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Studies on the Total Synthesis of Steroidal Antibiotics. 2. Two Convergent Schemes for the Synthesis of Tetracyclic Intermediates[1]

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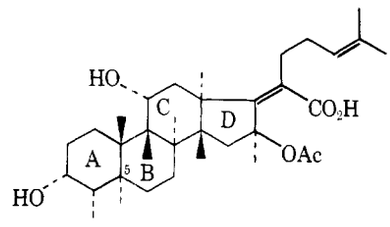
Two synthetic schemes are outlined for the construction of tetracyclic intermediates with the syn-trans-anti-trans backbone characteristic of the fusidic acid nucleus. Both entail the use of the α-methylene ketone **14** as the source of the C/D rings. One approach utilizes the conjugate addition of *m*-methoxybenzylmagnesium chloride as the means for the introduction of the remnants of the A/B ring system, as well as the placement of the C-8 angular methyl group. Modification of the aromatic ring through Birch reduction and then the Eschenmoser hydrazone cleavage of the derived epoxy ketone leads to the enone **13**. A new, versatile annelation procedure is demonstrated by utilization of the α-methylene ketone **14** as a heterodienophile in the Diels–Alder condensation with acrylates. Reductive fragmentation of the phosphorodiamidate derived from the adducts allows for introduction of the C-8 angular methyl group and provides for the ultimate formation of the enone **13** through aldol-type closure of the B ring. Further transformations of the enone **13** toward 11-deoxyfusidic acid type intermediates (**30**) as well as tricyclic substances that contain the 11α-hydroxy group (**37**) are outlined. Means are also presented for the conversion of the A-ring enone in tricyclic model compounds to the desired trans-syn-trans structures characteristic of fusidic acid.

An integral part of any program concerned with the total synthesis of the steroidal antibiotic fusidic acid (**1**)[4] must be the development of means for the construction of the highly



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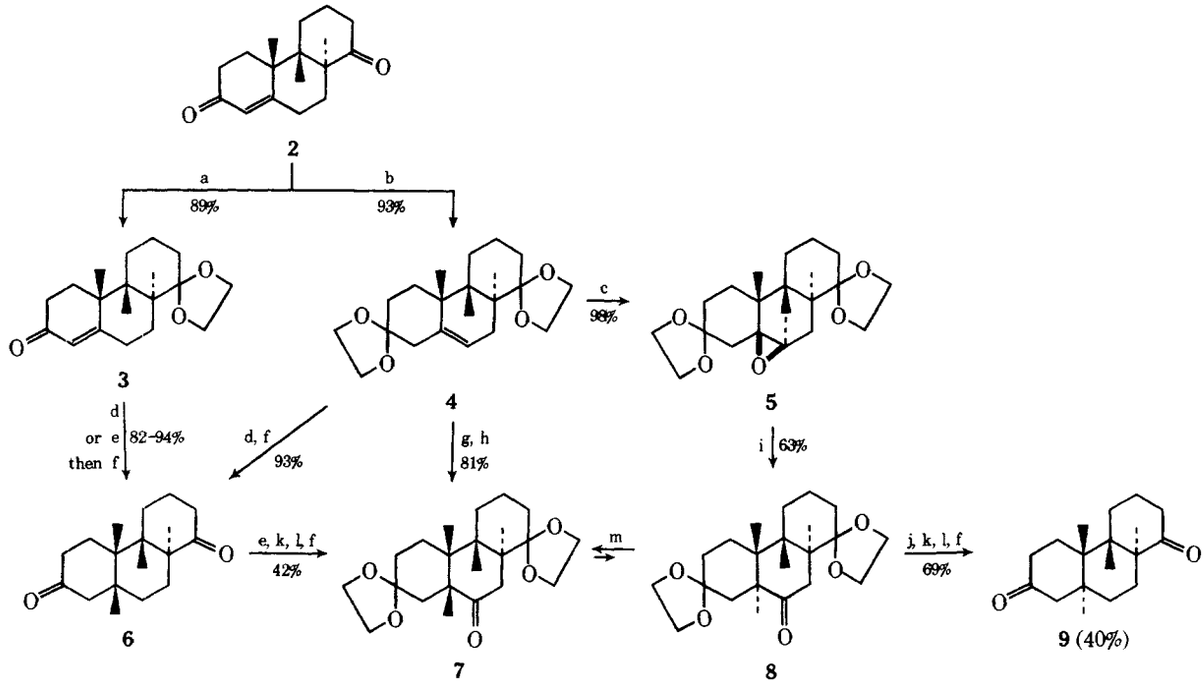
strained *trans-syn-trans*-perhydrophenanthrene system that represents the A, B, and C rings of this molecule. In such an arrangement, the B ring is fixed in a full boat conformation, and isomerization at either of the obvious synthetically accessible C-5 and C-9 positions leads to a more stable structure. The system thus dictates precise stereochemical control during synthesis and greatly circumscribes the methodology that is suitable.

To explore the problems posed by this system a tricyclic model was investigated[5] first. The purpose of this work was the development of a scheme for the reduction of the readily accessible Δ^4-3-ketone system to the desired A/B-trans structure. Thus, the transformation of the enedione **2**[6] (Chart I) to the trans-syn-trans diketone **9** was pursued. From the results[5] of reduction of the enone **2** by either metal in ammonia or catalytic hydrogenation, it became apparent that direct saturation of the double bond in this system leads only to A/B-cis fused material. Even catalytic hydrogenation of the 5(6) double bond in the intermediate bisketal **4** results[5] in only the cis isomer. The propensity for such syn-trans tricyclic systems to interact with reagents on the β face of the molecule is understandable from models in which it is apparent that the B ring is already in a virtual boat conformation. The α-C-8 methyl group very effectively shields the α side of the C-5 carbon toward approach by any external reagent.

To overcome this problem a sequence (Chart I) was used in which the desired C-5 α hydrogen was introduced by the intramolecular rearrangement of the oxide **5**. Despite the multistage nature of this process the overall yield of the diketone **9** was quite acceptable in view of the strain introduced. In retrospect it is particularly interesting that in this tricyclic system none of the product of C-9 methyl group migration could be identified as a result of rearrangement of the oxide **5**. The ketone function at C-6 in the diketal **8**, while efficiently removable without isomerization at C-5 for the fusidic acid (**1**) scheme, could be viewed as an asset for a potential helvolic acid[7] synthesis.

With this sequence available work was initiated on the synthesis of a tetracyclic analogue of the enone **2** with fusidic acid (**1**) as the ultimate objective. The basic approach employed was patterned after the later stages of the synthesis of the enone **2**[6] in which the syn relationship between the C-9 H and the C-10 CH_3 was established through the reductive methylation[8] of an intermediate α,β-unsaturated ketone. For this work the unsaturated ketone required was the tricyclic bisketal **13** (Chart II), and two different schemes were explored for its synthesis.

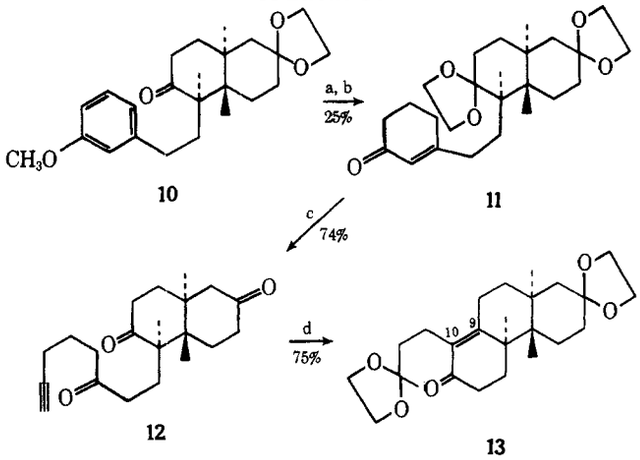
Chart I. Synthesis of *trans-syn-trans-* and *cis-syn-trans*-Perhydrophenanthrene System[a]



[a] a, $(CH_2OH)_2$, H^+, CH_2Cl_2–*n*-C_5H_{12}; b, $(CH_2OH)_2$, H^+, C_6H_6; c, *m*-$ClC_6H_4CO_3H$, CH_2Cl_2; d, H_2, Pd/C, EtOH; e, K or Li, NH_3, THF; f, H_3O^+, acetone; g, B_2H_6, THF; H_2O_2, OH^-; h, CrO_3·2Pyr, CH_2Cl_2; i, BF_3·Et_2O, CH_2Cl_2; j, $LiAlH_4$, Et_2O; k, *n*-BuLi, DME, Et_3N; $ClPO(N(CH_3)_2)_2$; l, Li, $EtNH_2$, THF, *t*-BuOH; m, NaOH, C_2H_5OH.

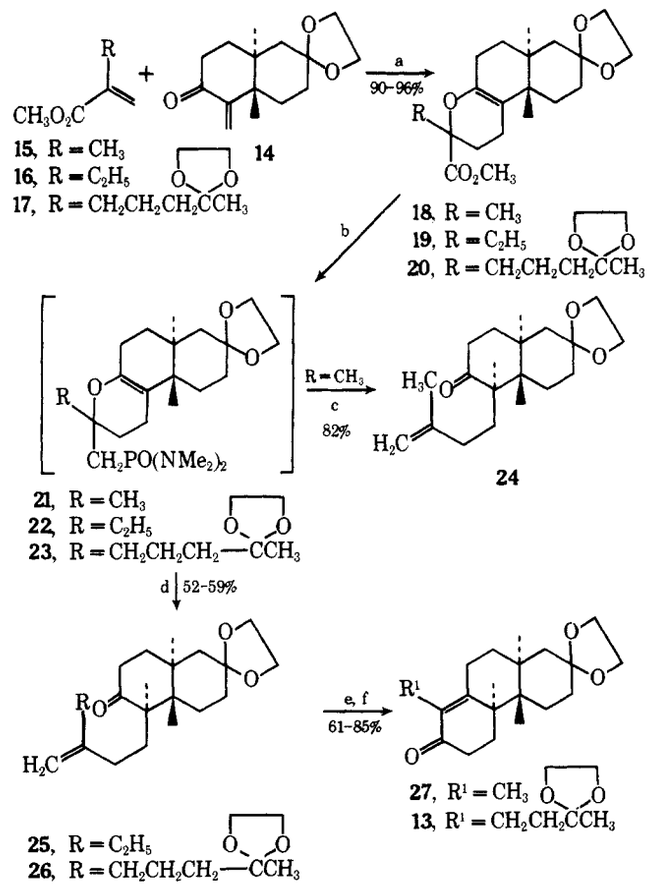
The first approach (Chart II) began from the ketone **10** in which the aromatic ring was envisaged as the ultimate source of the A ring in the desired tetracyclic ketone **30** (Chart IV). The conversion of this aromatic ring to a saturated carbon chain without oxidative loss of carbon entailed first Birch reduction sequence to the enone **11** and then Eschenmoser cleavage[10] of the derived epoxy ketone with aminodiphenylaziridine.[11] A similar sequence was recorded recently in the total synthesis of (±)-shionone.[12] After aldol-type condensation to form the B ring, hydrolysis of the terminal acetylene[13] and selective ketalization of the saturated ketones afforded the desired α,β-unsaturated ketone intermediate **13** in 14% overall yield [7% from the α-methylene ketone **14** (Chart III) common to both approaches]. While this sequence accomplished the intermediary objective, the frequent necessity to protect carbonyl functionality led to an unsatisfying overall yield as a result of the numerous manipulations required.

Chart II. Conjugate Addition Approach to the Synthesis of Enone 13[a]



[a] a, $(CH_2OH)_2$, $C_6H_5CH_3$, *p*-TsOH; b, Li, NH_3, THF–*t*-BuOH; 5% aqueous $(CO_2H)_2$; Al_2O_3 (activity II); c, H_2O_2, NaOH, CH_2Cl_2, 0°C; R_2NNH_2, C_6H_6, Δ; H_3O^+; d, 0.18 N KOH, H_2O–CH_3OH; $(CH_2OH)_2$, C_6H_6, *p*-TsOH; $HqSO_4$, 1% H_2SO_4, CH_3OH; $(CH_2OH)_2$, C_6H_6, *p*-TsOH.

Chart III. Diels–Alder Approach to the Synthesis of Enone 13[a]



[a] a, 180°C; b, $LiAlH_4$, Et_2O; *n*-BuLI, THF–TMEDA, $ClPO(NMe_2)_2$; c, Li, CH_3NH_2; H_2O; d, Li, $(C_6H_5)_2$, THF; CH_3I; e, O_3, CH_3OH; CH_3SCH_3; f, 0.18 N KOH, H_2O–CH_3OH.

A second approach (Chart III) to the synthesis of the unsaturated ketone **13** was shown to have broader general application as well as to provide the desired ketone **13** in higher overall yield. This scheme, like the foregoing route, relies on the α-methylene ketone **14**[9] as a substrate for both the addition of the carbon chain destined to become the A and B rings and the generation in the process of the masked enolate used to introduce the second of the vicinal angular methyl groups characteristic of these triterpenoids. The Diels–Alder condensation between the α-methylene ketone **14**[9] and various methyl α-substituted acrylates admirably served this purpose. An important facet of this reaction is that while the acrylate dienophile is used best in a fivefold excess over the α-methylene ketone **14**,[9] unreacted dienophile may be recovered very efficiently in reusable condition—a necessary feature for this condensation to be the core reaction in a convergent synthesis in which *both* the α-methylene ketone **14**[9] and the acrylate **17**, for instance, are valuable materials.

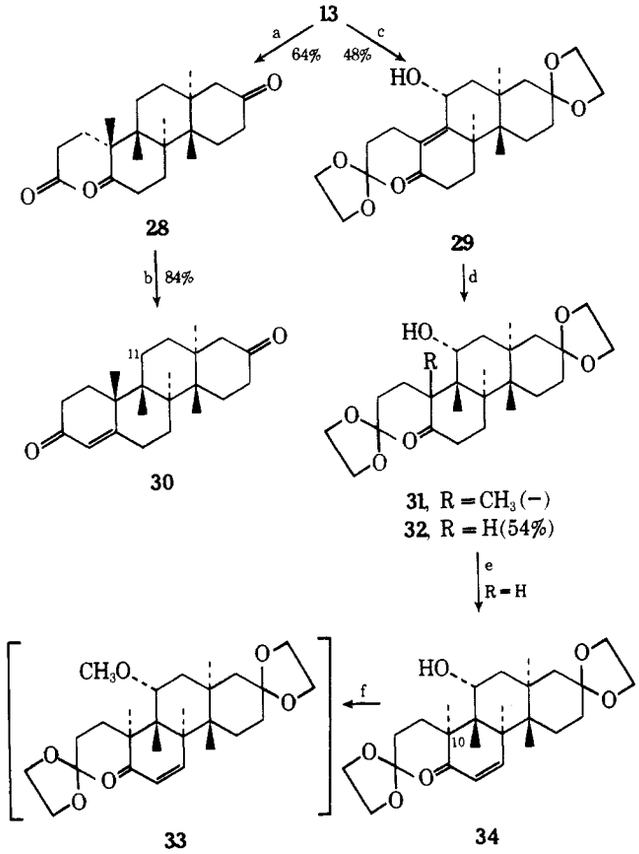
The planned subsequent cleavage of the dihydropyran ring so as to generate the desired enolate initially presented some difficulties. It was necessary to carry out this cleavage under conditions such that the enolate formed was not protonated and then reenolized to the more stable isomeric enolate. In addition, it was necessary to arrange the cleavage reaction in a manner such that the carbomethoxyl bearing carbon of the esters **18–20** became ultimately a ketone function. The cleavage sequence chosen made use of the recently developed phosphorodiamidate grouping[14] as a means for the final deoxygenation with fragmentation of the carbomethoxydihydropyran system. However, reduction of the primary phosphorodiamidates **21–23** was unsuccessful in ammonia and overreduction of the terminal methylene group generated by the fragmentation took place in ethylamine. While a solution to the latter overreduction problem was found when methylamine was used as a solvent, this solvent was too basic to permit direct methylation of the enolate generated by the fragmentation reaction, and only the ketone **24** was readily available from the phosphorodiamidate **21** under these conditions. In order to effect both fragmentation and then direct methylation, the phosphorodiamidates **22** and **23** were reduced with the biphenyl radical anion in tetrahydrofuran solution. The reductive fragmentation process took place efficiently as evidenced by the good yield of the derived enol acetate formed by trapping the intermediate enolate with acetic anhydride. The limitation on the overall yield of the process again appears to be the methylation of this intermediate enolate which leads not only to the desired ketones **25** and **26** but also to the corresponding β-methylated ketone (cis methyl groups, 5–14%) and the methyl enol ether (14–12%).

Final completion of the tricyclic construction was accomplished by ozonization of the terminal methylene group and then aldol-type condensation. The α,β-unsaturated ketone **13** was available in 45% overall yield from the methylene ketone **14**[9] by this scheme, which represents a significant improvement over the foregoing aromatic approach.

Further modification (Chart IV) of the α,β-unsaturated ketone **13** followed two different avenues. The first objective—the synthesis of the tetracyclic analogue **30** of the model tricyclic enone **2**—was accomplished by the same reductive methylation[8] and then aldol-type condensation sequence used before. Again the methylation reaction produced the α-methylated ketone and the methyl enol ether as well as the desired ketone **28** as the major product. While the enone **30** lacked the necessary oxygen function at C-11 for fusidic acid, this material can serve as an intermediate in a fusidane[4] or helvolic acid[7] synthesis after formation of an A/B-trans fusion by the method developed above.

Efforts to introduce a C-11 oxygen function at this stage were not nearly as successful. Through peracid oxidation of

Chart IV. Transformations of Enone 13[a]



[a] a, Li, NH_3, THF, H_2O; CH_3I; H_3O^+; b, 0.18 N KOH, H_2O –CH_3OH; c, NaH, THF, Ac_2O; *m*-$ClC_6H_4CO_3H$, dioxane/H_2O; d, LDA; Li, NH_3; NaOBz, then CH_3I or NH_4Cl; e, LDA, THF; C_6H_5SeBr; H_2O, Py; f, KO-*t*-Bu or LDA, *t*-BuOH or THF, CH_3I.

the enol acetate[15] derived from the enone **13** the hydroxy enone **29** became available. As expected,[16] direct lithium–ammonia reduction of this hydroxy enone **29** led only to products of hydrogenolysis of the hard-won alcohol grouping. Relative success in the retention of this alcohol function during lithium–ammonia reduction was found by initial conversion of the alcohol to the lithium alcoholate with lithium diisopropylamide. In this manner the saturated hydroxy ketone **32** was available, but again the problems associated with the previous direct reductive methylation reactions attended the attempts to form the ketone **31**. While it appeared probable that the desired ketone **31** was formed in approximately 15–25% yield by such a sequence, preparative isolation of the material from the complex product mixture was not possible. In addition to the methylation products observed before in similar reductive methylations, there appeared to be products from O-methylation of the C-11 alcohol function as well as those of α'-methylation of both starting hydroxy enone **29** and the expected saturated ketones **31** and **32**. The latter products must arise from enolization reactions promoted by the lithium C-11 alcoholate, the presence of which is necessary to prevent hydrogenolysis of this group.

Although at this stage in this phase of the synthesis the overall yield of the hydroxy ketone **32** was unsatisfactorily low, a final attempt was made to effect C-10 methylation through the isomeric enone **34**. Available from the saturated hydroxy ketone **32** by the procedures[17] of Sharpless and Reich, this enone **34** can only enolize toward the desired C-10 position. Unfortunately, the only methylation product identifiable by spectral examination of the crude product from several different methylation procedures was the O-methyl ether **33**. The presence of a similar product was noted earlier in the direct

reductive methylation reaction, and its reoccurrence here attests to the problems that attend the formation of the syn backbone in these systems by these means.

With a relatively efficient scheme available for the formation of the C-11-deoxygenone **30**, further work on the synthesis of tetracyclic derivatives in the trans-syn-trans-anti-trans series used this enone **30** as the substrate.

Experimental Section[18]

1,1,7,7-Bisethylenedioxy-4bβ,10aα-dimethyl-1,2,3,4aβ,4b,-5,6,7,8,10,10a-dodecahydrophenanthrene. A solution of 618 mg (2.50 mmol) of the enedione **2** (mp 134–137 °C, prepared in 23% overall yield as outlined in ref 5), 1.34 g (21.6 mmol) of ethylene glycol, and 10 mg of *p*-toluenesulfonic acid monohydrate in 30 mL of benzene was heated at reflux for 2 h under a Dean-Stark water separator in a nitrogen atmosphere. After cooling, the reaction mixture was diluted with 50 ml of ether, and the ethereal layer was washed with saturated $NaHCO_3$ solution (30 mL), water (30 mL), and brine (30 mL) and then dried ($MgSO_4$). Evaporation of the solvent at reduced pressure afforded 829 mg of a crystalline residue, which on purification by chromatography on 75 g of silica gel with petroleum ether–ether (1:1) gave 781 mg (93%) of the crystalline bisketal **4**, mp 157.5–159 °C. The analytical sample obtained by one crystallation from ether–*n*-pentane melted at 158–159 °C: IR ($CHCl_3$) 1675 cm^{-1} (C=C, weak); NMR ($CDCl_3$) δ 1.10 (s, 6, 2 CH_3), 3.94 (br s, 8, 2 OCH_2CH_2O), 5.40 (m, 1, C-9 H). Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.80; H, 9.12.

Ketal Enone 3. To a solution of 286 mg (1.16 mmol) of the enedione **2** in 3 mL of CH_2Cl_2 and 20 mL of *n*-pentane containing 5 mg of *p*-toluenesulfonic acid was added under a nitrogen atmosphere 335 mg (5.54 mmol) of ethylene glycol, and the mixture was stirred and heated under reflux for 3.5 h. After cooling, the mixture was diluted with 75 mL of ether, and the product was isolated by ether extraction including a base wash.[19] Purification of the crude, oily product by chromatography on 40 g of silica gel with 1:2 petroleum ether–ether afforded 23 mg of the diketal **4** in the first 160 mL of eluent and then 301 mg (89%) of the ketal enone **3** as a colorless oil in the next 160 mL of eluent. The analytical sample was obtained by evaporative distillation of a portion of this material at 165 °C (0.05 mm): NMR ($CDCl_3$) δ 1.06 (s, 3, CH_3), 1.23 (s, 3, CH_3), 3.98 (s, 4, OCH_2 CH_2O), and 5.83 (s, 1, C=CH); IR ($CHCl_3$) 16 60 (C=O) and 1625 cm^{-1} (C=C).

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.52; H, 9.05.

Cis-Syn-Trans Diketone 6. A. From Ketal Enone 3 by Hydrogenation. A mixture of 45.4 mg (0.16 mmol) of the ketal enone **3** and 42 mg of 10% palladium on carbon in 5 mL of absolute EtOH was stirred at room temperature in a hydrogen atmosphere for 45 min. After filtration, evaporation of the solvents from the filtrate at reduced pressure afforded 45.4 mg (99%) of the crystalline, saturated ketone ketal, mp 152–153 °C. Further purification of the product by chromatography on 8 g of silica gel with 1:2 petroleum ether–ether gave 43.1 mg (94%) of the saturated ketone ketal, mp 154–155 °C. The analytical sample, obtained after one crystallization from benzene–*n*-hexane and sublimation at 125 °C (0.03 mm), melted at 154.5–155.5 °C: NMR ($CDCl_3$) δ 1.07 (s, 3, CH_3), 1.27 (s, 3, CH_3), and 3.94 (m, 4, OCH_2CH_2O); IR ($CHCl_3$) 1705 cm^{-1} (C=O).

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.83; H, 9.72.

Hydrolysis of the ketal was accomplished when a solution of 40 mg (0.14 mmol) of the ketone ketal was stirred at room temperature in 5 mL of acetone and 1.2 mL of 10% aqueous HCl. Isolation of the product by ether extraction including a base wash[19] afforded 34.7 mg (100%) of the diketone **6**, mp 141–142 °C. The analytical sample, obtained after one crystallization from acetone–*n* hexane, melted at 142–143.5 °C: TLC (CH_2Cl_2–Et_2O) R_f 0.49; NMR ($CDCl_3$) δ 1.18 (s, 3, CH_3) and 1.31 (s, 3, CH_3); IR ($CHCl_3$) 1705 cm^{-1} (C=O); VPC (4% SE-30, 192 °C) t_R 3.00 min.

Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.47; H, 9.60.

The melting range of a mixture of this diketone **6**, mp 142–143 °C, and the isomeric trans-syn-trans diketone **9**, mp 134–135 °C, was 123–130 °C. Mixtures of samples of the two diketones **6** and **9** were resolved on TLC and VPC.

B. From the Ketal Enone 3 by Metal–Ammonia Reduction. To a solution of 50 mg (1.3 mg-atoms) of potassium in 10 mL of dry ammonia under a nitrogen atmosphere was added a solution of 67 mg (0.23 mmol) of the ketal enone **3** in 2 mL of dry THF. After stirring for 5 min, the blue reaction mixture was quenched with 0.5 ml of absolute EtOH, and after evaporation of the ammonia, the product was isolated by ether extraction.[19] A solution of the crude, crystalline product (69.5 mg) dipyridine complex[20] in 8 ml of dry CH_2Cl_2 was stirred for 15 min at room temperature, and then the mixture was filtered through 1 g of alumina with the aid of 10 mL of CH_2Cl_2. Evaporation of the solvent from the eluent afforded 65 mg of crystalline product which on chromatography on 15 g of silica gel with 80 mL of 1:2 petroleum ether–ether afforded 55.3 mg (82%) of the saturated ketone ketal, mp 154–155 °C. Further elution with 45 mL of the same eluent afforded 4.5 mg (7%) of the starting ketal enone **3**. There was no evidence in the product from this reduction, or that with lithium, of the corresponding trans-syn-trans ketone ketal, and the NMR, IR, TLC, and VPC spectra of this saturated ketone ketal were identical with those of the material obtained above from hydrogenation of the ketal enone **3**. Hydrolysis of a sample of this material in acetone–10% aqueous HCl afforded a quantitative yield of the diketone **6**.

C. From the Diketal 4. A mixture of 47.5 mg (0.142 mmol) of the diketal **4** and 12 mg of 10% palladium on carbon in 6 mL of absolute EtOH was stirred in a hydrogen atmosphere for 2 h. After filtration, removal of the solvent from the filtrate left 49.0 mg of the saturated diketal as a colorless gum [IR ($CHCl_3$) no > C=O absorption; NMR ($CDCl_3$) δ 1.06 (s, 3 H, CH_3), 1.13 (s, 3, CH_3), and 3.92 (m, 8, 2 OCH_2CH_2O)] which was hydrolyzed by treatment of an acetone (6 mL) solution with 1.5 mL of 10% aqueous HCl at room temperature for 1 h. Isolation of the product by ether extraction including a base wash[19] afforded 32.7 mg (93%) of the diketone **6** as colorless crystals, mp 141.5–142.5 °C. The NMR, IR, TLC, and VPC spectra of this material were identical with those of the diketone **6** prepared above.

D. From the Ketone Diketal 7. To a solution of 19 mg (2.7 mg-atoms) of lithium in 12 mL of dry NH_3 under a nitrogen atmosphere was added a solution of 76 mg (0.216 mmol) of the ketone diketal **7** (judged to be 91% cis-syn-trans and 9% trans-syn-trans by NMR) in 4 mL of dry THF, and the mixture was stirred for 30 min. The blue reaction mixture was quenched with 2 mL of absolute EtOH, and after evaporation of the NH_3, the product was isolated by ether extraction.[19] Purification of the crude product by chromatography on 42 g of silica gel, 230 mL of ether, and then 550 mL of 5% acetone–ether afforded first 11 mg (14%) of starting cis-syn-trans ketone ketal **7** and then 63 mg (81%) of the diketal alcohol as a colorless gum. The IR, NMR, TLC, and VPC spectra of this material were identical with those of the β alcohol obtained from hydroboration of the diketal **4**.

In a manner similar to that described below for the reductive removal of the hydroxyl group from the trans-syn-trans diketal alcohol from the diketal ketone **8**, 26 mg (0.073 mmol) of the cis-syn-trans diketal alcohol above was phosphorylated with 70 μl of a 2.66 M *n*-C_4H_9Li–hexane solution (0.19 mmol), 0.15 mL of NEt_3, 0.3 mL of dry HMPA, and 0.1 mL of $ClPO[N(CH_3)_2]_2$ in 2 mL of dry DME.

The crude phosphorodiamidate formed in this manner was reduced with 22 mg (3 mg-atoms) of lithium and 10 mg of *t*-BuOH in 8 mL of dry $EtNH_2$. Finally, the crude diketal obtained from this reduction was hydrolyzed in 4 mL of acetone with 0.8 mL of 10% aqueous HCl at room temperature for 1 h. Purification of the crude gum obtained from this sequence by chromatography on 2 g of silica gel with 10:1 CH_2Cl_2–Et_2O afforded 11 mg (58%) of the diketone **6**, mp 141–142 °C. The IR, NMR, TLC, and VPC spectra of this material were identical with those of the diketone **6** prepared above.

Hydroboration of Diketal 4. To a solution of 653 mg (1.95 mmol) of the diketal **4** in 100 mL of dry THF was added 10.0 mL of a 0.9 M borane–THF solution, and the clear solution was stirred at room temperature for 3 h. The reaction mixture was cooled in an ice bath, and then treated sequentially with 2 mL of H_2O, 10 mL of 3 N aqueous NaOH, and 10 mL of 30% H_2O_2. After the mixture had stirred at room temperature for 3 h, the product was isolated by benzene extraction.[19] Purification of the crude product by chromatography on 130 g of silica gel with 150 mL of benzene–EtOAc–acetone (10:5:3) and then 400 mL of the same solvents in the ratio 10:5:5 afforded 85 mg (12%) of the *tertiary* diketal alcohol, mp 175–178 °C, and 579 mg (84%) of the desired *secondary* diketal alcohol as a colorless oil.

The analytical sample of the *tertiary* diketal alcohol, obtained after two crystallizations from acetone–*n*-hexane, melted at 179–180 °C: NMR (CDCl) δ 1.04 (s, 3, CH_3), 1.13 (s, 3, CH_3), and 3.91, 3.93 (2 s, 8, 2 OCH_2CH_2O); IR ($CHCl_3$) 3605 cm^{-1} (OH); TLC (benzene–EtOAc–acetone, 10:5:2) R_f 0.37.

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.29; H, 9.24.

Attempted oxidation of 17 mg (0.048 mmol) of this alcohol with 1.5 mL of a 0.24 M solution of Collins reagent[20] in CH_2Cl_2 led to a

quantitative recovery of the starting alcohol (IR, NMR, TLC). Hydrolysis of 18.5 mg (0.05 mmol) of this diketal alcohol in 1 mL of acetone with 0.25 mL of 10% aqueous HCl at room temperature for 2 h led to the formation of 11 mg (90%) of the enedione **2**, mp 131–133 °C, as shown by identical IR, NMR, and VPC.

The analytical sample of the *secondary* diketal alcohol was obtained as a colorless oil by evaporative distillation at 195 °C (0.05 mm): TLC (benzene–EtOAc–acetone, 10:5:2) R_f 0.28; NMR ($CDCl_3$) δ 1.10 (s, 3, CH_3), 1.17 (s, 3, CH_3), 3.92 (s, 8, 2 OCH_2CH_2O), and 4.3 (m, 1, CHOH); IR ($CHCl_3$) 3620 cm^{-1} (OH).

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.16; H, 9.04.

Diketal Ketone 7. To 24 mL (5.76 mmol) of 0.24 M Collins reagent[20] in CH_2Cl_2 was added a solution of 328 mg (0.93 mmol) if the cis-syn-trans diketal alcohol in 8 mL of dry CH_2Cl_2, and the mixture was stirred at room temperature for 20 min. Filtration of the mixture through 10 g of alumina (activity III) with the aid of 60 mL of CH_2Cl_2 and then evaporation of the solvents at reduced pressure afforded 313 mg (96%) of the diketal ketone **7**, mp 147.5–149 °C. The analytical sample, obtained after two crystallizations of a portion of this material from acetone–*n*-hexane, melted at 150.5–151.5 °C: TLC (ether) R_f 0.37; NMR ($CDCl_3$) δ 1.13 (s, 3, CH_3), 1.28 (s, 3, CH_3), and 3.8–4.3 (m, 8, 2 OCH_2CH_2O); IR ($CHCl_3$) 1705 cm^{-1} (C=O).

Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.58 H, 8.67.

Equilibration Studies on Diketal Ketones 7 and 8. A. From Diketal Ketone 7. A solution of 53 mg (0.15 mmol) of the diketal ketone **7** in 20 mL of EtOH and 0.4 mL of 2 N aqueous NaOH was heated under reflux in a nitrogen atmosphere for 2 h. After dilution with 20 mL of H_2O, isolation of the product by ether extraction[19] afforded 52 mg of crystalline material, mp 142–144 °C. The TLC, VPC, and IR of this material were identical with those of the starting diketal ketone **7**, but the NMR ($CDCl_3$) showed the appearance of two new singlets at δ 0.89 and 1.38, integration of which indicated 8–10% of the diketal ketone **8**.

B. From Diketal Ketone 8. A solution of 35 mg (0.1 mmol) of the diketal ketone **8**, mp 169.5–171.5 °C, in 6 mL of EtOH and 1.4 mL of 10% aqueous NaOH was heated under reflux for 2 h. The progress of the reaction was followed by VPC (4% SE-30, 190 °C) and after the reflux period the peak due to diketal ketone **8** at 23.4 min had diminished to ~8% of the volatile material while that due to the diketal ketone **7** at 21.6 min had increased to ~92%.

Dilution of the reaction mixture with 60 mL of H_2O and isolation of the product by ether extraction[19] afforded 35 mg of crystalline material, mp 144.5–146.5 °C. The IR, TLC, and VPC spectra of this material were identical with those of the diketal ketone **7**, but again the NMR ($CDCl_3$) showed the additional two resonances at δ 0.89 and 1.38 due to the presence of ~8–10% of the diketal ketone **8** by integration. Further purification of this material by chromatography on 6 g of silica gel with 3:1 ether–petroleum ether and then crystallization of the recovered solid from acetone–*n*-hexane gave 32 mg (92%) of the purer diketal ketone **7**, mp 150–152.5 °C, alone or in admixture with authentic material, mp 151.5–152.5 °C, from the hydroboration–oxidation of the diketal olefin **4**.

1,1,7,7-Bisethylenedioxy-4bβ,10aα-dimethyl-8aβ,9β-oxidoperhydrophenanthrene (5). A solution of 470 mg (2.32 mmol) of *m*-chloroperoxybenzoic acid (85%) in 10 mL of CH_2Cl_2 was added dropwise to an ice-cold solution of 672 mg (2.01 mmol) of the diketal **4** in 10 mL of CH_2Cl_2 over a period of 10 min. Stirring was continued at room temperature for 1.5 h, and then the reaction mixture was diluted with 100 mL of ether, washed with 10% aqueous sodium sulfite solution (50 mL), saturated $NaHCO_3$ solution (50 mL), water (50 mL), and brine (50 mL), and finally dried ($MgSO_4$). Evaporation of the solvents at reduced pressure afforded 703 mg of a crystalline residue, which on purification by chromatography on 75 g of silica gel with petroleum ether–ether (2:1) gave 691 mg (98%) of the crystalline epoxide **5**, mp 167–168 °C. The analytical sample, obtained after one crystallization from acetone–*n*-hexane, melted at 167–168 °C: NMR ($CDCl_3$) δ 1.13 and 1.19 (2 s, 6, 2 CH_3), 3.05 (d, J = 6 Hz, 1, C-9 H), 3.94 (s, 8, 2, OCH_2CH_2O).

Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.56; H, 8.57.

1,1,7,7-Bisethylenedioxy-4bβ,10aα-dimethyl-9(8a*H*)-perhydrophenanthrone (8). To a well-stirred solution of 367 mg (1.05 mmol) of the epoxide **5** in 30 mL of dry CH_2Cl_2 under a nitrogen atmosphere at room temperature was added by syringe 0.35 mL of freshly distilled BF_3·Et_2O. The clear solution was stirred for 5 min and then 2 mL of dry Et_3N followed by 25 mL of saturated $NaHCO_3$ solution were added. The heterogeneous mixture was stirred for an additional 5 min and then the organic phase was separated with the aid of 125 mL of ether and washed with water (50 mL) and brine (50 mL). The dried ($MgSO_4$) organic solution was evaporated at reduced pressure, and the semicrystalline residue (358 mg) was chromatographed on 80 g of silica gel with petroleum ether–ether (1:2). The first 415-mL fraction contained 5.5 mg less polar impurities. Further elution with 270 mL of the same solvent mixture gave 230 mg (63%) of the crystalline ketone **8**, mp 170.5–172 °C. There was no evidence for the concomitant formation of the cis-syn-trans diketal ketone **7** or the rearranged alcohol. An analytical sample, prepared by crystallization from acetone–*n*-hexane, melted at 171.5–172.5 °C: IR ($CHCl_3$) 1705 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.90 (s, 3, CH_3), 1.39 (s, 3, CH_3), 3.94 (br s, 8, 2 OCH_2CH_2O).

Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.53; H, 8.65.

4bβ,10aα-Dimethyl-*trans*-syn-*trans*-1(2*H*),7(8*H*)-perhydrophenanthrenedione (9). A solution of 99 mg (0.282 mmol) of the diketal ketone **8** in 3 mL of benzene–ether (1:1) was added dropwise to a stirred slurry of 23 mg (0.61 mmol) of $LiAlH_4$ in 5 mL of ether under a nitrogen atmosphere over a period of 5 min. After the mixture has stirred at 25 °C for 1.5 h, excess hydride was decomposed with water and the ethereal solution was dried ($MgSO_4$) overnight. The crude alcohol, obtained as a foam (100.2 mg) after evaporation of the ether at reduced pressure, was dissolved in 4 ml of dry glyme under a nitrogen atmosphere, and then treated with 140 mL of 2.7 M n-C_4H_9Li in *n*-hexane. To this solution were added sequentially 0.2 mL of dry Et_3N and 0.17 mL of *N,N,N,N*-tetramethyldiamidophosphorochloridate [$ClPO(NMe_2)_2$]. The clear solution was stirred for 75 min and then added dropwise to a stirred solution of 45 mg of lithium in 20 mL of dry $EtNH_2$ under an argon atmosphere at 5 °C over a 2-min period. The blue mixture was stirred for an additional 15 min at 5 °C, and then quenched with 4 mL of 10% aqueous NH_4Cl solution after most of the $EtNH_2$ was evaporated at room temperature in a jet of argon; the residue was partitioned between water (100 mL) and 1:1 ether–*n*-pentane (120 mL). The organic extract was washed with water and brine and dried ($MgSO_4$). Evaporation of the solvents at reduced pressure gave 92.5 mg of the crude bisketal as a gum. A solution of the crude bisketal in 12 mL of acetone and 3 mL of 10% hydrochloric acid was stirred at room temperature for 2 h and then poured into 100 mL of water. After extraction of this solution with ether (3 × 50 mL), the combined extracts were washed with saturated $NaHCO_3$ solution (50 mL), water (50 mL), and brine (50 mL), and dried ($MgSO_4$). Purification of the crystalline residue, obtained by evaporation of the solvent at reduced pressure by chromatography on 20 g of silica gel with methylene chloride–ether ((8:1), gave 48.2 mg (69% overall) of the diketone **9**, mp 133–134 °C. The analytical sample, obtained by crystallization from acetone–*n*-hexane, melted at 134–135 °C: IR ($CHCl_3$) 1705 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.03 (s, 3, CH_3), 1.31 (s, 3, CH_3); TLC (CH_2Cl_2–Et_2O) R_f 0.52; VPC (4% SE-30, 1920) t_R 3.05 min.

Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.47, H. 9.76.

Bisketal 11. To a solution of 3.61 g (8.7 mmol) of the aromatic bisketal (prepared in 52% yield from the ketal ketone **10**[9] with ethylene glycol, *p*-toluenesulfonic acid catalyst in benzene under the standard conditions) in 300 mL of dry THF, 25 mL of dry *tert*-butyl alcohol, and ca. 750 mL of distilled ammonia was added 1.20 g (174 mmol) of lithium, and the deep blue solution was stirred for 8 h. After 25 mL of methanol was added, the ammonia was allowed to evaporate and brine was added to the residue. The crude product, isolated by ether extraction,[19] in 100 mL of dry THF was heated with 25 mL of 5% aqueous oxalic acid at 45–50 °C for 4 h, at which point TLC analysis (2:1 petroleum ether–ether) showed that none of the starting dihydroaromatic bisketal remained. After the solution was cooled and poured into 200 mL of saturated aqueous $NaHCO_3$ solution, the crude product was isolated by ether extraction.[19] This material was purified by medium-pressure liquid chromatography[18] on 410 g of silica gel in 1:2 petroleum ether–ether. Elution with 2100 mL of solvent afforded 1.2 g (35%) of the β,γ-unsaturated ketone bisketal: NMR δ 1.01 (s, 3, CH_3), 1.12 (s, 3, CH_3), 2.42 (br s, allylic H), 2.80 (br s, bisallylic H), 3.93 (s, 8, ketals), 5.59 (m, 1, vinyl); IR 1710 cm^{-1}; TLC (ether) R_f 0.54. An analytical sample was prepared by crystallization from ether, mp 144–146 °C.

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.29; H, 8.98.

The β,γ-unsaturated ketone was converted to the α,β isomer **11** by rechromatography on basic Al_2O_3 (II) in 95% yield.

Continued elution with 3200 mL of solvent afforded 1.36 g (39%) of the α,β-unsaturated ketone bisketal **11**: NMR δ 1.02 (s, 3, CH_3), 1.15 (s, 3, CH_3), 3.92 (s, 8, ketals), 5.85 (m, 1, enone H); IR 1660 cm^{-1} (unsaturated carbonyl); TLC (ether) R_f 0.38. An analytical sample

was prepared by crystallization from ether, mp 161.5–163 °C.

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.11; H, 8.94.

Acetylenic Triketone 12. A. Oxide Formation. To a solution of 0.82 g (2.03 mmol) of the α,β-unsaturated ketone **11** in 40 mL of CH_3OH and 5 mL of CH_2Cl_2 cooled in an ice bath were successively added 90 mg of KOH in 1 mL of MeOH and 2.0 mL (23 mmol) of 30% H_2O_2. After 1 h at 0 °C, another 90 mg of KOH in 1 mL of MeOH and 2.0 mL of 30% H_2O_2 were added, and the mixture was stirred for 1 h at 0 °C. The solution was then poured into cold, aqueous $Na_2S_2O_3$ solution, and the product was isolated by ether extraction.[19] The keto epoxide was isolated as a white solid (0.81 g), pure by TLC analysis: NMR δ 1.00 (s, 3, CH_3), 1.07 (s, 3, CH_3), 3.03 (s, 1, epoxide protons), 3.91 (s, 8, ketals); IR 1700 cm^{-1}; TLC (ether) R_f 0.59. An analytical sample was prepared by crystallization from ether, mp 176–178 °C.

Anal. Calcd for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.50; H, 8.75.

B. Eschenmoser Cleavage. A solution of 738 mg (1.76 mmol) of the above keto epoxide and 393 mg (1.80 mmol) of 2,3-*trans*-diphenyl-1-aminoaziridine[11] in 20 mL of dry benzene was stirred at 25 °C for 2 h. The benzene was evaporated at reduced pressure, and the resulting crude hydrozone (1.050 g) dissolved in 18.5 mL of dry DMF. This solution was then heated with stirring at 150–160 °C under an argon atmosphere for 2 h. After cooling, the solution was poured into saturated NaCl solution, and the product was isolated by ether extraction.[19] A solution of the crude product (1.350 g) in 15 mL of acetone containing 2 mL of 10% aqueous HCl was stirred at 25 °C for 4 h to effect ketal cleavage. Subsequent isolation of the product by ether extraction including a base wash[19] gave 1.010 g of a mixture of *trans*-stilbene and the acetylenic triketone **12**. Purification of this mixture by chromatography on 100 g of silica gel with ether afforded 419 mg (75%) of the acetylenic triketone **12**: mp 72–75 °C; NMR δ 1.00 (s, 3, CH_3), 1.16 (s, 3, CH_3); IR 3310 (C≡CH), 2130 (C≡C), 1705 cm^{-1} (carbonyl); TLC (ether) R_f 0.34; VPC t_R 2.4 min (280). An analytical sample was prepared by preparative TLC (1:1 petroleum ether–ether) and bulb-to-bulb distillation at 160 °C (0.03 mm).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.01; H, 9.23.

Enone 13. A solution of 308 mg (0.975 mmol) of the acetylenic triketone **12** in 100 ml of 1% aqueous KOH in 75% aqueous methanol was heated under reflux in an argon atmosphere for 15 h. After the mixture was cooled and then neutralized with 1 mL of acetic acid, the product was isolated by ether extraction including a base wash.[19] The resulting crude, solid acetylenic diketone amounted to 288 mg (99%), mp 148–150 °C, TLC (ether) R_f 0.40, UV active. The analytical sample was prepared after crystallization from ether and melted at 150–151 °C: NMR ($CDCl_3$) δ 1.09 (s, 3, CH_3), 1.33 (s, 3, CH_3); IR ($CDCl_3$) 3300 (C≡CH), 2120 (C≡C), 1710 (saturated C=O), and 1660 cm^{-1} (unsaturated C=O).

Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.60; H, 8.78.

This acetylenic diketone, together with similar material from another run (746 mg, 2.50 mmol) in 36 mL of CH_3OH was treated with 3.62 mL of saturated mericuric sulfate in 1% sulfuric acid solution, and the mixture stirred at 25 °C for 2 h. The crude product, isolated by CH_2Cl_2 extraction including a base wash,[19] amounted to 758 mg of a solid that showed no absorption due to –C≡CH in the infrared and only saturated and unsaturated carbonyl bands.

A solution of the above crude triketone (758 mg) in 125 mL of benzene and 20 mL of ethylene glycol containing 250 mg of *p*-toluenesulfonic acid was heated at reflux under a Dean-Stark water separator for 2.5 h. After cooling, the mixture was poured in 100 mL of saturated aqueous $NaHCO_3$, and the crude product was isolated by ether extraction.[19] Chromatography of the crude product (762 mg) over 50 g of silica gel with ether afforded 529 mg (52%) of the bisketal **13**, mp 113–116 °C: NMR ($CDCl_3$) δ 0.82 (s, 3, CH_3), 1.13 (s, 3, CH_3), 1.35 (s, 3, CH_3), 3.94 (s, 4, OCH_2CH_2O); IR ($CHCl_3$) 1670 cm^{-1} (unsaturated C=O); TLC (ether) R_f 0.43. The analytical sample, obtained after several crystallizations of a portion of this material from ether, melted at 115.5–116 °C.

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.30; H, 8.85.

Methyl 6,6-Ethylenedioxy-2-methyleneheptanoate (17). To a solution of 12 g (0.55 g-atom) of sodium in 220 mL of dry CH_3OH under an argon atmosphere was added 62.5 mL (72 g, 0.55 mol) of dimethyl malonate, and the mixture was heated to 75 °C to avoid precipitation of the sodiomalonate. To this mixture was added 140 g (0.545 mol) of 4,4-ethylenedioxy-1-iodopentane,[21] and the solution was heated at 75 °C for 3 h. The flask was cooled to room temperature and 30.6 g (0.55 mol) of KOH in 85 mL of CH_3OH was added in 2 min with vigorous stirring. After the reaction mixture had stirred for 15 h at room temperature, approximately 200 mL of CH_3OH was removed at reduced pressure and then replaced with 200 mL of ether. The ethereal slurry was cooled to 0 °C and acidified with 400 mL of precooled 1 N aqueous H_2SO_4. Isolation of the product by ether extraction[19] afforded 113 g of the crude monoacid.

Following the procedure of Mannich[22] this crude monoacid was neutralized at 0 °C with 51.5 mL (37.6 g, 0.5 mol) of $(C_2H_5)_2NH$ (no solvent) and the resulting salt was treated with 37 mL (40.5 g, 0.5 mol) of 37% aqueous HCHO solution. This mixture was stirred at room temperature for 1 h and then at 60 ° for 2 h. After the mixture was cooled, the product was isolated by ether extraction including both an acid and base wash.[19] Purification of the crude acrylate combined from two such runs (73 and 78 g) by distillation afforded 87.3 g (38%) of the acrylate **17**, bp 78–83 °C (0.5 mm). The analytical sample, obtained after redistillation of a portion of this material, boiled at 79–81 °C (0.5 mm): NMR ($CDCl_3$) δ 1.32 (s, 3, CH_3), 3.76 (s, 3, OCH_3), 3.96 (s, 4, OCH_2CH_2O), 5.60 (d, J = 1 Hz, 1, C=CH_2); IR ($CHCl_3$) 1725 (C=O) and 1630 cm^{-1} (C=C).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.62; H, 8.47.

Diels–Alder Reactions with Methylene Ketone 14. General Procedure. A mixture of five- to tenfold molar excess of the appropriate methyl acrylate **15**, **16**, or **17** and the α-methylene ketone **14**[9] was sealed under vacuum in an ampulla, and the tube was heated for 22–24 h in an oil bath at 180–185 °C. The products from the acrylates **15** and **16** were isolated by chromatography with 1:1 ether–petroleum ether on silica gel after first removing the excess acrylate on the rotary evaporator at reduced pressure.

In this manner 1.530 g (90%) of a 1:1 mixture of stereoisomeric adducts **18** was obtained from 1.200 g (5.08 mmol) of the α-methylene ketone **14** and a tenfold molar excess of methyl methacrylate (**15**, 5.10 g, 50.9 mmol). For identification purposes the stereoisomers were separated by rechromatography of a sample of this mixture on silica gel with 2:1 petroleum ether– ether, and both crystalline isomers were obtained pure for analytical purposes after two crystallizations from acetone–*n*-hexane. Isomer **18-I**: mp 96.5–98 °C; NMR ($CDCl_3$) δ 0.90 (s, 3, CH_3), 1.40 [s, 3, O=C–C(CH_3)O–], 3.75 (s, 3, OCH_3), and 3.96 (s, 4, OCH_2CH_2O–); IR ($CHCl_3$) 1730 (C=O) and 1675 cm^{-1} (enol ether C=C).

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 68.03; H, 8.45.

Isomer 18-II: mp 98–99 °C; NMR ($CDCl_3$) δ 0.91 (s, 3, CH_3), 1.46 [s, 3, O=C–]C(CH_3)O–, 3.71 (s, 3, OCH_3), and 3.94 (s, 4, –OCH_2CH_2O–); IR ($CHCl_3$) 1730 (C=O) and 1675 cm^{-1} (enol ether C=C).

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.99; H, 8.46.

Similarly, 663 mg (90%) of a mixture of the stereoisomeric adducts **19** was obtained from 500 mg (2.11 mmol) of the α-methylene ketone **14**[9] and a tenfold excess of the acrylate **16**.[22] This mixture was usually not further purified but used directly in the next experiments. For identification the two stereoisomers were separated by rechromatography on 60 g of silica gel with 1:1 ether–petroleum ether. The crystalline isomer was crystallized twice from 1:1 ether–petroleum ether for analysis, while the oily isomer was rechromatographed and dried at high vacuum.

Isomer 19-I: oil; TLC (Et_2O–petroleum ether) R_f 0.48; NMR ($CDCl_3$) δ 0.85 [t, J = 7 Hz, 3, CH_3(ethyl)], 0.88 (s, 3, CH_3), 3.72 (s, 3, OCH_3), and 3.92 (s, 4, OCH_2CH_2O); IR ($CHCl_3$) 1730 (ester C=O) and 1675 cm^{-1} (enol ether C=C).

Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.37; H, 8.49.

Isomer 19-II: mp 95–96.5 °C; TLC (Et_2O–petroleum ether) R_f 0.42; NMR ($CDCl_3$) δ 0.90 (t, J = 8 Hz, 3, ethyl CH_3), 0.91 (s, 3, CH_3), 3.70 (s, 3, OCH_3), and 3.94 (s, 4, OCH_2CH_2O); IR ($CHCl_3$) 1730 (ester C=O) and 1675 cm^{-1} (enol ether C=C).

Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.67; H, 8.66.

In the case of the acrylate **17** the reaction mixture from 1.50 g (6.36 mmol) of α-methylene ketone **14**[9] and 6.50 g (30.4 mmol) of acrylate **17** was cooled and then dissolved in 25 mL of ether. After the resulting ethereal solution was treated with 25 mL of petroleum ether the mixture was cooled at 5 °C in the refrigerator for 2 days. Collection of the crystalline product afforded 2.22 g (77%) of an approximately (NMR) 1:1 mixture of the stereoisomeric adducts **20**. Chromatography of the mother liquors (6 g) on 200 g of silica gel with 1:1 ether–petroleum ether afforded the following fractions.

Fraction I: 4.37 g (85% recovery) of unreacted acrylate **17** (NMR, IR) with 250 mL of eluent.

Fraction II: 0.535 g (19%) of a stereoisomeric mixture of the adduct **20** with 900 mL of eluent. The total combined yield of adduct **20** isolated was 2.755 g (96%). For further experimentation it was not necessary to separate these stereoisomers, but for analytical purposes, a sample was rechromatographed on silica gel with 1:1 ether–petroleum ether, and the individual crystalline isomers crystallized from chloroform–petroleum ether.

Isomer 20-I: mp 125.5–126.5 °C; TLC (Et_2O–petroleum ether) R_f 0.18; NMR ($CDCl_3$) δ 0.88 (s, 3, CH_3), 1.28 (s, 3, side-chain CH_3), 3.72 (s, 3, OCH_3) and 3.92 (s, 8, 2 OCH_2CH_2O); IR ($CHCl_3$) 1725 (ester C=O) and 1675 cm^{-1} (enol ether C=C).

Anal. Calcd for $C_{25}H_{38}O_7$: C, 66.64; H, 8.50. Found: C, 66.70; H, 8.53.

Isomer 20-II: mp 158–159 °C; TLC (Et_2O–petroleum ether) R_f 0.13; NMR ($CDCl_3$) δ 0.90 (s, 3, CH_3), 1.28 (s, 3, side-chain CH_3), 3.68 (s, 3, OCH_3), and 3.94 (s, 8, 2 OCH_2CH_2O); IR ($CHCl_3$) 1725 (ester C=O) and 1675 cm^{-1} (enol ether C=C).

Anal. Calcd for $C_{25}H_{38}O_7$: C, 66.64; H, 8.50. Found: C, 66.56; H, 8.66.

Ketone Ketal 24. A solution of 2.546 g (7.57 mmol) of the Diels–Alder adducts **18** (1:1) in 20 mL of dry ether was added to a well-stirred slurry of 435 mg (11.5 mmol) of $LiAlH_4$ in 80 mL of dry ether under an argon atmosphere at room temperature over a period of 15 min. After stirring for 1 h, the mixture was treated with 3 mL of pyridine, and then 1.00 mL of water and 10 g of anhydrous $MgSO_4$ were added. Stirring was continued for 90 min, and the mixture was then filtered. After removal of the ether at reduced pressure, the viscous residue was dissolved in 60 mL of dry THF and 10 mL of TMEDA under an argon atmosphere and then a few crystals of 1,10-phenanthroline were added. This solution was titrated with 2.2 M n-C_4H_9Li in hexane solution (4.2 mL, 9.2 mmol) to the phenanthroline color change The reaction flask was then immersed in an ice bath and 4.8 mL of $ClPO[N(CH_3)_2]_2$ was added in one lot. After the ice bath was removed, the clear, again yellow solution was stirred for 1 h. The reaction mixture was then poured into 500 mL of 1 N aqueous NaOH solution, and the product was isolated by ether extraction.[19] Purification of the residual gum by chromatography on 250 g of silica gel with 1:1 CH_2Cl_2–acetone afforded 3.070 g (92%) of the two epimeric phosphorodiamidates **21** as a semicrystalline solid: NMR ($CDCl_3$) δ 0.93 (s, 3, CH_3), 1.13 and 1.26 [2 s, 3, CH_2=C(CH_3)O], 2.67 (d, J = 10 Hz, 12, NCH_3), 3.78 (m, 2, $-CH_2O$), 3.94 (s, 4, OCH_2CH_2O–); IR ($CHCl_3$) 1675 cm^{-1} (enol ether C=C). This material was not further purified but used directly for the following type of experiment.

A solution of 104.0 mg (0.235 mmol) of the above phosphorodiamidate mixture **21** in 1.5 mL of dry THF was added in one lot to a well-stirred solution of 7.0 mg (1 mmol) of lithium in 8 mL of dry CH_3NH_2 (freshly distilled from lithium) under an argon atmosphere at reflux temperature. The blue mixture was stirred for 5 min and then quenched with 50 mg of $NaO_2CC_6H_5$, followed by 0.5 mL of water. The CH_3NH_2 was allowed to evaporate, and the residue was partitioned between 70 mL of dilute brine and 30 mL of ether. The aqueous phase was extracted with a second 30-mL portion of ether, and the combined ethereal phases were washed with water (30 mL) and brine (30 mL) and then dried ($MgSO_4$). Evaporation of the solvent at reduced pressure and purification of the residue by chromatography on 25 g of silica gel with 2:1 petroleum ether–ether gave 61.3 mg (89%) of the crystalline ketone ketal **24**, mp 78.5–80 °C. The analytical sample, obtained after crystallization from acetone–n-hexane, melted at 79–80.5 °C: NMR ($CDCl_3$) δ 0.67 (s, 3, CH_3), 3.95 (s, 4, OCH_2CH_2O), and 4.65 (br m, 2, CH_2); IR ($CHCl_3$) 1705 (C=O) and 1650 cm^{-1} (C=C).

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.93; H, 9.58.

Methylated Ketone Ketals 25 and 26. General Procedure. A. A solution of the stereoisomeric mixture of the esters **19** or **20** in ether was reduced with excess $LiAlH_4$ at room temperature for 1 h. After the addition of a twofold excess (volume/weight of esters) used of pyridine, the mixture was worked up with water and anhydrous $MgSO_4$. After removal of most of the solvents (leaving traces of pyridine to maintain a basic residue), the quantitative recovery of crude alcohols was not further purified but used directly in the following experiment.

B. A solution of the above crude alcohols in 5:1 THF–TMEDA containing a trace of 1,10-phenanthroline as indicator was titrated with an n-C_4H_9Li in hexane solution to the expected color change of the indicator. To this solution was added the calculated quantity of $ClPO[N(CH_3)_2]_2$, and the reaction mixture was stirred at room temperature for 1 h. The crude products **22** or **23**, quantitatively isolated by ether extraction including a base wash,[19] were spectrographically characterized (NMR, IR), but no further purified.

C. A solution of the above phosphorodiamates **22** or **23** in THF was added to a previously prepared blue solution of excess lithium and biphenyl in THF under an argon atmosphere at room temperature, and the mixture was stirred for 2–3 h. This blue-green mixture was cooled to −15 °C and then an eight- to tenfold excess (over phosphorodiamidate) of CH_3I was added. After this muddy brown mixture was stirred for 1.5 h at −10 °C, the suspension was poured into a tenfold volume excess of saturated aqueous $NaHCO_3$ solution, and the products were isolated by ether extraction.[19] After removal of the solvents at reduced pressure, the crude product, which showed the presence of three major components in addition to biphenyl on TLC (Et_2O–petroleum ether), was chromatographed on silica gel with 1:1 ether–petroleum ether. The following products were isolated by this procedure.

Ester 19. A. A solution of 1.67 g (4.77 mmol) of the ester **19** was reduced with 380 mg (10 mmol) of $LiAlH_4$ in 75 mL of ether, and worked up after the addition of 3 mL of pyridine: TLC (Et_2O–petroleum ether) R_f 0.21 and 0.13; NMR ($CDCl_3$) δ 0.87 (t, J = 7 Hz, 3, ethyl CH_3), 0.93 (s, 3, CH_3), 3.50 (m, 2, CH_2OH), and 3.94 (s, 4, OCH_2CH_2O); IR ($CHCl_3$) 3580 (OH) and 1680 cm^{-1} (enol ether C=C).

B. The crude alcohol mixture (1.62 g) in 54 ml of 5:1 THF–TMEDA containing a trace of 1,10-phenanthroline was titrated with 2.5 mL of 2.13 N n-C_4H_9Li solution and quenched with 3.1 mL of $ClPO[N(CH_3)_2]_2$: TLC (Et_2O) R_f ca. 0; NMR ($CDCl_3$) δ 0.98 (t, J = 6 Hz), B, ethyl CH_3), 0.92 (s, 3, CH_3), 2.65 (d, J = 10 Hz, 12, NCH_3), 3.80 (m, 2, CH_2O), and 3.92 (s, 4, OCH_2CH_2O); IR ($CHCl_3$) 1675 cm^{-1} (enol ether C=C).

C. A solution of the above crude phosphorodiamidate (402 mg, 0.88 mmol) in 4 mL of THF was reduced in a solution of 35 mg (1 cm, 5 mmol) of lithium and 300 mg (1.95 mmol) of biphenyl in 10 mL of THF. Methylation was accomplished by the addition of 1.0 mL (16 mmol) of CH_3I in 1 mL of THF. Chromatography of the product mixture afforded the following fractions.

Fraction I: oil, 39 mg (14%) of the O-methylated olefin ketal; TLC (Et_2O–petroleum ether) R_f 0.41; NMR ($CDCl_3$) δ 0.92 (s, 3, CH_3), 1.03 (t, J = 7 Hz, ethyl CH_3), 3.47 (s, 3, OCH_3), 3.94 (s, 4, OCH_2CH_2O), and 4.70 (br s, 2, C=CH_2); IR ($CHCl_3$) 1675 (enol ether C=C) and 1645 cm^{-1} (C=C). This sample was too hydrolytically labile for combustion analysis.

Fraction II: oil, 14 mg (5%) of the C-1 epimeric methylated olefin ketone ketal; TLC (Et_2O–petroleum ether) R_f 0.27; NMR ($CDCl_3$) δ 0.82 (s, 3, C-9 CH_3), 1.16 (t, J = 7 Hz, 3, ethyl CH_3), 1.18 (s, 3, $ClCH_3$), 3.94 (s, 4, OCH_2CH_2O), and 4.70 (br s, 2, C=CH_2); IR ($CHCl_3$) 1690 (C=O) and 1645 cm^{-1} (C=C).

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 74.79; H, 10.07.

Fraction III: oil, 168 mg (59%) of the ketone ketal **25**; TLC (Et_2O–petroleum ether) R_f 0.19; NMR ($CDCl_3$) δ 0.76 (s, 3, C-9 CH_3), 1.03 (t, J = 7 Hz, 3, ethyl CH_3), 1.20 (s, 3, $ClCH_3$), 3.94 (s, 4, OCH_2CH_2O), and 4.70 (br s, 2, C=CH_2); IR ($CHCl_3$) 1705 (C=O) and 1645 cm^{-1} (C=C).

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 75.00; H, 10.11.

Ester 20. A. A solution of 5.64 (12.5 mmol) of the ester **20** in 290 mL of THF was reduced with 950 mg (25 mmol) of $LiAlH_4$ and worked up after the addition of 10 mL of pyridine: TLC (Et_2O) R_f 0.31 and 0.25; NMR ($CDCl_3$) δ 0.92 (s, 3, CH_3), 1.30 (s, 3, side-chain CH_3), 3.52 (m, 2, CH_2OH), and 3.94 (s, 8, 2 OCH_2CH_2O); IR ($CHCl_3$) 3580, 3480 (OH), and 1675 cm^{-1} (enol ether C=C).

B. A solution of the above crude alcohol (6.0 g) in 120 ml of 5:1 THF–TMEDA containing a trace of 1,10-phenanthroline was titrated with 5.6 mL of 2.37 N n-C_4H_9Li and then quenched with 9.0 mL of $ClPO[N(CH_3)_2]_2$: TLC (CH_2Cl_2–acetone, 1:1) R_f 0.31; NMR ($CDCl_3$) δ 0.92 (s, 3, CH_3), 1.30 (s, 3, side-chain CH_3), 2.65 (d, J = 10 Hz, 12, NCH_3), 3.80 (m, 2, $-CH_2O$), and 3.94 (s, 8, 2 OCH_2CH_2O); IR ($CHCl_3$) 1675 cm^{-1} (enol ether C=C).

C. A solution of the above crude phosphorodiamidate (2.03 g, 3.65 mmol) in 18 mL of THF was reduced in a solution of 175 mg (5 cm, 25 mmol) of lithium and 1.5 g (9.75 mmol) of biphenyl in 40 mL of THF. Methylation was accomplished by the addition of 5.0 mL (80 mmol) of CH_3I in 5 mL of THF. Chromatography of the product mixture afforded the following fractions.

Fraction I: oil, 184 mg (12%) of the O-methylated olefin ketal; TLC (C_6H_6–EtOAc, 3:1) R_f 0.43; NMR ($CDCl_3$) δ 0.92 (s, 3, CH_3), 1.31 (s, 3, side-chain CH_3), 3.47 (s, 3, OCH_3), 3.94 (s, 8, 2 OCH_2CH_2O), and 4.72 (br s, 2, C=CH_2); IR ($CHCl_3$) 1665 (enol ether C=C) and 1645 cm^{-1} (C=C).

Anal. Calcd for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59. Found: C, 71.11; H, 9.57.

Fraction II: oil, 213 mg (14%) of the C-1 epimeric methylated olefin ketone ketal; TLC (C_6H_6–EtOAc, 3:1) R_f 0.35; NMR ($CDCl_3$) δ 0.82 (s, 3, C-9 CH_3), 1.17 (s, 3, $ClCH_3$), 1.31 (s, 3, side-chain CH_3), 3.92, 3.97 (2 s, 8, 2 OCH_2CH_2O), and 4.72 (br s, 2, $C=CH_2$); IR ($CHCl_3$) 1690 (C=O) and 1645 cm^{-1} (C=C).

Anal. Calcd for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59. Found: C, 71.31; H, 9.59.

Fraction III: oil, 796 mg (52%) of the ketone ketal **26**;TLC (C_6H_6–EtOAc, 3:1) R_f 0.27; NMR ($CDCl_3$) δ 0.77 (s, 3, C-9 CH_3), 1.20 (s, 3, C-1 CH_3). 1.31 (s, 3, side-chain CH_3), 3.94, 3.97 (2 s, 8, 2 OCH_2CH_2O), and 4.72 (br s, 2, $C=CH_2$); IR ($CHCl_3$) 1700 (C=O) and 1645 cm^{-1} (C=C).

Anal. Calcd for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59. Found: C, 71.36; H, 9.50.

Ozonization of Olefinic Ketone Ketals 25 and 26. General Procedure. A stream of ozonized oxygen was passed through a methanolic solution of the respective olefins **25** and **26** for the indicated time at −40 °C. After cooling to −60 °C, the reaction mixture was treated with CH_3SCH_3 and then stirred at −10 °C (1 h), 0 °C (1 H), and room temperature (4 h). Evaporation of the solvents at reduced pressure and isolation of the product from the residue by ether extraction[19] afforded the crude ketones, which were then purified by chromatography on silica gels indicated.

Olefinic Ketone Ketal 25. Ozonization of 137 mg (0.428 mmol) of the olefin **25** in 25 mL of CH_3OH for 7 min, workup with 2.0 mL of CH_SCH_3, and chromatography of the crude product on 20 g of silica gel with 3:1 C_6H_6–EtOAc afforded 118 mg (85%) of the corresponding diketone ketal as an oil which crystallized on standing. The analytical sample, obtained after two crystallizations of this material from EtOAc–hexane, melted at 64–65 °C; TLC (C_6H_6–EtOAc) R_f 0.25; NMR ($CDCl_3$) δ 0.77 (s, 3, C-9 CH_3), 1.05 (t, J = 7 Hz, side-chain CH_3), 1.16 (s, 3, C-1 CH_3), and 3.94 (s, 4, OCH_2CH_2O); IR ($CHCl_3$) 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.73; H, 9.33.

Olefinic Ketone Ketal 26. Ozonization was carried out on three equal batches of 6.0 g (14.25 mmol) of the olefin **26** in 600 mL of CH_3OH at −40 °C for 40 min, and each batch was worked up with 45 mL of CH_3SCH_3. The combined crude products were first filtered through 50 g of silica gl with EtOAc and then the residue from the eluent was rechromatographed on 410 g of silica gel in a medium-pressure chromatography apparatus[18] with gradient solvent elution. Solvents used in sequence were 1.2 L of C_6H_6, followed by adding the following amounts to a stirred reservoir: 1.2 L of 3:1 C_6H_6–EtOAc, 4 L of 2:1 C_6H_6–EtOAc, and 3 L of 1:1 C_6H_6–EtOAc. In this manner 13.0 g (72%) of the diketone diketal was obtained from the latter two eluent fractions as an oil. The analytical sample, obtained after another chromatogram with 2:1 C_6H_6–EtOAc, was also an oil: TLC (3:1 C_6H_6–EtOAc) R_f 0.11; NMR ($CDCl_3$) δ 0.78 (s, 3, C-9 CH_3), 1.15 (s, 3, C-1 CH_3), 1.31 (s, 3, side-chain CH_3), and 3.95, 3.98 (2 s, 8, 2 OCH_2CH_2O); IR ($CHCl_3$) 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.22; H, 9.06. Found: C, 68.29; H, 9.10.

Enone 27. In a manner similar to that described above for the formation of the enone **13** a solution of 115 mg (0.355 mmol) of the diketone in 35 ml of degassed 0.18 N 75% aqueous methanolic KOH was heated under reflux under an argon atmosphere for 14 h. The solution was neutralized with 0.36 mL of HOAc, cooled, and diluted with water, and the product was isolated by ether extraction.[19] The product obtained after removal of the solvent at reducd pressure amounted to 108 mg (98%) of the enone **27**, mp 126–127 °C. The analytical sample, obtained after one crystallization of a sample of this material from ether, melted at 127–128 °C: TLC (1:1 Et_2O–petroleum ether) R_f 0.17; NMR ($CDCl_3$) δ 0.82 (s, 3, C-9b CH_3), 1.30 (s, 3, C-4a CH_3), 1.78 (s, 3, C-1 CH_3), and 3.95 (s, 4, OCH_2CH_2O); IR ($CHCl_3$) 1655, 1605 cm^{-1} (C=C–C=O).

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.97: H. 9.24.

In the same manner of the above diketone diketal (12.4 g, 29.4 mmol) afforded 10.1 g (85%) of the enone **13** which was identical with that prepared above.

Triketone 28. To an argon-protected solution of 3.7 mg (1 mm, 0.53 mmol) of lithium in 6 mL of dry NH_3 and 1 mL of dry THF was added a solution of 80.8 mg (0.2 mmol) of the enone **13** in 1 mL of dry THF and 3.7 μL (0.2 mmol) of H_2O. After the blue mixture had stirred for 15 min a solution of 0.15 mL of CH_3I in 0.5 mL of dry THF was added, and the resulting mxiture was stirred for 45 min. After evaporation of the ammonia in an argon jet, the product was isolated by ether extraction.[19] Evaporation of the solvent at reduced pressure afforded 104 mg of crude solid product which was combined with 414 mg of similar material from the reductive methylation of 344.1 mg (0.85 mmol) of the enone **13** with 16.6 mg (4.5 mm, 2.37 mmol) of lithium and 0.52 mL of CH_3I in 26 mL of dry NH_3 and 10 mL of dry THF containing 15.8 μL (0.86 mmol) of H_2O.

A solution of these combined crude products (518 mg) in 35 mL of acetone and 6 mL of 10% aqueous hydrochloric acid was stirred at room temperature for 1 h. The reaction mixture was then poured into 100 mL of saturated aqueous $NaHCO_3$, and the product was isolated by ether extraction.[19] Purification of the crude product (414 mg) by chromatography on 100 g of silica gel with 3:1 benzene–ethyl acetate afforded 230 mg (64%) of the triketone **28**, mp 158–161 °C. The analytical sample obtained after crystallization of a portion of this material from ether, melted at 161–162.5 °C: TLC (ether) R_f 0.28; NMR ($CDCl_3$) δ 1.06 (s, 3, CH_3), 1.10 (s, 3, CH_3), 1.34 (s, 3, CH_3), and 2.06 (s, 3, $COCH_3$); IR (CHCl) 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.86; H, 9.63.

Enedione 30. A solution of 245 mg (0.74 mmol) of the triketone **28** in 74 mL of 1% aqueous methanolic (3:1) KOH was heated at reflux in an argon atmosphere for 1.5 h. After cooling, the reaction mixture was neutralized with 0.74 mL of glacial HOAc, and the product was isolated by ether extraction.[19] Purification of the crude solid product by chromatography on 100 g of silica gel with 2:1 benzene–ethyl acetate gave 195 mg (84%) of the crystalline enedione **30**, mp 250–252 °C. The analytical sample, obtained after crystallization of a portion of this material from CH_2Cl_2–C_2H_5OH, melted at 252–253 °C: TLC (1:1 benzene–ethyl acetate) R_f 0.38; NMR ($CDCl_3$) δ 0.97 (s, 3, CH_3), 1.15 (s, 3, CH_3), 1.27 (s, 3, CH_3), 5.82 (s, 1, C-4 H); IR ($CHCl_3$) 1705 (C=O), 1660 α,β-unsaturated C=O), and 1640 cm^{-1} (C=C).

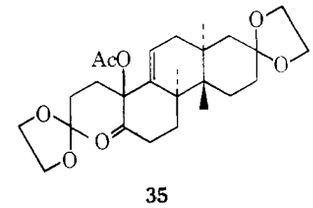
Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.08; H, 9.75.

Hydroxy Enone 29. A. Preparation of Dienol Acetate. A solution of 1.205 g (2.98 mmol) of the enone **13** in 120 mL of dry THF containing 5 drops of dry t-BuOH was stirred and heated under reflux in an argon atmosphere for 20 h with 145 mg (82.5 mg of NaH, 3.44 mmol) of a 57% mineral oil dispersion of NaH. After the mixture was cooled to −15 °C, 2.5 mL (26.5 mmol) of acetic anhydride was added, and stirring was continued for 18 min as the mixture was warmed to 10 °C. The mixture was then poured into 600 mL of ice-cooled, saturated $NaHCO_3$, and the product was isolated by ether extraction.[19] Purification of the crude product (1.378 g) on 150 g of silica gel with ether afforded 1.119 mg (84%) of the dienol acetate as an oil. Rechromatography of a portion of this material on silica gel with 1:1 ether–petroleum ether afforded the analytical sample as an oil: TLC (ether) R_f 0.48; NMR ($CDCl_3$) δ 0.82 (s, 3, CH_3), 1.05 (s, 3, CH_3), 1.30 (s, 3, CH_3), 2.15 (s, 3, $COCH_3$), 3.92 (s, 8, 2 OCH_2CH_2O), and 5.67 (t, $J \simeq 3$ Hz, 1, C=CH); IR ($CHCl_3$) 1745 (C=O) and 1655, 1630 cm^{-1} (C=C).

Anal. Calcd for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 69.96; H, 8.59.

B. Oxidation of Dienol Acetate. At nine 15-min intervals 0.1 mL of a 1.54 M solution of peracid (prepared from 1.25 g of 85% m-chloroperbenzoic acid and 12.5 mg of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide in 4 mL of pure dioxane) was added with stirring at room temperature to a solution of 1.100 g (2.46 mmol) of the dienol acetate above in 45 mL of dioxane and 17 mL of H_2O. A total of 2.25 equiv of peracid was added over the initial 2-h period, and then the mixture was stirred for an additional 4 h. After the reaction was quenched by the addition of 3 mL of 10% aqueous $NaHSO_3$ solution, the product was isolated by 4:6 CH_2Cl_2–ether extraction including a base wash.[19] Purification of the crude oily residue (1.299 g) was accomplished by chromatography on 150 g of silica gel. Fractions of 20 mL were collected in the following sequence: 1:1 benzene–ethyl acetate (fractions 1–25), 4:6 benzene–ethyl acetate (fractions 26–80), and 3:7 benzene–ethyl acetate (fractions 81–130).

I. Fractions 16–27 contained 399 mg (35%) of the acetoxy ketone **35**.



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This material crystallized, and the analytical sample, prepared by crystallization of a portion from ether and then CH_2Cl_2–petroleum ether, melted at 137–138 °C: TLC (ether) R_f 0.33; NMR ($CDCl_3$) δ 0.89 (s, 3, CH_3), 1.23 (s, 3, CH_3), 1.28 (s, 3, CH_3), 2.05 (s, 3, CH_3CO), 3.92

(s, 8, 2 OCH_2CH_2O), and 5.57 (m, 1, C=CH); IR ($CHCl_3$) 1745 (CH_3C=O), 1720 (C=O), and 1655 cm^{-1} (C=C).

Anal. Calcd for $C_{26}H_{38}O_7$: C, 67.51; H, 8.28. Found: C, 67.59; H, 8.23.

II. Fractions 56–130 contained 647 mg (59%) of the desired hydroxy enone **29** which crystallized on trituration with ether. The analytical sample, obtained after two crystallizations of a portion of this material from CH_2Cl_2–petroleum ether, melted at 182–183 °C: TLC (ether) R_f 0.125; NMR ($CDCl_3$) δ 0.80 (s, 3, CH_3), 1.34 (s, 3, CH_3), 1.49 (s, 3 CH_3), 3.92, 3.93 (2 s, 8, 2 OCH_2CH_2O), and 4.90 (m, 1, CHOH); IR ($CHCl_3$) 3590, 3450 (OH), 1650 (C=O), and 1575 cm^{-1} (C=C).

Anal. Calcd for $C_{24}H_{36}O_6$: C, 68.55; H, 8.63. Found: C, 68.39; H, 8.57.

Hydroxy Ketone 32. To an argon-protected solution of 8.3 mL (1.92 mmol) of 0.232 M lithium diisopropylamide in THF in 8.3 mL of dry THF cooled to −78 °C was added in 2 min a solution of 647 mg (1.54 mmol) of the hydroxy enone **29** in 4 mL of dry THF and stirring was continued at −78 °C for an additional 2 min. This "alkoxide" solution was then transferred via fine Teflon tubing under argon pressure to an argon-protected, cold (−78 °C) solution of 35 mg (1 cm, 5 mmol) of lithium in 70 mL of dry NH_3 and 20 mL of dry THF. The flask and tubing were rinsed with 1.0 mL of dry THF. After the reaction mixture had stirred at −78 °C for 45 min, $NaO_2CC_6H_5$ was added to discharge the blue color, and then 270 mg (5 mmol) of NH_4Cl was added. The ammonia was evaporated; water was added, and the products were isolated by extraction with 4:6 CH_2Cl_2–ether.[19] Purification of the crude product (590 mg) by one chromatogram on 150 g of silica gel with ether and then rechromatography of the mixed center fractions on 50 g of silica gel with ether afforded 240 mg (37%, 54% based on recovered hydroxy enone **29**) of the hydroxy ketone **32**, as a glass which crystallized on trituration with ether, and 302 mg (31%) of recovered hydroxy enone **29**.

The analytical sample of the hydroxy ketone **32**, obtained after two crystallizations of a portion of this material from ether, melted at 121–122 °C; TLC (ether) R_f 0.15; NMR ($CDCl_3$) δ 0.87 (s, 3, CH_3), 1.32 (s, 3, CH_3), 1.37 (s, 3, CH_3), 3.95 (s, 8, 2 OCH_2CH_2O), and 4.05 (m, 1, CHOH); IR ($CHCl_3$) 3610, 3475 (OH), and 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.22; H, 9.06. Found: C, 68.16; H, 9.13.

Reductive methylation of the hydroxy enone **29** by a similar process but with the substitution of CH_3I addition for the $NaO_2CC_6H_5$ quench led to a crude product with at least seven components as judged by TLC (ether). No pure products were obtained after extensive chromatography.

Enone 34. The hydroxy ketone **32** (74 mg) was converted in quantitative crude yield (yellow foam) to the α,β-unsaturated hydroxy ketone **34** with 2.16 equiv of lithium diisopropylamide and 1.18 equiv of phenylselenium bromide in 10 mL of dry THF at −78 °C and then 0.05 mL of 30% H_2O_2 in 10 mL of dry THF and 0.025 mL of pyridine. After chromatography of this material on 5 g of alumina (Woelm III) with 20:10:1 benzene–EtOAc–CH_3OH, a white foam was obtained with resisted crystallization: TLC (1:1 ethyl acetate–benzene) R_f 0.17; NMR ($CDCl_3$) δ 0.88 (s, 3, CH_3) 1.30 (s, 3, CH_3), 1.34 (s, 3, CH_3), 3.96 (s, 8, 2 OCH_2CH_2O), 4.05 (m, 1, CHOH), 5.86 (d, J = 10 Hz, 1, O=CCH=C), and 6.93 (d, J = 10 Hz, 1, O=CC=CH); IR ($CHCl_3$) 3600 (OH) and 1665 cm^{-1} (C=O); MS molecular ion peak at 420.253 (calcd, 420.251). No material was used in combustion analysis.

Attempted methylation of this enone **34** in *t*-BuOH or THF with KO-*t*-Bu and CH_3I led to no isolable C-methylated product. The NMR spectrum of the crude methylation mixture instead showed a major resonance at δ 3.72 ($CDCl_3$), probably due to O-methylation of the hydroxyl group, as, for example, **33**. No further experimentation on this process was conducted.

Registry No.—**2,** 38255-71-9; **3,** 38255-75-3; *cis*-**3** dihydro derivative, 61570-10-3; **4,** 38255-76-4; *cis*-**4** dihydro derivative, 61616-08-8; **4** tertiary alcohol derivative, 61570-11-4; **4** secondary alcohol derivative, 61570-12-5; **5,** 38255-78-6; **6,** 38255-77-5; **7,** 38255-80-0; **7** β-ol phosphorodiamidate, 61570-13-6; **8,** 38255-81-1; **8** deoxo derivative, 38255-79-7; **9,** 38255-84-4; **10,** 35890-75-6; **10** bisketal, 61570-14-7; **11,** 61570-15-8; **11** β,γ-unsaturated derivative, 61570-16-9; **11** epoxide, 61570-17-0; **11** epoxide hydrazone, 61570-18-1; **12,** 61570-19-2; **12** acetylenic diketone derivative, 61570-20-5; **12** triketone derivative, 61570-21-6; **13,** 61570-22-7; **13** dienol acetate, 61570-23-8; **14,** 35890-72-3; **15,** 80-62-6; **16,** 10500-08-0; **17,** 61570-24-9; **18-I** α-Me, 61570-25-0; **18-II** β-Me, 61616-09-9; **19-I** α-Et, 61570-26-1; **19-II** β-Et, 61616-10-2; **20-I** α-$(CH_2)_3$–$C(CH_3)$–O–O, 61570-27-2; **20-II** β-$(CH_2)_3$–$C(CH_3)$–O–O, 61616-11-3; **21** α-Me, 61570-28-3; **21** β-Me, 61616-12-4; **22,** 61570-29-4; **23,** 61617-67-2; **24,** 61570-30-7; **25,** 61570-31-8; **25** fraction I, 61570-32-9; **25** fraction II, 61616-13-5; **25** diketone ketal, 61618-15-3; **26,** 61665-00-7; **26** fraction I, 61570-33-0; **26** fraction II, 61570-34-1; **26** diketone diketal, 61618-16-4; **27,** 61570-35-2; **28,** 61570-36-3; **29,** 61570-37-4; **30,** 61616-14-6; **32,** 61570-38-5; **34,** 61570-39-6; **35,** 61570-40-9; ethylene glycol, 107-21-1; dimethyl malonate, 108-59-8; 4,4-ethylenedioxy-1-iodopentane, 369-28-1; $ClPO[N(CH_3)_2]_2$, 1605-65-8.

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.
(2) On study leave from the Centre National de la Recherche Scientifique, France.
(3) Fellow of Stiftung für Stipenden auf dem Gebiete der Chemie, Switzerland.
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(18) 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 of 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.
(19) 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.
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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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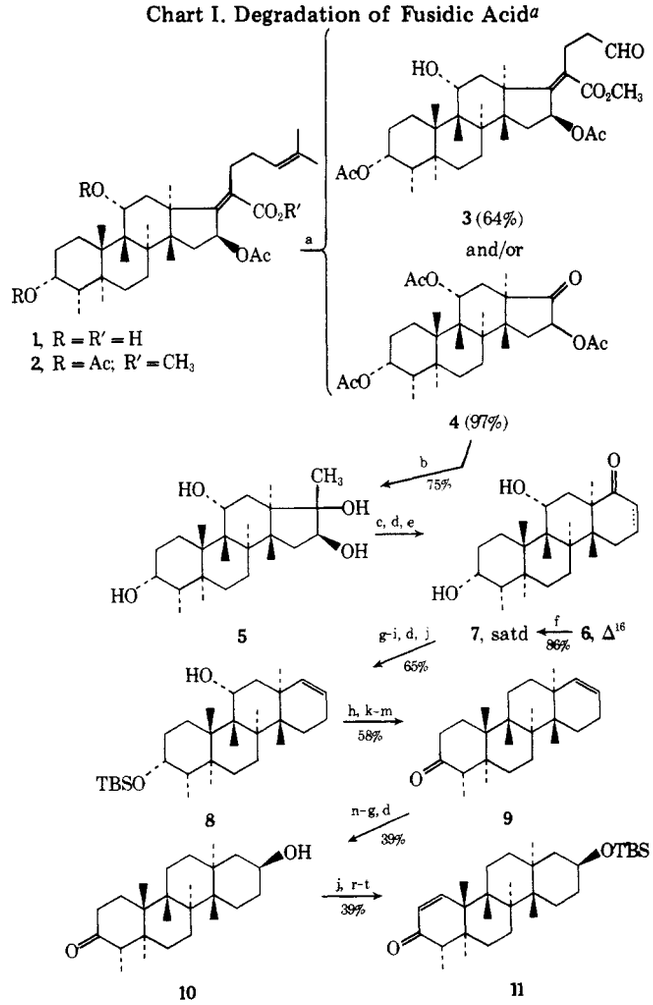
The degradation of fusidic acid (1) to the tetracyclic enone 11 is described. The principle phases of this conversion are the removal of the side chain and then expansion of the five-membered D ring. The racemic form of the enone 11 was prepared from the synthetic enedione 12. The central feature of 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.