Total Synthesis of the Quinazoline Alkaloids (−)-Fumiquinazoline G and (−)-Fiscalin B

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In 1992, Numata et al. reported[1] a series of cytotoxic fungal metabolites obtained from a strain of *Aspergillus fumigatus* isolated from the marine fish *Pseudolabrus japonicus*. Fumiquinazoline G (**1**, Figure 1) is a prototypical member, while others such as fumiquinazoline D (**2**) feature further intramolecular cyclizations. The related alkaloid fiscalin B (**3**), from the fungus *Neosartorya fischeri*, was discovered[2] at Sterling-Winthrop in the course of screening for substance P antagonists and also independently isolated[3] from the ascomycete *Corynascus setosus*. These examples demonstrate that the pyrazino[2,1-*b*]quinazoline-3,6-dione ring skeleton is used by nature as a scaffold for constrained peptidomimetics, and it has also attracted considerable attention[4] among medicinal chemists.

Retrosynthetically, dehydration of a peptide precursor (Figure 2) represents a concise and biomimetic route to the quinazoline ring of these natural products.[5] However, previous conditions for the dehydration have been fairly harsh, and suitable only for unhindered 2,3-disubstituted quinazolin-4-ones.[6] Syntheses of natural products involving more sterically demanding substrates have utilized indirect methods such as thioamide formation (asperlicin C[7]), oxidation of a dihydroquinazolinone (tryptoquivaline[8]), or aza-Wittig reaction (ardeemin[9]). Snider's recent synthesis[10] of *ent*-**1** (reported shortly after we began our work) also employed the aza-Wittig disconnection, requiring judicious manipulation of protecting groups and a total of 12 steps from Cbz-L-tryptophan.

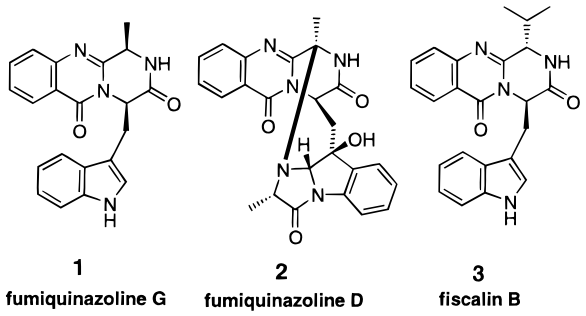


Figure 1.

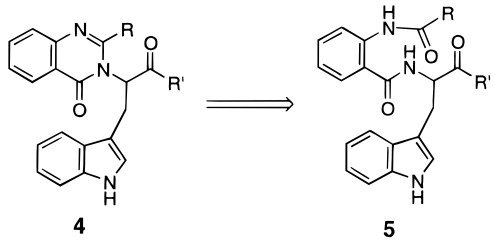
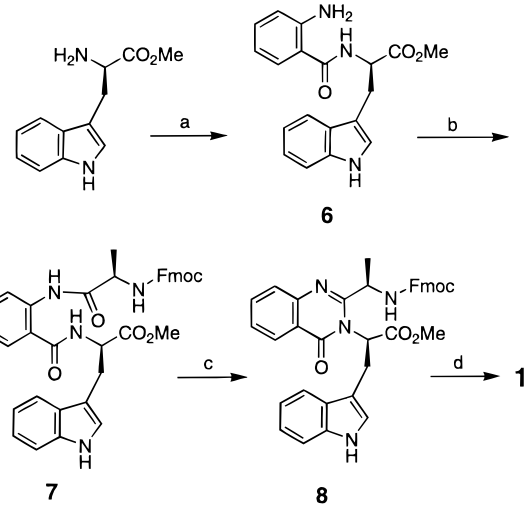


Figure 2.

Scheme 1[a]



[a] Reagents and conditions: (a) 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide·HCl (2.2 equiv), anthranilic acid (2.0 equiv), MeCN, rt, 3 h, 90%; (b) Fmoc-D-Ala-Cl (1.2 equiv), CH_2Cl_2/aqueous Na_2CO_3, rt, 1 h, 86%; (c) Ph_3P (5.0 equiv), I_2 (4.9 equiv), EtN(*i*-Pr)$_2$ (10.1 equiv), rt, 2.5 h, 65%; (d) (i) 20% piperidine in CH_2Cl_2, rt, 12 min, (ii) SiO_2 (75%).

Assuming a suitable means for peptide dehydration could be found, we proceeded with a synthesis of **1** along these lines. Tripeptide **7** (Scheme 1) was prepared in two steps from D-tryptophan methyl ester[11] by standard methods. At this stage, we became aware of Wipf's protocol[12] (triphenylphosphine, iodine, triethylamine) for the dehydration of β-keto amides to oxazoles. Among the amides in **7**, the anilide NH is the most acidic, suggesting that it can enolize

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

(3) Fujimoto, H.; Negishi, E.; Yamaguchi, K.; Nishi, N.; Yamazaki, M. *Chem. Pharm. Bull.* **1996**, *44*, 1843−1848.

(4) For examples, see: (a) Malamas, M. S.; Millen, J. *J. Med. Chem.* **1991**, *34*, 1492−1503. (b) Yu, M. J.; McCowan, J. R.; Mason N. R.; Deeter, J. B.; Mendelsohn, L. G. *J. Med. Chem.* **1992**, *35*, 2534−2542. (c) de Laszlo, S. E.; Quagliato, C. S.; Greenlee, W. J.; Patchett, A. A.; Chang, R. S. L.; Lotti, V. J.; Chen, T.-B.; Scheck, S. A.; Faust, K. A.; Kivlighn, S. S.; Schorn, T. S.; Zingaro, G. J.; Siegl, P. K. S. *J. Med. Chem.* **1993**, *36*, 3207−3210. (d) Hutchinson, J. H.; Cook, J. J.; Brashear, K. M.; Breslin, M. J.; Glass, J. D.; Gould, R. J.; Halczenko, W.; Holahan, M. A.; Lynch, R. J.; Sitko, G. R.; Stranieri, M. T.; Hartman, G. D.; *J. Med. Chem.* **1996**, *39*, 4583−4591. (e) Sánchez, J. D.; Ramos, M. T.; Avendaño, C. *Tetrahedron* **1998**, *54*, 969−980.

(5) For recent reviews on quinazoline alkaloids, see: (a) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 605−618. (b) Johne, S. In *Supplements to the 2nd Edition of Rodd's Chemistry of Carbon Compounds*; Ansell, M. F., Ed.; Elsevier: Amsterdam, 1995; Vol. IV I/J, pp 223−240.

(6) Brown, D. J. *Quinazolines. Supplement I*; Wiley: New York, 1996. For examples related to the synthesis of tryptoquivalines (R = H or Me), see: (a) Büchi, G.; DeShong, P. R.; Katsumura, S.; Sugimura, Y. *J. Am. Chem. Soc.* **1979**, *101*, 5084−5086. (b) Ohnuma, T.; Kimura, Y.; Ban, Y. *Tetrahedron Lett.* **1981**, *22*, 4969−4972. (c) Nakagawa, M.; Taniguchi, M.; Sodeoka, M.; Ito, M.; Yamaguchi, K.; Hino, T. *J. Am. Chem. Soc.* **1983**, *105*, 3709−3710.

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

(8) Nakagawa, M.; Ito, M.; Hasegawa, Y.; Akashi, S.; Hino, T. *Tetrahedron Lett.* **1984**, *25*, 3865−3868.

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

(10) He, F.; Snider, B. B. *Synlett* **1997**, 483−484.

(11) Our initial studies used the cheaper L-tryptophan methyl ester, eventually leading to *ent*-**1**. Details will be reported in a full paper, together with syntheses of fumiquinazoline F and glyantrypine.

(12) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604−3606.

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Table 1. Examples of Dehydrative Quinazolinone Synthesis[a]

substrate	R	R'	reaction time (h)	product	yield (%)	recovered substrate (%)
5a	Me	OMe	7	**4a**	99	0
5b	Ph	OMe	3.5	**4b**	93	2
5c	*i*-Pr	OMe	6	**4c**	88	12
5d	*t*-Bu	OMe	6	**4d**	17	83

[a] All substrates were prepared from L-tryptophan methyl ester. Reactions were carried out in CH_2Cl_2 solutions with Ph_3P (5.0 equiv), I_2 (5.0 equiv), $EtN(i\text{-}Pr)_2$ (10 equiv), and substrate (final concentrations were ca. 0.03 M) at rt.

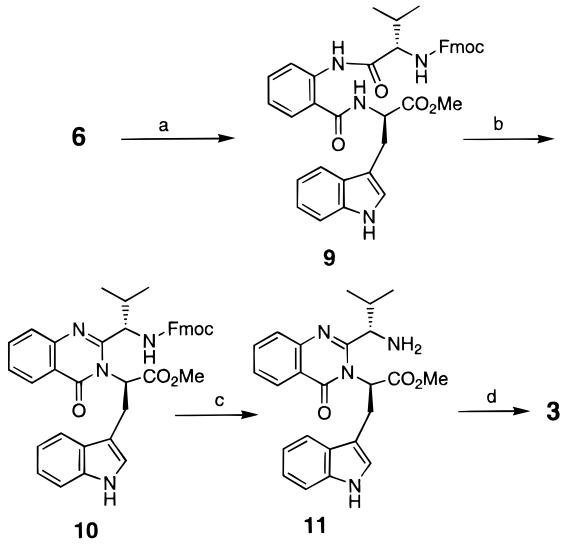
analogously to the ketone in the oxazole cyclization. To our delight, treatment of **7** under Wipf's conditions furnished the desired product **8** in 65% yield. Following removal of the Fmoc protecting group, attempted chromatographic purification of the free amine induced intramolecular cyclization, directly yielding (−)-fumiquinazoline G in a total of four steps and 38% overall yield.

Next, we investigated the sensitivity of the Wipf procedure to steric hindrance (Table 1). The successful quinazolinone formation with **4c** (R = *i*-Pr) is notable, as a previous attempt[6b] using phosphorus trichloride failed when R = *i*-Bu. Only the extremely hindered pivalamide **4d** did not provide a satisfactory yield of the quinazolinone. Even in this case, unreacted starting material was recovered intact, testifying to the mildness of the reaction conditions.

The synthesis of (−)-fiscalin B (Scheme 2) proceeded uneventfully up to and including Wipf dehydration of tripeptide **9**. However, amine **11** did not undergo spontaneous cyclization, and considerable experimentation was required for this transformation. Presumably, the increased bulk of the isopropyl side chain disfavors the desired reactive conformer. Success was finally realized by refluxing **11** in acetonitrile, providing (−)-fiscalin B in a total of five steps and 48% overall yield from D-tryptophan methyl ester.[13]

In summary, we have demonstrated that the Wipf oxazole synthesis is also applicable to quinazolinones and provides

Scheme 2[a]



[a] Reagents and conditions: (a) Fmoc-L-Val-Cl (1.4 equiv), CH_2Cl_2/aqueous Na_2CO_3, rt, 2 h, 90%; (b) Ph_3P (5.0 equiv), I_2 (4.9 equiv), $EtN(i\text{-}Pr)_2$ (10.4 equiv), rt, 8 h, 82%; (c) 20% piperidine in CH_2Cl_2, rt, 12 min; (d) MeCN, DMAP (1.3 equiv), reflux 19 h, 72%.

a powerful entry to this ring system. We are presently adapting the methodology to the combinatorial synthesis[14] of quinazolinone libraries for biological evaluation.

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Supporting Information Available: Experimental procedures and compound characterization data for the total synthesis of **1** and **3** (5 pages).

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(13) Synthetic **1** and **3** matched the spectroscopic data reported for the natural products. **1** had an optical rotation $[\alpha]^{26}_D = -456.2°$ (*c* 0.59, $CHCl_3$) [lit.[1] $[\alpha]_D = -462.8°$ (*c* 0.61, $CHCl_3$)], while **3** had an optical rotation $[\alpha]^{26}_D = -504°$ (*c* 0.64, MeOH) [lit.[3] $[\alpha]_D = -124°$ (*c* 0.021, MeOH)].

(14) For other approaches to the solid-phase synthesis of quinazolinones, see: (a) Chucholowski, A.; Masquelin, T.; Obrecht, D.; Stadlwieser, J.; Villalgordo, J. M. *Chimia* **1996**, *50*, 525−530. (b) Mayer, J. P.; Lewis, G. S.; Curtis, M. J.; Zhang, J. *Tetrahedron Lett.* **1997**, *38*, 8445−8448.