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Synthesis of circumdatin F and sclerotigenin. Use of the 2-nitrobenzyl group for protection of a diketopiperazine amide; synthesis of *ent*-fumiquinazoline G

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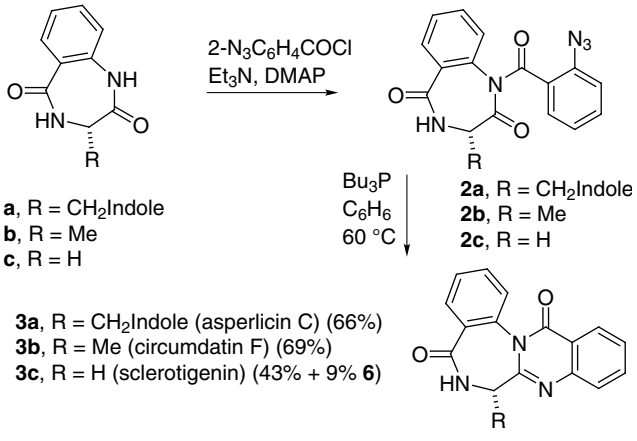
Abstract—The Eguchi aza Wittig protocol has been used for the synthesis of sclerotigenin and circumdatin F by selective acylation of the more acidic anilide nitrogen of a benzodiazepinedione without the need for protecting groups. The use of the 2-nitrobenzyl group as a photochemically labile protecting group for the amide nitrogen of a diketopiperazine permits the use of the aza Wittig procedure for the synthesis of fumiquinazoline G. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

A wide variety of quinazolinone natural products have been isolated in recent years. These fall into two general families with the quinazolinone fused to a benzodiazepinedione as in asperlicin C (**3a**)[1] (see Scheme 1) or to a diketopiperazine as in fumiquinazolines G (**4a**), and F (**4b**)[2] and fiscalin B (**4c**)[3] (see Scheme 2). Different applications of the Eguchi aza Wittig protocol[4] provide efficient entry to both classes of natural products. We recently reported an improved synthesis of asperlicin C (**3a**).[1] Selective acylation of the more acidic anilide nitrogen of **1a** with azidobenzoyl chloride, DMAP, and Et_3N in CH_2Cl_2, followed by aza Wittig cyclization[4] of the resulting imide **2a** with Bu_3P in benzene at 60°C afforded 66% of asperlicin C (**3a**). This sequence provides a short and efficient route to the fused quinazolinone ring system without the need for protection of the less acidic amide nitrogen. Since this work was completed, Rahbæk reported the isolation of the related quinazolinone circumdatin F (**3b**) as a minor component from the fungus *Aspergillus ochraceus*.[5] Gloer reported the isolation of the antiinsectan sclerotigenin (**3c**) from *Penicillium sclerotigenum*.[6] The selective acylation-aza Wittig sequence should provide an equally efficient route to these compounds.



Scheme 1.

Application of the Eguchi protocol to the synthesis of the fumiquinazolines and fiscalins (**4a–c**) requires the preparation of *N*-protected diketopiperazine **5**, since it is not possible to selectively acylate one of the two nitrogens of a diketopiperazine. We have previously reported a solution to this problem using the 2,4-dimethoxybenzyl protecting group.[7] We report here an improved solution using the photolabile 2-nitrobenzyl protecting group.

2. Synthesis of circumdatin F and sclerotigenin

Benzodiazepinedione **1b**[8] was insoluble in CH_2Cl_2, but could be selectively acylated with 2-azidobenzoyl chloride[4,9] and Et_3N and DMAP in THF to afford crude **2b**, which was treated with Bu_3P in benzene at 60°C to give 69% of (*S*)-(−)-circumdatin F (**3b**) with ^1H NMR spectral data identical to those reported (see Scheme 1).[5] Although the optical rotation of natural circumdatin F was not determined due to the small amount isolated, the absolute stereochemistry is probably the same as **3b** since

Keywords: aza Wittig reaction; alkaloids; photochemistry; protecting groups.

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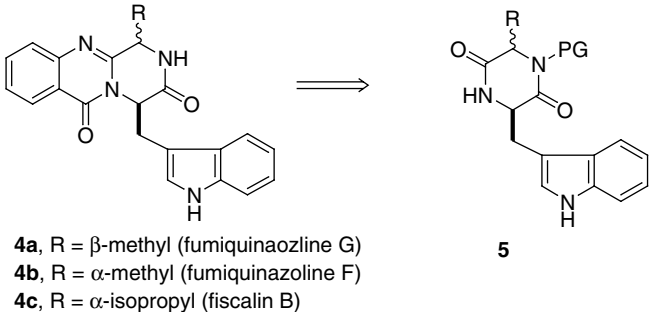


4a, R = β-methyl (fumiquinaozline G)
4b, R = α-methyl (fumiquinazoline F)
4c, R = α-isopropyl (fiscalin B)

5

Scheme 2.

the closely related alkaloid circumdatin C is derived from L-alanine.[5]

Acylation of the parent benzodiazepinedione (**1c**) was more challenging due to its insolubility in CH_2Cl_2, THF, and other common organic solvents. Eventually we found that acylation could be accomplished in modest yield in 2:1 CH_2Cl_2/DMSO. Treatment of crude imide **2c** with Bu_3P in benzene at 60°C provided 43% of sclerotigenin (**3c**) with spectral data identical to those of the natural product.[6,10]

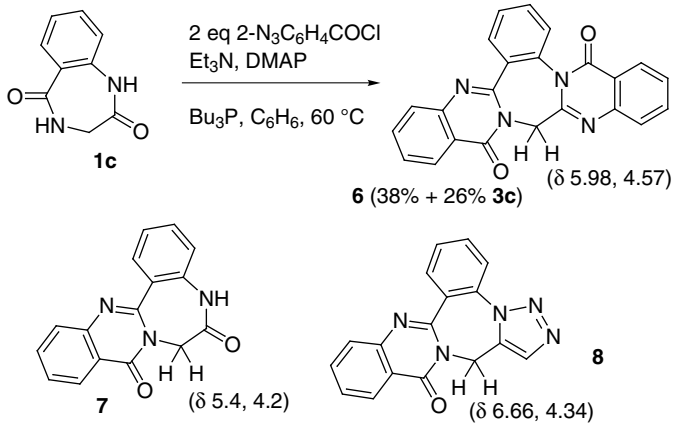
A second quinazolinone was isolated from this reaction in 9% yield. Initially, we thought that it might be **7** resulting from acylation of the other amide, which is less hindered in the parent **1c** than in the substituted analogues **1a** and **1b**. However, the ^{1}H NMR spectral absorptions for the methylene protons in DMSO-d_6 did not match those of authentic **7** (see Scheme 3).[11] Full NMR and MS characterization indicated that the minor product was the bis adduct **6**. The yield of this product could be improved by acylation with 2 equiv. of 2-azidobenzoyl chloride, which gave 38% of **6** and 26% of sclerotigenin (**3c**). The formation of the bis quinazolinone appears to be restricted to the unhindered parent **1c**, since none of the analogous product could be obtained from **1b** with 2 equiv. of 2-azidobenzoyl chloride.

The methylene protons of **3c** absorb at δ 4.24 and 4.31 in the ^{1}H NMR spectrum indicating that they are non-equivalent on the NMR time scale because of a significant barrier to flipping the seven-membered ring.[6] The chemical shifts of the methylene protons of **6** at δ 5.98 and 4.57 are remarkably different due to the slow flipping of the ring and the very anisotropic environment due to the adjacent carbonyl group.[12] Similar shift differences have been observed in **7** (δ 5.4 and 4.2)[11] and **8** (δ 6.66 and 4.34).[13]

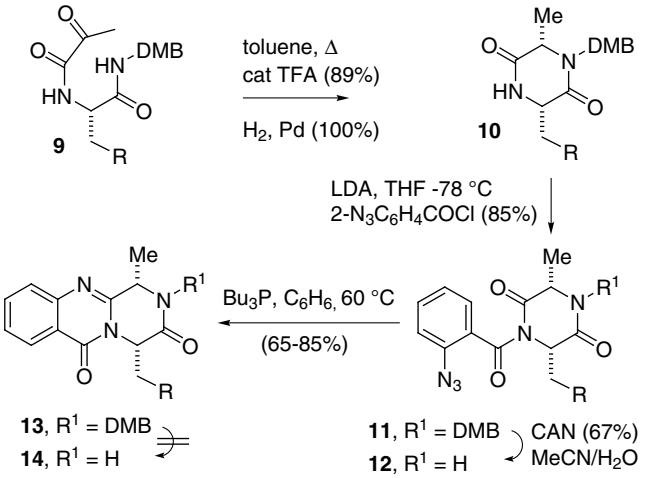
As expected, there is also a barrier to flipping the seven-membered ring of the substituted analogues **3a** and **3b**, although this had not been noted previously due to the small amount of the minor conformer present at equilibrium. The ^{1}H NMR spectrum indicates that circumdatin F (**3b**) exists as a 99:1 mixture of conformers in $CDCl_3$. The aliphatic protons of the major conformer absorb at δ 4.37 and 1.71, while those of the minor conformer absorb at δ 4.69 and 1.13. The ^{1}H NMR spectrum indicates that asperlicin C (**3a**) exists as a 27:1 mixture of conformers in DMSO-d_6.[1b] The aliphatic protons of the major conformer absorb at δ 4.40, 3.63 and 3.39, while those of the minor conformer absorb at δ 4.67, 2.80 and 2.49.

3. Synthesis of *ent*-fumiquinazoline G

A series of cytotoxic quinazolinones including fumiquinazolines G and F (**4a** and **4b**) were isolated by Numata from a strain of fungus *Aspergillus fumigatus* separated from the gastrointestinal tract of the fish *Pseudolabrus japonicus*.[2] Fiscalin B (**4c**), which inhibits binding of substance P to human U-373 MG intact cells, was isolated by a Sterling Winthrop group from the fungus *Neosartorya fischeri*.[3] We recently reported a synthesis of fumiquinazoline G (**4a**), which was carried out in the more available enantiomeric



Scheme 3.



Scheme 4.

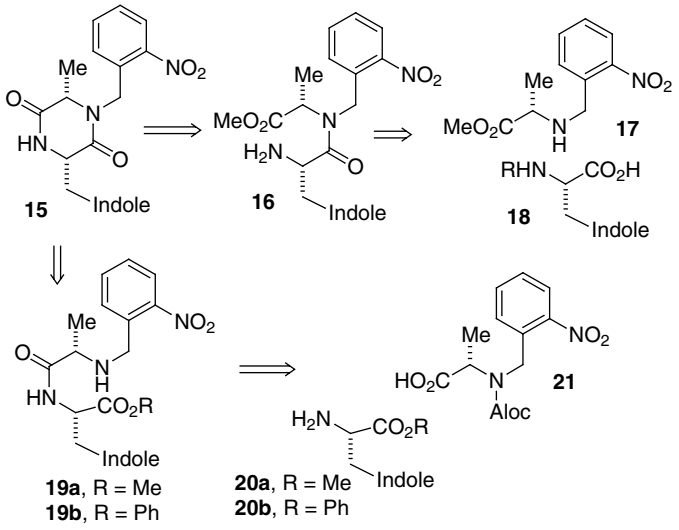
series using L-amino acids (see Scheme 4).[1b,7] Heating pyruvamide **9** in toluene at reflux containing a catalytic amount of TFA afforded the enamide, which was hydrogenated selectively from the less hindered β-face to give 89% of **10**. Formation of the amide anion with LDA in THF and acylation with 2-azidobenzoyl chloride afforded 85% of **11**, which was converted to quinazolinone **13** in 65–85% yield with Bu_3P in benzene at 60°C. Unfortunately, we were unable to cleanly remove the 2,4-dimethoxybenzyl (DMB) protecting group from **13** with either TFA or ceric ammonium nitrate (CAN) in aqueous MeCN.[1b,7] Avendaño and Menéndez have since reported similar problems cleaving the DMB group in related compounds with either CAN or TFA/anisole.[14] Fortunately, oxidative deprotection of acyclic imide **11** with CAN in aqueous MeCN afforded 67% of unprotected imide **12**, which could be cyclized with Bu_3P in benzene at 60°C to give 65–85% of quinazolinone **14**.

Although this sequence was successful, the harsh conditions required for deprotection of the DMB group, which can only be carried out on the imide and not the quinazolinone, are not ideal. Furthermore, the preparation of the diketopiperazine by condensation of the pyruvamide is limited to the preparation of alanine-derived diketopiperazines. We therefore needed a more general route to protected diketopiperazines that could be deprotected after the generation of the quinazolinone. We decided to investigate the 2-nitrobenzyl protecting group since it can be easily cleaved photochemically.[15]

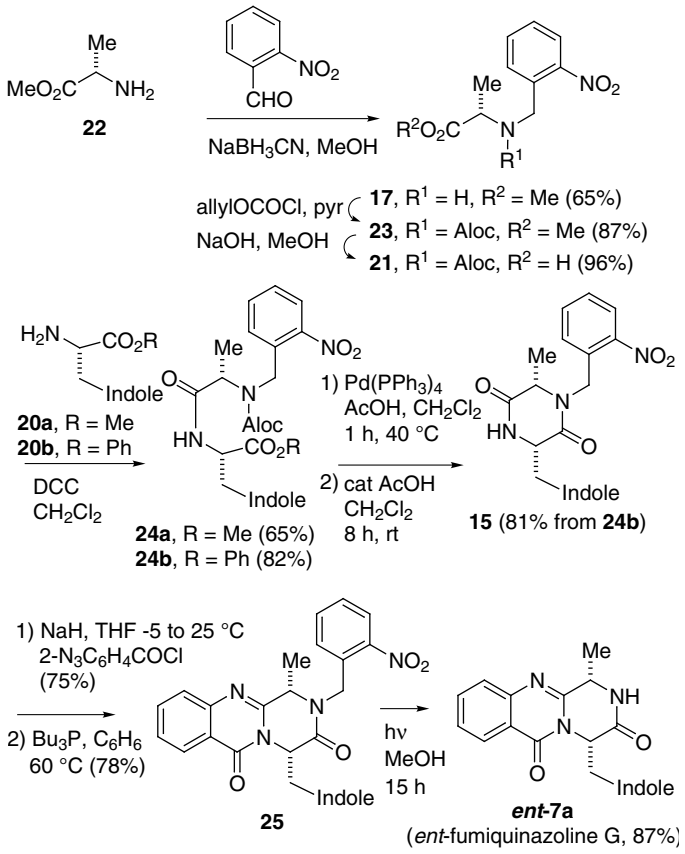
The shortest route to 2-nitrobenzyl diketopiperazine **15** is the cyclization of amino ester **16**, which could be prepared by coupling of the secondary amino ester **17** with the protected amino acid **18** (see Scheme 5). Alternatively, **15** could be prepared by cyclization of amino ester **19**, which could be prepared by coupling primary amino ester **20** with protected amino acid **21**. This sequence requires additional steps for the protection of the amino group of **17** and hydrolysis of the methyl ester to prepare **21**.

Reductive amination[16] of 2-nitrobenzaldehyde with alanine methyl ester (**22**) and $NaBH_3CN$ in MeOH afforded 65% of the required amino ester **17** (see Scheme 6). Unfortunately, attempted coupling of **17** with Troc- or Boc-tryptophan using DCC and DMAP, DCC and Et(*I*-Pr)$_2$N, HATU and Et(*I*-Pr)$_2$N, or HATU and HOBT was unsuccessful. We were also unable to acylate **17** with the acyl fluoride[17] prepared from Boc-tryptophan. Steric hindrance from the 2-nitrobenzyl group retards acylation of the hindered secondary amine of protected amino ester **17** as has been observed recently by Avendaño for related DMB protected amino acids.[14b]

The protected amino acid **21** was therefore prepared by coupling **17** with 10 equiv. of allyl chloroformate in pyridine/THF to give 87% of **23** and hydrolysis of the methyl ester to give 96% of **21**. A large excess of allyl chloroformate was needed to obtain good yields of **23**. Condensation of the acid of **21** with tryptophan methyl ester (**20a**) using DCC proceeded uneventfully to give 65% of dipeptide **24a**. Deprotection of the Aloc group with $Pd(PPh_3)_4$ gave the free dipeptide amino methyl ester. Unfortunately, diketopiperazine formation with the



Scheme 5.



Scheme 6.

hindered secondary amine could not be effected on heating in CH_2Cl_2 or $CHCl_3$ containing a catalytic amount of AcOH.

We therefore decided to use an activated phenyl ester to facilitate formation of the diketopiperazine since we had used this strategy effectively to form the benzodiazepinedione of asperlicin.[1,18] Treatment of Troc-tryptophan phenyl ester[1] with Zn in AcOH afforded amino ester **20b**,[18] which was condensed with **21** using DCC in CH_2Cl_2 to give 82% of dipeptide **24b**. Deprotection of the Aloc group with $Pd(PPh_3)_4$ in $AcOH/CH_2Cl_2$ afforded the more reactive dipeptide secondary amine phenyl ester, which cyclized on stirring in CH_2Cl_2 at 25°C containing a trace of AcOH for 8 h to afford 81% of the desired monoprotected diketopiperazine **15** and 13% of the easily separated epimerized diastereomer with a β-CH_2indole side chain.

The quinazolinone was introduced by acylation of **15** with NaH and 2-azidobenzoyl chloride[4,9] in THF at −5–25°C to give 75% of the imide, which was treated with Bu_3P in benzene at 60–70°C to afford 78% of protected *ent*-fumiquinazoline G (**25**). We were delighted to find that photolysis of a dilute MeOH solution of **25** at 254 nm through Pyrex provided 87% of *ent*-fumiquinazoline G (*ent*-**7a**). Neither the quinazolinone nor the indole interferes with the photochemical deprotection. Procedures using $NaHSO_3$ in aqueous MeOH to trap the nitrosobenzaldehyde produced in the photolysis were less successful.[15d]

In conclusion, we have shown that selective acylation of the more acidic anilide nitrogen of benzodiazepinediones **1** with 2-azidobenzoyl chloride followed by an aza Wittig reaction is general, providing very short and efficient syntheses of circumdatin F (**3b**) and sclerotigenin (**3c**). We have developed a general procedure for the synthesis of *N*-(2-nitrobenzyl)diketopiperazines, which can be deprotected cleanly on irradiation in MeOH through Pyrex at 254 nm. The utility of this sequence has been demonstrated in a short synthesis of *ent*-fumiquinazoline G (*ent*-**7a**).

4. Experimental

4.1. General

NMR spectral data are reported in $CDCl_3$ unless otherwise indicated. Chemical shifts are reported in δ and coupling constants in Hz.

4.1.1. (7*S*)-6,7-Dihydro-7-methylquinazolino[3,2-*a*][1,4]-benzodiazepine-5,13-dione (circumdatin F, 3b). Et_3N (350 μL, 2.5 mmol, 1.25 equiv.) was added to a solution of **1b**[8] (380 mg, 2 mmol) in dry THF (40 mL). The resulting mixture was stirred for 15 min and treated with DMAP (170 mg, 1.4 mmol, 0.7 equiv.). Freshly prepared 2-azidobenzoyl chloride[4,9] (from 408 mg, 2.5 mmol, 1.25 equiv. of 2-azidobenzoic acid)[9] in dry THF (2 mL) was added dropwise to the solution and the resulting mixture was stirred for 2 h at 20°C. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (30 mL), which was washed with water (3×30 mL) and dried

(Na_2SO_4). Concentration gave 650 mg of crude **2b** as a yellowish foamy solid.

Crude **2b** (650 mg) was dissolved in dry benzene (10 mL) and (n-Bu)$_3$P (485 μL, 1.9 mmol) was added to the solution in one portion. The resulting mixture was stirred at rt under N_2 for 2 min and at 60°C for 1 h. The reaction mixture was cooled and concentrated. The residue was diluted with CH_2Cl_2 (50 mL), which was washed with 0.5 M HCl (3×50 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated. Flash chromatography on silica gel (5:1 CH_2Cl_2/EtOAc) gave 403 mg (69% from **1b**) of **3b** as a white solid: mp 249.2–250.1°C; ^{1}H NMR 8.22 (d, 1, J=7.9 Hz), 7.97 (d, 1, J=7.3 Hz), 7.72 (t, 1, J=7.9 Hz), 7.68–7.50 (m, 4), 7.46 (t, 1, J=7.9 Hz), 7.28 (br, NH), 4.37 (dq, 1, J=6.7, 6.7 Hz), 1.71 (d, 3, J=6.7 Hz); ^{1}H NMR (CD_3OD) 8.26 (dd, 1, J=1.2, 7.9 Hz), 7.89–7.85 (m, 3), 7.78 (d, 1, J=7.9 Hz), 7.71–7.56 (m, 3), 4.43 (q, 1, J=6.7 Hz), 1.67 (d, 3, J=6.7 Hz); ^{13}C NMR 168.0, 161.5, 154.9, 146.0, 134.7, 133.5, 131.2, 130.6, 129.8, 128.8, 128.3, 127.6, 127.4, 127.2, 121.3, 49.9, 15.2; $[\alpha]_D$=176.0° (c 0.230, EtOH). The ^{1}H NMR spectral data in CD_3OD are identical to those of the natural product.[5]

4.1.2. 6,7-Dihydroquinazolino[3,2-*a*][1,4]benzodiazepine-5,13-dione (sclerotigenin, 3c). A solution of **1c**[8] (56 mg, 0.3 mmol) in dry DMSO (4 mL) was diluted with dry CH_2Cl_2 (4 mL). Et_3N (56 μL, 0.375 mmol, 1.25 equiv.) was added to the solution and the reaction mixture was stirred for 15 min, and treated with DMAP (28 mg, 0.21 mmol, 0.7 equiv.). Freshly prepared 2-azidobenzoyl chloride[4,9] (1.25 equiv.) in dry CH_2Cl_2 (4 mL) was added dropwise to the solution and the resulting mixture was stirred for 2 h at 20°C, diluted with CH_2Cl_2 (30 mL), washed with water (4×40 mL), dried (Na_2SO_4), and concentrated to give 75 mg of crude **2c** as a yellowish foamy solid.

Crude **2c** was dissolved in dry benzene (4 mL) and (n-Bu)$_3$P (60 μL, 0.24 mmol) was added to the solution in one portion. The resulting mixture was stirred under N_2 at rt for 2 min and at 60°C for 2 h. The reaction mixture was concentrated and the residue was dissolved in CH_2Cl_2 (30 mL). The resulting solution was washed with 0.5 M HCl (3×20 mL) and brine (20 mL), dried (Na_2SO_4) and concentrated giving 120 mg of crude **3c** as a thick brown oil. The crude mixture was triturated several times with hexane to remove most of the (n-Bu)$_3$PO. The hexane insoluble residue was purified on silica gel (1:1 CH_2Cl_2/EtOAc) giving 11 mg (9%) of **6** followed by 38 mg (43%) of **3c** as a white solid.

Data for **3c**: mp 277–280°C, lit. 6 mp 235–238°C; ^{1}H NMR 8.32 (d, 1, J=7.9 Hz), 7.97 (d, 1, J=7.3 Hz), 7.81 (t, 1, J=7.3 Hz), 7.70 (d, 1, J=7.9 Hz), 7.65–7.64 (m, 2), 7.58–7.53 (m, 2), 7.11 (br s, NH), 4.31 (dd, 1, J=6.1, 15.3 Hz), 4.24 (dd, 1, J=6.7, 15.3 Hz); ^{13}C NMR 168.2, 161.3, 153.6, 146.2, 135.1, 133.7, 131.4, 130.4, 129.8, 129.1, 128.1, 127.8, 127.6, 127.3, 121.5, 47.1. The ^{1}H and ^{13}C NMR spectral data are identical to those of the natural product.[6]

Data for **6**: mp 310.7–311.9°C; ^{1}H NMR 8.34 (br d, 1, J=7.9 Hz), 8.29 (br d, 1, J=7.9 Hz), 8.15 (br d, 1, J=7.9 Hz), 7.84–7.76 (m, 4), 7.76–7.67 (m, 2), 7.64 (ddd, 1, J=1.8, 6.3, 7.9 Hz), 7.58–7.48 (m, 2), 6.38 (d, 1, J=14.6 Hz), 4.44 (d, 1, J=14.6 Hz); ^{1}H NMR (DMSO-d_6) 8.17 (dd, 1, J=1.2, 7.3 Hz), 8.15 (dd, 1, J=1.2, 7.3 Hz), 8.06 (dd, 1, J=1.2, 7.3 Hz), 7.89–7.83 (m, 2), 7.79–7.71 (m, 3), 7.70 (dd, 1, J=1.8, 6.5 Hz), 7.66 (dd, 1, J=1.8, 6.5 Hz), 7.57 (ddd, 1, J=1.2, 7.3, 7.3 Hz), 7.56 (ddd, 1, J=1.2, 7.3, 7.3 Hz), 5.98 (d, 1, J=14.0 Hz), 4.57 (d, 1, J=14.0 Hz); ^{13}C NMR 161.1, 160.2, 151.4, 150.8, 147.5, 146.3, 135.0, 134.8, 134.4, 131.6, 131.4, 130.5, 129.1, 128.4, 128.1, 128.0, 127.8, 127.5, 127.34, 127.33, 121.7, 120.3, 46.3; HRMS (DEI) calculated for $C_{23}H_{14}N_4O_2$ (M^+) 378.1117, found 378.1118.

A similar reaction with (115 mg, 0.7 mmol, 2 equiv.) of 2-azidobenzoyl chloride,[4,9] (98 μL, 0.7 mmol, 2 equiv.) of Et_3N and 60 mg (0.34 mmol) of **1c** gave 49 mg (38%) of **6** and 25 mg (26%) of **3c**.

4.1.3. *N*-(2-Nitrobenzyl)-L-alanine methyl ester (17). NaOH (200 mg, 5 mmol) was added to a solution of L-alanine methyl ester hydrochloride (698 mg, 5 mmol) in anhydrous MeOH (15 mL) and resulting mixture was stirred for 5 min. 2-Nitrobenzaldehyde (831 mg, 5.5 mmol) and anhydrous Na_2SO_4 (500 mg) were added to this solution and the mixture was stirred at rt for 8 h under N_2. The mixture was cooled to 0°C and treated with $NaCNBH_3$ (315 mg, 5 mmol). The resulting mixture was stirred for 20 min at 25°C. Methanol was removed under reduced pressure and the residue was taken up in CH_2Cl_2 (50 mL). The resulting solution was washed with aqueous $NaHCO_3$ (2×50 mL), H_2O (50 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated to give a thick brown oil. Flash chromatography on silica gel (25:1 CH_2Cl_2/EtOAc) gave 770 mg (65%) of oily **17**: ^{1}H NMR 7.93 (d, 1, J=7.9 Hz), 7.63 (d, 1, J=7.3 Hz), 7.58 (dd, 1, J=7.3, 7.3 Hz), 7.41 (dd, 1, J=7.9, 7.3 Hz), 4.10 (d, 1, J=14.7 Hz), 3.98 (d, 1, J=14.7 Hz), 3.71 (s, 3), 3.38 (q, 1, J=7.3 Hz), 1.32 (d, 3, J=7.3 Hz); ^{13}C NMR 175.8, 149.1, 135.2, 133.1, 131.0, 128.0, 124.7, 56.4, 51.8, 48.9, 19.1; IR (neat) 1735, 1527, 1347; $[\alpha]_D$=−319.6° (c 0.310, EtOH).

4.1.4. *N*-(2-Nitrobenzyl)-*N*-Aloc-L-alanine methyl ester (23). Allyl chloroformate (2.23 mL, 21 mmol) was added dropwise to a solution of **17** (500 mg, 2.1 mmol) in pyridine (1.68 mL, 21 mmol) and dry THF (5 mL) at 0°C. The resulting mixture was stirred for 2 h. Ether (100 mL) was added to the reaction mixture and the organic phase was washed with H_2O (2×100 mL) and brine (100 mL), dried (Na_2SO_4) and concentrated. Flash chromatography on silica gel (CH_2Cl_2) gave 588 mg (87%) of **23** as a colorless oil: ^{1}H NMR (1:1 mixture of rotamers) 8.10–8.01 (m, 1), 7.71–7.59 (m, 2), 7.48–7.39 (m, 1), 5.91 (tdd, 0.5×1, J=5.5, 10.4, 17.1 Hz), 5.84–5.71 (m, 0.5×1), 5.32 (br d, 1, J=17.1 Hz), 5.23 (dd, 1, J=1.2, 10.4 Hz), 5.14–5.04 (m, 2), 4.81–4.54 (m, 2), 4.47–4.36 (m, 1), 3.73 (s, 0.5×3), 3.71 (s, 0.5×3), 1.42 (d, 3, J=7.3 Hz); ^{13}C NMR 171.9, 156.2, 134.5, 133.5, 132.2, 129.1, 128.6, 127.9, 125.0, (117.9, 117.7), (66.8, 66.5), (55.9, 55.7), 52.4, (47.9, 47.0), (15.7, 15.0); $[\alpha]_D$=−424.2° (c 0.240, EtOH).

4.1.5. *N*-(2-Nitrobenzyl)-*N*-Aloc-L-alanine (21). A solution of **23** (1.70 g, 5.3 mmol) in MeOH (10 mL) and 1 M

aqueous NaOH (5 mL) was stirred for 2 h at 25°C. The MeOH was evaporated, and the residue was diluted with water (50 mL) and washed with CH_2Cl_2 (2×50 mL). The pH of the aqueous phase was adjusted to 1–2 with 1 M HCl and the solution was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to give 1.57 g (96%) of **21** as a yellow oil: ^{1}H NMR (1:1 mixture of rotamers) 11.2–11.1 (br, 1, OH), 8.07 (br t, 1, J=8 Hz), 7.71–7.60 (m, 2), 7.50–7.40 (m, 1), 5.98–5.88 (m, 0.5×1), 5.81–5.73 (m, 0.5×1), 5.33 (br d, 0.5×1, J=17 Hz), 5.24 (br d, 0.5×1, J=10 Hz), 5.15–5.08 (m, 0.5×2), 5.12 (br d, 1, J=18 Hz), 4.80–4.41 (m, 4), 1.45 (d, 3, J=7.3 Hz); ^{13}C NMR (176.9, 176.8), 156.3, (147.7, 147.5), (134.0, 133.7), 133.5, 131.9, (128.9, 128.5), 127.8, 124.9, (118.0, 117.6), (66.9, 66.6), 55.6, (47.8, 47.1), (15.3, 14.6); HRMS (DEI) calculated for $C_{14}H_{17}N_2O_6$ (MH^+) 309.1087, found 309.1074.

4.1.6. Dipeptide 24b. A suspension of Troc-tryptophan phenyl ester[1] (910 mg, 2 mmol) and Zn dust (2.6 g, 40 mmol, 20 equiv.) in acetic acid (5 mL) was stirred for 30 min at rt. The solution was filtered through Celite and the filtrate was concentrated. The residue was dissolved in EtOAc (30 mL) and the resulting solution was washed with water (30 mL) and saturated $NaHCO_3$ (3×30 mL), dried (Na_2SO_4) and concentrated giving L-tryptophan phenyl ester **20b** that was dissolved in dry CH_2Cl_2 (3 mL) and used for the next step.

A solution of **21** (515 mg, 1.7 mmol) and 1,3-dicyclohexylcarbodiimide (362 mg, 1.75 mmol, 1.05 equiv.) in dry CH_2Cl_2 (5 mL) was stirred for 5 min at rt. The freshly prepared solution of **20b** was added and the resulting mixture was stirred for 25 min at rt. The insoluble by-product (DCU) was filtered off and the filtrate was concentrated giving crude **24b**. Flash chromatography on silica gel (20:1 CH_2Cl_2/EtOAc) gave **24b** (800 mg, 82%) as a yellowish foamy solid: mp 75.3–76.7°C; ^{1}H NMR (broadened due to mixture of rotamers) 8.32 (br s, NH), 8.01 (d, 1, J=7.9 Hz), 7.61 (d, 1, J=7.9 Hz), 7.50–7.41 (m, 1), 7.40–7.30 (m, 5), 7.24–7.17 (m, 2), 7.16–7.09 (m, 2), 6.94 (d, 2, J=7.3 Hz), 5.77–5.58 (m, 1), 5.20–5.00 (m, 3), 4.92–4.66 (m, 2), 4.61 (br d, 1, J=18 Hz), 4.45 (dd, 1, J=5.5, 13.4 Hz), 4.40–4.26 (m, 1), 3.47 (dd, 1, J=5.5, 14.7 Hz), 3.41 (dd, 1, J=6.7, 14.7 Hz), 1.27 (d, 3, J=7.3 Hz); $[\alpha]_D$=−611.52° (c 0.165, EtOH); HRMS (DEI) calculated for $C_{31}H_{30}N_4O_7$ (M^+) 570.2115, found 570.2126.

4.1.7. Diketopiperazine 15. A solution of **24b** (570 mg, 1 mmol) in AcOH (3 mL) and CH_2Cl_2 (5 mL) was treated with $Pd(PPh_3)_4$ (116 mg, 0.1 mmol) at rt, and the reaction mixture was stirred for 1 h in a 40°C water bath and concentrated. The residue was dissolved in EtOAc (30 mL), and the resulting solution was washed with saturated $NaHCO_3$ (3×30 mL), dried (Na_2SO_4) and evaporated to give crude amino phenyl ester.

A solution of the crude amino phenyl ester in CH_2Cl_2 (10 mL) was treated with AcOH (2 drops) dissolved in CH_2Cl_2 (2 mL), and the resulting mixture was stirred for 8 h at rt. The reaction mixture was washed with $NaHCO_3$ (10 mL), water (10 mL) and brine (10 mL), dried (Na_2SO_4), and evaporated. Flash chromatography on silica gel (EtOAc) gave 50 mg (13%) of the diastereomer, followed by 320 mg (81%) of **15** as a white solid: mp 221.7–223.3°C; ^{1}H NMR 8.17 (br s, NH), 8.04 (dd, 1, J=1.2, 7.9 Hz), 7.65 (br d, 1, J=7.9 Hz), 7.52–7.43 (m, 2), 7.41 (d, 1, J=7.9 Hz), 7.26 (t, 1, J=7.9 Hz), 7.21 (d, 1, J=7.9 Hz), 7.20 (d, 1, J=7.9 Hz), 7.14 (d, 1, J=2.4 Hz), 5.89 (br s, NH), 5.30 (d, 1, J=17.1 Hz), 4.58 (d, 1, J=17.1 Hz), 4.43 (ddd, 1, J=3.6, 3.6, 8.5 Hz), 3.87 (q, 1, J=7.3 Hz), 3.48 (dd, 1, J=3.6, 14.6 Hz), 3.29 (dd, 1, J=8.5, 14.6 Hz), 1.17 (d, 3, J=7.3 Hz); ^{1}H NMR (CD_3OD) 7.98 (dd, 1, J=1.2, 7.9 Hz), 7.59 (d, 1, J=7.9 Hz), 7.45–7.36 (m, 3), 7.14 (t, 1, J=7.9 Hz), 7.12 (s, 1), 7.06 (t, 1, J=7.9 Hz), 6.93 (d, 1, J=7.9 Hz), 4.88 (d, 1, J=17.1 Hz), 4.56 (d, 1, J=17.1 Hz), 4.46 (br t, 1, J=4.3 Hz), 3.75 (q, 1, J=6.7 Hz), 3.55 (dd, 1, J=4.3, 15.0 Hz), 3.18 (dd, 1, J=4.3, 15.0 Hz), 0.37 (d, 3, J=6.7 Hz); ^{13}C NMR (CD_3OD) 170.1, 168.9, 149.8, 138.0, 134.8, 132.6, 130.0, 129.5, 129.2, 126.1, 126.0, 122.9, 120.5, 120.3, 112.6, 109.6, 58.02, 57.97, 47.3, 31.1, 18.6, $[\alpha]_D$=−837.3° (c 0.108, EtOH); HRMS (DEI) calculated for $C_{21}H_{20}N_4O_4$ (M^+) 392.1485, found 392.1504. A ^{13}C NMR spectrum could not be obtained in $CDCl_3$ because of low solubility.

Data for the diastereomer: ^{1}H NMR 8.31 (br s, NH), 8.05 (dd, 1, J=1.2, 7.9 Hz), 7.69 (d, 1, J=7.9 Hz), 7.58–7.44 (m, 2), 7.41 (d, 1, J=7.9 Hz), 7.26, (t, 1, J=7.9 Hz), 7.18 (d, 1, J=7.9 Hz), 7.17 (d, 1, J=7.9 Hz), 7.14 (br s, 1), 5.91 (br s, NH), 5.40 (d, 1, J=16.5 Hz), 4.57 (d, 1, J=16.5 Hz), 4.41 (dd, 1, J=3.7, 9.8 Hz), 3.77 (q, 1, J=6.9 Hz), 3.75 (dd, 1, J=3.7, 14.7 Hz), 3.13 (dd, 1, J=9.8, 14.7 Hz), 1.46 (d, 3, J=6.9 Hz); ^{1}HMR (CD_3OD) 7.96 (dd, 1, J=1.2, 7.9 Hz), 7.61 (d, 1, J=7.9 Hz), 7.41 (d, 1, J=7.9 Hz), 7.35 (t, 1, J=7.9 Hz), 7.17 (t, 1, J=7.9 Hz), 7.11 (t, 1, J=7.9 Hz), 7.10 (s, 1), 7.00 (t, 1, J=7.9 Hz), 6.38 (d, 1, J=7.9 Hz), 4.95 (d, 1, J=17.1 Hz), 4.54 (br dd, 1, J=4.0, 4.3 Hz), 4.51 (d, 1, J=17.1 Hz), 3.57 (dd, 1, J=4.3, 14.7 Hz), 3.29 (q, 1, J=7.0 Hz), 3.22 (dd, 1, J=4.0, 14.7 Hz), 1.34 (d, 3, J=7.0 Hz); $[\alpha]_D$=−548.7° (c 0.170, EtOH).

4.1.8. Acylation of 15. NaH (24.5 mg of 60% mineral oil dispersion, 0.61 mmol, 1.2 equiv.) was added in one portion to a solution of **15** (200 mg, 0.51 mmol) in dry THF (5 mL) at −5°C, and the resulting mixture was stirred for 15 min. A solution of freshly prepared 2-azidobenzoyl chloride[4,9] in dry THF (1 mL) was added dropwise, and the reaction mixture warmed to rt and stirred for 2 h. The solvent was concentrated and the residue was dissolved in CH_2Cl_2 (30 mL). The resulting solution was washed with water (2×30 mL) and brine (30 mL), dried (Na_2SO_4) and concentrated. Flash chromatography on silica gel (20:1 EtOAc/CH_2Cl_2) gave 205 mg (75%) of pure imide: ^{1}H NMR 8.13 (br s, NH), 7.98 (d, 1, J=7.9 Hz), 7.63 (d, 1, J=7.9 Hz), 7.56–7.41 (m, 4), 7.39–7.32 (m, 2), 7.30–7.16 (m, 3), 7.11 (d, 1, J=7.9 Hz), 7.02 (d, 1, J=7.9 Hz), 5.37 (dd, 1, J=3.5, 5.2 Hz), 5.36 (d, 1, J=15.9 Hz), 4.25 (d, 1, J=15.9 Hz), 3.94 (q, 1, J=7.0 Hz), 3.78 (dd, 1, J=3.5, 15.3 Hz), 3.66 (dd, 1, J=5.2, 15.3 Hz), 0.35 (d, 3, J=7.0 Hz); ^{13}C NMR 170.0, 168.2, 166.5, 148.7, 135.84, 135.80, 133.7, 131.7, 130.9, 129.4, 128.8, 128.7, 128.2, 127.7, 125.4, 125.2, 124.4, 122.7, 120.3, 119.3, 118.0, 111.2, 109.3, 59.1, 56.4, 43.8, 28.7, 16.5; $[\alpha]_D$=317.0° (c 0.225, EtOH).

4.1.9. *N*-(Nitrobenzyl)fumiquinazoline G (25). A solution of the above imide (150 mg, 0.28 mmol) in dry benzene (10 mL) was treated with $(n\text{Bu})_3\text{P}$ (70 μL, 0.28 mmol). The resulting mixture was stirred under N_2 for 2 min at rt and 1.5 h at 75°C and concentrated. Flash chromatography of the residue on silica gel (15:1 CH_2Cl_2/EtOAc) gave 108 mg (78%) of **25** as a foamy solid: mp 128–129°C; ^{1}H NMR 8.39 (br d, 1, *J*=7.8 Hz), 8.08 (br s, NH), 7.99 (d, 1, *J*=7.8 Hz), 7.79 (t, 1, *J*=7.8 Hz), 7.58–7.52 (m, 2), 7.49–7.38 (m, 3), 7.30 (d, 1, *J*=7.8 Hz), 7.24 (d, 1, *J*=7.8 Hz), 7.15 (t, 1, *J*=7.8 Hz), 6.98 (t, 1, *J*=7.8 Hz), 6.81 (d, 1, *J*=2.4 Hz), 5.72 (dd, 1, *J*=4.3, 5.5 Hz), 5.46 (d, 1, *J*=16.5 Hz), 4.41 (d, 1, *J*=16.5 Hz), 4.37 (q, 1, *J*=6.7 Hz), 3.85 (dd, 1, *J*=5.5, 14.7 Hz), 3.80 (dd, 1, *J*=4.3, 14.7 Hz), 0.63 (d, 3, *J*=6.7 Hz); ^{13}C NMR 166.2, 160.7, 151.6, 147.2, 135.8, 134.9, 133.8, 131.0, 129.0, 128.6, 127.8, 127.1, 126.9, 126.7, 125.2, 123.4, 122.6, 120.1, 118.8, 111.2, 109.8, 64.2, 64.1, 57.3, 56.4, 43.9, 27.3, 20.3; $[\alpha]_D=-295.7°$ (*c* 0.175, EtOH); HRMS (DEI) calculated for $C_{28}H_{23}N_5O_4$ (M^+) 493.1750, found 493.1732.

4.1.10. *ent*-Fumiquinazoline G (*ent*-7a). A solution of **25** (25 mg, 0.05 mmol) in anhydrous MeOH (25 mL) in a Pyrex flask was purged with N_2 for 5 min. The reaction mixture was irradiated in a cylindrical photoreactor with seventeen, 12 in. long 254 nm lamps (G8T5 SYLVANIA) under N_2 for 14 h and concentrated. Flash chromatography of the residue on silica gel deactivated with 5% H_2O (1:1 CH_2Cl_2/EtOAc) gave 16 mg (87%) of *ent*-**7a** as a white solid: the ^{1}H and ^{13}C NMR spectral data are identical to those previously reported;[2,7] $[\alpha]_D=+477.8°$ (*c* 0.072, $CHCl_3$) (lit. 2 for enantiomer $[\alpha]_D=-462.8$ (*c* 0.61, $CHCl_3$)).

References

1. (a) He, F.; Foxman, B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1998**, *120*, 6417–6418. (b) He, F. PhD Dissertation, Brandeis University, Waltham, MA, 1999.
2. (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.
3. Wong, S. M.; Musza, L. L.; Kydd, G. C.; Kulling, R.; Gillum, A. M.; Cooper, R. *J. Antibiot.* **1993**, *46*, 545–553.
4. Takeuchi, H.; Hagiwara, S.; Eguchi, S. *Tetrahedron* **1989**, *45*, 6375–6386. For other applications of this reaction where selective acylation is not an issue see: Sugimori, T.; Okawa, T.; Eguchi, S.; Kakehi, A.; Yashima, E.; Okamoto, Y. *Tetrahedron* **1998**, *54*, 7997–8008. Depew, K. M.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11953–11963.
5. (a) Rahbæk, L.; Breinholt, J.; Frisvad, J. C.; Christophersen, C. *J. Org. Chem.* **1999**, *64*, 1689–1692. (b) Rahbæk, L.; Breinholt, J. *J. Nat. Prod.* **1999**, *62*, 904–905.
6. Joshi, B. K.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *J. Nat. Prod.* **1999**, *62*, 650–652.
7. (a) He, F.; Snider, B. B. *Synlett* **1997**, 483–484. (b) Wang, H.; Ganesan, A. *J. Org. Chem.* **1998**, *63*, 2432–2433 For another fumiquinazoline G synthesis see: . (c) Wang, H.; Ganesan, A. *J. Org. Chem.* **2000**, *65*, 1022–1030.
8. (a) Kim, D. H. J. *Heterocycl. Chem.* **1975**, *12*, 1323–1324. (b) Akssira, M.; Boumzebra, M.; Kasmi, H.; Dahdouh, A.; Roumestant, M. L.; Viallefont, Ph. *Tetrahedron* **1994**, *50*, 9051–9060. (c) Mohiuddin, G.; Reddy, P. S. N.; Ahmed, K.; Ratnam, C. V. *Indian J. Chem.* **1985**, 905–907.
9. Ardakani, M. A.; Smalley, R. K.; Smith, R. H. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2501–2506.
10. For an alternative synthesis see: Harrison, D. R.; Kennewell, P. D.; Taylor, J. B. *J. Heterocycl. Chem.* **1977**, *14*, 1191–1196.
11. Bock, M. G.; DiPardo, R. M.; Cochran, D. W.; Homnick, C. H.; Freidinger, R. M. *Heterocycles* **1985**, *23*, 273–276.
12. Sun, H. H.; Barrow, C. J.; Cooper, R. *J. Nat. Prod.* **1995**, *58*, 1575–1580.
13. Mohiuddin, G.; Reddy, P. S.; Ahmed, K.; Ratnam, C. V. *J. Chem. Res., Synop.* **1987**, *7*, 224–225.
14. (a) Buenadicha, F. L.; Bartolomé, M. T.; Aguirre, M. J.; Avendaño, C.; Söllhuber, M. *Tetrahedron: Asymmetry* **1998**, *9*, 483–501. (b) Caballero, E.; Avendaño, C.; Menéndez, J. C. *Heterocycles* **2000**, *53*, 1765–1782.
15. (a) Pillai, V. N. R. *Synthesis* **1980**, 1–26. (b) Pillai, V. N. R. *Org. Photochem.* **1987**, *9*, 225–323. (c) Henriksen, D. B.; Breddam, K.; Buchardt, O. *Int J. Pept. Protein Res.* **1993**, *41*, 169–180. (d) Miknis, G. F.; Williams, R. M. *J. Am. Chem. Soc.* **1993**, *115*, 536–547.
16. Gareau, Y.; Zamboni, R.; Wong, A. W. *J. Org. Chem.* **1993**, *58*, 1582–1585.
17. (a) Carpino, L. A.; Mansour, E. S. M. E.; Sadat-Aalaee, D. *J. Org. Chem.* **1991**, *56*, 2611–2614. (b) Carpino, L. A.; Mansour, E. S. M. E.; El-Faham, A. *J. Org. Chem.* **1993**, *58*, 4162–4164.
18. Galpin, I. J.; Hardy, P. M.; Kenner, G. W.; McDermott, J. R.; Ramage, R.; Seely, J. H.; Tyson, R. G. *Tetrahedron* **1979**, *35*, 2577–2582.