aqueous sodium bicarbonate solution or with dilute aqueous hydrochloric acid, respectively, prior to the aforementioned wash with water.
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Studies on the Total Synthesis of Steroidal Antibiotics. 3. Generation and Correlation of Tetracyclic Derivatives from the Degradation of Fusidic Acid and Total Synthesis[1]

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Received October 1, 1976

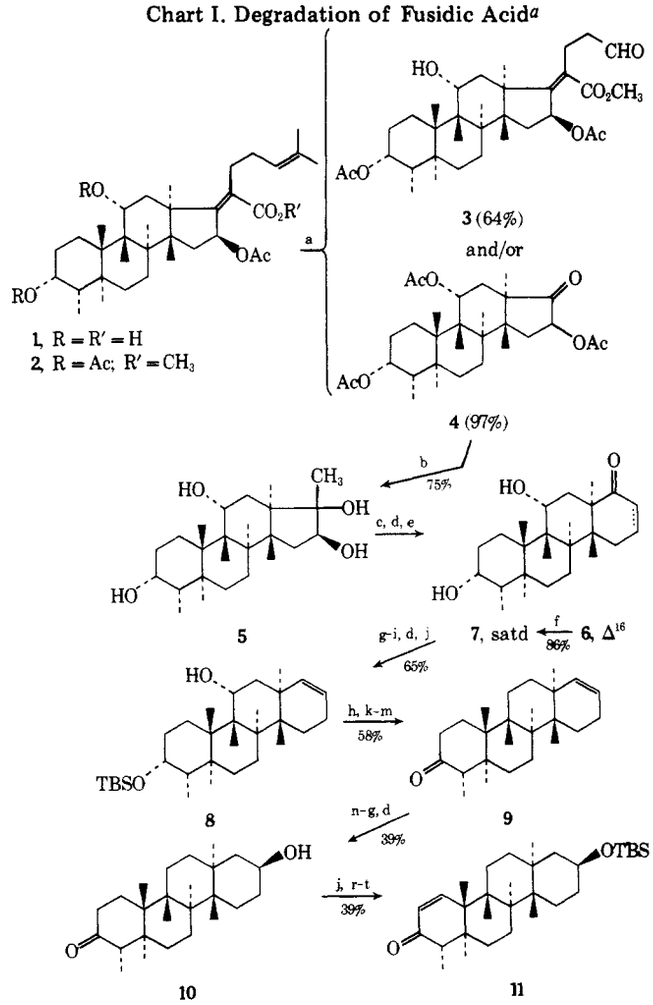
The degradation of fusidic acid (1) to the tetracyclic enone 11 is described. The principle phases of this conversion are the removal of the side chain and then expansion of the five-membered D ring. The racemic form of the enone 11 was prepared from the synthetic enedione 12. The central feature of this transformation entails the boron trifluoride etherate catalyzed rearrangement of the epoxide 14 and then removal of the C-6 ketone through reduction of the derived phosphorodiamidate. The identity of the racemic and naturally derived enones 11 establishes the stereochemical outcome of the synthetic plan employed.

In the preceding paper[2] in this series two convergent approaches to the synthesis of fusidic acid (1)[3] through tetracyclic intermediates, such as the diketone **12**, were presented. In addition to the necessary development of the logistics of the construction of such intermediates, the stereochemistry of these and subsequent substances was of the utmost importance. The availability of fusidic acid (1) from natural resources through the kind auspices of Dr. W. O. Godtfredsen (Leo Pharmaceuticals) and Hoffmann-La Roche and Co. made possible a project aimed at not only the production of comparison samples of tetracyclic derivatives of known stereochemistry through the selective degradation of the natural product, but also the generation of larger quantities of these materials suitable for use as relay substances for the synthetic effort. The latter consideration becomes of importance as a result of the low yields experienced in the synthetic phase of the work that is associated with the introduction of the C-11α OH and the formation of the trans A/B ring system. To these ends the degradation of fusidic acid (1) outlined in Chart I was undertaken and together with the further synthetic transformations of the diketone **12** (Chart II) forms the subject of this report.

In view of the previously reported[2] difficulties involved in attempts to introduce the C-11α OH function into tricyclic synthetic intermediates, this problem was shelved and efforts continued to develop a synthetic scheme for the C-11 deoxy series. In this series a logical junction between the synthetic and degradation sequences was at the enone **11**. This intermediate that had the required fusidic acid nuclear stereochemistry and was as well prestaged for the completion of the synthesis of C-11 deoxyfusidic acid through contraction of ring D and addition of the side chain. The ring A enone functionality in the intermediate **11** was necessary in the synthetic sequence (Chart II) in order to append the C-4 CH_3, but was also envisaged as possibly providing access through C-1 to C-11, and hence the ultimate introduction of a C-11α OH grouping.

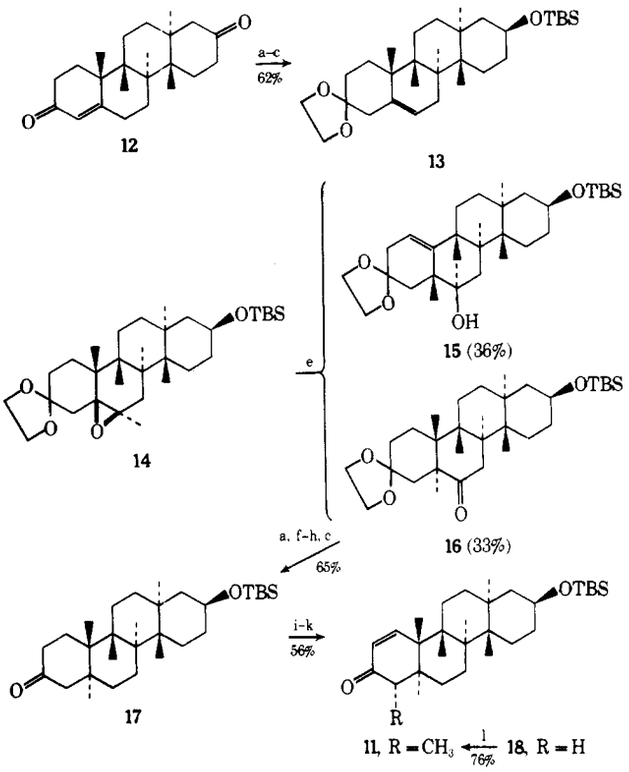
In the fusidic acid (1) degradation[3,4] removal of the side chain could be accomplished by stages whereby the isopropylidene grouping was cleaved first by brief treatment with ozone (aldehyde **3**) or completely in one more prolonged ozonization to the keto triacetate **4**. Expansion of the D ring to the enone **6** was accomplished through aldol-type cyclization of the *D*-secoketo aldehyde obtained by periodate

Chart I. Degradation of Fusidic Acid[a]



[a] a, O_3, CH_3OH, CH_3SCH_3; b, CH_3Li, THF; c, H_5IO_6, CH_3OH–H_2O; d, H_3O^+; e, KOH, CH_3OH–H_2O; f, 10% Pd/C, H_2, HOAc; g, DHP, H^+, C_6H_6; h, LDA, THF; $ClPO(NMe_2)_2$, HMPA–THF; i, Li, *t*-BuOH, NH_3(l); j, *t*-$BuMe_2SiCl$, imidazole, DMF; k, Li, *t*-BuOH, $EtNH_2$; l, $(n\text{-}Bu)_4NF$, THF; m, CrO_3, HOAc; n, $(HOCH_2)_2$, H^+, C_6H_6; o, Sia_2BH, H_2O_2, OH–THF; p, $CrO_3 \cdot 2Py$, CH_2Cl_2; q, Li(*t*-BuO)$_3$AlH, THF; r, NaH, HCO_2Et, C_6H_6; s, DDQ, C_6H_6; t, $[(C_6H_5)_3P]_3RhCl$, C_6H_6.

Chart II. Synthesis of Tetracycle Relay[a]



[a] a, Li(*t*-BuO)$_3$AlH, THF; b, $(CH_2OH)_2$, H^+, C_6H_6; c, *t*-Bu-Me_2SiCl, imidazole, DMF; d, MCPBA, CH_2Cl_2; e, $BF_3{\cdot}Et_2O$, CH_2Cl_2; f, LDA, THF; $ClPO(NMe_2)_2$, THF–HMPA; g, Li, *t*-BuOH, THF, $EtNH_2$; h, H_3O^+; i, NaH, HCO_2Et, C_6H_6; j, DDQ, C_6H_6; k, $[(C_6H_5)_3P]_3RhCl$, C_6H_6; l, LDA, THF; CH_3I.

cleavage of the tetrol **5**. Conversion of the dihydroxy ketone **7** to the olefinic ketone **9** utilized a sequence of phosphorodiamidate reductions.[5] First the 17(17a) olefin was generated through reduction of the enol phosphorodiamidate of the C-17a carbonyl and then C-11α OH was reductively removed through the phosphorodiamidate of the C-3 silyl ether **8**. Hydroboration of the ketal of the ketone **9** served to introduce the C-17 OH and then introduction of the C-1(2) unsaturation by the method of Caspi[6] led to the desired enone **11**. While the unimpressive overall yield of this multistage process (2–4% depending on the variations in the yields observed in the periodate cleavage step) leaves a lot to be developed before the enone **11** is a viable relay substance, sufficient naturally derived material was obtained for comparison with the enone **11** from the synthetic sequence (Chart II).

The key to the synthetic effort was the plan developed in the earlier tricyclic model series[7] for the introduction of the C-5α H. This process entailed the boron trifluoride etherate rearrangement of the initially formed C-5β,C-6β epoxide **14**, a substance that was efficiently formed from the enedione **12** as shown (Chart II). In contrast to the tricyclic model series, however, the yield of this rearrangement was not high. In the tricyclic model series an adequate 63% yield of the desired trans-syn-trans C-6 ketone resulted and no other skeletally rearranged by-products could be found. In the present tetracyclic series, the yield of the desired ketone **16** was only 33% and in this case skeletally rearranged alcohols such as **15** were equally as available. In spite of much variation of reaction conditions and substrate functionality, the best yield of the desired ketone **6** was obtained under the initial conditions. In view of this setback in the yield of this crucial rearrangement, it became particularly important to be certain of the stereochemistry of the ketone **16**. Since the results in this tetracyclic series differed so much from those of the tricyclic model series, doubt was even cast on the expected stereochemical outcome of the desired product. In order to assuage this doubt as well as investigate the subsequently planned transformations, the ketone **16** was converted into the enone **11**.

In the same manner as described for the tricyclic model series, the C-6 ketone was removed through the phosphorodiamidate reduction and the trans-syn-trans-anti-trans ketone **17** became available. In order to correlate this synthetic series with the derivatives from fusidic acid (**1**) itself it was necessary to introduce the C-4 CH_3. This process required the blocking of the C-2 position of the ketone **17** and the C-1(2) unsaturation was chosen for this purpose. Again the procedure developed by Caspi[6] proved satisfactory, and the ketone **11** was prepared through the unsaturated ketone **18**. It was gratifying to find that the spectral (NMR, IR, TLC, and MS) properties of this racemic sample of the ketone **11** and those of the naturally derived material above were indeed identical. It is thus possible to utilize this synthetic scheme for the further contraction of the D ring and the addition of the fusidic acid side chain with the aim toward completion of the total synthesis. As well, the naturally derived material may provide a useful relay substance for the synthesis after resolution of the synthetic sample and refinement of the degradation scheme. Work in these directions is in progress.

Experimental Section[8]

Methyl Diacetylfusidate (2). To a solution of 11.4 g (21.5 mmol) of methyl fusidate[3] [prepared in quantitative yield by the action of ethereal diazomethane on fusidic acid (**1**)[9]] in 100 mL (1.15 mol) of acetic anhydride and 40 mL (0.37 mol) of acetyl chloride was added 1 g (8.2 mmol, 0.38 equiv) of 4-dimethylaminopyridine,[10] and the mixture was stirred in the dark at room temperature for 2 h. After treatment of the reaction mixture with ice (500 g) and 120 mL of pyridine for 2 h, isolation of the product from this aqueous mixture by ether extraction[11] and then azeotropic distillation of toluene (3 × 100 mL) gave 12.2 g (quantitative) of the diacetate **2**, mp 135–137 °C. The analytical sample, obtained after crystallization of a portion of this material from EtOH, melted at 137–138 °C: TLC (1:1 benzene–EtOAc) R_f 0.64; IR ($CHCl_3$) 1710–1725 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.80 (d, J = 7 Hz, 3, C-4 CH_3), 0.94 (s, 3, CH_3), 0.98 (s, 3, CH_3), 1.36 (s, 3, CH_3), 1.56 (s, 3, CH_3C=C), 1.66 (s, 3, CH_3C=C), 1.99 (s, 3, CH_3CO), 2.04 (s, 3, CH_3CO), 3.62 (s, 3, CH_3O), 4.94 (m, 1, C-3β H), 5.02 (m, 1, C-24 H), 5.24 (m, 1, C-11β H), and 5.83 (d, J = 8 Hz, 1, C-16α H).

Anal. Calcd for $C_{36}H_{54}O_8$: C, 70.33; H, 8.85. Found: C, 70.42; H, 8.87.

Ozonolysis of Methyl Diacetylfusidate (2). A. Formation of Trisnoraldehyde 3. A solution of 93 mg (0.15 mmol) of methyl diacetylfusidate (**2**) in 8 mL of CH_3OH was cooled to −40 °C and ozonized oxygen was passed through the solution until the effluent gases liberated iodine (yellow coloration) from a test solution of 10% aqueous KI. After the temperature of the cooling bath was lowered to −60 °C and a stream of nitrogen had been passed through the solution for 5 min, 2 mL of CH_3SCH_3 was added, and the mixture was stirred for 1 h at −10 °C, 1 h at 0 °C, and 2 h at room temperature. Isolation of the products by ether extraction including a base wash[11] afforded 103 mg of a mixture of two products which was separated by preparative TLC (silica gel, 1:1 benzene–EtOAc). The material with R_f 0.51 (23 mg, 34%) was shown to be the keto triacetate **4** by comparison of its spectra (IR, NMR) with those of the material obtained in part B.

The material with R_f 0.41 amounted to 57 mg (64%) of the aldehyde **3**, an analytical sample of which was obtained by crystallization from benzene: mp 81–82 °C; IR ($CHCl_3$) 2820, 2720 (HC=O), and 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.82 (s, 3, CH_3), 0.95 (s, 3, CH_3), 1.00 (s, 3, CH_3), 1.38 (s, 3, CH_3), 3.64 (s, 3, CH_3O), 4.91 (m, 1, C-3β H), 5.27 (m, 1, C-11β H), 5.83 (d, J = 8 Hz, 1, C-16α H), and 9.72 (s, 1, HC=O).

Anal. Calcd for $C_{33}H_{49}O_9$: C, 67.32; H, 8.22. Found: C, 67.36; H, 8.15.

Reduction of a sample (100 mg) of this aldehyde **3** from another experiment with $NaBH_4$ (6.5 mg) in 10 mL of EtOH afforded 83 mg of crude alcohol which was acetylated with acetic anhydride (1 mL) and pyridine at room temperature for 2 h. Isolation of the product by azeotropic removal of 10 mL of toluene by distillation afforded 105 mg (98%) of crystalline tetraacetate, mp 146–150 °C. The analytical

sample, obtained after crystallization of this material from EtOH, melted at 153–154 °C: TLC (1:1 benzene–EtOAc) R_f 0.51; IR ($CHCl_3$) 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.82 (d, J = 6 Hz, 3, C-4 CH_3), 0.94 (s, 3, CH_3), 0.99 (s, 3, CH_3), 1.37 (s, 3, CH_3), 1.98, 2.04, 2.05 (3 s, 4 × 3, 4 CH_3CO), 3.63 (s, 3, CH_3O), 4.04 (t, J = 6 Hz, 2, CH_2OAc), 4.96 (m, 1, C-3β H), 5.29 (m, 1, C-11β H), and 5.88 (d, J = 8 Hz, 1, C-16α H).

Anal. Calcd for $C_{35}H_{52}O_{10}$: C, 66.43; H, 8.28. Found: C, 66.42; H, 8.28.

B. Formation of Keto Triacetate 4. A solution of 10 g (16.3 mmol) of methyl diacetylfusidate (**2**) in 1 L of CH_3OH was treated with ozonized oxygen at −40 °C for 85 min, and after a stream of nitrogen was run through the solution for 10 min, the mixture was treated with 40 mL of CH_3SCH_3. The reaction mixture was then allowed to warm and stand at room temperature for 14 h. Isolation of the product by ether extraction including a base wash[11] afforded 7.5 g (97%) of keto triacetate **4**, mp 158–162 °C, which was sufficiently pure for further experimentation. The analytical sample, obtained after three crystallizations of a portion of this material from EtOH, melted at 164–165 °C: TLC (1:1 benzene–EtOAc) R_f 0.54; IR ($CHCl_3$) 1745, 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.84 (d, J = 6 Hz, 3, C-4 CH_3), 0.94 (s, 3, CH_3), 1.27 (s, 3, CH_3), 1.47 (s, 3, CH_3), 2.00, 2.04, 2.10 (3 s, 3 × 3, 3 CH_3CO), 4.94 (m, 1, C-3β H), 5.30 (m, 1, C-11β H), and 5.35 (m, 1, C-16α H).

Anal. Calcd for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 68.13; H, 8.46.

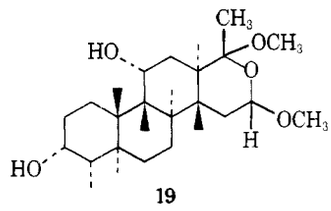
Tetrol 5. To an argon protected solution of 115 mL (180 mmol) of a 1.56 M ethereal CH_3Li solution in 165 mL of dry THF cooled at −70 °C was added dropwise over 1 h a solution of 5 g (10.5 mmol) of the keto triacetate **3** in 90 mL of dry THF. The mixture was then allowed to warm to room temperature, and stirring was continued for 15 h. The mixture was then cooled to 3 °C, quenched with 50 mL of H_2O, and the product isolated by 2:1 Et_2O–CH_2Cl_2 extraction.[11] Purification of the crude product (3.70 g) by chromatography on silica gel with 1:5 benzene–EtOAc afforded 2.86 g (75%) of the tetrol **5** as a white solid: TLC (1:1 benzene–EtOAc) R_f 0.03; IR ($CHCl_3$) 3600 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.88 (d, J = 6 Hz, 3, C-4 CH_3), 0.95 (s, 3, CH_3), 1.11 (s, 3, CH_3), 1.29 (s, 3, CH_3), 1.31 (s, 3, CH_3), 3.70 (m, 1, C-3β H), 3.96 (d, J = 9 Hz, 1, C-16α H), and 4.20 (m, 1, C-11β H).

For analytical purposes this tetrol **5** was characterized as its 3,16-diacetate, which was prepared from a 100-mg (0.27 mmol) sample with 1 mL of acetic anhydride and 1 mL of pyridine in the standard fashion. After crystallization from EtOH, the analytical sample melted at 226–227 °C: TLC (1:1 benzene–EtOAc) R_f 0.26; IR ($CHCl_3$) 3600 (OH) and 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.84 (d, J = Hz, 3, C-4 CH_3), 0.99 (s, 3, CH_3), 1.22 (s, 3, CH_3), 1.30 (s, 3, CH_3), 1.38 (s, 3, CH_3), 2.06, 2.11 (2 s, 2 × 3, 2 CH_3CO), 4.38 (m, 1, C-11β H), 4.88 (d, J = 8 Hz, 1, C-16α H), and 4.98 (m, 1, C-3β H).

Anal. Calcd for $C_{26}H_{42}O_6$: C, 69.30; H, 9.39. Found: C, 69.32; H, 9.41.

Dihydroxy Enone 6. A. Periodate Cleavage of Tetrol 5. To a stirred solution of 3 g (8.22 mmol) of the tetrol **5** in 400 mL of CH_3OH was added dropwise over a period of 20 min 2.625 g (12.38 mmol, 1.50 equiv) of H_5IO_6 in 60 mL of H_2O and 90 mL of CH_3OH, and the mixture was stirred in the dark for 3.5 h. The solution was then treated with 250 mL of saturated brine, and the resulting voluminous white precipitate removed by filtration. The filter cake was washed with 200 mL of ether, and the product was isolated from the combined filtrate by further ether extraction.[11] The crude product (3.3 g) was tentatively assigned the acetal structure **19** on the basis of the IR [($CHCl_3$) 3605 cm^{-1} (OH)] and NMR [($CDCl_3$) δ 0.90 (d, J = 6 Hz, 3, C-4 CH_3), 0.98 (s, 3, CH_3), 1.20 (s, 3, CH_3), 1.40 (s, 2 × 3, 2 CH_3), 3.28, 3.54 (2, 2 × 3, 2 CH_3O), 3.73 (m, 1, C-3β H), 4.34 (m, 1, C-11β H), and 4.66 (q, J = 4 Hz, 1, C-16β H)]. The TLC (1:1 benzene–EtOAc) showed two spots at R_f 0.15 and 0.21 which we have taken to be isomers of the acetal structure **19**. No further purification was attempted with this material, but samples from this and similar experiments were used directly in the following cyclizations.

B. Hydrolysis of Acetal 19. To a solution of 5.0 g (11.9 mmol) of the crude acetal **19** from an experiment similar to that above in 1100 mL of acetone was added with stirring 360 mL of 4% hydrochloric acid,



19

and the mixture was stirred at room temperature for 2 h. After 200 mL of saturated brine was added, the mixture was neutralized with solid K_2CO_3, and the product was isolated by ether extraction.[11] The total crude yield of what appeared to be a mixture of the enone **6** and its hydration product (TLC, IR, NMR) was 4.50 g, but this material was not further purified for the next experiments.

C. Base-Catalyzed Enone Formation. A 1.063-g (2.93 mmol) portion of the above crude hydrolysate in 160 mL of a 1.5% solution of KOH (2.4 g) in 1:1 CH_3OH–H_2O was thoroughly degassed with an argon stream for 30 min, and then the mixture was heated under reflux in an argon atmosphere for 5 h. Isolation of the product from the cooled reaction mixture by ether extraction[11] afforded 863 mg of crude enone **6**. Chromatography of this material combined with 314 mg of similar crude enone **6** from another experiment (1177 mg) on 60 g of silica with 2:3-benzene–EtOAc in a medium-pressure chromatographic apparatus[8] and then crystallization of the solid material eluted in fractions 5–14 (125 mL) from EtOH afforded 990 mg of the enone **6**, mp 210–212 °C. The analytical sample, obtained after two further crystallizations of a portion of this material from EtOH, melted at 213–215 °C: TLC (1:1 benzene–EtOAc) R_f 0.14; IR ($CHCl_3$) 3605 (OH) and 1660 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.84 (d, J = 6 Hz, 3, C-4 CH_3), 0.97 (s, 2 × 3, 2 CH_3), 1.53 (s, 3, CH_3), 3.65 (m, 1, C-3β H), 4.32 (m, 1, C-11β H), 5.88 (d, J = 10 Hz, 1, C-17 H), and 6.80 (m, 1, C-16 H).

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.27; H, 9.95.

In larger scale experiments, chromatographic purification of the enone **6** from this sequence of reactions was not necessary and the crystalline crude product was used directly in further experiments.

The 3-monoacetate of a sample of the 3,11-dihydroxy enone **6** (100 mg) was prepared with 2 mL of acetic anhydride and 2 mL of pyridine for identification purposes. After preparative TLC (silica gel, 1:1 benzene–EtOAc) and crystallization (twice) from ether, the analytical sample melted at 174–175 °C: TLC (1:1 benzene–EtOAc) R_f 0.41; IR ($CHCl_3$) 3640 (sh), 3600 (OH), 1720 (CH_3C=O), and 1665 cm^{-1} (α,β-unsaturated C=O); NMR ($CDCl_3$) δ 0.82 (d, J = 6 Hz, 3, C-4 CH_3), 1.00 (s, 2 × 3, 2 CH_3), 1.54 (s, 3, CH_3), 2.08 (s, 3, CH_3C=O), 3.06 (dd, J = 4, 12 Hz, C-13α H), 4.40 (m, 1, C-11β H), 4.98 (m, 1, C-3β H), 6.00 (dd, J = 3, 5 Hz, 1, C-17 H), and 6.88 (m, 1, C-16 H).

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.19; H, 9.34.

Dihydroxy Ketone 7. A mixture of 475 mg (1.37 mmol) of the enone **6** and 50 mg of 10% palladium on carbon in 16 mL of HOAc was stirred in a hydrogen atmosphere at room temperature for 3 h. After filtration removed the catalyst and most of the acetic acid was removed at the rotary evaporator at reduced pressure, the product was isolated by ether extraction including a base wash.[11] The crude product obtained after removal of the ether amounted to 413 mg (86%) of the dihydroxy ketone **7**, mp 199–201 °C. The analytical sample, obtained after crystallization of a portion of this material from CH_2Cl_2–EtOH, melted at 204–206 °C: TLC (1:1 benzene–EtOAc) R_f 0.11; IR ($CHCl_3$) 3605 (OH) and 1700 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.83 (s, 3, C-4 CH_3), 0.99 (s, 2 × 3, 2 CH_3), 1.51 (s, 3, CH_3), 2.95 (dd, J = 5, 10.5 Hz, 1, C-13α H), 3.70 (m, 1, C-3β H), and 4.35 (m, 1, C-11β H).

Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.82; H, 10.41. Found: C, 75.88; H, 10.38.

The 3-monoacetate of a sample of the 3,11-dihydroxy ketone **7** (100 mg) was prepared with 2 mL of acetic anhydride and 2 mL of pyridine for identification purposes. The analytical sample, obtained after two crystallizations of this material from CH_2Cl_2–EtOH, melted at 231–231.5 °C: TLC (1:1 benzene–EtOAc) R_f 0.45; IR ($CHCl_3$) 3640 (sh), 3600 (OH), and 1720–1705 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.79 (s, 3, CH_3), 0.90 (d, J = 6 Hz, 3, C-4 CH_3), 1.00 (s, 3, CH_3), 1.51 (s, 3, CH_3), 2.09 (s, 3, CH_3C=O), 2.96 (dd, J = 4, 11 Hz, 1, C-13α H), 4.35 (m, 1, C-11β H), and 4.98 (m, 1, C-3β H).

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Found: C, 73.80; H, 9.94.

6α,9α-Dihydroxy-6bβ,10α,12aα,12bβ-tetramethyl-1,2,4aα,5,6,6aβ,6b,7,8,9,10,10aα,11,12,12a,12b-hexadecahydrochrysene. A. To a stirred solution of 172 mg (0.495 mmol) of the dihydroxy ketone **7** in 35 mL of dry benzene was added 12 mg (0.14 mL, 1.5 mmol) of dihydropyran and 5 mg of *p*-toluenesulfonic acid monohydrate, and the mixture was stirred at room temperature for 15 h. After the mixture was treated with 20 mL of saturated aqueous $NaHCO_3$, isolation of the product by ether extraction[11] afforded 262 mg of the crude ditetrahydropyranyl derivative. This was used for next reaction without further purification.

B. To a stirred solution of 150 mg (0.21 mL, 1.5 mmol) of diisopropylamine in THF at −78 °C under an argon atmosphere was added dropwise 0.62 mL (1.5 mmol) of 2.4 M *n*-butyllithium in *n*-hexane

solution, and the mixture was stirred at −78 °C for 80 min and then at room temperature for 30 min. To this solution which was cooled again to −78 °C was added a solution of 262 mg of the ditetrahydropyranyl derivative above in 2.5 mL of THF, and the mixture was allowed to warm up to 0 °C and stir at 0 °C for 30 min. Then 3.5 mL of HMPA and 1.7 g (10 mmol) of $ClPO[N(CH_3)_2]_2$ were added, and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was poured into 50 mL of saturated aqueous $NaHCO_3$, and stirring was continued for 30 min before extraction. The product was isolated by ether extraction,[11] and the oily crude material was dried and used directly for the next reaction without further purification.

C. A solution of the crude enol phosphorodiamidate above and 741 mg (10 mmol) of *t*-BuOH in 10 mL of THF was added to a stirred solution of 77 mg (11 mg-atoms) of lithium in 50 mL of liquid ammonia, and the reaction mixture was stirred under reflux of ammonia for 3 h. Ammonium chloride was added to decompose excess lithium, and the ammonia was evaporated. The product was isolated by ether extraction[11] and was used for the next reaction without further purification.

D. The olefin above was dissolved in 30 mL of acetone and 10 mL of 2 N hydrochloric acid, and the mixture was stirred at room temperature for 2 h. Isolation of the product by ether extraction[11] and purification by preparative TLC (silica gel, 25% *n*-hexane–ether) afforded 116 mg (overall yield 71%) of solid olefinic diol, which proved difficult to purify by crystallization and was directly silylated below.

3α-*tert*-Butyl Dimethylsilyl Ether (8). To a solution of 328 mg (0.99 mmol) of the olefinic diol accumulated from several runs in 3 mL of dry DMF was added 150 mg (2.5 mmol) of imidazole and 186 mg (1.23 mmol) of *t*-$BuMe_2SiCl$ under an argon atmosphere, and the mixture was stirred at room temperature for 2 days. After evaporation of the DMF and treatment of the residue with 10 mL of saturated brine, the product was isolated by ether extraction.[11] Purification of the crude product by chromatography on 30 g of silica gel with 10% EtOAc–*n*-hexane afforded 412 mg (92%, 65% overall) of the crystalline monosilyl ether **8**. Crystallization of a portion of this material from Et_2O–CH_3OH gave the silyl ether **13** as colorless crystals: mp 128–129 °C; IR ($CHCl_3$) 3625 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.0 (s, 6), 0.77 (d, 3, J = 6 Hz), 0.79 (s, 3), 0.87 (s, 3), 0.90 (s, 3), 1.32 (s, 3), 3.67 (m, 1, $R_2CHOSiMe_2$-*t*-Bu), 4.25 (m, 1, R_2CHOH), 5.23 and 5.57 (two m, 1 each, CH=CH).

Anal. Calcd for $C_{28}H_{50}O_2Si$: C, 75.27; H, 11.28. Found: C, 75.24; H, 11.17.

Olefinic Ketone 9. A. To a stirred solution of 116 mg (0.16 mL, 1.15 mmol) of diisopropylamine in 1.5 mL of THF at −78 °C under an argon atmosphere was added dropwise 0.48 mL (1.15 mmol) of 2.4 M *n*-butyllithium in *n*-hexane solution, and the mixture was stirred at −78 °C for 30 min and then at room temperature for 30 min. To this solution, which was cooled again to −78 °C, was added a solution of 103 mg (0.23 mmol) of the alcohol **8** in 1.5 mL of THF. The cooling bath was removed, and the mixture was stirred at room temperature for 30 min. Then 1 mL of HMPA and 392 mg (2.3 mmol) of $ClPO[N(CH_3)_2]_2$ were added, and the mixture was stirred at room temperature for 3 h. The mixture was poured into 30 mL of saturated aqueous $NAHCO_3$, and stirring was continued for 1 h before extraction[11] and used directly for the next reaction without further purification.

B. The above crude phosphorodiamidate and 341 mg (4.6 mmol) of *t*-BuOH were dissolved in 1 mL of THF and 15 mL of ethylamine, and to this solution 35.5 mg (5.1 mg-atoms) of lithium was added. The mixture was stirred under reflux of ethylamine and an argon atmosphere for 1 h. The excess lithium was destroyed with NH_4Cl, and most of ethylamine was evaporated. After treatment of the residue with 10 mL of saturated brine, isolation of the product by ether extraction[11] and purification by chromatography on 20 g of silica gel with 5% EtOAc–*n*-hexane afforded 92 mg (93%) of crystalline 11-deoxysilyl ether. Crystallization of a portion of this material from Et_2O–CH_3OH gave colorless crystals: mp 115–116 °C; NMR ($CDCl_3$) δ 0.0 (s, 6), 0.80 (d, 3, J = 6 Hz), 0.83 (s, 6), 0.88 (s, 9), 1.13 (s, 3), 3.67 (m, 1, $R_2CHOSiMe_2$-*t*-Bu), 5.22 and 5.50 (two m, 1 each, CH=CH).

Anal. Calcd for $C_{28}H_{50}OSi$: C, 78.06; H, 11.70. Found: C, 77.94; H, 11.53.

C. A solution of 380 mg (0.88 mmol) of the 11-deoxysilyl ether above and 2.3 g of *tert*-butylammonium fluoride in 5 mL of THF was stirred at room temperature for 4 days. Isolation of the product by ether extraction and purification by chromatography on 20 g of silica gel with 5% EtOAc–*n*-hexane afforded 251 mg (94%) of the corresponding alcohol: IR ($CHCl_3$) 3600, 3300–3550 cm^{-1} (OH); NMR ($CDCl_3$) δ 3.75 (m, 1, $R_2CHOSiMe_2$-*t*-Bu), 5.27 and 5.56 (two m, 1 each, CH=CH). This material was not further purified, but used directly in the following experiment.

D. To a solution of 261 mg (0.83 mmol) of the above alcohol in 4 mL of HOAc which was cooled in an ice bath was added a solution of 105 mg (1.05 mmol) of chromium trioxide in 2 mL of 95% HOAc and the mixture was stirred at room temperature for 30 min. After CH_3OH was added to destroy excess oxidant, the solvent was evaporated under reduced pressure, and the product was isolated by $HCCl_3$ extraction.[11] Purification of the crude product by chromatography on 20 g of silica gel with 20% EtOAc–*n*-hexane afforded 187 mg (72%) of crystalline ketone **9**. Crystallization of a portion of this material from CH_2Cl_2–CH_3OH gave colorless crystals: mp 159–161 °C; IR ($CHCl_3$) 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.81 (s, 3), 0.98 (s, 3), 0.99 (d, 3, J = 6 Hz), 1.07 (s, 3), 5.28 and 5.57 (two m, 1 each, CH=CH).

Anal. Calcd for $C_{22}H_{34}O$: C, 84.02; H, 10.90. Found: C, 84.03; H, 10.88.

Hydroxy Ketone 10. A. A solution of 222 mg (0.71 mmol) of the ketone **9**, 10 mg of *p*-toluenesulfonic acid monohydrate, and 1 mL of ethylene glycol in 50 mL of benzene was heated under reflux in an argon atmosphere for 50 h in an apparatus equipped with a Dean-Stark water separator and molecular sieves (4A). After cooling, 10 mL of saturated aqueous $NaHCO_3$ was added to the mixture, and isolation of the product by ether extraction[11] afforded 248 mg (98%) of the crystalline ketal. Crystallization of a portion of this material from Et_2O–CH_3OH gave colorless crystals: mp 142–143 °C; NMR ($CDCl_3$) δ 0.64 (s, 3), 0.69 (d, 3, J = 6 Hz), 0.81 (s, 3), 1.02 (s, 3), 3.80 (s, 4, $-OCH_2CH_2O-$), 5.13 and 5.45 (two m, 1 each, CH=CH).

Anal. Calcd for $C_{24}H_{38}O_2$: C, 80.39; H, 10.80. Found: C, 80.21; H, 10.66.

B. To a solution of 1.2 g (17 mmol) of 2-methyl-2-butene in 1 mL of THF at −78 °C under argon atmosphere was added dropwise in 10 min 7.15 mL (8.5 mmol) of 1.19 M BH_3–THF in THF solution. The mixture was then warmed to 3 °C, and stirring was continued for 4 h. This stirred solution was cooled again at −78 °C for 30 min, at 3 °C for 2 h, and at room temperature for 22 h. This mixture was cooled in an ice bath, and 8 mL of 3 N aqueous NaOH and 10 mL of 30% aqueous H_2O_2 were cautiously added. The mixture was stirred vigorously at 55–60 °C for 1 h. After cooling 20 mL of saturated aqueous $NaHCO_3$ solution was added, and the product was isolated by $HCCl_3$ extraction.[11] The crude product was separated by chromatography on 20 g of silica gel. From the fractions eluted with 10% EtOAc–*n*-hexane 40 mg (20%) of 17a-norfusidan-3-ethylene ketal was obtained. From the fraction eluted with 50% *n*-hexane–EtOAc 213 mg (81%) of the crude mixture of the 17- and 17a-hydroxy derivatives was obtained. This mixture was used for the next oxidation reaction without separation.

C. To a stirred suspension of 330 mg (3.3 mmol) of chromium trioxide in 10 mL of dry CH_2Cl_2 which was cooled with an ice bath was added dropwise 577 mg (0.59 mL, 7.3 mmol) of dry pyridine, and the mixture was stirred at room temperature for 15 min. To this mixture was added dropwise a solution of 208 mg (0.55 mmol) of the above mixture of hydroxy derivatives in 5 mL of CH_2Cl_2, and the mixture was stirred for an additional 15 min. After treatment of the mixture with 40 mL of saturated aqueous $NaHCO_3$, the product, isolated by ether extraction,[11] amounted to 188 mg (90%) of a crude crystalline mixture of ketones, which was used directly for the next reaction without further purification.

D. To a stirred solution of 188 mg (0.5 mmol) of the above ketone mixture in 20 mL of THF which was cooled with an ice bath was added 635 mg (2.5 mmol) of Li(*t*-$BuO)_3AlH$, and the mixture was stirred at 3 °C for 2 h and at room temperature for 15 h. The mixture was cooled with an ice bath, and the excess reagent was decomposed with 1.25 mL of 2 N aqueous NaOH. The mixture was filtered through 10 g of silica with suction, and the filter was washed with CH_2Cl_2. Removal of the solvent afforded 190 mg of crude crystalline mixture of hydroxy derivatives. This material was dissolved in 20 mL of acetone and 2 mL of 2 N hydrochloric acid, and the solution was stirred at room temperature for 2 h. Isolation of the product by 10% CH_2Cl_2–Et_2O extraction[11] and purification by chromatography on 21 g of silica gel with 50% *n*-hexane–EtOAc gave 55 mg (total yield from olefinic ketone **9** was 25%) of a less polar product which was identified as a mixture of 17(a)α- and 17(a)-β-hydroxy derivatives. Subsequently, 88 mg (total yield from olefinic ketone **9** was 39%) of a more polar product was identified as 17a-norfusidan-3-on-17β-ol (**10**). Crystallization of a portion of this material from CH_2Cl_2–Et_2O gave colorless crystals: mp 197–198 °C; IR ($CHCl_3$) 3590, 3250–3550 (OH), 1695 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.97, 1.00, 1.07 (three s, 3 each), 1.01 (d, 3, J = 6 Hz), 3.55 (br m, 1, R_2CHOH).

Anal. Calcd for $C_{22}H_{36}O_2$: C, 79.46; H, 10.91. Found: C, 79.49; H, 11.00.

Unsaturated Ketone 11. A. From Degradation Sequence. 1. To a solution of 47 mg (0.14 mmol) of keto alcohol **10** in 3 mL of dry DMF under an argon atmosphere was added 30.6 mg (0.45 mmol) of imidazole and 60.2 mg (0.4 mmol) of t-$BuMe_2SiCl$, and the mixture was stirred at room temperature for 6 h. After evaporation of the DMF under reduced pressure and treatment of the residue with 3 mL of saturated brine, the product, isolated by 20% CH_2Cl_2–Et_2O ether extraction[11] and purified by chromatography on 20 g of silica gel with 20% EtOAc–n-hexane, amounted to 58 mg (92%) of the crystalline silyl ether. Crystallization of a portion of this material from CH_2Cl_2–Et_2O gave colorless crystals: mp 200–201 °C; IR ($CHCl_3$) 1695 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.04 (s, 6), 0.88 (s, 12), 0.98 (s, 3), 1.02 (d, 3, J = 7 Hz), 1.08 (s, 3), 3.2–3.7 (br m, 1, $R_2CHOSiMe_2$-t-Bu).

Anal. Calcd for $C_{28}H_{50}O_2Si$: C, 75.27; H, 11.28. Found: C, 75.20; H, 11.33.

2. To a suspension of 47 mg (1.1 mmol) of rinsed 56% sodium hydride in mineral oil in 0.5 ml of benzene under argon atmosphere was added 3 mg (4 μL) of CH_3OH and the mixture was stirred at room temperature for 30 min. A solution of 48 mg (0.11 mmol) of the above ketone in 2.5 mL of benzene and 82 mg (0.09 mL, 1.1 mmol) of ethyl formate were added, and the mixture was stirred at room temperature for 12 h. The excess sodium hydride was destroyed with H_2O. The aqueous layer was acidified with 2 N hydrochloric acid, and the product was isolated by CH_2Cl_2 extraction. This process afforded 50 mg of crystalline material which was used directly in the next reaction without further purification: IR ($CHCl_3$) 1575, 1625 cm^{-1} (br absorption); NMR ($CDCl_3$) δ 0.05 (s, 6), 0.80 (s, 3), 0.88 (s, 12), 1.11 (s, 3), 1.18 (d, 3, J = 7 Hz), 3.2–3.7 (br m, 1, $R_2CHOSiMe_2$-t-Bu), 8.53 (m, 1, C=CHOH).

3. A solution of 50 mg of the crude formyl ketone from above and 27 mg (0.16 mmol) of 98% dichlorodicyanobenzoquinone in 3 mL of dry benzene was stirred at room temperature for 30 min. The mixture was then passed through a column of 20 g of silica gel, and the fraction eluted with 33% EtOAc–n-hexane (200 ml) was collected. Evaporation of the solvent gave 43 mg of product. Separation of the crude product by preparative TLC (silica gel, 20% EtOAc–n-hexane) afforded 11 mg of starting ketone and 30 mg of crystalline enone aldehyde: IR ($CHCl_3$) 1675, 1695, 1725 cm^{-1} [COC(CHO)=C]; NMR ($CDCl_3$) δ 0.05 (s, 6), 0.88 (s, 12), 0.92 (s, 3), 1.15 (s, 3), 1.18 (d, 1, J = 6.5 Hz), 3.2–3.7 (br m, 1, $R_2CHOSiMe_2$-t-Bu), 8.08 (s, 1, CH=C–CO), 9.91 (s, 1, CHO).

4. A solution of 30 mg (0.063 mmol) of the above enone aldehyde and 64.5 mg (0.07 mmol) of tris(triphenylphosphine)rhodium chloride in 3 mL of dry benzene was heated under reflux in an argon atmosphere for 2 h. After cooling, the product was separated by preparative TLC (silica gel, 20% EtOAc–n-hexane), and amounted to 20 mg (total yield from hydroxy ketone **10** was 39% of the enone **11**). Crystallization of a portion of this material from CH_2Cl_2–CH_3OH gave colorless crystals: mp 192–193 °C; IR ($CHCl_3$) 1660 cm^{-1} (COCH=CH); NMR ($CDCl_3$) δ 0.00 (s, 6), 0.82 (s, 12), 0.92 (s, 3), 1.06 (s, 3), 1.07 (d, 1, J = 6.5 Hz), 5.75 and 7.27 (two d, 1 each, COCH=CH, J = 10 Hz); mass measured $M^+ - 57$, 387.

Anal. Calcd for $C_{28}H_{48}O_2Si$: C, 75.61; H, 10.88. Found: C, 75.55; H, 10.87.

The TLC, IR, NMR, and mass spectra of this authentic fusidic acid derivative were identical with those of the synthetic sample prepared above.

B. From Synthetic Sequence. A solution of 0.35 M lithium diisopropylamide in 14% hexane–THF was prepared by adding 1.4 mL (3.5 mmol) of a solution of 2.52 M n-butyllithium in hexane solution to a solution of 390 mg (0.54 mL, 3.9 mmol) of diisopropylamine in 8 mL of THF at −78 °C. The volume of the solution was adjusted to 10 mL using a volumetric flask at room temperature.

To a stirred solution of 14 mg (0.033 mmol) of the enone **18** in 1.5 mL of THF was added 0.14 mL (0.049 mmol) of 0.35 M lithium diisopropylamide in 14% n-hexane–THF at 78 °C under an argon atmosphere, and the mixture was stirred at −78 °C for 10 min, after which it was allowed to warm up to room temperature. After stirring at room temperature for 15 min, 460 mg (0.2 mL, 3.25 mmol) of CH_3I was added in one portion to the mixture, and it was stirred at room temperature for 30 min. Isolation of the product by CH_2Cl_2 extraction[11] and purification of the crude product by preparative TLC (silica gel, 10% EtOAc–n-hexane) gave 11 mg (76%) of ketone **11**. Crystallization of this material from CH_2Cl_2–CH_3OH gave the ketone **11** as colorless crystals: mp 186–187 °C; IR ($CHCl_3$) 1660 cm^{-1} (COCH=CH); NMR ($CDCl_3$) δ 0.00 (s, 6), 0.82 (s, 12), 0.92 (s, 3), 1.06 (s, 3), 1.07 (d, 1, J = 6.5 Hz), 5.75 and 7.27 (two d, 1 each, COCH=CH, J = 10 Hz); mass measured $M^+ - 57$, 387.

Anal. Calcd for $C_{28}H_{48}O_2Si$: C, 75.61; H, 10.88. Found: C, 75.57; H, 10.81.

This product was identical with the compound derived from the natural fusidic acid in respect to TLC, IR, NMR, and mass spectra.

3β-Hydroxy-6bβ,12aα,12bβ,-trimethyl-1,2,3,4,4aα,5,6,6aβ,-6b,7,11,12,12a,12b-tetradecahydro-9(8*H*)-chrysenone. To a cooled (3 °C) solution of 170 mg (0.54 mmol) of the enedione **12**[2] in 42 mL of dry THF and 8.3 mL of dry benzene under an argon atmosphere was added a solution of 688 mg (2.71 mmol) of $Li(t\text{-}BuO)_3AlH$ in 10.5 mL of dry THF, and the solution was stirred for 110 min. After the addition of 1.13 mL (2.82 mmol) of 10% aqueous NaOH, the reaction mixture was stirred for 1 h at room temperature and then filtered through 10 g of silica gel with the aid of 150 mL of EtOAc. After removal of the solvent at reduced pressure, there remained 166 mg (67%) of crude, crystalline enone alcohol, mp 193–196 °C, which was sufficiently pure to be used directly in the following experiments. An analytical sample, obtained after crystallization of a portion of this material from CH_2Cl_2–CH_3OH, melted at 199–200 °C; tlc)1:1 benzene–EtOAc) R_f 0.24; IR ($CHCl_3$) 3600 (OH), 1650 (unsaturated C=O), and 1625 cm^{-1} (sh, C=C); NMR ($CDCl_3$) δ 0.93 (s, 6, 2 CH_3), 1.24 (s, 3, CH_3), 3.50 (br m, 1, C-17α H), and 5.82 (s, 1, C-4 H).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.74; H, 10.13.

Olefinic Ketal 13. A. A solution of 138 mg (0.44 mmol) of the above crude enone alcohol, 1.4 mL of ethylene glycol, and 14 mg of p-toluenesulfonic acid monohydrate in 125 mL of benzene was heated at reflux under a Dean-Stark water separator for 3 h. After cooling, the product was isolated by ether extraction including a base wash[11] and purified by chromatography on 20 g of silica gel with 3:1 benzene–EtOAc. In this manner there was obtained 147 mg (94%) of the hydroxy ketal, mp 178–181 °C, the analytical sample of which, obtained after three crystallizations from CH_2Cl_2–EtOH, melted at 183–184 °C: TLC (1:1 benzene–EtOAc) R_f 0.39; IR ($CHCl_3$) 3600 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.89 (s, 3, CH_3), 1.00 (s, 3, CH_3), 1.09 (s, 3, CH_3), 3.94 (s, 4, OCH_2CH_2O), and 5.37 (d, J = 5 Hz, 1, C-6 H).

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.06. Found: C, 76.48; H, 10.20.

B. To a solution of 688 mg (1.9 mmol) of the above hydroxy ketal in 25 mL of dry DMF under argon atmosphere was added with stirring 390 mg (5.7 mmol) of imidazole and 570 mg (3.8 mmol) of t-$BuMe_2SiCl$, and the mixture was allowed to react at room temperature for 15 h. After evaporation of the DMF under reduced pressure and then treatment of the residue with 20 mL of saturated brine, the product was isolated by ether extraction.[11] Purification of the crude product by chromatography on 50 g of silica gel with 33% EtOAc–n-hexane afforded 895 mg (99%) of the crystalline silyl ether **13**. Crystallization of a portion of this material from ether–ethanol gave colorless crystals: mp 146–147 °C; NMR ($CDCl_3$) δ 0.04 (s, 6), 0.88 (s, 12), 0.99 (s, 3), 1.09 (s, 3), 3.2–3.7 (br m, 1, $R_2CHOSiMe_2$-t-Bu), 3.93 (s, 4), 5.31 (m, 1, RCH=C).

Anal. Calcd for $C_{29}H_{50}O_3Si$: C, 73.36; H, 10.62. Found: C, 73.34; H, 10.50.

Epoxy Ketal 14. To a stirred solution of 895 mg (1.9 mmol) of the ketal **13** and 320 mg (3.8 mmol) of anhydrous $NaHCO_3$ in 20 mL of CH_2Cl_2 under an argon atmosphere at 3 °C was added 770 mg (3.8 mmol) of 85% m-chloroperbenzoic acid, and the mixture was stirred at 3 °C for 1 h. The mixture was diluted with 100 mL of ether, and the ethereal phase was washed with 20 mL of 10% aqueous $Na_2S_2O_3$, 5% aqueous $NaHCO_3$ (20 mL), and saturated brine (two 20-mL portions). The aqueous layer were extracted with either (two 50-mL portions), and the combined ethereal layers were dried over $MgSO_4$ and evaporated. Purification of the crude product by chromatography on 50 g of silica gel with 33% EtOAc–n-hexane afforded 917 mg (98%) of the crystalline epoxide **14**. Crystallization of a portion from ether–ethanol gave colorless crystals: mp 161–162 °C; NMR ($CDCl_3$) δ 0.04 (s, 6), 0.84 (s, 3), 0.88 (s, 9), 1.06 (s, 3), 1.13 (s, 3), 3.09 (m, 1, RCHOC), 3.2–3.7 (br m, 1, $R_2CHOSiMe_2$-t-Bu), 3.94 (s, 4).

Anal. Calcd for $C_{29}H_{50}O_4Si$: C, 70.97; H, 10.27. Found: C, 70.92; H, 10.14.

Ketal Ketone 16. To a stirred solution of 900 mg (1.83 mmol) of the epoxide **14** in 55 mL of dry CH_2Cl_2 which was cooled with an ice bath was added under argon atmosphere 313 mg (276 μL, 3.25 mmol) of boron trifluoride etherate. After stirring for 3 min at 3 °C, the reaction mixture was quenched with 5 mL of Et_3N and 40 mL of saturated aqueous $NaHCO_3$, and the product was isolated by ether extraction.[11] The mixture of the products (913 mg) was separated by chromatography on 60 g of silica gel with 25% EtOAc–n-hexane and two main products were isolated.

The less polar crystalline product, 298 mg (33%), was identified as 17a-homo-30-nor-5αa-fusida-17β-$tert$-butyldimethylsilyloxy-6-keto-3-ethylene ketal (**16**). Crystallization of a portion from

CH_2Cl_2–CH_3OH gave colorless crystals: mp 169–170 °C; IR ($CHCl_3$) 1695 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.05 (s, 6), 0.88 (s, 12), 1.31 (s, 6), 3.2–3.7 (br m, 1, $R_2CHOSiMe_2$-*t*-Bu), 3.92 (s, 4).

Anal. Calcd for $C_{29}H_{45}O_4Si$: C, 70.97; H, 10.27. Found: C, 71.04; H, 10.16.

The other polar product, 231 mg (36%), was tentatively assigned as unsaturated hydroxy ketal **15**: oil; IR ($CHCl_3$) 3490, 3300–3550 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.00 (s, 6), 0.76 (s, 3), 0.85 (s, 9), 0.97 (s, 3), 1.08 (s, 3), 3.4–3.8 (br m, 2, R_2CHOH and $R_2CHOSiMe_2$-*t*-Bu), 3.90 (s, 4), 5.12 (m, 1, RCH=C).

Anal. Calcd for $C_{29}H_{35}O_4Si$: C, 70.97; H, 10.27. Found: C, 71.09; H, 10.18.

Ketone 17. A. To a stirred solution of 300 mg (0.61 mmol) of the ketone **16** in 80 mL of THF which was cooled with an ice bath was added under an argon atmosphere a solution of 930 mg (3.66 mmol) of Li(*t*-BuO)$_3$AlH in 20 mL of THF. The mixture was stirred for 30 min, and then allowed to warm to room temperature for 4 h. The reaction mixture was cooled with an ice bath and excess reagent was decomposed with ca. 3 mL of saturated brine. The mixture was filtered and the filter cake was washed with EtOAc. Extraction of the product with EtOAc and purification by chromatography on alumina with CH_2Cl_2 afforded 263 mg (88%) of the corresponding alcohol. Crystallization of a portion of this material from CH_2Cl_2–CH_3OH gave colorless crystals: mp 205–206 °C; IR ($CHCl_3$) 3600 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.03 (s, 6), 0.88 (s, 9), 0.93 (s, 3), 1.07 (s, 3), 1.13 (s, 3), 3.3–3.7 (br m, 1, $R_2CHOSiMe_2$-*t*-Bu), 3.93 (s, 4, and m, 1, $-OCH_2CH_2O-$ and R_2CHOH).

Anal. Calcd for $C_{29}H_{52}O_4Si$: C, 70.75; H, 10.64. Found: C, 70.77; H, 10.72.

B. To a stirred solution of 115 mg (0.16 mL, 1.12 mmol) of diisopropylamine in 4 mL of THF at −78 °C under an argon atmosphere was added dropwise 0.47 mL (1.12 mmol) of 2.4 M *n*-butyllithium solution in *n*-hexane, and the mixture was stirred at −78 °C for 30 min and at room temperature for 30 min. To this solution of lithium diisopropylamide in THF–*n*-hexane was added under an argon atmosphere at room temperature a solution of 185 mg (0.38 mmol) of the above alcohol in 4 mL of THF. After stirring for 30 min at room temperature, 2 ml of HMPA and 638 mg (0.65 mL, 3.75 mmol) of $ClPO[N(CH_3)_2]_2$ were added, and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 50 mL of saturated aqueous $NaHCO_3$ and stirring was continued for 30 min before extraction. The product was isolated by ether extraction.[11] The oily product was dried and used for the next reaction without further purification.

To a solution of the above crude phosphoramidate derivative and 300 mg of (4 mmol) of *t*-BuOH in 20 mL of ethylamine and 2 mL of THF was added 35 mg (5 mg-atoms) of lithium, and the mixture was stirred under reflux for 1 h. Excess lithium was destroyed with NH_4Cl and most of the ethylamine was evaporated. The residue was treated with 10 mL of saturated brine, and the product was isolated by ether extraction.[11] Purification of the crude product by chromatography on silica gel with 25% EtOAc–*n*-hexane afforded 152 mg (85%) of crystalline 6-deoxyketal. Crystallization of a portion of this material from Et_2O–CH_3OH gave colorless crystals: mp 154–156 °C; NMR ($CDCl_3$) δ 0.03 (s, 6), 0.84 (s, 3), 0.88 (s, 12), 1.12 (s, 3), 3.3–3.7 (m, 1, $R_2CHOSiMe_2$-*t*-Bu), 3.93 (s, 4).

Anal. Calcd for $C_{29}H_{52}O_3Si$: C, 73.05; H, 10.99. Found: C, 73.02; H, 10.97.

C. To a stirred solution of 217 mg (0.46 mmol) of the above ketal in 20 mL of acetone at 3 °C was added 1.25 mL of 2 N hydrochloric acid (2.5 mmol), and then the mixture was stirred at room temperature for 1.5 h. Isolation of the product by ether extraction[11] afforded the corresponding hydroxy ketone, which on further purification by crystallization from CH_2Cl_2–CH_3OH, gave 125 mg (87%) of pure hydroxy ketone: mp 179–180 °C; IR ($CHCl_3$) 1700 (C=O), 3590, 3200–3550 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.88, 0.97, 1.10 (3 s, 3 each), 3.5 (m, 1, R_2CHOH).

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.10; H, 10.71.

D. To a solution of 120 mg (0.38 mmol) of the above hydroxy ketone in 5 mL of dry DMF under an argon atmosphere were added with stirring 82 mg (1.2 mmol) of imidazole and 150 mg (1.0 mmol) of *t*-$BuMe_2SiCl$, and the mixture was stirred at room temperature for 24 h. After evaporation of the DMF under reduced pressure and then treatment of the residue with 20 mL of saturated brine, the product was isolated by 25% CH_2Cl_2–Et_2O extraction.[11] Purification of the crude product by chromatography on silica gel with 33% EtOAc–*n*-hexane afforded 153 mg (100%) of crystalline silyl ether **17**. Crystallization of a portion of this material from CH_2Cl_2–CH_3OH gave pure silyl ether **17**: mp 195–196 °C; IR ($CHCl_3$) 1695 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.04 (s, 6), 0.87 (s, 12), 0.96 (s, 3), 1.09 (s, 3), 3.25–3.7 (br m, 1, $R_2CHOSiMe_2$-*t*-Bu).

Anal. Calcd for $C_{27}H_{48}O_2Si$: C, 74.93; H, 11.18. Found: C, 74.97; H, 11.17.

Unsaturated Ketone 18. A. To the stirred suspension of 24.5 mg (0.57 mmol) of rinsed 56% hydride in mineral oil in 0.5 mL of benzene under argon atmosphere was added 3 mg (0.3 μL) of CH_3OH and the mixture was stirred at room temperature for 30 min. Then a solution of 49 mg (0.113 mmol) of ketone **17** in 2.5 mL of dry benzene and 42.5 mg (0.043 mL, 0.57 mmol) of ethyl formate was added, and the mixture was stirred at room temperature for 6 h.

The excess sodium hydride was destroyed with H_2O, and the aqueous layer was acidified with 2 N hydrochloric acid. Isolation of the product by CH_2Cl_2 extraction[11] afforded 5.1 mg of the crystalline formyl ketone which was used directly in the next reaction without further purification: IR ($CHCl_3$) 1575, 1630 cm^{-1} (br absorption) (COC=CHOH); NMR ($CDCl_3$) δ 0.04 (s, 3), 0.77 (s, 3), 0.97 (s, 12), 1.09 (s, 3), 3.5–3.7 (m, 1, $R_3CHOSiMe_3$-*t*-Bu), 8.64 (s, 1, C=CHOH).

B. A solution of 51 mg of the crude formyl ketone above and 31.5 mg (0.13 mmol) of 98% dichlorodicyanobenzoquinone in 5 mL of dry benzene was stirred at room temperature for 1 h. The mixture was then passed through a column of 10 g of silica gel, and the fraction eluted with 33% EtOAc–*n*-hexane (300 mL) was collected. Evaporation of the solvent gave 43 mg of the residue. Purification of the crude product by preparative TLC (silica gel, 25% EtOAc–*n*-hexane) afforded 37 mg of crystalline enone aldehyde: IR ($CHCl_3$) 1670, 1685, 1720 cm^{-1} [–COC(CHO)=C]; NMR ($CDCl_3$) δ 0.04 (s, 6), 0.91 (s, 12), 0.96 (s, 3), 1.16 (s, 3), 2.46 (m, 2, $COCH_2$–), 3.3–3.7 (br m, 1, $R_2CHOSiMe_2$-*t*-Bu), 8.20 (s, 1, CH=CCO), 10.02 (s, 1, CHO).

C. A solution of 37 mg (0.08 mmol) of the above enone aldehyde and 82 mg (0.088 mmol) of tris(triphenylphosphene)rhodium chloride in 3.5 mL of dry benzene was heated under reflux in an argon atmosphere for 2 h. After cooling, the product was separated by preparative TLC (silica gel, 25% EtOAc–*n*-hexane) and 25 mg (total yield from the ketone **17** was 56%) of crystalline enone **18** was obtained. Crystallization of a portion of this material from Et_2O–CH_3OH gave the pure enone **18**: mp 203–204 °C; IR ($CHCl_3$) 1660 cm^{-1} (COCH=CH); NMR ($CDCl_3$) δ 0.04 (s, 6), 0.92 (s, 12), 1.00 (s, 3), 1.11 (s, 3), 2.37 (m, 2 H, CH_2CO), 5.79 and 7.32 (two d, 1 each, CH=CHCO, J = 10 Hz).

Anal. Calcd for $C_{27}H_{46}O_2Si$: C, 75.28; H, 10.77. Found: C, 75.16; H, 10.54.

Registry No.—**1**, 6990-06-3; **1** (R = H; R′ = Me), 21157-24-4; **2**, 14424-45-4; **3**, 61446-33-1; **3** alcohol, 61436-93-9; **3** alcohol tetraacetate, 61436-94-0; **4**, 14185-98-9; **5**, 61436-95-1; **5** 3,16-diacetate, 61436-96-2; **6**, 61436-97-3; **6** 3-acetate, 61436-98-4; **7**, 61436-99-5; **7** 3 acetate, 61437-00-1; **8**, 61437-01-2; **8** phosphorodiamidate, 61446-32-0; **8** 11-deoxy silyl ether, 61437-02-3; **8** diol, 61446-30-8; **9**, 61437-03-4; **9** alcohol, 61437-04-5; **9** ethylene ketal, 61437-05-6; **9** ketal 17,17a-dihydro-17-ol, 61437-06-7; **9** ketal 17,17a-dihydro-17a-ol, 61437-07-8; **9** ketal 17,17a-dihydro-17-one, 61462-87-1; **9** ketal 17,17a-dihydro-17a-one, 61437-08-9; **9** 17,17a-dihydro-17aα-ol, 61437-09-0; **9** 17,17a-dihydro-17aβ-ol, 61437-10-3; **10**, 61446-10-4; **10** TBS, 61446-11-5; **11**, 61446-12-6; **11** formyl ketone, 61446-13-7; **11** enone aldehyde, 61446-14-8; **12**, 61446-15-9; **12** 17β-ol, 61446-16-0; **13**, 61446-17-1; **13** 17β-ol, 61446-18-2; **14**, 61446-19-3; **15**, 61446-20-6; **16**, 61446-21-7; **16** ol, 61446-22-8; **16** phosphoramidate, 61476-92-4; **17**, 61446-23-9; **17** ol, 61446-24-0; **17** ketal, 61446-25-1; **17** formyl ketone, 61446-26-2; **17** enone aldehyde, 61446-27-3; **18**, 61446-28-4; **19**, 61446-29-5; *t*-$BuMe_2SiCl$, 18162-48-6.

References and Notes

(1) The authors are grateful for the support of this investigation by Public Health Service Research Grant AM 14160 from the National Institute of Arthritis and Metabolic Diseases and the Hoffmann-La Roche Foundation.
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(8) Boiling points are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 237B grating infrared spectrometer and nuclear magnetic resonance (NMR) spectra were recorded using a Varian T-70 spectrometer. Chemical shifts are reported as δ values in parts per million relative to Me_4Si (δ 0.0 ppm) as an internal standard. Deuteriochloroform for NMR

and chloroform for IR spectra were filtered through neutral alumina before use.

Vapor phase chromatographic (VPC) analyses were determined on either a Hewlett-Packard 5750 equipped with a flame ionization detector or a Varian 920 equipped with a thermal conductivity detector using helium as the carrier gas under the indicated conditions. The indicated liquid phase was absorbed on 60–80 mesh Chromosorb W AW DMCS.

Silica gel columns used the 0.05–0.2 mm silica gel manufactured by E. Merck and Co., Darmstadt, Germany. Acidic silica gel refers to Silicar CC-4 special "for column chromatography", sold by Mallinckrodt Chemical Works, St. Louis, Mo. Preparative medium-pressure chromatography was performed using glass columns of the indicated length and diameter with fittings supplied by Laboratory Data Control, Riviera Beach, Fla., and an instrument minipump supplied by Milton Roy Co., St. Petersburg, Fla. (instrumentation designed by R. H. Mueller, those laboratories, and copies are available on request). The columns were packed with silica gel H "for TLC acc. to Stahl" (10–40 μ) manufactured by E. Merck and Co., Darmstadt, Germany. Solvents were degassed under water aspirator vacuum prior to use.

Analytical thin layer chromatography was conducted on 2.5 × 10 cm precoated TLC plates, silica gel 60 F-254, layer thickness 0.25 mm, manufactured by E. Merck and Co., Darmstadt, Germany.

"Dry" solvents were dried immediately prior to use. Ether and tetrahydrofuran (THF) were distilled from lithium aluminum hydride; pyridine, triethylamine, diisopropylamine, *N*-isopropylcyclohexylamine, trimethylchlorosilane (Me_3SiCl), hexamethylphosphoramide (HMPA), and benzene were distilled from calcium hydride; dichloromethane, methyl iodide, and hexane were distilled from phosphorus pentoxide. "Petroleum ether" refers to the "analyzed reagent" grade hydrocarbon fraction, bp 30–60 °C, which is supplied by J. T. Baker Co., Phillipsburg, N.J., and was not further purified.

Standard solutions of *tert*-butyldimethylchlorosilane (*t*-$BuMe_2SiCl$) in hexane (ca. 3.3 M) or HMPA (ca. 1.5 M) were employed.

Reactions were run under an argon atmosphere arranged with a mercury bubbler so that the system could be alternately evacuated and filled with argon and left under a positive pressure.

Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(9) Generously supplied by Dr. G. O. Godtfredsen (Leo Pharmaceutical Co.) and A. Brossi (Hoffmann-La Roche and Co.).
(10) H. Immer and K. Huber, *Helv. Chim. Acta*, **54**, 1347 (1971).
(11) In cases where the products were isolated "by solvent extraction", the procedure generally followed was to dilute the reaction mixture with the indicated solvent or to extract the aqueous solution with several portions of the indicated solvent; then the combined organic layers were washed with several portions of water followed by saturated brine. The organic layer was dried over anhydrous sodium or magnesium sulfate, then filtered, and the solvent was evaporated from the filtrate under reduced pressure (water aspirator) using a rotary evaporator. The use of the terms "base wash" or "acid wash" indicate washing the organic solution with saturated aqueous sodium bicarbonate solution or with dilute aqueous hydrochloric acid, respectively, prior to the aforementioned wash with water.

Carbon-13 Nuclear Magnetic Resonance Studies on a New Antitubercular Peptide Antibiotic LL-BM547β

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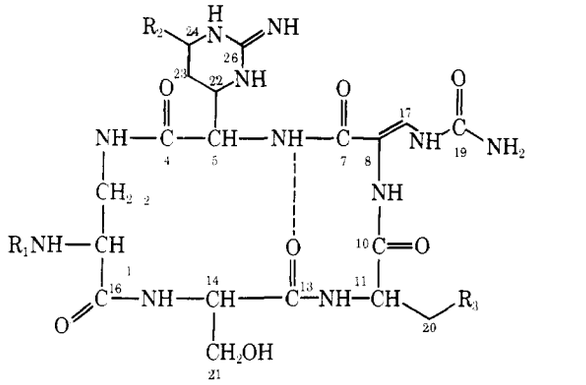
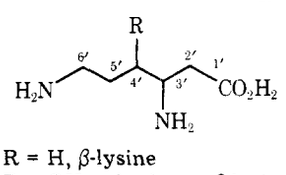
Received October 26, 1976

LL-BM547β, a new member of the viomycin family of antibiotics, is described. ^{13}C NMR studies on the antibiotic itself and on a hydrolytic product show that this antibiotic contains the new amino acid N^{β}-methyl-β-arginine as the appendaged amino acid.

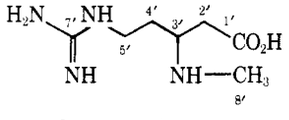
The antitubercular agent viomycin was first described in 1951.[1] Since that time other members of the same family have been isolated, namely the capreomycins[2] and the tuberactinomycins.[3] The structures of tuberactinomycin N[4] and viomycin[5] have been determined by x-ray crystallography.

A *Nocardia* species, Lederle culture BM547, produces two antibiotic components that belong to this same chemical class. By ^{13}C NMR spectroscopy, in conjunction with hydrolytic studies, LL-BM547β was shown to be I. The novelty of I stems from the fact that the appendaged amino acid is *N*-methyl-β-arginine as opposed to β-lysine or γ-hydroxy-β-lysine in the known members (Table I) of this family. The minor component, LL-BM547α or II, was identified as the known de-β-lysylviomycin.[6]





R = H, β-lysine
R = OH, γ-hydroxy-β-lysine



N^{β}-methyl-β-arginine

Isolation of I and II. The antibiotic components of culture BM547 in common with most water-soluble basic substances can be removed from the broth filtrate by passage over a weak cation exchange resin in the sodium cycle. The neutralized acid eluate from this resin may be applied directly to a dextran exchanger in the ammonium cycle. I and II may then be selectively eluted from this resin by using an ammonium chloride salt gradient as eluent. The eluate may be desalted over a granular carbon column. The pure antibiotic materials are recovered in about 50–60% yield from carbon columns by elution with 50% aqueous acetone solution. The solid antibiotic is obtained from this eluate by either lyophilization or precipitation with acetone.

Characterization of I and II. These two antibiotics, in common with all the other members of this peptide antitubercular group, have a vinyl urea chromophore which absorbs

Table I. Summary of the Known Antitubercular Peptide Antibiotics

Antibiotic	R_1	R_2	R_3
LL-BM547β (I)	N^{β}-CH_3-β-arginyl	OH	OH
LL-BM547α (II) delysylviomycin	H	OH	OH
Viomycin	β-Lysyl	OH	OH
Capreomycin	β-Lysyl	H	H
Tuberactinomycin A	γ-OH-β-lysyl	OH	OH
Tuberactinomycin N	γ-OH-β-lysyl	H	OH
Tuberactinomycin O	β-Lysyl	H	OH