* = 7.9, H-10), 8.03 (br, 1, NH, H-2), 7.86−7.76 (m, 2, H-7 and H-8), 7.58 (d, 1, *J* = 7.9, H-24), 7.54 (d, 1, *J* = 7.9, H-27), 7.49 (dd, 1, *J* = 7.9, 7.9, H-9), 7.35 (dd, 1, *J* = 7.9, 7.9, H-25), 7.34−7.28 (m, 4, $PhCH_2$), 7.22 (d, 1, *J* = 7.9, H-26), 7.05 (br, 1, $PhCH_2$), 5.75 (s, 1, H-18), 5.70 (br, 1, H-14), 4.46−4.35 (m, 1, H-20), 4.40−4.25 (m, 2, CH_2Ph), 2.79 (dd, 1, *J* = 15.3, 3.7, H-15b), 2.30 (dd, 1, *J* = 15.3, 3.7, H-15a), 2.13 (s, 3, H-16), 1.44 (d, 3, *J* = 6.7, H-29); ^{13}C NMR 169.6, 168.8, 159.9, 154.5, 150.2, 147.5, 139.9, 135.6, 134.9, 134.6, 129.8, 128.5 (2 C), 128.4, 128.2, 128.1 (2 C), 127.4, 127.3, 126.6, 124.4, 121.1, 116.7, 87.6, 85.1, 83.6, 67.7, 59.0, 51.9, 31.7, 24.6, 18.4; IR (KBr) 3462 (br), 1719, 1684, 1624, 1609; a ROESY experiment showed cross-peaks between H-16 and H-2, H-16 and CH_2Ph, H-15a and H-14, H-15b and H-14, H-15a and H-29, H-29 and H-20, H-16 and H-18, H-2 and H-27, H-9 and H-10; HRMS (FAB, DCM/NBA) calcd for $C_{32}H_{28}N_5O_6^+$ (MH^+) 578.2040, found 578.2048.

Fumiquinazoline C (7). To a solution of **60** (12 mg, 0.02 mmol) in EtOH (2 mL) was added Pd (5%) on carbon (6 mg). The suspension was stirred at room temperature under H_2 (60 PSI) for 30 h. The catalyst was filtered off and the filtrate was evaporated to give crude **7**. Flash chromatography on silica gel (1:1 CH_2Cl_2/EtOAc) gave 7.1 mg (77%) of fumiquinazoline C (**7**) as a light yellow solid: mp 179−182 °C (lit.[1] mp 178−182 °C); $[\alpha]_D$ −191.2 (*c* 0.15 in $CHCl_3$) (lit.[1] $[\alpha]_D$ −193.7); λ_{max} (EtOH) nm 207 (4.58), 225 (4.47), 260 (4.09), 271 (3.97), 282 (3.90), 304 (3.56), 317 (3.50); ^{1}H NMR 8.38 (d, 1, *J* = 7.4), 7.86 (dd, 1, *J* = 7.4, 6.3), 7.81 (d, 1, *J* = 7.4), 7.62 (dd, 1, *J* = 7.4, 6.3), 7.46 (d, 1, *J* = 7.4), 7.37 (d, 1, *J* = 7.9), 7.32 (td, 1, *J* = 7.9, 1.1), 7.21 (t, 1, *J* = 7.9), 7.03 (br, 1, NH), 5.74 (d, 1, *J* = 7.4), 5.35 (br d, 1, *J* = 6.7), 3.71 (qd, 1, *J* = 6.7, 6.7), 2.99 (dd, 1, *J* = 15.3, 7.4), 2.14 (d, 1, *J* = 15.3), 2.06 (s, 3), 1.07 (d, 3, *J* = 6.7), 1.03 (dd, 1, *J* = 6.7, 6.7, NH); ^{13}C NMR 170.8, 170.2,

159.5, 150.3, 146.3, 138.3, 135.7, 134.9, 130.3, 128.6, 128.4, 127.0, 126.2, 124.8, 121.4, 115.5, 87.2, 87.0, 84.1, 58.6, 51.4, 31.4, 24.6, 18.7; IR (KBr) 3440 (br), 1715, 1611. The spectral data are identical with those previously reported.[1]

***N*-19-Cbz-fumiquinazoline E (59).** A 0.2 M HCl solution was prepared by adding 0.284 mL of AcCl into 20 mL of dry MeOH and stirring for 2 h. A 28-mg (0.05 mmol)sample of **54b** was dissolved in a solution of HCl in MeOH (0.2 M, 1.0 mL). The solution was stirred at room temperature for 5 min, diluted with water, neutralized with NH_4OH, and extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel (5:1 CH_2Cl_2/EtOAc) gave 18 mg (61%) of **59** as a white solid: mp 151−152 °C; $[\alpha]_D$ −149.7 (*c* 0.50 in $CHCl_3$); ^{1}H NMR 8.17 (d, 1, *J* = 7.9), 7.77 (dd, 1, *J* = 7.9, 7.9), 7.72 (d, 1, *J* = 7.9), 7.59 (d, 1, *J* = 7.9), 7.49 (dd, 1, *J* = 7.9, 7.9), 7.45−7.25 (m, 8), 7.10 (br, 1, NH), 5.78 (s, 1), 5.66 (dd, 1, *J* = 10.4, 4.7), 5.24 (br, 2), 4.54 (q, 1, *J* = 6.7), 3.26 (br, 3), 2.76 (dd, 1, *J* = 14.0, 10.4), 2.01 (dd, 1, *J* = 14.0, 4.7), 1.94 (s, 3), 1.43 (d, 3, *J* = 6.7); ^{13}C NMR 168.0, 167.6, 160.0, 155.4, 149.2, 146.2, 136.1, 135.5 (2 C), 134.7, 128.9, 128.6 (3 C), 128.5, 128.2 (2 C), 127.9 (3 C), 127.1, 120.5, 116.4, 87.4, 84.8, 80.2, 68.2, 59.6, 52.7, 49.8, 38.7, 20.8, 18.2; IR (KBr) 3418 (br), 1716, 1684, 1602; HRMS (FAB, DCM/NBA) calcd for $C_{33}H_{31}N_5O_7Na^+$ (MNa^+) 632.2121, found 632.2101.

Fumiquinazoline E (3). To a solution of **59** (12 mg, 0.02 mmol) in methanol (2 mL) was added Pd (5%) on carbon (6 mg). The suspension was stirred at room temperature under H_2 (1 atm) for 30 min. The catalyst was filtered off and the filtrate was evaporated to give crude **3**. Flash chromatography on silica gel (3:2 CH_2Cl_2/EtOAc) gave 8.0 mg (84%) of pure fumiquinazoline E (**3**) as a light yellow solid: mp 168−170 °C (lit.[1] mp 168−172 °C); $[\alpha]_D$ −144.6 (*c* 0.32 in $CHCl_3$) (lit.[1] $[\alpha]_D$ −143.3); λ_{max} (EtOH) nm (log ϵ) 210 (4.52), 226 (4.44), 234 (4.36), 256 (4.10), 278 (4.01), 304 (3.55), 317 (3.41); ^{1}H NMR 8.26 (d, 1, *J* = 6.8), 7.80 (ddd, 1, *J* = 7.9, 7.9, 1.0), 7.76 (d, 1, *J* = 7.9), 7.59 (d, 1, *J* = 7.2), 7.58 (dd, 1, *J* = 7.2, 1.0), 7.54 (dd, 1, *J* = 7.9, 6.8), 7.35 (dd, 1, *J* = 7.9, 7.2), 7.17 (dd, 1, *J* = 7.9, 7.2), 6.86 (br, 1, NH), 5.94 (dd, 1, *J* = 9.2, 4.9), 5.46 (br s, 1), 4.51 (s, 1, OH), 4.16 (q, 1, *J* = 6.7), 3.34 (s, 3), 2.83 (dd, 1, *J* = 14.4, 9.2), 2.80 (br, 1, NH), 2.48 (dd, 1, *J* = 14.4, 4.9), 1.97 (s, 3), 1.34 (d, 3, *J* = 6.7); ^{13}C NMR 172.6, 171.3, 161.0, 148.2, 146.2, 138.6, 136.8, 134.8, 129.7, 128.0 (2 C), 126.9, 125.2, 124.7, 120.6, 115.1, 86.3, 84.8, 80.1, 59.2, 53.4, 50.8, 38.9, 20.9, 17.9; IR (KBr) 3420 (br), 1685, 1608. A 2-D NOESY experiment showed correlations between OMe and H-15a, OMe and H-15b, OMe and H-16, H-14 and OH, H-14 and H-27. The data are identical with those previously reported.[1]

Tetracyclic Lactone 42b. To a solution of **41b** (450 mg, 0.68 mmol) in methanol (5 mL) was added Pd (5%) on carbon (100 mg). The suspension was stirred at room temperature under H_2 (1 atm) for 30 min. The catalyst was filtered off and the filtrate was concentrated under reduced pressure to give the crude amine alcohol. To a solution of the crude amine alcohol in CH_2Cl_2 (20 mL) was added silica gel (EM 9385, silica gel 60, 230−400 mesh, 15 g). The mixture was stirred at room temperature for 24 h. The silica gel was filtered off and the filtrate was evaporated under reduced pressure. Flash chromatography on silica gel (10:1 CH_2Cl_2/EtOAc) gave 215 mg (65%) of the lactone amine **42b** as a white solid: mp 102−104 °C; $[\alpha]_D$ −16.4 (*c* 0.45 in $CHCl_3$); ^{1}H NMR 7.52 (d, 1, *J* = 7.9), 7.45−7.38 (m, 2), 7.25 (t, 1, *J* = 7.9), 5.69 (s, 1), 5.63 (d, 1, *J* = 6.7, NH), 4.76 (s, 2), 4.72 (dd, 1, *J* = 11.8, 8.4), 3.98−3.91 (m, 1), 3.19 (dd, 1, *J* = 12.5, 8.4), 2.22 (dd, 1, *J* = 12.5, 11.8), 1.93−1.80 (m, 1), 1.73−1.57 (m, 2), 1.62 (br, 1, NH), 1.04 (d, 3, *J* = 6.1), 1.01 (d, 3, *J* = 6.1); ^{13}C NMR 173.9, 173.1, 154.1, 137.6, 133.6, 130.9, 126.4, 124.6, 116.4, 95.0, 91.0, 84.3, 74.8, 62.9, 51.0, 42.9, 36.2, 25.4, 23.0, 21.8; IR (KBr) 3356, 1793, 1718, 1608; HRMS (FAB, DCM/NBA) calcd for $C_{20}H_{23}Cl_3N_3O_5^+$ (MH^+) 490.0703, found 490.0689.

Fmoc-tetracyclic Lactone 66b. To a solution of the free lactone amine **42b** (150 mg, 0.30 mmol) in CH_2Cl_2 (1 mL) was added FmocCl (140 mg, 3 equiv) and (*i*-Pr)$_2$NEt (0.1 mL, 2 equiv). The reaction mixture was stirred at room temperature for 24 h, and quenched with saturated $NaHCO_3$. The organic layer was washed with brine, dried, and concentrated. Flash chromatography on silica gel (50:1 CH_2Cl_2/EtOAc) gave 150 mg (70%) of **66b** as a white solid: mp 75−78 °C; $[\alpha]_D$ +34.9 (*c* 0.90 in $CHCl_3$); ^{1}H NMR (5:1 mixture of rotamers, major rotamer) 7.80−7.76 (m, 2), 7.77 (d, 1, buried), 7.57 (d, 2, *J* = 7.3), 7.45 (d, 1, *J* = 7.9), 7.44−7.28 (m, 5), 7.25 (t, 1, *J* = 7.9), 5.80 (d, 1, *J* = 6.7, NH), 5.78 (s, 1), 4.91−4.84 (m, 1), 4.80 (d, 1, *J* = 12.2), 4.76−4.67 (m, 1), 4.71 (d, 1, *J* = 12.2), 4.28−4.18 (m, 2), 4.01−3.94 (m, 1), 2.60 (dd, 1, *J* = 14.0, 11.0), 2.17 (dd, 1, *J* = 14.0, 9.2), 1.78−1.66 (m, 1), 1.53−1.46 (m, 2), 0.75 (d, 3, *J* = 6.7), 0.73 (d, 3, *J* = 6.7); ^{1}H NMR (minor rotamer, partial) 7.61 (d, 1, *J* = 7.3), 5.64 (s, 1), 4.05 (t, 1, *J* = 6.1), 0.94 (d, 3, *J* = 6.7), 0.87 (d, 3, *J* = 6.7); ^{13}C NMR (major rotamer) 173.7, 168.5, 154.1, 153.8, 143.3, 143.0, 141.5, 141.4, 135.9, 135.7, 130.7, 127.9 (2 C), 127.2 (2 C), 125.7, 124.7, 124.5, 124.4, 120.32, 120.27, 116.0, 95.1, 89.5, 83.3, 74.9, 66.8, 62.0, 51.8, 47.3, 39.2, 34.9, 23.7, 23.3, 21.7; ^{13}C NMR (minor rotamer, partial) 144.3, 131.2, 127.5, 126.9, 124.7, 120.0, 65.1, 50.3, 47.1; IR (KBr) 3308, 1797, 1734, 1690, 1608; HRMS (FAB, DCM/NBA/PPG) calcd for $C_{35}H_{33}Cl_3N_3O_7^+$ (MH^+) 712.1384, found 712.1408.

Aniline Precursor to 67b. To a solution of **66b** (80 mg, 0.11 mmol) in acetic acid (1.0 mL) was added zinc dust (300 mg). The mixture was stirred at room temperature for 30 min. The mixture was diluted with EtOAc (10 mL) and the zinc dust was filtered off. The filtrate was washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated under reduced pressure to give the crude amine.

To a mixture of the crude amine and EDAC (55 mg, 0.24 mmol) in MeCN (1 mL) was added anthranilic acid (33 mg, 0.22 mmol) in several portions over 60 min at room temperature with stirring. The reaction mixture was stirred for an additional 20 min, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, which was washed with water and saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel (20:1 CH_2Cl_2/EtOAc) gave 64 mg (91%) of the aniline as a white solid: mp 147−150 °C; $[\alpha]_D$ +76.2 (*c* 0.32 in $CHCl_3$); ^{1}H NMR (10:1 mixture of rotamers, major) 8.01 (d, 1, *J* = 7.9), 7.78 (d, 1, *J* = 7.3), 7.77 (d, 1, *J* = 7.3), 7.62 (d, 1, *J* = 7.3), 7.59 (dd, 2, *J* = 7.3, 7.3), 7.44 (d, 1, *J* = 7.9), 7.41 (dd, 2, *J* = 7.3, 7.3), 7.38−7.29 (m, 3), 7.24 (dd, 1, *J* = 7.9, 7.9), 7.19 (dd, 1, *J* = 7.9, 7.9), 6.71 (d, 1, *J* = 6.7, NH), 6.64 (d, 1, *J* = 7.9), 6.63 (1, *J* = 7.9, 7.9), 5.81 (s, 1), 5.56 (br, 2, NH), 4.92 (dd, 1, *J* = 10.9, 5.5), 4.68 (dd, 1, *J* = 10.9, 4.9), 4.23 (dd, 1, *J* = 5.5, 4.9), 4.18 (ddd, 1, *J* = 11.0, 9.2, 6.7), 4.01 (t, 1, *J* = 6.7), 2.55 (dd, 1, *J* = 13.7, 11.0), 2.27 (dd, 1, *J* = 13.7, 9.2), 1.81−1.68 (m, 1), 1.58−1.49 (m, 2), 0.77 (d, 3, *J* = 6.7), 0.76 (d, 3, *J* = 6.7); ^{1}H NMR (minor rotamer, partial) 7.73 (d, 2, *J* = 7.3), 5.67 (s, 1), 2.79−2.64 (m, 1), 2.35−2.27 (m, 1), 0.93 (d, 3, *J* = 6.7), 0.86 (d, 3, *J* = 6.7); ^{13}C NMR 174.6, 168.9, 168.6, 154.0, 149.2, 143.5, 143.1, 136.1, 135.9, 133.0, 130.6, 127.9, 127.347, 127.293, 127.2, 127.1, 126.2, 124.50, 124.46, 120.4, 120.3, 117.5, 116.7, 116.0, 113.7, 89.61, 83.57, 66.8, 62.1, 51.4, 47.4, 39.4, 35.0, 23.8, 23.4, 21.8; IR (KBr) 3483, 3354, 1793, 1733, 1695, 1653, 1611. Anal. Calcd for $C_{39}H_{36}N_4O_6 \cdot H_2O$: C, 69.42; H, 5.68; N, 8.30. Found: C, 68.91; H, 5.53; N, 8.06.

Diamide Precursor to 67b. To a solution of the aniline (66 mg, 0.10 mmol) and EDAC (60 mg, 3 equiv) in MeCN (3 mL) was added *N*-Fmoc-phenylselenyl-L-alanine (40 mg, 0.20 mmol, 2 equiv). The resulting mixture was stirred at 35 °C for 1 h and concentrated. The residue was dissolved in CH_2Cl_2, which was washed with water and saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel (20:1 CH_2Cl_2/EtOAc) gave 78 mg (71%) of the diamide as a white solid: mp 136−138 °C; $[\alpha]_D$ −154.2 (*c* 0.45 in $CHCl_3$); ^{1}H NMR 11.2 (s, 1, NH), 8.28 (br d, 1, *J* = 8.0), 8.05 (d, 1, *J* = 7.3, NH), 7.86−7.78 (m, 1), 7.77−7.68 (m, 4), 7.65−7.57 (m, 1), 7.54 (d, 1, *J* = 8.0), 7.49−7.19 (m, 18), 7.07−

6.98 (m, 3), 5.96 (d, 1, J = 7.7, NH), 5.72 (s, 1), 5.09 (dd, 1, J = 10.7, 4.7), 4.78−4.68 (m, 1), 4.55 (dd, 1, J = 10.7, 3.5), 4.39−4.20 (m, 3), 4.21−4.13 (m, 2), 3.94−3.84 (m, 1), 3.56−3.45 (m, 2), 2.41 (dd, 1, J = 13.7, 10.7), 2.17 (dd, 1, J = 13.7, 8.7), 1.75−1.64 (m, 1), 1.55−1.43 (m, 2), 0.77 (d, 3, J = 6.7), 0.72 (d, 3, J = 6.7); ^{13}C NMR 175.3, 168.7, 168.6, 168.4, 156.0, 153.9, 144.0, 143.6, 143.5, 143.2 (2 C), 141.6, 141.4, 141.23, 141.15, 138.8, 136.0, 135.7, 133.4 (3 C), 133.2, 130.9, 129.0 (2 C), 127.9, 127.6 (2 C), 127.4, 127.3, 127.2, 127.1 (2 C), 127.0, 126.7, 126.2, 125.4, 125.1, 124.4, 124.3, 123.4, 121.9, 120.4, 120.3, 119.9 (2 C), 119.0, 116.1, 90.2, 83.4, 67.4, 66.9, 61.9, 55.9, 51.9, 47.5, 46.9, 39.5, 34.5, 30.5, 23.8, 23.4, 21.7; IR (KBr) 3365 (br), 1792, 1729, 1684, 1649, 1603. Anal. Calcd for $C_{53}H_{45}N_5O_9Se\cdot H_2O$: C, 67.37; H, 5.12; N, 6.24. Found: C, 67.85; H, 5.05; N, 6.10.

Iminobenzoxazine 67b. To a solution of Ph_3P (52 mg, 0.2 mmol, 4 equiv) in dry CH_2Cl_2 (2 mL) was added a Br_2 solution in CH_2Cl_2 (1.0 M, 0.19 mmol, 3.8 equiv) under N_2. The resulting solution was stirred at room temperature for 5 min, and (i-Pr)$_2$NEt (0.04 mL, 4 equiv) and the diamide (55 mg, 0.05 mmol) were added. The resulting mixture was stirred at room temperature for 5 min and concentrated. The residue was washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. Flash chromatography on silica gel (50:1 CH_2Cl_2/EtOAc) gave 50 mg (91%) of **67b** as a light-yellow solid: mp 127−130 °C; $[\alpha]_D$ +18.4 (c 0.44 in $CHCl_3$); ^{1}H NMR (6:1 mixture of rotamers, major rotamer) 8.01 (d, 1, J = 7.9), 7.77 (d, 2, J = 7.3), 7.73 (d, 2, J = 7.3), 7.64 (t, 2, J = 7.3), 7.60−7.52 (m, 4), 7.53−7.47 (m, 2), 7.46−7.22 (m, 13), 7.04−6.95 (m, 3), 6.10 (d, 1, J = 8.5, NH), 5.90 (s, 1), 4.94−4.84 (m, 4), 4.37−4.30 (m, 2), 4.27−4.21 (m, 2), 4.11−4.03 (m, 1), 3.57 (dd, 1, J = 13.1, 4.6), 3.41 (dd, 1, J = 13.1, 6.1), 2.72 (dd, 1, J = 14.0, 9.8), 2.13 (dd, 1, J = 14.0, 6.7), 1.81−1.68 (m, 1), 1.55−1.41 (m, 2), 0.75 (d, 3, J = 6.7), 0.74 (d, 3, J = 6.7); ^{1}H NMR (minor rotamer, partial) 6.14 (d, 1, J = 7.9, NH), 5.86 (s, 1), 5.03−4.96 (m, 4), 4.54−4.48 (m, 2), 3.53−3.45 (m, 1), 3.28−3.20 (m, 1), 2.84−2.76 (m, 1), 2.09−2.01 (m, 1), 0.99 (d, 3, J = 6.7), 0.92 (d, 3, J = 6.7); ^{13}C NMR (major rotamer) 174.3, 168.6, 156.6, 155.5, 154.0, 149.2, 143.8 (2 C), 143.5 (2 C), 141.4 (2 C), 141.3 (2 C), 140.8, 136.1, 136.0, 133.6, 133.3 (3 C), 130.6, 129.0 (2 C), 128.5, 128.3, 127.9 (2 C), 127.7 (2 C), 127.3, 127.1 (2 C), 126.9, 126.6, 126.0, 125.3 (2 C), 125.2, 125.0, 124.4, 124.2, 120.3 (2 C), 119.9 (2 C), 118.9, 116.5, 90.1, 83.3, 67.3, 67.0, 62.3, 55.6, 53.2, 47.3, 47.0, 39.1, 38.0, 30.3, 23.8, 23.3, 21.7; ^{13}C NMR (minor rotamer, partial) 143.0, 133.7, 128.6, 128.0, 82.7, 46.6; IR (KBr) 3418 (br), 1792, 1725, 1717, 1677, 1607. Anal. Calcd for $C_{63}H_{54}N_5O_8Se$: C, 69.61; H, 4.91; N, 6.44. Found: C, 69.28; H, 4.97; N, 6.24. HRMS (FAB, DCM/NBA) calcd for $C_{63}H_{54}N_5O_8Se^+$ (MH^+) 1088.3138, found 1088.3102.

Fumiquinazoline H (6). To a solution of **67b** (23 mg, 0.02 mmol) in dry EtOAc (0.10 mL) was added dry piperidine (0.01 mL, 10 equiv). The resulting mixture was stirred at room temperature for 10 min, diluted with hexane, and concentrated under reduced pressure to give the crude amidine **68b** as solid, which was dissolved in dry MeCN (4 mL). The solution was refluxed for 1 h, cooled, and concentrated to give a light-red residue. Flash chromatography on silica gel (5:1 CH_2Cl_2/EtOAc) gave 3.3 mg (34%) of **6** as a white solid: mp 145−147 °C (lit.[2] mp 144−147 °C); $[\alpha]_D$ −60.8 (c 0.12 in $CHCl_3$) (lit.[2] $[\alpha]_D$ −59); ^{1}H NMR ($CDCl_3$) 8.32 (dd, 1, J = 7.9, 1.2), 7.83 (ddd, 1, J = 7.9, 7.9, 1.2), 7.78 (d, 1, J = 7.9), 7.58 (ddd, 1, J = 7.9, 7.9, 1.2), 7.52 (d, 1, J = 7.9), 7.30 (ddd, 1, J = 7.9, 7.9, 1.8), 7.08−7.00 (m, 2), 6.62 (br, 1, NH), 5.80−5.74 (m, 2), 3.94 (dd, 1, J = 8.5, 4.5), 3.16 (dd, 1, J = 15.3, 6.5), 2.56 (br, 1, NH), 2.08 (s, 3), 1.94 (dd, 1, J = 15.3, 1.8), 1.90−1.77 (m, 2), 1.72−1.60 (m, 1), 1.04 (d, 3, J = 6.7), 1.00 (d, 3, J = 6.7); ^{1}H NMR (acetone-d_6) 8.71 (br s, 1, NH, H-2), 8.22 (dd, 1, J = 7.9, 1.2, H-10), 7.87 (ddd, 1, J = 7.9, 7.9, 1.2, H-8), 7.75 (d, 1, J = 7.9, H-7), 7.60 (ddd, 1, J = 7.9, 7.9, 1.2, H-9), 7.43 (d, 1, J = 7.8, H-24), 7.29 (ddd, 1, J = 7.8, 7.8, 1.2, H-25), 7.24 (d, 1, J = 7.8, H-27), 7.04 (ddd, 1, J = 7.8, 7.8, 1.2, H-26), 5.92 (dd, 1, J = 5.8, 1.2, H-18), 5.54 (ddd, 1, J = 5.6, 1.8, 1.8, H-14), 3.82 (t, 1, J = 7.3, H-20), 3.17 (dd, 1, J = 14.9, 5.6, H-15a), 2.56 (br d, 1, J = 5.8, NH, H-19), 2.07 (dd, 1, J = 14.9, 1.8, H-15b), 2.01 (s, 3, H-16), 1.92−1.80 (m, 1, H-30), 1.75−1.65 (m, 2, H-29), 1.02 (d, 3, J = 6.7, H-31), 0.98 (d, 3, J = 6.7, H-32); ^{13}C NMR (acetone-d_6) 173.6 (C-21), 169.7 (C-1), 160.1 (C-12), 153.0 (C-4), 148.3 (C-6), 138.9 (C-28), 138.4 (C-23), 135.5 (C-8), 130.8 (C-25), 129.1 (C-7), 128.4 (C-9), 127.7 (C-10), 127.1 (C-27), 126.2 (C-26), 122.1 (C-11), 115.6 (C-24), 88.9 (C-18), 88.0 (C-17), 85.6 (C-3), 63.4 (C-24), 54.2 (C-14), 42.7 (C-29), 35.5 (C-15), 26.4 (C-30), 24.6 (C-16), 23.3 (C-31), 22.4 (C-32). The data are identical with those previously reported.[2]

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Supporting Information Available: Experimental procedures for those compounds not provided in the Experimental Section and copies of ^{1}H and ^{13}C NMR spectra of key intermediates and fumiquinazolines A, B, C, E, H, and I. This material is available free of charge via the Internet at http://pubs.acs.org.

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