Evaporation of the washed and dried ether extract followed by TLC of the residue gave 8 mg of 12,15-epoxylabda-8(17),12,14-triene (**22**): mp 85–86 °C (not recrystallized because of sample size) (lit.[21] mp 88–89 °C); IR 3075, 1640, 1620, 1510, 885, 725 cm^{-1}; NMR 7.18 (d, J = 2 Hz, H-15), 6.12 (d, J = 2 Hz, H-14), 4.78 and 4.59 (both br, H-17), 2.00 (H-16), 0.92, 0.86, and 0.86 ppm (C-4 and C-10 Me).

Anal. Calcd for $C_{20}H_{30}O$: mol wt 286.2296. Found: mol wt (mass spectroscopy) 286.2296 (15.6%).

Reaction of 5 mg of **21** with $FeSO_4 \cdot 7H_2O$ in the same manner gave 3 mg of **22** after purification by TLC.

(21) Raldugin, V. A.; Demenkova, L. I.; Pentegova, V. A. *Khim. Prir. Soedin.* **1978**, *14*, 345.

Registry No. (*E*)-**2**, 76467-03-3; (*Z*)-**2**, 76467-04-4; (*E*)-**3**, 10483-51-9; (*Z*)-**3**, 10395-41-2; **4**, 76498-70-9; **5**, 10395-42-3; **6**, 17990-20-4; **7** (isomer 1), 76467-05-5; **7** (isomer 2), 76497-67-1; **8**, 76467-06-6; **9**, 76467-07-7; **10** (isomer 1), 76467-08-8; **10** (isomer 2), 76497-68-2; **11**, 76497-69-3; **12a**, 596-85-0; **12b**, 1438-62-6; **13** (isomer 1), 61091-79-0; **13** (isomer 2), 61091-80-3; **14**, 511-02-4; **15**, 76467-09-9; **16**, 76467-10-2; **17** (isomer 1), 76467-11-3; **17** (isomer 2), 76497-70-6; **18**, 61604-71-5; **19**, 76467-12-4; **20**, 76467-13-5; **21**, 76467-14-6; **22**, 67779-53-7; manool, 596-85-1; 14,15-dihydromanool, 40768-86-3.

Supplementary Material Available: Mass spectral data (2 pages). Ordering information is given on any current masthead page.

Synthesis of 7,9-Di-*O*-methyl-11-oxosibiromycinone

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The synthesis of 7,9-di-*O*-methyl-11-oxosibiromycinone (**8**) is described. Nitration of methyl 4-methyl-3,5-dimethoxybenzoate (**18**) gave the corresponding nitro derivative **20** which was converted to 4-methyl-3,5-dimethoxy-2-nitrobenzoyl chloride (**24**). Ethyl 4-formylpyrrole-2-carboxylate (**10**) was treated with ethylmagnesium bromide and the resulting secondary alcohol **25** heated in dimethyl sulfoxide to afford ethyl (*E*)-4-(1-propenyl)pyrrole-2-carboxylate (**26**). Amide bond formation between acid chloride **24** and the sodium salt of pyrrole derivative **26** gave **29**. Reduction of the nitro group of **29** with triirondodecacarbonyl gave the corresponding amine **31** which cyclized to the desired compound **8** on heating with *p*-toluenesulfonic acid in toluene. Preliminary attempts to convert **8** to sibiromycinone were unsuccessful.

Introduction

Sibiromycin (**1**)[1] is a naturally occurring antitumor antibiotic first isolated[2] in the Soviet Union from *Streptosporangium sibiricum*.[3] It binds strongly to DNA and is active against a number of tumor cells, including transplanted solid tumors in mice. Its biological activity has been attributed to covalent binding to DNA through the electrophilic N(10)–C(11) carbinolamine[4].

Sibiromycin is characterized by a number of structural features which present challenges to chemical synthesis, especially when compared to other pyrrolo[1,4]benzodiazepine antibiotics such as anthramycin (**2**).[5,6] Sibiromycin (**1**) differs from **2** in that not only is **1** the glycoside of a branched-chain amino sugar (sibirosamine) but it also incorporates an aromatic pyrrole ring into its structure as opposed to the dihydropyrrole found in **2**. Both **1** and **2** undergo ready dehydration to the corresponding imines anhydrosibiromycin (**3**) and anhydroanthramycin (**4**) (see Scheme I). While the carbinolamine–imine interconversion is readily reversible for anthramycin,[7] the equilibrium is strongly biased toward the conjugated imine **3** for **1**.[2] Anhydrosibiromycin (**3**) is biologically inactive.[2] Another significant difference is that the amide bond to the pyrrole ring nitrogen in **1** is less stable toward nucleophilic cleavage than is the corresponding amide bond in **2**.

The labile carbinolamine function apparently presents the major obstacle to any synthesis of **1** or of its aglycon sibiromycinone (**5**). In a recent synthetic effort, Parker[8] found that dehydration of 7,9-di-*O*-methylsibiromycinone (**6**) occurred spontaneously under the cyclization conditions used for its formation, giving, as the only isolable product, 7,9-di-*O*-methylanhydrosibiromycinone (**7**). An alternative approach would be to introduce the carbinolamine functionality in a separate reduction step following construction of the pyrrolo[1,4]benzodiazepine skeleton, analogous to the approach taken by Leimgruber in the synthesis of **2**.[9] We report here the synthesis of the key intermediate required to pursue this approach, 7,9-di-*O*-methyl-11-oxosibiromycinone (**8**).

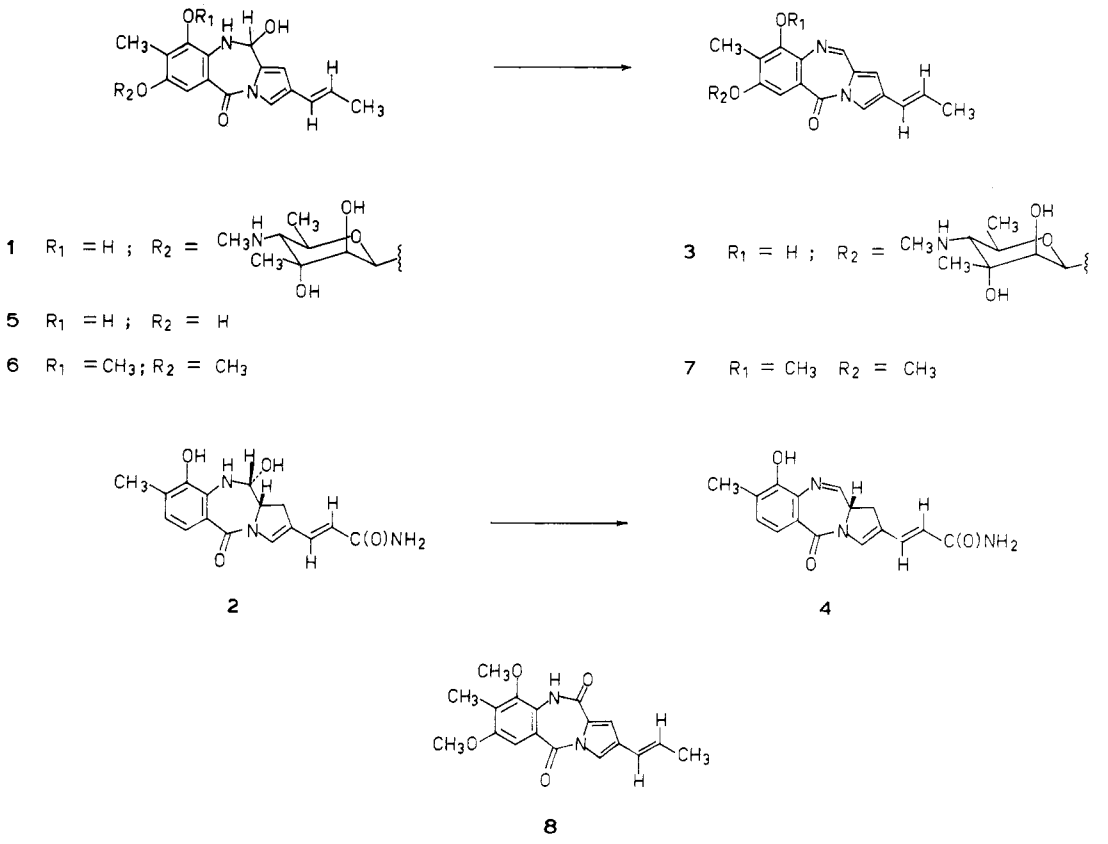
Results and Discussion

The synthetic plan is outlined in Scheme II. The diazepine ring is constructed in two stages: first, amide formation between 4-methyl-3,5-dimethoxy-2-nitrobenzoyl chloride (**24**) and ethyl (*E*)-4-(1-propenyl)pyrrole-2-

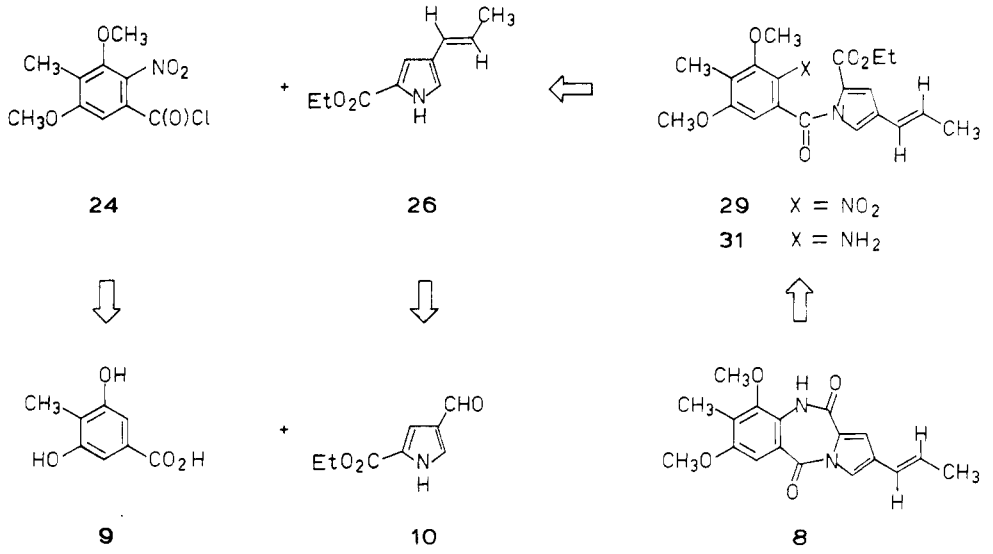
(1) For reviews see: (a) Gause, G. F. "Antibiotics III"; Corcoran, J. W., Hahn, F. E., Eds.; Springer-Verlag: New York, 1975; pp 269–273; (b) Hurley, L. H. *J. Antibiot.* **1977**, *30*, 349–370.
(2) Brazhnikova, M. G.; Konstantinova, N. V.; Mesentsev, A. S. *J. Antibiot.* **1972**, *25*, 668–673.
(3) For a review of biosynthetic studies, see: Hurley, L. H. *Acc. Chem. Res.* **1980**, *13*, 263–269.
(4) Hurley, L. H.; Petrusek, R. *Nature* **1979**, *282*, 529–531.
(5) Structure of sibiromycin: Mesentsev, A. S.; Kuljaeva, V. V.; Rubasheva, L. M. *J. Antibiot.* **1974**, *27*, 866–873.
(6) Structure of anthramycin: Leimgruber, W.; Batcho, A. D.; Schenker, F. *J. Am. Chem. Soc.* **1965**, *87*, 5793–5795.
(7) Leimbruger, W.; Stefanovic, V.; Schener, F.; Karr, A.; Berger, J. *J. Am. Chem. Soc.* **1965**, *87*, 5791–5793.
(8) Parker, K. A.; Fedynyshyn, T. H. *Tetrahedron* Lett. **1979**, 1657–1660.
(9) Leimgruber, W.; Batcho, A. D.; Czajkowski, R. C. *J. Am. Chem. Soc.* **1980**, *102*, 5641–5644.

0022-3263/81/1946-1366$01.25/0

Scheme I



Scheme II



carboxylate (**26**) to give **29**, and, in the second stage, closure of the central diazepine ring by amide bond formation between an amino group on the benzene nucleus and the ester carbonyl of the pyrrole fragment. The starting materials required for this approach are 4-methyl-3,5-dihydroxybenzoic acid (**9**) and ethyl 4-formylpyrrole-2-carboxylate (**10**).

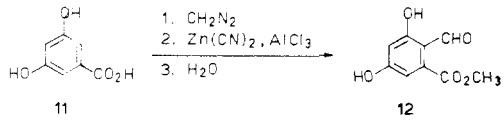
Synthesis of 4-Methyl-3,5-dimethoxy-2-nitrobenzoyl Chloride (24). The preparation of 4-methyl-3,5-dihydroxybenzoic acid (**9**) from *p*-toluic acid as reported in the early literature[10] is unreliable and not conducive to the preparation of even moderate amounts of material.[11] We turned our attention to alternative synthesis of **9** based on introducing a methyl group into the 4-position of 3,5-dihydroxybenzoic acid (**11**).

One approach envisioned introduction of the methyl group by formylation of the ring followed by reduction. Reaction of **11**, as its methyl ester, with zinc cyanide–aluminum chloride[12] afforded a formyl derivative in good yield, but NMR analysis revealed that the formyl group has been introduced at the 2-position.

Iodination[13] of **11** gave a single product, apparently the 4-iodo derivative **13**, as evidenced by a sharp singlet in its

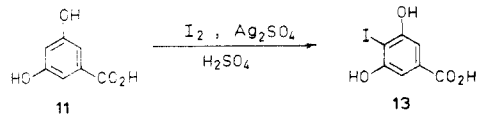
(10) (a) Asahina, Y.; Asano, J. *Chem. Ber.* **1933**, *66*, 687–688. (b) Charlesworth, E. H.; Robinson, R. *J. Chem. Soc.* **1934**, 1531–1533.

(11) Tyman, J. H. P. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1639–1647.
(12) Whalley, W. B. *J. Chem. Soc.* **1949**, 3278–3280.
(13) Barker, I. R. L.; Waters, W. A. *J. Chem. Soc.* **1952**, 150–152.



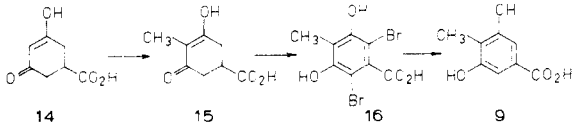
11 12

NMR spectrum for the aromatic protons at δ 7.15. Attempts to replace the iodo substituent by methyl were not successful.



11 13

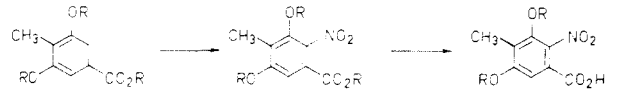
Whalley[14] has described a preparation of **9** involving base-catalyzed methylation of 3,5-cyclohexanedionecarboxylic acid (**14**),[15] followed by oxidation with excess bromine, to give **16** which was subsequently converted to **9** by hydrogenolysis. We have found



14 15 16 9

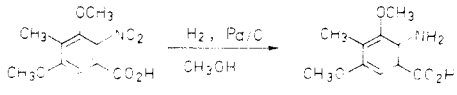
Whalley's procedure can be modified slightly to increase its efficiency and believe it to be the preferred method for the preparation of **9**. Oxidation of **15** with 1 equiv of bromine in acetic acid is rapid and produces **9** directly. Material prepared in this way is contaminated with small amounts of **16** and/or the monobromo derivative but is sufficiently pure to be carried through subsequent steps.

Compound **9** was converted to the tri-*O*-benzyl derivative **17** in 80% yield with benzyl chloride–potassium carbonate in dimethyl formamide. Alternatively, alkylation of **9** with methyl sulfate–potassium carbonate–acetone gave the known[8,10a] methyl 3,5-dimethoxy-4-methylbenzoate (**18**) in 81% yield. Nitration of **17** or **18** with cupric nitrate



17 R = CH_2Ph 19 R = CH_2Ph 21 R = CH_2Ph
18 R = CH_3 20 R = CH_3 22 R = CH_3

in acetic anhydride occurred smoothly to give the 2-nitro derivatives **19** (92%) and **20** (83%) which were hydrolyzed to the corresponding nitro acids **21** and **22**. The structure of **22** was confirmed by reduction to the known 3,5-dimethoxy-4-methylanthranilic acid (**23**) in quantitative yield. This compound has been previously described by Mesentsev who obtained it by degradation of 1.[5] The ^1H NMR spectrum of **23** was identical with that reported by Mesentsev.

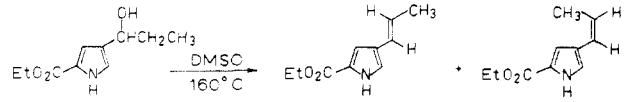


22 23

Subsequent work was carried out on the di-*O*-methyl series only. Nitro acid **22** was converted to the acid chloride **24** in the usual way with thionyl chloride.

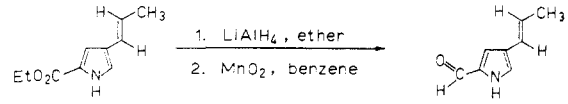
Synthesis of Ethyl (*E*)-4-(1-Propenyl)pyrrole-2-carboxylate (26). Ethylidenation of the formyl group of ethyl 4-formylpyrrole-2-carboxylate (**10**) to produce ethyl (*E*)-4-(1-propenyl)pyrrole-2-carboxylate (**26**) has been achieved by Parker[8] using the Schlosser modification of the Wittig reaction. In the interests of economy, however, an alternative means of effecting the conversion of **10** to **26** was sought—especially one which avoids the necessity of chromatographic purification of **26**.

Addition of excess ethylmagnesium bromide to **10** afforded alcohol **25** which was dehydrated by heating in dimethyl sulfoxide (160 °C, 2.5 h).[16] After distillation, a 6:1 mixture of **26** and its *Z* isomer **27** was obtained in 28% yield. The desired isomer **26** was obtained by recrystallization. Although the overall yield in absolute terms is low, the simplicity of the synthesis suggests it may be useful for large-scale preparation of **26**.



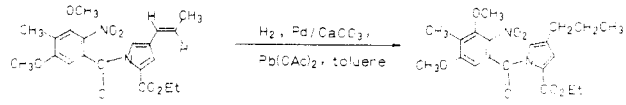
25 26 27

As confirmation of its structure, compound **26** was converted to 4-(1-propenyl)pyrrole-2-carboxaldehyde (**28**) by reduction to the primary alcohol with lithium aluminum hydride, followed by oxidation with activated manganese dioxide. Aldehyde **28** has been isolated as a hydrolysis product of sibiromycin by Mesentsev.[2,5] The IR and NMR spectra of **28** were identical with those reported.



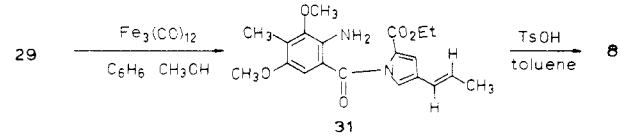
26 28

Synthesis of 7,9-Di-*O*-methyl-11-oxosibiromycinone (8). Pyrrole derivative **26** was converted to its sodium salt (NaH, THF) and coupled directly to nitro acid chloride **24** to give amide **29** in 89% yield. Conversion of the nitro group in **29** to an amino function was difficult since catalytic hydrogenation of the propenyl side chain proved to be faster than reduction of the nitro group. The propyl side-chain analogue **30** of nitro compound **29** was isolated in 87% yield on hydrogenation of **29** over the Lindlar catalyst.



29 30

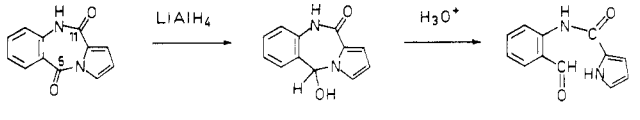
Attempts at chemical reduction of **29** were complicated in many cases by nucleophilic cleavage of the amide bond. The best conditions found of those we surveyed utilized triirondodecacarbonyl as the reducing agent[17] in benzene containing 2% methanol at reflux (1.5 h). The desired amine **31** was obtained as a yellow oil in 30% yield. Amine **31** cyclized to the desired 11-oxo-7,9-di-*O*-methylsibiromycinone (**8**) in 63% yield on refluxing in toluene containing a trace of *p*-toluenesulfonic acid.



31

(14) Briggs, D. R.; Whalley, W. B. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1382–1384.
(15) van Tamelen, E. E.; Hildahl, G. T. *J. Am. Chem. Soc.* **1956**, *78*, 4405–4410.
(16) Traynelis, V. J.; Hergenbother, W. L.; Livingston, J. R.; Valicenti, J. A. *J. Org. Chem.* **1962**, *27*, 2377–2383.
(17) Landesberg, J. M.; Katz, L.; Olsen, C. *J. Org. Chem.* **1972**, *37*, 930–936.

Selective Amide Reduction in an 11-Oxosibiromycinone Model System. A preliminary investigation into the feasibility of reducing the C(11) carbonyl group of diamide 8 indicated that it is the carbonyl group attached to the pyrrole nitrogen which is the more reactive toward hydride reducing agents. Thus, lithium aluminum hydride reduction of the model pyrrolo(1,4)benzodiazepine **32** gave the aldehyde **34** in 84% yield, presumably via the C(5) carbinolamine **33**.

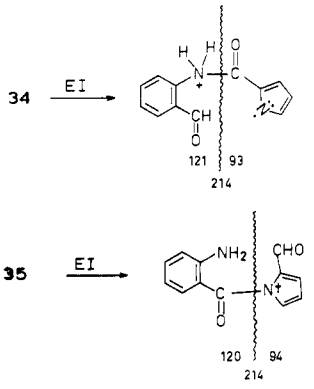


32 33 34

That C(5) was reduced rather than C(11) was concluded on the basis of a number of considerations. First, the alternative reduction product **35** is of a type without

35 36

precedent in these kinds of compounds and should exist in the carbinolamine form as in sibiromycin. Further **35** should exhibit a tendency toward dehydration to give the corresponding imine **36**. No such tendency was observed. The mass spectrum of the reduction product had its most intense peaks at m/e 93 and 94; there was another intense ion (42% of m/e 93) at m/e 121. Structure **34** is more in accord with such a fragmentation than is **35** which should produce m/e 120 and 94.



Thus, direct reduction of 8 to 7,9-di-O-methylsibiromycinone **6** with simple reducing agents does not seem feasible at present. We are exploring alternative methods to effect reduction of 8 or some derivative of 8 so as to incorporate the essential carbinolamine functionality.

Experimental Section

Infrared spectra were obtained on a Perkin-Elmer 337 grating spectrometer as KBr disks or as thin films. Melting points and boiling points are uncorrected. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, GA. Proton NMR spectra were obtained at 90 MHz on a Varian EM-390 instrument. Low-resolution mass spectra were measured by using a Hitachi Perkin-Elmer RMU-6E spectrometer. High-resolution mass spectra were determined by the Mass Spectrometry Center, University of Pennsylvania (D. T. Terwilliger, Director), and by the Middle Atlantic Mass Spectrometry Laboratory, Baltimore, MD (C. Fenselau, Director).

Formylation of Methyl 3,5-Dihydroxybenzoate. To a solution of 1.54 g (10 mmol) of 3,5-dihydroxybenzoic acid (11) in 25 mL of anhydrous ether was added an ether solution of diazomethane until the yellow color persisted. A few drops of acetic acid were added and the solution was extracted with saturated sodium bicarbonate solution and water and then dried over anhydrous sodium sulfate. The ether was evaporated to yield the desired methyl ester (1.4 g, 83%) as a syrup which soon crystallized, mp 147–149 °C.

A 0.50-g (2.9 mmol) portion of the ester was dissolved in ether and cooled to 0 °C and 1.25 g of anhydrous aluminum chloride added followed by 1.09 g (8.0 mmol) of zinc cyanide. The reaction mixture was stirred for 10 min and then saturated with anhydrous hydrogen chloride. After the mixture stood overnight, the ether was decanted, leaving a reddish oil which was heated for 20 min on a steam bath with water (20 mL). On cooling, the solution deposited 0.234 g (40%) of methyl 2-formyl-3,5-dihydroxybenzoate (**12**) which was crystallized from water: mp 156–157 °C; ^{1}H NMR ($CDCl_3$) δ 10.35 (s, 1, CHO), 6.93 (m, 1, arom), 6.48 (m, 1, arom), 3.90 (s, 3, OCH_3).

Anal. Calcd for $C_9H_8O_5$: C, 55.10; H, 4.08. Found: C, 54.86; H, 4.13.

Iodination of 3,5-Dihydroxybenzoic Acid (11). To a stirred solution of 3,5-dihydroxybenzoic acid (11, 0.308 g, 2 mmol) in 20 mL of concentrated H_2SO_4 at 55–60 °C was added silver sulfate (0.6 g, 2.9 mmol) followed by pulverized iodine (0.63 g, 5 mmol) over a period of 2.5 h. The resulting brick red solution was poured onto ice and the mixture extracted with ether. The combined ether extracts were washed once with aqueous sodium sulfite and evaporated to afford 0.38 g (68%) of 4-iodo-3,5-dihydroxybenzoic acid (**13**) as a yellow solid. The analytical sample was obtained by recrystallization from water: mp 231.5–234 °C; ^{1}H NMR (acetone-d_6) δ 7.15 (s, arom); mass spectrum (EI), m/e (relative intensity) 280 (M^+, 29), 263 (8), 154 (71), 137 (100).

Anal. Calcd for $C_7H_5IO_4$: C, 30.00; H, 1.79; I, 45.36. Found: C, 30.12; H, 1.84; I, 45.25.

3,5-Dihydroxy-4-methylbenzoic Acid (9). Bromine (1.0 mL, 0.039 mol) was added to 6.0 g (0.035 mol) of 4-methyl-3,5-dioxocyclohexanecarboxylic acid (**15**)[14] in acetic acid (25 mL) at room temperature with stirring. An additional 75 mL of acetic acid was added and the solution was stirred under reflux for 46 h. Gas evolution was vigorous during the first few hours. The solution was evaporated under reduced pressure, leaving a reddish-brown solid which was taken up in boiling water (100 mL) and treated with decolorizing carbon. Filtration through Celite and removal of the solvent left a tan solid: 6.2 g; mp 242–246 °C. A second purification with charcoal gave 5.62 g (95%) of **9**, mp 244–246 °C (lit.[10] mp 245–250 °C, 264–265 °C). Material obtained by this procedure was suitable for the preparation of benzyl 4-methyl-3,5-dibenzyloxybenzoate and methyl 4-methyl-3,5-dimethoxybenzoate.

Benzyl 3,5-Bis(benzyloxy)-4-methylbenzoate (17). A mixture containing 4.0 g (0.024 mol) of 3,5-dihydroxy-4-methylbenzoic acid (**9**), 19.6 g (0.076 mol) of benzyl chloride, and 13 g of potassium carbonate in 45 mL of dry dimethylformamide was stirred at 110–120 °C for 20 h. After cooling, the mixture was filtered, and the solid was washed with DMF (10 mL). Water (20 mL) was added slowly and the solution was refrigerated overnight. The crystals which deposited were collected, washed with several portions of water, and dried under vacuum to give 8.3 g (80%) of **17**, mp 112.5–114.5 °C. The analytical sample was obtained by preparative thin-layer chromatography on silica gel ($CHCl_3$) and recrystallized twice from absolute ethanol to give needles: mp 118–119 °C; ^{1}H NMR ($CDCl_3$) δ 7.50–7.30 (m, 17, arom), 5.33 (s, 2, CO_2CH_2Ph), 5.10 (s, 4, $ArOCH_2Ph$), 2.24 (s, 3, CH_3).

Anal. Calcd for $C_{29}H_{26}O_4$: C, 79.42; H, 5.98. Found: C, 79.45; H, 6.02.

Methyl 4-Methyl-3,5-dimethoxybenzoate (18). A mixture of 3,5-dihydroxy-4-methylbenzoic acid (**9**, 2.0 g, 12 mmol), methyl sulfate (36 mL, 38.5 mmol), potassium carbonate (9 g), and anhydrous acetone (150 mL) was stirred under reflux for 20 h. An additional 1.6 mL of methyl sulfate was added in two portions over the next 6 h. The reaction mixture was cooled to room temperature and filtered, and the filter cake was washed with acetone. The filtrate and washings were concentrated under reduced pressure to a volume of ca. 25 mL. Methanol (5 mL) was added and the solution was kept overnight in a freezer (−13 °C). Crystals deposited and were collected. The mother liquor was concentrated and a few drops of water was added. After standing for several hours in the freezer the solution was again filtered and

the crystals were washed with water. There was obtained 2.02 g (81%) of **18**, mp 100.5–102 °C (lit.[10a] mp 105 °C). The product was recrystallized from ethanol–water: mp 102–103 °C; ^{1}H NMR ($CDCl_3$) δ 7.2 (s, 2, arom), 3.90 (s, 6, CO_2CH_3), 3.86 (s, 3, OCH_3), 2.12 (s, 3, CH_3).

Benzyl 3,5-Bis(benzyloxy)-4-methyl-2-nitrobenzoate (19). To a stirred solution of 9.2 g (0.021 mol) of **17** in 50 mL of acetic anhydride was slowly added 6.34 g (0.026 mol) of cupric nitrate over a period of 20 min. After being stirred 1.5 h, the reaction mixture was poured onto ice and extracted with ether. The combined ether extracts were washed with 1.5 N sodium hydroxide solution, saturated sodium bicarbonate, water, and brine. The yellow solution was dried over sodium sulfate and evaporated to leave 9.34 g (92%) of **19** as a syrup which was homogeneous on TLC. The analytical sample was obtained by column chromatography on silica gel with chloroform and recrystallization from absolute ethanol: mp 85.5–86 °C; ^{1}H NMR ($CDCl_3$) δ 7.35–7.20 (m, 16, arom), 5.24 (s, 2, CO_2CH_2Ph), 5.10 (s, 2, $ArOCH_2Ph$) 4.92 (s, 2, $ArOCH_2Ph$), 2.23 (s, 3, CH_3); IR (thin film) 3030, 3000, 1725, 1570, 1530, 1450, 1260, 1325 cm^{-1}; mass spectrum (EI), *m/e* (relative intensity) 483 (M^+, 3), 465 (10), 438 (9), 392 (13), 286 (11), 271 (40), 181 (100), 150 (40).

Anal. Calcd for $C_{29}H_{25}NO_6$: C, 72.04; H, 5.21; N, 2.89. Found: C, 71.86; H, 5.27; N, 2.88.

Methyl 4-Methyl-3,5-dimethoxy-2-nitrobenzoate (20). In a manner similar to that of the preparation of **19** described above, 1.64 g (7.8 mmol) of **18** was nitrated, giving 1.71 g (83%) of **20** as yellow crystals, mp 92–93 °C. Recrystallization from ethanol gave material melting at 95–95.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.20 (s, 1, arom), 3.92 (s, 3, OCH_3), 3.88 (s, 3, CO_2CH_3), 3.80 (s, 3, OCH_3), 2.22 (s, CH_3).

3,5-Bis(benzyloxy)-4-methyl-2-nitrobenzoic Acid (21). A solution of 2.3 g (4.76 mmol) of **19** in 30 mL of methanol–water (2:1) containing 1.5 g of potassium hydroxide was refluxed for 1.5 h, cooled to 0 °C, and acidified with concentrated hydrochloric acid. The product which crystallized on standing overnight at −13 °C was filtered and recrystallized from absolute ethanol to afford 1.13 (60%) of **21**: mp 203–205 °C; ^{1}H NMR (acetone-d_6) δ 7.6–7.3 (m, 11, arom), 5.34 (s, 2, OCH_2Ph), 5.02 (s, 2, OCH_2Ph), 2.33 (s, 3, CH_3); IR (KBr) 3000, 1675, 1575, 1530, 1420, 1360 cm^{-1}; mass spectrum (EI), *m/e* (relative intensity) 393 (M^+, 7), 375 (7), 359 (97), 268 (100).

Anal. Calcd for $C_{22}H_{19}NO_6$: C, 67.16; H, 4.87; N, 3.58. Found: C, 67.24; H, 4.89; N, 3.57.

4-Methyl-3,5-dimethoxy-2-nitrobenzoic Acid (22). Saponification of methyl ester **20** (1.7 g, 6.7 mmol) was effected in a similar manner to give 1.45 g (95%) of crude **22**, mp 208–210 °C. Pure material, mp 209–210 °C, was obtained (1.12 g, 70%) by recrystallization from absolute ethanol: ^{1}H NMR (acetone-d_6) δ 8.3 (br s, 1, CO_2H), 7.27 (s, 1, arom), 3.91 (s, 3, OCH_3), 3.80 (s, 3, OCH_3), 2.20 (s, 3, CH_3); IR (KBr) 2880, 1640, 1530, 1350 cm^{-1}.

Reduction of 22 to 4-Methyl-3,5-dimethoxyanthranilic Acid (23). A mixture of 60 mg (0.25 mmol) of **22**, 10% palladium on carbon (20 mg), and methanol (5 mL) was hydrogenated at room temperature and atmospheric pressure for 3 h. Hydrogen uptake was 9.4 mL (56% of theoretical) after 20 min but slowed as the reaction proceeded. The addition of another 10 mg of catalyst resulted in complete reduction. A thin-layer chromatogram (silica gel; 20% methanol–chloroform) showed a single spot. The catalyst was removed by centrifugation and the colorless solution was evaporated under reduced pressure to afford 52 mg (quantitative) of white crystalline product, mp 173–174 °C. Recrystallization from ethanol gave plates, mp 175–176 °C (lit[4a] mp 175–177 °C. The ^{1}H NMR spectrum was identical with that reported.[4a]

Ethyl (*E*)-4-(1-Propenyl)pyrrole-2-carboxylate (26). To a solution of ethylmagnesium bromide (1.0 mol; from 75 mL of ethyl bromide and 24 g of magnesium) in 300 mL of dry ether at 0 °C (N_2 atmosphere) was added 17 g (0.1 mol) of ethyl 4-formylpyrrole-2-carboxylate (**10**) in 1:1 ether-tetrahydrofuran. The reaction mixture was stirred at 0 °C for 2.5 h during which the disappearance of the aldehyde was monitored by TLC (silica gel; 5% methanol–chloroform). When starting material was no longer detectable the reaction mixture was poured carefully onto ice and the organic phase isolated and dried (Na_2SO_4). Removal of the solvent afforded ethyl 4-(1-hydroxypropyl)pyrrole-2-carboxylate (**25**) as a syrup; ^{1}H NMR ($CDCl_3$) δ 6.90 (m, 2, C(3)-H and C(5)-H), 4.57 (t, J = 7 Hz, 1, CHOH), 4.30 (q, J = 7 Hz, 2, OCH_2), 3.5 (s, 1, OH), 1.80 (m, 2, CCH_2C), 1.35 (t, J = 7 Hz, 3, CH_3), 0.95 (t, J = 7 Hz, 3, CH_3).

The crude unstable alcohol was taken up in 100 mL of dimethyl sulfoxide and heated at 160 °C for 2.5 h. After the mixture cooled to room temperature water was added and the mixture was extracted thoroughly with ether. The combined ether extracts were dried (Na_2SO_4) and evaporated to a residue which was distilled to give 5.1 g (28%) of material, mp 135–142 °C (2 torr), which crystallized on standing, mp 55–60 °C. NMR analysis indicated that the product was a 6:1 mixture of the desired compound **26** and its *Z* isomer **27**. Two recrystallizations from hexane gave the pure *E* isomer **26**: mp 74–75 °C; ^{1}H NMR ($CDCl_3$) δ 9.5 (br s, 1, NH), 6.94 (m, 1, C(5)-H), 6.85 (m, 1, C(3)-H), 6.25 (d, J = 16 Hz, 1, vinyl H), 5.9 (dq, J = 6, J = 16 Hz, 1, vinyl H), 4.31 (q, J = 7 Hz, 2, OCH_2), 1.80 (d, J = 6 Hz, 3, CH_3), 1.32 (t, J = 7 Hz, 3, CH_3); IR (KBr) 3270, 2900, 1660, 1365 cm^{-1}.

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.04; H, 7.26; N, 7.82. Found: C, 66.83; H, 7.30; N, 7.75.

Conversion of 26 to (*E*)-4-(1-Propenyl)pyrrole-2-carboxaldehyde (28). To a refluxing solution of ethyl (*E*)-4-(1-propenyl)pyrrole-2-carboxylate (**26**, 0.179 g, 1 mmol), in anhydrous ether (10 mL) was added a suspension of lithium aluminum hydride (10 mg, 1.26 equiv) in dry ether (5 mL) dropwise with stirring. The progress of the reaction was monitored by TLC (silica gel; 4% methanol/chloroform). After 1.5 h another 10 mg of LAH (total 1.53 equiv) was added and refluxing was continued for 30 min. Sodium sulfate decahydrate was added and the aluminum salts were removed by filtration through Celite. The resulting solution was dried briefly over Na_2SO_4 and evaporated under reduced pressure to give (*E*)-4-(1-propenyl)pyrrole-2-methanol as a reddish syrup; ^{1}H NMR ($CDCl_3$) δ 8.3 (br s, NH), 6.80 (m, C(5)-H), 6.64 (m, C(3)-H), 6.34–6.12 (m, CH_3CH=CH), 5.90 (m, CH_3CH=CH), 4.54 (s, CH_2OH), 1.95 (br s, OH), 1.80 (d, CH_3CH=CH).

Without further purification, the product was taken up in 5 mL of dry benzene and 0.390 g (5 equiv) of activated manganese dioxide was added. After the mixture was stirred overnight at ambient temperature, an additional 0.156 g of manganese dioxide was added and the reaction allowed to proceed for an additional 24 h. The reaction mixture was filtered and evaporated to leave 40 mg (30%) of aldehyde **28**, mp 110.5–112 °C, after crystallization from hexane. Recrystallization from hexane gave needles, mp 112–114 °C (lit.[10a] mp 115–116 °C). The ^{1}H NMR spectrum was identical with that reported by Mesentsev:[4a] ^{1}H NMR ($CDCl_3$) δ 9.6 (br s, 1, NH), 9.49 (s, 1, CHO), 7.04 (m, 1, C(5)-H), 6.95 (m, 1, C(3)-H), 6.25 (d, J = 16 Hz, 1, vinyl H), 5.95 (dq, J = 6, J = 16 Hz, 1, vinyl H), 1.80 (d, J = 6 Hz, 3, CH_3); IR (thin film) 3260, 3200, 2950, 2855, 1650, 1450, 1395, cm^{-1}.

Ethyl 1-(2-Nitro-4-methyl-3,5-dimethoxybenzoyl)-(*E*)-4-(1-propenyl)pyrrole-2-carboxylate (29). A mixture of 2-nitro-4-methyl-3,5-dimethoxybenzoic acid (**22**, 0.66 g, 2.74 mmol), thionyl chloride (0.78 mL, 4 equiv), dry chloroform (12 mL), and a drop of pyridine was stirred under reflux for 10 min. Solvent was removed under reduced pressure and dry benzene (10 mL) was added. The mixture was filtered and evaporated under reduced pressure, and the residue stored under vacuum until use.

The sodium salt of ethyl (*E*)-4-propenylpyrrole-2-carboxylate (**26**) was prepared from the pyrrole (0.441 g, 0.9 equiv based on acid) and sodium hydride (0.134 g of 55% dispersion in oil, ca. 1.2 equiv of NaH; washed with dry hexane) in dry THF. The yellow solution was stirred for 30 min at 40 °C and then added dropwise to a solution of the acid chloride in dry THF (8 mL) with stirring at room temperature. The mixture was stirred for 1.25 h and then poured into a separatory funnel containing ether (100 mL) and dilute sodium bicarbonate solution. The ether was washed with water and brine and then dried (Na_2SO_4). Removal of the solvent left a syrup which was lyophilized from benzene to afford 0.98 g (98%) of the desired nitro ester as a brittle residue.

A 40-mg sample of this material was purified by preparative thin-layer chromatography to give 20 mg of **29** as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 7.09 (m, 2, pyrrole ring H), 6.70 (s, 1, arom H), 6.10 (m, 2, vinyl H), 4.08 (q, J = 7 Hz, 2, OCH_2), 3.89 and 3.84 (s, 3 each, OCH_3), 2.23 (s, 3, $ArCH_3$), 1.81 (d, J = 6 Hz, 3, CH_3CH), 1.18 (t, J = 7 Hz, 3, CH_2CH_3); IR (thin film) 3020, 2910,

1690, 1560, 1360, 1325 cm^{-1}; mass spectrum (EI), m/e (relative intensity) 402 (M^+, 11), 373 (4), 224 (100) 179 (63), 167 (37), 149 (84), 133 (85); exact mass calcd for $C_{20}H_{22}N_2O_7$ 402.1427, found 402.1436.

Attempted Catalytic Reduction of 29. A mixture containing 30 mg (0.075 mol) of **29**, Lindlar's catalyst (10 mg of 5% Pd/$CaCO_3$/$Pb(OAc)_2$), and toluene (5 mL) was hydrogenated at room temperature and atmospheric pressure for 7 h. Catalyst was removed by centrifugation and the solvent evaporated to leave a residue which was purified by preparative thin-layer chromatography (silica gel; chloroform) to give 26 mg (87%) of a colorless syrup identified as ethyl 1-(2-nitro-4-methyl-3,5-dimethoxybenzoyl)-4-propylpyrrole-2-carboxylate (**30**) by its spectroscopic properties: ^1H NMR ($CDCl_3$) δ 7.1–6.8 (m, 3, arom and pyrrole ring H), 4.09 (q, J = 7 Hz, 2, CH_3CH_2), 3.87 and 3.82 (s, each 3 H, OCH_3), 2.40 (m, 2 H, CH_2), 2.22 (s, 3, CH_3), 1.60 (m, 2, CH_2), 1.34 (t, 3 H), 1.18 (t, 3, CH_3); IR (thin film) 3010, 2950, 1690, 1560, 1530, 1390, 1325 cm^{-1}; mass spectrum (EI), m/e (relative intensity) 404 (M^+, 3), 386 (4), 375 (13), 357 (15), 224 (100), 152 (37); exact mass calcd for $C_{20}H_{24}N_2O_7$ 404.1583, found 404.1591.

Ethyl 1-(2-Amino-4-methyl-3,5-dimethoxybenzoyl)-(*E*)-4-(1-propenyl)pyrrole-2-carboxylate (31). A solution of ethyl 1-(2-nitro-4-methyl-3,5-dimethoxybenzoyl)-(*E*)-4-propenylpyrrole-2-carboxylate (**29**, 0.9 g, 2.24 mmol), triirondodecacarbonyl (1.3 g of 95% $Fe_3(CO)_{12}$ containing 5% methanol, 1.1 equiv), and dry methanol (0.5 mL) in dry benzene (25 mL) was stirred under reflux in an atmosphere of nitrogen for 1.7 h. The reaction mixture was filtered through Celite and the green solution was evaporated under reduced pressure to a residue which was chromatographed on a silica gel column (90 g of 70–230 mesh, chloroform). The material obtained was purified further by preparative thin-layer chromatography (silica gel plates, 2-mm thickness, chloroform) and the bright yellow bands were isolated to afford 252 mg (30%) of the pure amine **31** as a yellow syrup: ^1H NMR ($CDCl_3$) δ 7.01 (m, 2, pyrrole ring H), 6.32 (s, 1, arom), 6.2 (d, 1, J = 16 Hz, vinyl H), 5.9 (dq, 1, vinyl H), 5.7 (br s, 2, NH_2), 4.04 (q, J = 7 Hz, 2, OCH_2), 3.68 and 3.51 (s, each 3, OCH_3), 2.12 (s, 3, CH_3), 1.76 (d, J = 6 Hz, 3, CH_3), 1.10 (t, J = 7 Hz, 3, CH_3CH_2); IR (thin film) 3495, 3380, 3020, 2960, 1690, 1675, 1585, 1560, 1465, 1400, 1380 cm^{-1}; mass spectrum (EI), m/e (relative intensity) 372 (M^+, 24), 326 (2), 299 (21), 225 (5), 210 (5), 194 (100), 179 (11), 133 (21); exact mass calcd for $C_{20}H_{24}N_2O_5$ 372.1685, found 372.1689.

7,9-Di-*O*-methyl-11-oxosibiromycinone (8). A mixture of 218 mg (0.586 mmol) of ethyl 1-(2-amino-4-methyl-3,5-dimethoxybenzoyl)-(*E*)-4-propenylpyrrole-2-carboxylate (**31**) and *p*-toluenesulfonic acid (25 mg) in dry toluene (18 mL) was stirred under reflux for 40 min. Chloroform (45 mL) was added and the soltuion was washed with sodium bicarbonate solution, water, and brine and then dried (Na_2SO_4). Evaporation of the solvent under reduced pressure afforded 120 mg (63%) of the crystalline benzodiazepine **8**, mp 177–182 °C, which could be recrystallized from dichloromethane–hexane, mp 188–191 °C. The analytical sample was obtained by preparative thin-layer chromatography (silica gel, chloroform) followed by crystallization from petroleum ether (bp 30–60 °C)–dichloromethane: mp 193–195 °C; ^1H NMR ($CDCl_3$) δ 8.70 (br, s, 1, NH), 7.96 (br s, 1, pyrrole ring H), 7.64 (br s, 2, pyrrole ring H and arom H), 6.23 (m, 2, vinyl H), 3.90 and 3.81 (s, each 3, OCH_3), 2.26 (s, 3, CH_3), 1.87 (d, J = 6 Hz, 3, CH_3); IR (KBr) 3350, 3220, 1665, 1640, 1615, 1475, 1460, 1315 cm^{-1}; mass spectrum (EI), m/e (relative intensity) 326 (M^+, 100).

Anal. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.24; H, 5.56; N, 8.58. Found: C, 66.01; H, 5.62; N, 8.49.

Synthesis of 5,11-Dioxo-10,11-dihydro-5*H*-pyrrolo[2,1-*c*](1,4)benzodiazepine (32). The sulfinamide anhydride of anthranilic acid was prepared by refluxing the acid (1.1 g, 8 mmol) with thionyl chloride (2.9 mL, 5 equiv) for 2.5 h. Solvent and excess thionyl chloride were removed under reduced pressure and the yellow syrup was dried under vacuum for ca. 30 min. The sodium salt of ethyl pyrrole-2-carboxylate was prepared from the pyrrole (1.0 g, 0.9 equiv based on anthranilic acid) and sodium hydride (0.62 g of a 55% dispersion in oil; washed with dry hexane) in dry THF. The solution was stirred for 30 min at room temperature and then added dropwise to a solution of the sulfinamide anhydride in dry THF (10 mL). The reaction mixture was stirred overnight and then partitioned between water and ether. The ether was washed with water, saturated sodium bicarbonate solution, and then saturated sodium chloride solution to leave a yellow solution which was dried over sodium sulfate. Solvent was evaporated under reduced pressure to leave an amber syrup which was taken up in dry toluene (25 mL) and refluxed for 3 h with *p*-toluenesulfonic acid (35 mg). The reaction mixture was cooled to room temperature and diluted with chloroform. Crystals deposited and were collected to afford 0.38 g (25%) of the crude benzodiazepine which was crystallized from ethyl acetate. The analytical sample was prepared by preparative thin-layer chromatography (silica gel; 2% methanol–chloroform) followed by crystallization from ethyl acetate to give needles: mp 230–231 °C; ^1H NMR (Me_2SO-d_6) δ 8.30 (dd, 1, H-6), 8.05 (m, 1, H-9), 7.70 (m, 1, H-7), 7.49 (m, 1, H-3), 7.42 (m, 1, H-1), 7.25 (m, 1, H-8), 6.67 (m, 1, H-2); IR (KBr) 3500, 3400, 3160, 3020, 1655, 1622, 1552, 1435, 1385 cm^{-1}; mass spectrum (EI), m/e (relative intensity) 212 (100), 184 (48), 170 (32), 119 (74).

Anal. Calcd for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.68; H, 3.90; N, 13.14.

Reaction of 32 with Lithium Aluminum Hydride. To a solution of 53 mg (0.25 mmol) of **32** in 5 mL of dry tetrahydrofuran at 0 °C was added 10 mg (0.26 mmol) of $LiAlH_4$. The reaction mixture was allowed to warm to room temperature and another 10-mg portion of $LiAlH_4$ added. After the mixture was stirred for a further 40 min, saturated ammonium chloride was added. The solution was decanted from insoluble salts and evaporated to a residue which was extracted with ether. The pale yellow ethereal solution was dried (Na_2SO_4) and evaporated under reduced pressure to afford 45 mg (84%) of *N*-(*o*-formylbenzene)-pyrrole-2-carboxamide, mp 149–153 °C. Purification by preparative thin-layer chromatography on silica gel (ethyl acetate) and crystallization from hexane–chloroform gave needles: mp 163–166 °C; ^1H NMR (acetone-d_6) δ 10.05 (s, 1 H, CHO), 8.80, 7.89, 7.65, 7.26, 7.10, 6.92, 6.25 (each 1 H); IR (KBr) 3260, 1650, 1595, 1568, 1535, 1520, 1436, 1310 cm^{-1}; mass spectrum (EI), m/e (relative intensity) 214 (M^+, 69), 197 (35), 121 (42), 93 (100).

Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.70; N, 13.07. Found: C, 67.08; H, 4.76; N, 13.04.

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Registry No. **8**, 76447-12-6; **9**, 28026-96-2; **10**, 7126-57-0; **11**, 99-10-5; **11** methyl ester, 2150-44-9; **12**, 16849-78-8; **13**, 76447-13-7; **15**, 76447-14-8; **17**, 76447-15-9; **18**, 60441-79-4; **19**, 76447-16-0; **20**, 76447-17-1; **21**, 76447-18-2; **22**, 76447-19-3; **22** acid chloride, 76447-20-6; **23**, 71955-96-9; **25**, 76447-21-7; **26**, 76447-22-8; **26** Na, 76447-23-9; **27**, 76447-24-0; **28**, 76447-25-1; **29**, 76447-26-2; **30**, 76447-27-3; **31**, 76447-28-4; **32**, 76447-29-5; **34**, 76447-30-8; (*E*)-4-(1-propenyl)-pyrrole-2-methanol, 76479-85-1; anthranilic acid, 118-92-3; ethyl pyrrole-2-carboxylate sodium salt, 76447-31-9.