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The Total Synthesis of *dl*-Quadrone

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Abstract: A regio- and stereospecific total synthesis of *dl*-quadrone (**1**) is described. The synthesis, which starts with 4,4-dimethylcyclopent-2-en-1-one (**5**), is accomplished in 19 steps in 3.1% yield. The key intermediates are the enone ester **4**, the iodo ketal **15**, the tricyclic keto ester **16**, and the hydroxymethyl keto acid **22**. The latter as well as the seco acid **2** afford quadrone upon thermolysis.

Background and Strategy

The isolation, characterization, and structural determination of the sesquiterpene quadrone (**1**) was described in 1978 by a group from the W. R. Grace Co.[1,2] As is becoming increasingly common practice, the proof of structure of **1** arose solely from X-ray crystallographic evidence. Thus, there were no recorded investigations from which one might draw inferences as to the chemical personality of this novel natural product.

It was not improbable for our laboratory to interest itself in pursuing the total synthesis of quadrone. Two of its key structural features are the presence of a bicyclo[3.3.0]octane system (see A:B rings) and a cyclopentanopyranone arrangement (see A:D rings). As such, quadrone is possessed of characteristics similar to those found in pentalenolactone[3] and the coriolins,[4] substances with which we developed some familiarity. In its cyclohexanopyranone substructure (see C:D rings), quadrone bore some resemblance to vernolepin, another sesquiterpene which had previously been the object of our attentions.[5,6a]

As is the case with each of the systems cited above, antitumor properties have been asserted on behalf of quadrone. The paucity of hard in vivo biological information which might broaden these initial findings is such that the actual chemotherapeutic potential of quadrone must be perceived with appropriate reserve. Nonetheless, the apparently similar antitumor profiles of these structurally related sesquiterpenes is surely worthy of investigation.

In devising a prospectus for the total synthesis of the tetracyclic quadrone, it was helpful to focus upon the nature of its four ring fusions. These are specified in Figure 1.

The structure of quadrone, *per se*, offers no apparent rationale for its antitumor properties. However, it is seen on inspection that the α-methylene keto acid **2**, nominally related to quadrone in a retro-Michael sense, and bearing as it does an electrophilic α-methylene ketone, might well be the carrier of biological activity.[6b] While this formulation of the mode of action is purely conjectural, it did serve to raise an interesting chemical question as to the independent viability of **2** and the activation-energy requirements for passing between **1** and **2**. On such grounds, as well as on obvious retrosynthetic considerations, compound **2** emerged as an attractive subgoal.

The six-membered C ring of **2** was to be constructed by an alkylation reaction of precursor **3**, wherein the substituent, indicated as X, and the ketone protecting group, shown as P, need not be specified with precision.

It will be noted that the quaternary carbon 8b (see asterisk in Figure 1) of quadrone is a core center for each of its four fusions. Accordingly, adequate provision for development of a broad range of functionality at this carbon, during the "trial and error" stage of the synthesis, could well be crucial for success. An intermediate of the type **4** appeared to satisfy this goal. In such a system, the relevant center (see asterisk in Figure 2) appears as the β' carbon of an α,β'-unsaturated β-keto ester. It seemed likely that a variety of nucleophiles could be appended by Michael-like processes to this center.

In planning access to system **4**, the possibility suggested by Figure 3 presented itself. A nucleophilic specie would be added, also in a Michael sense, to the β position of enone **5** and the resultant enolate would be alkylated by a suitable electrophile at its α center. Further progress would involve transformation of Nu to the subunit CH_2CH_2L (L = leaving group) in a way which could be coordinated with the conversion of E^+ to the subunit $CH_2C(O)CH_2CO_2Me$. Intramolecular aldolization would give rise to the desired **4**.

In this paper we describe the experiments by which this general scheme was reduced to practice and through which a reasonably satisfactory total synthesis of *dl*-quadrone was achieved.[7] Before relating these results and experimental procedures, it is important to emphasize that the formulations implicit in this paper were arrived at after our inability to reduce to practice a variety of related schemes. Indeed, what is presented below was, to a great extent, an exercise in regroupment and improvisation. Accounts of these ancillary investigations, which served to illuminate a synthetic path to quadrone, are provided elsewhere.[8,9]

Results

The specie formed from the interaction of vinylmagnesium bromide and tri-*n*-butylphosphine–cuprous iodide iodide reacted with the well-known 4,4-dimethylcyclopentenone[10] (**5**). This initial addition reaction was effected in dry tetrahydrofuran from −45 °C → −20 °C. The resultant metalloenolate reacts with methyl 4-iodo-3-methoxycrotonate (**6**). To achieve this alkylation reaction it was necessary to dilute the THF solution with hexamethylphosphoric triamide (HMPA). After standard workup and purification by flash chromatography on silica gel, compound **7** was obtained in 55% yield. When carried out on smaller scales (1–10 mmol) than those indicated in the Experimental Section (100 mmol), the isolated yield of **7** was ~10% higher. Iodide **6** was obtained by a Finkelstein reaction on the corresponding bromide.[11] The yields of **7** obtained by using the iodide were uniformly higher than those realized from the bromide[7] by ~15–20%. Reaction

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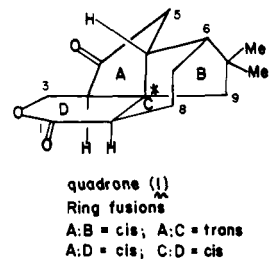

Figure 1.

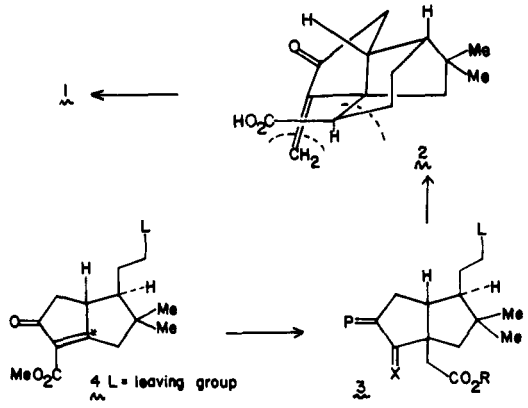

Figure 2.

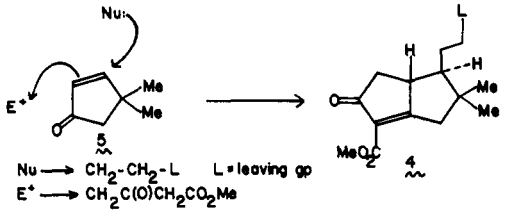

Figure 3.

of compound **7** with ethylene glycol in toluene under reflux (Dean–Stark trap) with catalysis by *p*-toluenesulfonic acid afforded the diketal **8**.

With both ketone functions protected, attentions were directed to the modification of the vinyl group along constructive lines. Hydroboration (BH_3–THF)–oxidation ($NaOH$–H_2O_2) of **8** led to the formation of **9a**. Mesylation of **9a**, in a standard way, followed by reaction of the resultant **9b** with lithium bromide in acetone under reflux afforded bromide **9c**. In many runs, this lithium bromide process also served to bring about deketalization leading to the formation of **10**. If this adventitious deketalization did not occur, the desired **10** could be obtained from **9c** by deliberate acid treatment.

Smooth aldolization–dehydration was achieved by reaction of **10** with sodium methoxide in methanol at 0 °C. The key intermediate **4** was obtained in 47% yield from **7**.

It is recognized that no evidence has yet been summoned in support of the indicated stereochemical assignment of **4** or its precursors. Indeed, this issue could not be decided from analysis of the NMR spectra of the members of this series.

Our disposition to favor the indicated arrangement, wherein the bromoethyl function is cis to the junction hydrogen, was based on considerations of chemical probability. First, it seemed likely that the enolate-trapping sequence by which **7** was produced would be likely to afford, even at the kinetic level, a trans orientation of the two alkyl substituents. Furthermore, in the unlikely event that this were not the case, ample opportunity for equilibration to the thermodynamically more stable product existed in the conversions of **7** → **8**, **9** → **10**, or **10** → **4**. A rigorous definition of the stereochemistry of **4** arose from X-ray crystallographic examination of the product of its reaction with methyl 3-(trimethylsilyloxy)-3-methoxyacrylate under very mild Mukaiyama-type conditions.[8,12]

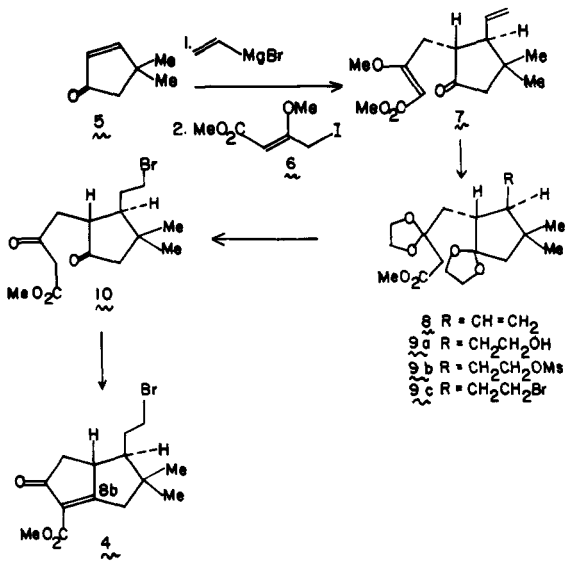

Figure 4.

The "alkylidene acetoacetate" arrangement did allow for the introduction of a variety of nucleophiles at C_{8b} (quadrone numbering). Unfortunately, as described elsewhere, this amenability did not extend to ring-forming reactions with intramolecular nucleophiles attached in various ways to the two-carbon side chain (see arrow in Figure 5).[8,9]

Accordingly, attentions were centered on the ring-forming possibilities of a system of the type **3** (see Figure 3). In this connection, the reaction of **4** with the silyl ketene acetal **11** was studied. Compound **11** was prepared simply from *tert*-butyl acetate by enol silylation (see Experimental Section) by using standard procedures.[13]

Michael-type addition of **11** to **4** occurred under the usual Mukaiyama conditions.[12,14] A very clean reaction ensued and the only product noted was the silyl ester **12a**. *Thus, the tert-butyl, rather than the tert-butyldimethylsilyl group, had been cleaved in the Mukaiyama reaction.* Mild acid hydrolysis allowed for the isolation of the monoester monoacid **12b**. However, for the purposes of this synthesis, crude **12a** was subjected to the action of aqueous HCl in dioxane under reflux for 1.5 h. These conditions brought about decarboxylation of the β-keto acid but did not visibly damage the primary bromide. Esterification with diazomethane afforded a 74% yield of ester **13**. For maximization of the opportunity for intramolecular alkylation (cf. Figure 2), the ketone group was protected in the standard way to afford **14**. Additionally, the bromine was replaced with an iodine atom by reaction of **14** with sodium iodide in acetone (containing small amounts of pyridine) under reflux. The crucial substrate **15** was thus obtained (93% from **13**).

It will be appreciated that in placing reliance on an intramolecular alkylation of the ester enolate to be derived from **15**, we were not providing, at the planning level, systematic control over the configuration of the carbomethoxy group in the resultant product. Needless to say, future progress in the desired direction was predicated upon the availability of **16**. Assuming a chairlike arrangement of the six-membered ring, an axial disposition for the carbomethoxy function is required.

Again, we note that in many of our earlier schemes we did attempt to deal with the configuration at this chiral center in a logically persuasive way.[8,9] However, none of those schemes could be reduced to practice. Thus, the study of the attempted cyclization of **15** was not carried out as a consequence of any rationale at the stereochemical level.

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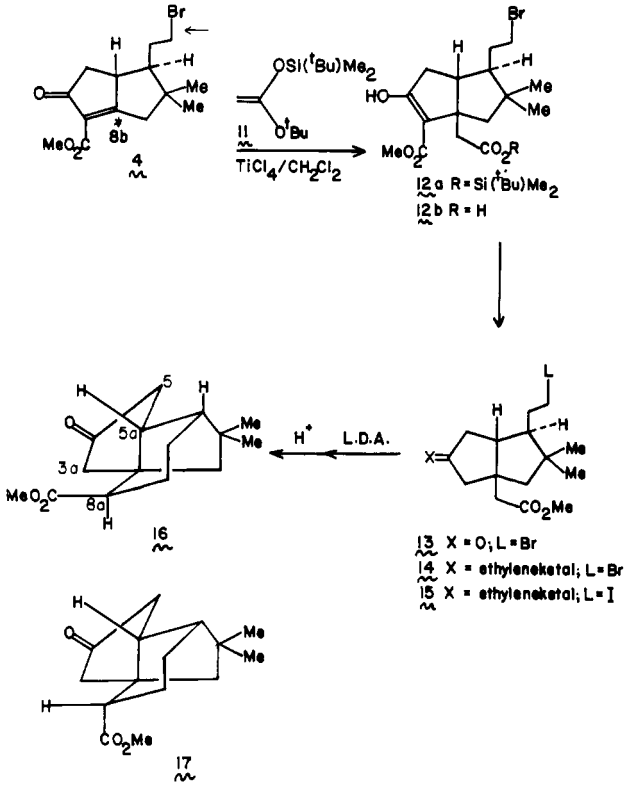

Figure 5.

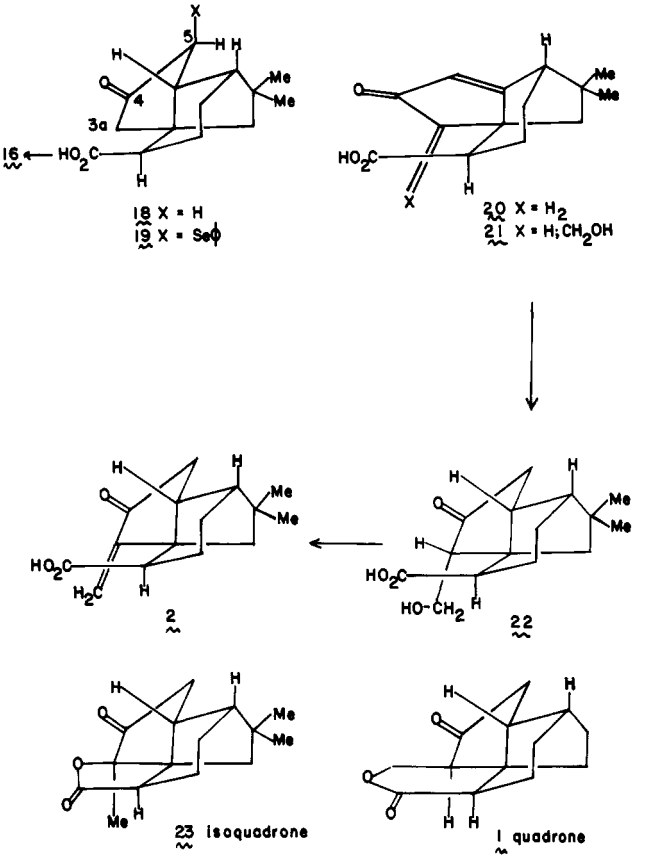

Figure 6.

In the event, deprotonation of **15** could be achieved by its reaction with lithium diisopropylamide in THF at −78 °C → −23 °C. To this solution was added HMPA and the temperature was allowed to increase to ambience where it was maintained for an additional hour. A standard workup was followed directly by acid-catalyzed deketalization (tosyl acid–acetone). There was thus obtained the tricyclic keto ester **16**, mp 49–51 °C, in ~55% yield.

The evidence that the stereochemistry at C_{8a} was indeed that shown in **16** rested largely on interpretations of its NMR spectrum (600 MHz). Particularly persuasive was the multiplicity of H_{8a} ($CDCl_3$, δ 2.76, apparent doublet, J = 7.5 Hz) and the anomalously "low field" (δ 2.83, apparent triplet, J = 10.2 Hz) absorption of H_{5a}. We could rationalize this chemical shift only by invoking a 1,3-diaxial deshielding relationship of the proton at C_{5a} and the axial carbomethoxyl group at C_{8a} of a flattened C ring. Of course, the success of the total synthesis further served to strengthen this assignment.

When cycloalkylation of **15** was carried out with a nearly stoichiometric equivalency of lithium diisopropylamide the only tricyclic product isolated or detected with certainty was **16**. However, when the reaction was carried out with 1.5 equiv of the same base, in addition to **16** there was produced and isolated in 5% yield an isomer to which we assign the structure **17**. Indeed, in keeping with the spectral interpretations offered above, the proton at C_{8a} in **17** emerges as a doublet of doublets, J_1 = 11.0 Hz, J_2 = 6.2 Hz. Moreover, the proton at C_{5a} is not displaced to low field and is, in fact, not uniquely resolved.

We believe that the cycloalkylation reaction is essentially stereospecific in its kinetic production of **16**. It seems likely that with excess lithium diisopropylamide the resultant **16** suffers deprotonation. Protonation of the resultant enolate (either on workup or by nonenolized **16**) accounts for the formation of significant amounts of "equatorial" carbomethoxy isomer **17**.

While the result was surely gratifying, its explanation is far from clear. One interpretation which might be advanced is that the geometry which leads to **16** is the one which minimizes any steric interactions between the carbomethoxy function and the iodide leaving group. In the same direction it can be argued that in the "pre-**16**" conformer, steric interactions between the carbomethoxy group and the B ring are minimized, as are the interactions between the leaving group and the β-geminal methyl group. In any case, this highly stereoselective result was as welcome as it was surprising. The setting for the final attack on quadrone was at hand.

Elsewhere[9] we have dealt in some detail with the difficulties which awaited us in this, the final stage of the investigation. Here we will only note that, not unexpectedly, a variety of functionalization reactions of the C_4 ketone occurred at C_5 rather than at C_{3a}. Moreover, serious problems were encountered in the alkaline hydrolysis of the axial ester at several advanced stages of the synthesis. Accordingly, the route shown in Figure 6 was developed.

Saponification (KOH–methanol, reflux) of **16** afforded the acid **18**, mp 132–135 °C. Selenenylation of **18** in ethyl acetate without catalysis[15] afforded the C_5-phenylseleno compound **19** (stereochemistry undetermined). Oxidative deselenylation[16] in the usual way provided the enone acid **20**, mp 142–146 °C.

The C_5–C_{5a} double bond was used to ensure enolization of the C_4 ketone toward C_{3a}. Indeed, treatment of **20** with 3 equiv of lithium diisopropylamide followed by reaction of the enolate carboxylate with formaldehyde[17,18] gave a 60–70% yield of **21**, mp 156–159 °C.

As expected, catalytic reduction (H_2/Pd–C, methanol) of **21** afforded the cis-fused (AB) hydroxymethyl keto acid **22**, mp 156–159 °C. The stereochemistry at C_{3a} in **21** and **22** remains undetermined, though the failure to observe any spontaneous lactonization to quadrone (**1**) suggests that it might well be formulated as shown. Treatment of **22** with tosyl acid in benzene at 40–50 °C allowed us to reach a major subgoal, the α-methylene keto acid **2**, in 94% yield. It was of some interest to discover that compound **2** is indeed capable of independent existence and that

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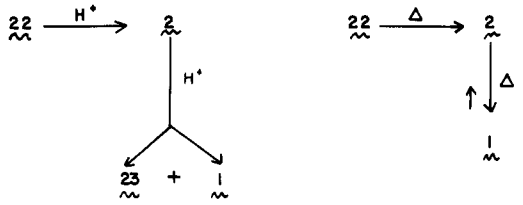

Figure 7.

its transformation to quadrone was far from automatic.

Reaction of **2** with tosyl acid in benzene under reflux did indeed produce the first discernible quantities of synthetic *dl*-quadrone. However, the major product of this reaction was clearly a γ-lactone containing three methyl singlets—a substance we formulate as isoquadrone (**23**). (See Figure 6.)

It seemed likely to us that isoquadrone arises from enolization of the cyclopentanone of **2**. This would be followed by protonation of the terminal methylene group to a 2-hydroxyallylic cation which is captured by the carboxyl group.[9] Apparently, the stereoelectronics for the expected Michael-type closure of **2** → **1** are difficult, thus allowing for intercession of the pathway leading to isoquadrone.

Fortunately, direct pyrolysis of the methylene acid **2** at 190–195 °C for several minutes afforded quadrone (**1**), free of its isomer **23**. The acid **2** was also present. The approximate (integration of relevant NMR peaks) ratio of **2**/**1** was 1:4. The separation of **1** from **2** could be carried out either by direct chromatography on silica gel or by aqueous extraction followed by chromatography. Essentially the same ratio of **2**:**1** could be generated by pyrolysis of quadrone (**1**), thus supporting the interpretation of a real equilibrium between **1** and **2** under the thermolytic conditions.

Furthermore, it was found that pyrolysis of **22** also gave *dl*-quadrone free of the iso compound **23**. The first stage of this pyrolysis seems (by TLC examination) to be a dehydration to **2**, which then goes on to quadrone (**1**). However, the occurrence of some direct lactonization to quadrone is not excluded. The isolated yield of *dl*-quadrone (**1**) was 51%, excluding the recyclable amounts **2**. The NMR (270 MHz), infrared, and mass spectra as well as the chromatographic properties of synthetic *dl*-quadrone (mp 140–142 °C) were identical with those of a specimen of the natural product kindly furnished by Dr. Matthew Suffness of the National Cancer Foundation.

The total synthesis of quadrone is thus achieved by 19 steps in 3.1% overall yield.

Experimental Section[19]

Methyl 4-Iodo-3-methoxy-2-butenoate (6). A solution of methyl 4-bromo-3-methoxy-2-butenoate[11] (20 g, 96 mmol) in reagent grade acetone (125 mL) was added to sodium iodide (43 g, 287 mmol) in one portion. The mixture was stirred at room temperature for 3 h, and the volatiles were removed in vacuo. The residue was diluted with hexanes (400 mL) and this solution was extracted with aqueous sodium thiosulfate followed by brine. The organic phase was dried, and the volatiles were removed in vacuo, affording 24 g (98%) of **6** as a clear yellow oil, which was used in the next experiment without further purification: ν ($CHCl_3$) 1708, 1635 cm^{-1}; δ ($CDCl_3$) 3.70 (s, 3 H), 3.73 (s, 3 H), 4.48 (s, 2 H), 5.08 (s, 1 H).

Methyl (*Z*)-(1*R,2*R**)-β-Methoxy-3,3-dimethyl-5-oxo-2-vinylcyclopentanecrotonate (7).** To a 500-mL three-neck flask equipped with a mechanical stirrer, nitrogen inlet, and septum were added $(Bu_3P{\cdot}CuI)_4$[20] (5 g, 12.7 mol % Cu^{1+}) and THF (25 mL). This solution was cooled to −45 °C, and vinylmagnesium bromide (135 mL of a 1.1 M solution in THF; 0.148 mol) was added over ~15 min. The resulting purplish black solution was stirred for 15 min at −45 °C, and then 4,4-dimethylcyclopentenone[10] (11 g, 0.1 mol) was added neat over ~15 min. The solution was stirred for 1 h, during which time the temperature of the bath came to −20 °C. Hexamethylphosphoric triamide (HMPA, 100 mL) was rapidly added, followed immediately by **6** (56.5 g, 0.22 mol). The cooling bath was removed, and the solution (which turned orange over several minutes) was stirred for 1 h at room temperature. After quenching the solution with saturated NH_4Cl (20 mL), the reaction mixture was diluted with hexanes (1.5 L). The organic phase was extracted successively with dilute NH_4OH [3 × (250 mL of H_2O containing 5 mL of concentrated NH_4OH)], H_2O (3 × 250 mL), and brine (100 mL) and dried, and the volatiles were removed in vacuo. The resulting oil was flash chromatographed[21] in two portions on a 50-cm column by using hexane/ethyl acetate (8:1, v/v). The mixed fractions were reflashed, affording a total of 14.4 g of **7** (54%) as an oil, suitable for use in the next steps: ν ($CHCl_3$) 3085, 1738, 1709, 1629, 1440, 1211, 1144, 932 cm^{-1}; δ ($CDCl_3$) 0.85 (s, 3 H), 1.05 (s, 3 H), 2.1–3.25 (m, 6 H), 3.50 (s, 3 H), 3.60 (s, 3 H), 4.85–5.02 (m, 3 H), 5.4–5.76 (m, 1 H); *m/e* 266 (M^+).

Methyl *trans*-2-[(7-Vinyl-8,8-dimethyl-1,4-dioxaspiro[4.4]non-6-yl)-methyl]-1,3-dioxolane-2-acetate (8). A solution of **7** (1.60 g, 6.02 mmol), ethylene glycol (1.88 g, 30 mmol), and $TsOH{\cdot}H_2O$ (30 mg, 2.6 mol %) in toluene (35 mL) was heated under a nitrogen atmosphere with use of a Dean–Stark water trap for 3 h. The cooled reaction mixture was diluted with 150 mL of hexanes and extracted successively with saturated $NaHCO_3$ (30 mL), water (3 × 50 mL), and brine (50 mL). The organic layer was dried, and the volatiles were removed in vacuo to afford crude **8** as an oil: ν ($CHCl_3$) 1733, 1438 cm^{-1}; δ ($CDCl_3$) 0.86 (s, 3 H), 0.88 (s, 3 H), 1.06–2.30 (m, 6 H), 2.60 (s, 2 H), 3.60 (s, 6 H), 3.7–3.9 (m, 8 H), 4.88–5.12 (m, 2 H), 5.44–5.80 (m, 1 H); *m/e* 340 (M^+). This was used directly in the next experiment.

Methyl *trans*-2-[(7-(2-Hydroxyethyl)-8,8-dimethyl-1,4-dioxaspiro-[4.4]non-6-yl)methyl]-1,3-dioxolane-2-acetate (9a). To a solution of the above crude diketal **8** in THF (55 mL) was added $BH_3{\cdot}THF$ (4 mL of a 0.98 M solution in THF (Ventron), 4.1 mmol, 2 equiv of hydride based on starting **7**) at 0 °C over 5 min. The reaction mixture was stirred at 0 °C for 15 min and then allowed to come to room temperature. After TLC analysis indicated complete reaction (~1.5 h), the mixture was cooled to 0 °C and MeOH (1.5 mL) was slowly added. Aqueous NaOH (0.97 mL of a 3 M solution) was then *cautiously* added followed by 30% H_2O_2 (0.67 mL). The solution was warmed at 40–50 °C for 1 h. After cooling, the solution was diluted with ether (150 mL), washed with brine (2 × 50 mL), and dried, and the volatiles were removed in vacuo, giving crude **9a** as an oil: ν ($CHCl_3$) 3600–3150, 1725, 1430 cm^{-1}; δ ($CDCl_3$) 0.92 (s, 3 H), 0.96 (s, 3 H), 1.2–2.48 (m, 8 H), 2.64 (s, 2 H), 3.61 (s, 3 H), 3.54–3.92 (m, 10 H); *m/e* 358 (M^+). This was used directly in the next experiment.

Methyl *trans*-2-(2-Bromoethyl)-3,3-dimethyl-5-oxocyclopentane-acetoacetate (10). To a solution of the above crude alcohol **9a** in dry ether (50 mL) at 0 °C was added triethylamine (4.2 mL, 30 mmol) followed by methanesulfonyl chloride (1.4 mL, 18 mmol). The reaction mixture was brought to room temperature and stirred for 3 h. Ether (200 mL) was added, and the solution was extracted with H_2O (2 × 50 mL) followed by saturated sodium bicarbonate (2 × 20 mL). The organic layer was dried and the solvent removed in vacuo to afford crude mesylate **9b**: δ ($CHCl_3$) δ 2.94 (s, 3 H), 4.28 (t, 2 H). To this was added reagent grade acetone (50 mL) and LiBr (1.6 g, ~ 3 equiv). The mixture was refluxed under a drying tube for 6 h. The volatiles were removed in vacuo, and the residue taken up in 200 mL of ether. This was extracted with 50% brine (50 mL) and brine (50 mL) and dried, and the solvent was removed in vacuo. The resulting oil was flash chromatographed[21] by using hexanes–EtOAc (3:2, v/v), affording relatively pure **10** (1.25 g, 62% from **7**) as an oil: ν ($CHCl_3$) 1740, 1720, 1440 cm^{-1}; δ ($CDCl_3$) 0.97 (s, 3 H), 1.22 (s, 3 H), 1.83–2.33 (m, 6 H), 2.97 (d, *J* = 5 Hz, 1

(19) Melting points were determined on a Thomas–Hoover melting point apparatus and are uncorrected. NMR spectra were recorded at 90 MHz (Varian EM-390), 100 MHz (Jeol MH-100), 270 MHz (Brücker 270), or 600 MHz (NIH NMR Facility for Biomedical Studies, Mellon Institute). Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane as an internal standard (δ_{TMS} = 0.00) in the indicated solvent. Resonance patterns are reported as s (singlet), d (doublet), t (triplet), m (multiplet), and b (broad). Coupling constants (*J*) are reported in hertz. IR spectra were recorded on a Perkin-Elmer 137, a Perkin-Elmer 247, or a Perkin-Elmer 710B instrument and are reported in cm^{-1}. Mass spectra were recorded on either a LKB 9000A GC–MS (interfaced with a Varian Data Machine 620/L-100) or a Hewlett-Packard 5985 GC–MS and are reported in *m/e* units. Thin-layer chromatography (TLC) analyses were carried out by using precoated silica gel F-254 plates (Merck). Visualization was accomplished by using UV light (254 nm), iodine vapor, and an oxidizing spray (ammonium molybdate–cerric sulfate/10% aqueous sulfuric acid) followed by heating to maximum visibility of the spot(s). Flash chromatography[21] was carried out with 15-, 20-, 40-, or 50-cm columns by using Merck silica gel 60. High-pressure liquid chromatographics (HPLC) were carried out on a Waters Model 6000A solvent delivery system equipped with a Model U6K injector and a R401 differential refractometer. The column used was either an analytical or preparative μ-Porasil, depending on the scale of the reaction. All solvents used in chromatographics were distilled. Dry solvents were obtained by using standard procedures. *n*-Butyllithium was titrated prior to use by using (−)-menthol (1,10-phenanthroline as indicator). Vinylmagnesium bromide was used as supplied (Ventron). All organic solutions which were "dried" in workup refer to the addition of magnesium sulfate, followed by filtration.

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H), 3.35–3.63 (m, 4 H), 3.77 (s, 3 H); *m/e* 332, 334 (M^+).

Methyl (3a*R,4*R**)-4-(2-Bromoethyl)-2,3,3a,4,5,6-hexahydro-5,5-dimethyl-2-oxo-1-pentalenecarboxylate (4).** To a solution of **10** (1.25 g, 3.75 mmol) in absolute MeOH (40 mL) at 0 °C was added NaOMe (~0.19 g, 3.52 mmol). The solution was stirred at 0 °C for 2 h. The volatiles were removed in vacuo at <40 °C (bath temperature). Several milliliters of saturated NH_4Cl was added, and the residue was diluted with 200 mL of ether. The organic phase was washed with acidic brine (50 mL of brine, 0.5 mL of 10% HCl) and brine (50 mL) and dried, and the solvent was removed in vacuo. The resulting oil was carefully flash chromatographed[21] by using hexanes–EtOAc (3:2, v/v). Several mixed fractions were rechromatographed, affording a total of 880 mg of **4** (47% from **7**) as an oil, suitable for use in the next step: ν ($CHCl_3$) 1745, 1713, 1642, 1440 cm^{-1}; δ ($CDCl_3$) 1.08 (s, 3 H), 1.20 (s, 3 H), 1.4–3.0 (m, 8 H), 3.25–3.67 (m, 2 H), 3.85 (s, 3 H); *m/e* 314, 316 (M^+). Crystallization of a sample from hexanes provided analytically pure **4**, mp 93–94 °C. Anal. Calcd for $C_{14}H_{19}O_3Br$: C, 53.34; H, 6.08; Br, 25.35. Found: C, 53.37; H, 5.99; Br, 25.66.

1-(*tert*-Butyldimethylsilyloxy)-1-*tert*-butoxyethylene (11). To a solution of diisopropylamine (7.0 g, 49.7 mmol) in THF (40 mL) at 0 °C was added BuLi (29.6 mL, 1.6 M, 47.4 mmol) over a period of 5 min. The solution was stirred at 0 °C for 10 min and then placed in a −78 °C bath, *tert*-butyl acetate (5.0 g, 43.1 mmol) was added neat, dropwise, over 10 min. The reaction was stirred for an additional 15 min and then HMPA (6.5 mL) was added in one portion, followed by *tert*-butyldimethylsilyl chloride (6.8 g, 45.3 mmol, dissolved in 15 mL of THF). The reaction was allowed to come to room temperature; then the solvent was removed in vacuo. The residue was taken up in hexanes (250 mL) and extracted successively with water (3 × 100 mL) followed by brine (50 mL). The organic phase was dried and the solvent removed in vacuo, affording 9.94 g (100%) of crude ketene acetal **11** as a clear, yellow liquid, suitable for use without further purification: ν ($CHCl_3$) 1647, 1465, 1365, 1250, 845 cm^{-1}; δ (CCl_4) 0.13 (s, 6 H), 0.92 (s, 9 H), 1.3 (s, 9 H), 3.32 (d, J = 0.9 Hz, 1 H), 3.37 (d, J = 0.9 Hz, 1 H).

Methyl (1*R,3a*R**,6a*R**)-1-(2-Bromoethyl)hexahydro-2,2-dimethyl-5-oxo-3a(1*H*)-pentaleneacetate (13).** To a solution of **4** (515 mg of the above oil, 1.64 mmol) in dry CH_2Cl_2 (15 mL) at −78 °C was added $TiCl_4$ (380 mg, 2.0 mmol). This solution was stirred at −78 °C for 5 min and then ketene acetal **11** (1.37 mL, d ~ 0.83, 1.14 g, 4.9 mmol) was added. The solution went immediately from a wine-red color to a very dark orange–wine red. This was stirred at −78 °C for 5 min and then brought to room temperature for 30 min. The solution was treated with 10% HCl (10 mL) followed by H_2O (10 mL) and CH_2Cl_2 (30 mL). The aqueous layer was salted, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried and the volatiles removed in vacuo to provide an oil whose NMR was consistent with a mixture of the diester **12a** and its corresponding ester acid **12b**: δ ($CDCl_3$) 0.08 (s), 0.14 (s), 0.79 (s), 10.32 (b s, enol proton).

This crude oil was heated under reflux in a solution of 1 M HCl (9 mL) and dioxane (9 mL) for 1.5 h. Brine (10 mL) was added after cooling. This was extracted with ether (3 × 30 mL) and CH_2Cl_2 (2 × 20 mL). The combined organic phases were extracted successively with saturated $NaHCO_3$ (3 × 12 mL), 1 M NaOH (2 × 10 mL), and water (10 mL). These combined aqueous layers were acidified (pH < 2) with concentrated HCl and extracted with CH_2Cl_2 (5 × 30 mL). The combined organic layers were dried, and the solvent was removed in vacuo to afford an oil. This was treated as a CH_2Cl_2 solution with excess ethereal diazomethane. Acetic acid was added and the solution was evaporated in vacuo to give an oil which was flash chromatographed[21] by using hexanes–ethyl acetate (2:1, v/v). This afforded 400 mg of keto ester **13** (74% from **4**) as an oil: ν ($CHCl_3$) 1740, 1736, 1435 cm^{-1}; δ ($CDCl_3$) 0.93 (s, 3 H), 1.03 (s, 3 H), 1.3–2.7 (m, 12 H), 3.52 (t, 2 H), 3.62 (s, 3 H); *m/e* 330, 332 (M^+).

Methyl (3'a*R,6'*R**,6'a*R**)-6'-(2-Bromoethyl)tetrahydro-5',5'-dimethylspiro[1,3-dioxolane-2,2'(1*H*)-pentalene]-3'a(3'*H*)-acetate (14).** A solution of **13** (400 mg, 1.21 mmol), ethylene glycol (~440 mg, 7.2 mmol), TsOH·H_2O (10 mg, 0.052 mmol), and toluene (13.5 mL) was heated under reflux with a Dean–Stark trap and drying tube for 3.75 h. The reaction mixture was cooled and diluted with 80 mL of ether. The organic phase was extracted successively with saturated $NaHCO_3$ (15 mL), neutral water (3 × 30 mL), and brine (10 mL). Drying and evaporation of the volatiles in vacuo followed by flash chromatography[21] with hexanes–EtOAc (4:1, v/v) provided 420 mg of ketal ester **14** (93%) as an oil: ν ($CHCl_3$) 1725, 1433 cm^{-1}; δ ($CDCl_3$) 0.88 (s, 3 H), 1.00 (s, 3 H), 1.6–2.2 (m, 10 H), 2.42 (d, J = 15 Hz, 1 H), 2.68 (d, J = 15 Hz, 1 H), ~3.6 (m, 2 H), 3.66 (s, 3 H), 3.88 (bs, 4 H); *m/e* 374, 376 (M^+).

Methyl (3'a*R,6'*R**,6'a*R**)-6'-(2-Iodoethyl)tetrahydro-5',5'-dimethylspiro[1,3-dioxolane-2,2'(1'*H*)-pentalene]-3'a(3'*H*)-acetate (15).** To a solution of **14** (420 mg, 1.12 mmol) in reagent grade acetone (9 mL) were added NaI (680 mg, >4.53 mmol) and 2 drops of pyridine. The solution was refluxed for 15 h under a drying tube. The solvent was removed in vacuo and ether (70 mL) was added. This was extracted with 50% brine (25 mL) and brine (15 mL) and dried, and the solvent was removed in vacuo. The resulting oil (480 mg, >100% mass yield) was used immediately in the next step without purification [δ ($CDCl_3$) 3.26 (m, 2 H, CH_2I)]. The rest of the NMR spectrum was superimposable with that of **14**.

Methyl (3a*R,4*S**,7*S**,7a*S**)-Octahydro-8,8-dimethyl-2-oxo-3a,7-ethano-3a*H*-indene-4-carboxylate (16).** To a solution of diisopropylamine (1.59 g, 15.8 mmol) in THF (120 mL) at 0 °C was added BuLi (8.9 mL, 1.6 M, 14 mmol). The solution was stirred at 0 °C for 5 min and then cooled to −78 °C. Iodo ketal **15** (4.00 g, 9.48 mmol) in THF (6 mL) was added dropwise over 10 min. The reaction mixture was stirred for 20 min at −78 °C, 15 min at −45 °C, then brought to −23 °C. HMPA (10 mL) was immediately added. The solution was stirred at −23 °C for an additional 15 min and then brought to room temperature for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), diluted with hexanes (~600 mL), and extracted with water (3 × 150 mL) followed by brine (100 mL). The organic layer was dried, and the volatiles were removed in vacuo, providing the crude ketal ester as an oil: ν ($CHCl_3$) 1726, 1436 cm^{-1}; δ ($CDCl_3$) 1.12 (s, 3 H), 1.26 (s, 3 H), 1.4–2.3 (m, 11 H), 2.5–2.75 (m, 2 H), 3.7 (s, 3 H), 3.87 (bs, 4 H); *m/e* 294 (M^+).

This material was dissolved in acetone (100 mL) containing TsOH·H_2O (50 mg, ~3 mol %) and the solution was stirred for 1 h at room temperature. Solid sodium bicarbonate (1 g) was added, and the mixture was stirred for an additional 30 min. Filtration followed by evaporation of the solvent in vacuo afforded an oil which was carefully flash chromatographed (hexanes–ethyl acetate, 5:1, v/v), affording 1.32 g of pure **16** (55.5%), along with ~120 mg of its equatorial isomer **17**. Spectral data for **16**: ν ($CHCl_3$) 1730, 1436 cm^{-1}; δ ($CDCl_3$) (600 MHz) 1.17 (s, 3 H), 1.19 (s, 3 H), 1.76–2.0 (m, 5 H), 1.58 (d, J = 14.8 Hz, 1 H), 1.76 (d, J = 14.8 Hz, 1 H), 2.24 (d, J = 17.7 Hz, 1 H), 2.36 (d, J = 17.7 Hz, 1 H), 2.48 (d, J = 10.2 Hz, 2 H), 2.76 (d, J = 7.5 Hz, 1 H), 2.88 (t, J = 10.2 Hz, 1 H), 3.68 (s, 3 H); *m/e* 250 (M^+). Crystallization from hexanes provided an analytically pure sample, mp 49–51 °C. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.96; H, 8.79. Spectral data for **17**: ν ($CHCl_3$) 1728, 1450, 1432, 1160 cm^{-1}; δ ($CDCl_3$) 1.17 (s, 3 H), 1.21 (s, 3 H), 1.56 (m, 1 H), 1.79–2.19 (m, 7 H), 2.29 (d, J = 18.3 Hz, 1 H), 2.40 (d, J = 18.3 Hz, 1 H), 2.52 (2 overlapping dd, J = 15.3, 5.9 Hz, 2 H), 2.65 (dd, J = 11.0, 6.16 Hz, 1 H), 3.65 (s, 3 H).

In other runs wherein the amount of base was limited to 0.95–1.05 equiv, the amount of **17** to **16** never exceeded 4:96 (by NMR integration). In the limiting case (0.95 equiv of base), the ratio was <3:>97. Yields in all cases were 55–60%.

(3a*R,4*S**,7*S**,7a*S**)-Octahydro-8,8-dimethyl-2-oxo-3a,7-ethano-3a*H*-indene-4-carboxylic Acid (18).** To 1.37 g of **16** (5.48 mmol) were added aqueous KOH (40 mL of a 0.15 M solution, 6 mmol) and methanol (15 mL). This solution was heated under reflux under N_2 for 1.5 h, cooled, and concentrated in vacuo to ca. one-half the original volume. It was then acidified (concentrated HCl), diluted with brine (50 mL), and extracted with ether (4 × 50 mL). The combined ethereal layers were extracted with saturated sodium bicarbonate (50 mL), 1 M NaOH (2 × 25 mL), and water (25 mL). These combined aqueous extracts were acidified (concentrated HCl) and extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were dried, and the solvent was removed in vacuo, affording 1.30 g of crude **18** (100%), suitable for use in the next steps. Crystallization of a small amount of acid thus prepared from hexanes–ether provided crystals melting at 132–135 °C: ν ($CHCl_3$) 3550–2400, 1731, 1700, 1115 cm^{-1}; δ ($CDCl_3$) 1.18 (s, 3 H), 1.22 (s, 3 H), 1.57 (d, J = 15 Hz, 1 H), 1.82 (d, J = 15 Hz, 1 H), 1.7–2.05 (m, 5 H), 2.24 (d, J = 19.5 Hz, 1 H), 2.51 (distorted t, J = 8.25, 10.5 Hz, 2 H), 2.73 (d, J = 19.5 Hz, 1 H), ~2.8 (d, 1 H), 2.87 (dd, J = 8.25, 10.5 Hz, 1 H), 9.3 (bs, 1 H); *m/e* 236 (M^+).

(3a*R,4*R**,7*S**)-2,3,4,5,6,7-Hexahydro-8,8-dimethyl-2-oxo-3a,7-ethano-3a*H*-indene-4-carboxylic Acid (20).** To a solution of **18** (1.30 g, 5.5 mmol) in ethyl acetate (50 mL) was added phenylselenyl chloride (1.2 g, 6.26 mmol). The resulting solution was stirred under N_2 at room temperature for 3 h and then diluted with water (50 mL) and ether (150 mL). After separation, the organic layer was washed with brine (40 mL) and dried, and the solvent was removed in vacuo, affording an unweighed amount of the crude selenide (**19**).

This was dissolved in CH_2Cl_2 (~40 mL), and pyridine (2.2 mL, ~27 mmol) was added, followed immediately by 30% H_2O_2 (3.8 mL, ~43 mmol). This solution was stirred at room temperature for 45 min. It was then diluted with CH_2Cl_2 (100 mL), extracted with 10% HCl (2 × 25 mL), and washed with brine (25 mL). The organic layer was dried and the solvent removed in vacuo. The resulting crude product was quickly flash chromatographed[21,22] (hexanes–EtOAc, 1:1, v/v, containing

0.5% AcOH), affording 1.00 g of **20** (78%) as a crystalline solid. Recrystallization from hexanes/EtOAc afforded analytically pure material melting at 142–146 °C: ν ($CHCl_3$) 3530–2400, 1702, 1636 cm^{-1}; δ ($CDCl_3$) 0.95 (s, 3 H), 1.25 (s, 3 H), 1.42 (d, J = 13.5 Hz, 1 H), 1.82–2.19 (m, 5 H), 2.20 (d, J = 18.3 Hz, 1 H), 2.49 (bs, 1 H), 2.78 (d, J = 18.3 Hz, 1 H), 2.95 (d, J = 5.1 Hz, 1 H), 5.88 (s, 1 H); m/e 234 (M^+). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.45; H, 7.58.

(3*R,3a*R**,4*R**,7*S**)-2,3,4,5,6,7-Hexahydro-3-(hydroxymethyl)-8,8-dimethyl-2-oxo-3a,7-ethano-3a*H*-indene-4-carboxylic Acid (21).** To a solution of **20** (125 mg, 0.534 mmol) in THF (3.3 mL) at −23 °C was added lithium diisopropylamine (freshly prepared from 0.25 mL of diisopropylamine in THF and 1 mL of 1.6 M BuLi at 0 °C, diluted to 2-mL total volume, 0.8 M, 1.6 mmol) dropwise. The resulting solution was stirred at −23 °C for 1.25 h, and then CH_2O gas (from pyrolysis of >1 g of paraformaldehyde at 145–150 °C under a slow flow of N_2) was bubbled into the solution for 5 min. The cloudy and thick reaction mixture was brought to room temperature, quenched with saturated NH_4Cl (1 mL), diluted with CH_2Cl_2 (40 mL), and washed with 10% HCl (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL), and the organic layers were combined. This was washed with brine (25 mL) and dried, and the solvent was removed in vacuo. The resulting oil was flash chromatographed [hexanes–EtOAc (1:1, v/v, containing 1.5% AcOH), going to hexanes–EtOAc (1:3, v/v, containing 1.5% AcOH)] to afford a crude crystalline solid. This was triturated with hexanes and hexanes containing ~25% ether, then a small amount of ether, affording 85 mg of almost pure **21** (60%) melting at 156–159 °C. On a smaller scale, the combined yield of two 50-mg reactions was 68%. ν ($CHCl_3$) 3550–2400, 3023, 1701 (shoulder), 1686, 1641, 1178 cm^{-1}; δ ($CDCl_3$) 0.92 (s, 3 H), 1.26 (s, 3 H), 1.56 (d, J = 13.5 Hz, 1 H), 1.69 (d, J = 13.5 Hz, 1 H), 1.75–2.22 (m, 5 H), 2.49 (s, 1 H), 2.75 (t, J = 7 Hz, 1 H), 2.99 (d, 1 H), 3.72 (d, J = 7 Hz, 2 H), 5.88 (s, 1 H).

(3*R,3a*R**,7*R**,7a*R**)-Octahydro-3-(hydroxymethyl)-8,8-dimethyl-2-oxo-3a,7-ethano-3a*H*-indene-4-carboxylic Acid (22).** To a solution of **21** (50 mg, 0.189 mmol) in methanol (2 mL) was added 5% Pd–C (10 mg). The reaction mixture was stirred vigorously at room temperature under a hydrogen atmosphere (balloon) until the reaction was complete (TLC, ~1 h). Filtration through Celite and evaporation of the volatiles in vacuo afforded the crude crystalline keto acid **22**. Recrystallization of another sample from hexanes–EtOAc afforded material melting at 156–159 °C: ν ($CHCl_3$) 3633–2404, 1730, 1452 cm^{-1}; δ ($CDCl_3$) 1.12 (s, 3 H), 1.18 (s, 3 H), 1.52 (d, J = 15 Hz, 1 H), 1.61 (d, J = 15 Hz, 1 H), 1.72–2.09 (m, 6 H), 2.26 (dd, J = 19.8, 7 Hz, 1 H), 2.58 (dd, J = 19.8, 11.7 Hz, 1 H), 2.78 (dd, J = 7, 11.7 Hz, 1 H), 2.91 (dd, J = 4.8, 8.4 Hz, 1 H), 3.01 (d, J = 6.6 Hz, 1 H), 3.64 (dd, J = 11, 8.4 Hz, 1 H), 3.98 (dd, J = 11, 4.8 Hz, 1 H); m/e 266 (M^+).

(3a*R,5a*S**,6*S**,8a*S**,8b*S**)-Octahydro-10,10-dimethyl-6,8b-ethano-8b*H*-indeno[1,7-*cd*]pyran-1,4-dione (*dl*-Quadrone).** The above material (in a 25-mL flask) was heated directly at 190–195 °C under a slow flow of nitrogen for 5.75 min. TLC and NMR analysis indicated the *exclusive* presence of quadrone (**1**) and the α-methylene keto acid **2**. The residue was dissolved in CH_2Cl_2 (15 mL) and extracted with saturated sodium bicarbonate (2 × 5 mL). The organic layer was dried and the solvent removed in vacuo, affording an oil which was flash chromatographed (hexanes–ethyl acetate, 3:2, v/v), giving *dl*-quadrone (**1**)[1,2] as a crystalline homogeneous solid (24 mg, 0.096 mmol, 51% from **21**), mp 138–142 °C. Its properties (TLC mobility, FT IR, 270 MHz NMR, MS, HPLC) were identical with those of a sample of natural quadrone provided by the National Cancer Institute. Recrystallization of synthetic quadrone from either hexanes–ether or MeOH–H_2O gave crystals melting at 140–142 °C.[23]

(3a*R,4*S**,7*S**,7a*S**)-Octahydro-8,8-dimethyl-3-methylene-2-oxo-3a,7-ethano-3a*H*-indene-4-carboxylic Acid (2).** To a solution of **22** (8 mg, 0.03 mmol) in benzene (0.5 mL) was added two crystals of tosyl acid hydrate. The mixture was heated at 40–50 °C until TLC analysis indicated complete reaction (~20 min). The reaction mixture was cooled to room temperature and chromatographed directly by using a pipet column (1:1 hexanes–ethyl acetate), affording 7 mg of essentially pure enone acid **2** (94%) as a solid. Crystallization from hexanes/ether afforded crystals melting at 177–79 °C: ν ($CHCl_3$) 3550–2400, 1719, 1707 (shoulder), 1637, 1410, 1391, 1222, 1155, 739 cm^{-1}; δ ($CDCl_3$) 1.20 (s, 3 H), 1.26 (s, 3 H), ~1.5–2.2 (m, 7 H), 2.53 (dd, J = 19, 10 Hz, 1 H), 2.66 (dd, J = 19, 10 Hz, 1 H), 2.98 (t, J = 10 Hz, 1 H), 3.05 (d, J = 7.3 Hz, 1 H), 5.22 (s, 1 H), 5.98 (s, 1 H). On a larger scale (~25 mg), the yield was 78% of pure **2**, mp 177–79 °C.

(2a*R,5*R**,5a*R**,7a*R**,7b*S**)-Hexahydro-7a,9,9-trimethyl-2-*H*-5,7b-ethanoindeno[1,7-*bc*]furan-2,7(7a*H*)-dione (Isoquadrone, 23).** In a separate experiment, a solution of **22** (7.8 mg) in 1 mL of benzene containing two crystals of tosyl acid hydrate was heated under reflux for 1 h. The solution was cooled and directly chromatographed on 5 g of silica gel. Elution with 1:1 hexanes–ethyl acetate afforded a mixture of **23** and **1**. These were separated by HPLC to provide 4.8 mg of relatively pure **23**, mp 164–167 °C, and 2.2 mg of **1**. For 23: ν ($CHCl_3$) 1778, 1757, 1454, 1223, 1186 cm^{-1}; δ $CDCl_3$ 1.21 (s, 3 H), 1.23 (s, 3 H), 1.32 (s, 3 H), 1.64 (d, J = 14.2 Hz, 1 H), 1.71 (m, 1 H), 1.76 (d, J = 14.2 Hz, 1 H), 1.92–2.14 (m, 5 H), 2.48 (dd, J = 12.8, 19.0 Hz, 1 H), 2.66 (dd, J = 8, 19.0 Hz, 1 H), 2.82 (d, J = 8.8 Hz, 1 H); m/e 248 (M^+).

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(22) It should be noted that, for this and the remaining compounds in this series, purification (even by chromatography) is extremely difficult owing to their highly insoluble nature in anything except ethyl acetate, methanol, or large volumes of methylene chloride (used in extractions).

(23) Attempted recovery of the acid **2** from the aqueous layer by careful acidification gave a mixture of products. In other runs, the residue was chromatographed directly, allowing the possibility of recyclization. That the reaction was an equilibrium was demonstrated by melting a sample of a synthetic quadrone, affording the same mixture as before. Prolonged heating did not appreciably change this ratio, though decomposition became apparent.