A Diels–Alder Approach to the Pyridine C Ring of Streptonigrin

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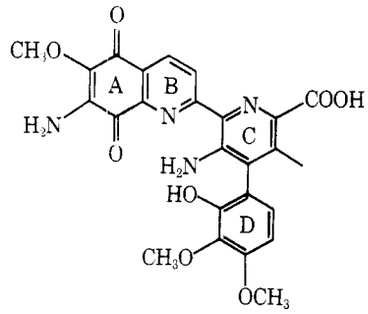
A model synthetic approach to synthesis of the pyridine C ring of the antitumor agent and antibiotic streptonigrin (1) is described. A hetero-Diels–Alder reaction is used as the method of ring construction. Studies of the reaction of dienophile **6** with dienes **13–16** and **18** are described in detail, particularly in regard to regioselectivity. A mechanistic model is proposed to rationalize the results. Adduct **27** has been converted to an acetylpyridine **42**, which possesses four of the five substituents present in the desired streptonigrin synthon **3**.

Streptonigrin (**1**) is a tetracyclic antitumor antibiotic produced by *Streptomyces flocculus*.[2] Considerable work has appeared describing approaches to the synthesis of streptonigrin and of streptonigrin analogues.[3-7] Progress has also been made in elucidating the mechanism of action of **1** as an antitumor agent.[8]



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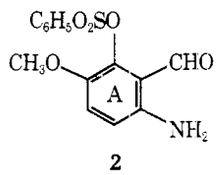
We have recently been engaged in studies directed toward the total synthesis of this challenging molecule. Our projected approach involves coupling aminoaldehyde **2** with pentasubstituted acetylpyridine **3** in a Friedlander condensation to give tetracyclic quinoline **4**. Elaboration of the A-ring



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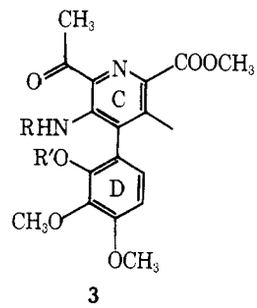

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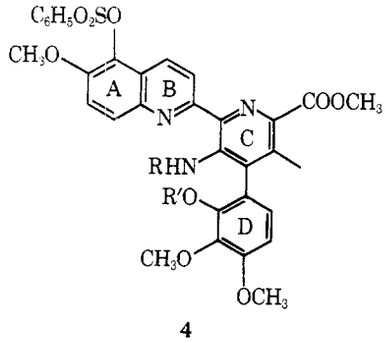

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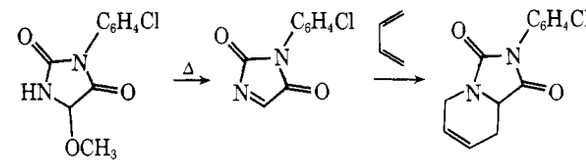
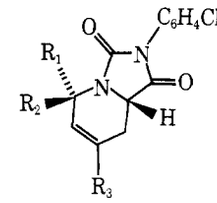
functionality and removal of the protecting groups would lead to streptonigrin (**1**). We have tested the final steps of this synthetic strategy and reported[7] synthesis of a model streptonigrin quinolinequinone AB-ring system. In this and the following paper[9] is described the synthesis of model CD-ring pyridines related to **3** using a hetero-Diels–Alder reaction to construct the C ring.

It has been reported [10a] that 1-(*p*-chlorophenyl)-2,5-imidazolidinedione (**6**), which can be formed in situ by elimination of methanol from readily available 3-(*p*-chlorophenyl)-5-methoxyhydantoin (**5**),[11] undergoes Diels–Alder reactions with a variety of simple dienes either thermally or under Lewis acid catalysis to produce adducts such as **7**. Al-

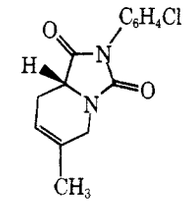


5 **6** **7**

though the stereochemistry of this reaction has been studied,[10] relatively little was known at the outset of our work about the orientational preferences of this cycloaddition when using unsymmetrically substituted dienes. It was known that thermal condensation of **6** with isoprene gives about a 1:1 mixture of the orientational isomers **8** and **11**. However,



8, $R_1 = R_2 = H$; $R_3 = CH_3$
9, $R_2 = R_3 = H$; $R_1 = CH_3$
10, $R_1 = R_2 = R_3 = CH_3$



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thermal condensation of **6** with *trans*-piperylene or acid-catalyzed condensation of **6** with 1,1,3-trimethylbutadiene gives exclusively isomers **9** and **10**, respectively.[10a] We have prepared several substituted dienes of potential use in synthesis of pyridine **3** and studied the regiochemistry of their reactions with dienophile **6**.

Aldehyde **12**, which is readily prepared by aldol condensation of phenylacetaldehyde with acetaldehyde,[12] was converted to dienes **13** and **14** by treatment with propylene and ethylene Wittig reagents, respectively. Both dienes were isolated as mixtures of isomers about the disubstituted double bond. The ratio of trans to cis isomers varied depending upon the solvent used. In ether solvent the trans isomer predominated by about 2:1 whereas in THF about a 3:4 mixture of trans to cis was obtained. The overall yield of dienes was best, however, if the reaction was run in THF. No serious attempt was made to find optimum reaction conditions for synthesis of the trans isomer in this model series. Since the cis isomers do not react in the Diels–Alder step (vide infra), a procedure will have to be found in the real D-ring series to prepare

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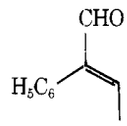

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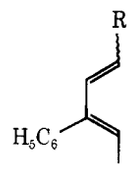
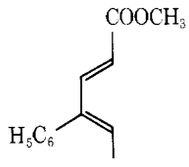
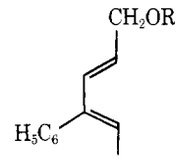


13, R = CH_2CH_3
14, R = CH_3
15, R = H



16



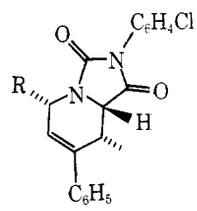
17, R = H
18, R = $COCH_3$

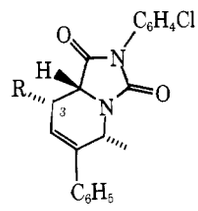
stereochemically pure trans dienes. This work is now in progress.

Treatment of aldehyde **12** with the methylene ylide produced diene **15** in 53% yield.[18] Condensation of aldehyde **12** with the anion derived from trimethylphosphonoacetate gave diene **16** as the stereochemically pure trans product in 77% yield. Reduction of **16** with lithium aluminum hydride produced alcohol **17** (87%) which could be acetylated with acetic anhydride in pyridine to provide **18** stereochemically pure in 84% yield. Dienes **13–16** and **18** were refluxed with methoxyhydantoin **5** in xylene for 3 days. The ratios of Diels–Alder orientation products were determined by NMR integration of the crude reaction mixture or by careful isolation by preparative TLC of an aliquot. The products were then isolated by column chromatography and fully characterized by complete 100-MHz NMR decoupling. Stereochemistry was also determined by NMR decoupling.

The reaction by diene **16** with dienophile **6** was quite sluggish and after 3 days a considerable amount of starting material remained. The sole product of this reaction was adduct **20** which on attempted purification by preparative TLC gave a 1:1 mixture of C-3 epimers. None of isomer **19** was detected. Diene **15** reacted with dienophile **6** somewhat faster to give primarily adduct **22** along with a small amount of **21.** Here again, starting material remained after 3 days in refluxing xylene but no serious attempt was made to push the reaction to completion.[13] The major isomers formed in the above two cases are in the undesired series of adduct (i.e., phenyl and N in a "meta" relationship).

On the other hand, dienes **13, 14,** and **18** showed a different orientational preference in the Diels–Alder reaction from dienes **15** and **16.** In these cases the desired (i.e., phenyl and N are "para") adducts **23, 25,** and **27** were the major products and lesser amounts of the undesired isomers **24, 26,** and **28**

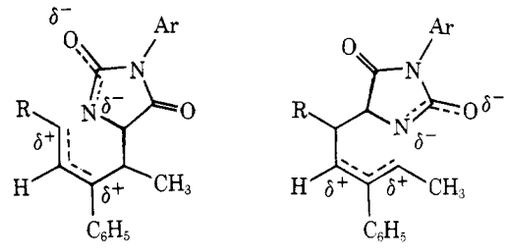




	Ratio, %	
19, R = $COOCH_3$	0:100	**20**, R = $COOCH_3$
21, R = H	8:92	**22**, R = H
23, R = CH_2OCOCH_3	55:45	**24**, R = CH_2OCOCH_3
25, R = CH_3	67:33	**26**, R = CH_3
27, R = CH_2CH_3	75:25	**28**, R = CH_2CH_3

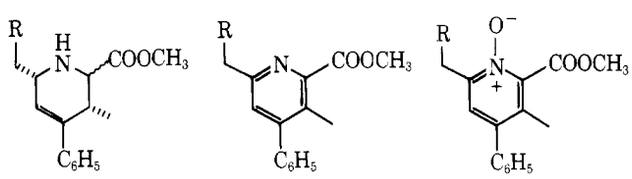
were found. In these cases also, starting material remained after 3 days.[13] However, with dienes **13** and **14,** recovered starting material was highly enriched in the cis isomers which apparently do not react with **6.** No adducts could be detected which had stereochemistry expected from cycloaddition of a *cis*-diene.

These results might be rationalized if one postulates nonsynchronous[14] bond formation in the [4 + 2] cycloaddition and that the transition state for the reaction has dipolar character.[10b] With these assumptions one might envision transition states such as **29** and **30** leading to the "desired" and "undesired" series of products, respectively. The difference between these two transition states is that in **29** a positive charge is adjacent to both R and phenyl and in **30** the charge is adjacent to both H and CH_3. As the group R becomes more capable of stabilizing a positive charge (i.e., $COOCH_3 \rightarrow AcOCH_2 \rightarrow H \rightarrow CH_3 \rightarrow CH_2CH_3$) transition state **29** gradually becomes favored over transition state **30.** It appears that the substituents at the 1 and 4 positions of the dienes (i.e., R and CH_3) have the strongest effect upon orientation. This is in accord with the greater rate-enhancing ability of 1,4 substituents vs. 2, 3 substituents on butadiene in the Diels–Alder reaction.[15,16] Thus, when using diene **19** (R = $COOCH_3$) transition state **29** is destabilized since there is a positive charge adjacent to the R group at C-1. With diene **15** (R = H) the C-4 methyl substituent has a greater effect on stabilization of **30** than the 3-phenyl substituent has on stabilizing **29.** In the cases where R = CH_2OAc, CH_3, and CH_2CH_3, the C-1 and C-4 substituents nearly cancel each other, and orientation is governed mainly by the relative stabilizing abilities of phenyl vs. H. Although these interrelationships are complex, using this model one might qualitatively predict the major orientational isomer in these hetero-Diels–Alder reactions.



29 30

Adduct **27,** on hydrolysis with barium hydroxide followed by esterification with methanolic HCl, gave amino ester **31** as a mixture of epimers. This mixture could be aromatized to the ethylpyridine **33** by treatment with either chloranil (59%) or

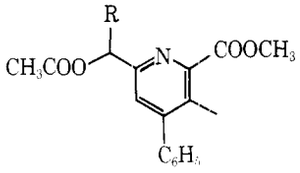


31, R = CH_3
32, R = H

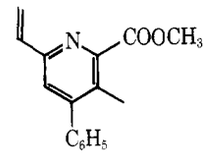
33, R = CH_3
34, R = H

35, R = CH_3
36, R = H

5% Pd/C in refluxing toluene (50%). Although the yield was slightly better using chloranil, the ease of purification of product using Pd/C made this the reagent of choice. Likewise, adduct **25** could be converted to the methylpyridine **34** via **32** by an identical sequence of reactions. Oxidation of pyridines **33** and **34** with *m*-chloroperbenzoic acid in methylene chloride (100% in both cases) gave pyridine *N*-oxides **35** and **36,** respectively. On heating with acetic anhydride, **35** smoothly rearranged to give the acetoxy compound **37** (86% yield) along with a small amount (9%) of vinylpyridine **39.**[17] Similarly, *N*-oxide **36** could be transformed to acetate **38** in 83% yield. Hydrolysis of esters **37** and **38** with potassium carbonate in anhydrous methanol gave alcohols **40** and **41,** respectively.



37, R = CH_3
38, R = H



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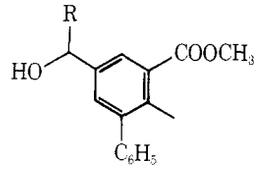
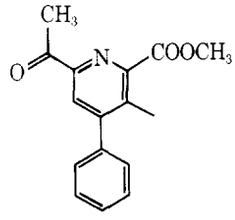


40, R = CH_3
41, R = H

Oxidation of alcohol **40** with activated manganese dioxide gave the acetylpyridine **42** in 81% yield.



42

Thus, we can readily construct a pyridine similar to **3** but still lacking a 3-amino substituent. In the following paper we describe studies dealing with introduction of this final C-ring substituent.[9]

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were measured on either a Perkin-Elmer 137 or 197 spectrometer. NMR spectra were taken at 60 MHz on Varian A-60A or Perkin-Elmer R-12 spectrometers. The 100-MHz spectra were recorded on a Varian XL-100 instrument. All spectra were taken in deuteriochloroform. The 270-MHz NMR spectra were obtained on a Bruker 270 HX instrument at Yale University on a facility supported by NIH Grant 1-PO7-PROO798. High-resolution mass spectra were obtained on a CEC 21-110B spectrometer at MIT under NIH Grant PR 00317. Elemental analyses were done by Microtech Laboratories, Skokie, Ill. E. M. Merck silica gel 60 (0.05–0.20 mm) was used for column chromatography and silica gel PF_{254} was used for both analytical and preparative TLC.

3-Phenyl-2,4-heptadiene (13). To a suspension of 25.4 g (66 mmol) of *n*-propyltriphenylphosphonium bromide in 500 mL of anhydrous ether was slowly added 33 mL (60 mmol) of 1.82 M *n*-butyllithium in hexane in 20 mL of anhydrous ether at room temperature under nitrogen. To this mixture, cooled in an ice bath, was added 8.7 g (60 mmol) of aldehyde **12**, and the mixture was stirred overnight at room temperature. The reaction mixture was filtered and the filter cake was washed well with ether. The filtrate was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was distilled in vacuo to give 4.2 g (40%) of a mixture of dienes **13:** NMR δ 1.0 (3 H, t, J = 7 Hz), 1.5–2.3 (5 H, m), 5.0–6.4 (3 H, m), 7.3 (5 H, m).

3-Phenyl-2,4-hexadiene (14). To a suspension of 50 g (135 mmol) of ethyltriphenylphosphonium bromide in 800 mL of anhydrous THF was added dropwise 60 mL (130 mmol) of 2.17 M *n*-butyllithium in hexane at room temperature under nitrogen with stirring during 1.5 h and the mixture was stirred for an additional 1 h until a negative Gilman test was observed. To this deep orange-red solution, cooled in an ice bath, was added a solution of 18 g (123 mmol) of aldehyde **12** in 20 mL of anhydrous THF and the resulting mixture was stirred for 18 h at room temperature. The mixture was filtered and the filter cake was washed well with ether. The organic filtrate was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was vacuum distilled to give 15.3 g (78%) of a mixture of dienes **14:** NMR δ 1.5 (6 H, m), 4.8–6.4 (3 H, m), 7.3 (5 H, m).

3-Phenyl-1,3-pentadiene (15). To a suspension of 12.86 g (36 mmol) of methyltriphenylphosphonium bromide in 300 mL of anhydrous ether was added 16.7 mL of 1.8 M *n*-butyllithium (30 mmol) in 10 mL of anhydrous ether at room temperature. To this solution was added dropwise 4.39 g (30 mmol) of 2-phenylcrotonaldehyde (**12**) in 20 mL of anhydrous ether, and the mixture was stirred for 2 h at room temperature. The mixture was filtered, and the organic filtrate was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was vacuum distilled to give 2.2 g (53%) of diene **15:** bp 40 °C (3 Torr); [lit.[18] bp 72–73 °C (12 Torr)]; NMR δ 1.6 (3 H, d, J = 7 Hz), 4.9 (2 H, m), 5.8 (1 H, q, J = 7 Hz), 6.7 (1 H, m), 7.3 (5 H, m).

Methyl 4-Phenyl-2,4-hexadienoate (16). A flame-dried 3-L three-necked round-bottom flask equipped with a mechanical stirrer, dropping funnel, and gas inlet tube was charged with 11 g (229 mmol) of a 50% dispersion of sodium hydride in mineral oil and 1 L of dry benzene under a nitrogen atmosphere. To this stirred mixture was added dropwise 45 g (247 mmol) of trimethyl phosphonoacetate. During the addition period the temperature was maintained at 30–35 °C. After the addition was complete, the mixture was stirred for 1 h at room temperature. To this mixture was added dropwise 30 g (205 mmol) of aldehyde **12** while maintaining the temperature at 20–25 °C. The resulting mixture was stirred overnight and diluted with benzene. The organic phase was washed with water and saturated brine, dried over anhydrous $MgSO_4$, and clarified. Evaporation of the solvent and vacuum distillation gave 32 g (77%) of ester **16:** bp 100–104 °C (0.35 Torr); IR (neat) 1720 cm^{-1}; NMR δ 1.2 (3 H, d, J = 7 Hz), 3.7 (3 H, s), 5.45 (1 H, d, J = 17 Hz), 6.3 (1 H, q, J = 7 Hz), 7.3 (5 H, m), 7.6 (1 H, d, J = 17 Hz).

1-Hydroxy-4-phenyl-2,4-hexadiene (17). To a suspension of 6 g (158 mmol) of lithium aluminum hydride in 500 mL of anhydrous ether was added 32 g (158 mmol) of ester **16** at ice-bath temperature under nitrogen. The mixture was warmed to room temperature, stirred for 4 h, and hydrolyzed by successive addition of 6 mL of water, 6 mL of 15% NaOH, and 18 mL of water. The mixture was filtered, and the collected solid was washed well with ether. The combined solution was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. Distillation under reduced pressure gave 24 g (87%) of alcohol **17:** bp 104–107 °C (0.9 Torr); NMR δ 1.6 (3 H, d, J = 7 Hz), 4.1 (2 H, d, J = 6 Hz), 5.3 (1 H, t of d, J = 17, 6 Hz), 5.7 (1 H, q, J = 7 Hz), 6.0 (1 H, d, J = 17 Hz), 7.3 (5 H, m).

1-Acetoxy-4-phenyl-2,4-hexadiene (18). To a solution of 4.05 g (23.2 mmol) of alcohol **17** in 15 mL of pyridine was added dropwise 3 mL of acetic anhydride at ice-bath temperature. The solution was warmed to room temperature, allowed to stand for 20 h, and evaporated to dryness in vacuo. Vacuum distillation gave 4.24 g (84%) of acetate **18:** IR (neat) 1725 cm^{-1}; NMR δ 1.6 (3 H, d, J = 7 Hz), 2.0 (3 H, s), 4.5 (2 H, d, J = 6 Hz), 5.1 (1 H, t of d, J = 6, 16 Hz), 5.8 (1 H, q, J = 7 Hz), 6.5 (1 H, d, J = 16 Hz), 7.3 (5 H, m).

***N*-(*p*-Chlorophenyl)-6α-ethyl-3β,6β-dihydro-3α-methyl-4-phenyl-1,2β(2*H*)-pyridinedicarboximide (27) and *N*-(*p*-Chlorophenyl)-3α-ethyl-3β,6β-dihydro-6α-methyl-5-phenyl-1,2β(2*H*)-pyridinedicarboximide (28).** A solution of 1.0 g (5.8 mmol) of dienes **13** and 1.4 g (5.8 mmol) of 3-(*p*-chlorophenyl)-5-methoxyhydantoin (**5**) in 3 mL of *p*-xylene was refluxed for 3 days. The mixture was evaporated to dryness and the residue was chromatographed on silica gel (100 g) in hexane–ethyl acetate (9:1), affording 828 mg (37%) of adduct **27** and 200 mg (9%) of adduct **28.** The initial ratio of **27** to **28** (75:25) was determined by integration of the vinyl protons in the NMR spectrum of the crude mixture. **27:** IR (film) 1740 and 1780 cm^{-1}; NMR δ 1.1 (6 H, m), 2.5 (2 H, br m), 3.4 (1 H, br m), 4.35 (1 H, d, J = 4 Hz), 4.5 (1 H, br m), 5.9 (1 H, d, J = 3 Hz), 7.5 (9 H, m). For **28** an analytical sample obtained by recrystallization from $CHCl_3$–hexane had mp 162–163 °C; IR (film) 1740 and 1780 cm^{-1}; NMR δ 1.0–1.8 (5 H, m), 1.55 (3 H, d, J = 7 Hz), 2.9 (1 H, br m), 4.23 (1 H, d, J = 3 Hz), 4.7 (1 H, q, J = 7 Hz), 6.18 (1 H, d, J = 7 Hz), 7.5 (9 H, m). Anal. Calcd for $C_{22}H_{21}N_2O_2Cl$: C, 69.38; H, 5.56; N, 7.24. Found: C, 69.32; H, 5.57; N, 7.24.

***N*-(*p*-Chlorophenyl)-3β,6β-dihydro-3α,6α-dimethyl-4-phenyl-1,2β(2*H*)-pyridinedicarboximide (25) and *N*-(*p*-Chlorophenyl)-3β,6β-dihydro-3α,6α-dimethyl-5-phenyl-1,2β(2*H*)-pyridinedicarboximide (26).** A solution of 15.3 g (97 mmol) of a mixture of dienes **14** and 25 g (104 mmol) of 3-(*p*-chlorophenyl)-5-methoxyhydantoin (**5**) in 35 mL of *p*-xylene was refluxed for 3 days. The mixture was chromatographed on a column of silica gel in hexane–ethyl acetate (9:1), affording 9.1 g (26%) of pure adduct **25** and 4 g (11%) of pure adduct **26.** The ratio of **25** to **26** (67:33) was determined by careful preparative TLC of a small reaction aliquot. For **25** a sample recrystallized from ether–hexane had mp 129–131 °C; IR (film) 1720 and 1780 cm^{-1}; NMR δ 1.1 (3 H, d, J = 7 Hz), 1.75 (3 H,

d, J = 7 Hz), 2.35 (1 H, m), 4.3 (1 H, d, J = 7 Hz), 4.9 (1 H, m), 5.9 (1 H, d, J = 3 Hz), 7.4 (9 H, m). Anal. Calcd for $C_{21}H_{19}N_2O_2Cl$: m/e 366.11351. Found: m/e 366.11589. For **26** a sample recrystallized from ethyl acetate–hexane had mp 156–158 °C; IR (film) 1720 and 1780 cm^{-1}; NMR δ 1.1 (3 H, d, J = 7 Hz), 1.6 (3 H, d, J = 7 Hz), 3.0 (1 H, m), 4.25 (1 H, d, J = 4 Hz), 4.8 (1 H, q, J = 7 Hz), 6.25 (1 H, d, J = 7 Hz), 7.4 (9 H, m). Anal. Calcd for $C_{21}H_{19}N_2O_2Cl$: C= 68.76: H, 5.26. Found: C, 68.97; H, 5.37.

***N*-(*p*-Chlorophenyl)-3,6β-dihydro-6α-methyl-5-phenyl-1,2β(2*H*)-pyridinedicarboximide (22) and *N*-(*p*-Chlorophenyl)-3βb,6-dihydro-3α-methyl-4-phenyl-1,2β(2*H*)-pyridinedicarboximde (21).** A solution of 428 mg (3.0 mmol) of diene **15** and 510 mg (2.0 mmol) of 3-(*p*-chlorophenyl)-5-methoxyhydantoin (**5**) in 3 mL of *p*-xylene was refluxed for 3 days. The mixture was chromatographed on neutral alumina in benzene to give a solid, which was recrystallized from CH_2Cl_2–hexane to afford 200 mg (22%) of adduct **22** and 20 mg (2%) of adduct **21**. For **22** an analytical sample was obtained by recrystallization from methylene chloride–hexane: mp 199–201 °C; IR (film) 1720 and 1780 cm^{-1}; NMR δ 1.2 (3 H, d, J = 7 Hz), 2.7 (2 H, m), 4.2 (1 H, m), 5.2 (1 H, m), 6.0 (1 H, m), 7.5 (9 H, m). Anal. Calcd for $C_{20}H_{17}N_2O_2Cl$: m/e 352.0977. Found: m/e 352.0972. For **21** a sample recrystallized from ethyl acetate–hexane had mp 150–153 °C; IR (film) 1720 and 1775 cm^{-1}; NMR δ 1.0 (3 H, d, J = 7 Hz), 3.4 (1 H, m), 3.8–5.0 (3 H, m), 6.0 (1 H, t, J = 3 Hz), 7.4 (9 H, m).

6α-Acetoxymethyl-*N*-(*p*-chlorophenyl)-3β,6β-dihydro-3α-methyl-4-phenyl-1,2β(2*H*)-pyridinedicarboximide (23) and 3α-Acetoxymethyl-*N*-(*p*-chlorophenyl)-3β,6β-dihydro-6α-methyl-5-phenyl-1,2β(2*H*)-pyridinedicarboximide (24). A solution of 3.04 g (14.0 mmol) of diene **18** and 4.0 g (16.6 mmol) of 3-(*p*-chlorophenyl)-5-methoxyhydantoin (**5**) in 10 mL of *p*-xylene was refluxed for 3 days. The mixture was chromatographed on a column of silica gel in hexane–ethyl acetate (8:2) to give 2 g (34%) of pure adduct **23** and 1.3 g (22%) of pure adduct **24**. The initial ratio of **23** to **24** (55:45) was determined by the integration of the vinyl protons in the NMR spectrum of the crude reaction mixture. For **23**, an analytical sample obtained by recrystallization from ether–hexane had mp 134–135 °C; IR 1720, 1740, and 1775 cm^{-1}; NMR δ 1.1 (3 H, d, J = 7 Hz), 2.0 (3 H, s), 3.45 (1 H, m), 4.35 (1 H, d, J = 4 Hz), 4.6 (1 H, m), 5.0 (2 H, m), 5.85 (1 H, d, J = 3 Hz), 7.4 (9 H, m). Anal. Calcd for $C_{23}H_{21}N_2O_4Cl{\cdot}CH_3COOH$: m/e 364.09786. Found: m/e 364.09844. **24** gave NMR δ 1.6 (3 H, d, J = 7 Hz), 2.0 (3 H, s), 3.4 (1 H, m), 4.2 (3 H, m), 4.8 (1 H, q, J = 7 Hz), 6.1 (1 H, d, J = 7 Hz), 7.4 (9 H, m).

3α-Carbomethoxy-*N*-(*p*-chlorophenyl)-3β,6β-dihydro-6α-methyl-5-phenyl-1,2β(2*H*)-pyridinedicarboximide (20). A mixture of 168 mg (0.83 mmol) of diene **16** and 260 mg (1.0 mmol) of 3-(*p*-chlorophenyl)-5-methoxyhydantoin (**5**) in 3 mL of *p*-xylene was refluxed for 3 days. The mixture was evaporated to dryness, and the residue was purified by preparative TLC using hexane–ethyl acetate (8:2) to give 50 mg (13%) of a 1:1 mixture of adducts epimeric at C-3. Adduct **20** was initially formed exclusively but was partially epimerized on preparative TLC purification. The NMR of the mixture showed the C-3 proton in **20** at δ 4.3 (1 H, d, J = 4 Hz) and in the C-3 epimer at δ 4.9 (1 H, d, J = 11 Hz).

Methyl 6-Ethyl-1,2,3,6-tetrahydro-3-methyl-4-phenylpyridinecarboxylate (31). A mixture of 2.0 g (5.25 mmol) of Diels–Alder adduct **27** and 5.0 g of $Ba(OH)_2{\cdot}8H_2O$ in 50 mL of a 1:1 mixture of *p*-dioxane and water was refluxed under nitrogen for 17 h. A stream of CO_2 was passed through the mixture until no further precipitate was formed. The mixture was filtered and the filter cake was washed well with water. The aqueous filtrate was extracted with ether to remove neutral material and evaporated to dryness. A mixture of the residue and methanolic HCl (prepared from 200 mL of methanol and 20 mL of acetyl chloride) was refluxed for 22 h. The mixture was evaporated to dryness, taken up in water basified with 5% NaOH, and extracted with CH_2Cl_2. The organic fraction was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to give 916 mg (67%) of crude amine **31** as an oil which was used for the next step without further purification: IR (film) 1735 and 3330 cm^{-1}; NMR δ 3.8 (3H, s), 5.9 (1 H, d, J = 3 Hz).

Methyl 6-Ethyl-3-methyl-4-phenyl-2-pyridinecarboxylate (33). A. A mixture of 526 mg (3.18 mmol) of amine **31** and 150 mg of 5% Pd/C in 30 mL of toluene was gently refluxed for 22 h. The reaction mixture was filtered and evaporated to dryness. The residue was chromatographed on silica gel (30 g) in CH_2Cl_2–hexane–ethyl acetate (2:8:1), affording 255 mg (50%) of ethyl pyridine **33** as an oil: IR (film) 1600 and 1730 cm^{-1}; NMR δ 1.3 (3 H, t, J = 7 Hz), 2.3 (3 H, s), 2.87 (2 H, q, J = 7 Hz), 4.0 (3 H, s), 7.25 (1 H, s), 7.4 (5 H, m). Anal. Calcd for $C_{16}H_{17}NO_2$: m/e 255.12592. Found: m/e 255.12408.

B. A solution of 55 mg (0.21 mmol) of amine **31** and 210 mg (0.85 mmol) of chloranil in 10 mL of dry benzene was stirred at room temperature for 20 h, and the reaction mixture was diluted with ethyl acetate. The organic layer was washed with 1% sodium dithionite–1% NaOH solution, saturated $NaHCO_3$, and saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was purified by preparative TLC in CH_2Cl_2–ethyl acetate (85:15) to give 32 mg (59%) of ethylpyridine **33** identical with that prepared in part A.

Methyl 6-Ethyl-3-methyl-4-phenyl-2-pyridinecarboxylate 1-Oxide (35). A solution of 400 mg (1.57 mmol) of pyridine **33** and 400 mg (1.85 mmol) of 85% *m*-chloroperbenzoic acid in 30 mL of CH_2Cl_2 was stirred at room temperature for 24 h. The solution was evaporated to dryness and the residue was taken up in ethyl acetate. The solution was washed with 5% $NaHCO_3$ and saturated brine, dried over anhydrous $MgSO_4$, and evaporated to give 440 mg (100%) of **35** which was homogeneous by TLC and NMR. An analytical sample was obtained by preparative TLC (hexane–ethyl acetate–methanol, 8:1:1): IR (film) 1740 cm^{-1}; NMR δ 1.3 (3 H, t, J = 7 Hz), 2.15 (3 H, s), 2.96 (2 H, q, J = 7 Hz), 4.03 (3 H, s), 7.15 (1 H, s), 7.4 (5 H, m). Anal. Calcd for $C_{16}H_{17}NO_3$: m/e 271.1208. Found: m/e 271.1204.

Methyl 6-(1-Acetoxyethyl)-3-methyl-4-phenyl-2-pyridinecarboxylate (37) and Methyl 3-Methyl-4-phenyl-6-vinyl-2-pyridinecarboxylate (39). A solution of 440 mg (1.62 mmol) of pyridine *N*-oxide **35** was heated in 5 mL of freshly distilled acetic anhydride at 120 °C. The solution was evaporated to dryness in vacuo and the residue was purified by preparative TLC, affording 35 mg (9%) of vinlypyridine **39** and 420 mg (86%) of acetate **37** as oils. **37:** IR (film) 1740 cm^{-1}; NMR δ 1.63 (3 H, d, J = 7 Hz), 2.14 (3 H, s), 2.38 (3 H, s), 4.03 (3 H, s), 6.05 (1 H, q, J = 7 Hz), 7.4 (6 H, m). **39:** IR (film) 1735 cm^{-1}; NMR δ 2.4 (3 H, s), 5.5, 6.2, 7.0 (1 H each, AMX), 7.5 (6 H, m).

Methyl 6-(1-Hydroxyethyl)-3-methyl-4-phenyl-2-pyridinecarboxylate (40). To a solution of 380 mg (1.21 mmol) of acetate **37** in 30 mL of anhydrous methanol cooled in an ice bath was added 35 mg of anhydrous K_2CO_3. The resulting mixture was warmed to room temperature and stirred for 2 h. The solution was diluted with ethyl acetate, washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to give 340 mg (100%) of alcohol **40** (mp 62–63 °C) as an oil which was found to be almost homogeneous by TLC. An analytical sample crystallized from ether–hexane had mp 62–63 °C: IR (film) 1730 cm^{-1}; NMR δ 1.5 (3 H, d, J = 7 Hz), 2.37 (3 H, s), 4.02 (3 H, s), 5.0 (1 H, q, J = 7 Hz), 7.4 (6 H, m). Anal. Calcd for $C_{16}H_{17}NO_2$: m/e 271.1208. Found: m/e 271.1192.

Methyl 1,2,3,6-Tetrahydro-3,6-dimethyl-4-phenyl-2-pyridinecarboxylate (32). A mixture of 1.76 g (4.8 mmol) of adduct **25** and 5 g of $Ba(OH)_2{\cdot}8H_2O$ in 50 mL of a 1:1 mixture of *p*-dioxane and water was refluxed under nitrogen for 17 h. A stream of CO_2 was passed through the mixture until no further precipitate was formed. The mixture was filtered and the filter cake was washed well with water. The filtrate was extracted with ether to remove neutral material and evaporated to dryness. A mixture of the residue and methanolic HCl (prepared from 200 mL of methanol and 20 mL of acetyl chloride) was refluxed for 45 h. The mixture was evaporated to dryness, taken up in water, basified with 5% NaOH, and extracted with CH_2Cl_2. The organic layer was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to give 900 mg (77%) of crude amine **32** as an oil which was used in the next step without purification: NMR δ 3.8 (3 H, s), 5.8 (1 H, d, J = 3 Hz).

Methyl 3,6-Dimethyl-4-phenyl-2-pyridinecarboxylate (34). A mixture of 4.29 g (17.5 mmol) of **32** and 400 mg of 5% Pd/C in 150 mL of toluene was refluxed for 24 h. The reaction mixture was filtered and evaporated to dryness. The residue was chromatographed on silica gel in hexane–ethyl acetate (9:1) to give 2.1 g (50%) of pyridine **34** as an oil: NMR δ 2.35 (3 H, s), 2.6 (3 H, s), 4.0 (3 H, s), 7.2 (1 H, s), 7.4 (5 H, m).

Methyl 3,6-Dimethyl-4-phenyl-2-pyridinecarboxylate 1-Oxide (36). A solution of 340 mg (1.4 mmol) of pyridine **34** and 400 mg (1.97 mmol) of 85% *m*-chloroperbenzoic acid in 30 mL of CH_2Cl_2 was stirred at room temperature for 16 h. The solution was evaporated to dryness and the residue was taken up in ethyl acetate. The organic layer was washed with 10% $NaHSO_3$, 2% NaOH, and saturated brine, dried over anhydrous $MgSO_4$, and evaporated to give 362 mg (100%) of *N*-oxide **36**, which was homogeneous by TLC and NMR: mp 107–108 °C; NMR δ 2.2 (3 H, s), 2.55 (3 H, s), 4.1 (3 H, s), 7.2 (1 H, s), 7.45 (5 H, m). Anal. Calcd for $C_{15}H_{15}NO_2$: m/e 257.1050. Found: m/e 257.1052.

Methyl 6-Acetoxymethyl-3-methyl-4-phenyl-2-pyridinecarboxylate (38). A solution of 1.55 g (5.83 mmol) of *N*-oxide **36** in 30 mL of acetic anhydride was heated at 120 °C for 2 h. The solution was evaporated to dryness in vacuo, and the residue was chromatographed on silica gel (30 g) in hexane–ethyl acetate (8:2) to afford 1.5

g (83%) of acetate **38** as a white solid: mp 85–87 °C; IR (film) 1740 cm^{-1}; NMR δ 2.1 (3 H, s), 2.35 (3 H, s), 4.0 (3 H, s), 5.3 (2 H, s), 7.4 (6 H, m).

Methyl 6-Hydroxymethyl-3-methyl-4-phenyl-2-pyridinecarboxylate (41). To a solution of 1.5 g (5 mmol) of acetate **38** in 50 mL of absolute methanol cooled in an ice bath was added 100 mg of anhydrous K_2CO_3. The resulting mixture was warmed to room temperature and stirred for 2 h. The mixture was evaporated to dryness and taken up in ethyl acetate. The organic phase was washed with saturated brine, dried over anhydous $MgSO_4$, and evaporated to give 1.3 g (100%) of alcohol **41** which was homogeneous by TLC: IR (film) 1730 and 3400 cm^{-1}; NMR δ 2.35 (3 H, s), 4.0 (3 H, s), 4.8 (2 H, s), 7.4 (6 H, m).

Methyl 6-Acetyl-3-methyl-4-phenyl-2-pyridinecarboxylate (42). A mixture of 30 mg (0.11 mmol) of alcohol **40** and 60 mg of activated MnO_2 in 25 mL of $CHCl_3$ was stirred at room temperature for 3 days. The mixture was filtered with the aid of Celite and evaporated to dryness. The residue was chromatographed on a small column of silica gel (5 g) in $CHCl_3$, affording 16 mg (81% based on reacted starting material) of **42** and 10 mg of recovered **40.** An analytical sample obtained by recrystallization from ether–hexane had mp 111 °C: IR (film) 1695 and 1735 cm^{-1}; NMR δ 2.43 (3 H, s), 2.76 (3 H, s), 4.04 (3 H, s), 7.4 (5 H, m), 8.03 (1 H, s). Anal. Calcd for $C_{16}H_{15}NO_2$: *m/e* 269.105. Found: *m/e* 269.105.

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Registry No.—**5,** 30454-96-7; **12,** 54075-09-1; (*E,Z*)-**13,** 64034-98-6; (*Z,Z*)-**13,** 64034-99-7; (*E,Z*)-**14,** 64035-00-3; (*Z,Z*)-**14,** 64035-01-4; **15,** 64035-02-5; **16,** 64035-03-6; **17,** 64035-04-7; **18,** 64035-05-8; **20,** 64035-06-9; 3β-**20,** 6406974-5; **21,** 64035-07-0; **22,** 64035-08-1; **23,** 64035-09-2; **24,** 64035-10-5; **25,** 64035-11-6; **26,** 64035-12-7; **27,** 64035-13-8; **28,** 64035-14-9; **31** (isomer I), 64035-15-0; **31** (isomer II), 64035-16-1; **32,** 64035-17-2; **33,** 64035-18-3; **34,** 64035-19-4; **35,** 64034-90-8; **36,** 64034-91-9; **37,** 64034-92-0; **38,** 64034-93-1; **39,** 64034-94-2; **40,** 64034-95-3; **41,** 64034-96-4; **42,** 64034-97-5; propyltriphenylphosphonium bromide, 6228-47-3; trimethyl phosphonoacetate, 5927-18-4.

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Elaboration of the Pyridine C-Ring Functionality in a Streptonigrin Precursor

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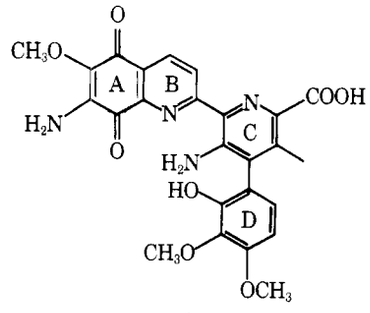
Model studies directed toward total synthesis of streptonigrin (1) are outlined. A number of attempts to introduce a 3-amino substituent into compounds **6** and **18,** prepared previously by Diels–Alder reactions, are described. A successful method for introduction of this substituent into a preformed pyridine via introduction of a functionalized carbon followed by Curtius rearrangement has been developed. Compound **52** has been prepared which contains all of the features present in the pyridine C ring of streptonigrin synthon **3.**

The antitumor agent and antibiotic streptonigrin (**1**)[2] has been the object of numerous synthetic studies in several laboratories.[3–8] Our projected synthetic strategy is based upon coupling of *o*-aminobenzaldehyde **2** with the highly substituted acetylpyridine **3** via a Friedlander condensation to give the tetracyclic quinoline **4.** Elaboration of the A-ring functionality will provide streptonigrin.[3]



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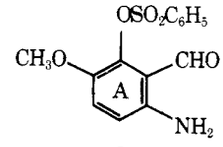

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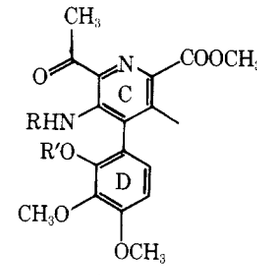

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