Rearrangement of 4-Imino-4*H*-3,1-benzoxazines to 4-Quinazolinones via Amidine Carboxamides

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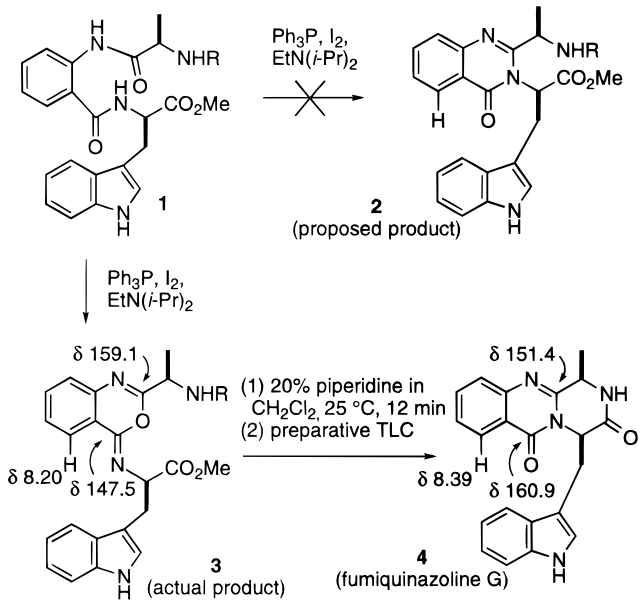
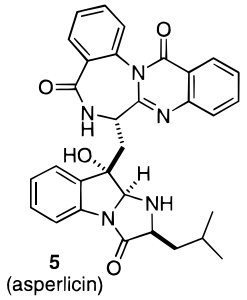
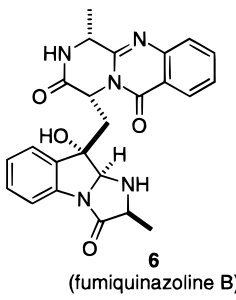
Ganesan recently reported a very short synthesis of fumiquinazoline G, in which the key step is the cyclization of *N*-acylanthranilamide **1**, R = Fmoc, with PPh_3, I_2, and $EtN(i\text{-}Pr)_2$ in CH_2Cl_2 at 25 °C to give a cyclization product that they reported to be 4-quinazolinone **2**, R = Fmoc, in 65% yield.[1,2] Deprotection of the Fmoc group with 20% piperidine in CH_2Cl_2 followed by preparative TLC of the crude product gives 75% of fumiquinazoline G (**4**) from the cyclization product.



We recently reported the first synthesis of asperlicin (**5**) which was based on a novel, efficient route to the hydroxyimidazoindolone moiety.[3] We reexamined Ganesan's fumiquinazoline G synthesis as part of a plan to use his 4-quinazolinone synthesis and our route to hydroxyimidazoindolones for the synthesis of fumiquinazoline B (**6**).

The spectral data and chemical reactivity of Ganesan's cyclization product suggested that it is not quinazolinone **2**, R = Fmoc, but rather 4-imino-4*H*-3,1-benzoxazine **3**, R = Fmoc. The downfield aromatic proton absorbs at δ 8.20 rather than at δ 8.39 as in fumiquinazoline G (**4**). The downfield ^{13}C NMR absorptions, which were assigned by HMBC correlation, are even more problematic. C-2 absorbs at δ 159.1, as opposed to δ 151.4 in fumiquinazoline G, and C-4 absorbs at δ 147.5 as opposed to δ 160.9 in fumiquinazoline G.[4] Furthermore, there are no NOEs between the aliphatic protons of the two different side chains, which is consistent with 4-imino-4*H*-3,1-benzoxazine **3** but not with 4-quinazolinone **2**. Finally, the product hydrolyzes to regenerate **1**, R = Fmoc, on silica gel chromatography unless Et_3N is present in the eluent. 4-Imino-4*H*-3,1-benzoxazines are expected to be hydrolytically unstable, while 4-quinazolinones are known to be hydrolytically stable.[5]





We have previously prepared 4-imino-4*H*-3,1-benzoxazines by the addition of primary amines to acid chlorides such as **7**, which provides 85% of **8** with spectral data similar to those of **3**.[6] Of even greater significance, Mazurkiewicz reported in 1989 that treatment of *N*-acylanthranilamides **9a**, **9b**, **9d**, and **9e** with PPh_3, Br_2, and Et_3N in CH_2Cl_2 for 0.2−1 h at reflux (conditions very similar to those of Ganesan) provides 84−95% of the corresponding 4-imino-4*H*-3,1-benzoxazine **10**.[7,8] Mazurkiewicz reported that 4-imino-4*H*-3,1-benzoxazines **10a** and **10b** isomerize to 4-quinazolinones **11a** and **11b** on treatment with excess HCl in $ClCH_2CH_2Cl$ for 120 h at 25 °C or 2−6 h at 70 °C.[7]

*Despite this compelling evidence that the structure of the cyclization product is **3**, not **2**, we are able to reproduce Ganesan's fumiquinazoline G synthesis.* Treatment of **3**, R = Fmoc, with piperidine to deprotect the Fmoc group affords an intermediate that is converted to fumiquinazoline G (**4**) on preparative TLC. However, deprotection of the Fmoc group with DMAP provides **3**, R = H, that does not cyclize to fumiquinazoline G on preparative TLC. Moreover, deprotection of **3**, R = allyloxycarbonyl, with $Pd(PPh_3)_4$ also gives **3**, R = H, that does not cyclize to fumiquinazoline G on preparative TLC. These results suggest that piperidine plays a crucial role in the conversion of **3** to **4** beyond that of deprotecting the Fmoc group.

We prepared simpler systems that were more amenable to detailed study to determine the function of piperidine. Cyclization of **9a**−**c** with PPh_3, I_2, and EtN-

(1) Wang, H.; Ganesan, A. *J. Org. Chem.* **1998**, *63*, 2432−2433.
(2) For the first synthesis of fumiquinazoline G see: He, F.; Snider, B. B. *Synlett* **1997**, 483−484.
(3) He, F.; Foxman, B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1998**, *120*, 6417−6418.
(4) Takahashi, C.; Matsushita, T.; Doi, M.; Minoura, K.; Shingu, T.; Kumeda, Y.; Numata, A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2345−2353.
(5) (a) Brown, D. J. *Quinazolines, Supplement 1*; Wiley: New York, 1996; Chapter 4. (b) Sinha, S.; Srivastava, M. In *Progress in Drug Research*; Jucker, E., Ed.; Birkhäuser: Basel, 1994; Vol. 43, pp 143−238.
(6) He, F., Snider, B. B. Unpublished results.
(7) Mazurkiewicz, R. *Monatsh. Chem.* **1989**, *120*, 973−980.
(8) For other reports of 4-imino-4*H*-3,1-benzoxazines see: (a) Molina, P.; Alajarin, M.; Vidal, A.; De la Concepcion Foces-Foces, M.; Hernandez Cano, F. *Tetrahedron* **1989**, *45*, 4263−4286. (b) Colonna, M.; Poloni, M. *Ann. Chim. (Rome)* **1973**, *63*, 287−290.

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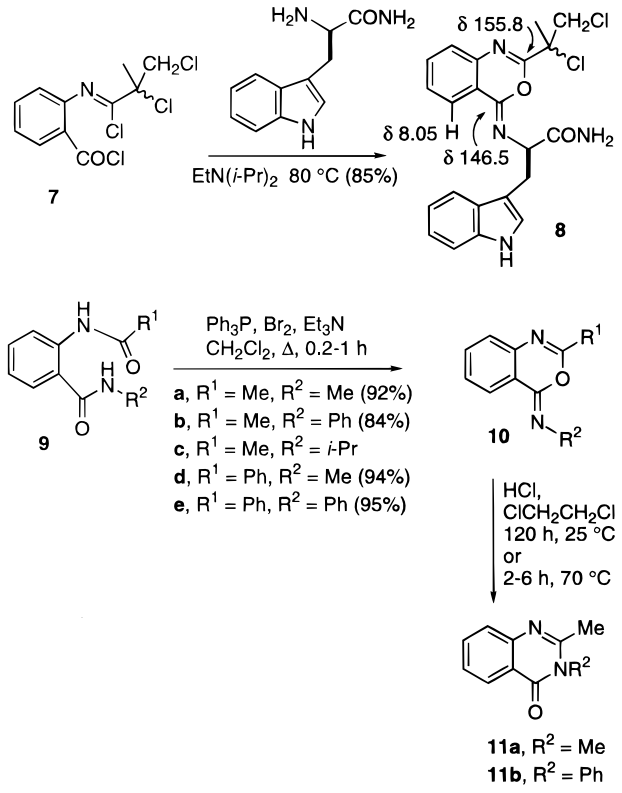
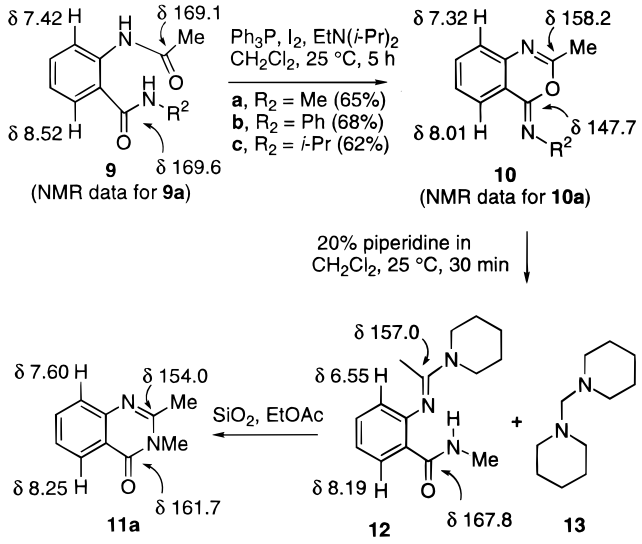
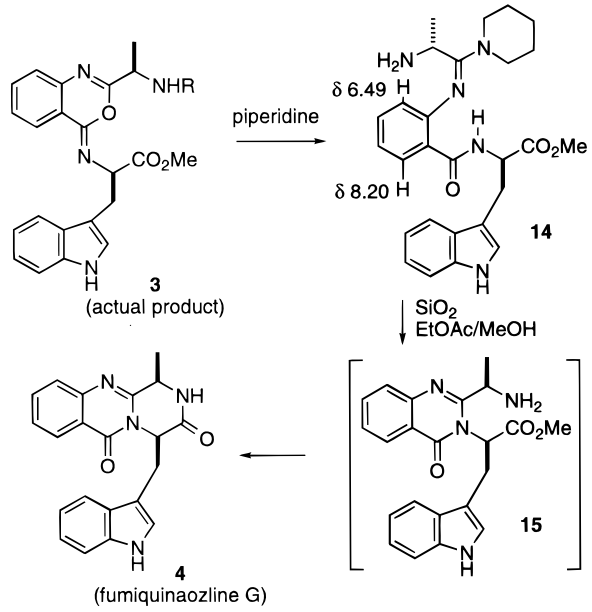


(*i*-Pr)$_2$ yields 62−65% of 4-imino-4*H*-3,1-benzoxazines **10a**−**c**. The ^{1}H NMR spectral data for **10a** and **10b** are identical to those reported by Mazurkiewicz.[7] The ^{13}C NMR spectral data as assigned by HMBC correlation are analogous to those of **3** and **8**. C-2 of **10a** absorbs at δ 158.2 and C-4 absorbs at δ 147.7, while C-2 of 4-quinazolinone **11a** absorbs at δ 154.0 and C-4 absorbs at δ 161.7.[9]



Treatment of **10a** with 20% piperidine in CH_2Cl_2 for 30 min at 25 °C provides a complex mixture of amidine carboxamide **12** and 1,1′-methylenebis(piperidine) (**13**), which results from the well-known reaction of piperidine with CH_2Cl_2.[10] Dissolution of **10a** in neat piperidine for 1 h or in 20% piperidine in EtOAc overnight, followed by concentration, affords 82% of amidine carboxamide **12**. The ^{1}H NMR spectrum shows a characteristic absorption at δ 6.55 which fits well with that reported for the parent amidine lacking the *N*-methylcarboxamide,[11] and the absorption at δ 8.19 is shifted downfield from δ 8.01 in **10a**. The configuration of the amidine carbon−nitrogen double bond was established by the strong NOE between the hydrogen at δ 6.55 and the methyl group at δ 1.92. An NOE between the NH proton at δ 8.97 and the piperidine hydrogens at δ 3.60 suggests that **12** exists primarily in the conformation shown, possibly because of intramolecular hydrogen bonding between the amide hydrogen and the amidine nitrogen. The ^{13}C NMR spectrum also fits well with that reported for the parent amidine lacking the *N*-methylcarboxamide.[12] Amidine carboxamide **12** cyclizes quantitatively to 4-quinazolinone **11a** on stirring with silica gel in EtOAc for overnight. Cyclization also occurs slowly in $CDCl_3$ solution which presumably contains traces of DCl.

The conversion of 4-imino-4*H*-3,1-benzoxazine **3**, R = Fmoc, to fumiquinazoline G (**4**) proceeds through amidine carboxamide **14**, which is formed quantitatively on dissolution in 20% piperidine in EtOAc for 1 h at 25 °C. Flash chromatography gives 93% of **14** containing only 5−10% of **4** if 2% Et_3N is present in the eluent to prevent cyclization. The ^{1}H NMR spectrum of **14** shows absorptions at δ 8.20 and 6.49 indicating that an amidine carboxamide is present. Amidine carboxamide **14** cyclizes to 4-quinazolinone **15**, which spontaneously cyclizes with loss of methanol to give 82% of fumiquinazoline G on stirring overnight in 2:1 EtOAc/MeOH containing silica gel.



The rearrangement of 4-imino-4*H*-3,1-benzoxazines to 4-quinazolinones via amidine carboxamides provides a

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(10) (a) Mills, J. E.; Maryanoff, C. A.; McComsey, D. F.; Stanzione, R. C.; Scott, L. *J. Org. Chem.* **1987**, *52*, 1857−1859. (b) Matsumoto, K.; Hashimoto, S.; Ikemi, Y.; Otani, S.; *Heterocycles* **1984**, *22*, 1417−1420.

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(12) Oszczapowicz, J.; Raczynska, E.; Osek, J. *Magn. Reson. Chem.* **1986**, *24*, 9−14.

valuable route to quinazolinones, since the 4-imino-4*H*-3,1-benzoxazines are readily available by treatment of *N*-acylanthranilamides with PPh_3, Br_2, or I_2, and a tertiary amine. We are currently exploring the scope of the two-step rearrangement with respect to substituents on the 4-imino-4*H*-3,1-benzoxazine, primary and secondary amine for amidine formation, and conditions for isomerization of the amidine carboxamide to the 4-quinazolinone.

Experimental Section

General. NMR spectra were recorded in $CDCl_3$ at 400 MHz. Chemical shifts are reported in δ, coupling constants are reported in hertz, and IR data are reported in cm^{-1}.

2-Methyl-4-(methylimino)-4*H*-3,1-benzoxazine (10a). To a solution of amide **9a** (48 mg, 0.25 mmol) in CH_2Cl_2 (15 mL) were added Ph_3P (327.5 mg, 1.25 mmol), *N*,*N*-diisopropylethylamine (404 mg, 545 μL, 3.13 mmol), and I_2 (310.9 mg, 1.23 mmol). The reaction mixture was stirred at room temperature for 5 h, quenched with aqueous Na_2CO_3 solution, dried (Na_2SO_4), and concentrated. The dark residue was purified by flash chromatography on silica gel (5:1 hexane/EtOAc with 2% Et_3N) to give 28.3 mg (65%) of **10a** as a white solid: mp 77−80 °C (lit.[7] mp 82−83 °C); ^{1}H NMR 8.01 (dd, 1, J = 1.5, 8.0), 7.51 (ddd, 1, J = 1.5, 7.2, 8.0), 7.34−7.16 (m, 2), 3.19 (s, 3), 2.34 (s, 3); ^{13}C NMR 158.2, 147.7, 141.5, 132.7, 127.7, 125.6, 125.2, 119.4, 33.2, 21.0; IR (KBr) 1680, 1654, 1603. The ^{1}H NMR and IR spectra are consistent with those previously reported.[7]

2-Methyl-4-(phenylimino)-4*H*-3,1-benzoxazine (10b) was produced following the procedure for **10a** in 68% yield as an oil: ^{1}H NMR 8.24 (dd, 1, J = 1.2, 8.0), 7.59 (ddd, 1, J = 1.2, 7.6, 8.8), 7.43−7.33 (m, 4), 7.20−7.10 (m, 3), 2.26 (s, 3); ^{13}C NMR 158.0, 145.8, 145.3, 142.4, 133.6, 128.7 (2 C), 128.0, 126.4, 125.8, 124.1, 122.5 (2 C), 119.2, 20.9; IR (neat) 1674, 1654, 1594. The ^{1}H NMR and IR spectra are consistent with those previously reported.[7]

2-Methyl-4-((1-methylethyl)imino)-4*H*-3,1-benzoxazine (10c) was produced following the procedure for **10a** in 62% yield as an oil: ^{1}H NMR 8.06 (dd, 1, J = 1.6, 8.4), 7.49 (ddd, 1, J = 1.6, 7.6, 8.8), 7.32−7.26 (m, 2), 4.16 (hept, 1, J = 6.4), 2.32 (s, 3), 1.21 (d, 6, J = 6.4); ^{13}C NMR 158.4, 144.6, 141.7, 132.5, 127.5, 125.7, 125.5, 119.6, 46.1, 23.5 (2 C), 21.1; IR (neat) 1679, 1654, 1606.

Amidine Carboxamide 12. A solution of **10a** (10.2 mg, 0.0586 mmol) in piperidine (distilled from CaH_2, 0.25 mL) was stirred at room temperature for 1 h. The resulting mixture was evaporated under reduced pressure to give crude **12**. Flash chromatography on silica gel (1:1 CH_2Cl_2/EtOAc with 2% Et_3N) afforded 12.4 mg (82%) of pure **12** as a colorless oil: ^{1}H NMR 8.97 (br s, 1, NH), 8.19 (dd, 1, J = 1.2, 8.0), 7.29 (ddd, 1, J = 1.2, 7.2, 8.0), 7.05 (ddd, 1, J = 1.2, 7.2, 8.0), 6.55 (dd, 1, J = 1.2, 8.0), 3.60 (br t, 4, J = 4.8), 2.94 (d, 3, J = 4.8), 1.92 (s, 3), 1.77−1.69 (m, 2), 1.67−1.59 (m, 4); ^{13}C NMR 167.8, 157.0, 149.4, 131.1, 130.8, 125.3, 123.1, 121.9, 45.9 (br, 2 C), 26.1, 26.0 (2 C), 24.7, 15.3; IR (neat) 3462 (br), 3207 (br), 1652, 1589, 1538. The ^{1}H and ^{13}C NMR spectra correspond to those of closely related amidines.[11, 12]

2,3-Dimethyl-4(3*H*)-quinazolinone (11a). To a solution of **12** (6.2 mg, 0.024 mmol) in EtOAc (0.25 mL) was added silica gel (EM 9385, silica gel 60, 230−400 mesh, 60 mg). The mixture was stirred at room-temperature overnight. The silica gel was filtered off, and the filtrate was evaporated under reduced pressure to give 4.2 mg (100%) of **11a** as a white solid: mp 107−109 °C (needles, hexane) (lit.[7] mp 109−109.5 °C); ^{1}H NMR 8.26 (dd, 1, J = 1.2, 8.0), 7.72 (ddd, 1, J = 1.2, 7.2, 8.0), 7.61 (br d, 1, J = 8.0), 7.44 (ddd, 1, J = 1.2, 7.2, 8.0), 3.63 (s, 3), 2.63 (s, 3); ^{13}C NMR 162.3, 154.4, 147.2, 134.1, 126.8, 126.6, 126.4, 120.2, 31.0, 23.6; IR (KBr) 1670, 1601. The data are consistent with those previously reported.[9]

4-Imino-4*H*-3,1-benzoxazine 3, R = Fmoc, was prepared as described by Ganesan:[1] the ^{1}H NMR and IR spectra are identical to those reported; ^{13}C NMR ($CDCl_3$) 172.8, 159.1, 155.4, 147.5, 143.9, 143.8, 141.3 (2 C), 141.0, 135.9, 133.3, 128.3, 127.7 (2 C), 127.4, 127.1 (2 C), 126.4, 126.1, 125.1, 125.0, 122.8, 122.0, 120.0 (2 C), 119.4, 119.3, 118.9, 112.2, 111.1, 66.7, 59.8, 52.2, 49.0, 47.2, 29.5, 18.8.

4-Imino-4*H*-3,1-benzoxazine 3, R = H. To a solution of **3**, R = Fmoc, (3 mg, 0.005 mmol) in MeCN (0.2 mL) was added DMAP (20 mg). The mixture was stirred at 75 °C for 4 h and evaporated under reduced pressure to give a residue. Flash chromatography of this residue on silica gel (5:1 EtOAc/MeOH with 2% Et_3N) afforded 1.5 mg (77%) of **3**, R = H: ^{1}H NMR 8.21 (dd, 1, J = 1.6, 8.0), 8.04 (br s, 1, NH), 7.73 (d, 1, J = 7.6), 7.54 (ddd, 1, J = 1.6, 8.0, 8.0), 7.36 (ddd, 1, J = 1.2, 7.6, 7.6), 7.32 (d, 1, J = 7.6), 7.31 (d, 1, J = 7.6), 7.17 (ddd, 1, J = 1.2, 8.0, 8.0), 7.10 (ddd, 1, J = 1.2, 7.2, 8.4), 7.05 (d, 1, J = 2.4), 4.93 (dd, 1, J = 4.4, 8.4), 3.72 (s, 3), 3.51 (ddd, 1, J = 0.4, 4.4, 14.0), 3.47 (q, 1, J = 6.8), 3.26 (ddd, 1, J = 0.4, 8.4, 14.0), 1.17 (d, 3, J = 6.8).

Amidine Carboxamide 14. To a suspension of **3**, R = Fmoc (24.5 mg, 0.04 mmol), in EtOAc (0.4 mL) was added piperidine (distilled from CaH_2, 0.1 mL). The mixture was stirred at room temperature for 1 h. TLC (4:1 EtOAc/MeOH) indicated that the deprotection was complete in 10 min and the conversion of the resulting amine **3**, R = H, to amidine carboxamide **14** was complete in 45 min. The mixture was evaporated under reduced pressure to give a residue which was purified by flash chromatography on silica gel (2:1 CH_2Cl_2/EtOAc with 2% of Et_3N, then 2:1 EtOAc/MeOH with 2% of Et_3N) to afford 17.2 mg (93%) of amidine carboxamide **14** as a colorless oil containing 5−10% of fumiquinazoline G (**4**): ^{1}H NMR 9.37 (br d, 1, J = 8.0, NH), 8.46 (br s, 1, NH), 8.20 (d, 1, J = 7.2), 7.50 (d, 1, J = 8.0), 7.29 (d, 1, J = 8.8), 7.27 (ddd, 1, J = 1.6, 7.6, 8.0), 7.12 (ddd, 1, J = 1.2, 8.0, 8.0), 7.05−6.97 (m, 3), 6.49 (d, 1, J = 7.2), 5.26 (td, 1, J = 5.6, 8.0), 3.83 (br q, 1, J = 6.8), 3.67 (s, 3), 3.38 (dd, 1, J = 5.6, 15.2), 3.33 (dd, 1, J = 5.6, 15.2), 3.28−3.20 (m, 2), 3.18−3.10 (m, 2), 1.68 (br s, 2, NH_2), 1.51−1.44 (m, 2), 1.44−1.34 (m, 4), 1.06 (d, 3, J = 6.8); ^{13}C NMR 173.0, 166.6, 163.0, 150.2, 136.1, 131.7, 131.1, 127.6, 122.6, 121.9 (2 C), 121.3, 119.4, 118.7, 111.1, 110.6, 53.1, 52.2, 47.5, 47.2 (2 C), 28.3, 25.8 (2 C), 24.3, 21.5 (one quaternary carbon was not observed); IR (neat) 3252, 1739, 1634, 1591, 1520.

Conversion of 14 to Fumiquinazoline G (4). To a solution of amidine carboxamide **14** (6.6 mg, 0.014 mmol) in a 2:1 mixture of EtOAc and MeOH (0.3 mL) was added silica gel (EM 9385, silica gel 60, 230−400 mesh, 66 mg). The suspension was stirred at room-temperature overnight. The silica gel was filtered off, and the filtrate was evaporated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (EtOAc) to give 4.2 mg (82%) of **4** with ^{1}H NMR and ^{13}C NMR spectra identical to those previously reported.[1,2,4]

Acknowledgment. We are grateful to the National Institutes of Health (GM50151) for generous financial support.

Supporting Information Available: ^{1}H and ^{13}C NMR spectral data for **3**, R = Fmoc, **10a−c, 11a**, **12**, and **14**, and HMBC spectra for **3**, R = Fmoc, and **10a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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