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Total Syntheses of (−)-Fumiquinazolines A, B, and I

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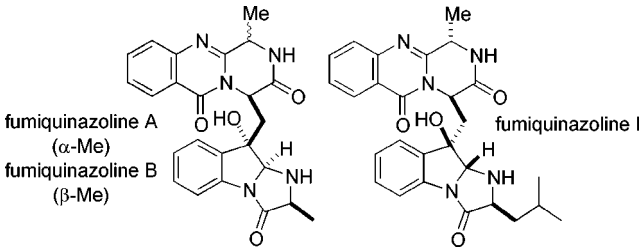
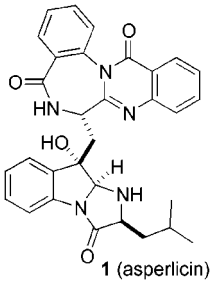
ABSTRACT

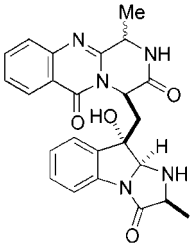


The first total syntheses of (−)-fumiquinazolines A, B, and I have been accomplished efficiently using the Pd-catalyzed cyclization of an iodoindole carbamate to construct the imidazoindolone moiety and the dehydrative cyclization of a diamide followed by rearrangement through an amidine to construct the quinazolone moiety.

We recently reported the first synthesis of the potent cholecystokinin antagonist asperlicin (**1**).[1] The key steps in this synthesis include the use of the Buchwald palladium-catalyzed cyclization[2] of iodoindole carbamate **4** to form the novel imidazoindolone **5** (see Scheme 1). Selective acylation of the more acidic anilide nitrogen of **6** with azidobenzoyl chloride and cyclization to quinazolone **7** by the Eguchi aza Wittig protocol (see Scheme 1) provides an efficient route to the fused quinazolinone ring system without the use of protecting groups.[3] Finally, epoxidation of **8** with the saccharine-derived oxaziridine in MeOH affords **9** with the desired α-hydroxy group in 75−92% selectivity depending on the R group. Directed reduction of **9** with $NaBH(OAc)_3$ proceeds through **10**, which leads exclusively to **11** with the desired cis H and OH substituents on the less hindered α-face.



1 (asperlicin)



2, α-Me (fumiquinazoline A)
3, β-Me (fumiquinazoline B)

Numata and co-workers isolated the moderately cytotoxic fumiquinazolines A (**2**) and B (**3**) from a strain of *Aspergillus fumigatus* isolated from the gastrointestinal tract of the fish *Pseudolabrus japonicus*.[4] The imidazoindolone moieties of the fumiquinazolines can be constructed using the protocol developed in our asperlicin synthesis. However, the Eguchi

(1) He, F.; Foxman B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1998**, *120*, 6417−6418.
(2) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525−7546.
(3) Takeuchi, H.; Hagiwara, S.; Eguchi, S. *Tetrahedron* **1989**, *45*, 6375−6386.
(4) (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.
(5) Wang, H.; Ganesan, A. *J. Org. Chem.* **1998**, *63*, 2432−2433. (b) Wang, H.; Ganesan, A. *J. Org. Chem.* **2000**, *65*, 1022−1030.
(6) He, F.; Snider, B. B. *J. Org. Chem.* **1999**, *64*, 1397−1399. See also: Hart, D. J.; Magomedov, N. *Tetrahedron Lett.* **1999**, *40*, 5429−5432.
(7) Mazurkiewicz, R. *Monatsh. Chem.* **1989**, *120*, 973−980.

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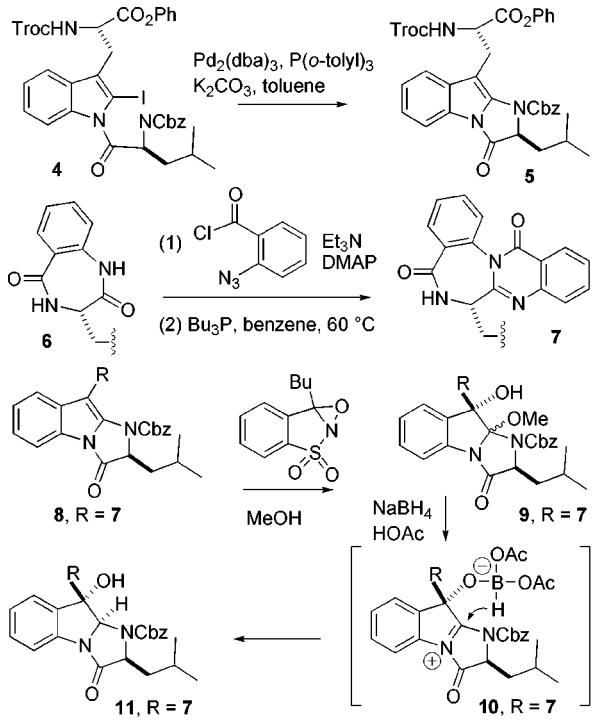
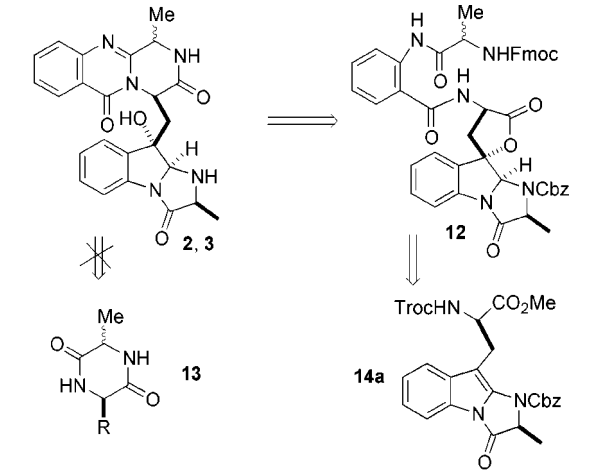
Scheme 1



aza Wittig procedure is not attractive since selective acylation of diketopiperazine **13** will not be selective (see Scheme 2).

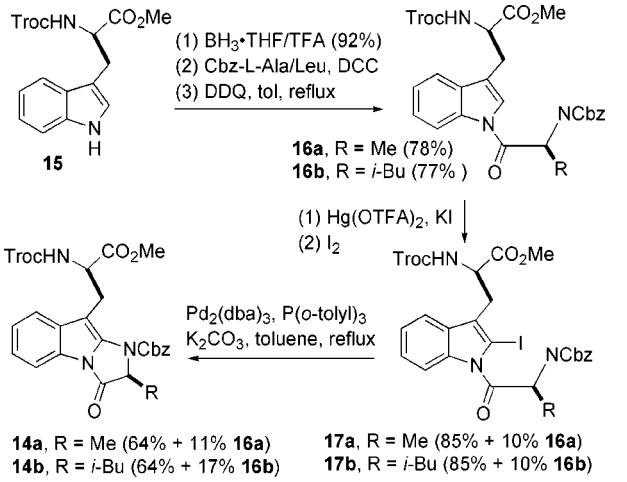
Scheme 2



Dehydrative cyclization of diamide **12** should form the quinazolone of **2** and **3**. Wang and Ganesan reported that treatment of analogous simpler anthranilamides with Ph_3P, I_2, and Et(*i*-Pr)$_2$N affords the desired quinazolinones.[5] We showed[6] that this procedure actually gives an iminobenzoxazine,[7] e.g., **23**, which is converted to an amidine, e.g., **24**, by the piperidine used to deprotect the Fmoc group. The desired quinazolinone is formed during TLC purification. Diamide **12** can be prepared easily from imidazoindolone **14a**. Since the amide bond of **14a** is not stable to the basic conditions needed to rearrange the iminobenzoxazine to the quinazolone, we introduced the hydroxy group by epoxidation and reduction prior to quinazolinone formation and protected it intramolecularly as the lactone of **12**.

Reduction of protected D-tryptophan **15**[8] with BH_3·THF in TFA[9] provides 92% of the indoline, which is acylated with *N*-CBZ-L-alanine and DCC to afford 79% of *N*-acylindole **16a** after oxidation with DDQ[10] (see Scheme 3).

Scheme 3



Mercuration[11] of **16a** with $Hg(OTFA)_2$, addition of KI, and iodination give 85% of iodoindole **17a** and 10% of recovered **16a**. The Buchwald palladium-catalyzed cyclization[2] of **17a** affords 64% of **14a** and 11% of indole **16a**, which can be recycled.

Epoxidation of **14a** with the saccharine-derived oxaziridine[12] yields 65% of **18a** as a mixture of diastereomers with an α-hydroxy group and 23% of **19a** as a mixture of diastereomers with a *β*-hydroxy group (see Scheme 4). Reduction of **18a** with $NaBH(OAc)_3$ provides exclusively the isomer with an α-hydrogen as described above for the conversion of **9** to **11**.[13] Lactonization to give 66% of **20a** is accomplished by stirring with silica gel in CH_2Cl_2 for 12 h. Mild conditions are necessary since the lactone is easily epimerized.[14] A similar sequence converts **19a** to 70% of **21a**.

Reductive deprotection of **20a** with Zn in AcOH affords the amine, which is coupled with anthranilic acid and EDAC

(8) Prepared in >95% yield by reaction of D-tryptophan methyl ester hydrochloride with Troc chloride in a two-phase system of ether and aqueous $NaHCO_3$ for 4 h: Vedejs, E.; Wang, J. *Org. Lett.* **2000**, *2*, 1031−1032.

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

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

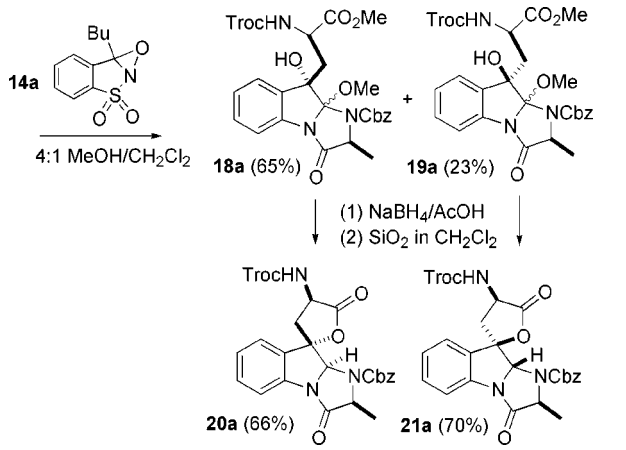
(11) Mingoia, Q. *Gazz. Chim. Ital*. **1930**, *60*, 509−515.

(12) (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.

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

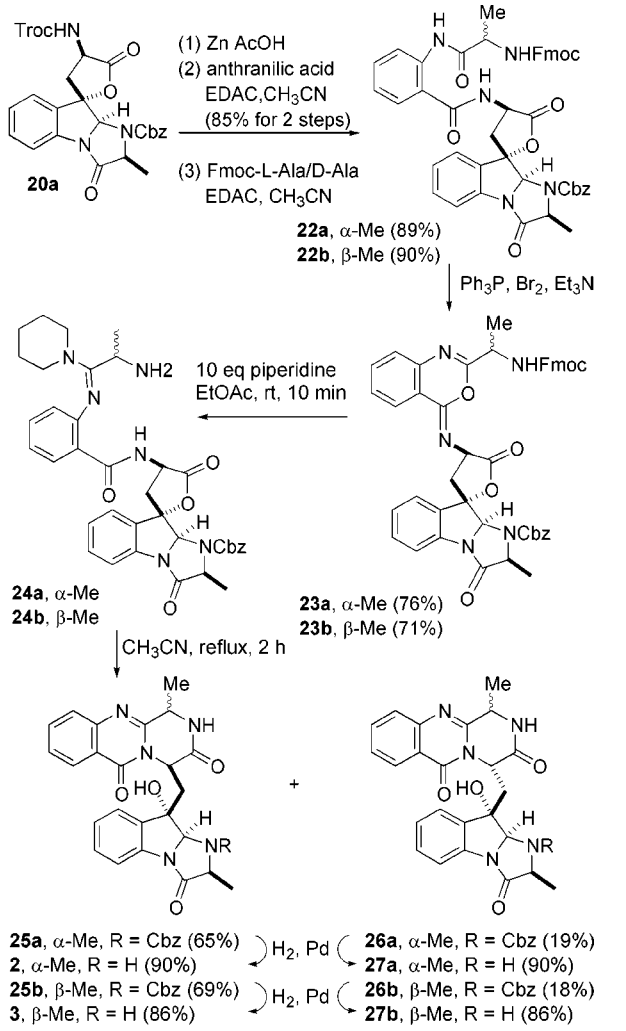
(14) Michl, K.; *Liebigs Ann. Chem.* **1981**, 33−39.

Scheme 4



in CH_3CN to yield 85% of the aniline (see Scheme 5). A second coupling with Fmoc-L-alanine yields 89% of **22a**. Treatment of **22a** with Ph_3P, Br_2, and Et_3N in CH_2Cl_2 at room temperature provides 76% of iminobenzoxazine **23a**.[5−7,15]

Scheme 5



Reaction of **23a** with 10 equiv of piperidine in EtOAc at 25 °C for 10 min gives crude amidine amine **24a**, which is refluxed in CH_3CN for 2 h to give 65% of Cbz-fumiquinazoline A (**25a**) and 19% of the readily separable isomer **26a** resulting from epimerization of the sensitive lactone[14] prior to formation of the diketopiperazine. Cyclization at lower temperatures proceeds with less epimerization but gives a lower yield of **25a**. Hydrogenolysis of **25a** affords 90% of fumiquinazoline A (**2**) with spectral data and optical rotation identical to that reported for the natural product.[4] Hydrogenolysis of **26a** gives 90% of **27a** with spectral data identical to that reported for a base-catalyzed rearrangement product of fumiquinazolines A and B.[4,16]

A similar sequence coupling the aniline formed from **20a** with FMOC-D-alanine provides 90% of **22b**. Dehydrative cyclization affords 71% of iminobenzoxazine **23b**, which is rearranged via amidine **24b** to give 69% of Cbz-fumiquinazoline B (**25b**) and 18% of epimer **26b**. Hydrogenolysis of **25b** affords 90% of fumiquinazoline B (**3**) with spectral data and optical rotation identical to that reported for the natural product.[4,17] Hydrogenolysis of **26b** gives 90% of **27b** with spectral data identical to that reported for a base-catalyzed rearrangement product of fumiquinazolines A and B.[4,16]

Belofsky, Köck, and co-workers recently reported the isolation of the antifungal fumiquinazoline I (**30**) from a fungus *Acremonium* sp. isolated from the surface of the Caribbean tunicate *Ecteinascidia turbinata*.[18] Fumiquinazoline I differs from fumiquinazoline A in two respects. The substituent on the imidazolinone ring is an isobutyl group from leucine, rather than a methyl substituent from alanine. More significantly, the hydrogen and hydroxyl substituents on the indoline ring are cis to the alkyl substituent on the imidazolinone ring, rather than trans as in fumiquinazoline A. In our model study for the asperlicin synthesis, we found that epoxidation of imidazoindolone **8**, R = Me, with dimethyldioxirane,[19] rather than the saccharine-derived oxaziridine, affords a 2:1 mixture rich in the isomer required for fumiquinazoline I with the hydroxy group cis to the isobutyl substituent.[1] It was therefore a simple matter to adapt the synthesis of fumiquinazoline A to the synthesis of fumiquinazoline I.

Imidazoindolone **14b** derived from Cbz-L-leucine is prepared analogously to **14a** in the yields indicated in Scheme 3. Epoxidation of **14b** with dimethyldioxirane in 15:4:1

(15) Longer reaction times were required with I_2 instead of Br_2 so that more FMOC cleavage occurs with either Et_3N or $Et(i\text{-}Pr)_2N$ as the base.

(16) The spectral data for **27a** correspond exactly to those reported for **6** in ref 4b, while those for **27b** correspond exactly to those reported for **5**. The stereochemistry of **5** and **6** is switched in this reference.

(17) The ^1H NMR spectrum of fumiquinazoline B is concentration dependent. The spectrum of a 0.08 M solution in $CDCl_3$ matches that reported,[4] while the spectrum of a 0.01 M solution is shifted by as much as 0.1 ppm.

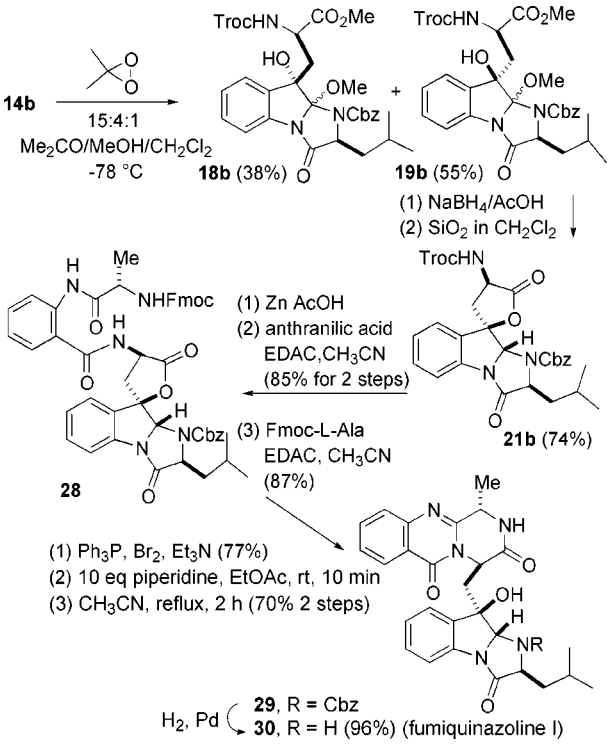
(18) Belofsky, G. N.; Anguera, M.; Jensen, P. R.; Fenical, W.; Köck, M. *Chem. Eur. J.* **2000,** *6*, 1355−1360.

(19) (a) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377. (b) Adam, W.; Reinhardt, D.; Reissig, H.-U.; Paulini, K. *Tetrahedron* **1995**, *51*, 12257−12262.

(20) 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.

acetone/MeOH/CH_2Cl_2 provides 55% of the desired alcohol **19b** with the hydroxy group cis to the isobutyl group and only 38% of the alcohol **18b**, which is the major product with the saccharine-derived oxaziridine (see Scheme 6).

Scheme 6



Reduction of **19b** with $NaBH(OAc)_3$ and lactonization with silica gel in CH_2Cl_2 yields 72% of **21b**. Diamide **28** is prepared analogously to **22a** in the yields indicated. Dehydrative cyclization of **28** with Ph_3P, Br_2, and Et_3N in CH_2Cl_2 affords 77% of the iminobenzoxazine. Deprotection and ring opening of the iminobenzoxazine with piperidine and cyclization in CH_3CN at reflux give 70% of Cbz-fumiquinazoline I (**29**) and 10% of the impure epimer corresponding to **26a**. Hydrogenolysis of **29** affords 96% of fumiquinazoline I (**30**) with spectral data identical to those reported.[20]

In conclusion, we have completed the first syntheses of (−)-fumiquinazolines A, B, and I which proceed in 16 steps from protected tryptophan, leucine, and alanine in 7% overall yield, making this family of compounds and a wide variety of analogues readily available. The oxidation of **14a** with the saccharine-derived oxaziridine for fumiquinazolines A and B and of **14b** with dimethyldioxirane for fumiquinazoline I selectively forms the appropriate imidazoindolone stereoisomer. Application of these methods to the syntheses of the more highly oxidized fumiquinazolines C, D, E and H is currently in progress.

Acknowledgment. We are grateful to the National Institutes of Health (GM-50151) for generous financial support. We thank Dr. Feng He for technical advice, Professor Numata for helpful discussions, and Prof. Belofsky for copies of the spectral data of fumiquinazoline I.

Supporting Information Available: Full experimental procedures for the preparation of **2**, **3**, and **30**. This material is available free of charge via the Internet at http://pubs.acs.org.

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