ORGANIC LETTERS

2002
Vol. 4, No. 7
1087−1090

Total Syntheses of (−)-Fumiquinazolines C, E, and H

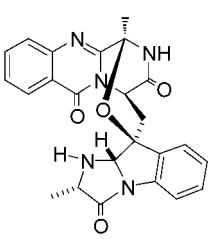
Barry B. Snider* and Hongbo Zeng

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

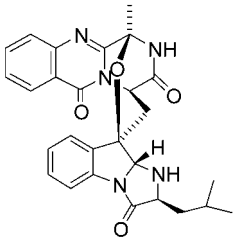
snider@brandeis.edu

Received December 12, 2001

ABSTRACT



fumiquinazoline C

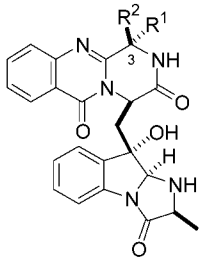


fumiquinazoline H

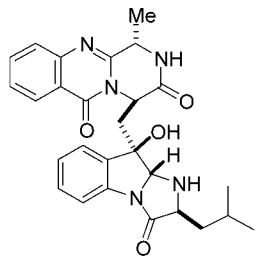
Total syntheses of the heptacyclic fumiquinazolines C and H have been accomplished efficiently using FmocNHCH(CH_2SePh)CO_2H as the precursor for the requisite dehydrofumiquinazoline.

Numata and co-workers isolated the moderately cytotoxic fumiquinazolines A−G (**1**−**3**, **5**) from a strain of *Aserpgillus fumigatus* found in the gastrointestinal tract of the fish *Pseudolabrus japonicus*.[1] Belofsky, Köck, and co-workers isolated the antifungal fumiquinazolines H (**6**) and I (**4**) from a fungus *Acremonium* sp. isolated from the surface of the Caribbean tunicate *Ecteinascidia turbinata*.[2]

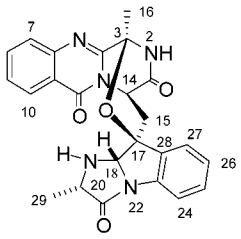
The challenge for the syntheses of fumiquinazolines A (**1**), B (**2**), and I (**4**) is the modification of the tryptophan indole to introduce the imidazolinone ring and hydroxy group.[3] We recently reported syntheses of fumiquinazolines A, B, and I,[4] using indole modification chemistry initially developed for the synthesis of asperlicin.[5] Fumiquinazolines C (**5**), E (**3**), and H (**6**) present an additional challenge because they are more highly oxidized with a methoxy group at C-3 in fumiquinazoline E (**3**) and a seven-membered ring formed between C-3 and the oxygen on C-17 in fumiquinazolines C (**5**) and H (**6**).



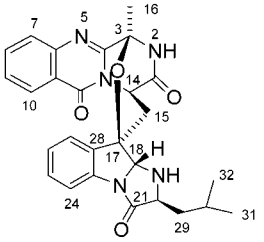
1, R^1 = Me, R^2= H (fumiquinazoline A)
2, R^1 = H, R^2= Me (fumiquinazoline B)
3, R^1 = Me, R^2 = OMe (fumiquinazoline E)



4 (fumiquinazoline I)



5 (fumiquinazoline C)



6 (fumiquinazoline H)

(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**, 2345−2343.

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

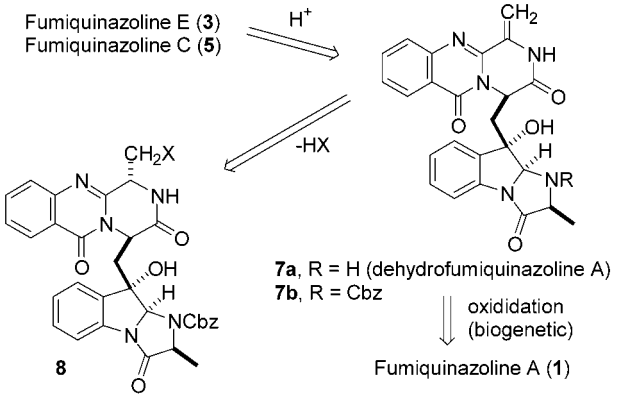
(3) The simpler fumiquinazolines F and G, in which the indole ring of tryptophan has not been modified, have been synthesized several times: (a) He, F.; Snider, B. B. *Synlett* **1997**, 483−484. (b) Wang, H.; Ganesan, A. *J. Org. Chem.* **1998**, *63*, 2432−2433. (c) Wang, H.; Ganesan, A. *J. Org. Chem.* **2000**, *65*, 1022−1030. (d) Snider, B. B.; Busuyek, M. V. *Tetrahedron* **2001**, *57*, 3301−3307. (e) Hernández, F.; Lumetzberger, A.; Avendaño, C.; Söllhuber, M. *Synlett* **2001**, 1387−1390.

(4) Snider, B. B.; Zeng, H. *Org. Lett.* **2000**, *2*, 4103−4106.

10.1021/ol017215d CCC: $22.00
Published on Web 03/13/2002

Fumiquinazolines C (**5**) and E (**3**) are probably biosynthesized by oxidation of fumiquinazoline A or B (**1** or **2**) to form dehydrofumiquinazoline A (**7a**) (Scheme 1). Protonation and cyclization will give fumiquinazoline C (**5**); protonation and reaction with MeOH will give fumiquinazoline E (**3**). Such an oxidation is hard to carry out chemically, but our synthetic route to **1** and **2** can be easily modified by use of Fmoc-L-NHCH(CH_2X)CO_2H instead of Fmoc-L-alanine to give **8**. X can be any functional group that can be eliminated to give Cbz-dehydrofumiquinazoline A (**7b**).

Scheme 1

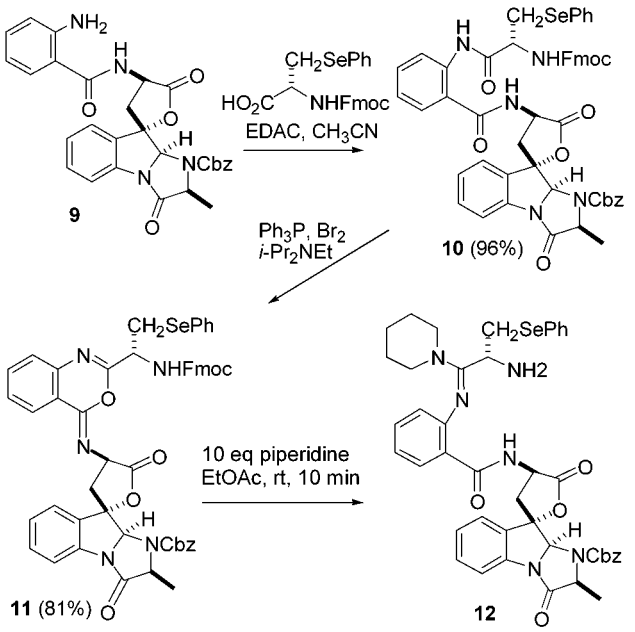


Numerous dehydroalanine precursors have been developed, including *O*-acetylserine, *O*-tosylserine, and *S*-methylcysteine,[6,7] which has been used by Hart and Magomedov for the syntheses of dehydrofumiquinazoline F and alantrypinone.[7] van der Donk recently reported the synthesis of FmocNHCH(CH_2SePh)CO_2H and its use as a dehydroalanine precursor.[8] The facile elimination by oxidation to the selenoxide with $NaIO_4$ in aqueous THF at 25 °C was particularly appealing because these conditions were likely to be compatible with the functionality in **8**.

Reaction of fumiquinazoline A intermediate **9**[4] with FmocNHCH(CH_2SePh)CO_2H and EDAC in CH_3CN affords 96% of **10** (Scheme 2). Mazurkiewicz−Ganesan cyclization,[3bc,9,10] provides 81% of **11**, which is treated with 10 equiv of piperidine in EtOAc at 25 °C for 10 min to cleave the Fmoc group and open the iminobenzoxazine to give amidine **12**.

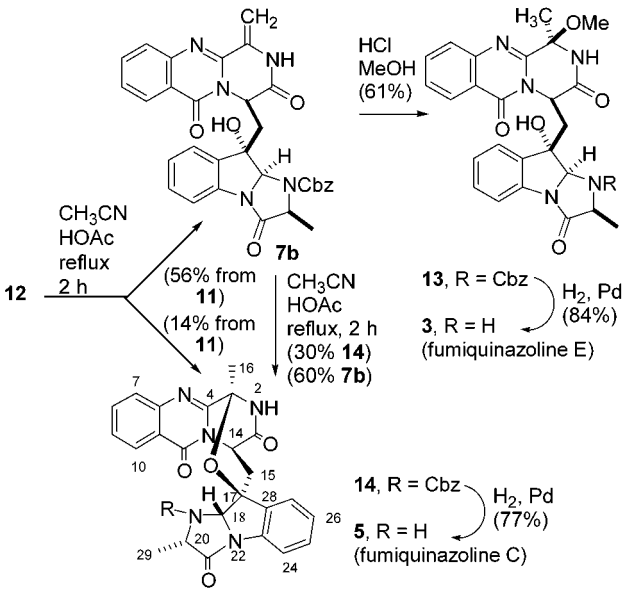
We were delighted to find that heating crude **12** in 25:1 CH_3CN/HOAc at reflux for 2 h forms Cbz-dehydrofumiquinazoline A (**7b**, 56% from **11**) and Cbz-fumiquinazoline C (**14**, 14% from **11**) (Scheme 3). Under these reaction conditions, **12** undergoes four sequential reactions. The amidine amide cyclizes to form the quinazolinone. The amine lactone reacts to give the piperazine ring. At this point, benzeneselenol is eliminated without the need for oxidation to the selenoxide. Finally, under the acidic conditions, the double bond is protonated to give a cation that reacts with the alcohol to form the seven-membered ether ring of fumiquinazoline C.

Scheme 2



Further heating of **7b** in 100:1 CH_3CN/HOAc at reflux for 2 h affords 30% of **14** and 60% of recovered **7b**, which

Scheme 3



(5) He, F.; Foxman B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1998**, *120*, 6417−6418

(6) Chai, C. L. L.; King, A. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1173−1182. Miao, Z.; Tam, J. P. *Org. Lett.* **2000**, *2*, 3711−3713 and references therein.

(7) (a) Freed, J. D.; Hart, D. J.; Magomedov, N. *J. Org. Chem.* **2001**, *66*, 839−852. (b) Hart, D. J.; Magomedov, N. A. *J. Am. Chem. Soc.* **2001**, *123*, 5892−5899.

(8) (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.

(9) Mazurkiewicz, R. *Monatsh. Chem.* **1989**, *120*, 973−980.

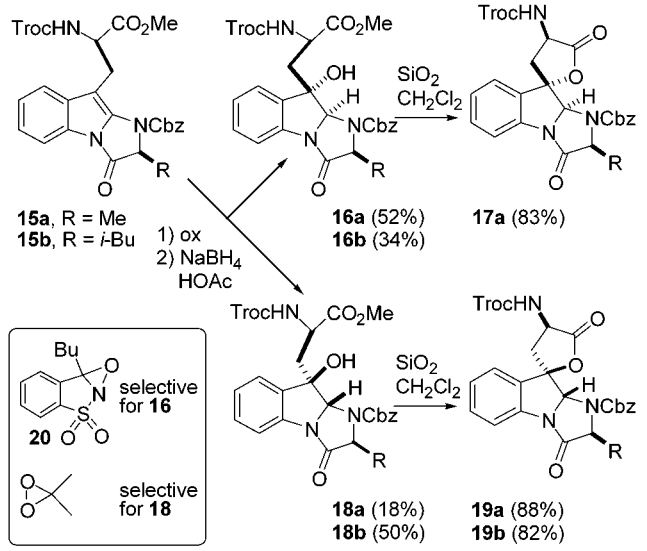
(10) He, F.; Snider, B. B. *J. Org. Chem.* **1999**, *64*, 1397−1399.

can be recycled. Slow decomposition occurs on longer heating, so that reaction for 12 h consumes all of **7b** but gives only 40−50% of **14**. Treatment of **7b** with 0.2 M HCl in MeOH at 25 °C for 5 min provides 61% of Cbz-fumiquinazoline E (**13**). Hydrogenolysis of **13** with Pd/C under 1 atm of H_2 for 30 min proceeds cleanly, giving 84% of (−)-fumiquinazoline E (**3**).[11] The additional ring of **14** forces the Cbz group into a more hindered environment. Hydrogenolysis with Pd/C under 4 atm of H_2 for 30 h affords 77% of (−)-fumiquinazoline C (**5**).[11]

We next turned to the preparation of fumiquinazoline H (**6**) by coupling FmocNHCH(CH_2SePh)CO_2H with the aniline intermediate in our fumiquinazoline I synthesis.[4] The hydrogen and hydroxy substituents on the indoline ring are cis to the alkyl substituent on the imidazoline ring in fumiquinazoline I (**4**) rather than trans as in fumiquinazoline A (**1**). Therefore on formation of the seven-membered ether ring, the imidazoline ring is over the quinazolinone ring in fumiquinazoline C (**5**), while the indoline is over the quinazolinone in fumiquinazoline H (**6**). MM2 calculations indicate that the fumiquinazoline H ring system is more hindered by about 2 kcal/mol.

Epoxidation of **15a**[4] with oxaziridine **20**[12] occurs selectively on the bottom face, leading to the fumiquinazoline A, B, C, and E precursors (Scheme 4). Ring opening by MeOH

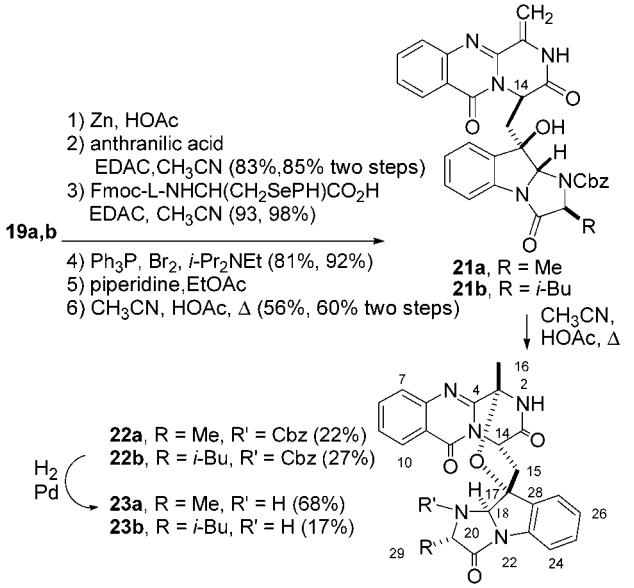
Scheme 4



gives a mixture of methoxy alcohols. Reductive cleavage of the methoxy group by NaBH(OAc)$_3$ occurs by intramolecular hydride delivery from the alkoxyborohydride[4] to give 52% of **16a** and 18% of **18a**, both of which have the hydrogen and hydroxy groups cis. On the other hand, oxidation of **15b** with dimethyldioxirane proceeds selectively on the top face as needed for fumiquinazolines H and I giving 50% of **18b** and only 34% of **16b** after reduction. Lactonization of **18a** and **18b** by stirring with SiO_2 in CH_2Cl_2 gives lactones **19a** and **19b** in 88% and 82% yield, respectively.

Elaboration of both **19a** and **19b** to Cbz-dehydro-fumiquinazolines **21a** and **21b** by the procedure developed for the preparation of **7b** proceeds uneventfully as shown in Scheme 5. To our surprise, cyclization of **21a** by heating in

Scheme 5



25:1 CH_3CN/HOAc was slow. After heating for 12 h, we obtain 22% of a 2:1 mixture of **22a** and the enantiomer of **14**, 33% of recovered **21a**, and no Cbz-fumiquinazoline H analogue. Epimerization at C-14 prior to cyclization leads to the formation of **22a**, while epimerization at both C-14 and C-20 leads to the enantiomer of **14**. Cyclization of **21b** by heating in 25:1 CH_3CN/HOAc for 12 h provides 27% of **22b** and 33% of recovered **21b**. Hydrogenolysis of **22a** under 4 atm of H_2 for 24 h gives 68% of **23a**, while the isobutyl group of **22b** makes the Cbz group even more hindered so that hydrogenolysis under 4 atm of H_2 for 24 h yields only 17% of **23b**. These experiments indicate that the additional steric hindrance of the fumiquinazoline H ring system prevents the cyclization of **21**. Facile epimerization at C-14[1] leads to an intermediate that cyclizes more readily to give **22** with the fumiquinazoline C ring system.[13]

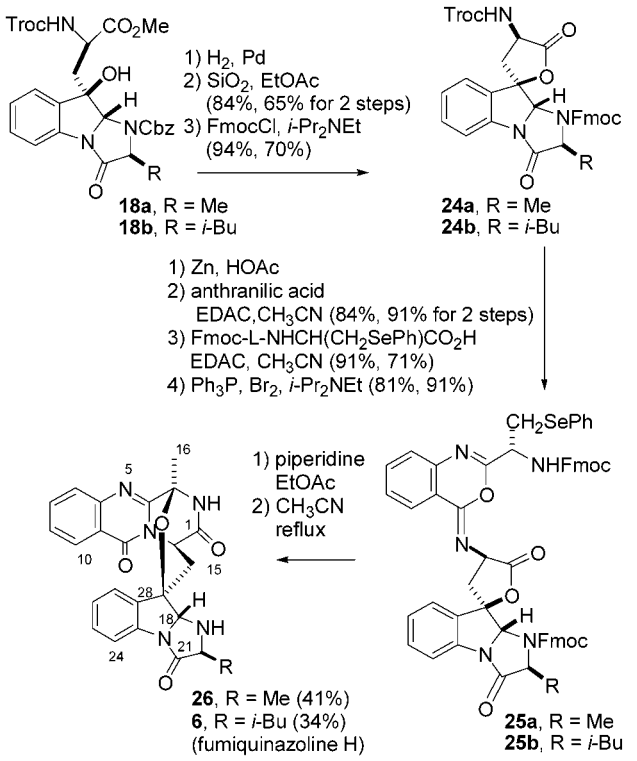
MM2 calculations indicate that Cbz-fumiquinazoline H is also 2 kcal/mol more hindered than Cbz-fumiquinazoline C. Even though the Cbz group does not affect the relative stability, examination of models indicates that it severely hinders the approach of the hydroxy group to a cation at

(11) The spectral data, melting point, and optical rotation are identical to those reported for the natural product.[1]

(12) 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) In fumiquinazoline C (**5**), **14**, **22**, and **23** there is an NOE between H-2 and H-27. In fumiquinazoline H (**6**) there is an NOE between H-2 and H-18. In Cbz-fumiquinazoline C (**14**) and **22**, the Cbz benzyl protons are shifted upfield to δ 4.40−4.25 as a result of shielding by the quinazolinone ring.

Scheme 6



C-3 to form the fumiquinazoline H ring system. Finally, the isobutyl group of **22b** retards hydrogenolysis, suggesting that even if we could obtain Cbz-fumiquinazoline H, deprotection would be difficult. Nature does cyclize dehydrofumiquinazoline I to fumiquinazoline H. Therefore we decided to adapt our route to prepare unprotected dehydrofumiquinazoline I, with the expectation that it would cyclize to fumiquinazoline H without epimerization.

Replacement of the Cbz of **18** with an Fmoc group should lead to iminobenzoxazine **25**. Both Fmoc groups should be deprotected during the rearrangement with piperidine. Hydrogenolysis of **18b** with Pd/C under 1 atm H_2 for 30 min followed by lactonization with silica gel in CH_2Cl_2 gives 65% of the tetracyclic lactone. Reaction with FmocCl and *i*-Pr_2NEt affords 70% of **24b**. Conversion of **24b** to **25b** proceeds analogously to the preparation of **11** in the yields indicated in Scheme 6.

Treatment of **25b** with 10 equiv of piperidine in EtOAc for 10 min cleaves both Fmoc groups and opens the iminobenzoxazine. Heating the crude product in CH_3CN at reflux for 1 h effects ring closure of the amidine to the quinazolinone, formation of the piperazine ring, and elimination of benzeneselenol to give dehydrofumiquinazoline I.[14] In the absence of the bulky Cbz group, cyclization proceeds spontaneously without epimerization at C-14 to give 34% of (−)-fumiquinazoline H (**6**).[11] The conversion of **25b** to **6** involves seven distinct chemical steps! A similar sequence converts **18a** to iminobenzoxazine **25a**, which rearranges to give 41% of fumiquinazoline H analogue **26**.

Fumiquinazoline D,[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 (**7a**) 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 can be prepared easily from **16a** analogously to the preparation of **25**. Treatment of the iminobenzoxazine with piperidine in EtOAc for 10 min and then heating at reflux in CH_3CN for 1.5 h affords **7a**, which cyclizes to give 40% of fumiquinazoline C (**5**) and no fumiquinazoline D.

In conclusion, we have completed efficient 13-step syntheses of (−)-fumiquinazolines C (**5**) and E (**3**) and a 14-step synthesis of (−)-fumiquinazoline H (**6**) using Fmoc-NHCH(CH_2SePh)CO_2H as a dehydroalanine precursor that spontaneously eliminates benzeneselenol without oxidation under the cyclization conditions.[15,16]

Acknowledgment. We are grateful to the National Institutes of Health (GM-51051) for financial support.

Supporting Information Available: Spectral data and full experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL017215D

(14) The rearrangements of Cbz-protected amidines such as **12** are best carried out in CH_3CN containing 2−5 equiv of HOAc to prevent epimerization at C-14. These conditions will reduce the epimerization that was observed in our syntheses of fumiquinazolines A, B, and I.[4] The rearrangement of the unprotected amidine from **25** proceeds much more cleanly in CH_3CN without HOAc.

(15) We previously acylated the indole by a three-step sequence involving reduction to the indoline, acylation, and reoxidation. This can be accomplished in a single step in 90−95% yield by reaction of TrocNHtrypOMe with CbzNHalaOPhNO_2 or CbzNHLeuOPhNO_2, KF, 18-crown-6, and *i*-Pr_2NEt in CH_3CN.[16]

(16) Nakagawa, M.; Sodeoka, M.; Yamaguchi, K.; Hino, T. *Chem. Pharm. Bull.* **1984**, *32*, 1373−1384.