The residue was passed through a small column of silica gel. Elution with chloroform afforded 1.44 g (64%) of **18**: mp (from ethanol) 148–150 °C; λ_{max} ($CHCl_3$) 6.17, 6.25 μ; $\delta(CDCl_3)$ 2.3, 2.5 (singlets, combined 3 H), 3.98 (s, 6), 6.72 (s, 1), 8.0 (br s, 1) ppm; *m/e* 270.029 46 (calcd for $C_{12}H_{11}O_5Cl$, 270.029 06).

Preparation of 7-Chloro-4,6-dimethoxy-2-(1-phenylthioethylidene)-3(2*H*)-benzofuranone (19). A solution of benzofuranone, **18** (1.440 g, 5.3 mmol), thiophenol (2.44 g, 2.28 mL, 22.3 mmol), and *p*-toluenesulfonic acid monohydrate (0.2 g, 1.06 mmol) in 80 mL of degassed benzene was heated under reflux with azeotropic removal of water for 36 h. The dark solution was freed of solvent and the residue was chromatographed on 100 g of silica gel (Brinkmann silica gel 60). Elution with 5% ethyl acetate–benzene gave 1.4 g (73%) of **19** as a mixture of geometric isomers: λ_{max} ($CHCl_3$) 5.95, 6.13, 6.27 μ; $\delta(CDCl_3)$ 1.96–2.15 (singlets, combined 3 H), 3.98 (s, 6), 6.10 (s, 1), 7.4 (m, 5) ppm; *m/e* 362.0380 (calcd for $C_{18}H_{15}O_4ClS$, 362.0379).

Preparation of 7-Chloro-4,6-dimethoxy-2-(1-phenylsulfinylethylidene)-3(2*H*)-benzofuranone (20). To a solution of **19** (1.400 g, 3.86 mmol) in 40 mL of CH_2Cl_2, cooled to −20 °C, was added, over 2 h, a solution of *m*-chloroperoxybenzoic acid (0.785, 3.86 mmol) in 20 mL of CH_2Cl_2. The reaction mixture was stirred for an additional 1 h and filtered. The filtrate was extracted 5 × with 5% $KHCO_3$ (50 mL). The yellow organic solution was dried (Na_2SO_4) and concentrated to give 1.32 g (91%) of **20** as a yellow solid which was not purified further: λ_{max} ($CHCl_3$) 5.88, 6.06, 6.21, 6.25 μ; $\delta(CDCl_3)$ 2.05 and 2.20 (singlets, combined 3 H), 3.88 and 3.94 (singlets, combined 6 H), 6.04 (s, 1), 7.4 (m, 5) ppm; *m/e* 362 (P − 16).

Preparation of *dl*-Dehydrogriseofulvin (13). The sulfoxide **20** (1.000 g, 2.64 mmol) and 1,1-dimethoxy-3-trimethylsilyloxy-1,3-butadiene (**4**, 2.13 g, 10.5 mmol) in 10 mL of dry toluene in a sealed tube were heated from 100 to 135 °C over a 6-h period. The solution was cooled, diluted with ethyl acetate, and extracted with 1 N HCl and brine. Evaporation of the dried organic layer afforded a residue which was chromatographed on 100 g of Brinkmann silica gel 60. Elution with 5% ethyl acetate–benzene afforded 500 mg (54%) of *dl*-dehydrogriseofulvin (**13**), mp 285–286 °C (lit.[4b] 288–290 °C), whose infrared and NMR spectra coincided with those of an authentic sample, obtained by selenium dioxide dehydrogenation of **1**.[4b]

Preparation of *dl*-Griseofulvin (1). A solution of synthetic dehydrogriseofulvin (**13**, 50 mg, 0.14 mmol) in 8 mL of EtOH was injected into a reaction vessel containing prereduced 10% Pd/C (100 mg) slurried in 3 mL of EtOH. After 6 min, the reaction mixture was filtered (under nitrogen) and the filtrate was concentrated to afford 49 mg of an off-white foam. Chromatography (1 g, Brinkmann silica gel 60) and elution with 10% ethyl acetate–benzene afforded 30 mg (58%) of griseofulvin, mp 219.5–221 °C (lit.[4b] 222–223.5 °C). The infrared and NMR spectra as well as mobility on TLC of this material were identical with those of authentic (+)-griseofulvin.[11]

Acknowledgments. This research was supported by PHS Grant AI-13939-02. NMR spectra were obtained on facilities supported by RR-00297-08. We also wish to thank Mr. Glen Herman for mass spectral determinations.

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(11) We thank Dr. David Taub of Merck Sharp and Dohme for providing us with a generous sample of griseofulvin for comparison for preparing an authentic sample of **13**.
(12) Regio- and stereoselectivity in the catalytic reduction of **13** appear to be complete. The only side reaction is that of hydrogenolysis, affording in ca. 24% yield the well-known 3-chloro-2,4′-dihydroxy-4,6,2′-trimethoxy-6′-methylbenzophenone, which can be recycled by the Merck procedure (cf. ref 4b) to **13**.
(13) Melting points are uncorrected. Combustion analyses were conducted by Galbraith Associates. Infrared spectra were obtained on a Perkin-Elmer Model 137 or 237 spectrometer. High-resolution mass spectra were measured on a Varian Associates CH-5 instrument by direct insertion. NMR spectra were measured in the indicated solvents with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ) from the Me_4Si resonance.

Total Synthesis of *dl*-Pentalenolactone

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Abstract: The synthesis of *dl*-pentalenolactone has been achieved in a stereospecific way. The key features of the synthesis were (1) a Diels–Alder route to 5-acylcyclohexenones via selective deacylation of a 4,5-diacylcyclohexenone (see **30** → **31**), (2) a new route to α-methylene-δ-lactones via the Brederick reagent (see **4** → **64** → **65** → **66** → **66a** → **5**), and (3) the stereospecific introduction of an epoxymethylenelactone via an epoxyhemiacetal (see **5** → **6**).

Background

In a 1957 disclosure from the Pfizer Co., Celmer reported the isolation of a new antibiotic from a *Streptomyces* broth culture.[1] The substance, named PA-132, was reported to have excellent antibiotic activity against Gram-positive and Gram-negative bacteria as well as against pathogenic and saprophytic fungi. In 1969, Takeuchi described the isolation of PA-132 from *Streptomyces* sp no. 8403-MC.[2] It was also shown to have inhibitory activity against nucleic acid synthesis in bacterial cells. This substance, named pentalenolactone, was obtained as a white, hygroscopic powder. Preliminary chemical and spectroscopic studies led to the provisional assignment of structure **2** to this antibiotic.

Subsequently, an Upjohn group, using antitumor assays, described the isolation of pentalenolactone from a fermentation broth of *Streptomyces* UC 5319. Its structure assignment was

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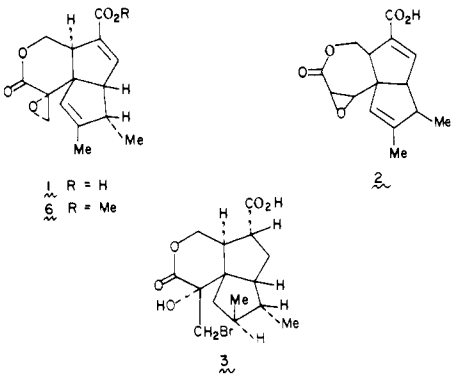
now revised. Crystallographic examination of its derived tetrahydrobromohydrin showed the latter to be **3**, and pentalenolactone itself was accordingly formulated as **1**.[3]

Pentalenolactone is thus seen to share structural features with the hirsutic[4a] and coriolin[4b] families. More recently, there have been isolated from natural sources a variety of pentalenolactone analogues including pentalenolactones G and H.[5] Also, one should note the relationship of **1** with another recently reputed tumor-inhibitory sesquiterpene, quadrone.[6] It would appear that the reduced pyranopentalene system found in **1** may well have rather widespread occurrence.

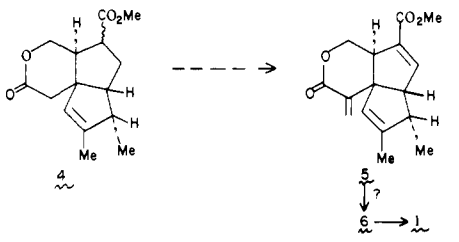


To those who would undertake its total synthesis, pentalenolactone offers challenges of some substance. A program for mastering its novel pentalenopyranone ring system must be devised. The relative relationship of its five centers of chirality must be arranged. Included among these is the chiral center at the provocative spiroepoxymethylenelactone attachment.

Herein is provided an account of the total synthesis of pentalenolactone.[7]

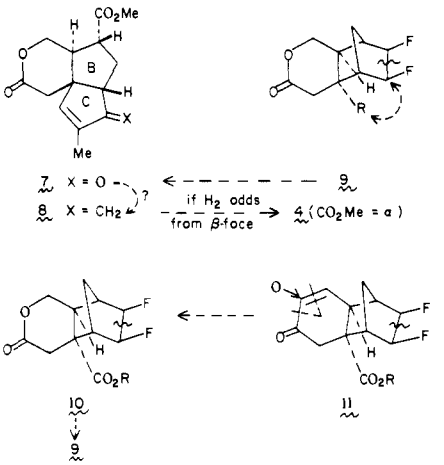
Synthetic Strategy

At the outset, we operated on the assumption that the hypothetical compound **4**, while less than ideally functionalized, could serve as an operationally acceptable precursor of **1**. The thought was that the prototropic behavior of the two carbonyl groups, undifferentiated in terms of oxidation level, might, in fact, be subject to control, thereby allowing for the conversion of **4** to **5**. It was further assumed that epoxidation of **5** or a derivative thereof might be carried out at the exocyclic methylene group in the required stereochemical sense to give **6** and, after hydrolysis, **1**.



Provision for the required α configuration of the secondary methyl group was a central element of our plan. It will be seen that this corresponds to the more hindered, concave face of the BC ring system. Accordingly, a kinetic solution appeared to be required. It was felt that selective reduction of **8** might occur from the convex (β) face of the BC system to afford **4**. To maximize the probability that reduction of **8** would occur from the desired β surface, it seemed advantageous for the carbomethoxy function to be disposed in the α configuration, thus further hindering the concave side. Henceforth, this α configuration is thus defined in **4**.[8]

It was further assumed that compound **8** might be generated from precursor **7** by a Wittig or synthetically equivalent transformation. This, in turn, suggested the possibility that the two cis disposed carbonyl residues in **7** might arise from oxidative degradation of a two-carbon bridge in the hypothetical progenitor, **9**. In structure **9**, we leave unspecified the precise



nature of this bridge. We also leave unspecified the structure of R. These will be considered with more precision as the synthesis unfolds. However, even without defining the structure of R in detail, it seemed likely that it might be produced from a carboxyl or equivalent function. This led us to consider system **10** as a reasonable type of precursor. The functions F are such as to facilitate degradation of the two-carbon bridge.

In our total synthesis of vernolepin[9a,b] we had, drawing from prior art,[10] demonstrated the utility of cyclohexenones as antecedents of δ-lactones. To be applied to the case at hand, there would be required access to system **11**.

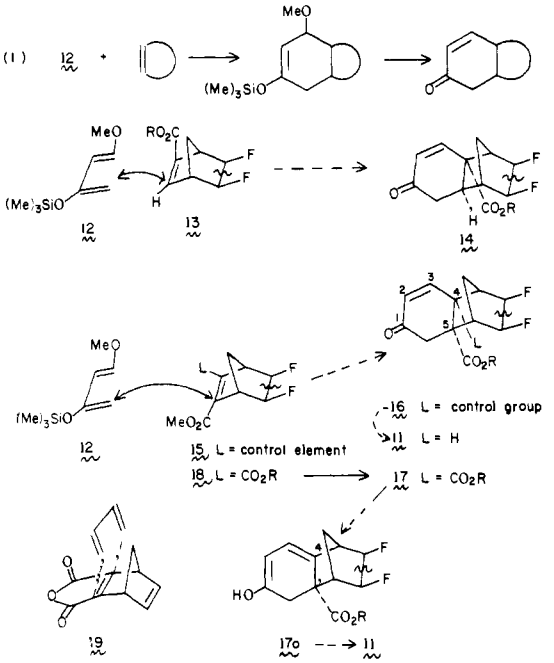
It could be proposed that a cyclohexenone such as **11** might arise from the Diels–Alder schematic, formulated in eq 1. However, for the synthesis of **11** a problem of some seriousness emerges, since one could predict that cycloaddition of the dienophile type **13** with the diene **12**[11a,b] followed by unraveling would lead, inexorably, to the 4-acylcyclohexenone **14**—a system of no readily seen value for our program.

In principle, one could consider a dienophile such as **15**, bearing a control element, L, which would guide its reaction with **12** to give **16**, and that somehow **16** would be converted to the required **11**. An attractively simple variation of this potentially complicated formulation presented itself. *If we consider the case where the "control element", L, was itself equal to CO_2R, we are led to the symmetrical dienophile* ***18.*** Its reaction with **12** would lead to **17**—a 4,5-diacylcyclohex-2-en-1-one. It was recognized that the extraneous 4-acyl group is part of a nonenolizable vinylogous β-dicarbonyl system, vis-à-vis the enone. It is accordingly, in principle, subject to deacylation under acidic or basic conditions. The 5-acyl group, not being part of such a network, should not be comparably vulnerable, and should thus survive in the conversion of **17** to **11**.

Of course, base-induced cleavage reactions of vinylogous β-dicarbonyl systems owe their facility to the intermediacy of conjugated dienols (or dienolates). In the case of **17** the intermediate **17a** would be produced. Its orderly conversion to the desired **11** depends on positional and stereochemical control in the ketonization of the dienol, either at the kinetic or thermodynamic levels. In this respect we could foresee a major advantage in the two-carbon bridge method of housing the latent 1,5-dicarbonyl functionality necessary to reach **7**. *The angle strain imposed by the fusion of the norbornane and cyclohexano rings would only be exacerbated if species* ***17a*** *ketonized to give either the β,γ-unsaturated system or the α,β-unsaturated trans-fused epimer.* Accordingly, ketonization of **17a**, certainly under equilibrating conditions, would

be expected to afford the cis-fused α,β-unsaturated system, **11**.

Finally, at the planning level, one must consider the likely topological sense of Diels–Alder reaction of a dienophile such as **18** with **12**. Clearly, the success of the enterprise demands

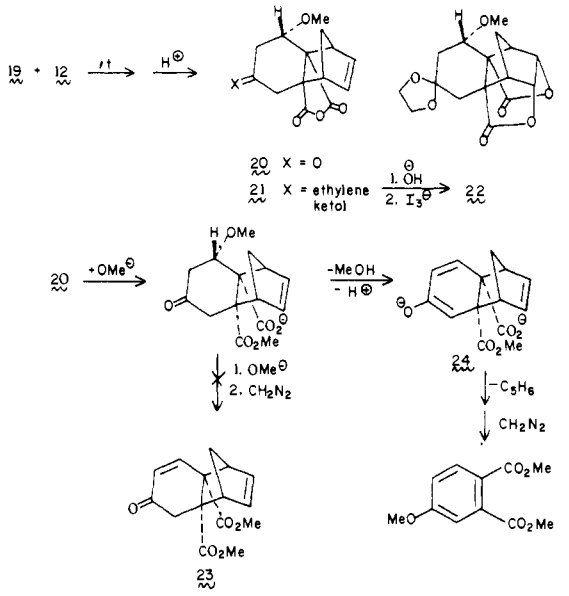


that cycloaddition occur cis to the one- rather than two-carbon bridge. An encouraging precedent was available via the detailed studies of Simmons, who reported that cycloaddition of anhydride **19** with 1,3-butadiene occurs cis to the one-carbon bridge.[12] Indeed, the Simmons dienophile, **19**, was the starting point of our journey toward *dl*-pentalenolactone. Our findings are described below.

Discussion of Results

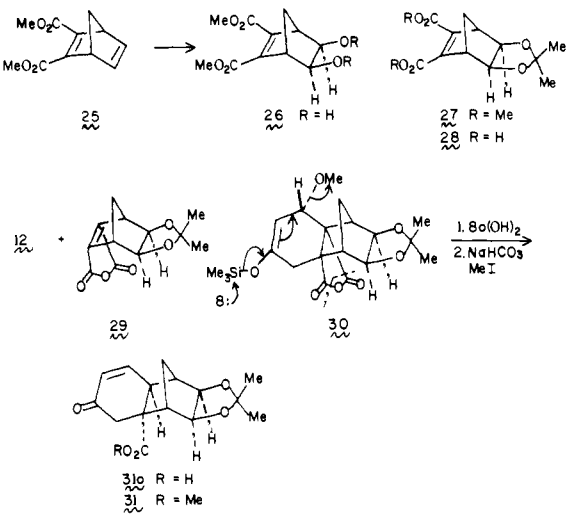
(1) Synthesis of Enone Ester 31. Cycloaddition of **19** with **12** took place in benzene at room temperature. The adduct was not characterized. After its exposure to aqueous acetic acid, there was thus obtained in 71% yield the β-methoxy ketone[13] **20**, mp 99–100 °C. The configuration of the methoxy function, drawn as shown on the basis of the usual endo selectivity in Diels–Alder reactions, is, in fact, not known with certainty. That the substituted succinic anhydride in **20** is cis to the etheno bridge was, however, rigorously established. Reaction of **20** under quite standard ketalizing conditions afforded **21**, mp 127–128 °C, in 81% yield—a tribute to the stability of the anhydride. Compound **21** was treated with aqueous sodium hydroxide followed by potassium triiodide. There was obtained the highly crystalline dilactone **22**.

With this confirmation accomplished, we returned to ketone **20** and attempted to achieve its conversion to cyclohexenone **23** by a seemingly simple β-elimination of methanol. In the event, reaction of **20** with sodium methoxide in methanol even at room temperature, followed by reaction with diazomethane, afforded, not the expected **23**, but rather dimethyl 4-methoxyphthalate in yields of 60–70%. A probable interpretation of this unexpected reaction is that the monoacid monoester version of **23** was in fact, produced. However, its ready enolization in the α' sense, giving rise to **24**, sets the stage for a notably rapid retro-Diels–Alder reaction, releasing cyclopentadiene and a phenolic monoacid monoester which is converted to dimethyl 4-methoxyphthalate after reaction with diazomethane. Similar remarkably facile cycloreversions have recently been reported from other laboratories.[14]



It was thus necessary to retain the capacity for cleaving the two-carbon bridge at the required stage of the synthesis, while eliminating the vulnerability of the enone to base-catalyzed cycloreversion. For this purpose, we started with the readily available diester **25**.[15] This was converted in 76% yield to diol **26** through the action of catalytic osmium tetroxide, which is continuously recycled by *N*-morpholine *N*-oxide.[16] The diester acetonide **27**, obtained from **26** by standard methods, was saponified to diacid **28**. The latter responded well to the action of ethoxyacetylene[12] to give an 83% yield of **29**, mp 159–160 °C.

The reaction of **29** and **12** in benzene under reflux for 3 h afforded a virtually quantitative yield of the crystalline adduct, **30**, mp 141–142 °C. After considerable experimentation, it was found that treatment of **30** with 1.2 equiv of barium hydroxide brought about the desired cleavage of the anhydride, unraveling of the β-methoxysilyl enol ether, and decarboxylation of the vinylogous β-keto barium carboxylate to afford acid **31a** *in one operation* in 99% yield. For large-scale work it was most convenient to convert **31a** to **31** by methylation of its sodium salt with methyl iodide. The yield of **31**, mp 104–105 °C, from **30** was 80%.



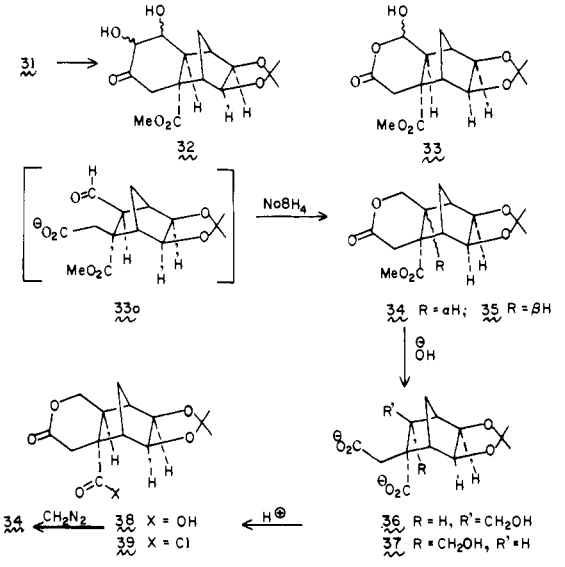
The assignment of a cis fusion to the hydrindenone system in this compound was not rigorously ascertained at this point. This was demonstrated, convincingly, at a later stage (vide infra). TLC and spectroscopic examination of the mother liquors from the crystallization of **31** left open the possibility that trace amounts of double bond and/or a stereoisomeric modi-

fication of **31** were produced from this sequence. However, we were unable to obtain such products in sufficient purity for characterization.

(2) Preparation of Acid Chloride 39. Treatment of **31** with osmium tetroxide in the presence of barium chlorate[9a,b] served to effect its conversion to the crystalline diol **32**, mp 158–159 °C, in virtually quantitative yield. The configurations of the two hydroxyl functions in **32** are left unspecified and are, in any case, of no moment since, from the next step (lead tetraacetate–aqueous acetic acid), there was obtained the pseudolactone system, **33**. This was treated with 1 equiv of aqueous sodium hydroxide (presumably generating **33a**) and excess sodium borohydride. Acidification afforded the crystalline δ-lactone methyl ester **34** (mp 181–182 °C) in 85% yield from **31**.

Of course, the stereochemical assignment shown in **34** rested on two assumptions, i.e., that the decarboxylation–ketonization of **30** had given cis-fused **31a** and that no epimerization of the aldehyde had occurred during reductive cyclization. Either of these occurrences could have given rise to the hypothetical trans-fused lactone represented as **35**. That the product was a δ- rather than a γ-lactone was in consonance with its infrared spectrum, and seemed very probable, in any case, since the product was still a methyl ester lactone rather than a carboxylic acid lactone.

The assignment of cis stereochemistry to the δ-lactone was strongly supported by the next series of reactions. The presumed **34** reacted with 4.5 equiv of aqueous sodium hydroxide to give a water-soluble disodium salt, **36**. Acidification of **36** afforded a lactone acid, mp 264–265 °C, which on treatment with diazomethane restored the original lactone ester, mp 181–182 °C.



Were the original lactone ester to be properly represented by **35**, it seemed highly improbable that it would have been reconstructed by the sequence of reactions described above, since acidification of its saponification product, **37**, would most likely have afforded a cis-fused γ-lactone. Accordingly, the formulation of the lactone ester as **34** and its derived lactone acid as **38** seemed secure. Treatment of **38** with thionyl chloride in benzene afforded a nearly quantitative yield of the acid chloride **39**.

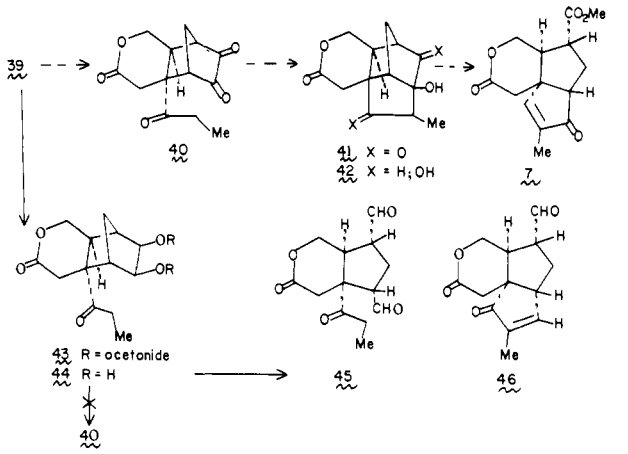
(3) Synthesis of Pentalenopyranone 4. The acid chloride **39** served as a branching point for several initiatives aimed at enone **7**. Our preferred route involved an intramolecular aldol condensation of the hypothetical trione **40** wherein compound **41** would be produced. Reduction of such a β-aldol acyloin would give triol **42** which would be subjected to oxidative cleavage and β-elimination, leading to the desired enone **7**.

The first phases of this plan could be reduced to practice. Thus, **39** reacted with 2.6 equiv of ethylmagnesium bromide in THF at −78 °C to afford a 60% yield of the ethyl ketone **43**, mp 172.5–173.5 °C. From this, by acid-catalyzed cleavage of the acetonide, was obtained the highly crystalline dihydroxyketolactone **44**, mp 174–175 °C. It was now our intention to oxidize the vicinal diol to the α-diketone **40**.

A variety of possibilities were explored to reach this goal. Early emphasis was placed on Jones-type oxidations and on Moffatt–Pfitzner[17] or conceptually related variations thereof. While no products were fully characterized from the chromic acid oxidations of **44**, it was clear that even under mild conditions the bulk of reaction was occurring with cleavage of the carbon–carbon bond leading to acidic products.

Attempted Moffatt–Pfitzner reactions afforded material which, on the basis of TLC and mass spectral analyses, appeared to consist of largely starting **44** and some monooxidation product. Only the slightest amount of double oxidation was indicated. Also unsuccessful in our hands was the *N*-halosuccinimide dimethyl sulfide variation of Corey,[18] which had, in fact, been used by Büchi[19] to convert a vicinal diol to an α-diketone. Applied to substrate **44** these conditions gave largely starting material and complex mixtures.

With a view toward achieving monooxidation of diol **44** (to either hydroxy diketone) it was subjected to the action of silver carbonate on Celite.[20] Again, reaction was quite slow, but such, reaction as did occur produced largely the keto dialdehyde **45**. Finally, it was found that reaction of diol **44** with a large excess of activated manganese dioxide, in chloroform under reflux, afforded a virtually quantitative yield of the keto dialdehyde **45**.[21] It should be noted that this compound was also produced by a more classical periodate cleavage of **44** but in a much lower state of purity. Apparently dialdehyde **45** is extensively hydrated in aqueous medium.[22]

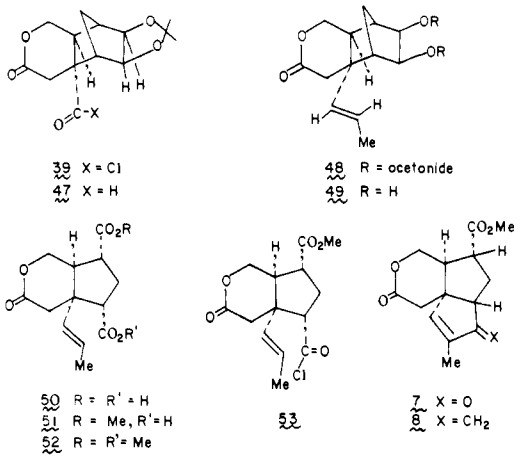


Several attempts were made to achieve aldol cyclization of the unstable keto dialdehyde **45**. The only conditions where some measure of success was attained involved heating **45** with piperidine in acetic acid. There was thus obtained, for the first time, the desired pentalenopyranone ring system in the form of the unstable enone aldehyde **46**. While it was gratifying to enter, at last, into the required ring system, the yields for the aldolization–dehydration were most disappointing (20–40%).

Rather extensive manipulations would be necessary to convert **46** into the desired **4**. Owing to the difficulties associated with its synthesis, and to some unfavorable early attempts to carry compound **46** further, an alternate approach was pursued. We returned to acid chloride **39** and studied its conversion to aldehyde **47**. After some less than satisfying attempts to bring about this transformation, in high yield, with a variety of metal hydride reducing agents, it was found that classical Rosenmund reduction suffices to convert **39** to **47**, mp 158–159

°C, in essentially quantitative yield. The latter reacted smoothly with ethylidenetriphenylphosphorane in dimethoxyethane to afford the propenyl lactone **48**, mp 180–181 °C, in 88% yield. Treatment of **48** with aqueous HCl in dimethoxyethane under reflux produced the diol **49**, mp 135–136 °C, in 96% yield.

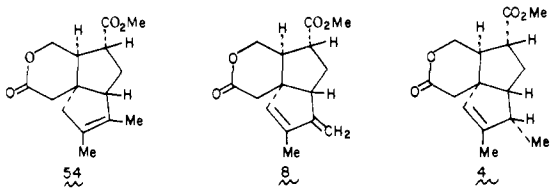
Oxidation, according to Jones,[24] converted **49** to the crude dicarboxylic acid **50**, which was treated with methanol–H_2SO_4 in the hope of bringing about its conversion to monoester monoacid **51**. The crude material thus received reacted with thionyl chloride in benzene to give crude acid chloride **53**. The olefinic acid chloride ester was treated with aluminum chloride at room temperature. There was thus obtained a 41% yield of the long-desired enone **7**, mp 110–111 °C, and 19% of the oily *seco*-dimethyl ester **52**, which had clearly arisen from nonselectivity in the attempted monoesterification. The latter could be converted by saponification to its precursor **50**, which, when recycled through the sequence, afforded an additional 8% of **7**.



In our hands, the conversion of **7** to **8** by Wittig-type methodology was best carried out under the conditions of Uda.[25] Unfortunately, the yield of **8**, mp 73–74.5 °C, was only 46% at maximum. In principle, one might consider alternatives to the Wittig method, but these were in practice not investigated. At last we were in a position to study the introduction of the secondary methyl group required for **4**, by catalytic semireduction of diene **8**.[26]

It was a matter of some consternation to find that heterogeneous catalysis (Pd/C–ethanol) gave almost exclusively the tetrasubstituted olefin **54**. This compound was not rigorously purified but the resonances in the "*C*-methyl region" of its NMR spectrum, the absence of signals attributable to any olefinic protons in the same spectrum, and its mass spectrum (*m/e* 264) sufficed to convey the unwanted news—that semihydrogenation had indeed occurred—but that **54** was the product.

We do not know whether the formation of **54** is the result of actual 1,4 reduction of the s-trans diene or, more likely, the consequence of subsequent tautomerization on the catalytic surface. Fortunately, for our purpose, it was not necessary to investigate this matter because hydrogenation of **8** in the presence of the Wilkinson system $(Ph_3P)_3$–RhCl[27] afforded the dihydro compound **4**, mp 88–90 °C. The major loss (ca. 20–25%) involved a poor product balance upon chromatographic separation of **4** from catalyst, or products derived therefrom. While no other pure dihydro or tetrahydro product could be obtained, when the reaction was conducted on a sufficiently large scale (250 mg), the NMR spectrum of the mother liquors of crystallization did suggest, in the *C*-methyl region (δ 1.1 d, J = 7 Hz), that traces of such products may be present. The mass spectrum of the mother liquors indicated only a parent *m/e* of 264, consistent with the dihydro nominal mass. In almost all of our work, the total dihydro material rather than the crystalline version of **4** was carried further, with no apparent disadvantage.



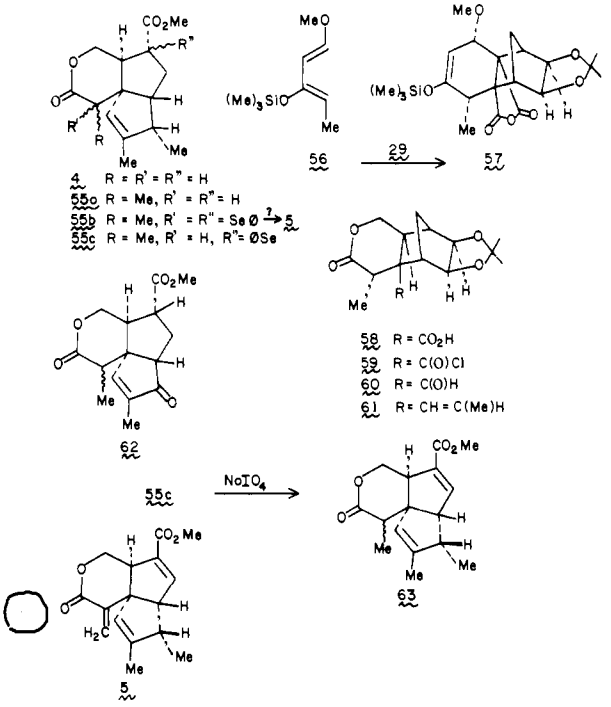
That the stereochemistry of **4** is as shown was not known rigorously at this point, but was subsequently established at the stage of deoxypentalenolactone methyl ester (**5**, vide infra).

(4) Synthesis of Deoxypentalenolactone Methyl Ester (5). In principle, the conversion of **4** to **5** might be achieved in three steps. The first would involve the introduction of a methyl group α to the lactonic carbonyl function (**4** → **55a**). This would be followed by concurrent base-induced selenenylation at each of the two enolizable centers (**55a** → **55b**) and then concurrent oxidative elimination (**55b** → **5**).[28]

The first projected step, **4** → **55a**, was, in our hands, not satisfactory. While only limited amounts of material were devoted to this possibility, we could not reproducibly introduce the single methyl group required for this transformation. We, of course, relied on a nonnucleophilic base (lithium diisopropylamide) in varying stoichiometric relations to **4**. The presumed deprotonation was followed by quenching with methyl iodide. In practice, considerable starting material was recovered. Small amounts (20–30%) of desired **55a** could be isolated. The presence of di- and possibly trimethylated products was also indicated. Worst of all, the reactions carried out on small scale (10–20 mg of **4**) were not reproducible.

Furthermore, attempts to achieve the bisselenenylation of **55a** with a view toward obtaining **55b** were uniformly unsuccessful. At best, we could introduce a single phenylseleno function adjacent to the carbomethoxy group, thus affording **55c**. Repeated efforts to achieve the conversion of **55a** or **55c** to the desired **55b** were in every case unsuccessful.

While these activities were in progress, we also sought to provide for a more orderly synthesis of **55a**. For this purpose



we returned to the original dienophile **29**, and investigated its Diels–Alder reaction with the modified diene **56**.[29] Indeed there was obtained in 71% yield the crystalline adduct **57**,[30] mp 115–118 °C. This was now the starting material for a series of reactions which precisely paralleled those described above, starting with the nor adduct **30**. We thus reached the acid **58**,[30] mp 280–282 °C. Rosenmund reduction of its derived acid chloride **59** did provide aldehyde **60**,[30] mp 246–247 °C, but only in 49% yield. The Wittig reaction **60** → **61**[30] (mp 222–223 °C) was also apparently complicated by the presence of the proximate methyl group and was achieved, at best, in 45% yield. Compound **61** was carried further to the level of **62**[30] by a sequence again comparable to that which was reasonably successful in the case of the demethyl compounds (vide supra, **49** → **50** → **51** → **7** → **8** → **4**). Unfortunately, the yields were uniformly lower than those of the nor series, and this attempt at inclusion of what was thought to be the "strategic" methyl group was abandoned.[30]

The only solace which was available from this disastrous phase of the inquiry arose in the oxidative deselenenylation of **55c** with sodium metaperiodate. This did indeed provide, in ca. 70% yield, the trisubstituted olefinic ester **63**. No apparent competition from the alternate mode of elimination could be detected.

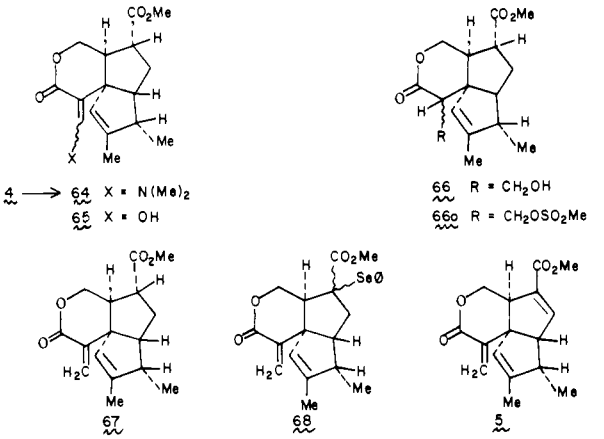
The studies described above had established the feasibility of base-induced selenenylation α to the ester (cf. **55a** → **55c**) and the likely favorable outcome in an oxidative deselenenylation (cf. **55c** → **63**) in a suitable precursor. However, they had failed to achieve a satisfactory synthesis of **55a** and, more seriously, had cast considerable doubt on the likelihood of base-induced selenenylation at the secondary neopentyl center α to the lactone, since neither **55a** nor **55c** could be converted to **55b**.

It was thus necessary to decouple the prototropic reactions of the lactone and ester functions. We focused on the conversion of **4** to the α-methylenelactone **67**. We sought to achieve this in a manner which would not be likely to perturb the enolizable center adjacent to the ester.

The de novo introduction of a methylene function α to a lactonic carbonyl group is an area in which considerable effort has been expended.[31,32] Nonetheless, in projecting a conversion of **4** to **67**, we were obliged to operate in the face of an unusual set of constraints, since schemes involving stoichiometric deprotonation α to the lactone seemed to be questionable in the presence of the ester. Furthermore, electrophilic attack on the hindered enolate seemed to be an additional complication. We therefore sought a reaction where forcing conditions could be applied to the lactone area of **4** without fostering undesired protropic reactions in the environs of the carbomethoxyl function. Fortunately, this could be accomplished.

Treatment of **4** with an excess of the Brederick reagent,[33] bis(dimethylamino)-*tert*-butoxymethane (neat), at 96 °C for 40 h afforded a virtually quantitative yield of **64**. The enaminolactone was smoothly cleaved through the action of silica gel at room temperature for 1 h, providing the enol **65**. No "aldehydo" character could be gleaned from the NMR spectrum of this product. Nonetheless, reaction of **65** with sodium borohydride in methanol for 30 min at 0 °C afforded a high yield of the hydroxymethyl lactone **66**. The components of this epimeric mixture were not characterized in detail. Rather the mixture was converted, by way of the derived mesylates **66a**, to the homogeneous α-methylenelactone **67**, mp 68–70 °C. The overall yield for the five-step conversion of **4** to **67** was, reproducibly, 60–65%.

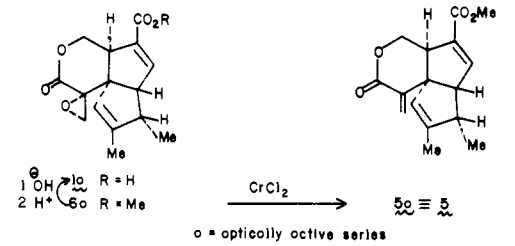
It was now necessary to achieve base-induced selenenylation α to the carbomethoxy function. Fortunately, this was possible in the presence of the α-methylenelactone. Treatment of **67** with 3 equiv of lithium diisopropylamide, followed by 2 equiv of phenylselenenyl chloride at −78 °C for 30 min, afforded



47% of the epimeric mixture **68**. This mixture was not characterized in detail. Instead it was subjected to oxidative deselenenylation[28] to afford, in 97% yield, *dl*-deoxypentalenolactone **5**.

Before embarking on the introduction of the required epoxy function, it was first useful to establish that compound **5** was indeed correctly formulated. It will be recalled that the stereochemical sense of the semihydrogenation reaction (**8** → **4**) had not been defined in a rigorous way.

Toward this end, samples of naturally occurring pentalenolactone **1** were obtained.[34] Esterification of **1** with diazomethane afforded the more stable methyl ester, **6a**. Treatment of **6a** with chromous chloride in acetone gave a 52% yield of optically active **5a**, $[\alpha]^{24}_D$ −190° (*c* 1.09, methanol). *The solution infrared and NMR spectra of fully synthetic* **5** *and naturally derived* **5a** *were identical. Their chromatographic properties were also identical.*[35] *There could be no doubt that the synthesis of deoxypentalenolactone methyl ester had been achieved.*



(5) Synthesis of Pentalenolactone (1). Thus reassured, all efforts were now directed toward the introduction of the properly configured spiroepoxide. That this was the last remaining problem was clear, since in the optically active series saponification of **6a** followed by careful acidification did indeed restore optically active pentalenolactone **1a**. The success of the venture thus rested on the conversion of **5** to **6**.[36]

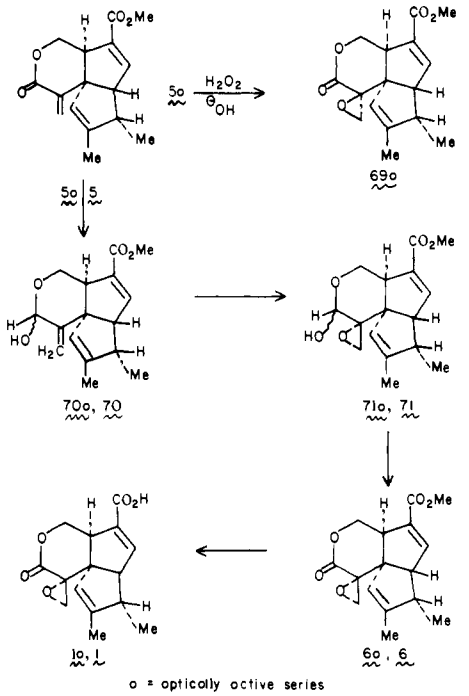
In pursuing this objective, we carried out our opening reactions with a most reliable model, i.e., the optically active deoxy compound **5a**, confident that any successes could be transferred to the fully synthetic racemic series.

Compound **5a** was treated with alkaline hydrogen peroxide under conditions related to those of Trost[36a] and Payne.[37] Epoxidation did occur at the exocyclic methylene group. Unfortunately, the only characterized compound (32%) was **69a**, clearly different from **6a** in both its chromatographic and spectral (see Experimental Section for NMR spectroscopic data) properties. Small amounts of the desired **6a** could be detected by thin layer chromatographic analysis of the reaction mixture. The TLC mobilities of **6a** and **5a** are, in fact, very close. Thus, the traces of **6a** isolated from this reaction were contaminated with some starting **5a**. At best, the yield of the direct epoxidation of **5a** to **6a** was 10%.

The cis-fused oxahydrindan section of **5a** is sufficiently flexible such that examination of molecular models fails to reveal, a priori, a clear bias in favor of α- or β-face attack. Empirically, β-attack appeared to be heavily favored (**5a** → **69a**). We reasoned that an axially oriented anomeric hydroxyl group of a hemiacetal derivable from **5a** might be disposed toward the α configuration wherein it resides on the convex surface of the oxahydrindan system. So stationed, this hydroxyl, which would also be allylic to the exocyclic methylene group, might provide the required guidance for α-epoxidation.[38,39]

Accordingly, compound **5a** was treated with diisobutylaluminum hydride to afford **70a**. Epoxidation of **70a** according to Sharpless[39] provided the epoxyhemiacetal **71a**. Jones oxidation of **71a** gave, as the overwhelmingly predominant product, pentalenolactone methyl ester (**6a**). Analysis of the thin layer chromatogram of the crude Jones oxidation product revealed the possibility, at most, of traces of the undesired, more polar epoxide **69** in amounts too small for isolation. Compound **6a** thus obtained from **5a** was recycled to **1a** by alkaline hydrolysis (2.5 equiv of 2 N KOH/H_2O/THF, room temperature, 21 h) followed by careful acidification. The spectral and chromatographic properties of reconstituted pentalenolactone (**1a**) were identical with those of **1a** obtained via natural sources.[34]

The formalities necessary for the total synthesis of **1** involved the repetition of this sequence on racemic **5**. This was done two times, starting in each case with ca. 25 mg of fully synthetic material. Compound **5** was converted as above to the *dl*-hemiacetal **70** which upon epoxidation gave *dl*-epoxyhemiacetal **71**. Oxidation of **71** gave *dl*-pentalenolactone methyl ester (**6**). The NMR spectrum and LC trace of the fully synthetic



6 revealed the presence of two impurities in a combined total of ca. 10%. In the synthetic series, it was thus necessary to resort to LC purification to obtain a fully homogeneous sample of **6**. This was done (see Experimental Section). The infrared, NMR, mass spectra, and LC properties of *dl*-pentalenolactone methyl ester (**6**) were the same as those of **6a**. Alkaline hydrolysis as above followed by careful acidification gave the unstable free *dl*-pentalenolactone **1**, whose spectra (infrared, NMR, and mass) and chromatographic properties were the same as those of **1a** obtained via the benzylamine salt of the natural product[34] or from **5a**. The total synthesis of *dl*-pentalenolactone was thus completed.

Summary

With the readily available **12** and **25** as our starting materials, 33 synthetic operations were required to produce *dl*-pentalenolactone in an overall yield of 0.2%. It is of interest to recall some of the adversities which occasioned this rather lengthy route. The cycloreversion of **23** added three steps (**25** → **26**, **26** → **27**, and **48** → **49**) to the original plan. Most seriously, what might, in principle, have been a four-step conversion (**4** → **55a** → **55b** → **5** → **6**) escalated, in the light of unfavorable findings described above, into a ten-step series (**4** → **64** → **65** → **66** → **66a** → **67** → **68** → **5** → **70** → **71** → **6**) in 13% overall yield. Other notably serious losses occurred in the sequence **49** → **8** → **7** → **4** (16%). Given these reverses, this synthesis is not destined to play a significant role in the availability of pentalenolactone.

Nonetheless, several synthetic demonstrations of importance were achieved. In this connection we would point to the expansion of our functionalized activated diene methodology[11,29] to embrace the goal of 5-acylcyclohexenones (cf. **30** → **31**). Furthermore, it appears likely that the α-methylenation method which was used for the conversion of **4** to **67** is probably the most generally useful to date, in terms of functional group and steric hindrance tolerance. Finally, the control of the sense of epoxidation via an anomeric hydroxyl group may well have general value in synthesis.[42] It is on such applications that the ultimate value of the exercise must depend. An efficient total synthesis of pentalenolactone remains, to our knowledge, an unsolved problem.

Experimental Section[43]

(1β,4β,4aα,5α,8aα)-1,4,4a,5,6,8a-Hexahydro-5-methoxy-7-oxo-1,4-methanonaphthalene-4a,8a-dicarboxylic Anhydride (20). To a solution of norbornadiene-2,3-dicarboxylic anhydride (**19**),[12] 2.35 g, 0.015 mol) in 25 mL of benzene at room temperature was added in one portion 1-methoxy-3-trimethylsiloxy-1,3-butadiene[11a,b] (**12**, 2.60 g, 0.015 mol) in 5 mL of benzene. The reaction became mildly exothermic. The solution was stirred at room temperature under nitrogen for 1 h, after which time the volatiles were removed completely in vacuo. Dimethoxyethane (40 mL), water (15 mL), and glacial acetic acid (7.5 mL) were added and the solution was stirred at room temperature for 1 h. A solution of 75 mL of saturated sodium bicarbonate was added and the solution extracted with ethyl acetate (4 × 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo to afford an oil which readily crystallized. Trituration with pentane containing a small amount of ether afforded 2.70 g (71%) of **20** as a crystalline solid: mp 99–100 °C; λ_{max} ($CHCl_3$) 5.44, 5.85 μ; δ ($CDCl_3$) 1.7 (m, 2), 2.5–3.4 (m, containing s at 3.4, 9), 4.2 (t, J = 4 Hz, 1), 6.2–6.6 (m, 2) ppm; *m/e* 262.083 42 (calcd for $C_{14}H_{14}O_5$, 262.084 12 (parent)).

(1'β,4'β,4a'α,5'α,8a'α)-1',4',4a',5',6',8a'-Hexahydro-5'-methoxyspiro[1,3-dioxolane-2,7'](8'*H*)-[1',4']methanonaphthalene-4'a,8'a-dicarboxylic Anhydride (21). A solution of ketone **20** (2.50 g, 0.0095 mol) in 300 mL of benzene, containing 25 mL of ethylene glycol and *p*-toluenesulfonic acid (0.250 g, 0.0013 mmol), was heated under reflux under nitrogen with azeotropic removal of water for 17 h. The reaction mixture was cooled to room temperature and 250 mL of ether added. The organics were extracted with saturated aqueous sodium bicarbonate (3 × 100 mL), dried (Na_2SO_4), and evaporated to afford an oil which easily crystallized. Trituration with pentane gave 2.418 g (83%) of **21**: mp 127–128 °C; λ_{max} ($CHCl_3$) 5.42, 5.62 μ; δ($CDCl_3$) 1.4–3.0 (m, 8), 3.4 (s, 4), 4.9 (br s, 4), 6.4 (m, 2) ppm; *m/e* 306.108 45 (calcd for $C_{16}H_{18}O_6$, 306.110 34 (parent)).

Dilactone of 21. To a solution of ethylene ketal **21** (0.306 g, 0.001 mol) in 1 mL of tetrahydrofuran was added sodium hydroxide (0.120 g, 0.003 mmol) in 4 mL of water. The solution was stirred at room temperature for 19 h, at which time 2.5 mL of iodine–potassium iodide solution (89 g, 0.350 mol of I_2; 330 g, 1.77 mol of KI; 500 mL of H_2O) was added. The solution was stirred in the dark at room temperature for 4 days. Ethyl acetate (50 mL) was added, followed by 10 mL of

10% $Na_2S_2O_3$. The aqueous phase was extracted with ethyl acetate (4 × 10 mL). The combined organic extracts were washed with 1 × 10 mL of 10% $Na_2S_2O_3$ and dried (Na_2SO_4) and the volatiles removed in vacuo. The sticky solid which remained was triturated with ether to afford 0.1619 g (50%) of dilactone **22:** mp 180 °C dec; λ_{max} ($CHCl_3$) 5.53 μ; δ(acetone-d_6) 1.6–2.5 (m, 8), 3.0 (br s, 4), 3.4 (s, 3), 4.0 (m, 2), 4.8 (t, J = 3 Hz, 1) ppm;[44] *m/e* 322.104 30 (calcd for $C_{16}H_{18}O_7$, 322.105 25 (parent)).

Dimethyl 4-Methoxyphthalate. To a solution of ketone **20** (0.250 g, 0.009 54 mol) in 10 mL of methanol was added 1 mL of 1 M sodium methoxide in methanol solution. The solution was stirred for 1 h under nitrogen at room temperature, and 1 mL of the methoxide solution was added. Stirring was continued for an additional 2 h, followed by the addition of excess Dowex 50W-X8 (H^+) resin. After stirring for 10 min the solution was filtered and the resin washed with methanol. The total methanol solution was treated with excess ethereal diazomethane for 1 h. Removal of the volatiles in vacuo gave an oil which was chromatographed on silica gel (20 g). Elution with hexane–ethyl acetate (9:1) afforded 0.138 g (65%) of dimethyl 4-methoxyphthalate: λ_{max} ($CHCl_3$) 5.81 μ; $\delta(CDCl_3)$ 3.9 (s, 6), 4.0 (s, 3), 6.8–7.1 (m, 2), 7.7 (d, J = 8.5 Hz, 1) ppm.

Dimethyl 5,6-Dihydroxynorborn-2-ene-2,3-dicarboxylate (26). To a solution of *N*-methymorpholine *N*-oxide (137.5 g, 0.898 mol) and osmium tetroxide[16] (1.0 g, 0.004 mol) in 1600 mL of *tert*-butyl alcohol, 530 mL of tetrahydrofuran, and 170 mL of water at 0 °C (ice bath) was added dropwise diester **25** (185.1 g, 0.889 mol) over a period of 0.5 h. After 4 h at room temperature, TLC analysis showed the reaction to be complete. The reaction mixture was filtered through a pad of Celite and the volatiles were removed to afford a dark, oily residue. The oil was dissolved in 300 mL of ethyl acetate and washed with cold 10% aqueous hydrochloric acid (3 × 500 mL). The organic layer was dried (Na_2SO_4) and evaporated in vacuo to yield 165.4 g (76%) of diol **26:** λ_{max} ($CHCl_3$) 2.75, 5.75 μ; $\delta(CDCl_3)$ 2.0 (m, 2), 3.2 (br s, 2), 3.5 (br s, 2), 3.8 (s, 6), 4.0 (br s, 2) ppm.

Dimethyl (3aα,4β,7β,7aα)-3a,4,7,7a-Tetrahydro-2,2-dimethyl-4,7-methano-1,3-benzodioxole-5,6-dicarboxylate (27). To a solution of diol **26** (165.4 g, 0.683 mol) in 4000 mL of dry acetone was added anhydrous copper(II) sulfate[45] (656 g, 4.1 mol). The solution was heated under reflux under a nitrogen blanket for 40 h, cooled to room temperature, then filtered through a Celite pad. The volatiles were removed in vacuo, and the residual oil was chromatographed on 1800 g of silica gel. Elution with 30% ethyl acetate in hexane afforded 143.2 g (74%) of **27:** mp 56–57 °C; λ_{max} ($CHCl_3$) 5.75 μ; $\delta(CDCl_3)$ 1.3 (s, 3), 1.4 (s, 3), 2.0 (m, 2), 3.2 (m, 2), 3.8 (s, 6), 4.4 (m, 2) ppm.

Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.67; H, 6.55.

(3aα,4β,7β,7aα)-3a,4,7,7a-Tetrahydro-2,2-dimethyl-4,7-methano-1,3-benzodioxole-5,6-dicarboxylic Acid (28). To a solution of diester **27** (45.12 g, 0.16 mol) in 320 mL of tetrahydrofuran was added aqueous sodium hydroxide (0.25 M, 1885 mL, 0.48 mol) at room temperature. After stirring for 18 h, the pH of the solution was adjusted with concentrated hydrochloric acid to equal 2, and the aqueous system was extracted with ethyl acetate (6 × 1 L). The combined organic layers were dried (Na_2SO_4) and the volatiles removed in vacuo to yield a light yellow solid, which was triturated with a pentane–ether (20:1) solution to afford diacid **28,** 40.5 g (100%), as a white solid: mp 230–231 °C; δ(acetone-d_6) 1.3 (s, 3), 1.4 (s, 3), 1.9 (m, 2), 3.3 (m, 2), 4.4 (m, 2), 8.7 (br s, 2) ppm.

Anal. Calcd for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.75; H, 5.61.

(3aα,4β,8β,8aα)-3a,4,8,8a-Tetrahydro-2,2-dimethyl-4,8-methanofuro[3,4-*f*]-1,3-benzodioxole-5,7-dione (29). To a solution of diacid **28** (40.5 g, 0.159 mol) in 3 L of methylene chloride at reflux was slowly added 40 mL of ethoxyethyne.[12] The solution was heated and refluxed for 18 h and cooled to room temperature and activated charcoal was added. After stirring for 30 min, the reaction mixture was filtered through a pad of Celite and the volatiles were removed in vacuo. The residue was triturated with pentane–ether (20:1), filtered, and dried to afford 31.2 g (83%) of white, crystalline anhydride **29:** mp 159–160 °C: λ_{max} ($CHCl_3$) 5.40, 5.65 μ; $\delta(CDCl_3)$ 1.3 (s, 3), 1.5 (s, 3), 2.2 (m, 2), 3.4 (m, 2), 4.4 (m, 2) ppm.

Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.02; H, 5.12. Found: C, 60.97; H, 5.26.

(3aα,4β,4aα,5α,8aα,9β,9aα)-Octahydro-5-methoxy-2,2-dimethyl-7-trimethylsiloxy-4,9-methanonaphtho[2,3-*d*]-1,3-dioxole-4a,8a-dicarboxylic Anhydride (30). To a solution of acetonide anhydride **29** (26.8 g, 0.113 mol) in 2300 mL of dry benzene was added 1-methoxy-3-trimethylsiloxy-1,3-butadiene **12**[11a,b] (29.3 g, 0.170 mol). The solution was stirred for 18 h at room temperature, then concentrated in vacuo to yield a solid, which upon washing with cold (0 °C) pentane afforded 41.6 (89%) of adduct **30:** mp 141.5–142.5 °C; λ_{max} ($CHCl_3$) 5.42, 5.63, 5.79, 6.07 μ; $\delta(CDCl_3)$ 0.2 (s, 9), 1.3 (s, 3), 1.5 (s, 3), 2.0 (m, 2), 2.15 (br d, J = 16 Hz, 1), 2.5 (m, 1), 2.8 (m, 1), 2.9 (br d, J = 16 Hz, 1), 3.4 (s, 3), 4.05 (br d, J = 4 Hz, 1), 4.1 (br d, J = 5 Hz, 1), 4.4 (br d, J = 5 Hz, 1), 5.0 (br d, J = 4 Hz, 1) ppm.

Anal. Calcd for $C_{20}H_{28}O_7Si$: C, 58.80; H, 6.91; Si, 6.87; *m/e* 408.160 42 (P). Found: C, 59.01; H, 7.04; Si, 6.83; *m/e* 408.159 59.

(3aα,4β,4aα,8aα,9β,9aα)-Hexahydro-2,2-dimethyl-6-oxo-4,9-methanonaphtho[2,3-*d*]-1,3-dioxole-4a(4*H*)-carboxylic Acid (31a). To a solution of trimethylsilyl enol ether **30** (20.4 g, 0.05 mol) in 1200 mL of water was added $Ba(OH)_2 \cdot 8H_2O$[46] (18.93 g, 0.06 mol). The solution was refluxed for 5 h, then cooled to room temperature, and concentrated hydrochloric acid was added until the solution was acidic to pH paper. The solution was extracted with ethyl acetate (4 × 800 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to yield a crude enone acid. The crude product was triturated with pentane–ether (20:1), filtered, and dried to yield 13.5 g (99%) of enone acid **31a:** mp 219–221 °C; λ_{max} ($CHCl_3$) 5.90, 5.95 μ; $\delta(CDCl_3)$ 1.2 (s, 3), 1.35 (s, 3), 1.5 (br d, J = 10 Hz, 1), 1.75 (br d, J = 10 Hz, 1), 2.1 (br s, 2), 2.5 (d, J = 17 Hz, 1), 2.7 (m, 1), 2.75 (d, J = 17 Hz, 1), 4.2 (s, 2), 5.9 (d of d, J_{BA} = 10, J_{BX} = 2 Hz, 1), 6.8 (d of d, J_{AB} = 10, J_{AX} = 4 Hz, 1) ppm; *m/e* 263.090 31 (calcd for $C_{14}H_{15}O_5$, 263.091 94 (P − Me)).

Methyl (3aα,4β,4aα,8aα,9β,9aα)-Hexahydro-2,2-dimethyl-6-oxo-4,9-methanonaphtho[2,3-*d*]-1,3-dioxole-4a(4*H*)-carboxylate (31). A solution of enone acid **31a** (10.4 g, 0.037 mol), sodium bicarbonate (13.23 g, 0.157 mol), and methyl iodide (22.33 g, 0.157 mol) in 275 mL of *N*,*N*-dimethylformamide was heated under a nitrogen blanket at 65 °C for 5 h, then cooled to room temperature. The volatiles were removed in vacuo and the residue was suspended in 100 mL of ethyl acetate. The resulting suspension was washed with water (2 × 50 mL). The combined washings were extracted with ethyl acetate (3 × 50 mL) and the ethyl acetate layers combined and dried (Na_2SO_4). The volatiles were removed in vacuo to yield a crude enone ester which was chromatographed on silica gel (170 g). Elution with 20% ethyl acetate in hexane afforded 8.0 g (74%) of ester **31:** mp 104–105 °C; λ_{max} ($CHCl_3$) 5.7, 5.85 μ; $\delta(CDCl_3)$ 1.2 (s, 3), 1.35 (s, 3), 1.40 (br d, J = 11 Hz, 1), 1.8 (br d, J = 11 Hz, 1), 2.2 (m, 2), 2.4 (d, J = 17 Hz, 1), 2.8 (m, 1), 2.9 (d, J = 17 Hz, 1), 3.8 (s, 3), 4.0 (br d, J = 6 Hz, 1), 4.2 (br d, J = 6 Hz, 1), 5.9 (d of d, J_{BA} = 10, J_{BX} = 2 Hz, 1), 6.5 (d of d, J_{AB} = 10, J_{AX} = 4 Hz, 1) ppm.

Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.40; H, 7.06.

Methyl Octahydro-7,8-dihydroxy-2,2-dimethyl-6-oxo-4,9-methanonaphtho[2,3-*d*]-1,3-dioxole-4a(4*H*)-carboxylate (32). To a stirred solution of enone **31** (10.03 g, 0.034 mol) and barium chlorate (7.08 g, 0.0219 mol) in 250 mL of water and 25 mL of tetrahydrofuran was added osmium tetroxide[9a,b] (2.0 g, 0.007 87 mol) in one portion. After stirring for 1 h, the volatiles were removed in vacuo and the resulting salts were extracted with hot ethyl acetate. The solution was treated with activated charcoal, then filtered through a pad of Celite. The volatiles were removed in vacuo to yield 11.2 g (100%) of a light green diol **32:** mp 158–159 °C; λ_{max} ($CHCl_3$) 2.9, 5.8 μ; $\delta(CDCl_3)$ 1.3 (s, 3), 1.5 (s, 3), 1.6 (m, 1), 2.0 (m, 1), 2.45 (m, 1), 2.5 (m, 1), 2.6 (d, J = 18 Hz, 1), 3.1 (d, J = 18 Hz, 1), 3.2 (m, 1), 3.8 (s, 3), 4.0–4.2 (m, 4) ppm.

Anal. Calcd for $C_{16}H_{22}O_7$: C, 58.89; H, 6.79. Found: C, 58.50; H, 7.08.

Methyl (3aα,4β,4aα,8aα,9β,9aα)-Octahydro-5-hydroxy-2,2-dimethyl-7-oxo-4,9-methano-8a*H*-1,3-dioxolo[4,5-*g*][2]benzopyran-8a-carboxylate (33). Diol **32** (11.2 g, 0.0343 mol) was dissolved in 2500 mL of an acetic acid–water (9:1) solution. Lead tetraacetate[9a,b] (60.8 g, 0.137 mol) was added in one portion followed by stirring at room temperature for 18 h. The acetic acid and water were removed in vacuo and the white, sticky solid was dissolved in 600 mL of water and extracted with ethyl acetate (4 × 700 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford 10.7 g (100%) of lactol ester **33** as a light yellow oil: λ_{max} ($CHCl_3$) 3.0, 5.75 μ; $\delta(CDCl_3)$ 1.2 (s, 3), 1.4 (s, 3), 1.45–2.0 (m, 2), 2.2 (m, 2), 2.7–3.0 (m, 4), 3.7 (s, 3), 3.9–4.2 (m, 2) ppm; *m/e* 297.095 93 (calcd for $C_{14}H_{17}O_7$, 297.097 43 (P − Me)).

Methyl (3aα,4β,4aα,8aα,9β,9aα)-Octahydro-2,2-dimethyl-7-oxo-4,9-methano-8a*H*-1,3-dioxolo[4,5-*g*][2]benzopyran-8a-carboxylate (34). Lactol **33** (10.7 g, 0.0343 mol) was dissolved in 334 mL of a 0.1026 M aqueous sodium hydroxide solution by gently warming the solution on a steam bath. After dissolution, the solution was cooled to room temperature. Water (300 mL) was added and the solution was cooled to 0 °C (ice bath). Sodium borohydride[10] (8.145 g, 0.214 mol) was added in small portions, followed by stirring at 0 °C for 30 min, then at room temperature for 18 h. The solution was acidified to pH 2 with concentrated hydrochloric acid and extracted with chloroform (5 × 500 mL). The combined chloroform extracts were dried (Na_2SO_4) and concentrated in vacuo to afford 7.97 g (79%) of lactone ester **34**: mp 181–182.5 °C; λ_{max} ($CHCl_3$) 5.65, 5.75 μ; δ($CDCl_3$) 1.3 (s, 3), 1.5 (s, 3), 1.7 (br d, J = 10 Hz, 1), 1.9 (br d, J = 10 Hz, 1), 2.1 (m, 1), 2.45 (m, 1), 2.55 (m, 1), 2.6 (d, J = 15 Hz, 1), 2.9 (d, J = 15 Hz, 1), 3.8 (s, 3), 3.9 (d, J = 5.5 Hz, 1), 3.95 (d of d, J_{BA} = 12, J_{BX} = 12 Hz, 1), 4.1 (d, J = 5.5 Hz, 1), 4.4 (d of d, J_{AB} = 12, J_{AX} = 7 Hz, 1) ppm.

Anal. Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 60.59; H, 6.75.

(3aα,4β,4aα,8aα,9β,9aα)-Octahydro-2,2-dimethyl-7-oxo-4,9-methano-8a*H*-1,3-dioxolo[4,5-*g*][2]benzopyran-8a-carboxylic Acid (38). A solution of lactone ester **34** (7.2792 g, 0.0244 mol) in 488 mL of 0.2248 M aqueous sodium hydroxide and 275 mL of water was heated at reflux for 24 h, then cooled to room temperature. The solution was acidified to pH 2 with concentrated hydrochloric acid and extracted with ethyl acetate (4 × 500 mL). The combined organic layers were dried (Na_2SO_4) and the volatiles removed in vacuo. The crude lactone acid was triturated with pentane–ether (1:1), filtered, and dried to yield 6.350 g (92%) of lactone acid **38** as a white solid: mp 264–265 °C; λ_{max} (KBr) 2.90, 5.65, 5.80 μ; δ(acetone-d_6) 1.2 (s, 3), 1.4 (s, 3), 1.8 (br d, J = 11.5 Hz, 1), 1.95 (br d, J = 11.5 Hz, 1), 2.1 (br s, 1), 2.6 (br s, 1), 2.80 (br d of d, J_{XB} = 11, J_{XA} = 6.6 Hz, 1), 2.9 (d, J = 15.5 Hz, 1), 3.25 (d, J = 15.5 Hz, 1), 4.0 (d of d, J_{BA} = 11, J_{BX} = 11 Hz, 1), 4.3 (br d, J = 5.5 Hz, 1), 4.4 (d of d, J_{AB} = 11, J_{AX} = 6.6 Hz, 1), 4.6 (br d, J = 5.5 Hz, 1) ppm.

Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.37; H, 6.53.

(3aα,4β,4aα,8aα,9β,9aα)-Octahydro-2,2-dimethyl-7-oxo-4,9-methano-8a*H*-1,3-dioxolo[4,5-*g*][2]benzopyran-8a-carbonyl Chloride (39). A solution of lactone **38** (6.3506 g, 0.0225 mol) in 170 mL of dry benzene and 17 mL of thionyl chloride (distilled) was refluxed for 18 h. The volatiles were removed in vacuo to afford 6.75 g (100%) of acid chloride **39**: λ_{max} ($CHCl_3$) 5.7, 5.75 μ; δ($CDCl_3$) 1.3 (s, 3), 1.5 (s, 3), 1.6 (br d, J = 12 Hz, 1), 1.9 (br d, J = 12 Hz, 1), 2.75 (m, 1), 2.5 (m, 1), 2.6 (m, 1), 2.8 (d, J = 15 Hz, 1), 3.1 (d, J = 15 Hz, 1), 4.0 (d of d, J_{BA} = 12, J_{BX} = 12 Hz, 1), 4.1 (m, 2), 4.4 (d of d, J_{AB} = 12, J_{AX} = 7 Hz, 1) ppm; *m/e* 285.051 92 (calcd for $C_{13}H_{14}O_5Cl$, 285.052 97 (P − Me)).

(3aα,4β,4aα,8aα,9β,9aα)-Octahydro-2,2-dimethyl-8a-(1-propionyl)-4,9-methano-7*H*-1,3-dioxolo[4,5-*g*][2]benzopyran-7-one (43). A solution of acid chloride **39** (2.58 g, 0.0086 mol) in 50 mL of dry tetrahydrofuran was cooled to −78 °C (dry ice–acetone) and ethylmagnesium bromide (1.3 M, 7.2 mL, 0.0223 mol) was added over a period of 15 min. The reaction mixture, after stirring for an additional 1.5 h at −78 °C, was allowed to warm to room temperature and concentrated hydrochloric acid was added to adjust the pH to equal 2. Water (50 mL) was added and the resulting solution extracted with chloroform (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and the volatiles removed in vacuo. The residual solid was chromatographed on silica gel (250 g). Elution with ether afforded 1.532 g (60%) of ketone acetonide **43**: mp 172.5–173.5 °C; λ_{max} ($CHCl_3$) 5.7, 5.82 μ; δ($CDCl_3$) 1.1 (t, J = 7 Hz, 3), 1.25 (s, 3), 1.44 (s, 3), 1.65 (br d, J = 12 Hz, 1), 1.9 (br d, J = 12 Hz, 1), 2.2 (br s, 1), 2.5 (br s, 1), 2.6 (d of d, J_{XB} = 9, J_{XA} = 6 Hz, 1), 2.7 (m, 4), 3.75 (br d, J = 5 Hz, 1), 4.0 (d of d, J_{BA} = 12, J_{BX} = 9 Hz, 1), 4.1 (br d, J = 5 Hz, 1), 4.4 (d of d, J_{AB} = 12, J_{AX} = 6 Hz, 1) ppm.

Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.38; H, 7.70.

(4aα,5β,6β,7β,8β,8aα)-Hexahydro-6,7-dihydroxy-4a-(1-propionyl)-5,8-methano-1*H*-2-benzopyran-3-one (44). A solution of ketone acetonide **43** (1.0639 g, 0.0036 mol) in 35 mL of an acetic acid–water mixture (3:2) was heated at reflux for 18 h. The reaction mixture was cooled to room temperature, the volatiles were removed in vacuo, and the residual solid was recrystallized from ethyl acetate to afford 0.5733 g (63%) of diol **44**: mp 174–175 °C; λ_{max} ($CHCl_3$) 2.8, 5.7, 5.83 μ; δ(acetone-d_6) 1.0 (t, J = 7 Hz, 3), 1.8 (s, 2), 2.4 (br s, 1), 2.55 (br s, 1), 2.6 (d, J = 15 Hz, 1), 2.7 (m, 3), 2.8 (d, J = 15 Hz, 1), 3.4 (br s, 1), 3.6 (br s, 1), 3.8–4.4 (m, 4) ppm.

Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.41; H, 7.14. Found: C, 61.55; H, 7.30.

(4aα,5α,7α,7aα)-Hexahydro-3-oxo-4a-(1-propionyl)cyclopenta[*c*]-pyran-5,7-dicarboxaldehyde (45). To a stirring solution of diol **44** (50.8 mg, 0.2 mmol) in 20 mL of chloroform at room temperature was added activated manganese dioxide[21] (278.4 mg, 3.2 mmol) in one portion. The reaction mixture was stirred for 3 h, then filtered through a Celite pad. The manganese dioxide was washed twice with chloroform and the volatiles were removed in vacuo to afford 50.2 mg (100%) of unstable dialdehyde **45** which was used immediately: δ($CDCl_3$) 1.0 (t, J = 7 Hz, 3), 2.0 (m, 2), 2.1–3.0 (m, 5), 2.9 (d, J = 16 Hz, 1), 3.3 (d, J = 16 Hz, 1), 4.3 (d of d, J_{BA} = 12, J_{BX} = 3 Hz, 1), 4.6 (d of d, J_{AB} = 12, J_{AX} = 4 Hz, 1), 9.9 (s, 2) ppm.

(4aα,5α,6aβ,9aS*)-1,2,4,4a,5,6,6a,9-Octahydro-8-methyl-2,9-dioxopentaleno[1,6a-*c*]pyran-5-carboxaldehyde (46). Dialdehyde **45** (50.2 mg, 0.2 mmol) was dissolved in dry benzene and 0.1 mL of acetic acid and 0.1 mL of piperidine[47] were added. The solution was heated at 100 °C (oil bath) in a slow stream of dry nitrogen for 3 h. The temperature was then reduced to 80 °C and stirring was continued for 18 h. The reaction mixture was cooled to room temperature, 6 mL of chloroform was added, and the solution was washed with water (3 × 5 mL). The organic layers were dried (Na_2SO_4) and the volatiles removed in vacuo. The residual oil was chromatographed on silica gel (2.5 g). Elution with ether afforded 18.9 mg (39%) of aldehyde **46** as an oil: λ_{max} ($CHCl_3$) 5.70, 5.80, 5.85 μ; δ($CDCl_3$) 1.8 (s, 3), 2.2–2.6 (m, 2), 2.3 (d, J = 14 Hz, 1), 2.9 (d, J = 14 Hz, 1), 2.9 (m, 1), 3.0–3.2 (m, 2), 4.3 (d of d, J_{BA} = 12, J_{BX} = 3 Hz, 1), 4.5 (d of d, J_{AB} = 12, J_{AX} = 4 Hz, 1), 7.2 (m, 1), 9.7 (s, 1) ppm; *m/e* 234.090 55 (calcd for $C_{13}H_{14}O_4$: 234.089 21 (parent)).

(3aα,4β,4aα,8aα,9β,9aα)-Octahydro-2,2-dimethyl-7-oxo-4,9-methano-8a*H*-1,3-dioxolo[4,5-*g*][2]benzopyran-8a-carboxaldehyde (47). A solution of acid chloride **39** (6.75 g, 0.0225 mol) in 455 mL of dry toluene with 6.80 g of palladium on barium sulfate[23] was refluxed for 15 h under a constant stream of hydrogen gas. The reaction mixture was cooled to room temperature and filtered through a pad of Celite. The catalyst was washed with methylene chloride (2 × 100 mL) and the combined reaction mixture and washings were concentrated in vacuo to afford 5.7109 g (95%) of lactone aldehyde **47**: mp 158–159 °C; λ_{max} ($CHCl_3$) 5.70, 5.80 μ; δ($CDCl_3$) 1.3 (s, 3), 1.4 (s, 3), 1.7 (br d, J = 10 Hz, 1), 2.0 (br d, J = 10 Hz, 1), 2.2 (br s, 1), 2.5 (m, 1), 2.6 (br s, 1), 2.7 (d, J = 17 Hz, 1), 2.9 (d, J = 17 Hz, 1), 4.1 (d of d, J_{BA} = 12, J_{BX} = 12 Hz, 1), 4.2 (m, 2), 4.5 (d of d, J_{AB} = 12, J_{AX} = 7 Hz, 1), 9.9 (s, 1) ppm.

Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 63.17; H, 7.03.

(3aα,4β,4aα,8aα(*E*),9β,9aα)-Octahydro-2,2-dimethyl-8a-(1-propenyl)-4,9-methano-7*H*-1,3-dioxolo[4,5-*g*][2]benzopyran-7-one (48). To a vigorously stirred suspension of freshly prepared ethyltriphenylphosphonium bromide (11.4639 g, 0.0309 mol) in 130.65 mL of dry ($LiAlH_4$) dimethoxyethane at 0 °C under nitrogen blanket was slowly added 19.35 mL of 1.55 M (standardized) *n*-butyllithium in hexane. After the addition was complete, the resulting deep red solution was stirred for an additional 1 h. The solids remaining in suspension were allowed to settle to the bottom of the flask, and 112 mL of the 0.2 M ylide solution was removed via syringe and transferred to a dry addition funnel. The ylide solution was added as quickly as possible to a stirred solution of aldehyde **47** (5.00 g, 0.0187 mol) in 500 mL of dry dimethoxyethane at −5 °C (ice–methanol). At the end of the addition period, the reaction mixture was allowed to warm to room temperature while being stirred for 1 h. A solution of dimethoxyethane saturated with hydrochloric acid was added dropwise until the reaction mixture became clear. The volatiles were removed in vacuo and the residue was chromatographed on 260 g of silica gel. Elution with benzene (750 mL) followed by ether (4 L) afforded 4.2674 g (82%) of ethylidene acetonide **48**: mp 180–181 °C; λ_{max} ($CHCl_3$) 5.75 μ; δ($CDCl_3$) 1.3 (s, 3), 1.4 (s, 3), 1.4–1.8 (m, 3), 1.7 (d of d, J_{XA} = 6, J_{XB} = 1.5 Hz, 3), 1.9 (s, 1), 2.4 (s, 1), 2.45 (s, 2), 3.6 (d of d, J_{BA} = 11, J_{BX} = 11 Hz, 1), 3.8 (d, J = 6 Hz, 1), 4.1 (d, J = 6 Hz, 1), 4.1 (d of d, J_{AB} = 11, J_{AX} = 6 Hz, 1), 4.9 (d of q, J_{BA} = 11, J_{BX} = 1.5 Hz, 1), 5.2 (d of q, J_{AB} = 11, J_{AX} = 6 Hz, 1) ppm.

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.89; H, 8.06.

(4aα(*E*),5β,6α,7α,8β,8aα)-Hexahydro-6,7-dihydroxy-4a-(1-pro-

penyl)-5,8-methano-1*H*-2-benzopyran-3-one (49). A solution of ethylidene acetonide **48** (2.500 g, 0.0089 mol) in 300 mL of dimethoxyethane, 150 mL of water, and 28 mL of concentrated hydrochloric acid was heated under reflux for 18 h. The volume of the solution was reduced by ca. two-thirds in vacuo, and the aqueous mixture was extracted with chloroform (4 × 250 mL). The combined organic layers were dried (Na_2SO_4) and the volatiles were removed in vacuo to afford 2.1369 g (99%) of ethylidene diol **49:** mp 135–136 °C; λ_{max} ($CHCl_3$) 3.0, 5.75 μ; δ($CDCl_3$) 1.6–1.9 (m, 2), 1.8 (d of d, J_{XA} = 6, J_{XB} = 1.5 Hz, 3), 1.9 (br s, 2), 2.4 (m, 1), 2.5 (s, 2), 2.9 (br d, 1, -OH), 3.1 (br d, 1, -OH), 3.7 (d, J = 6 Hz, 1), 3.9 (d of d, J_{BA} = 11, J_{BX} = 11 Hz, 1), 4.1 (d, J = 6 Hz, 1), 4.2 (d of d, J_{AB} = 11, J_{AX} = 6 Hz, 1), 5.3 (d of q, J_{BA} = 11, J_{BX} = 1.5 Hz, 1), 5.6 (d of q, J_{AB} = 11, J_{AX} = 6 Hz, 1) ppm.

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.83; H, 7.61; *m/e* 238.120 51 (parent). Found: C, 65.41; H, 7.63; *m/e* 238.122 41.

(4aα(*E*),5α,7α,7aα)-Hexahydro-3-oxo-4a-(1-propenyl)cyclopenta[*c*]pyran-5,7-dicarboxylic Acid (50). To a solution of diol **49** (1.5155 g, 0.006 37 mol) in 100 mL of acetone at 0 °C (ice bath) was added 13.7 mL of 1.4 M Jones reagent[24] over a period of 30 min. After stirring for an additional 30 min at 0 °C, the reaction mixture was allowed to warm to room temperature and 100 mL of water and 100 mL of ethyl acetate were added. To this mixture was slowly added solid sodium bisulfite until the ethyl acetate layer became clear. The solution was concentrated in vacuo to remove the acetone, followed by extraction with ethyl acetate (4 × 100 mL). The combined organic layers were dried (Na_2SO_4) and the volatiles removed in vacuo to yield 1.6217 g (95%) of diacid **50** as a light yellow oil which by spectroscopic analysis was suitable for use in the following steps: λ_{max} ($CHCl_3$) 5.7, 5.9 μ; δ($CDCl_3$) 1.8 (d, J = 6 Hz, 3), 2.1 (m, 1), 2.3 (m, 1), 2.5–3.0 (m, 3), 3.05 (s, 2), 4.0–4.4 (m, 2), 5.4–5.8 (m, 2) ppm.

(4aα(*E*),5α,7α,7aα)-Hexahydro-7-methoxycarbonyl-3-oxo-4a-(1-propenyl)cyclopenta[*c*]pyran-5-carboxylic Acid (51) and Dimethyl (4aα(*E*),5α,7α,7aα)-Hexahydro-3-oxo-4a-(1-propenyl)cyclopenta-[*c*]pyran-5,7-dicarboxylate (52). A solution of diacid **50** (1.6217 g, 0.0061 mol) in 110 mL of methanol containing 0.7 mL of concentrated sulfuric acid was stirred at 0 °C for 1 h and 18 h at 5 °C. The reaction mixture was concentrated in vacuo to a volume of ca. 5 mL followed by the addition of 75 mL of water and extraction with ethyl acetate (5 × 100 mL). The organics were dried (Na_2SO_4) and the volatiles were removed in vacuo to afford 1.6718 g (98%) of a clear oil containing 80% acid ester **51** and 20% diester **52.**

Acid ester **51:** λ_{max} ($CHCl_3$) 2.9, 5.7, 5.75 μ; δ($CDCl_3$) 1.85 (d, J = 7 Hz, 3), 2.05–2.4 (m, 2), 2.6–3.2 (m, 5), 3.8 (s, 3), 4.4 (m, 2), 5.1–5.8 (m, 2) ppm.

Diester **52;** δ($CDCl_3$) 1.8 (d, J = 7 Hz, 3), 2.1–2.4 (m, 2), 2.5–3.0 (m, 3), 3.1 (m, 2), 3.75 (s, 3), 3.8 (s, 3), 4.2 (m, 2), 5.2–5.9 (m, 2) ppm.

Methyl (4aα,5α,6aβ,9a*S)-1,2,4,4a,5,6,6a,7-Octahydro-8-methyl-2,7-dioxopentaleno[1,6a-*c*]pyran-5-carboxylate (7).** A solution of acid ester **51** (1.6718 g, 0.0059 mol) in 140 mL of dry benzene and 22 mL of thionyl chloride was refluxed for 18 h under nitrogen. The reaction mixture was cooled and the volatiles were removed in vacuo. The crude acid chloride, after being dissolved in 250 mL of distilled (P_2O_5) methylene chloride, was cooled to 0 °C under nitrogen and freshly sublimed aluminum chloride (2.523 g, 0.0189 mol) was added. The reaction mixture was stirred at 0 °C for 1 h, then at room temperature for 40 h. Ice was slowly added, followed by 150 mL of water, and the reaction mixture was stirred for an additional 15 min. The methylene chloride layer was removed and the aqueous layer was extracted with ethyl acetate (4 × 100 mL). The combined organic layers were dried (Na_2SO_4) and the volatiles were removed in vacuo. The residual oil was chromatographed on silica gel (140 g). Elution with benzene (1 L), then benzene–ethyl acetate (2:1), afforded 0.3022 g (19%) of diester **52** and 0.6389 (41%) of enone **7**: mp 110–111.5 °C; λ_{max} ($CHCl_3$) 5.68, 5.75, 5.82 μ; δ($CDCl_3$) 1.7 (br s, 3), 1.7–2.0 (m, 1), 2.25 (m, 1), 2.4 (d, J = 16 Hz, 1), 2.6 (m, 2), 2.7 (d, J = 16 Hz, 1), 3.05 (m, 1), 3.6 (s, 3), 4.25 (d of d, J_{BA} = 10, J_{BX} = 4 Hz, 1), 4.4 (d of d, J_{AB} = 10, J_{AX} = 5 Hz, 1), 7.0 (m, 1) ppm.

Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10; *m/e* 264.099 77 (parent). Found: C, 63.51; H, 6.30; *m/e* 264.098 57.

Hydrolysis of 52 to 50. A solution of diester **52** (0.379 g, 0.001 28 mol) in 43 mL of water containing sodium hydroxide (0.2041 g, 0.0051 mol) was refluxed for 16 h. After the reaction mixture was cooled to room temperature, concentrated hydrochloric acid was added until the solution was acidic toward pH paper. The solution was extracted with ethyl acetate (4 × 50 mL) and the organic layers were dried (Na_2SO_4), treated with activated charcoal, and evaporated in vacuo to yield 0.2463 g (72%) of a diacid whose spectral properties were identical with those of diacid **50** previously prepared by Jones oxidation of diol **49.**

Methyl (4aα,5α,6aβ,9a*R)-1,2,4,4a,5,6,6a,7-Octahydro-8-methyl-7-methylene-2-oxopentaleno[1,6a-*c*]pyran-5-carboxylate (8).** To a dried flask under nitrogen was added sodium hydride, 50% dispersion (0.216 g, 0.0045 mol). After the sodium hydride was washed three times with dry hexane and residual hexane was removed in vacuo, 2.25 mL of dry (CaH_2) dimethyl sulfoxide was introduced via syringe and the suspension heated at 70 °C (oil bath) for 1 h. The solution was cooled to 10 °C and freshly washed (dry benzene) and dried methyltriphenylphosphonium bromide (1.6065 g, 0.0045 mol) in 4.5 mL of dry dimethyl sulfoxide[25] was added over a period of 10 min. The solution was stirred for an additional 20 min at room temperature, then allowed to stand, letting all solids settle to the bottom of the flask. The ylide solution (3.9 mL 0.002 63 mol) was withdrawn via syringe and slowly added to a solution of enone **7** (0.5778 g, 0.002 19 mol) in 7.7 mL of dry (CaH_2) benzene at room temperature. The reaction mixture was stirred for 30 min and 10 mL of ethyl ether and 7 mL of water were added. The solution was made acidic with the addition of 2 N HCl and extracted with ethyl ether (3 × 10 mL). The combined organic layers were washed with saturated brine solution and dried (Na_2SO_4) and the volatiles removed in vacuo. The residual oil was chromatographed on silica gel (42 g). Elution with benzene–ethyl acetate (10:1) afforded 0.2638 g (46%) of diene **8**: mp 73–74.5 °C; λ_{max} ($CHCl_3$) 5.72, 5.76 μ; δ($CDCl_3$) 1.6 (m, 3), 2.05–2.55 (m, 5), 2.6–3.0 (m, 2), 3.6 (s, 3), 4.2 (m, 2), 4.8 (m, 2), 5.5 (m, 1) ppm; *m/e* 262.119 38 (calcd for $C_{15}H_{18}O_4$, 262.120 51 (parent)).

Methyl (4aα,5α,6aβ,7α,9a*R)-1,2,4,4a,5,6,6a,7-Octahydro-7,8-dimethyl-2-oxopentaleno[1,6a-*c*]pyran-5-carboxylate (4).** A solution of diene **8** (0.2920 g, 1.110 mmol) and tris(triphenylphosphonium)rhodium chloride[26] (0.1031 g, 0.11 mmol) in 34 mL of benzene was hydrogenated at 1 atm for 12 **h.** The volatiles were removed in vacuo and the residue stirred with 50 mL of ethyl ether. The solids were filtered through a Celite pad, and the filtrate was concentrated in vacuo to afford an oily residue which was chromatographed on silica gel (36 g). Elution with benzene–ether (20:1) afforded 0.2230 (76%) of **4** as a light brown oil which slowly crystallized: mp 88–90 °C; λ_{max} ($CHCl_3$) 5.75, 5.80 μ; δ($CDCl_3$) 1.0 (d, J = 7 Hz, 3), 1.6 (m, 3), 1.55–1.65 (m, 1), 1.8 (m, 1), 2.1–2.5 (m, 4), 2.6–2.9 (m, 2), 3.6 (s, 3), 4.2 (d, J = 3 Hz, 2), 5.1 (m, 1) ppm.

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63; *m/e* 264.136 16 (parent). Found: C, 67.90; H, 7.58; *m/e* 264.136 31.

Methyl (4aα,5α,6aβ,7α,9a*S)-1,2,4,4a,5,6,6a,7-Octahydro-7,8-dimethyl-1-dimethylaminomethylene-2-oxopentaleno[1,6a-*c*]-pyran-5-carboxylate (64).** A solution of **4** (0.1347 g, 0.510 mmol) in 7.7 mL of bis(dimethylamino)-*tert*-butoxymethane[33] was heated to 96 °C (oil bath). The temperature was allowed to rise from 25 to 60 °C in 1 h and from 60 to 96 °C in 3 h. The solution was stirred for 40 h at 96 °C and cooled to room temperature. The volatiles were removed in vacuo to afford a quantitative yield of crude enaminolactone **64** which was used without further purification: λ_{max} ($CHCl_3$) 3.45, 5.70, 6.0, 6.25 μ; δ($CDCl_3$) 0.9 (d, J = 8 Hz, 3), 1.6 (br s, 3), 1.6 (m, 1), 2.2 (m, 1), 2.3 (m, 2), 2.8 (m, 2), 2.85 (s, 6), 3.6 (s, 3), 4.0 (m, 2), 5.05 (m, 1), 6.2 (s, 1) ppm; *m/e* 319.1770 (calcd for $C_{18}H_{25}O_4N$, 319.1783 (parent)).

Methyl (4aα,5α,6aβ,7α,9a*S)-1,2,4,4a,5,6,6a,7-Octahydro-1-hydroxymethylene-7,8-dimethyl-2-oxopentaleno[1,6a-*c*]pyran-5-carboxylate (65).** To a stirred slurry of 2.6 g of silica gel in 11 mL of methylene chloride was added 0.26 mL of water. After 15 min of continued stirring, all the aqueous phase disappeared due to absorption on the silica gel surface, and enamino lactone **64** (0.1627 g, 0.510 mmol) in 4 mL of methylene chloride was added. The slurry was stirred for 1 h and filtered. The silica gel was washed with methylene chloride (3 × 10 mL), the combined organic layers were dried (Na_2SO_4), and the volatiles were removed in vacuo to afford 0.1481 g (99%) of crude hydroxymethylenelactone **65** which was determined to be of suitable purity by spectroscopic analysis: λ_{max} ($CHCl_3$) 5.75, 5.80, 6.0 μ; δ($CDCl_3$) 1.05 (d, J = 7 Hz, 3), 1.7 (br s, 3), 1.8–2.1 (m, 1), 2.2–2.5 (m, 2), 2.6–3.0 (m, 3), 3.7 (s, 3), 4.0–4.4 (m, 2), 5.1 (br s, 1), 7.0 (br s, 1) ppm; *m/e* 292.131 07 (calcd for $C_{16}H_{20}O_5$, 292.130 71 (parent)).

Methyl (4aα,5α,6aβ,7α,9a*S)-1,2,4,4a,5,6,6a,7-Octahydro-1-hydroxymethyl-7,8-dimethyl-2-oxopentaleno[1,6a-*c*]pyran-5-car-**

boxylate (66). To hydroxymethylenelactone **65** (0.1481 g, 0.507 mmol) in 6 mL of methanol at 0 °C (ice bath) was slowly added sodium borohydride (0.0096 g, 0.253 mmol). After the reaction mixture was stirred for 30 min at 0 °C, it was allowed to warm to room temperature and 10 mL of water and 10 mL of chloroform were added. The pH of the solution was adjusted with 2 N hydrochloric acid to pH 2 and the resulting solution was extracted with chloroform (3 × 10 mL). The organics were washed with brine and dried (Na_2SO_4) and the volatiles removed in vacuo to afford 0.1459 g (98%) of a light yellow oil identified by its spectral properties as a mixture of epimeric hydroxymethyllactones **66**: λ_{max} ($CHCl_3$) 2.8, 5.7, 5.75 μ; δ($CDCl_3$) 1.0 (d, J = 7 Hz, 3), 1.3 (m, 2), 1.6 (m, 3), 1.8–2.1 (m, 1), 2.2–3.0 (m, 5), 3.6 (s, 3), 3.5–4.0 (m, 2), 4.2 (m, 2), 4.9 (5.1) (m, 1) ppm; *m/e* 294.146 76 (calcd for $C_{16}H_{22}O_5$, 294.146 72 (parent)).

Mesylation of 66. To a solution of hydroxymethyllactones **66** (0.1359 g, 0.462 mmol) in 2.7 mL of dry pyridine at 0 °C was added methanesulfonyl chloride (0.1588 g, 1.38 mmol, 0.108 mL). The solution was stirred for 2 min at 0 °C, then 2 h at room temperature, followed by the addition of 5 mL of water and 5 mL of chloroform. Hydrochloric acid (2 N) was added until the solution was acidic to pH paper. The resulting solution was extracted with chloroform (3 × 15 mL) and the organic layers were washed with saturated sodium bicarbonate and brine and dried (Na_2SO_4). Evaporation of the volatiles in vacuo afforded 0.172 g (100%) of an epimeric mixture of mesylates **66a**: λ_{max} ($CHCl_3$) 5.75, 5.80 μ; δ($CDCl_3$) 1.0 (d, J = 7 Hz, 3), 1.3 (m, 2), 1.6 (m, 3), 1.8–2.9 (m, 5), 3.0 (s, 3), 3.6 (s, 3), 3.9–4.1 (m, 2), 4.2–4.6 (m, 2), 4.8 (5.1) (m, 1) ppm; *m/e* 372.124 17 (calcd for $C_{17}H_{24}O_7S$: 372.124 27 (parent)).

Methyl (4α*a*,5α,6a*β*,7α,9a*S)-1,2,4,4a,5,6,6a,7-Octahydro-7,8-dimethyl-1-methylene-2-oxopentaleno[1,6a-*c*]pyran-5-carboxylate (67).** To a stirring solution of mesylates **66a** (0.1719 g, 0.462 mmol) in 6.2 mL of dry benzene was added 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU, 0.287 g, 0.001 89 mol, 0.282 mL) over a period of 3 min. After the solution was stirred for 15 min, 6 mL of saturated ammonium chloride solution was added followed by extraction with benzene (3 × 6 mL). The organic layers were dried (Na_2SO_4) and the volatiles removed in vacuo. The residual oil was chromatographed on silica gel (7.5 g). Elution with benzene–ethyl acetate (10:1) afforded 0.0786 g (61%) of α-methylene lactone **67**: mp 68–70 °C; λ_{max} ($CHCl_3$) 5.75, 5.82 μ; δ($CDCl_3$) 1.0 (d, J = 7 Hz, 3), 1.7 (m, 1), 1.73 (br s, 3), 1.9–2.0 (m, 1), 2.3–2.4 (m, 1), 2.4–2.5 (m, 1), 2.6–2.7 (m, 1), 2.9–3.0 (m, 1), 3.6 (s, 3), 4.2 (d of d, J_{BA} = 11.8, J_{BX} = 2.8 Hz, 1), 4.3 (d of d, J_{AB} = 11.8, J_{AX} = 1.6 Hz, 1), 5.2 (br s, 1), 5.4 (d, J = 1.5 Hz, 1), 5.9 (d, J = 1.5 Hz, 1) ppm; *m/e* 276.136 31 (calcd for $C_{16}H_{20}O_4$, 276.136 16 (parent)).

Methyl (4a*α*,6a*β*,7*α*,9a*S)-1,2,4,4a,5,6,6a,7-Octahydro-7,8-dimethyl-1-methylene-2-oxo-5-phenylselenenylpentaleno[1,6a-*c*]-pyran-5-carboxylate (68).** To a rapidly stirred solution of diisopropylamine (53.8 mg, 0.533 mmol) in 0.5 mL of dry ($LiAlH_4$) tetrahydrofuran at −78 °C (dry ice–acetone) under nitrogen was added dropwise *n*-butyllithium (0.326 mL, 0.522 mmol). After the solution was stirred at −78 °C for 20 min, α-methylene lactone **67** (48.1 mg, 0.174 mmol) in 0.5 mL of dry tetrahydrofuran was added via syringe and the resulting enolate solution was stirred for an additional 30 min. To the enolate solution at −78 °C was quickly added phenylselenenyl chloride[27] (66.7 mg, 0.348 mmol) in 0.5 mL of dry tetrahydrofuran and stirring was continued for 30 min. The reaction mixture was warmed to room temperature and 3 mL of saturated ammonium chloride was added. The solution was extracted with methylene chloride (3 × 5 mL), the combined organic layers were dried (Na_2SO_4), and the volatiles were removed in vacuo. The residue was chromatographed on silica gel (4.6 g). Elution with benzene–ethyl acetate (30:1) afforded 34.8 mg (47%) of phenylselenides **68** as a mixture of epimers: λ_{max} ($CHCl_3$) 5.75, 5.85 μ.

Methyl (4a*α*,6a*β*,7*α*,9a*S)-1,2,4,4a,6a,7-Hexahydro-7,8-dimethyl-1-methylene-2-oxopentaleno[1,6a-*c*]pyran-5-carboxylate (*dl*-Deoxypentalenolactone Methyl Ester, 5).** To a solution of selenide **68** (45.5 mg, 0.106 mmol) in 1.8 mL of methanol was added dropwise 0.9 mL of water. To the resulting cloudy solution was added solid sodium metaperiodate[28] (112.9 mg, 0.527 mmol) in one portion. The reaction mixture was stirred for 30 min, then 6 mL of water was added, followed by extraction with methylene chloride (3 × 6 mL). The organic layers were dried (Na_2SO_4), the volatiles were removed in vacuo, and the residual oil was chromatographed on silica gel (2.2 g). Elution with benzene–ethyl acetate (30:1) afforded 28.0 mg (97%) of triene **5**, whose spectral properties were identical with those of natural triene **5a** (vide infra): *m/e* 274.121 36 (calcd for $C_{16}H_{18}O_4$, 274.120 51 (parent)).

Methyl (4a*α*,6a*β*,7*α*,9a*S)-Hexahydro-2-hydroxy-7,8-dimethyl-1-methylenepentaleno[1,6a-*c*]pyran-5-carboxylate (70).** To a solution of triene **5** (34 mg, 0.124 mmol) in 1.1 mL of dry dimethoxyethane and 2.2 mL of dry toluene under nitrogen at −78 °C was added diisobutylaluminum hydride (0.180 mL of a 0.9 M solution in hexane, 0.162 mmol) over a period of 5 min. The solution was stirred for 25 min and 0.9 mL of a saturated aqueous sodium bicarbonate solution was added. The resulting solution was stirred at −78 °C for 10 min, then allowed to warm to room temperature. After the solution was stirred for 10 min at room temperature, 3.5 mL of water was added. After evaporation of most of the toluene in vacuo, the system was extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and the volatiles were removed in vacuo to afford 31.1 mg (92%) of lactol **70** which was used without further purification: λ_{max} ($CHCl_3$) 2.9, 5.92 μ; δ($CDCl_3$) 1.1 (d, J = 7 Hz, 3), 1.7 (br s, 3), 2.7–3.0 (m, 2), 3.4 (m, 1), 3.7 (m, 1), 3.8 (s, 3), 3.9 (m, 1), 5.1 (m, 1), 5.2 (m, 1), 5.35 (m, 1), 5.6 (m, 1), 7.0 (m, 1) ppm.

Methyl (1′*S,4′a*α*,6′a*β*,7′*α*,9′a*S**)-4′,4′a,6′a,7′-Tetrahydro-2′-hydroxy-7′,8′-dimethylspiro[oxirane-2,1′(2′*H*)-pentaleno-[1,6a-*c*]pyran]-5-carboxylate (71).** A solution of lactol **70** (29.7 mg, 0.108 mmol), vanadyl acetylacetonate (2.2 mg), and *tert*-butyl hydroperoxide[39] (19.3 μL, 17.3 mg, 0.174 mmol) in 2.2 mL of dry benzene was heated under reflux for 35 min. The mixture was cooled to room temperature, 3 mL of saturated aqueous sodium bisulfite was added, and the resulting system was extracted with ethyl acetate (3 × 5 mL). The organic extracts were dried (Na_2SO_4) and the volatiles removed in vacuo to afford 31.0 mg (99%) of crude epoxy lactol **71**, which was used immediately in the next step: λ_{max} ($CHCl_3$) 2.8, 5.92 μ; δ 1.1 (d, J = 7 Hz, 3), 1.7 (br s, 3), 2.2–3.2 (m, 5), 3.4–4.1 (m, 2), 3.8 (s, 3), 5.1 (m, 1), 5.4 (m, 1), 7.0 (m, 1) ppm.

Methyl (1′*S,4′a*α*,6′a*β*,7′*α*,9′a*S**)-4′,4′a,6′a,7′-Tetrahydro-7′,8′-dimethyl-2′-oxospiro[oxirane-2,1′(2′*H*)-pentaleno[1,6a-*c*]pyran]-5-carboxylate (*dl*-Pentalenolactone Methyl Ester, 6).** Epoxylactol **71** (31.0 mg, 0.107 mmol) was dissolved in 3.1 mL of acetone and cooled to 0 °C (ice bath). Jones reagent (1.3 M, 82.7 μL, 0.107 mol) was slowly added and the reaction mixture stirred for 30 min at 0 °C. Saturated aqueous sodium sulfite (3 mL) was added and the resulting solution extracted with chloroform (3 × 5 mL). The combined organic extracts were washed once with saturated aqueous sodium chloride and dried (Na_2SO_4), and the volatiles removed in vacuo. The residual oil was chromatographed on silica gel (1.45 g). Elution with benzene–ethyl acetate (10:1) afforded 7.1 mg (23%) of *dl*-pentalenolactone methyl ester (**6**): λ_{max} ($CHCl_3$) 5.7, 5.85 μ; δ($CDCl_3$) 1.05 (d, J = 7 Hz, 3), 1.65 (br s, 3), 2.6 (d, J = 5 Hz, 1), 2.8 (m, 1), 3.1 (d, J = 5 Hz, 1), 3.1 (m, 1), 3.35 (m, 1), 3.70 (s, 3), 4.6 (m, 2), 5.1 (m, 1), 6.8 (m, 1) ppm. Though homogeneous on thin layer chromatography in a variety of systems, the NMR spectrum of fully synthetic **6** showed the presence of two impurities (ca. 10%), δ 1.0 (J = 7 Hz) and 1.1 (J = 7 Hz). A homogeneous sample lacking these impurities was obtained by purification on a Waters LC: 6000A solvent delivery system equipped with a R 401 differential refractometer. Using a 3.9 i.d. × 30 cm μ Bondapak CN column and elution with 9:1 hexane–chloroform at a solvent flow rate of 3 mL/min, k' for **6** = 3.8.

(1′*S,4′a*α*,6′a*β*,7′*α*,9′a*S**)-4′,4′a,6′a,7′-Tetrahydro-7′,8′-dimethyl-2′-oxospiro[oxirane-2,1′(2′*H*)-pentaleno[1,6a-*c*]pyran]-5-carboxylic Acid (*dl*-Pentalenolactone, 1.** To a solution of **6** (12.0 mg, 0.041 mmol) in 2.0 mL of tetrahydrofuran was added 0.5 mL of water. The solution was cooled to 0 °C (ice bath) and 52 μL of a 2 N aqueous potassium hydroxide solution (0.103 mmol) was added. The reaction mixture was stirred at 0 °C for 30 min, then for 21 h at room temperature. The solution was acidified to pH 2 and extracted with chloroform (15 × 1 mL), followed by ethyl acetate (3 × 15 mL). The combined organic layers were washed with saturated sodium chloride and dried (Na_2SO_4). The volatiles were removed in vacuo and the residue was chromatographed twice on silica gel (1.5 g). Elution with chloroform–ethanol (20:1) afforded 6.8 mg (55%) of synthetic *dl*-pentalenolactone (**1**) whose spectral properties were identical with those of **1a** (vide infra).

Pentalenolactone (1a). To a methanol (3 mL) of natural pentalenolactone benzylamine[34] salt (75.0 mg, 0.196 mmol) was added 18 mL of pH 2 buffer (KCl–HCl). The solution was extracted with chloroform (4 × 23 mL), and the organic extracts were washed with brine and dried (Na_2SO_4). The volatiles were removed in vacuo to afford

54 mg (100%) of natural pentalenolactone (**1a**): λ_{max} ($CHCl_3$) 5.7, 5.9 μ; δ($CDCl_3$) 1.1 (d, J = 7 Hz, 3), 1.6 (br s, 3), 2.7 (d, J = 5 Hz, 1), 2.8–3.0 (m, 1), 3.2 (d, J = 5 Hz, 1), 3.2 (m, 1), 3.4 (m, 1), 4.8 (m, 2), 5.2 (m, 1), 7.1 (m, 1) ppm.

Pentalenolactone Methyl Ester (6a). A sample of **1a** (54 mg, 0.195 mmol) in 3 mL of methanol was treated with excess ethereal diazomethane at room temperature for 30 min. The volatiles were removed in vacuo to afford 56.0 mg (100%) of natural pentalenolactone methyl ester (**6a**): λ_{max} ($CHCl_3$) 5.7, 5.85 μ; δ($CDCl_3$) 1.05 (d, J = 7 Hz, 3), 1.65 (br s, 3), 2.6 (d, J = 5 Hz, 1), 2.8 (m, 1), 3.1 (d, J = 5 Hz, 1), 3.1 (m, 1), 3.35 (m, 1), 3.70 (s, 3), 4.6 (m, 2), 5.1 (m, 1), 6.8 (m, 1) ppm.

Deoxypentalenolactone (5a). A 1.5 M solution of chromous chloride was prepared as follows. To a mixture of zinc dust (1.0 g, 0.0178 mol) and mercuric chloride (0.10 g, 0.37 mmol) was added 2 mL of a 2 N hydrochloric acid solution. After the mixture was stirred for 15 min at room temperature, the aqueous layer was decanted off. The residue amalgam was stirred under nitrogen with 5 mL of a degassed 2 N hydrochloric acid solution for 15 min.

Chromic chloride (5.0 g, 0.0187 mol) was stirred in a separate flask with 7.5 mL of degassed 2 N hydrochloric acid for min, then filtered. The filtered chromic chloride solution was added to the zinc amalgam solution and stirring was continued for 3.5 h. The solution turned slowly to light blue. This solution was used immediately. Pentalenolactone methyl ester (**6a**, 56.0 mg, 0.193 mmol) was dissolved in 5.5 mL of acetone. The chromous chloride solution (1.5 M, 1.28 mL, 1.93 mmol) was added slowly and the reaction mixture stirred for 1 h. Water (6 mL) was added and the resulting solution extracted with chloroform (4 × 9 mL). The organic extracts were washed with brine and dried (Na_2SO_4) and the volatiles removed in vacuo. The residue was chromatographed on silica gel (4.6 g). Elution with benzene–ethyl acetate (30:1) afforded 27.5 mg (52%) of **5a**: λ_{max} ($CHCl_3$) 5.75, 5.80 μ; δ($CDCl_3$) 1.0 (d, J = 7 Hz, 3), 1.65 (br s, 3), 2.75–2.95 (m, 1), 3.0–3.2 (m, 1), 3.2–3.4 (m, 1), 3.7 (s, 3), 4.1–4.5 (m, 2), 5.2 (br s, 1), 5.45 (s, 1), 6.0 (s, 1), 6.8 (br s, 1).

Epipentalenolactone Methyl Ester (69a). To a solution of **5a** (7.5 mg, 0.027 mmol) in 0.5 mL of methanol at 0 °C were added aqueous sodium bicarbonate (0.5 M, 0.16 mL, 0.081 mmol) and 30% hydrogen peroxide[36a,37] (18.6 μL, 0.164 mmol). The reaction mixture was allowed to warm to room temperature and stirring was continued for 16 h. Water (2 mL) and chloroform (2 mL) were added followed by the slow addition of solid sodium bisulfite until a negative starch–potassium iodide test was obtained. The mixture was acidified to pH 2 with 2 N hydrochloric acid, then extracted with chloroform (3 × 5 mL). The organic layers were dried (Na_2SO_4) and the volatiles removed in vacuo. The oily residue was chromatographed on silica gel (0.7 g). Elution with benzene–ethyl acetate (20:1) afforded 2.5 mg (32%) of epipentalenolactone methyl ester (**69a**): λ_{max} ($CHCl_3$) 5.7, 5.85 μ; δ($CDCl_3$) 0.9 (d, J = 7 Hz, 3), 1.6 (br s, 3), 2.9 (s, 2), 3.2 (m, 2), 3.5–3.8 (m, 1), 3.7 (s, 3), 4.35 (d of d, J_{BA} = 12, J_{BX} = 5 Hz, 1), 4.6 (d of d, J_{AB} = 12, J_{BX} = 3 Hz, 1), 4.9 (m, 1), 6.8 (m, 1).

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Supplementary Material Available: NMR spectra of **5** and **5a**, **6** and **6a**, and **1** and **1a** as well as infrared spectra (10 pages). Ordering information is given on any current masthead page.

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(34) We wish to thank Professor David Cane of Brown University and Drs. Arthur Nagel and Robert Volkmann of Pfizer, Inc., for supplying us with samples of pentalenolactone as its benzylammonium salt. The free acid, which is unstable, was converted to its methyl ester **5a**, which is more durable.
(35) The NMR spectrum of fully synthetic **5** contains trace impurities with resonances in the regions δ 0.9, 1.2, and 1.6. These do not appear to be interpretable in terms of any other relevant obvious product which might have arisen in the series. The spectrum is registered in the microfilm edition.
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(44) The resonance which is assigned to the proton on the tertiary center bearing the methoxyl group occurs at anomalously (0.5 ppm) low field relative to that encountered in somewhat related model systems.[11] This may be related to a solvent effect from acetone-d_6. All other properties of the compound seem uniquely consistent with its proposed structure.
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