JOC*Note*

A Reinvestigation of 4-Hydroxyindole-6-carboxylate Synthesis from Pyrrole-2-carboxaldehyde: A Facile Synthesis of Indoles and Indolizines

Musong Kim and Edwin Vedejs*

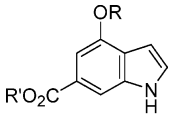
Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109

edved@umich.edu

Received May 6, 2004

Abstract: Cyclization of the Stobbe product **3** under the literature conditions (acetic anhydride/sodium acetate) affords both the indole **6** and the indolizine **8**. The presence of base promotes the formation of indolizine products, and using acetic anhydride/triethylamine leads to indolizine products in good yield. Improved conditions for conversion to indoles **2**, **5**, and **6** are reported, and inconsistencies in some of the literature structure assignments and characterization data are noted.

In the course of a synthesis project, we were interested in rapid access to 4-hydroxyindole-6-carboxylic acid derivatives **1** and **2**. Given the frequent occurrence of similar indoles in biologically active compounds[1] and their relationship to FR900482 and related structures,[2,3] there was no shortage of potential approaches. However, we could find only three demonstrated strategies in the literature for preparation of specific indoles having the substitution pattern of **1** or **2**.[2a,3,4]



1 R= R'= H
2 R= R'= Me

One of the published approaches is rather lengthy, eight steps from 3-acetyl-1-phenylsulfonylpyrrole to an acetal corresponding to a protected analogue of **1** ($PhSO_2N$ in place of NH; 1,3-dioxan-2-yl in place of $R'O_2C$).[2a] A more concise route was developed by Ziegler et al. using the Batcho−Leimgruber indole synthesis to prepare a 4-benzyloxy indole (**2** with R= Bn in place of Me), but six steps were required.[3] The shortest sequence to related indoles has been reported by El-Rayyes[4] from the Stobbe condensation product **3** and NaOAc/Ac_2O, a cyclization procedure that appears to involve a vinyl ketene intermediate **4** (Scheme 1).[5,6] Several other groups have cited this chemistry,[6,7] but we were surprised that it has not been used more often in view of the apparent simplicity and the longer alternatives in the literature.[2,3] Another concern was that only partial NMR data had been included in the original work,[4] not sufficient to confirm the structures. Here, we report our attempts to reproduce the annulation from **3**, along with revised procedures that afford the desired indole **2**. Spectroscopic characterization of products is also included along with cautionary comments regarding data reported in the original paper and in subsequent work.[4,6,7]

Half-ester **3** was prepared by Stobbe condensation of pyrrole-2-carboxaldehyde and dimethyl succinate as described,[4a] and the *E*-geometry was confirmed by NOE methods. However, treatment of **3** with sodium acetate and acetic anhydride following the published procedure[4a] resulted in a mixture of two isomeric acetates that proved to be **6** and **8**, corresponding to cyclization of the vinyl ketene **4** via the phenolic intermediates **5** and **7**. The identity of **6** and **8** was not immediately clear, so conditions were varied in attempts to favor one of the pathways (Table 1). The combination of Et_3N/Ac_2O afforded a single product according to NMR assay (entry 3), and a similar reaction using Et_3N/methyl chloroformate was especially clean and gave a major product in 80% yield after crystallization. However, the chloroformate product proved to be the indolizine **9** according to ^1H and ^{13}C NMR data, including a decisive DEPT experiment that revealed the presence of five vinylic CH carbons. Based on similarities in the NMR spectra, the Et_3N/Ac_2O product was therefore assigned as the acetoxy indolizine **8**.

The assignment of structure **8** supported the conclusion that indole **6** is indeed the major product under the El-Rayyes conditions (Table 1, entry 1) and stimulated attempts to improve the product ratio in favor of **6**. Heating with acetic anhydride in the absence of base (entry 5) was promising in the sense that **8** was not detected, but this experiment gave the diacylated indole **10** as well as **6**. Better results were obtained in toluene using a limited amount of the anhydride. This prevented the formation of **10** and gave better ratios of **6**:**8**. Finally, the optimal conditions for indole formation were found by refluxing **3** in toluene with acetic anhydride and an equivalent of acetic acid (entry 7). These results suggest that the undesired cyclization to the indolizine **7** is

(1) General reviews: Gribble, G. W. In *Rodd's Chemistry of Carbon Compounds*, 2nd ed.; 1997; Vol. 4, p 69. Lounasmaa, M. *Curr. Org. Chem*. **1998**, *2*, 63. Leonard, J. *Nat. Prod. Rep*. **1999**, *16*, 319. Gribble, G. W. *J. Chem. Soc., Perkin Trans 1* **2000**, *7*, 1045. Scholz, U.; Winterfeldt, E. *Nat. Prod. Rep*. **2000**, *17*, 349.

(2) (a) Utsunomiya, I.; Muratake, H.; Natsume, M. *Chem. Pharm. Bull*. **1995**, *43*, 37. (b) Fukuyama, T.; Goto, S. *Tetrahedron Lett*. **1989**, *30*, 6491. (c) Williams, R. M.; Rollins, S. B.; Judd, T. C. *Tetrahedron* **2000**, *56*, 521.

(3) Ziegler, F. E.; Belema, M. *J. Org. Chem*. **1997**, *62*, 1083.

(4) (a) El-Rayyes, N. R. *J. Prakt. Chem*. **1973**, *315*, 295. (b) A related study has appeared using *N*-methylpyrrole derivatives where the alternative cyclization pathway is blocked: El-Rayyes, N. R.; Al-Salman, N. A. *J. Prakt. Chem*. **1976**, *318*, 816.

(5) (a) Perri, S. T.; Moore, H. W. *J. Am. Chem. Soc*. **1990**, *112*, 1897. (b) Turnbull, P.; Moore, H. W. *J. Org. Chem*. **1995**, *60*, 644. (c) Karady, S.; Amato, J. S.; Reamer, R. A.; Weinstock, L. M. *Tetrahedron Lett*. **1996**, *37*, 8277.

(6) (a) Brenna, E.; Fuganti, C.; Perozzo, V.; Serra, S. *Tetrahedron* **1997**, *53*, 15029. (b) Fuganti, C.; Serra, S. *J. Chem. Res., Synop*. **1998**, 638. (c) Fuganti, C.; Serra, S. *J. Chem. Res., Miniprint* **1998**, 2726. (d) Serra, S.; Fugante, C.; Moro, A. *J. Org. Chem*. **2001**, *66*, 7883.

(7) (a) Kampe, W.; Stach, K.; Thiel, M.; Bartsch, W.; Schaumann, W. Ger. Offen. DE 2508251, 1976; *Chem. Abstr*. **1977**, *86*, 55280. (b) Kampe, W.; Stach, K.; Thiel, M.; Bartsch, W.; Dietmann, K.; Roesch, E.; Schaumann, W. US 4,152,446, 1980; *Chem. Abstr*. **1981**, *94*, 156743. (c) Berthold, R.; Vogel, A. Eur. Pat. Appl. EP 191724, 1986; *Chem. Abstr*. **1987**, *106*, 102290. (d) Berthold, R.; Ott, H. Ger. Offen. DE 3524955, 1986; *Chem. Abstr*. **1987**, *106*, 84635. (e) Mattei, P.; Pflieger, P. PCT Int. Appl. WO 0183474, 2001; *Chem. Abstr*. **2001**, *135*, 357939.

10.1021/jo040191e CCC: $27.50
Published on Web 09/09/2004

SCHEME 1

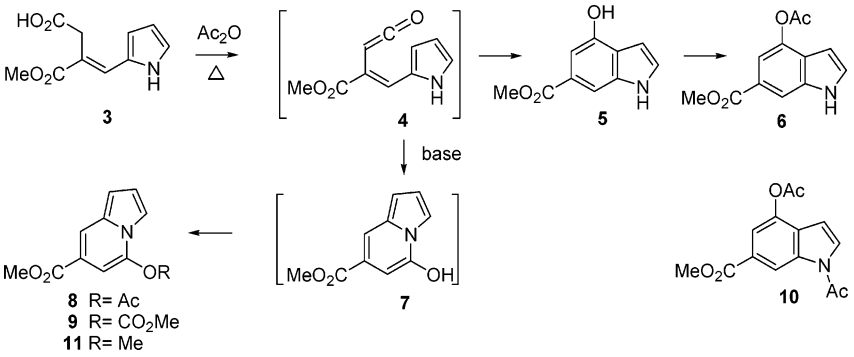


TABLE 1. Cyclization of 3 to 6, 8, or 10

entry	additive (equiv)	amt of Ac_2O (equiv)	time (h)	solvent/*T* (°C)	products
1	NaOAc	excess	*a*	Ac_2O (rt to 75)	**6**:**8** (1.8:1)
2	NaOAc	excess	4	Ac_2O (reflux)	**8**:**10** (1:2)
3	Et_3N (5)	excess	1	Ac_2O (rt)	**8** (>95%)
4	K_2CO_3	excess	2	Ac_2O (reflux)	**8**:**10** (1:1.3)
5	None	excess	8	Ac_2O (75)	**6**:**10** (1:1)
6	None	10	16	toluene (reflux)	**6**:**8** (5:1)
7	AcOH (1)	10	16	toluene (reflux)	**6**:**8** (8:1)
8	AcOH (4)	10	6	toluene (reflux)	**6**:**8** (7:1)

[a] The reaction mixture was stirred 14 h at rt and was then warmed for 6 h at 75 °C.[4a]

catalyzed by base, but we have not determined whether cyclization occurs from the vinyl ketene **4** or at the stage of the mixed anhydride intermediate from **3**.

The best conditions gave **6** contaminated with a significant amount of **8**, so we explored the possibility of purification at a later stage. Crystallization was easier after saponification of **6** to **5**, and subsequent *O*-methylation gave the desired **2**. Similarities in the NMR spectra of **2** and **6** indicate that both structures belong to the indole series. A DEPT experiment confirmed that **2** has four vinylic CH carbons as required, and the presence of an NH proton at 8.63 ppm (br s) in the ^{1}H NMR spectrum confirmed the connectivity. Although the overall yield of **2** from **3** was moderate (38%), the procedure was easy to carry out on a multigram scale and solved our preparative problem.

Comparisons with literature structures proved somewhat difficult because El-Rayyes reported no NMR data beyond the methyl chemical shifts in **6** (δ 3.75, 2.3 ppm in $CDCl_3$).[4a] Our values for **6** are somewhat different (δ 3.92, 2.41 ppm), but the methyl shifts do not distinguish **6** from **8** (δ 3.90, 2.45 ppm). Because **6** is the major product under the reported conditions,[4a] the original structural assignment is confirmed. However, El-Rayyes did not comment on the formation of the isomer **8**, resulting in questions regarding other structural assignments in his paper. For example, saponification of "**6**" to "**1**" and conversion of "**1**" to "**2**" were reported. The products were characterized without including NMR data, but melting points were provided, "**1**" (mp 265 °C); "**2**" (mp 102 °C); "**6**" (mp 151 °C). Only one of these values agrees with our data: **1** (mp 264−7 °C, crystallized from hexane/EtOAc); **2** (mp 135−6 °C, crystallized from hexane/EtOAc); **6** (mp 137−8 °C, crystallized from hexane). The discrepancies cannot be fully explained because of the limited data available for comparison, but we note that the methoxy indolizine **11** (from saponification of **9** and *O*-methylation) has similar ^{1}H NMR methyl shifts compared to **2**, while the melting point is 103−104 °C, nearly the same as the reported value for "**2**".[4a] This raises the possibility that some of the original experiments may have used cyclization products containing both **6** and **8** to explore the preparation of derivatives and that some of the data reflect the enrichment of one isomer or the other (indole or indolizine) by crystallization. We were able to reproduce the mp data for "**1**" = **1**, but not for "**2**" or "**6**". We cannot comment further on the El-Rayyes characterization data, although the structural assignments appear to be correct as published.[4a]

The procedure used for the synthesis of **9** is nearly identical to a method reported in 1998 by Serra et al. for cyclization of the Stobbe condensation product from pyrrole-2-carboxaldehyde.[6c] The latter workers did not isolate the mixed carbonate ester, but reported saponification to a product assigned as 4-hydroxyindole-6-carboxylic acid "**1**" (mp 262−4 °C). The melting point is nearly the same as that provided by El-Rayyes for **1**, and Serra's NMR data are similar to our chemical shift data for **1**. However, we obtained only the indolizine **8** when using Serra's procedure, and our attempts to saponify **8** did not give **1**.[8]

Several patents also describe the synthesis of indole derivatives using the El-Rayyes method.[7] Relevant NMR data were not provided in these reports, so we have no basis to suggest that the structures were not the desired indoles. Nevertheless, it would be prudent to look closely at the spectroscopic data for the resulting indoles in view of the structural issues and the possibility of contamination by indolizines.[9,10]

In conclusion, the cyclization of **3** under the literature conditions (acetic anhydride/sodium acetate)[4a] affords

(8) Under the conditions reported by Serra,[6c] saponification of **8** gave a mixture of structures, apparently including the phenol **7** and tautomeric unsaturated lactams expected from acetate cleavage, but with the methyl ester intact. Under more forcing conditions (15% NaOH, reflux 1 h), both the ester and the lactam were cleaved to give 2-(1*H*-pyrrol-2-ylmethylene)succinic acid, the diacid corresponding to the Stobbe condensation product **3**.

(9) The patent literature reports a phenol assigned structure **5**, mp 80−81 °C, but includes no NMR data for this substance;[7d] we find a melting point of 148−149 °C for **5**.

(10) (a) General reviews: Swinbourne, F. J.; Hunt, J. H.; Klinkert, G. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1978; vol. 23, pp 104−170. Flitsch, W. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: New York, 1984; Vol. 4, pp 443−495. (b) Padwa, A.; Austin, D. J.; Precedo, L.; Zhi, L. *J. Org. Chem.* **1993**, *58*, 1144.

both the indole **6** and the indolizine **8**. The presence of base promotes the formation of indolizine products, especially in the case of the soluble base triethylamine. Although mechanistic details have not been investigated, vinyl ketene intermediates have been invoked to explain similar annulations starting from carbocyclic analogues of **3**.[5,6] The best ratio in favor of indole products was obtained using 1 equiv of acetic acid and 10 equiv of acetic anhydride in refluxing toluene, resulting in preparatively useful conversion to the 4,6-disubstituted indoles **2** and **5**. Under basic conditions, the indolizines **8** and **9** are formed, and **9** can be isolated in good yield. Few methods are known for the preparation of 5-oxygenated indolizines,[10] and the base-modified El-Rayyes conditions may have some potential in this context.

Experimental Section

2-(1*H*-Pyrrol-2-ylmethylene)succinic Acid 1-Methyl Ester (3). Following the El-Rayyes procedure,[4a] dimethyl succinate (41.3 mL, 316 mmol) was added to a stirring solution of 1*H*-pyrrole-2-carbaldehyde (20.0 g, 210 mmol) in benzene (140 mL). The solution was cooled (ice bath), and 60% NaH suspended in mineral oil (16.8 g, 421 mmol) was added. The resulting suspension was allowed to warm to rt and was then stirred for 16 h. The reaction mixture was quenched with water at 0 °C, and the aqueous layer was washed with ether and 5% KOH, followed by addition of NaCl (5 g) to the combined aqueous layers. After acidification with concd HCl to pH < 1 at 0 °C, the precipitate was filtered to afford **3** (42.3 g, 96%) as a brown solid, mp = 134−136 °C, that was used without purification: ^{1}H NMR (400 MHz, CD_3OD) δ 10.94 (1H, br s) 7.72 (1H, s), 6.96 (1H, ddd, J = 2.7, 2.7, 1.4 Hz) 6.52 (1H, dm, J = 2.5 Hz) 6.26 (1H, m) 3.77 (3H, s) 3.62 (2H, s); ^{13}C NMR (125 MHz, CD_3OD) δ 175.2, 170.5, 133.4, 133.3, 128.8, 123.4, 123.3, 118.4, 114.6, 114.5, 112.1, 112.0; IR (neat) 3323, 1684, 1613 cm^{-1}; MS (DCI/NH_3) m/z 210 (MH^+, 40), 209 (15), 194 (14), 193 (19), 192 (100), 191 (46), 178 (20), 166 (30); HRMS calcd for $C_{10}H_{12}NO_4$ (MH^+) 210.0766, found m/z 210.0765.

4-Hydroxy-1*H*-indole-6-carboxylic Acid Methyl Ester (5). Acetic acid (2.73 mL, 47.8 mmol) and acetic anhydride (45.1 mL, 478 mmol) were added to a stirring solution of **3** (10 g, 47.8 mmol) in toluene (400 mL) and refluxed for 16 h. After being cooled to 0 °C, the resulting suspension was diluted with ether (200 mL) and quenched with satd $NaHCO_3$. The aqueous layer was extracted with ether, and the combined organics were washed with satd $NaHCO_3$, H_2O, brine, and dried (Na_2SO_4) to afford a brown solid (9.42 g). The crude product was redissolved in MeOH (350 mL), and NaOMe (10.9 g, 201 mmol) was added. The resulting solution was refluxed for 1 h. After being cooled to 0 °C, the reaction mixture was diluted with ether (150 mL) and acidified with 1 N HCl. The aqueous layer was extracted with ether, and the combined organic layers were washed with H_2O and brine and dried (Na_2SO_4) to give crude hydroxy indole (8.84 g) as a brown oil. Crystallization from CH_2Cl_2 afforded **5** (4.23 g, 46% over two steps) as a shiny light brown solid: mp = 148−149 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 10.83 (1H, br s) 7.70 (1H, t, J = 1.1 Hz) 7.31 (1H, d, J = 3.3 Hz) 7.08 (1H, d, J = 1.5 Hz) 6.61 (1H, dd, J = 2.9, 0.7 Hz) 3.88 (1H, s); ^{13}C NMR (100 MHz, CD_3OD) δ 170.2, 151.1, 138.6, 127.4, 124.8, 123.4, 107.4, 104.5, 100.0, 52.3; IR (neat) 3399, 1676, 1584 cm^{-1}; MS calcd for $C_{10}H_9NNaO_3$ 214.1 (ES/Na), found m/z 214.1 ($M + Na^+$).

4-Methoxy-1*H*-indole-6-carboxylic Acid Methyl Ester (2). Solid K_2CO_3 (5.58 g, 40.4 mmol) and MeI (0.839 mL, 13.5 mmol) were added to a stirring solution of **5** (2.58 g, 13.5 mmol) in DMF (68 mL) at 0 °C. After being stirred for 16 h at 0 °C, the resulting suspension was quenched with 1 N HCl (30 mL) and the aqueous layer was extracted with ether. The combined organic phase was washed with H_2O and brine and dried over Na_2SO_4 to give a brown solid (2.66 g). The crude product was dissolved in CH_2Cl_2 and filtered through a plug of silica gel. Concentration of eluent afforded **2** (2.31 g, 84%) as a light yellow solid. The analytical sample was prepared by recrystallization from ethyl acetate/hexanes to give light yellow crystals: mp = 135−136 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (1H, br s) 7.84 (1H, t, J = 1.0 Hz) 7.26 (1H, d, J = 5.6 Hz) 7.21 (1H, d, J = 1.0 Hz) 6.70 (1H, ddd, J = 2.9, 2.0, 0.7 Hz) 4.00 (3H, s) 3.93 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 152.8, 136.2, 125.9, 124.5, 122.4, 107.6, 100.3, 100.0, 55.4, 52.0; IR (neat) 3323, 1690, 1580 cm^{-1}; MS (EI) 205 (M^+, 100), 190 (50), 174 (42), 146 (32), 132 (23), 131 (24), 103 (28); HRMS calcd for $C_{11}H_{11}NO_3$ (M^+) 205.0739, found m/z 205.0744.

4-Acetoxy-1*H*-indole-6-carboxylic Acid Methyl Ester (6) and 7-Acetoxy-7a*H*-indene-5-carboxylic Acid Methyl Ester (8). The published procedure of El-Rayyes was followed,[4a] but the products were isolated by flash chromatography on silica gel using 1:1 hexane/ethyl acetate instead of direct crystallization. **6**: R_f 0.51; mp 137−8 °C, crystallized from hexane (lit.[4] mp 151 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (1H, bs), 7.97 (1H, s), 7.54 (1H, d, J = 1.1 Hz), 7.25 (1H, dd, J = 3.3, 2.6 Hz), 6.44 (1H, m), 3.92 (3H, s), 2.41 (3H, s). **8**: R_f 0.74, mp 73−75 °C (crystallized from hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (1H, s), 7.33 (1H, d, J = 1.1 Hz), 6.94 (1H, d, J = 1.5 Hz), 6.91 (1H, dd, J = 2.9, 1.1 Hz), 6.8 (1H, dd, J = 4.0, 1.1 Hz), 3.9 (3H, s), 2.45 (3H, s).

5-Methoxycarbonyloxyindolizine-7-carboxylic Acid Methyl Ester (9). Methyl chloroformate (5.91 mL, 76.3 mmol) and triethylamine (25.3 mL, 181.6 mmol) were added to a stirring solution of **3** (7.6 g, 36.3 mmol) in THF (300 mL) at 0 °C. The resulting solution was allowed to warm to rt and then stirred for 2 h followed by evaporation (aspirator). The resulting paste was redissolved in hexane/ethyl acetate (1:1) and filtered through a plug of silica gel to give a brown oil (12.57 g). Crystallization from hexane/ethyl acetate afforded **9** (7.24 g, 80%) as a light orange solid: mp = 92−94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (1H, d, J = 0.7 Hz), 7.42 (1H, m), 7.03 (1H, d, J = 1.5 Hz), 6.93 (1H, dd, J = 4.0, 2.9 Hz), 6.82 (1H, dd, J = 4.0, 1.5 Hz), 4.00 (3H, s), 3.91 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 152.0, 139.2, 133.3, 120.5, 118.8, 115.9, 110.7, 105.9, 98.3, 56.4, 52.1; IR (neat) 1779, 1713 cm^{-1}; MS (DCI/NH_4) m/z 250 (MH^+, 100), 205 (21), 192 (24), 191 (20), 190 (44); HRMS calcd for $C_{12}H_{12}NO_5$ (MH^+) 250.0715, found m/z 250.0715.

4-Acetoxy-1-acetyl-1*H*-indole-6-carboxylic Acid Methyl Ester (10). The procedure described for cyclization was performed as described for the preparation of **5**, except that toluene was replaced by acetic anhydride as the solvent (4 h, reflux). Chromatography as described for preparation of **8** gave a polar fraction consisting of **10**. Crystallization from hexane/ethyl acetate gave **10** as fine filament-like crystals: mp 165−7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (1H, s), 7.75 (1H, s), 7.57 (1H, d, J = 3.7 Hz), 6.59 (1H, d, J = 3.7 Hz), 3.95 (3H, s), 2.68 (3H, s), 2.41 (3H, s); MS calcd for $C_{14}H_{13}NNaO_5$ 298.0691 (ES/Na), found m/z 298.0679 ($M + Na^+$).

5-Methoxyindolizine-7-carboxylic Acid Methyl Ester (11). Sodium methoxide (95%, 4.22 g, 72.2 mmol) was added to a stirring solution of **9** (4.50 g, 18.1 mmol) in methanol (150 mL) at 0 °C. The resulting solution was quenched with pH 3 phosphate buffer after 20 min. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4 to give a brown solid (3.49 g). Attempts to carry out the *O*-alkylation using iodomethane/KO-*t*-Bu[7e] gave products of *C*-methylation. For this reason, the crude product was dissolved in CH_2Cl_2 (180 mL) and cooled to 0 °C, and methyl trifluoromethanesulfonate (3.10 mL, 27.4 mmol) was added (no added base). The resulting mixture was quenched with satd NH_4Cl (40 mL) after stirring for 20 h at rt. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4 and evaporated (aspirator) to give a dark green oil (4.17 g). Filtration through a plug of silica gel (1:1 hexanes/ethyl acetate) afforded **11** (3.13 g, 84% over two steps) as an off-white solid. A sample was prepared by flash chromatography (3:1,

hexanes/ethyl acetate) and crystallization from hexane: mp = 103−104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (1H, d, J = 0.7 Hz) 7.53 (1H, ddd, J = 1.5, 1.5, 0.7 Hz) 6.87 (1H, dd, J = 3.7, 2.6 Hz) 6.71 (1H, dd, J = 4.0, 1.5 Hz) 6.36 (1H, d, J = 1.1 Hz) 4.10 (3H, s) 3.91 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 148.5, 132.6, 119.6, 115.8, 115.0, 110.7, 104.44, 83.59, 56.1, 51.98; IR (neat) 3167, 1703, 1625 cm^{-1}; MS (EI) m/z 205 (M^+, 83), 190 (100), 131 (14), 103 (11); HRMS calcd for $C_{11}H_{11}NO_3$ (M^+) 205.0739, found m/z 205.0730.

Acknowledgment. This work was supported by the National Institutes of Health (CA17918).

Supporting Information Available: NMR spectra of key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO040191E