g (83%) of acetate **38** as a white solid: mp 85–87 °C; IR (film) 1740 $cm^{-1}$; NMR $\delta$ 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 $\delta$ 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 $\delta$ 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.

**Acknowledgment.** This work was supported by the National Science Foundation (MPS 75-01558) and by Eli Lilly and Co.

**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; 3$\beta$-**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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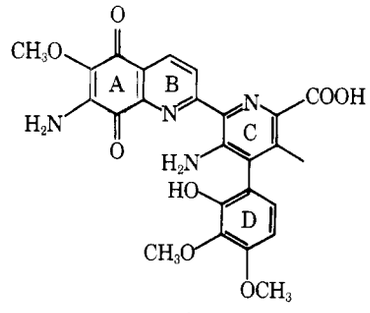
Model studies directed toward total synthesis of streptonigrin (1) are outlined. A number of attempts to introduce a 3-amino substituent into compounds **6** and **18,** prepared previously by Diels–Alder reactions, are described. A successful method for introduction of this substituent into a preformed 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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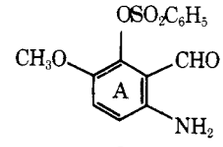
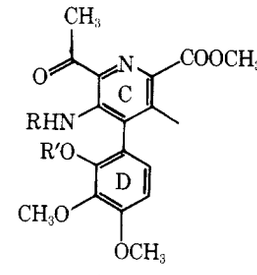



2

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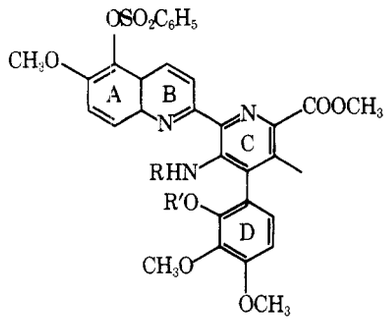

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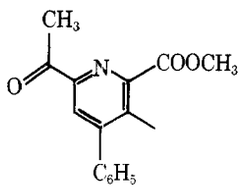
In the preceding paper were described studies directed toward synthesis of an analogue of acetylpyridine **3**. We reported preparation of pyridine **5** from compound **6**, a product



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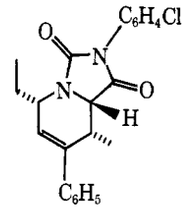
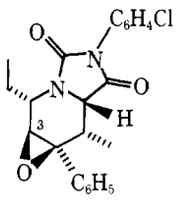


6

of a hetero-Diels–Alder reaction. Compound **5** contains four of the five substituents present in the desired pyridine **3** but lacks a 3-amino substituent. This paper describes the introduction of such functionality.

Our initial approach to the elaboration of this final C-ring functional group was directed toward introduction of a 3-nitrogen substituent at an early stage into a nonaromatic precursor such as **6**, followed by aromatization as described previously for preparation of pyridine **5**.[8] Thus, compound **6**[8] was treated with *m*-chloroperbenzoic acid in methylene chloride to give exclusively the β-epoxide **7** in 91% yield. An attempt was made to rearrange epoxide **7** to the C-3 ketone **8**, but on brief treatment with $BF_3$ etherate, epoxide **7** underwent ring contraction to afford only aldehyde **9**. Compound **9** is a single stereoisomer with an unknown configuration at



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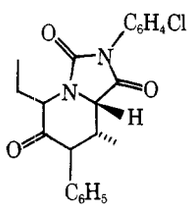

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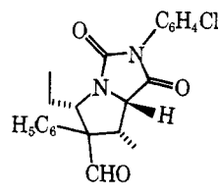
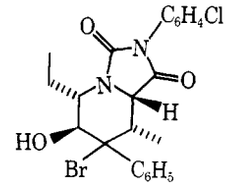


9

the quaternary carbon. Epoxide **7** could be opened cleanly to bromohydrin **10** on treatment with 48% hydrobromic acid in chloroform. However, attempts to oxidize **10** to the corresponding bromo ketone resulted only in recovery of starting material. The fact that this secondary alcohol is inert toward oxidation might be due to steric hindrance of removal of the carbinol proton from the crowded α face of the molecule.[9]

Treatment of epoxide **7** with acetic acid containing a small amount of *p*-toluenesulfonic acid, to our surprise, gave acetate **13** rather than the expected product **11**, as was evident from NMR spectroscopy. Likewise, treatment of **7** with trifluoroacetic acid gave trifluoroacetate **14** rather than **12**. The structure of **13** was also confirmed chemically: hydrolysis of trifluoroacetate **14** to diol **15**, followed by acetylation with acetic anhydride gave acetate **13**, identical with material formed by epoxide opening. Esters **11** and **12** are probably formed initially but rearrange to minimize steric crowding. In all of the above reactions single stereoisomers are formed, but the configuration of the quaternary center is unknown.[10]



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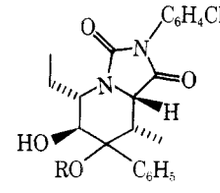
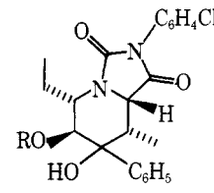


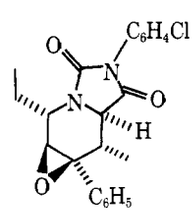
11, R = $COCH_3$
12, R = $COCF_3$



13, R = $COCH_3$
14, R = $COCF_3$
15, R = H
16, R = $SO_2CH_3$

Diol **15** was transformed to the monomesylate **16** with methanesulfonyl chloride in pyridine (75%) but all attempts to displace the mesyl group with nucleophiles such as azide, cyanide, and ammonia gave no characterizable products. Similarly, attempts were made to open epoxide **7** with the same nucleophiles, but in general only epimerization of the hydantoin occurred to give **17**.[11,12] We attribute our inability to displace a β-substituent at C-3 to steric interference of attack of a nucleophile from the α side of the molecule.

It appeared to us that the best way to overcome this steric problem would be to introduce a C-3 leaving group with an α configuration, thus requiring attack of a nitrogen nucleophile from the less hindered β face. Since all stereochemistry will ultimately be destroyed, the relative configuration of the various functional groups at this stage is presumably of no consequence. Therefore, adduct **18**, prepared as described in the previous paper,[8] was hydrolyzed with aqueous potassium carbonate to give alcohol **19**. Epimerization of the C-6 hydantoin proton also occurred under these conditions to give the thermodynamically favored stereoisomer shown in structure **19**.[11,12] Epoxidation of **19** with *m*-chloroperbenzoic acid gave the α-epoxide **20** as the major product (65%) along with a small amount of the β-epoxide **21** (13%). A syn-directing effect of a homoallylic alcohol on the stereochemistry of epoxidation has considerable precedence.[13] Epoxide configurations were established by the NMR coupling constant between the epoxide proton ($H_3$) and the adjacent proton ($H_2$) ($J_{2,3}$ = 4 Hz in **20** and $J_{2,3}$ = 0 Hz in **21** due to a 90° dihedral angle). In order to chemically confirm this stereochemical



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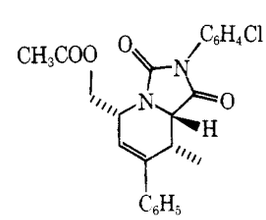

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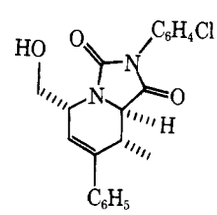

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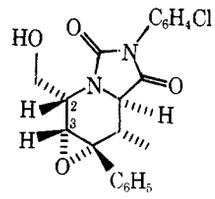

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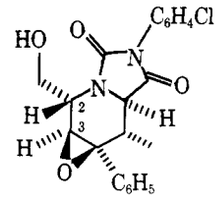

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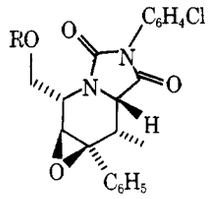
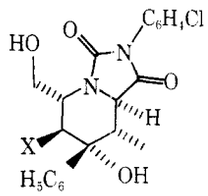
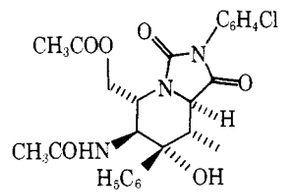


22, R = $COCH_3$
23, R = H

assignment, acetate 18 was epoxidized to give, as anticipated, exclusively the β-epoxide **22** (73%), which on hydrolysis afforded a mixture of alcohols **21** and **23**. Epoxy alcohol **21** prepared in this way was identical with material synthesized by direct epoxidation of alcohol **19**. α-Epoxide **20** could be readily opened with sodium azide using phase-transfer catalysis[14] to produce azido alcohol **24**. Reduction of **24** by catalytic hydrogenation gave amine **25** which on acetylation afforded amide **26**. Although compound **26** now has a nitrogen



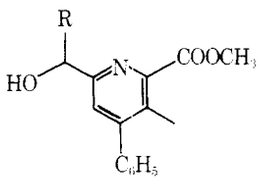
24, X = $N_3$
25, X = $NH_2$



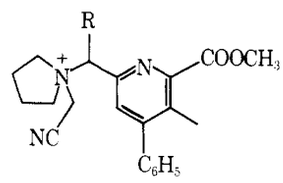
26

substituent in the desired C-3 position, we anticipated that serious problems might arise in the aromatization of this intermediate due to its high degree of functionalization. Rather than pursue this approach further at present, we have instead investigated introduction of a C-3 nitrogen substituent into a system which has already been aromatized to a pyridine. In this alternative approach our strategy was to introduce a functionalized carbon into the C-3 position of a preformed tetrasubstituted pyridine and by a suitable rearrangement (Hoffmann, Curtius, Schmidt, or Beckmann) subsequently put nitrogen into the pyridine nucleus.

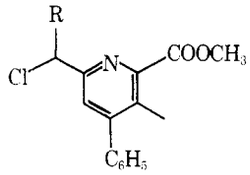
Therefore, alcohol **27**[8] was converted to the chloride **29** with thionyl chloride in pyridine (99% yield) which on warming at



27, R = H
28, R = $CH_3$

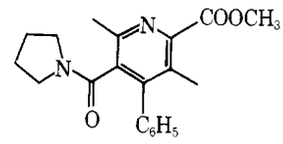


31, R = H
32, R = $CH_3$



29, R = H
30, R = $CH_3$

60 °C with *N*-cyanomethylpyrrolidine in $Me_2SO$ gave the quaternary salt **31** (93%).[15] When this salt was treated with potassium *tert*-butoxide in THF–$Me_2SO$ for several hours under nitrogen without rigorous exclusion of oxygen, the only isolable product was amide **33** (30%). We believe **33** is formed by a series of steps involving [2,3] sigmatropic rearrangement[16,17] of the ylide derived from **31** giving aminonitrile **34**, which is deprotonated to anion **36**.[18] Reaction of **36** with molecular oxygen would give peroxide **37**, which on reduction by



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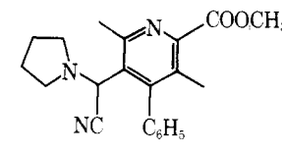

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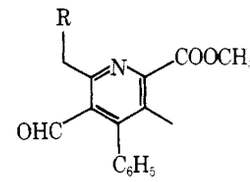
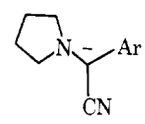


35a, R = H
35b, R = $CH_3$



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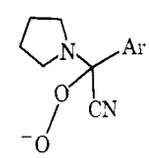

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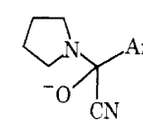
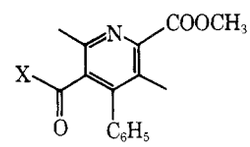


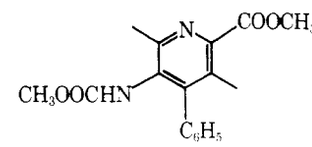
38

dimethyl sulfoxide[19] to **38** and loss of cyanide ion would give the observed amide **33**. After extensive experimentation, it was found that the initial [2,3] sigmatropic rearrangement product **34** could be isolated if salt **31** is treated with potassium *tert*-butoxide at −30 °C for 5 min in THF–HMPA–$Me_2SO$ solvent under deoxygenated[20] argon. Hydrolysis of **34** with aqueous oxalic acid gave the aldehyde **35a** (43% yield from **31**). In a similar series of experiments, alcohol **28**[8] was converted to chloride **30** and a number of unsuccessful attempts were made to prepare the quaternary salt **32** by treatment of **30** with *N*-cyanomethylpyrrolidine. We had hoped that quaternary salt **32** could be transformed to the ethylpyridine aldehyde **35b** with a side chain having the correct number of carbons for eventual conversion to an acetylpyridine. We have thus been forced to concentrate our synthetic efforts on the 2-methyl series of compounds, with the hope of future conversion of methyl to acetyl.

Aldehyde **35a** was oxidized to the carboxylic acid **39** in 92% yield with potassium permanganate in aqueous acetone at room temperature, and this acid was then transformed to the amide **40** via the corresponding acid chloride. Amide **40** cleanly underwent a Hoffmann rearrangement[5b,21,22] on treatment with bromine and sodium methoxide in methanol, producing the urethane **41** in 100% yield. Alternatively, acid **39** could be directly converted to urethane **41** by a modified Curtius rearrangement[23] on treatment with diphenylphosphoryl azide and triethylamine in refluxing benzene, followed by addition of methanol (100% yield).

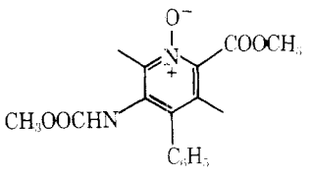


39, X = OH
40, X = $NH_2$

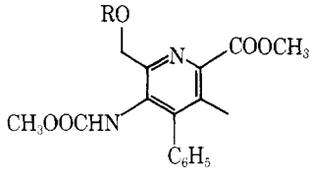


41

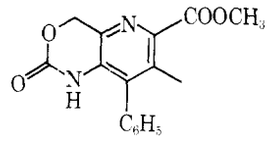
We next turned to the problem of functionalization of the 2-methyl group of **41**. Conversion of **41** into the *N*-oxide **42** was effected with *m*-chloroperbenzoic acid. Upon heating in acetic anhydride, **42** rearranged cleanly to the acetoxymethyl compound **43**.[24] Hydrolysis of **43** with potassium carbonate in methanol did not give the desired alcohol **44**, but instead afforded the cyclic urethane **45** in 100% yield.[25] Since a free 2-



**42**



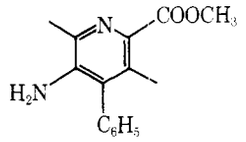
**43**, R = $COCH_3$
**44**, R = H



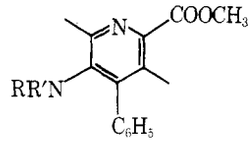
**45**

hydroxymethyl group was needed for further transformations, and since we envisioned potential future problems due to this sort of cyclization, we decided to protect the 3-amino functionality in a different manner.

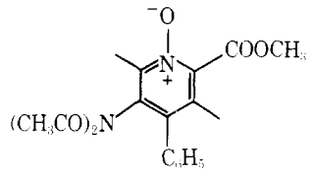
Acid **39** was transformed directly to amine **46** by the modified Curtius rearrangement using water rather than methanol.[23] This amine proved to be quite nonbasic and did not react with acetic anhydride in pyridine at room temperature. On heating at 130 °C **46** was slowly converted to the imide **48** and not into the expected amide **47**. The low nucleophilicity of amine **46** may be partly due to steric factors and partly due to delocalization of electrons on nitrogen into the carbomethoxyl group. Thus, the reactivity of **46** might be expected



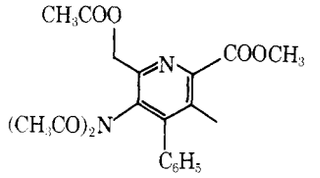
**46**



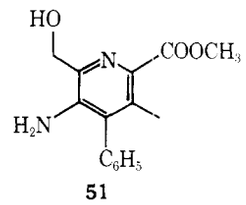
**47**, R = H; R′ = $COCH_3$
**48**, R = R′ = $COCH_3$



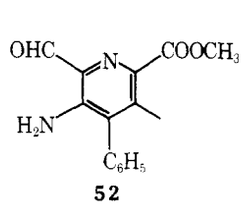
**49**



**50**



**51**



**52**

to be similar to a vinylogous urethane. On treatment with *m*-chloroperbenzoic acid, imide **48** was converted to the corresponding *N*-oxide **49**, which on heating in acetic anhydride[24] was transformed to the acetoxymethylpyridine **50**. Upon being stirred at room temperature in methanol containing anhydrous potassium carbonate, **50** was transformed into the amino alcohol **51**. The ease of removal of both *N*-acetyl groups under such mild conditions is again indicative of the low basicity of the 3-amino nitrogen in these compounds. Amino alcohol **51** was stirred at room temperature with activated manganese dioxide in chloroform[26] to afford the stable, crystalline aminoaldehyde **52**.

We are now using the methodology described in this and the preceding paper[8] for the synthesis of the required synthon **3**. This work will be reported shortly.

## 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. 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-P07-PR00798. 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.

***N*-(*p*-Chlorophenyl)-2α-ethyl-5α-methyl-6α-phenyl-7-oxa-3-azabicyclo[4.1.0]heptane-3,4-dicarboximide (7).** A solution of 240 mg (0.63 mmol) of olefin **6** and 183 mg (0.90 mmol) of 85% *m*-chloroperbenzoic acid in 10 mL of $CH_2Cl_2$ was stirred at room temperature for 25 h, and the reaction mixture was diluted with $CHCl_3$. The organic layer was washed with 5% NaOH and saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was crystallized from ether–hexane to give 228 mg (91%) of epoxide **7** as white crystals. An analytical sample prepared by recrystallization from ether–hexane had mp 169–170 °C: IR (film) 1720 and 1775 $cm^{-1}$; NMR δ 1.13 (6 H, m), 2.45 (2 H, m), 3.1 (1 H, m), 3.5 (1 H, s), 4.15 (1 H, t), 4.66 (1 H, d, $J$ = 3 Hz), 7.5 (9 H, s). Anal. Calcd for $C_{22}H_{21}N_2O_3Cl$: C, 66.58; H, 5.33; N, 7.06. Found: C, 66.75; H, 5.42; N, 7.05.

***N*-(*p*-Chlorophenyl)-5α-ethyl-3-formyl-3α-methyl-4-phenyl-1,2-pyrrolidinedicarboximide (9).** To a solution of 150 mg (0.38 mmol) of epoxide **7** in 3 mL of dry benzene was added 1 mL of boron trifluoride etherate at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ after 10 min, and the mixture was diluted with ether. The organic layer was washed with saturated brine, dried over anhydrous $Na_2SO_4$, and evaporated to dryness to give 180 mg of crude solid material. Recrystallization from $CHCl_3$–hexane gave 90 mg (60%) of aldehyde **9** as white crystals. An analytical sample obtained by recrystallization from $CH_2Cl_2$–hexane had mp 205–207 °C: IR (film) 1720 and 1770 $cm^{-1}$; NMR δ 1.35 (6 H, m), 1.6–3.0 (3 H, br m), 4.1 (1 H, m), 4.4 (1 H, d, $J$ = 11 Hz), 7.5 (9 H, m), 10.0 (1 H, br s). Anal. Calcd for $C_{22}H_{21}N_2O_3Cl$: C, 66.58; H, 5.33; N, 7.06. Found: C, 66.74; H, 5.35; N, 7.02.

**4-Bromo-*N*-(*p*-chlorophenyl)-6α-ethyl-4β-hydroxyl-3α-methyl-4-phenyl-1,2α-piperidinedicarboximide (10).** To a solution of 130 mg (0.33 mmol) of epoxide **7** in 2 mL of $CHCl_3$ was added 0.5 mL of 48% HBr at room temperature. The mixture was stirred overnight, washed with saturated $NaHCO_3$ and saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was purified by preparative TLC developing in $CHCl_3$ to afford 137 mg (88%) of bromohydrin **10** as a white foamy solid: IR (film) 1720, 1770 $cm^{-1}$; NMR δ 0.4 (3 H, d, $J$ = 7 Hz), 1.3 (3 H, t, $J$ = 7 Hz), 1.8 (1 H, d, $J$ = 11 Hz, exchangeable), 2.4 (2 H, m), 3.0 (2 H, m), 3.7 (1 H, t, $J$ = 11 Hz), 4.4 (1 H, d, $J$ = 4 Hz), 7.0 (9 H, m).

**5β-Acetoxy-*N*-(*p*-chlorophenyl)-6α-ethyl-4-hydroxy-3α-methyl-4-phenyl-1,2-piperidinecarboximide (13). A.** A solution of 108 mg (0.27 mmol) of epoxide **7** in 5 mL of acetic acid was heated at 60 °C for 6 h in the presence of a catalytic amount of *p*-TosOH, and the reaction mixture was diluted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ and saturated brine and evaporated to dryness. The residue was purified by preparative TLC in hexane–ethyl acetate (7:3) to give 60 mg (48%) of acetate **13** as white crystals. An analytical sample obtained by recrystallization from ether had mp 197–200 °C: IR (film) 1715, 1740, and 1780 $cm^{-1}$; NMR δ 0.7 (3 H, d, $J$ = 7 Hz), 1.2 (3 H, t, $J$ = 7 Hz), 1.3–2.7 (4 H, br m), 1.9 (3 H, s), 3.8 (1 H, m), 4.8 (1 H, d, $J$ = 4 Hz), 5.75 (1 H, d, $J$ = 10 Hz), 7.4 (9 H, s). Anal. Calcd for $C_{24}H_{25}N_2O_5Cl$: *m/e* 456.1450. Found: *m/e* 456.1440.

**B.** To a solution of 27 mg (0.07 mmol) of diol **15** in 1 mL of dry pyridine was added 0.1 mL of acetic anhydride. The resulting solution was stirred at room temperature for 22 h and evaporated to dryness in vacuo to afford 35 mg (100%) of acetate **14**, which was identical with material prepared in part A.

***N*-(*p*-Chlorophenyl)-6α-ethyl-5β-(trifluoroacetoxy)-4-hydroxy-3α-methyl-4-phenyl-1,2α-piperidinecarboximide (14).** To a solution of 100 mg (0.25 mmol) of epoxide **7** in 1 mL of chloroform was added 0.2 mL of trifluoroacetic acid. The solution was allowed to stand at room temperature for 22 h and diluted with ethyl acetate. The organic phase was washed with saturated $NaHCO_3$ and saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was purified by preparative TLC in hexane–ethyl acetate (8:2) to give 102 mg (80%) of trifluoroacetate **14:** IR (film) 1725 and 1795 $cm^{-1}$; NMR δ 0.8 (3 H, d, $J$ = 7 Hz), 1.3 (3 H, t, $J$ = 7 Hz), 1.8–2.9 (4 H, br m), 4.0 (1 H, br m), 4.85 (1 H, d, $J$ = 4 Hz), 5.9 (1 H, d, $J$ = 10 Hz), 7.4 (9 H, s).

***N*-(*p*-Chlorophenyl)-6α-ethyl-4,5β-dihydroxy-3α-methyl-4-phenyl-1,2α-piperidinecarboximide (15).** A solution of 65 mg (0.13 mmol) of trifluoroacetate **14** in 5 mL of methanol was stirred at room temperature for 2 h. The solution was evaporated to dryness to give 59 mg (100%) of diol **15** as white crystals: mp 175–178 °C; IR (film) 1710, 1770, and 3500 $cm^{-1}$; NMR δ 1.65 (3 H, d, $J$ = 7 Hz), 1.2 (3 H, t, $J$ = 7 Hz), 2.35 (4 H, br m), 3.55 (1 H, br m), 4.3 (1 H, br d, $J$ = 10 Hz), 4.68 (1 H, d, $J$ = 4 Hz), 7.4 (9 H, m). Anal. Calcd for $C_{22}H_{23}N_2O_4Cl$: $m/e$ 414.1345. Found: $m/e$ 414.1346.

**5β-Methanesulfonyloxy-*N*-(*p*-chlorophenyl)-6α-ethyl-4-hydroxy-3α-methyl-4-phenyl-1,2α-piperidinecarboximide (16).** A solution of 40 mg (9.096 mmol) of diol **15** and 0.05 mL of methanesulfonyl chloride in 1 mL of dry pyridine was stirred at room temperature for 24 h. The reaction mixture was evaporated to dryness, and the residue was purified by preparative TLC in hexane–ethyl acetate (6:4) to give 35 mg (75%) of mesylate **16:** NMR δ 0.9 (3 H, d, $J$ = 7 Hz), 1.3 (3 H, t, $J$ = 7 Hz), 2.2 (3 H, s), 2.4 (4 H, m), 3.8 (1 H, m), 4.7 (1 H, d, $J$ = 6 Hz), 5.4 (1 H, d, $J$ = 10 Hz), 7.4 (9 H, m).

***N*-(*p*-Chlorophenyl)-2α-ethyl-5α-methyl-6α-phenyl-7-oxa-3-azabicyclo[4.1.0]heptane-3,4β-dicarboximide (17).** A mixture of 200 mg of epoxide **7**, 3 mL of toluene, 200 mg of sodium azide dissolved in a minimum amount of water, and 0.1 mL of Aliquat 336[14] was refluxed at 105 °C. After 4 days the reaction mixture was diluted with $CHCl_3$. The organic layer was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was purified by preparative TLC in hexane–ethyl acetate (8:2) to give 72 mg (36%) of epimer **17:** NMR δ 1.1 (5 H, m), 1.8 (2 H, m), 2.7 (1 H, m), 3.35 (1 H, s), 3.75 (1 H, d, $J$ = 9 Hz), 4.6 (1 H, br t), 7.4 (9 H, m).

***N*-(*p*-Chlorophenyl)-3β,6β-dihydro-6α-(hydroxymethyl)-3α-methyl-4-phenyl-1,2α(2*H*)-pyridinedicarboximide (19).** To a solution of 218 mg (0.51 mmol) of acetate **18** in 15 mL of MeOH–THF–$CHCl_3$ (7:7:1) was added 1 mL of 2.5% aqueous $K_2CO_3$ solution at 0 °C. The resulting solution was warmed to room temperature and stirred for 6 h, and the reaction mixture was diluted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was purified by preparative TLC in hexane–ethyl acetate (6:4) to give 130 mg (66%) of alcohol **19:** NMR δ 1.2 (3 H, d, $J$ = 7 Hz), 2.9 (1 H, m), 3.8 (2 H, m), 4.03 (1 H, d, $J$ = 10 Hz), 4.75 (1 H, m), 5.75 (1 H, d of d, $J$ = 3.5 Hz), 7.3 (9 H, m).

***N*-(*p*-Chlorophenyl)-2α-(hydroxymethyl)-5α-methyl-6β-phenyl-7-oxa-3-azabicyclo[3.1.0]heptane-3,4β-dicarboximide (20) and *N*-(*p*-Chlorophenyl)-2α-(hydroxymethyl)-5α-methyl-6α-7-oxa-3-azabicyclo[4.1.0]heptane-3,4β-dicarboximide (21).** A solution of 181 mg (0.47 mmol) of alcohol **19** and 174 mg (0.69 mmol) of 85% *m*-chloroperbenzoic acid in 10 mL of $CH_2Cl_2$ was stirred at room temperature for 2 days. The solution was evaporated to dryness and the residue was taken up in ethyl acetate. The organic phase was washed with 5% $NaHSO_3$, saturated $NaHCO_3$, and saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was purified by preparative TLC in hexane–ethyl acetate (7:3) giving 120 mg (65%) of α-epoxide **20** and 25 mg (13%) of β-epoxide **21. 20:** mp 192–194 °C; IR (film) 1715, 1770, and 3450 $cm^{-1}$; NMR δ 1.2 (3 H, d, $J$ = 7 Hz), 2.7 (2 H, m), 3.3 (1 H, d, $J$ = 4 Hz), 3.9 (3 H, m), 4.55 (1 H, m), 7.3 (9 H, m). Anal. Calcd for $C_{21}H_{19}N_2O_4Cl$: $m/e$ 398.10333. Found: $m/e$ 398.10778. **21:** IR (film) 1715, 1770, and 3450 $cm^{-1}$; NMR δ 1.0 (3 H, d, $J$ = 7 Hz), 2.3 (2 H, br m), 3.4 (1 H, s), 4.1 (3 H, m), 4.6 (1 H, m), 7.3 (9 H, m).

**2α-(Acetoxymethyl)-*N*-(*p*-chlorophenyl)-5α-methyl-6α-phenyl-7-oxa-3-bicyclo[4.1.0]heptane-3,4α-dicarboximide (22).** A solution of 40 mg (0.09 mmol) of olefin **18** and 25 mg (0.12 mmol) of *m*-chloroperbenzoic acid in 2 mL of $CHCl_3$ was stirred at room temperature for 20 h. The solution was evaporated to dryness, and the residue was taken up in ethyl acetate. The solution was washed with saturated $NaHCO_3$ and saturated brine, dried over anhydrous $MgSO_4$, and evaporated to give 50 mg of crude product. Recrystallization from ether–pentane gave 30 mg (73%) of epoxide **22** as white crystals: mp 163 °C; IR (film) 1720, 1740, and 1775 $cm^{-1}$; NMR δ 1.0 (3 H, d, $J$ = 7 Hz), 2.1 (3 H, s), 3.1 (1 H, m), 3.6 (1 H, s), 4.2–5.4 (4 H, m), 7.3 (9 H, s). Anal. Calcd for $C_{23}H_{21}N_2O_5Cl$: $m/e$ 440.11390. Found: $m/e$ 440.11542.

***N*-(*p*-Chlorophenyl)-2α-(hydroxymethyl)-5α-methyl-6α-phenyl-7-oxa-3-azabicyclo[4.1.0]heptane-3,4α-dicarboximide (23) and Epoxide 21.** To a solution of 30 mg (0.07 mmol) of epoxide **22** in 3.5 mL of THF–MeOH–$CHCl_3$ (3:1:1) was added 0.2 mL of 5% aqueous $K_2CO_3$ at room temperature. The mixture was evaporated to dryness and the residue was purified by preparative TLC (hexane–ethyl acetate, 7:3) to give 15 mg (55%) of alcohol **23** and 13 mg (45%) of alcohol **21,** which was identical with material prepared by epoxidation of **19. 23** gave the following spectral data: IR (film) 1715, 1770, and 3450 $cm^{-1}$; NMR δ 1.0 (3 H, d, $J$ = 7 Hz), 3.1 (1 H, m), 3.6 (1 H, s), 4.0–5.0 (4 H, m), 7.5 (9 H, m).

**5β-Azido-*N*-(*p*-chlorophenyl)-4α-hydroxy-6α-(hydroxymethyl)-3α-methyl-4β-phenyl-1,2β-piperidinedicarboximide (24).** A mixture of 66 mg (0.17 mmol) of epoxide **20,** 50 mg of 99% sodium azide, 4 mL of toluene, 1 mL of $H_2O$, and 7 drops of Aliquat 336[14] was heated at 110 °C for 6 h, and the reaction mixture was diluted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was purified on a small column of silica gel (5 g) in hexane–ethyl acetate (1:1) to give 55 mg (75%) of azide **24** as white crystals which was used in the next step without further purification: IR (film) 1710, 1780, 2120, and 3400 $cm^{-1}$; NMR δ 1.2 (3 H, d, $J$ = 6 Hz), 2.5–4.7 (8 H, m), 7.5 (9 H, m).

**5β-*N*-(Acetylamino)-*N*-(*p*-chlorophenyl)-4α-hydroxy-6α-(acetoxymethyl)-3α-methyl-4β-phenyl-1,2β-piperidinedicarboximide (26).** A mixture of 50 mg (0.11 mmol) of azide **24** and 15 mg of 5% Pd/C in 5 mL of ethyl acetate was hydrogenated at room temperature and atmospheric pressure for 7 h. The mixture was filtered and evaporated to give 20 mg of amine **25.** A solution of this crude product and 0.1 mL of acetic anhydride in 15 mL of pyridine was allowed to stand at room temperature overnight. The solution was evaporated to dryness in vacuo and the residue was purified by preparative TLC in hexane–ethyl acetate (1:1) to give 16 mg (30%) of amide **26** as white crystals: mp 254 °C; IR (Nujol) 1720, 1740, 1770, and 3350 $cm^{-1}$; NMR δ 1.65 (3 H, s), 1.75 (3 H, s), 2.05 (3 H, s), 2.7 (2 H, m), 4.0–5.2 (5 H, m), 6.0 (1 H, m), 7.4 (9 H, m). Anal. Calcd for $C_{25}H_{26}N_3O_6Cl$: $m/e$ 499.1506. Found: $m/e$ 499.1501.

**Methyl 6-(Chloromethyl)-3-methyl-4-phenyl-2-pyridinecarboxylate (29).** To a solution of 600 mg (2.33 mmol) of alcohol **27** in 20 mL of dry benzene was added 320 mg (2.69 mmol) of thionyl chloride at 0 °C. The resulting mixture was slowly warmed to room temperature and stirred for 1 h. The mixture was evaporated to dryness, and the residue was taken up in ether. The solution was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was chromatographed on silica gel (20 g) in hexane–ethyl acetate (9:1) to give 638 mg (99%) of chloride **29:** IR (film) 1735 $cm^{-1}$; NMR δ 2.35 (3 H, s), 4.0 (3 H, s), 4.7 (3 H, s), 7.4 (6 H, m).

**Methyl 6-(1-Chloroethyl)-3-methyl-4-phenyl-2-pyridinecarboxylate (30).** To a solution of 25 mg (0.092 mmol) of alcohol **28** in 1 mL of dry benzene was added a solution of 25 mg of thionyl chloride in 1 mL of dry benzene at 0 °C. The solution was warmed to room temperature and stirred for 2 h. The mixture was evaporated to dryness, and the residue was purified on a small column of silica gel (5 g) in $CHCl_3$ to give 20 mg (75%) of chloride **30:** IR (film) 1735 $cm^{-1}$; NMR δ 1.85 (3 H, d, $J$ = 7 Hz), 2.3 (3 H, s), 4.0 (3 H, s), 5.4 (1 H, q, $J$ = 7 Hz), 7.5 (5 H, s), 7.6 (1 H, s).

**Preparation of Quaternary Salt 31.** A solution of 250 mg (0.91 mmol) of chloride **29** and 200 mg (1.81 mmol) of *N*-cyanomethylpyrrolidine in 2 mL of dimethyl sulfoxide was heated at 50–60 °C for 1 day and at 40 °C for 2 days.[15] The solution was evaporated to dryness in vacuo, and the residue was crystallized from ethyl acetate–ether to give 327 mg (93%) of salt **31:** IR (Nujol) 1730 $cm^{-1}$; NMR δ 2.4 (4 H, br s), 2.43 (3 H, s), 4.0 (3 H, s), 4.3 (4 H, br m), 5.35 (2 H, s), 5.85 (2 H, s), 7.4 (5 H, m), 8.0 (1 H, s).

**Preparation of Amide 33.** A solution of 20 mg (0.07 mmol) of chloride **29** and 40 mg (0.36 mmol) of *N*-cyanomethylpyrrolidine[15] in $Me_2SO$-$d_6$ in an NMR tube was allowed to stand at room temperature for 48 h until quaternization was complete. The solution was transferred to a round-bottomed flask, diluted with small amount of dry THF, and cooled to −10 °C. To this solution was added 30 mg of potassium *tert*-butoxide, and the mixture was stirred for 2 h under nitrogen. The mixture was diluted with ether, and the organic layer was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was purified by preparative TLC in hexane–ethyl acetate (3:7) to give 7 mg (30%) of amide **33:** IR (film)

1640 and 1735 $cm^{-1}$; NMR $\delta$ 1.65 (4 H, m), 2.2 (3 H, s), 2.55 (3 H, s), 2.9 (2 H, m), 3.2 (2 H, m), 4.0 (3 H, s), 7.3 (5 H, m). Anal. Calcd for $C_{20}H_{22}N_2O_3$: *m/e* 338.1628. Found *m/e* 338.1626.

**Methyl 5-Formyl-3,6-dimethyl-4-phenyl-2-pyridinecarboxylate (35a).** To a solution of 120 mg (0.31 mmol) of quaternary salt **31** in 15 mL of HMPA–$Me_2SO$–THF (2:4:9) was added 70 mg of potassium *tert*-butoxide at −15 °C under oxygen-free argon.[20] The solution was stirred for 10 min and quenched with saturated $NH_4Cl$ solution. The mixture was diluted with ethyl acetate, and the organic fraction was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. A mixture of the residue and 20 mg of oxalic acid in 7 mL of THF–$H_2O$ (5/2) was refluxed for 1 h. The mixture was evaporated to dryness, and the residue was purified by chromatography on a column of silica gel (10 g) in ethyl acetate–hexane (2:8) to give 36 mg (43%) of aldehyde **35a** as a white solid: IR (film) 1700 and 1740 $cm^{-1}$; NMR $\delta$ 2.2 (3 H, s), 2.8 (3 H, s), 4.07 (3 H, s), 7.2–7.7 (3 H, m), 9.9 (1 H, s); mass spectrum *m/e* 269 ($M^+$).

**Methyl 5-Carboxyl-3,6-dimethyl-4-phenyl-2-pyridinecarboxylate (39).** To a solution of 36 mg (0.134 mmol) of aldehyde **35a** in 6 mL of acetone–$H_2O$ (2:1) was added 30 mg of potassium permanganate at room temperature. The mixture was stirred at room temperature for 1 h, and a small amount of sodium bisulfite was added. The mixture was filtered and the filtrate was washed well with acetone. The acetone was removed by evaporation and the remaining aqueous phase was extracted with $CHCl_3$. The organic layer was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness to give 35 mg (92%) of acid **39** as a white, crystalline solid, which was recrystallized from chloroform: mp 245 °C; IR (Nujol) 1720, 1740, and 2600 $cm^{-1}$; NMR $\delta$ 2.2 (3 H, s), 2.62 (3 H, s), 4.0 (3 H, s), 7.2–7.6 (5 H, m).

**Methyl 5-Amido-3,6-dimethyl-4-phenyl-2-pyridinecarboxylate (40).** A solution of 22 mg (0.077 mmol) of acid **39** in minimum amount of pyridine was diluted with 4 mL of $CHCl_3$. To this solution was added 5 drops of thionyl chloride and the solution was stirred for 3 h at room temperature. A stream of anhydrous ammonia was passed through the solution cooled in an ice bath for 5 min, and the mixture was stirred for 20 min at room temperature. The mixture was partitioned between chloroform and water, and aqueous layer was extracted with $CHCl_3$. The combined $CHCl_3$ extract was washed with saturated brine, dried over anhydrous $Na_2SO_4$, and evaporated to dryness. The residue was purified by preparative TLC in ethyl acetate to give 15 mg (70%) of amide **40:** IR ($CHCl_3$) 1680, 1735, 3400, and 3520 $cm^{-1}$; NMR $\delta$ 2.2 (3 H, s), 2.7 (3 H, s), 4.0 (3 H, s), 5.3–5.8 (2 H, br s), 7.2–7.6 (5 H, m).

**Methyl 5-Carbamoyl-3,6-dimethyl-4-phenyl-2-pyridinecarboxylate (41). A.** To a solution of 18 mg (0.063 mmol) of amide **40** in 5 mL of absolute methanol was added 70 mg of sodium methoxide followed by 60 mg of bromine in a small amount of absolute methanol in an ice bath. The solution was stirred for 30 min at ice-bath temperature and then refluxed for 20 min. The solution was partitioned between $CHCl_3$ and $H_2O$, and the aqueous layer was extracted with $CHCl_3$ several times. The combined organic layer was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness to give 19 mg (100%) of urethane **41:** IR ($CHCl_3$) 1735 and 3420 $cm^{-1}$; NMR $\delta$ 2.2 (3 H, s), 2.6 (3 H, s), 3.7 (3 H, s), 4.0 (3 H, s), 5.8 (1 H, br s), 7.0–7.7 (5 H, m). Anal. Calcd for $C_{17}H_{18}N_2O_4$: *m/e* 314.1266. Found: *m/e* 314.1272.

**B.** A solution of 10 mg (0.035 mmol) of acid **39,** 2 drops of triethylamine, and 2 drops of diphenylphosphoryl azide in 3 mL of anhydrous benzene was refluxed for 1 h. To the solution was added 0.5 mL of dry methanol and the solution was refluxed for an additional 30 min. The solution was evaporated to dryness, and the residue was purified by preparative TLC in ethyl acetate–hexane (7:3) to give 10 mg (100%) of urethane **41** identical with material prepared in part A.

**Methyl 5-Carbamoyl-3,6-dimethyl-4-phenyl-2-pyridinecarboxylate 1-Oxide (42).** A solution of 13 mg (0.04 mmol) of pyridine **41** and 24 mg (0.1 mmol) of 85% *m*-chloroperbenzoic acid in 3 mL of $CHCl_3$ was stirred at room temperature for 18 h. The solution was evaporated to dryness and the residue was taken up in ethyl acetate. The organic phase was washed with saturated $NaHSO_3$, $NaHCO_3$, and brine, dried over anhydrous $MgSO_4$, and evaporated to give 15 mg (100%) of solid **42** which was homogeneous by TLC and NMR: NMR $\delta$ 2.0 (3 H, s), 2.5 (3 H, s), 3.7 (3 H, s), 4.05 (3 H, s), 6.1 (1 H, br s), 7.0–7.6 (5 H, m).

**Methyl 6-Acetoxymethyl-5-carbamoyl-3-methyl-4-phenyl-2-pyridinecarboxylate (43).** A solution of 15 mg (0.045 mmol) of pyridine *N*-oxide **42** in 2 mL of acetic anhydride was heated at 110 °C for 2 h. The solution was evaporated to dryness in vacuo to give 15 mg (88%) of acetate **43:** IR ($CHCl_3$) 1740 and 3400 $cm^{-1}$; NMR $\delta$ 2.1 (3 H, s), 2.2 (3 H, s), 3.6 (3 H, s), 4.0 (3 H, s), 5.3 (3 H, s), 6.4 (1 H, br s), 7.1–7.7 (5 H, m). Anal. Calcd for $C_{19}H_{20}N_2O_6$: *m/e* 372.133. Found: *m/e* 372.132.

**Preparation of Urethane 45.** A mixture of 15 mg (0.04 mmol) of acetate **43** and 35 mg of anhydrous $K_2CO_3$ in 3 mL of absolute methanol was stirred at room temperature for 1 h. The mixture was diluted with ethyl acetate, washed with saturated brine, dried over anhydrous $Na_2SO_4$, and evaporated to dryness to give 12 mg (100%) of cyclic urethane **45:** IR ($CHCl_3$) 1735 and 3400 $cm^{-1}$; NMR $\delta$ 2.3 (3 H, s), 4.0 (3 H, s), 6.53 (2 H, s), 6.7 (1 H, br s), 7.3–7.7 (5 H, m). Anal. Calcd for $C_{16}H_{14}N_2O_4$: *m/e* 298.0952. Found: *m/e* 298.096.

**Methyl 5-Amino-3,6-dimethyl-4-phenyl-2-pyridinecarboxylate (46).** A solution of 50 mg (0.175 mmol) of acid **39,** 0.1 mL of triethylamine, and 0.1 mL of diphenylphosphoryl azide in 5 mL of dry benzene was refluxed for 1 h.[23] To the solution was added 0.5 mL of water and the mixture was refluxed for an additional 30 min. The mixture was evaporated to dryness, and the residue was purified by chromatography on a column of silica gel (5 g) in hexane–ethyl acetate (8:2; 100 mL) followed by ethyl acetate (50 mL) to give 39 mg (87%) of aminopyridine **46:** IR ($CHCl_3$) 1720, 3400, and 3500 $cm^{-1}$; NMR $\delta$ 2.2 (3 H, s), 2.5 (3 H, s), 4.0 (3 H, s), 7.2–7.7 (5 H, m); mass spectrum *m/e* 256 ($M^+$).

**Preparation of Imide 48.** A solution of 39 mg (0.152 mmol) of aminopyridine **46** and 1 mL of acetic anhydride in 3 mL of pyridine was refluxed for 8 h (oil bath temperature 130 °C). The solution was evaporated to dryness in vacuo to give 49 mg (95%) of imide **48:** IR (film) 1720 and 1780 $cm^{-1}$; NMR $\delta$ 2.1 (6 H, s), 2.2 (3 H, s), 2.5 (3 H, s), 4.05 (3 H, s), 7.0–7.7 (5 H, m).

**Methyl 5-Amino-6-hydroxymethyl-3-methyl-4-phenyl-2-pyridinecarboxylate (51).** A solution of 49 mg (0.144 mmol) of imide **48** and 100 mg of 85% *m*-chloroperbenzoic acid in 10 mL of $CHCl_3$ was stirred at room temperature for 34 h. The solution was taken up in ethyl acetate. The organic phase was washed with saturated $NaHSO_3$, $NaHCO_3$, and brine, dried over anhydrous $MgSO_4$, and evaporated to give *N*-oxide **49.** A solution of the *N*-oxide **49** in 2 mL of acetic anhydride was heated at 110 °C (oil bath temperature) for 2 h. The solution was evaporated to dryness in vacuo to give crude acetate **50.**

A mixture of the crude acetate **50** and 70 mg of anhydrous $K_2CO_3$ in 5 mL of dry methanol was stirred at room temperature for 7 h. The mixture was evaporated to dryness, and the residue was taken up in ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous $MgSO_4$, and evaporated to dryness to give 37 mg of crude amino alcohol **51.**

**49:** NMR $\delta$ 2.05 (3 H, s), 2.15 (6 H, s), 2.45 (3 H, s), 4.1 (3 H, s), 7.0–7.77 (5 H, m). **50:** NMR $\delta$ 2.1 (3 H, s), 2.5 (6 H, s), 2.25 (3 H, s), 4.05 (3 H, s), 5.17 (2 H, s), 7.0–7.7 (5 H, s). **51:** NMR $\delta$ 2.2 (3 H, s), 4.0 (3 H, s), 4.83 (2 H, s), 7.0–7.7 (5 H, m).

**Methyl 5-Amino-6-formyl-3-methyl-4-phenyl-2-pyridinecarboxylate (52).** A mixture of 37 mg of crude amino alcohol **51** and 100 mg of activated manganese dioxide[25] in 5 mL of chloroform was stirred at room temperature for 1 h. The mixture was filtered through a pad of Celite, and the filtrate was evaporated to dryness. The residue was purified by preparative TLC in ethyl acetate–hexane (4:1) to give 16 mg (34% in six steps from **48**) of aminoaldehyde **52:** IR (film) 1680, 1720, 3350, and 3475 $cm^{-1}$; NMR $\delta$ 2.3 (3 H, s), 4.0 (3 H, s), 5.8–6.5 (2 H, br s), 7.2–7.8 (5 H, m), 10.3 (1 H, s). Anal. Calcd for $C_{15}H_{14}N_2O_3$: *m/e* 270.1004. Found: *m/e* 270.1001.

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**Registry No.**—**6,** 64035-13-8; **7,** 64090-71-7; **9,** 64035-32-1; **10,** 64035-33-2; **13,** 64035-34-3; **14,** 64035-35-4; **15,** 64035-36-5; **16,** 64035-37-6; **17,** 64035-38-7; **18,** 64035-09-2; **19,** 64035-39-8; **20,** 64035-40-1; **21,** 64069-75-6; **22,** 64035-41-2; **23,** 64069-76-7; **24,** 64035-42-3; **25,** 64035-43-4; **26,** 64035-44-5; **27,** 64034-96-4; **28,** 64034-95-3; **29,** 64035-45-6; **30,** 64035-46-7; **31,** 64035-47-8; **33,** 64056-86-6; **35a,** 64035-48-9; **39,** 64035-20-7; **40,** 64035-21-8; **41,** 64035-22-9; **42,** 64035-23-0; **43,** 64035-24-1; **45,** 64035-25-2; **46,** 64035-26-3; **48,** 64035-27-4; **40,** 64035-28-5; **50,** 64035-29-6; **51,** 64035-30-9; **52,** 64035-31-0; trifluoroacetic acid, 76-05-1; methanesulfonyl chloride, 124-63-0; *N*-cyanomethylpyrrolidine, 29134-29-0.

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# Mercury in Organic Chemistry. 12.[1] Synthesis of β-Chloro-$\Delta^{\alpha,\beta}$-butenolides via Mercuration–Carbonylation of Propargylic Alcohols[2]

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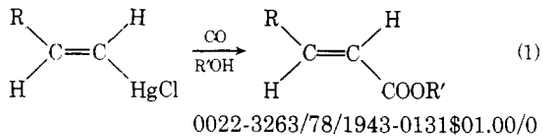
A number of propargylic alcohols react with mercuric chloride to give (*E*)-β-chloro-γ-hydroxyvinylmercuric chlorides. These can be readily carbonylated in a variety of solvents using stoichiometric amounts of palladium chloride and 1 atm of carbon monoxide to give essentially quantitative yields of the corresponding β-chloro-$\Delta^{\alpha,\beta}$-butenolides. Carbonylation can be effected using only catalytic amounts of palladium chloride if cupric chloride is used as a reoxidant and benzene as the solvent.

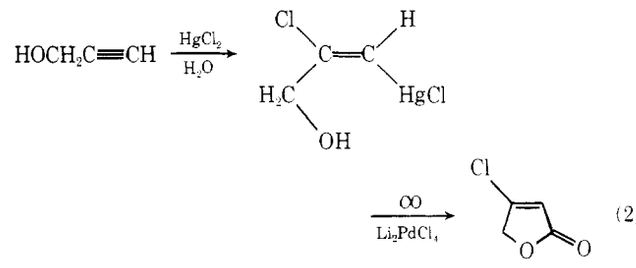
Unsaturated five-member ring lactones, butenolides, occur widely in nature[5] and possess an unusual range of biological activity.[6] They appear throughout the plant kingdom from the simple metabolites of lichens, mold, and fungi[7] to the more complex sesquiterpenes of the family Compositae[8] and steroidal glycosides of the families Ranunculaceae, Liliaceae, Scrophulariaceae, and Apocyanaceae.[9] More recently butenolides have been observed in such diverse animal species as sponges,[10-15] butterflies,[16] and insects.[17] In the latter species they appear to play a significant role as chemical defense weapons. Butenolides also hold promise as insecticides,[18] herbicides,[19] and seed and plant growth regulators.[20-22] Of considerable importance is their widespread allergenic,[23,24] antibacterial,[25,26] and antifungal[27-29] activity. Undoubtedly, vitamin C is the most physiologically important butenolide, but tremendous interest has also been generated by the cardiac glycosides which have the remarkable ability to reduce the frequency, but increase the amplitude of the heart beat.[9] Although in some cases carcinogenic,[30,31] an increasing number of butenolides exhibit cytotoxic and/or tumor inhibitory properties toward a variety of cancers.[32,33]

The unusual range of biological activity of butenolides has stimulated considerable research on the synthesis of these valuable compounds.[34] Of foremost interest are the $\Delta^{\alpha,\beta}$-butenolides. Recent work in our laboratory on the palladium promoted carbonylation of vinylmercurials (eq 1)[35] suggested




(1)

a novel new route to these butenolides. During that work we found that the β-chlorovinylmercurial[36] obtained by mercuric chloride addition to propargyl alcohol could be readily carbonylated to give β-chloro-$\Delta^{\alpha,\beta}$-butenolide [4-chloro-2(5*H*)-furanone] in 96% isolated yield (eq 2). The ease with which




(2)

both mercuration and carbonylation could be effected and the high yield of butenolide encouraged us to examine the full scope of both of these reactions. We wish now to report the complete experimental details of that investigation.

## Results and Discussion

**Mercuration of Propargylic Alcohols.** The first step in our new approach to butenolides involves the mercuration of propargylic alcohols. Nesmeyanov and Kochetkov reported in 1949 that propargyl alcohol (55% yield), 2-methyl-3-butyn-2-ol (38%), 2-butyne-1,4-diol (87%), and 2,5-dimethyl-3-hexyne-2,5-diol (95%) readily react at room temperature with saturated aqueous solutions of sodium chloride

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