Synthetic Studies of the Antitumor Antibiotic Streptonigrin. 3. Synthesis of the C–D Ring of Streptonigrin by an Unsymmetrical Ullmann Reaction

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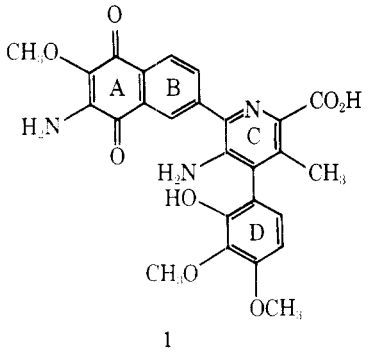
Received August 8, 1978

In our synthetic studies on the antitumor antibiotic streptonigrin **1**, we have pursued the problem by initially dividing this polyfunctional molecule into two parts: the quinolinedione A/B moiety **2** and the heterocyclic biaryl C–D moiety **3**.



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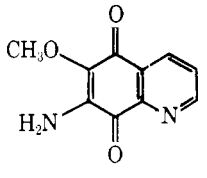

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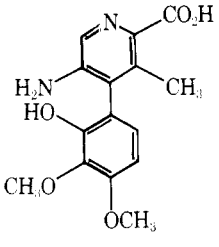

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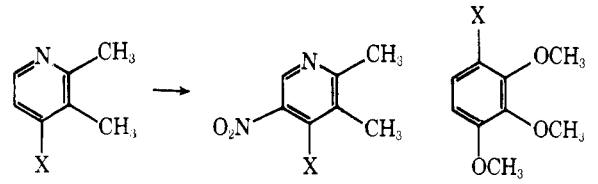
Both **2** and **3** have since been synthesized in this laboratory.[1,2]

During the development of synthetic routes to the C–D system, our attention was directed to a study on the feasibility of forming the backbone of the C–D ring system by coupling the pyridine and the phenyl rings, with appropriate substituents, to form an unsymmetrical heterobiaryl intermediate. Subsequent conversion of the substituents to the desired functional groups would then yield the C–D ring unit. This approach, if successful, should not only afford the C–D moiety of streptonigrin by a shorter synthetic route, but the information gained by this study may also be useful for the coupling of the A/B to the C–D ring unit for the eventual synthesis of this antibiotic.

Considerable attention has been devoted to the copper-promoted reactions recently reported on the Ullmann reaction.[3,4] Many examples of heterocyclic ring couplings using furan, thiophene, selenophene, pyrrole, pyridine, quinoline, and pyrimidine were reported. Although most of the reactions described deal with the synthesis of symmetrical biaryls and no examples were given wherein the ring systems had many functional groups, the Ullmann reaction was believed the method of choice for our present study.

For the synthesis of unsymmetrical biaryls by the Ullmann method, it was reported that optimum yields can best be achieved when one of the starting aryl halides is activated and the other is relatively inactive.[4] Thus the condensation reaction between 4-chloro-2,3-dimethyl-5-nitropyridine (**5b**) and 4-iodo-1,2,3-trimethoxybenzene (**6a**) was studied initially. Compound **5b** was prepared from 2,3-dimethyl-4-nitropyridine (**4a**) via **4b**, **4c**, and **5a**. The iodotrimethoxybenzene **6a**

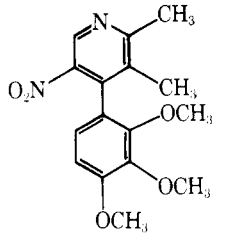


4a, X = NO_2
b, X = $OCOCH_3$
c, X = OH

5a, X = OH
b, X = Cl

6a, X = I
b, X = Br

was prepared in 90% yield from 1,2,3-trimethoxybenzene and iodine in chloroform in the presence of silver trifluoroacetate, according to a similar procedure of Janssen and Wilson for the iodination of veratrole.[5] The Ullmann reaction between **5b** and **6a** was conducted in dimethylformamide to give a 55% yield of the coupling product **7**. It was found in subsequent



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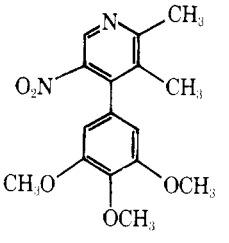

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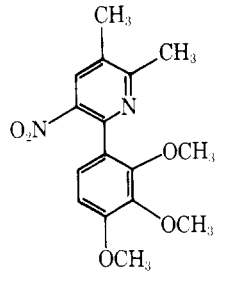

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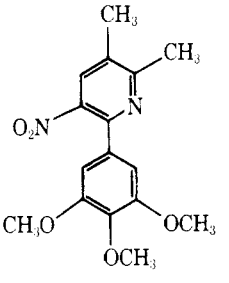

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experiments that the reaction temperature plays an important role in the yields of products: lower reaction temperature resulted in no coupling and higher temperature drastically reduced the yield. Attempted Ullmann condensation of **5b** with 4-bromo-1,2,3-trimethoxybenzene[6] (**6b**) could not be realized under similar reaction conditions.

The NMR spectra of **7**, however, raised some questions as to the validity of the assigned structure. The ortho protons on the aryl ring showed a sharp singlet. The remaining protons gave characteristic chemical shifts consistent with the proposed structure. Nevertheless, three alternative structures, **8**, **9**, and **10**, which would furnish a similar NMR pattern, could not be ruled out since Ullmann reactions are known to occasionally yield isomeric products during coupling. Consequently, three additional Ullmann reactions using 4-chloro-2,3-dimethyl-5-nitropyridine (**5b**) or 6-chloro-2,3-dimethyl-5-nitropyridine[6] in combination with 4-iodo-1,2,3-trimethoxybenzene (**6a**) or 5-iodo-1,2,3-trimethoxybenzene[7] were conducted. These Ullmann coupling products (**7–10**) were characterized. Since none of the four positional isomers was identical with any of the others, it was concluded that all of the compounds obtained were normal coupling products and that the structural assignment for compound **7** was therefore confirmed.

Oxidation of **7** with selenium dioxide yielded the corresponding carboxaldehyde **11a**. Catalytic hydrogenation of **7** afforded the 3-amino analogue **11b**. The latter compound resisted oxidation by selenium dioxide, illustrating the importance of the presence of a strong electron-withdrawing group at the para position with respect to the α-methyl group.

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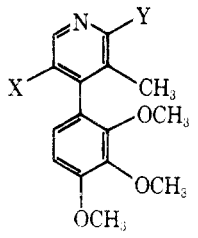
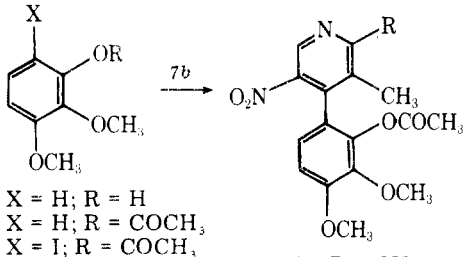


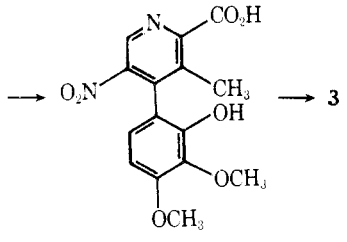
11a, X = NO_2; Y = CHO
b, X = NH_2; Y = CH_3

Based on the preceding chemical information, synthesis of the C–D ring component of streptonigrin was conducted as follows. 2-Acetoxy-3,4-dimethoxy-1-iodobenzene (**12c**), one of the required starting materials, was prepared by acetylation of 2,3-dimethoxyphenol (**12a**) followed by iodination of the intermediate **12b** with iodine monochloride in methylene chloride. Ullmann condensation of **12c** with 4-chloro-2,3-dimethyl-5-nitropyridine (**5b**) in dimethylformamide gave a 33% yield of the coupling product **13a**.



12a, X = H; R = H
b, X = H; R = $COCH_3$
c, X = I; R = $COCH_3$

13a, R = CH_3
b, R = CHO
c, R = CO_2H



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As in the case of the biaryl **7**, compound **13a** was readily oxidized to the aldehyde **13b** in 80–90% yield with selenium dioxide in dioxane. As expected, purification of the aldehyde was rather troublesome due to the presence of selenium. Subsequent oxidation and hydrolysis to the nitro acid **14** was achieved by silver oxide in basic aqueous ethanol. Direct oxidation of the α-methyl group in **13a** to a carboxylic acid function, using a variety of reagents and conditions including the use of selenium dioxide in acetic acid, was not realized. In most cases only the aldehyde **13b** was isolated. Final conversion of **14** to the desired C–D ring component **3** was brought about by catalytic reduction. The product was found to be identical in every respect with that prepared by our earlier stepwise synthesis.[2]

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 127. The NMR spectra were obtained on a Varian EM 360A using tetramethylsilane as an internal standard. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

2,3-Dimethyl-4-nitropyridine (4a). A solution of 75.6 g (0.45 mol) of 2,3-dimethyl-4-nitropyridine *N*-oxide[8] in 300 mL of CH_2Cl_2 was cooled to −15 to −20 °C by occasional contact with a dry ice–acetone bath. To the solution was slowly added, over 30 min, a solution of 44 mL (0.5 mol) of PCl_3 in 60 mL of CH_2Cl_2. After the addition was complete, the reaction was maintained at the same temperature for 15 min, then warmed to room temperature. After another 15 min, the reaction mixture was again cooled with the dry ice–acetone bath while 50 mL of H_2O was slowly added. The mixture was then neutralized by aqueous NaOH (85 g in 300 mL of H_2O). The resulting mixture was allowed to stand and the CH_2Cl_2 layer was separated and dried ($MgSO_4$). Evaporation of the organic solvent gave 65 g (95% yield) of **4a** as a low-melting, unstable solid: NMR ($CDCl_3$) δ 2.43 (s, 3 H, CH_3), 2.66 (s, 3 H, CH_3), 7.43 (d, 1 H, J = 10 Hz, aromatic H), 8.55 (d, 1 H, J = 10 Hz, aromatic H).

2,3-Dimethyl-4-hydroxy-5-nitropyridine (5a). A mixture of 45.6 g (0.3 mol) of **4a**, 49 g (0.5 mol) of anhydrous KOAc, and 300 mL of Ac_2O was refluxed for 16 h, then allowed to cool. To the dark mixture was added 400 mL of anhydrous Et_2O. The mixture was stirred for 1 h then filtered through Celite, and the filtrate was evaporated in vacuo. The oily residue was mixed with 400 mL of anhydrous Et_2O and allowed to stir for 1 h. The mixture was again filtered through Celite and the filtrate evaporated in vacuo, giving 45 g (91% yield) of crude 4-acetoxy-2,3-dimethylpyridine (**4b**) as a dark viscous oil. This was mixed with 250 mL of H_2O and heated on a steam bath for 4 h, then allowed to stand at room temperature overnight. The aqueous mixture was washed once with 150 mL of Et_2O and the aqueous solution evaporated in vacuo to give 32.6 g of 2,3-dimethyl-4-hydroxypyridine (**4c**) as a dark viscous oil. It is important that as much water be removed from the residual oil as possible prior to nitration.

The oil was dissolved in 120 mL of concentrated H_2SO_4 and the solution warmed to 60 °C. To this solution was slowly added a solution of 40 mL of 90% fuming HNO_3 in 30 mL of concentrated H_2SO_4 over 45 min while maintaining the reaction temperature at 60–65 °C. After the addition was complete, the reaction temperature was maintained at 65 °C for 2 h, then warmed to 75 °C for an additional 30 min. The mixture was then cooled and added to crushed ice. The solution was neutralized to pH 5–6 with NH_4OH while cooling, during which time a pale yellow solid was formed. The solid was collected by filtration, washed with cold water, and dried at 80–90 °C in vacuo to give 34.5 g (68% yield) of **5a**, mp 260–270 °C dec, as a pale yellow amorphous powder, which was of sufficient purity for subsequent reactions. An analytical sample was prepared by recrystallization from aqueous CH_3CN: mp 260–270 °C dec; IR (Nujol) 1650, 1600, 1525, 1350, 1325, 1250, and 1180 cm^{-1}; NMR (TFA) δ 2.54 (s, 3 H, CH_3), 2.87 (s, 3 H, CH_3), 9.35 (s, 1 H, aromatic H). Anal. Calcd for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 49.60; H, 4.80; N, 16.66.

4-Chloro-2,3-dimethyl-5-nitropyridine (5b). To 85 mL of $POCl_3$ was added 26.8 g (0.16 mol) of **5a**. After a mild exothermic reaction had subsided and the solid had dissolved, 33.3 g (0.16 mol) of PCl_5 was added and the resulting solution refluxed for 2 h. After standing at room temperature overnight, the dark solution was cautiously poured onto crushed ice with vigorous stirring. The resulting icy mixture was neutralized with 28% NH_4OH to pH 5 and then extracted with Et_2O (3 × 150 mL). The Et_2O extract was washed with saturated NaCl solution, dried ($MgSO_4$), and evaporated. The solid residue was dissolved in Et_2O–C_6H_{14} (1:1) and treated with dry activated charcoal. Recrystallization from Et_2O–C_6H_{14} gave 19.7 g (66% yield) of **5b** as pale yellow needles: mp 77–78 °C; IR (Nujol) 1565, 1540 and 1520 cm^{-1}; NMR ($CDCl_3$) δ 2.47 (s, 3 H, CH_3), 2.66 (s, 3 H, CH_3), and 8.77 (s, 1 H, aromatic H). Anal. Calcd for $C_7H_7ClN_2O_2$: C, 45.06; H, 3.78; N, 15.01. Found: C, 45.05; H, 3.92; N, 15.07.

2,3-Dimethyl-5-nitro-4-[(2,3,4-trimethoxy)phenyl]pyridine (7). A mixture of 7.5 g (0.04 mol) of the chloronitropyridine **5b**, 14.7 g (0.05 mol) of the iodobenzene **6a**, and 15.9 g (0.25 g-atom) of electrolytic Cu dust in 30 mL of $HCONMe_2$ was heated at 129 ± 2 °C under N_2 in an oil bath. The reaction was monitored by TLC. After 3 h, the mixture was cooled, diluted with 100 mL of CH_2Cl_2, and filtered through Celite. The filtrate was diluted with 400 mL of Et_2O and once again filtered to remove a small amount of solid material. The filtrate was then washed well with H_2O, dried, and evaporated. Column chromatography of the residue on silica gel with stepwise petroleum ether–Et_2O elution, followed by recrystallization from CH_2Cl_2–Et_2O, gave 7.0 g (55% yield) of the Ullmann product **7** as yellow prisms: mp 83–85 °C; IR (Nujol) 1605, 1550, 1530, 1505, 1425, and 1360 cm^{-1}; NMR ($CDCl_3$) δ 2.13 (s, 3 H, CH_3), 2.65 (s, 3 H, CH_3), 3.73 (s, 3 H, OCH_3), 3.92 (s, 6 H, OCH_3), 6.75 (s, 2 H, aromatic H), and 8.88 (s, 1 H, pyridine aromatic H). Anal. Calcd for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 59.99; H, 5.84; N, 8.96.

2,3-Dimethyl-5-nitro-4[(3,4,5-trimethoxy)phenyl]pyridine (8). A mixture of 1.4 g (0.0075 mol) of 4-chloro-2,3-dimethyl-5-nitropyridine (**5b**), 4.4 g (0.015 mol) of 5-iodo-1,2,3-trimethoxybenzene,[7] and 4 g of Cu dust in 20 mL of $HCONMe_2$ was heated at mild reflux, 153–155 °C, for 4 h. The workup was analogous to that for the preparation of the aforementioned Ullmann product **7**. There was obtained 0.6 g (25% yield) of **8** as yellow prisms: mp 111–112 °C; IR (Nujol) 1590, 1550, 1515, 1420, and 1360 cm^{-1}; NMR ($CDCl_3$) δ 2.17

(s, 3 H, CH_3), 2.66 (s, 3 H, CH_3), 3.85 (s, 3 H, OCH_3), 3.92 (s, 6 H, OCH_3), 6.42 (s, 2 H, aromatic H), and 8.42–9.09 (broad, 1 H, pyridine aromatic H). Anal. Calcd for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.77; H, 5.86; N, 8.79.

5,6-Dimethyl-3-nitro-2-[(2,3,4-trimethoxy)phenyl]pyridine (9). This compound was prepared in a manner similar to that used for the preceding compound (reaction temperature 153–155 °C, 1 h) from 1 g of 6-chloro-2,3-dimethyl-5-nitropyridine,[6] 3.2 g of 4-iodo-1,2,3-trimethoxybenzene, and 3.2 g of Cu: 0.2 g (11%) yield; mp 109–111 °C; IR (Nujol) 1600, 1580, 1560, 1515, 1490, 1410, and 1340 cm^{-1}; NMR ($CDCl_3$) δ 2.36 (s, 3 H, CH_3), 2.58 (s, 3 H, CH_3), 3.69 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 6.81 (d, 1 H, J = 9 Hz, aromatic H), 7.34 (d, 1 H, J = 9 Hz, aromatic H), and 8.00 (s, 1 H, pyridine aromatic H). Anal. Calcd for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.02; H, 5.70; N, 8.99.

5,6-Dimethyl-3-nitro-2-[(3,4,5-trimethoxy)phenyl]pyridine (10). This compound was prepared in a manner similar to that used for the preparation of the preceding compound from 1.3 g of 6-chloro-2,3-dimethyl-5-nitropyridine, 2.1 g of 5-iodo-1,2,3-trimethoxybenzene, and 3.2 g of Cu: 0.3 g (13%) yield; mp 133–135 °C; IR (Nujol) 1590, 1565, 1525, and 1335 cm^{-1}; NMR ($CDCl_3$) δ 2.39 (s, 3 H, CH_3), 2.62 (s, 3 H, CH_3), 3.87 (s, 9 H, OCH_3), 6.77 (s, 2 H, aromatic H), and 7.86 (s, 1 H, pyridine aromatic H). Anal. Calcd for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.20; H, 5.67; N, 8.76.

5-Amino-2,3-dimethyl-4-[(2,3,4-trimethoxy)phenyl]pyridine (11b). A solution of 4.2 g (0.013 mol) of the nitropyridine **7** in CH_3OH was hydrogenated in a Parr hydrogenator at 3.5 kg/cm^2 in the presence of 10% Pd/C. After H_2 uptake ceased, the mixture was filtered and the filtrate evaporated in vacuo. Trituration with Et_2O gave 2.7 g (71% yield) of the amine **11b** as a white granular solid, mp 143–145 °C. Recrystallization from CH_2Cl_2–Et_2O gave an analytical sample: mp 145–147 °C; IR (Nujol) 3500, 3330, 3200, 1585, 1540, 1490, 1310, 1280, 1275, 1260, 1200, 1165, 1135, and 1085 cm^{-1}; NMR ($CDCl_3$) δ 1.93 (s, 3 H, CH_3), 2.39 (s, 3 H, CH_3), 3.30 (s, 2 H, NH_2), 3.58 (s, 3 H, OCH_3), 3.87 (s, 6 H, OCH_3), 6.72 (s, 2 H, aromatic H), and 7.90 (s, 1 H, pyridine aromatic H). Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.82; H, 6.76, N, 9.69.

2-Acetoxy-3,4-dimethoxy-1-iodobenzene (12c). A solution of 15.4 g (0.1 mol) of 2,3-dimethoxyphenol (**12a**) in 75 mL of Ac_2O and 15 mL of pyridine was stirred at room temperature for 5 h. The majority of the solvent was removed in vacuo and the residue dissolved in 150 mL of Et_2O. To the solution was added 150 mL of H_2O and the mixture was stirred overnight. The Et_2O layer was then separated and washed twice with aqueous Na_2CO_3, twice with 1 N HCl, and finally with H_2O. After drying ($MgSO_4$) and evaporation of the solvent there was obtained 19.3 g (98% yield) of the crude acetate **12b.** This was dissolved in 100 mL of CH_2Cl_2 and the solution was cooled in an ice bath. To the stirred solution was added, over a period of 30 min, a 1:1 mixture of ICl (ca. 60–75%) and CH_2Cl_2 while maintaining the reaction temperature at 5 °C. After the addition was complete, the reaction mixture was stirred at 5 °C for another 30 min. The reaction was monitored by removing an aliquot from the mixture, working up, and examining with NMR. If starting material was still present, an appropriate amount of ICl was added to the reaction mixture. When no starting material was detected, 50 mL of CH_2Cl_2 was added and the resulting dark solution was washed thoroughly with an aqueous $Na_2S_2O_3$ solution until the dark, organic layer was clear. It was then washed with water, dried, and evaporated in vacuo. The residue was recrystallized from Et_2O–C_6H_{14} to give 19.5 g (61% yield) of **12c** as white prisms: mp 70–71 °C; IR (Nujol) 1755, 1620, and 1575 cm^{-1}; NMR ($CDCl_3$) δ 2.35 (s, 3 H, $COCH_3$), 3.83 (s, 6 H, OCH_3), 6.60 (d, 1 H, J = 9 Hz, aromatic H), 7.44 (s, 1 H, J = 9 Hz, aromatic H). Anal. Calcd for $C_{10}H_{11}IO_4$: C, 37.29; H, 3.44. Found: C, 37.65, H, 3.49.

4-(2-Acetoxy-3,4-dimethoxy)phenyl-2,3-dimethyl-5-nitropyridine (13a). A mixture of 7.5 g (0.04 mol) of 4-chloro-2,3-dimethyl-5-nitropyridine (**5b**), 15.6 g (0.049 mol) of 2-acetoxy-3,4-dimethoxy-1-iodobenzene (**12c**), and 19.1 g (0.3 g-atom) of electrolytic Cu dust in 50 mL of $HCONMe_2$ was heated under N_2 at 140 ± 1 °C in an oil bath. The reaction was monitored by TLC. After 90 min, no starting chloronitropyridine was present. Workup of this compound was analogous to those reported previously to give 4.6 g (33% yield) of **13a** as yellow prisms: mp 141–143 °C; IR (Nujol) 1775, 1610, 1585, 1540, 1525, and 1515 cm^{-1}; NMR ($CDCl_3$) δ 2.01 (s, 3 H, $COCH_3$), 2.11 (s, 3 H, CH_3), 2.65 (s, 3 H, CH_3), 3.87 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 6.83 (d, 1 H, J = 9 Hz, aromatic H), 6.97 (d, 1 H, J = 9 Hz, aromatic H), and 8.89 (s, 1 H, pyridine aromatic H). Anal. Calcd for $C_{17}H_{18}N_2O_6$: C, 58.95; H, 5.24; N, 8.09. Found: C, 58.99; H, 5.20; N, 8.05.

4-(2-Acetoxy-3,4-dimethoxy)phenyl-3-methyl-5-nitro-2-pyridinecarboxaldehyde (13b). A mixture of 4.0 g (0.012 mol) of the nitropyridine **13a** and 1.7 g (0.015 mol) of SeO_2 in 75 mL of dioxane was refluxed for 3 h. Total consumption of the starting material was indicated by TLC. The mixture was cooled and filtered through Celite, using a small amount of CH_2Cl_2 for washing. The combined filtrate and wash solution was evaporated in vacuo to yield a yellow-orange oil heavily contaminated with Se. The residual oil was dissolved in 75 mL of 1:1 CH_2Cl_2–Et_2O and allowed to stand at room temperature for 3 days at which time more Se separated from the solution. The mixture was filtered and evaporated in vacuo. The residue was chromatographed on silica gel using petroleum ether–Et_2O stepwise elution. Fractions containing the aldehyde were combined and evaporated and the residue was recrystallized from CH_2Cl_2–Et_2O to give 3.0 g (72% yield) of the desired aldehyde **13b** as yellow prisms: mp 117–118 °C; IR (Nujol) 1780, 1720, 1615, 1585, 1535, and 1505 cm^{-1}; NMR ($CDCl_3$) δ 2.02 (s, 3 H, OCH_3), 2.47 (s, 3 H, CH_3), 3.86 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 6.84 (d, 1 H, J = 9 Hz, aromatic H), 7.02 (d, 1 H, J = 9 Hz, aromatic H), 9.03 (s, 1 H, pyridine aromatic H), and 10.25 (s, 1 H, CHO). Anal. Calcd for $C_{17}H_{16}N_2O_7$: C, 56.67. H, 4.48; N, 7.78. Found: C, 56.68; H, 4.66; N, 7.71.

4-(3,4-Dimethoxy-2-hydroxy)phenyl-3-methyl-5-nitro-2-pyridinecarboxylic Acid (14). To a freshly prepared cold mixture of silver oxide in water [prepared by combining a solution of 1.7 g (0.01 mol) of $AgNO_3$ in 10 mL of H_2O and a solution of 0.8 g (0.02 mol) of NaOH in 10 mL of H_2O] was slowly added, over 5 min, a solution of 1.8 g (0.005 mol) of the aldehyde **13b** in 20 mL of EtOH. The temperature during the addition was maintained below 10 °C. After the addition was complete, the reaction mixture was kept in the ice bath for 20 min, then allowed to warm to room temperature. It was filtered and a small amount of H_2O was used to wash the filter cake. To the combined filtrate and washings (containing **13c**) was added 2 g (0.05 mol) of NaOH and the solution was warmed at 40 °C for 2 h. It was then neutralized with dilute HCl and evaporated to dryness. The residue was chromatographed on silica gel with stepwise CH_2Cl_2–MeOH elution to give 1 g (58% yield) of the acid **14** as a pale yellow powder, mp 230–236 °C dec, upon evaporation of the eluent: IR (Nujol) 3500, 3400, 1600, 1590, 1515, 1335, 1280, 1185, 1115, 1085, and 995 cm^{-1}. The product was used for the preparation of the target compound without further purification.

5-Amino-4-(3,4-dimethoxy-2-hydroxy)phenyl-3-methyl-2-pyridinecarboxylic Acid (3). A solution of 0.5 g of the hydroxynitro acid **14** in 40 mL of MeOH was hydrogenated in a Parr bomb at 3.5 kg/cm^2 of H_2 in the presence of 5% Pd/C. After 3 h, the mixture was filtered and the filtrate evaporated in vacuo to dryness. The residue was recrystallized from H_2O to give 0.1 g (22% yield) of an off-white solid, mp 213–214 °C dec. This product was found to be identical in every respect with that of an authentic sample of the C–D ring component of streptonigrin prepared in this laboratory by another synthetic route.[2]

Acknowledgment. This investigation was supported by Contract No. N01-CM-33743 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare. The authors thank Dr. Harry B. Wood, Jr., and Mr. Robert B. Ing of the National Cancer Institute and Professor A. I. Meyers of Colorado State University for their interest, and Mrs. Margaret L. Rounds for performing instrumental measurements.

Registry No.—**3,** 61948-43-4; **4a,** 68707-69-7; **4b,** 68707-70-0; **4c,** 68707-71-1; **5a,** 68707-72-2; **5b,** 68707-73-3; **6a,** 25245-37-8; **7,** 68707-74-4; **8,** 68707-75-5; **9,** 68707-76-6; **10,** 68707-77-7; **11b,** 68707-78-8; **12a,** 5150-42-5; **12b,** 27257-08-5; **12c,** 68707-79-9; **13a,** 68707-80-2; **13b,** 68707-81-3; **14,** 68707-82-4; 2,3-dimethyl-4-nitropyridine *N*-oxide, 37699-43-7; 5-iodo-1,2,3-trimethoxybenzene, 25245-29-8; 6-chloro-2,3-dimethyl-5-nitropyridine, 65213-96-9.

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