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Three-Component One-Pot Total Syntheses of Glyantrypine, Fumiquinazoline F, and Fiscalin B Promoted by Microwave Irradiation†

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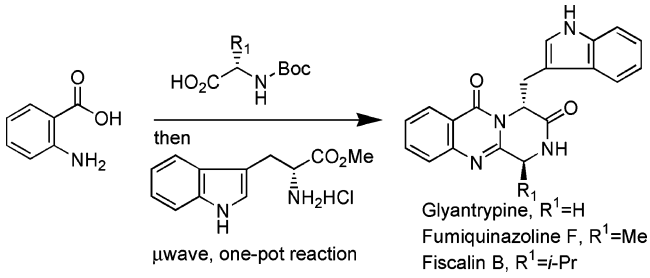
Received April 20, 2005



A microwave-promoted three-component one-pot reaction has been developed to provide access to the core pyrazino[2,1-*b*]quinazoline-3,6-dione (**1**) scaffold, which is common to several families of alkaloids with significant biological activities. By adapting this synthetic strategy through the use of selected Boc-amino acids and amino acid esters, we have accomplished highly efficient and concise total syntheses of glyantrypine (**2**), fumiquinazoline F (**3**), and fiscalin B (**5**), achieving overall yields of 55, 39, and 20%, respectively.

Introduction

Fungal quinazolinone metabolites which incorporate the core pyrazino[2,1-*b*]quinazoline-3,6-dione (**1**) scaffold represent several families of alkaloids (Figure 1).[1] Representative natural products containing scaffold **1** include glyantripine (**2**),[2] fumiquinazolines F (**3**) and G (**4**),[3] fiscalin B (**5**),[4] alantripinione (**6**),[5] ardeemin (**7**),[6] and *N*-acetylardeemin (**8**), many of which have exhibited significant biological activities.[2−4,6a,b] Because of the unique structural features and pharmaceutical relevance of these alkaloids,[6] several research groups have devoted much effort to their total syntheses.[6e−11]

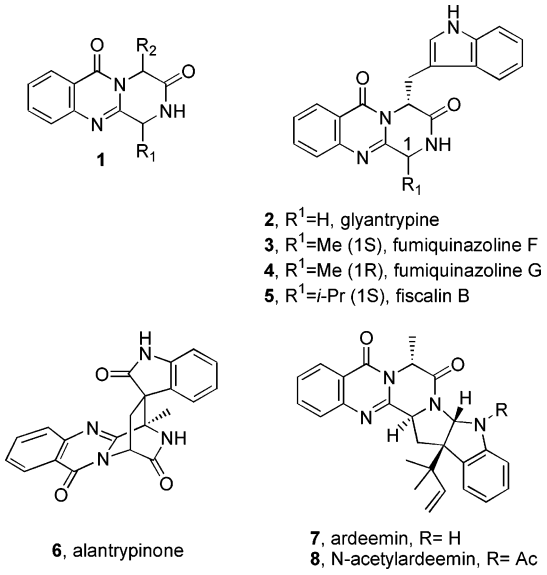


FIGURE 1. Pyrazino[2,1-*b*]quinazoline-3,6-dione (**1**) and representative natural products.

† This paper is dedicated with respect and affection to the memory of Professor Satoru Masamune who passed away on November 9, 2003.

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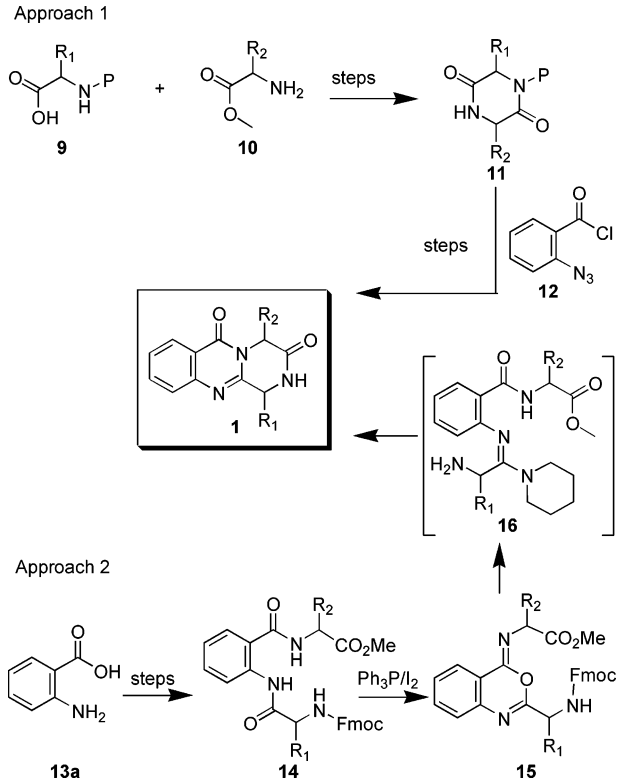
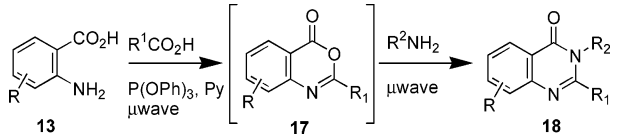
10.1021/jo0508043 CCC: $30.25
Published on Web 07/01/2005

SCHEME 1. Available Approaches for the Synthesis of Pyrazino[2,1-*b*]quinazoline-3,6-diones



Thus far, two major synthetic strategies have been reported to access the core ring system **1**, which have subsequently led to the total synthesis of several natural products (Scheme 1). Snider,[7] Avendaño,[8] and Söllhuber[8] took advantage of an aza-Wittig approach[9] (Approach 1) to construct **1** by reacting diketopiperazines **11** (derived from amino acids **9** and **10** via a multistep reaction sequence) with *o*-azidobenzoyl chloride (**12**), a protocol that was successfully employed in the total syntheses of glyantrypine (**2**),[8] fumiquinazoline F (**3**),[8a] fumiquinazoline G (**4**),[7a,b,8a] and fiscalin B (**5**).[8a] Alternatively, Ganesan[10] reported a remarkably straightforward approach (Approach 2) highlighted by the dehydration of intermediate **14** using Ph_3P/I_2 as a dehydrating agent, affording glyantrypine (**2**), fumiquinazoline F (**3**), fumiquinazoline G (**4**), and fiscalin B (**5**) in only four to five synthetic steps. This method has also been extended to the synthesis of more complex fumiquinazolines.[7c,11,12] The reaction mechanism was later verified by Snider,[13] confirming that the intermediacy of an iminobenzoxazine **15**[14] formed from the dehydrative cyclization of intermediate **14**. Hart and Magomedov have also shown that the rearrangement of the iminobenzoxazine **15** to the quinazolinones can be carried out with $Li(AlMe_3SPh)$.[11]

SCHEME 2. One-Pot Synthesis of 2,3-Disubstituted Quinazolin-4-ones



Very recently, we developed an efficient microwave-assisted three-component one-pot methodology for the synthesis of various 2,3-disubstituted quinazolin-4-ones **18** from readily available anthranilic acids **13** (Scheme 2).[15] This novel approach allows access to a broader chemistry scope relative to existing methods, accommodating an expanded array of carboxylic acids (R^1CO_2H) and amines (R^2NH_2). Although our microwave method readily provided substituted quinazolin-4-one cores such as **18** via a one-pot process, we were intrigued by the possibility of extending this methodology toward a one-pot total synthesis of the fungal quinazolin-4-one natural products.[16] This synthetic approach of quinazoline dehydration followed by diketopiperazine-like cyclization represents, in principle, the most efficient and straightforward route to fumiquinazoline alkaloids. Yet, it has not been successfully utilized to date in the total synthesis of natural products containing core **1**. In this paper, we report the application of this approach to the three-component one-pot[17] total syntheses of glyantrypine (**2**), fumiquinazoline F (**3**), and fiscalin B (**5**).

Results and Discussion

Synthesis Plan. Our retrosynthetic strategy (Scheme 3) envisions a highly efficient three-component one-pot reaction sequence that allows for the in situ construction of key intermediates and the necessity of only a single

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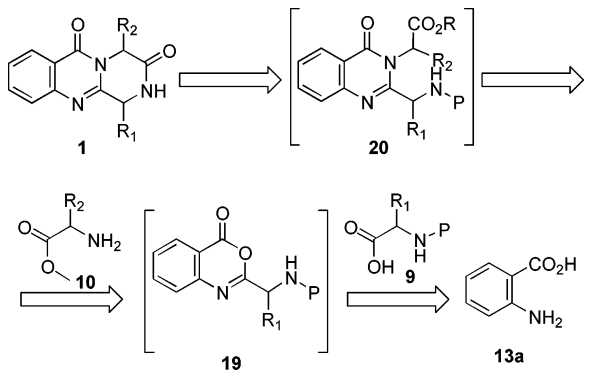
SCHEME 3. Retrosynthetic Strategy for the Total Synthesis of Fumiquinazoline Alkaloids



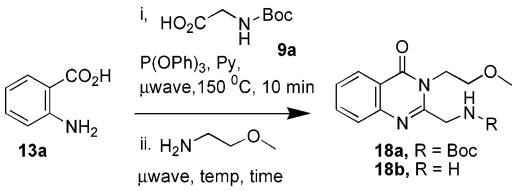
reagent ($P(OPh)_3$) to complete the total synthesis. The pyrazino[2,1-*b*]quinazoline-3,6-dione (**1**) could be obtained by a diketopiperazine-like cyclization after an N-deprotection of quinazolinone **20**, and the quinazolinone **20** could be formed in situ through the reaction of intermediate **19** with the amino acid ester **10** under the microwave conditions. N-protected benzoxazin-4-one (**19**) could be generated in situ from the reaction of anthranilic acid (**13a**) with a protected α-amino acid **9**. Although we have successfully applied this approach to a variety of model systems, the natural products presented a number of additional challenges. One critical hurdle was the identification of an appropriate protecting group for α-amino acid **9**. The ideal protecting group needed to be compatible with the microwave reaction conditions for the formation of **19** and **20** (typically 150−220 °C, pyridine/$P(OPh)_3$)[15] but labile enough to be deprotected in situ prior to the diketopiperazine-like cyclization.

Determination of Protecting Groups. To establish the forward synthetic route, we started our investigation by examining the formation of quinazolin-4-ones employing amino acids with standard protecting groups such as Boc, Cbz, Bn, and Fmoc. Boc-amino acids were identified as the optimal performers under the reaction conditions.[18] More importantly, when a Boc was used as the protecting group, we observed the desired quinazolinone ring formation to give **18a**, followed by the in situ deprotection of the *N*-Boc group to form **18b** (Table 1). Although **18a** was formed at a lower temperature (180 °C), the reaction conditions were optimized to yield **18b** as the only product once the reaction temperature was increased to 220 °C. These results pointed to the possibility of further simplifying the sequence by conducting a series of transformations to form the pyrazino-[2,1-*b*]quinazoline-3,6-dione (**1**) in one-pot, provided that the selection of an appropriate amino ester **10** compatible with the reaction conditions is made.

Synthesis of the Pyrazino[2,1-*b*]quinazoline-3,6-dione Core. With these encouraging results in hand, we began the construction of the simplified target pyrazino[2,1-*b*]quinazoline-3,6-dione (**1**) skeletons through the one-pot process (Scheme 4). Glycinemethylester hydrochloride (**10a**) was chosen as the simplest reactant that could be used to develop the diketopiperazine-like cyclization. With the addition of **10a** to the initially

(18) The reaction utilizing Boc-amino acids provided reaction mixtures with fewer side products.

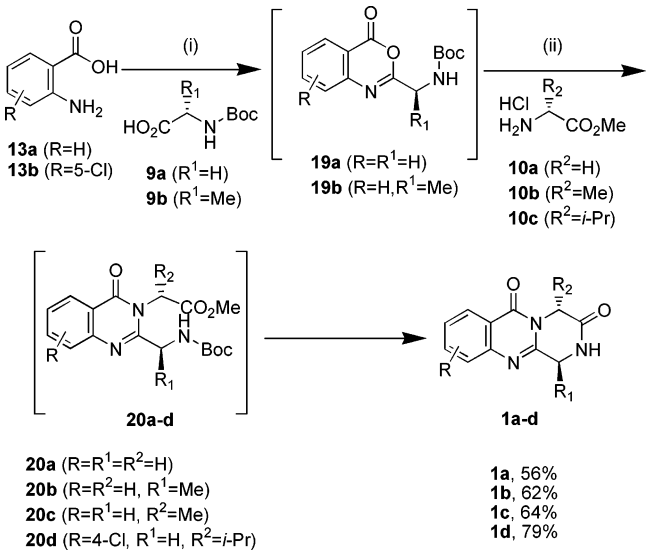
TABLE 1. In Situ N-Deprotection under Microwave Irradiation



entry	temp (°C)	time (min)	**18a/18b**[a]
1	180	3	100/0
2	200	3	80/20
3	210	3	10/90
4	220	4	0/100

[a] Determined by LC-MS (ELSD) of the crude reaction mixture. Compounds **18a** (60% yield) and **18b** (50% yield) were isolated on preparative HPLC and characterized.

SCHEME 4. Optimization of the One-Pot Microwave-Promoted Synthesis of Pyrazino[2,1-*b*]quinazoline-3,6-dione (1)[a]

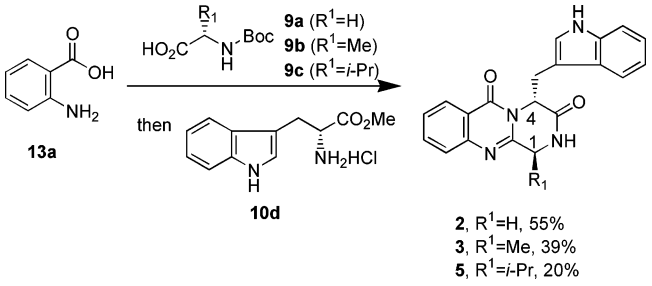


[a] Conditions (i) for **1a**, **1c**, and **1d**, mixture of the corresponding **13** (1.0 equiv), **9a** (1.0 equiv), and $P(OPh)_3$ (1.2 equiv) in pyridine, microwave heating, 150 °C, 10 min; for **1b**, mixture of corresponding **13a** (1.0 equiv), **9b** (1.0 equiv), and $P(OPh)_3$ (1.2 equiv) in pyridine, 55 °C, conventional heating, 16 h; (ii) addition of the corresponding **10** (1.0 equiv), microwave heating, 220 °C, 1.5 min.

generated benzoxazin-4-one (**19a**), the formation of the intermediate **20a** was observed at 150−200 °C under microwave irradiation. Gratifyingly, further irradiation of the reaction mixture at higher temperatures (200−220 °C) affected the ring closure, which yielded **1a** (50% unoptimized), thus achieving the one-pot synthesis of the target core scaffold. Isolation of intermediate **20a** (detailed in the Experimental Section) provided us with direct evidence for our distinct synthetic route to access scaffolds incorporating core **1**.

Once the reaction sequence had been established, it was desirable to optimize the conditions to apply the method to the total synthesis of the natural products (Scheme 4). It is important to note that for the formation of the Boc-protected benzoxazin-4-one (**19**) two different sets of heating conditions were developed to maximize

SCHEME 5. One-Pot Total Synthesis of Glyantrypine (2), Fumiquinazoline F (3), and Fiscalin B (5)[a]



[a] Conditions for **2**: **13a** (1.0 equiv), **9a** (1.0 equiv), and $P(OPh)_3$ (1.2 equiv), pyridine, microwave heating, 150 °C, 10 min; then **10d** (1.0 equiv), microwave heating, 220 °C, 1.5 min. Conditions for **3** or **5**: **13a** (1.0 equiv), **9b** (1.0 equiv) or **9c** (1.0 equiv), and $P(OPh)_3$ (1.2 equiv), pyridine, conventional heating, 55 °C, 16 h; then **10d** (1.0 equiv), microwave heating, 220 °C, 1.5 min.

the yields and accommodate the required functionality. For example, *N*-Boc-glycine (**9a**) was converted to **19a** using microwave heating at 150 °C for 10 min, whereas conventional heating of *N*-Boc-L-alanine (**9b**) at 55 °C for 16 h proved to be the best set of conditions to generate **19b**.[19] In either case, addition of the amino acid esters **10a**, **10b**, and **10c** to the in situ generated Boc-protected benzoxazin-4-one (**19**) followed by microwave heating at 220 °C for 1.5 min afforded the corresponding final products **1a**, **1b**, **1c**, and **1d** with yields of 62, 56, 64, and 79%, respectively. Therefore, these two complementary methods (microwave−microwave or thermal−microwave heating) provided maximum flexibility for applying our one-pot process to various natural products. Moreover, **1b**, a key intermediate in the total synthesis of alantrypinone (**6**) as reported by Kende,[12] could be readily synthesized in this fashion on a 5-g scale in 57% yield, reinforcing the practical advantages of this approach.

Total Synthesis of Glyantrypine, Fumiquinazoline F, and Fiscalin B. Finally, we report the application of this synthetic strategy to the one-pot total syntheses of the alkaloids glyantrypine (**2**), fumiquinazoline F (**3**), and fiscalin B (**5**) (Scheme 5). Microwave irradiation of anthranilic acid (**13a**) with *N*-Boc-glycine (**9a**) followed by the addition of D-tryptophan methylester hydrochloride (**10d**) provided glyantrypine (**2**) in 55% yield.[20,21] Because of epimerization at C4 under these reaction conditions, **2** was obtained with 70% ee as determined by chiral SFC/MS. Fortunately, enantiomerically pure **2** could be generated either via semipreparative chiral SFC or simply by recrystallization from methanol. The unnatural enantiomer of **2** was also synthesized by employing L-tryptophan methylester hydrochloride and purified via preparative chiral SFC.

To further investigate the impact of microwave heating on the stereogenic center at C4, we examined various sets of conditions for the ring closure by modifying the temperature and time of microwave irradiation. The results clearly identified that effective diketopiperazine-like cyclization occurred only at temperatures ranging from >210 to <230 °C, but the degree of epimerization and ratio of the side products increased as a function of prolonged reaction time and increasing temperature. For example, the reaction did not proceed to completion when heated at 210 °C for 3 min. A prolonged reaction time for **2** resulted in enantiomeric erosion (40% ee at 6 min). On the other hand, when the reaction was carried out at higher microwave temperatures (230 °C), unidentified side products emerged after 1.5 min of heating, presumably as a result of decomposition. Moreover, the ee of **2** was decreased to 52% when the reaction was carried out for 3 min at 220 °C. Thus, the optimal conditions for the ring closure were determined to be microwave irradiation at 220 °C for 1.5 min, and these optimized conditions were used in the syntheses of the target molecules.

A one-pot total synthesis of fumiquinazoline F (**3**) in 39% yield was also achieved using the thermal−microwave heating protocol (Scheme 5). The ee for **3** was determined to be 72% (by analytical chiral SFC/MS), which was improved to >99% ee through recrystallization from methanol, as described for **2**. It was observed that both the C1 and C4 stereogenic centers were epimerized partially under the reaction conditions.[22] An investigation of the impact of the reaction conditions on epimerization resulted in outcomes similar to those identified in the case of **2** (the ee for **3** decreased to 50% when the reaction was carried out for 3 min at 220 °C), where epimerization increased with prolonged reaction time and elevated temperatures. The combined remaining fractions after the isolation of **3** were concentrated and separated by preparative HPLC to yield fumiquinazoline G (**4**) as a minor byproduct in 3% yield.[23] Fiscalin B (**5**) was also obtained following the thermal−microwave heating protocol (Scheme 5) but only in 20% yield with 50% ee, which could be attributed to steric hindrance created by the isopropyl group.[24] Despite evidence of epimerization, the successful application of this methodology to access sterically hindered fiscalin B in a one-pot reaction demonstrates the utility of this new method.[25]

(19) In all cases where we have used conventional heating to generate intermediates corresponding to **19**, microwave heating could generate the same products, albeit in lower yields.

(20) As a comparison, a control reaction was carried out in a sealed tube under conventional heating in an oil bath at 210 °C (the minimal temperature required for the reaction to proceed) for 15 min. The product **2** was formed, but the crude reaction mixture was more complex with multiple side products and fully racemized products (LC/MS, ELSD = 60%, ee = 0%) as compared with the microwave conditions which provided the product in higher yield with minimal side reactions and with much less enantiomeric erosion (LC/MS, ELSD = 75%, ee = 70%). Additionally, the conventional heating conditions (sealed tube) are not practical for parallel synthesis of analogue libraries of the natural products, which is an effort that we are pursuing.

(21) The synthesis of **3** was also achieved with the use of D-tryptophan methylester, resulting in an identical yield and optical purity under the same microwave conditions as those used for D-tryptophan methylester hydrochloride (**10d**).

(22) This was evidenced by the fact that the ee of **3** was decreased with higher reaction temperature and longer reaction time. Both samples of **3**, with 72% ee and 50% ee, have identical ^1H NMR and ^{13}C NMR relative to enantiomerically pure **3**.

(23) ^1H NMR is identical with fumiquinazoline G in ref 9b. The chiral SFC/MS analysis confirmed that it is a racemate of **4**.

(24) The ee of **5** was determined by chiral SFC/MS. Enantiomerically pure (>99% ee) **5** could be obtained via preparative chiral SFC separation. The sample has $[\alpha]_D = -613$ (*c* 0.064, $CHCl_3$) {lit.[10b] $[\alpha]^{30}_D = -609$ (*c* 0.59, $CHCl_3$)}. See the Experimental Section for details.

(25) Steric hindrance is an important factor in unsuccessful quinazolinone ring formation in Fiscalin B total synthesis. See the discussion in: Buenadicha, F. L.; Avendaño, C.; Söllhuber, M. *Tetrahedron: Asymmetry* **2001**, *12*, 3019. See ref 10b.

Summary

We have developed a novel and highly efficient three-component one-pot reaction sequence promoted by microwave irradiation for the synthesis of 4-quinazoline-3,6-diones (**1**) and have also demonstrated the utility and versatility of this strategy through the total syntheses of several natural products from readily available starting materials. Notwithstanding the partial epimerization under the reaction conditions, the approach provides an efficient and practical entry into a broad range of natural products. In addition, the methodology features a significantly wide chemistry scope, enabling the construction of natural product-templated and diversity-oriented screening libraries, which will be described in due course.

Experimental Section

[3-(2-Methoxyethyl)-4-oxo-3,4-dihydroquinazolin-2-ylmethyl]carbamic Acid *tert*-Butyl Ester (18a). To a conical-bottomed Smith Process vial were added anthranilic acid (**13a**) (28 mg, 200 μmol), *N*-Boc-glycine (**9a**) (35 mg, 200 μmol), and triphenyl phosphite (63 μL, 220 μmol) along with 1 mL of anhydrous pyridine. The sealed vial was irradiated in the microwave for 10 min at 150 °C. After cooling the mixture to room temperature, we added 2-methoxyethylamine (17.5 μL, 200 μmol), and the resulting mixture was heated in the microwave at 180 °C for 3 min. The reaction mixture was then concentrated in vacuo, and the residue was purified by preparative HPLC[26] (ProntoSIL 120-10-C18 column (50 × 20 mm) with a flow rate of 44 mL/min utilizing an acetonitrile/water mobile phase) to afford **18a** as a white foam (40 mg, 60%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, 1H, J = 8.0, 1.2 Hz), 7.74 (td, 1H, J = 8.0, 1.2 Hz), 7.67 (d, 1H, J = 8.0 Hz), 7.47 (td, 1H, J = 8.0, 1.2 Hz), 6.07 (bs, 1H), 4.57 (d, 2H, J = 4.4 Hz), 4.24 (t, 2H, J = 5.2 Hz), 3.68 (t, 2H, J = 5.2 Hz), 3.28 (s, 3H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 156.0, 153.1, 146.8, 134.6, 127.2, 127.1, 127.0, 120.8, 80.0, 70.1, 59.3, 43.6, 43.1, 28.7; HRMS calcd for ($C_{17}H_{23}N_3O_4$ + Na) 356.1589, found 356.1578; MS *m/z* 334.29 (M + H).

2-Aminomethyl-3-(2-methoxyethyl)-3*H*-quinazolin-4-one (18b). To a conical-bottomed Smith Process vial were added anthranilic acid (**13a**) (28 mg, 200 μmol), *N*-Boc-glycine (**9a**) (35 mg, 200 μmol), and triphenyl phosphite (63 μL, 220 μmol) along with 1 mL of anhydrous pyridine. The sealed vial was irradiated in the microwave for 10 min at 150 °C. After cooling the mixture to room temperature, we added 2-methoxyethylamine (17.5 μL, 200 μmol), and the resulting mixture was heated in the microwave at 220 °C for 4 min. The reaction mixture was then concentrated in vacuo, and the residue was purified by preparative HPLC (ProntoSIL 120-10-C18 column (50 × 20 mm) with a flow rate of 44 mL/min utilizing an acetonitrile/water mobile phase and 0.1% trifluoroacetic acid as a modifier) to afford **18b** as a white solid TFA salt (35 mg, 50%): ^{1}H NMR (400 MHz, CD_3OD) δ 8.20 (dd, 1H, J = 8.4, 1.2 Hz), 7.81 (td, 1H, J = 8.4, 1.2 Hz), 7.72 (d, 1H, J = 8.4 Hz), 7.51 (td, 1H, J = 8.4, 1.2 Hz), 4.30 (t, 2H, J = 5.2 Hz), 4.09 (s, 2H), 3.70 (t, 2H, J = 5.2 Hz), 3.30 (s, 3H); HRMS calcd for ($C_{12}H_{15}N_3O_2$ + H) 234.1244, found 234.1238; MS *m/z* 234.24 (M + H).

[2-(*tert*-Butoxycarbonylaminomethyl)-4-oxo-4*H*-quinazolin-3-yl]acetic Acid Methyl Ester (20a). To a conical-bottomed Smith Process vial were added anthranilic acid (**13a**) (28 mg, 200 μmol), *N*-Boc-glycine (**9a**) (35 mg, 200 μmol), and triphenyl phosphite (63 μL, 220 μmol) along with 1 mL of anhydrous pyridine. The sealed vial was irradiated in the microwave for 10 min at 150 °C. After cooling the mixture to room temperature, we added glycine methylester hydrochloride (**10a**) (25 mg, 200 μmol), and the resulting mixture was heated in the microwave at 150 °C for 3 min. The reaction mixture was then concentrated in vacuo, and the residue was purified by preparative HPLC (ProntoSIL 120-10-C18 column (50 × 20 mm) with a flow rate of 44 mL/min utilizing an acetonitrile/water mobile phase) to afford **20a** as a white solid (38 mg, 55%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, 1H, J = 8.2, 1.2 Hz), 7.78 (ddd, 1H, J = 8.2, 7.6, 1.2 Hz), 7.70 (d, 1H, J = 7.6 Hz), 7.50 (ddd, 1H, J = 8.2, 7.6, 1.2 Hz), 5.93 (bs, 1H), 4.86 (s, 2H), 4.35 (t, 2H, J = 4.8 Hz), 3.80 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 161.9, 155.8, 151.6, 146.7, 135.0, 127.5, 127.4, 127.3, 120.5, 80.5, 53.2, 44.0, 43.2, 28.6; HRMS calcd for ($C_{17}H_{21}N_3O_5$ + Na) 370.1381, found 370.1371; MS *m/z* 348.12 (M + H).

2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (1a). To a conical-bottomed Smith Process vial were added anthranilic acid (**13a**) (28 mg, 200 μmol), *N*-Boc-glycine (**9a**) (35 mg, 200 μmol), and triphenyl phosphite (63 μL, 220 μmol) along with 1 mL of anhydrous pyridine. The sealed vial was irradiated in the microwave for 10 min at 150 °C. After cooling the mixture to room temperature, we added glycine methylester hydrochloride (**10a**) (25 mg, 200 μmol), and the resulting mixture was heated in the microwave at 220 °C for 1.5 min. The reaction mixture was then concentrated in vacuo, and the residue was purified by silica gel flash chromatography (dichloromethane/ethyl acetate/MeOH = 50:48:2) to afford **1a** as a white solid (24 mg, 56%): mp 285−287 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (bs, 1H), 8.12 (dd, 1H, J = 8.0, 1.6 Hz), 7.83 (ddd, 1H, J = 7.2, 6.0, 0.8 Hz), 7.63 (d, 1H, J = 8.0 Hz), 7.52 (dd, 1H, J = 8.0, 8.0 Hz), 4.51 (s, 1H), 4.42 (d, 1H, J = 2.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.7, 160.5, 150.8, 147.8, 135.4, 127.5, 127.4, 126.9, 45.43, 45.37; HRMS calcd for ($C_{11}H_9N_3O_2$ + H) 216.0768, found 216.0769; MS *m/z* 216.12 (M + H).

(1*S*)-1-Methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (1b). To a conical-bottomed Smith Process vial were added anthranilic acid (**13a**) (28 mg, 200 μmol), *N*-Boc-L-alanine (**9b**) (38 mg, 200 μmol), and triphenyl phosphite (63 μL, 220 μmol) along with 1 mL of anhydrous pyridine. The vial was then heated at 55 °C for 16 h. After cooling the mixture to room temperature, we added glycine methylester hydrochloride (**10a**) (25 mg, 200 μmol), and the resulting mixture was heated in the microwave at 220 °C for 1.5 min. The reaction mixture was then concentrated in vacuo, and the residue was purified by silica gel flash chromatography (dichloromethane/ethyl acetate/MeOH = 50:48:2) to afford **1b** as a white solid (28.5 mg, 62%): mp 238−240 °C; ^{1}H NMR (400 MHz, DMSO−d_6) δ 8.67 (bs, 1H), 8.13 (dd, 1H, J = 8.0, 1.2 Hz), 7.81 (ddd, 1H, J = 8.0, 7.2, 1.6 Hz), 7.63 (dd, 1H, J = 7.6, 0.8 Hz), 7.51 (ddd, 1H, J = 8.0, 7.2, 1.6 Hz), 4.63 (d, 1H, J = 17.6 Hz), 4.60 (dq, 1H, J = 7.0, 1.6 Hz), 4.48 (d, 1H, J = 17.6 Hz), 1.52 (dd, 3H, J = 7.0, 1.0 Hz); ^{13}C NMR (100 MHz, DMSO−d_6) δ 166.7, 160.7, 153.3, 147.4, 135.4, 127.8, 127.4, 126.8, 120.0, 50.9, 45.0, 19.9; HRMS calcd for ($C_{12}H_{11}N_3O_2$ + H) 230.0924, found 230.0925; MS *m/z* 230.27 (M + H).

Gram-Scale Synthesis of 1b. To a 40 mL glass vial were added anthranilic acid (**13a**) (1.37 g, 10 mmol), *N*-Boc-L-alanine (**9b**) (1.89 g, 10 mmol), triphenyl phosphite (2.62 mL, 12 mmol), and pyridine (15 mL). Four copies of this reaction were prepared, and the reaction mixtures were heated at 55 °C for 16 h. After cooling the mixtures to room temperature, we transferred the four reactions to four vessels for the Reactor HPR 100-mL rotor for the microwave labstation, and then glycine methylester hydrochloride (**10a**) (1.25 g, 10 mmol) was added to each vessel. These four reactions were then set on the rotor in parallel and heated in the microwave labstation at 210 °C for 7 min with an 18-min temperature ramp. The reaction mixtures were combined and then concentrated in vacuo, and the residue was purified by silica gel flash chromatography (dichloromethane/ethyl acetate/MeOH = 50:48:2) to afford **1b** as a white solid (5.2 g, 57%), with

(26) Goetzinger, W.; Zhang, X.; Bi, G.; Towle, M.; Cherrak, D.; Kyranos, J. N. *Int. J. Mass. Spectrom.* **2004**, *238*, 153.

analytical data consistent with that reported in the previous experiments.

(4*S*)-4-Methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (1c). To a conical-bottomed Smith Process vial were added anthranilic acid (**13a**) (28 mg, 200 μmol), *N*-Boc-glycine (**9a**) (35 mg, 200 μmol), and triphenyl phosphite (63 μL, 220 μmol) along with 1 mL of anhydrous pyridine. The sealed vial was irradiated in the microwave for 10 min at 150 °C. After cooling the mixture to room temperature, we added D-alanine methylester hydrochloride (**10b**) (28 mg, 200 μmol), and the resulting mixture was heated in the microwave at 220 °C for 1.5 min. The reaction mixture was then concentrated in vacuo, and the residue was purified by silica gel flash chromatography (dichloromethane/ethyl acetate/MeOH = 50:48:2) to afford **1c** as a white solid (29.4 mg, 64%): mp 217−219 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, 1H, *J* = 8.0 Hz), 7.78 (ddd, 1H, *J* = 8.0, 7.2, 0.8 Hz), 7.64 (d, 1H, *J* = 8.4 Hz), 7.52 (dd, 1H, *J* = 7.6, 3.4 Hz), 6.90 (bs, 1H, *N*-H), 5.46 (q, 1H, *J* = 7.2 Hz), 4.69 (d, 1H, *J* = 16.8 Hz), 4.51 (dd, 1H, *J* = 16.4, 4.8 Hz), 1.66 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 160.4, 147.8, 147.2, 135.1, 127.6, 127.21, 127.18, 120.6, 52.0, 45.3, 17.2; HRMS calcd for ($C_{12}H_{11}N_3O_2$ + H) 230.0924, found 230.0927; MS *m/z* 230.10 (M + H).

(4*S*)-4-(2-Methylpropyl)-9-chloro-2*H*-pyrazino[2,1-*b*]-quinazoline-3,6-(1*H*,4*H*)dione (1d). To a conical-bottomed Smith Process vial were added 4-chloroanthranilic acid (**13b**) (35 mg, 200 μmol), *N*-Boc-glycine (**9a**) (35 mg, 200 μmol), and triphenyl phosphite (63 μL, 220 μmol) along with 1 mL of anhydrous pyridine. The sealed vial was irradiated in the microwave for 10 min at 150 °C. After cooling the mixture to room temperature, we added D-valine methylester hydrochloride (**10c**) (34 mg, 200 μmol), and the resulting mixture was heated in the microwave at 220 °C for 1.5 min. The reaction mixture was then concentrated in vacuo, and the residue was purified by silica gel flash chromatography (dichloromethane/ethyl acetate/MeOH = 50:48:2) to afford **1d** as a white solid (46 mg, 79%): mp 219−221 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, 1H, *J* = 8.8 Hz), 7.63 (d, 1H, *J* = 2.0 Hz), 7.45 (dd, 1H, *J* = 8.6, 1.8 Hz), 6.73 (bd, 1H, *J* = 4.4 Hz), 5.24 (dd, 1H, *J* = 8.0, 1.2 Hz), 4.70 (d, 1H, *J* = 17.2 Hz), 4.43 (dd, 1H, *J* = 17.6, 5.2 Hz), 2.33−2.45 (m, 1H), 1.15 (d, 3H, *J* = 7.2 Hz), 1.08 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 160.4, 149.8, 148.2, 141.3, 128.9, 128.2, 126.8, 119.0, 61.0, 45.7, 32.0, 20.1, 19.0; HRMS calcd for ($C_{14}H_{14}N_3O_2C1$ + Na) 314.0667, found 314.0668; MS *m/z* 292.04 (M + H).

(*R*)-4-(1*H*-indol-3-ylmethyl)-2*H*-pyrazino[2,1-*b*]quinazoline-3,6(1*H*,4*H*)-dione (glyantrypine) (2). To a conical-bottomed Smith Process vial were added anthranilic acid (**13a**) (28 mg, 200 μmol), *N*-Boc-glycine (**9a**) (35 mg, 200 μmol), and triphenyl phosphite (63 μL, 220 μmol) along with 1 mL of anhydrous pyridine. The sealed vial was irradiated in the microwave for 10 min at 150 °C. After cooling the mixture to room temperature, we added D-tryptophan methylester hydrochloride (**10d**) (51 mg, 200 μmol), and the resulting mixture was heated in the microwave at 220 °C for 1.5 min. Using this procedure, we ran two copies of the reaction on the Personal Chemistry Creator and Smith stations and the combined reaction mixture was concentrated in vacuo, and the residue was purified by silica gel flash chromatography (dichloromethane/ethyl acetate/MeOH = 50:48:2) to afford **2** as a white crystal (76 mg, 55%). The ee of this sample was determined to be 70% on an analytical SFC/MS system equipped with a ChiralCel OD-H column (4.6 × 250 mm) with a flow rate of 3 mL/min and 25% MeOH in CO_2 as the mobile phase (30 °C, 130 bar outlet pressure). When the analytical HPLC was coupled with APCI sourced mass spectrometric detection, a makeup flow (0.3 mL/min) of 0.1% formic acid in MeOH was used. The chiral purification was carried out on a SFC MiniGram system equipped with a ChiralCel OJ-H Column (20 × 250 mm) with a flow rate of 60 mL/min and a mobile phase composed of 20% MeOH in CO_2. The column oven was set at 30 °C, and the outlet pressure was at 100 bar. Fraction collection was triggered on the basis of UV_{214nm} trace. After chiral purification, the ee of **2** was determined to be 100% using the analytical conditions described above. Alternatively, enantiomerically pure **2** (100% ee) could also be obtained after recrystallization from MeOH as light yellow crystals: mp 155−157 °C; $[\alpha]_D$ = −535 (*c* 0.028, $CHCl_3$) {lit.[10b] mp 159−161 °C (foam); $[\alpha]^{30}_D$ = −522 (*c* 0.24, $CHCl_3$)}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (bs, 1H), 8.31 (d, 1H, *J* = 4.4 Hz), 8.18 (d, 1H, *J* = 7.2 Hz), 7.82 (td, 1H, *J* = 7.7, 1.6 Hz), 7.54 (t, 2H, *J* = 8.4 Hz), 7.30 (dd, 1H, *J* = 8.0, 0.8 Hz), 7.24 (d, 1H, *J* = 7.6 Hz), 6.99 (t, 1H, *J* = 7.4 Hz), 7.85 (d, 1H, *J* = 2.8 Hz), 6.76 (t, 1H, *J* = 7.4 Hz), 5.26 (t, 1H, *J* = 5.0 Hz), 3.79 (dd, 1H, *J* = 17.2, 4.4 Hz), 3.41 (d, 2H, *J* = 5.0 Hz), 3.05 (d, 1H, *J* = 16.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.5, 160.7, 149.8, 147.5, 136.5, 135.6, 127.7, 127.6, 127.2, 127.0, 124.9, 122.1, 120.4, 119.4, 118.3, 112.1, 108.3, 57.2, 44.2, 27.1; HRMS calcd for ($C_{20}H_{16}N_4O_2$ + Na) 367.1165, found 367.1172; MS *m/z* 345.25 (M + H).

(1*S*,4*R*)-4-(1*H*-Indol-3-ylmethyl)-1-methyl-2*H*-pyrazino-[2,1-*b*]quinazoline-3,6(1*H*,4*H*)-dione (fumiquinazoline F) (3). To a conical-bottomed Smith Process vial were added anthranilic acid (**13a**) (28 mg, 200 μmol), *N*-Boc-L-alanine (**9b**) (38 mg, 200 μmol), and triphenyl phosphite (63 μL, 220 μmol) along with 1 mL of anhydrous pyridine. The vial was heated in a heating block at 55 °C for 16 h. After cooling the mixture to room temperature, we added D-tryptophan methylester hydrochloride (**10d**) (51 mg, 200 μmol), and the resulting mixture was irradiated in the microwave at 220 °C for 1.5 min. Using this procedure, we ran two copies of the reaction on the Personal Chemistry Creator and Smith stations and the combined reaction mixture was concentrated in vacuo, and the residue was purified by silica gel flash chromatography (dichloromethane/ethyl acetate/MeOH = 50:48:2) to give a desired product **3** as a white solid (56 mg, 39%). The combined remaining fractions were concentrated and separated by preparative HPLC employing a ProntoSIL 120-10-C18 column (50 × 20 mm). The flow rate was at 44 mL/min utilizing an acetonitrile/water mobile phase. After dry-down on the freeze-dryer, 4 mg (3%) of **4** was obtained as pale yellow foam.

The ee of **3** was determined to be 72% using the method and conditions described above for **2**. Light yellow cubical crystals were obtained after recrystallization from MeOH, and the ee was determined to be 100% using the same conditions as above. **3:** mp 134−136 °C; $[\alpha]_D$ = −479 (*c* 0.038, $CHCl_3$) {lit.[10b] mp 137 °C (foam); $[\alpha]^{30}_D$ = −516 (*c* 0.74, $CHCl_3$)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (dd, 1H, *J* = 8.0, 1.2 Hz), 8.14 (bs, 1H), 7.78 (td, 1H, *J* = 7.2, 1.2 Hz), 7.59 (d, 1H, *J* = 7.6 Hz), 7.53 (t, 1H, *J* = 6.8 Hz), 7.38 (d, 1H, *J* = 7.6 Hz), 7.29 (d, 1H, *J* = 8.0 Hz), 7.11 (t, 1H, *J* = 7.6 Hz), 6.90 (t, 1H, *J* = 7.6 Hz), 6.70 (d, 1H, *J* = 2.0 Hz), 6.27 (bs, 1H, NH), 5.68 (t, 1H, *J* = 4.0 Hz), 3.70 (dd, 1H, *J* = 15.2, 3.6 Hz), 3.64 (dd, *J* = 15.3, 5.2 Hz), 3.07 (q, 1H, *J* = 6.4 Hz), 1.36 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 160.8, 151.9, 147.2, 136.2, 134.9, 127.5, 127.3, 127.1, 123.7, 122.8, 120.4, 120.3, 118.7, 111.4, 109.6, 57.8, 49.4, 27.3, 19.4; HRMS calcd for ($C_{21}H_{18}N_4O_2$ + Na) 381.1322, found 381.1323; MS *m/z* 359.34 (M + H).

Fumiquinazoline G (4). The ee of **4** was determined to be 0% using the method and conditions as described above for **2**. ^{1}H NMR [lit.[10b]] δ 8.39 (dd, 1H, *J* = 8.0, 1.2), 8.05 (bs, 1H), 7.79 (td, 1H, *J* = 7.6, 1.6), 7.57 (d, 1H, *J* = 8.4), 7.54 (td, 1H, *J* = 8.0, 1.2), 7.29 (dd, 1H, *J* = 14.4, 8.0), 7.10 (td, 1H, *J* = 7.2, 0.8), 6.87 (td, 1H, *J* = 7.2, 0.8), 6.73 (d, 1H, *J* = 2.4), 6.26 (bs, 1H), 5.57 (dd, 1H, *J* = 5.6, 3.2), 4.46 (qd, 1H, *J* = 7.2, 2.8), 3.81 (dd. 1H, *J* = 14.8, 4.8), 3.73 (dd, *J* = 14.8, 3.2), 0.54 (d, 3H, *J* = 6.8); MS *m/z* 359.35 (M + H).

(1*S*,4*R*)-4-(1*H*-Indol-3-ylmethyl)-1-isopropyl-2*H*-pyrazino[2,1-*b*]quinazoline-3,6(1*H*,4*H*)-dione (fiscalin B) (5). To a conical-bottomed Smith Process vial were added anthranilic acid (**13a**) (28 mg, 200 μmol), Boc-L-valine (**9c**) (44 mg, 200 μmol), and triphenyl phosphite (63 μL, 220 μmol) along

with 1 mL of anhydrous pyridine. The vial was heated in a heating block at 55 °C for 16 h. After cooling the mixture to room temperature, we added D-tryptophan methylester hydrochloride (**10d**) (51 mg, 200 μmol), and the resulting mixture was irradiated in the microwave at 220 °C for 1.5 min. Using this procedure, we ran two copies of reactions on the Personal Chemistry Creator and Smith stations and the combined reaction mixture was concentrated in vacuo, and the residue was purified by silica gel flash chromatography (dichloromethane/ethyl acetate/MeOH = 50:48:2) to give the desired product **5** as a pale yellow solid (31 mg, 20%). The ee of **5** was determined to be 50% using the method and conditions described above for **2**. After chiral purification (carried out on the semi-prep SFC system as described above for **2**), the ee of **5** (now a white solid) was determined to be 100% (using the same method and conditions as for **2**): mp 167−169 °C; $[\alpha]_D = -613$ (*c* 0.064, $CHCl_3$) {lit.[10b] mp 176.5−178.5 °C; $[\alpha]^{30}_D = -609$ (*c* 0.59, $CHCl_3$)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (dd, 1H, J = 8.0, 1.2 Hz), 8.07 (bs, 1H), 7.77 (ddd, 1H, J = 8.4, 6.8, 1.6 Hz), 7.55 (d, 1H, J = 7.6 Hz), 7.53 (t, 1H, J = 7.2 Hz), 7.44 (d, 1H, J = 8.0 Hz), 7.28 (d, 1H, J = 7.6 Hz), 7.12 (t, 1H, J = 7.6 Hz), 6.93 (t, 1H, J = 7.2 Hz), 6.60 (d, 1H, J = 2.8 Hz), 5.76 (bs, 1H), 5.67 (dd, 1H, J = 5.6, 2.8 Hz), 3.74 (dd, 1H, J = 15.0, 3.2 Hz), 3.63 (dd, 1H, J = 15.0, 5.2 Hz), 2.70 (d, 1H, J = 2.1 Hz), 2.63 (m, 1H), 0.64 (d, 3H, J = 7.2 Hz), 0.63 (d, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 161.1, 150.5, 147.3, 136.2, 134.9, 127.4, 127.4, 127.3, 127.1, 123.8, 122.8, 120.4, 120.3, 119.0, 111.3, 109.6, 58.3, 57.0, 29.7, 27.6, 19.0, 15.0; HRMS calcd for ($C_{23}H_{22}N_4O_2$ + Na) 409.1635, found 409.1644; MS *m/z* 387.22 (M + H).

Acknowledgment. The authors thank Ms. Martina DeSomma, Ms. Jun Zhao, and Mr. Ted Manley for technical support.

Supporting Information Available: Copies of ^{1}HNMR and ^{13}CNMR spectra for compounds **1a**−**d**, **2**, **3**, **5**, **18a**, **18b**, and **20a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0508043