Total Synthesis of (+)-Fumiquinazoline G and (+)-Dehydrofumiquinazoline G

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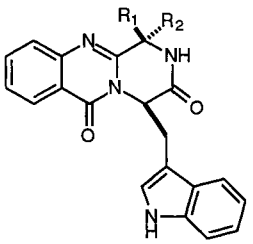
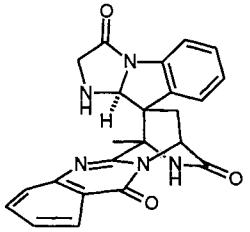
Dedicated to my mentor Professor E. J. Corey in honor of his remarkable contributions to organic chemistry

Abstract: An efficient twelve step synthesis of (+)-fumiquinazoline G (**16**) has been accomplished in 11% overall yield.

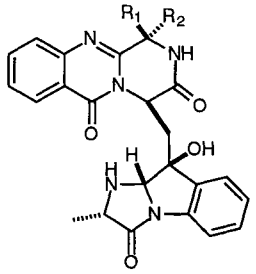
Numata reported the isolation of the moderately cytotoxic fumiquinazolines A-G (**1**, **2**, **5-8**) from a fungus separated from a *Pseudolabrus* fish in 1992.[1] Biogenetically, these molecules are tri- or tetrapeptides derived from anthranilic acid, tryptophan and one or two alanines. The absolute configuration has been established as shown by hydrolysis of fumiquinazoline D (not shown) to L-alanine. The fumiquinazolines must therefore be derived from D-tryptophan. In 1993, a Sterling Winthrop group isolated fiscalin B (**3**), which is identical to fumiquinazoline F (**2**) except for the substitution of an isopropyl group (from valine) for the methyl group, from the fungus *Neosartorya fischeri*.[2] The fiscalins inhibit the binding of substance P (SP) to human U-373 MG intact cells and therefore might be novel analgesics or anti-inflammatory agents. In 1994, another Sterling Winthrop group obtained spiroquinazoline (**4**), another SP inhibitor, from the fungus *Aspergillus flavipes*.[3]



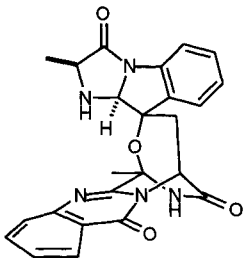
1, R_1 = Me, R_2 = H (fumiquinazoline G)
2, R_1 = H, R_2 = Me (fumiquinazoline F)
3, R_1 = H, R_2 = *i*-Pr (fiscalin B)



4 (spiroquinazoline)



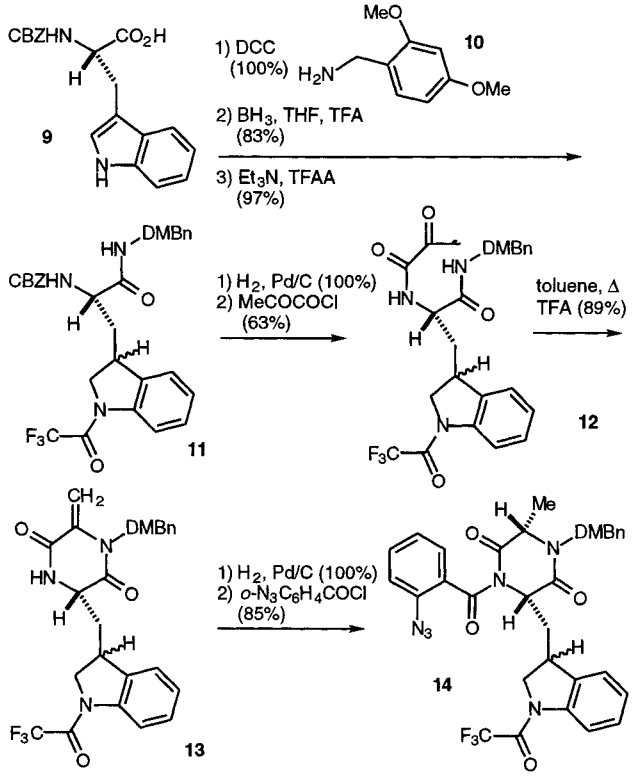
5, R_1 = Me, R_2 = H (fumiquinazoline B)
6, R_1 = H, R_2 = Me (fumiquinazoline A)
7, R_1 = OMe, R_2 = Me (fumiquinazoline E)



8 (fumiquinazoline C)

Spiroquinazoline (**4**) and fumiquinazoline C (**8**) both contain seven rings in an unusual spiro bridged arrangement. The unusual structures of these materials coupled with the potential for different types of interesting biological activity prompted us to consider synthetic routes to these targets. Relatively little is known about the chemistry of quinazolin-4-one peptide-derived antibiotics. Successful syntheses include those of the tryptoquivalines by Büchi,[4] Ban,[5] and Nakagawa and Hino,[6] asperlicins D and E by Bock,[7] and aredeemin by Danishefsky.[8]

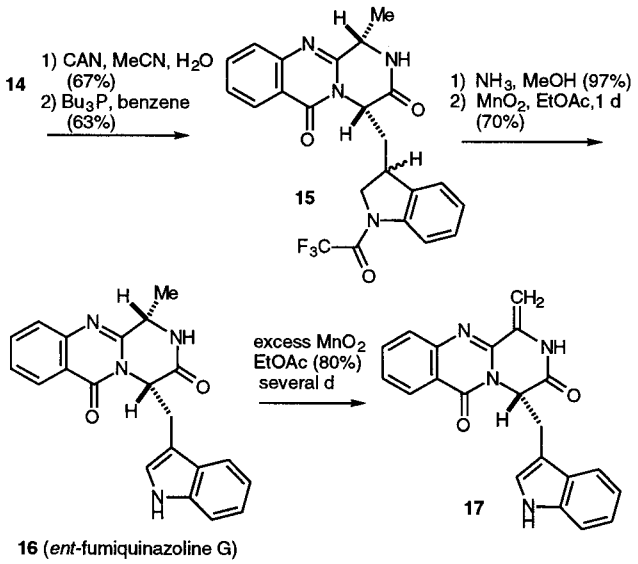
We chose the simpler fumiquinazolines, G (**1**) and F (**2**), as our initial targets. 2,3-Dialkylquinazolin-4-ones are very sterically hindered and surprisingly difficult to prepare.[9] Our initial attempts at closing the quinazolin-4-one ring prior to forming the piperazine ring were unsuccessful. We therefore used Eguchi's procedure for the annulation of a quinazolin-4-one onto an amide.[8,10]



Coupling of CBZ-L-tryptophan (**9**)[11] with dimethoxybenzylamine (**10**), reduction of the indole with BH_3 in TFA and THF,[12] and trifluoroacetylation of the indoline gave **11**. The dimethoxybenzyl protecting group was necessary for the cyclization of **12** to **13** and for the selective acylation of **13** to give **14**. The indole ring did not survive some of the later steps so it was reduced to the indoline and reoxidized in the last step of the synthesis. Hydrogenolysis of the CBZ group and reaction of the amine with pyruvoyl chloride[13] provided **12**. Dehydration (toluene, TFA, Δ) afforded methylenediketopiperazine **13** as reported by Ottenheijm for *N*-hydroxymethylenediketopiperazines.[14] Although the methylene group will be needed for the synthesis of **4** and **8**, it interfered with the oxidative removal of the dimethoxybenzyl group and was therefore reduced with complete selectivity from the less hindered ß-face to give the diketopiperazine, which was acylated with *o*-azidobenzoyl chloride[10,15] to give **14**.

With the azidobenzamide attached, the dimethoxybenzyl protecting group was removed by oxidation with CAN.[16] Formation of the aza-Wittig reagent with Bu_3P by Eguchi's procedure[10] led to **15**. Cleavage of the trifluoroacetamide with NH_3 in MeOH,[17] followed by oxidation of the indoline with MnO_2 in EtOAc for 1 d completed the synthesis, giving 70% of (+)-fumiquinazoline G (**16**) and 10-20% of (+)-dehydrofumiquinazoline G (**17**). Oxidation of **16** with excess MnO_2 for several days provided **17** in 80% yield.

The ^1H and ^{13}C NMR spectral data for **16** are identical to those reported.[1] The $[a]_D$ is +446°, while that of natural **16** is -463°, thereby confirming the stereochemical assignment of the natural product and establishing that the synthesis proceeds with little or no racemization. Treatment of fumiquinazoline F or G with base is reported to give a 3:2 equilibrium mixture.[1a] The synthesis of **16** therefore constitutes a formal synthesis of fumiquinazoline F (**2**) as well.



In conclusion, an efficient twelve step synthesis of (+)-fumiquinazoline G (**16**) has been accomplished in 11% overall yield. This scheme should be readily adaptable to the more complex fumiquinazolines and spiroquinazoline. The facile oxidation of **16** to dehydrofumiquinazoline (**17**) indicates that the functionality needed for the synthesis of **4** and **8** can be easily introduced. The glycine or alanine needed for the synthesis of **4** or **8** can be easily introduced late in the synthesis by acylation of the indoline prior to oxidative regeneration of the indole ring.[18]

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References and Notes

(1) (a) Takahashi, C.; Matsushita, T.; Doi, M.; Minoura, K.; Shingu, T.; Kumeda,Y.; Numata, A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2345-2353. (b) 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.

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

(3) Barrow, C. J.; Sun, H. H. *J. Nat. Prod.* **1994**, *57*, 471-476.

(4) Büchi, G.; DeShong, P. R.; Katsumura, S.; Sugimura, Y. *J. Am. Chem. Soc.* **1979**, *101*, 5084-5086.

(5) Ohnuma, T.; Kimura, Y.; Ban, Y. *Tetrahedron Lett.* **1981**, *22*, 4969-4972.

(6) (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.

(7) Bock, M. G.; DiPardo, R. M.; Pitzenberger, S. M.; Homnick C. F.; Springer, J. P.; Freidinger, R. M. *J. Org. Chem.* **1987**, *52*, 1644-1646.

(8) Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143-11144.

(9) See reference 6b and reference 6 therein.

(10)Takeuchi, H.; Hagiwara, S.; Eguchi, S. *Tetrahedron* **1989**, *45*, 6375-6386.

(11) Use of D-tryptophan will lead to natural (-)-fumiquinazoline G.

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

(13)Ottenheijm, H. C. J.; Tijhuis, M. W. *Organic Syntheses, Coll. Vol. VII*, Freeman, J. P., Ed.; Wiley: New York, 1990, pp 467-469.

(14)(a) Ottenheijm, H. C. J.; Plate, R.; Noordik, J. H.; Herscheid, J. D. M. *J. Org. Chem.* **1982**, *47*, 2147-2154. (b) Plate, R.; Nivard, R. J. F.; Ottenheijm, H. C. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2473-2480. (c) Plate, R.; Akkerman, M. A. J.; Ottenheijm, H. C. J.; Smits, J. M. M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2481-2490.

(15)Ardakani, M. A.; Smalley, R. K.; Smith, R. H. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2501-2506.

(16)Yamaura, M.; Suzuki, T.; Hashimoto, H.; Yoshimura, J.; Okamoto, T.; Shin, C.-g. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1413-1420.

(17)Epimerization at the CHMe center occurred during hydrolysis of the trifluoroacetamide with aqueous base.

(18)Neklyudov, A. D.; Shchukina, L. A.; Suvorov, N. N. *J. Gen. Chem. USSR* **1967**, *37*, 747-750.