δ 0.894 (3 H, t, J = 5.5 Hz), 4.105 (1 H, br m, 3-H), 4.80–6.20 (5 H, olefinic protons and ABX system); mass spectrum, m/z (relative intensity) M^+ absent, 318 (0.1), 264 (0.2), 149 (0.5), 135 (1.5), 111 (10.6), 94 (11.8), 55 (65), 43 (100).

The trans aldehyde **8** (418 mg) was converted to the allylic alcohol **16** in the same way: IR ($CHCl_3$) 3600 (OH), 3010 (C-H=CH), 967 (CH=CH trans). The ^1H NMR spectrum of **16** was similar to that of **10**.

(4*E*,8*Z*)- and (4*E*,8*E*)-4,8-Pentacosadienoic Acid, Methyl Ester (11 and 17). A solution of the cis alcohol **10** (420 mg, 1.25 mmol), trimethyl orthoacetate (5 mL), and a few drops of propionic acid was heated under argon at 140 °C for 1 h with removal of methanol. Evaporation of the excess trimethyl orthoacetate under vacuum and chromatography on 14.0 g of silica gel with hexane–ether (1:1) as eluent afforded 465 mg (95%) of **11** as a yellowish oil: R_f 0.79; IR ($CHCl_3$) 3006 (CH=CH), 1741 (C=O), 966 (CH=CH trans); ^1H NMR (300 MHz) δ 0.886 (3 H, t, J = 5.5 Hz), 1.258 (28 H, br s, aliphatic CH_2), 2.328 (2 H, t, J = 6.5 Hz, 3-CH_2), 2.338 (2 H, t, J = 6.5 Hz, 2-CH_2), 3.682 (3 H, s, OCH_3), 5.35–5.51 (4 H, br m, olefinic protons); mass spectrum, m/z (relative intensity) 392 (M^+, 0.3), 168 (0.6), 136 (2.5), 95 (14), 43 (100).

Claisen rearrangement of the trans alcohol **16** under the same conditions as for **10** gave the ester **17**: IR ($CHCl_3$) 3006 (CH=CH), 1741 (C=O), 966 (CH=CH trans). The ^1H NMR and mass spectra of **17** were similar to those of **11**.

(4*E*,8*Z*)- and (4*E*,8*E*)-4,8-Pentacosadienol (12 and 18). To a suspension of lithium aluminum hydride (229 mg, 6 mmol) in dry THF (10 mL) was added dropwise a solution of the ester **11** (465 mg) in dry ether (5 mL) at 0 °C, and the mixture was stirred at room temperature for 1 h. Addition of 986 mg (9 mmol) of oxalic acid dihydrate and filtration over Celite afforded the alcohol **12**: 358 mg (90%); R_f 0.36; IR (neat) 3605 (OH), 967 (CH=CH trans); ^1H NMR (300 MHz) δ 0.901 (3 H, t, J = 5.5 Hz), 3.671 (2 H, t, J = 6.5 Hz, 1-CH_2), 5.435 (4 H, m, olefinic protons); mass spectrum, m/z (relative intensity) M^+ absent, 346 (0.1), 207 (1.4), 83 (20), 55 (65), 43 (100).

The ester **17** was reduced in the same way to give the alcohol **18**. Its spectroscopic data were identical with those of **12**.

(4*E*,8*Z*)- and (4*E*,8*E*)-4,8-Pentacosadienol Methanesulfonate (13 and 19). A solution of the alcohol **12** (358 mg, 1.18 mmol) in 5 mL of CH_2Cl_2 and 0.5 mL of Et_3N was treated dropwise with 0.2 mL of MsCl at 0 °C and stirred for 1 h. The usual workup afforded the mesylate **13**: 438 mg (93%) after purification on chromatography on silica gel using hexane–ether (1:1), R_f 0.33.

The alcohol **18** was converted to the mesylate **19** in the same way. Both isomers **13** and **19** have the same spectral properties: IR ($CHCl_3$) 1371, 1350, 1178 (OSO_2CH_3); ^1H NMR (300 MHz) δ 0.890 (3 H, t, J = 5.5 Hz), 2.978 (3 H, s, CH_3SO_3), 4.256 (2 H, t, J = 6 Hz, 1-CH_2), 5.432 (4 H, br m, olefinic protons).

(4*E*,8*Z*)- and (4*E*,8*E*)-1-Cyano-4,8-pentacosadiene (14 and 20). The mesylate **13** (410 mg, 0.92 mmol) dissolved in 5 mL of THF was added dropwise to a solution of NaCN (196 mg, 4 mmol) in Me_2SO (5 mL) at 65 °C and stirred for 3 h. The usual workup and chromatography on silica gel with hexane–ether (1:1) as the eluent gave the cyanide **14** in 90% yield (311 mg): IR (neat) 3006 (CH=CH), 2240 (CN), 966 (CH=CH trans); ^1H NMR (300 MHz) δ 0.890 (3 H, t, J = 5.5 Hz), 2.605 (2 H, t, J = 6 Hz, 2-CH_2), 5.433 (4 H, br m, olefinic protons); mass spectrum, m/z (relative intensity) 373 (M^+, 0.3), 218 (0.3), 190 (0.6), 176 (1.5), 97 (12.0), 83 (31.2), 55 (67.1), 41 (100).

Similarly, the mesylate **19** was converted to the cyanide **20** whose spectroscopic data were identical with those of **14**.

(5*E*,9*Z*)- and (5*E*,9*E*)-5,9-Hexacosadienoic Acid (15 and 21). The cyanide **14** (290 mg, 0.77 mmol) was hydrolyzed in 2 N KOH/ethanol for 48 h under refluxing conditions to give the acid **15a** (159 mg). Similarly, the cyanide **20** afforded the 5*E*,9*E* acid **21a**. The spectroscopic data of **15b** and **21b** were identical with those of **9b**.

Acknowledgment. Financial support was provided by NIH grant GM 06840. We thank Dr. Lois J. Durham for the ^{13}C NMR spectra. Use of the NMR center at the Stanford 500-MHz and 300-MHz facility (NSF Grant GP 23633) is gratefully acknowledged. P.L.M. and O.P. thank the Swiss National Science Foundation for postdoctoral fellowships.

Registry No. **1**, 1552-12-1; **2a**, 72195-80-3; **2b**, 82861-01-6; **3**, 90913-48-7; **4**, 90913-49-8; **5a**, 52715-55-6; **5b**, 90913-50-1; **6**, 90913-51-2; **7**, 90913-52-3; **8**, 90913-53-4; **9a**, 90913-54-5; **9b**, 90913-55-6; **10**, 90913-56-7; **11**, 90913-57-8; **12**, 90913-58-9; **13**, 90913-59-0; **14**, 90913-60-3; **15a**, 90913-61-4; **15b**, 90913-62-5; **16**, 90913-63-6; **17**, 90913-64-7; **18**, 90913-65-8; **19**, 90913-66-9; **20**, 90913-67-0; **21a**, 90913-68-1; **21b**, 90913-69-2; (4-carboxybutyl)-triphenylphosphonium bromide, 17814-85-6; vinylbromide, 593-60-2; trimethyl orthoacetate, 1445-45-0.

A Synthetic Approach to the Quassinoids

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A synthetic route to the quassinoids has been developed. Two-stage annelation of 2-methylcyclohexanone with 1-chloro-3-pentanone gives tricyclic dienone **9** (60%), which is oxidized by acetyl chromate in acetic acid to give dienedione **27** (80%). Bisketalization of this material followed by hydrolysis of the conjugated enone ketals provides monoketal **30** (77%), along with recovered **27**. Ring C of **30** is functionalized by the Stiles and Reich methods to obtain the unsaturated keto ester **33** (73%). The latter material reacts with ketene acetal **35** at 5–6 kbar and room temperature to give an adduct that is desilylated by treatment with aqueous KF; keto diester **39** is produced in 95% yield. Epoxidation of **39** occurs smoothly with *m*-CPBA to give **46** (88%), which is converted into allylic alcohol **40** by the two-step Sharpless procedure (78%). Finally, pyridinium chlorochromate induces solvolytic cyclization of **40**, affording **41** in 55% yield. In the course of the investigation, it was also discovered that β-keto ester **46** is oxidized by *m*-CPBA to **47** in quantitative yield.

The quassinoids are a group of diterpenoids that occur in genera of the family Simaroubaceae.[4] Those members of the group that have been obtained from the genus *Brucea* are known as bruceolides.[5-9] In 1973, S. M.

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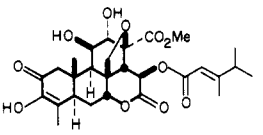
Kupchan and co-workers reported an investigation of *B. antidysenterica* Mill., a simaroubaceous tree which is indigenous to Upper Guinea, the Cameroons, and Ethiopia, and which is used in the latter country in the treatment of cancer.[10,11] Eight quassinoids were isolated, several of which subsequently proved to have significant antitumor and antileukemic properties.[12] The most promising of these materials, from the standpoint of potential utility for treatment of cancer, is bruceantin (1). Kupchan's



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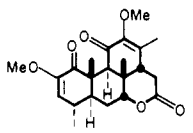
disclosure of the antineoplastic activity of bruceantin focused considerable attention on the quassinoids in general, and on the bruceolides in particular, and several investigations have subsequently turned up other naturally occurring bruceolides.[13,14] It has also been found that some quassinoids other than the bruceolides have antineoplastic activity.[15-17]

The initial findings by the National Cancer Institute that bruceantin is active against the L-1210 lymphoid leukemia, the Lewis lung carcinoma, and the B-16 melanocarcinoma resulted in its being selected for clinical trial.[18-21] Because of the promising activity that has been found in the series, synthetic studies have been initiated by several research groups. Although no bruceolides have yet been prepared by total synthesis, considerable progress has been made. The most significant advance to date has been Grieco's synthesis of the prototypical quassinoid, quassin itself (2).[22] Other synthetic reports have come

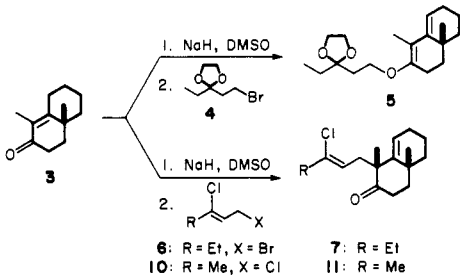


2

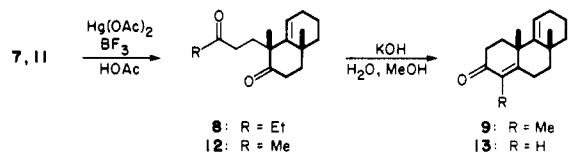
from the laboratories of Valenta,[23] Dias,[24] Watt,[25] Mandell,[26] Kraus,[27] and Fuchs.[28] In this paper, we report our own investigations of the quassinoid problem. We will present a reasonably straightforward synthetic route to the quassin skeleton, lacking the tetrahydrofuran ring D that is characteristic of the bruceolides. Although the ultimate product of this investigation is probably not a viable intermediate for conversion into the bruceolides, it may be useful for the synthesis of simpler quassinoids. In addition, the chemistry worked out to date provides a model study for an eventual assault on the bruceolides.

At the outset, we recognized that the central problems of bruceolide synthesis are elaboration of the heterocyclic D and E rings. Thus, the first problem is the relatively simple task of constructing a suitably functionalized perhydrophenanthrene system to which these rings can be appended.

Unsaturated ketone 3 is available in 60% yield by the acid-catalyzed Robinson annelation of 2-methylcyclohexanone with ethyl vinyl ketone.[29] Treatment of this



enone successively with sodium hydride/dimethyl sulfoxide and bromo ketal 4[30] affords only the O-alkylated product 5, in 62% yield. However, utilization of the same procedure with the allyl bromide 6 gives the C-alkylated product 7 in 64% yield. Hydrolysis of the vinyl chloride is accomplished by treatment of 7 with mercuric acetate and boron trifluoride etherate in acetic acid. The intermediate unsaturated diketone 8 is cyclized by treatment



with aqueous, methanolic KOH; tricyclic dienone 9 is obtained in an overall yield of 61%. A similar sequence, utilizing the commercially available allyl chloride 10, provides the tricyclic dienone 13, by way of 11 and 12, in an overall yield of 30%.

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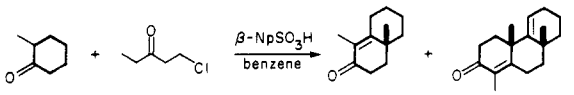
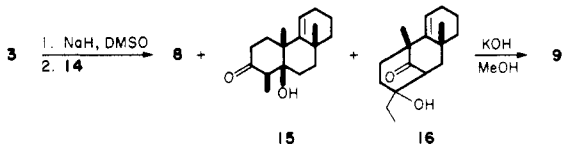
A more convenient synthesis of **9** was found subsequently. When 2-methylcyclohexanone is treated with 1-chloro-3-pentanone (**14**) and 2-naphthalenesulfonic acid



14 **3** **9**

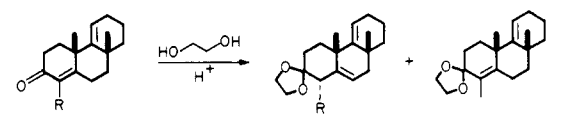
in benzene,[31] there is obtained a mixture of the bicyclic enone **3** (64%) and the tricyclic dienone **9** (18%). Treatment of **3** with sodium hydride/dimethyl sulfoxide and **14** affords a mixture of enedione **8** and aldols **15** and **16**. When this mixture is treated with hot, methanolic



15 **16**

KOH, the tricyclic dienone **9** is obtained in 65% yield. The combined yield of **9** in this two-step procedure is 60%, based on 2-methylcyclohexanone.

The synthetic strategy that we envisioned called for functionalization of ring B (at C-7) for eventual introduction of the axial lactone oxygen, and functionalization of ring C for attachment of the other terminus of the lactone ring. The method chosen for accomplishing the first goal was ketalization of the ring A enone. With compound **13**, standard ketalization with ethylene glycol and toluenesulfonic acid in benzene affords the diene ketal **17**, uncontaminated by isomers, in 82% yield.

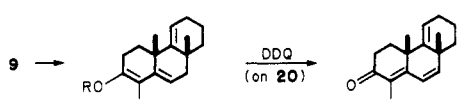


13: R = H
9: R = Me

17: R = H
18: R = Me

19

However, in the case of dienone **9**, ketalization provides an approximate 1:1 mixture of isomeric ketals **18** and **19**. The failure of the double bond to undergo complete isomerization to the distal position in this case is presumably due to the stabilizing effect of the C-4 alkyl group.[32] The desired movement of the C-4,C-5 double bond into ring B in **9** was achieved by formation of the enol ether **20** (87%) and enol acetate **21** (67%). Oxidation of enol

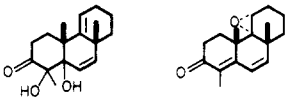


20: R = Et
21: R = MeCO

22

ether **20** to trienone **22** is brought about by treatment of **20** with dichlorodicyanobenzoquinone (DDQ). Treatment of enol acetate **21** under similar conditions gives trienone **22**, contaminated by a number of by products, in poor yield.

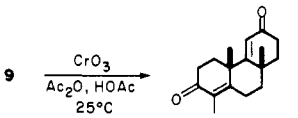
The ring B double bond in **22** proved to be unexpectedly inert. The compound is recovered unchanged after treatment with alkaline hydrogen peroxide,[33] sodium hypochlorite in pyridine,[34] and lithium bis(1-methoxyvinyl)cuprate.[35] Surprisingly, osmium tetroxide attacks the ring A double bond, giving a product (presumably **23**)



23 **24**

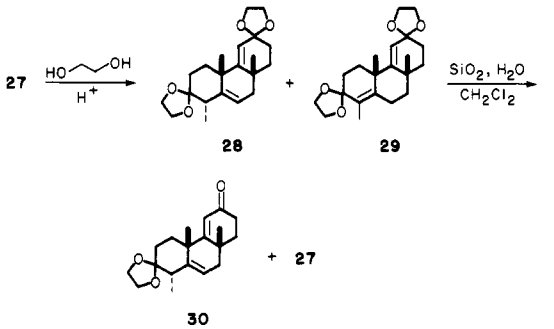
that retains the ring B and ring C double bonds. Not surprisingly, *m*-chloroperoxybenzoic acid attacks the ring C double bond, providing **24**, and catalytic hydrogenation reduces the ring B double bond, regenerating **9**.

Having experienced unexpected difficulty in the introduction of functionality into ring B, we turned our attention temporarily to the problem of functionalizing ring C. Allylic oxidation of dienone **9** with chromic anhydride in acetic anhydride–acetic acid gives dienedione **27** in more than 80% yield. Treatment of this material with ethylene



27

glycol and 2-naphthalenesulfonic acid in refluxing benzene gives a mixture of isomeric bisketals **28** and **29** in quantitative yield. Hydrolysis of the mixture with wet silica gel in methylene chloride[36] gives monoketal **30** (77%), along with a small amount of returned dienedione **27**.

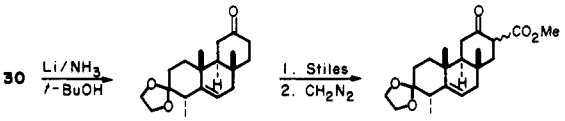


28 **29**

30 + **27**

The success of this ketalization, relative to that of the related dienone **9**, in which a 1:1 mixture of **18** and **19** is produced, was a fortuitous but welcome result. Integration of the ^{1}H NMR resonance at about δ 5.45 ppm in the mixture of ketals **28** and **29** indicates that the ratio of these two isomers is about 6:1, which agrees relatively well with the isolated yields of **30** and recovered **27** (77% and 10%, respectively) from the two-step procedure of bisketalization followed by hydrolysis. It is possible that the presence of the C-12 geminal dioxy substituent affects the conformation of the tricyclic system in such a way as to slightly favor the C-5,C-6 unsaturated isomer at equilibrium. The facile hydrolysis of the ketals of the conjugated enone systems is precedented.[36]

Reduction of **30** with lithium/ammonia/*tert*-butyl alcohol provides the saturated ketone **31** in nearly quantitative yield. The syn,trans stereochemistry of **31**, expected



31 **32**

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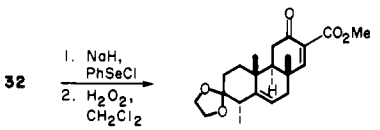
on the basis of ample analogy,[37] was eventually confirmed by X-ray analysis (vida infra). Treatment of this material with Stiles' reagent (methoxymagnesium methyl carbonate, MMC),[38] followed by methylation with diazomethane gives β-keto ester **32** in 90% yield. Although the non-enolic nature of this intermediate is vouchsafed by its infrared spectrum (strong absorption at 1710 and 1735 cm^{-1}), its stereostructure remains uncertain, in light of the finding that a related compound (vida infra) exists in a conformation with a boat ring C.

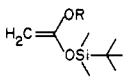
Ring C is readied further for installation of the elements of ring D by introduction of unsaturation at C-13,C-14. Treatment of the sodium salt of β-keto ester **32** with



33

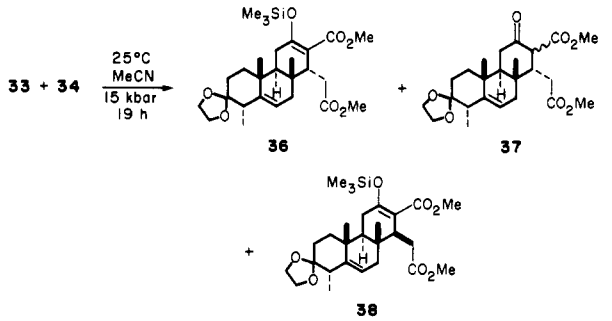
benzeneselenenyl chloride in THF, after the method of Reich,[39] provides a mixture of selenides, which is oxidized by hydrogen peroxide in a two-phase system consisting of methylene chloride and pH 7 phosphate buffer. The crystalline unsaturated keto ester **33** is obtained in an overall yield of 84%.

Treatment of intermediate **33** with ketene acetals **34** or **35** in the presence of titanium tetrachloride[40,41] or a 1:1 mixture of titanium tetrachloride and titanium tetraisopropoxide[40] results in complete reaction of the unsaturated keto ester moiety, but extensive reaction of the C-3 ketal occurs, leading to complex product mixtures. Although



34: R = Me
35: R = *t*-Bu

such additions are known to proceed without the aid of a catalyst in hot acetonitrile, the reaction of **33** and ketene acetal **34** gives only 10% yield of adduct after 21 h at 155 °C. However, the report by Matsumoto that sluggish Michael addition reactions may be driven to completion under conditions of high pressure[42] encouraged us to investigate this parameter. Indeed, an acetonitrile solution 0.15 M in **33** and 0.45 M in **34** reacts smoothly at 15 kbar



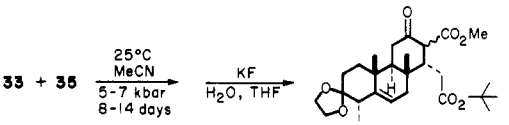
36 **37**

38

for 24 h to give adduct **36** (84%), along with minor amounts of the unsilylated product **37** (9%) and an isomer presumed to be the C-14 diastereomer **38** (7%).[43]

Treatment of the major product, **36**, with aqueous KF provides keto diester **37**.

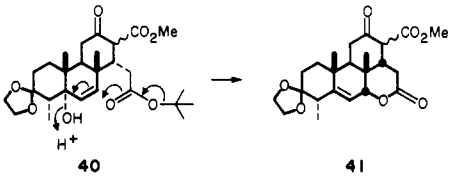
Somewhat better results are obtained in the high-pressure reaction of **33** with ketene acetal **35**, in that less of



39

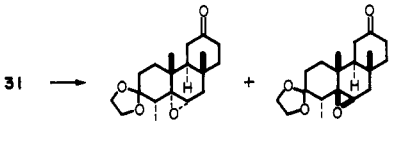
the diastereomeric product corresponding to **38** is produced. In addition, it was found that the reaction can be carried out at pressures as low as 5 kbar on a scale that produces 3–5 g of adduct. In actual practice, the crude reaction product is desilylated by treatment with KF in aqueous THF. In a typical run, crystalline **39** is produced in 95% yield for the two steps.[44] The stereochemistry depicted at C-14 in adducts **36**, **37**, and **39** is that expected on stereoelectronic grounds (axial attack by the nucleophile); it was confirmed for **39** by subsequent X-ray analysis of a derivative (vide infra).

With the elements of ring D installed at C-14, we turned our attention to the proper functionalization of C-7. One appealing scheme that presented itself was the solvolysis of the allylic alcohol **40**; it might reasonably be expected that the carbonyl oxygen of the proximate *tert*-butyl ester would participate as shown to provide a tetracyclic lactone such as **41**. To this end, we examined the epoxidation of



40 **41**

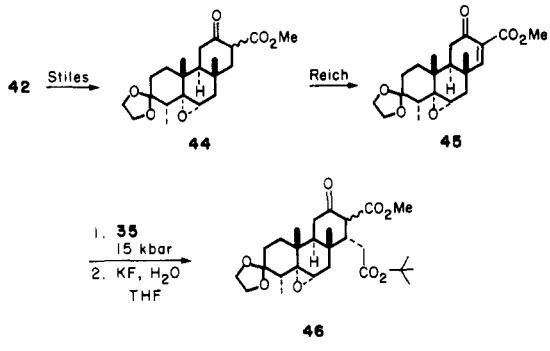
the simple unsaturated ketone **31**. Treatment of **31** with buffered *m*-CPBA in methylene chloride at room temperature affords a 7:1 mixture of epoxides **42** and **43** (59% yield), along with products resulting from Baeyer–Villiger oxidation (25% yield). On the other hand, the recently introduced tetrachloroacetone peroxyhemiketal[45] gives only keto epoxide **42**, although the reaction is relatively slow, giving a conversion of **31** to **42** of only 55% after 2.5 days at room temperature. However, the unreacted **31** is readily recovered, and the yield of epoxide, based on consumed reactant, is 82%.



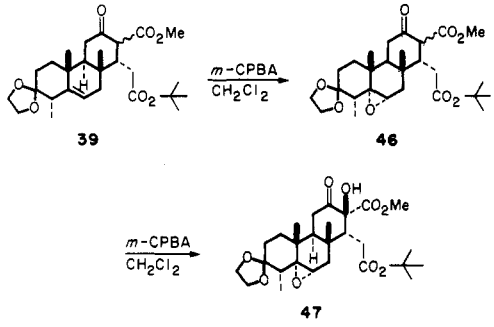
42 **43**

Functionalization of keto epoxide **42** by the Stiles and Reich procedures provides unsaturated keto ester **45**. Application of the high-pressure ketene acetal addition to this substance provides intermediate **46**. We later found that epoxide **46** may also be obtained by oxidation of **39** with *m*-CPBA in methylene chloride. In contrast to the behavior seen with the simple unsaturated ketone **31**, compound **39** gives *only* epoxide **46**, in 88% yield. Significantly, if excess peroxy acid is used, a second oxidation

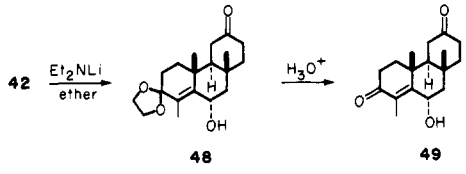
(37) Caine, D. *Org. React. (N.Y.)* **1976**, *23*, 1.
(38) Finkbeiner, H. L.; Stiles, M. *J. Am. Chem. Soc.* **1963**, *85*, 616.
(39) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.
(40) Saigo, K.; Osaki, M.; Mukaiyama, T. *Chem. Lett.* **1976**, 163.
(41) Danishefsky, S.; Vaughan, K.; Gadwood, R.; Tsuzuki, K. *J. Am. Chem. Soc.* **1981**, *103*, 4136.
(42) Matsumoto, K. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1013.
(43) Bunce, R. A.; Schlecht, M. F.; Dauben, W. G.; Heathcock, C. H. *Tetrahedron Lett.* **1983**, *24*, 4943.
(44) We thank Professor W. Pirkle, of the University of Illinois, for carrying out several large-scale reactions for us in his apparatus at Champaign-Urbana.
(45) Stark, C. J. *Tetrahedron Lett.* **1981**, *22*, 2089.



occurs, converting **46** into intermediate **47**; the latter substance can be obtained in quantitative yield! Thus, the preferred route to epoxide **46** is the sequence **31** → **32** → **33** → **39** → **46**, which proceeds in an overall yield of more than 70% for the four steps.



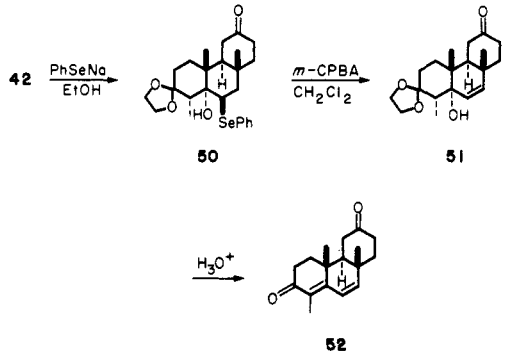
We had intended to rearrange the epoxide ring of **47** to an allylic alcohol by the Rickborn–Crandall procedure.[46] There is an obvious question of regiochemistry, since deprotonation might occur either at C-4 or C-7. However, mechanistic investigations by Kissel and Rickborn have shown that syn elimination is preferred, and we therefore expected elimination to proceed solely from C-7 deprotonation. Thus, we were surprised to find that treatment of the model epoxide **42** with excess lithium diethylamide



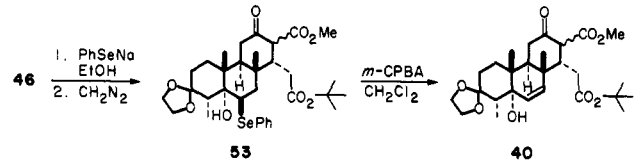
in ether, followed by acidic hydrolysis gives only **49**, resulting from deprotonation of **42** at C-4. The reason for this unexpected behavior probably lies in the oxygen substituents at C-3. If the lithium cation of the base is coordinated with the 3β oxygen, intramolecular deprotonation would result in removal of the 4β hydrogen, leading to the formation of **48**.[47]

Epoxide **42** is successfully rearranged to allylic alcohol **51** by the Sharpless procedure, wherein the epoxide ring is first opened by sodium phenylselenide, and the resulting phenylseleno derivative **50** is then oxidatively eliminated.[48] By this route, **51** is obtained in an overall yield of 73% from epoxide **42**; mild acidic hydrolysis of **51** provides the crystalline dienedione **52** in 93% yield.

The Sharpless procedure can also be applied to epoxide **46**. In this case, however, the situation is complicated by

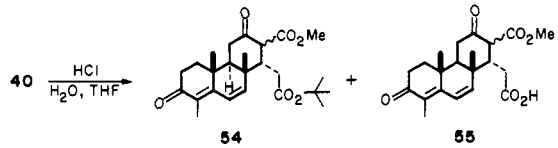


the fact that epoxide **46** is much less soluble in ethanol

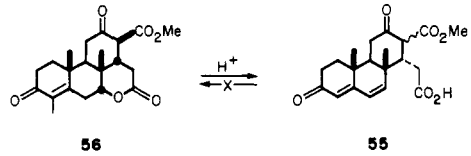


than epoxide **42** and also by the presence of the methyl ester in **46**. Because of the reduced solubility of **46**, the reaction must be carried out under more dilute conditions. In addition, a significant amount (10–30%) of nucleophilic demethylation occurs, giving the β-keto acid corresponding to product **53**. Therefore, it is necessary to treat the crude product with diazomethane in order to maximize the yield of **53**. By this method, epoxide **46** can be converted into **40** in 78% yield, based on consumed starting material.

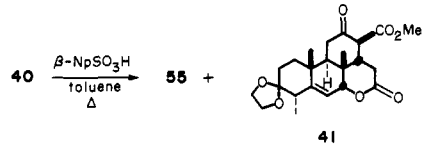
Initial attempts to bring about solvolytic ring closure of the 6-valerolactone ring (**40** → **41**) by the use of aqueous or anhydrous acid were unsuccessful. Treatment of **40** with



HCl in aqueous THF for periods of time ranging from 4 to 72 h provides a mixture of **54** (38–39%) and acid **55** (14–17%). Control experiments showed that acid **55** is *not* formed from ester **54**. Thus, we believe that the solvolytic ring closure does occur to a degree, but that the product (**56**) is unstable to acidic conditions, and undergoes elim-



ination to give **55**. Attempts to bring about the reverse of this reaction, Michael addition of the carboxyl group to the δ position of the dienone of **55**, were uniformly unsuccessful. The foregoing hypothesis obviously suggests that the solvolytic cyclization may succeed under anhydrous conditions. However, the use of anhydrous 2-naphthalenesulfonic acid in refluxing toluene leads mainly to acid **55** (38% yield) and a trace amount of lactone **41**.



The problem was solved in an unexpected manner. Treatment of allylic alcohol **40** with pyridinium chloro-

(46) (a) Kissel, C. L.; Rickborn, B. *J. Org. Chem.* **1972**, *37*, 2060. (b) Crandall, J. K.; Lin, L. C. *Ibid.* **1968**, *46*, 2375.
(47) Similar results have been observed by Holland, H. L. and Jahangir *Can. J. Chem.* **1983**, *61*, 2165.
(48) Sharpless, K. B.; Hauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697.

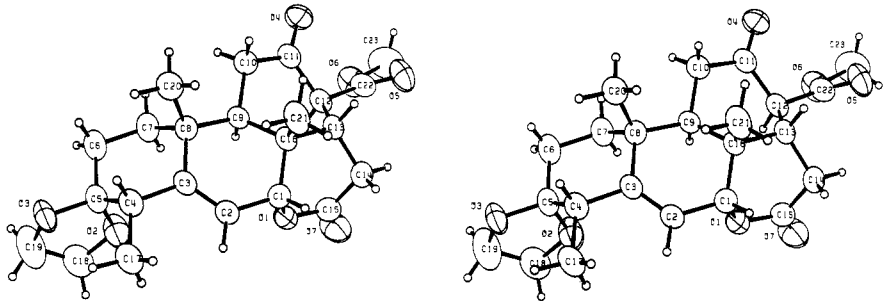
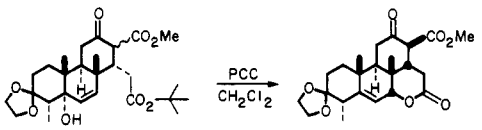
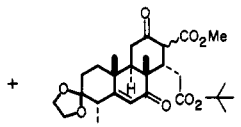


Figure 1. ORTEP stereoscopic projection of lactone 41.

chromate[49] in methylene chloride gives a mixture of the crystalline lactone 41 (55%) and enone 57 (14%).



40 41



57

The mechanism of the foregoing reaction presumably involves solvolysis by the initially formed chromate ester, leading to an allyl cation that is trapped by the *tert*-butyl ester carbonyl oxygen. The by product enone **57** arises from the expected[50] oxidative rearrangement. A variety of attempts to bring about this reaction by other, more traditional procedures for generating an allylic cation from an allylic alcohol were uniformly unsuccessful. The stereostructure of **41** was elucidated by single-crystal X-ray analysis, which revealed that rings C and D are both in boat conformations and that the C-13 methoxycarbonyl substituent has the β configuration (Figure 1).

Thus, a tetracyclic quassinoid precursor is available in 10% overall yield from 2-methylcyclohexanone by the sequence: **3** → **9** → **27** → **30** → **31** → **32** → **33** → **39** → **46** → **53** → **40** → **41**. In addition, the remarkable discovery that β-keto ester **46** is cleanly oxidized to alcohol **47** provides a method for introduction of the requisite oxygen for formation of the tetrahydrofuran ring E of the bruceolides. A brief investigation of the possible application of the Barton–Kalvoda reaction[51] to **47** was, in fact, carried out. Not surprisingly, however, simple cleavage of the α-hydroxy carbonyl moiety occurs upon treatment of this material with lead tetraacetate; no tetrahydrofuran-containing products were obtained. We are now investigating the application of the chemistry reported in this paper, starting with 2-(methoxycarbonyl)cyclohexanone. In this way, we expect to prepare an analogue of **41** having an alkoxymethyl group at C-8.

Experimental Section

General Procedures. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Methylene chloride, benzene, pyridine, and acetonitrile were dried over 3A molecular sieves. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone under nitrogen. Dimethyl sulfoxide and dimethylformamide were distilled from calcium hydride at reduced pressure. Absolute methanol was obtained by distillation from magnesium. Chromium trioxide was pulverized and dried for several days under reduced pressure over P_2O_5. 2-Naphthalenesulfonic acid was dried azeotropically in benzene, and then under reduced pressure for several days. Boiling points and melting points are uncorrected. The high-pressure reactions were performed by sealing the reaction mixture in a length of teflon tubing with metal screw-caps, and placing the tube within the piston cavity of a hydraulic oil press, at either 15 kbar or 7 kbar, for varying lengths of time. Large-scale high-pressure reactions were carried out by Professor William Pirkle at the University of Illinois. Infrared spectra (IR) were determined with a Perkin-Elmer Model 297 infrared recording spectrophotometer. ^{1}H NMR spectra were determined with a Varian EM 390 or the UCB 200 and 250 spectrometers (superconducting, FT instruments operating at 200 or 250 MHz). Chemical shifts are expressed in ppm downfield from internal tetramethylsilane (Me_4Si). Significant ^{1}H NMR data are tabulated in order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constant in Hertz. ^{13}C NMR spectra were measured with the UCB 250 and are expressed in ppm downfield from Me_4Si. High-performance liquid chromatography (HPLC) was done with a Waters PrepLC/system 500. Elemental analyses were performed by the Microanalytical Laboratory, operated by the College of Chemistry, University of California, Berkeley, CA. Column chromatography was performed by the "flash" technique of Still et al.[52]

(*Z*)-1-Bromo-3-chloro-2-pentene (6). To a rapidly stirring mixture of 3.8 g (0.1 mol) of lithium aluminum hydride and 10.8 g (0.2 mol) of sodium methoxide in 500 mL of THF was slowly added 8.4 g (0.1 mol) of 2-pentyn-1-ol (Farchem). The reaction mixture was refluxed for 3 h and then cooled to room temperature. Excess lithium aluminum hydride was destroyed by addition of 10 mL (0.1 mol) of ethyl acetate. The resulting solution was placed in a dry ice cooling bath and, after 10 min, a solution of 20 g (0.15 mol) of *N*-chlorosuccinimide in 50 mL of THF was added. After 10 min, the cooling bath was removed and stirring was continued for 1.5 h at room temperature. At the end of this period 10% aqueous NaOH and 250 mL of petroleum ether were added and the precipitate was removed by filtration. The filtrate was washed with water and saturated brine, dried over Na_2SO_4, concentrated, and distilled [bulb-to-bulb, 65 °C (2 torr)] to give 7.94 g (66%) of colorless oil: ^{1}H NMR (CCl_4) δ 1.16 (t, 3 H, J = 6), 2.35 (q, 2 H, J = 6), 3.2 (broad s, 1 H), 4.2 (d, 2 H, J = 6), and 5.6 (d, 1 H, J = 6).

To a solution of 7.9 g (65.6 mmol) of 3-chloro-2-penten-1-ol and 160 mg (2 mmol) of pyridine in 30 mL of dry ether was added 6.77 (25 mmol) of phosphorus tribromide in 10 mL of ether, and the reaction mixture was refluxed for 2 h. The cooled solution was poured into an equal volume of ice water, the organic phase was separated, and the aqueous layer was extracted with 2 × 20 mL of ether. The combined ethereal solution was washed with 2 × 20 mL of 10% K_2CO_3 solution and 25 mL of saturated brine, dried over Na_2SO_4, concentrated, and distilled [bulb-to-bulb, 60 °C (5 torr)] to give 10.22 g (85%) of a colorless oil (which turned yellow upon standing): ^{1}H NMR (CCl_4) δ 1.2 (t, 3 H, J = 7), 2.42 (q, 2 H, J = 7), 4.03 (d, 2 H, J = 8), and 5.76 (t, 1 H, J = 8).

1-Chloro-3-pentanone (14). A 2-L three-necked flask was charged with 1.2 L of methylene chloride and 305 g of anhydrous

(49) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(50) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682.
(51) Kalvoda, J.; Heusler, K. *Synthesis* **1971**, 501.
(52) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

aluminum chloride was added, followed by 200 mL (213 g, 2.3 mols) of propionyl chloride, with efficient stirring. The reaction mixture was chilled to 0 °C with an ice/salt bath. Ethylene was bubbled through the stirring solution by means of a fritted glass tube. The inlet gas flow was recorded with a flow meter, and the outlet gas flow with a "GC-type" bubble gas flow meter. The inlet flow rate was adjusted to allow most of the ethylene to be absorbed by the solution, e.g., an outlet flow rate of about 30 mL/min. The rate of absorption (more than 1 L/min initially) dropped to zero after 90 min. The reaction mixture was then poured into 2 L of ice and 500 mL of 35% HCl. The organic phase was then washed with 10% aqueous HCl (6 × 500 mL) and saturated aqueous $NaHCO_3$ (500 mL) and dried ($MgSO_4$). Solvent removal and distillation at 11 torr gave 207 g (76%) of 1-chloro-pentanone (14), bp 65–70 °C (11 torr).

(±)-2-Ethyl-2-[2-[(3,4,4a,5,6,7-hexahydro-1,4a-dimethyl-2-naphthalenyl)oxy]ethyl]-1,3-dioxolane (5). In a dry flask, 13 mmol of hexane-washed NaH (547 mg of 57% in oil) was allowed to react with 20 mL of dry Me_2SO at 65 °C for 1 h. After the solution was cooled to room temperature, a solution of enone 3 (1.78 g, 10 mmol) in 15 mL of Me_2SO was added. Stirring was continued for 1.5 h and a solution of 2.3 g (11 mmol) of 1-bromo-3-pentanone ethylene ketal in 10 mL of Me_2SO was introduced. The reaction mixture was stirred at room temperature for 14 h and was then poured into 50 mL of saturated NH_4Cl and extracted with 3 × 50 mL of ether. The combined ethereal solution was washed with 50 mL of water, 50 mL of saturated brine, and dried over $MgSO_4$. Removal of solvent left 2.99 g of pale yellow oil which was purified by HPLC (15% ether:hexanes) to give 1 g (62% based on the consumed starting material) of the O-alkylated product 5, 0.83 g (47%) of starting material, and 0.15 g of volatile 1-penten-3-one ethylene ketal. Compound 5: ^1H NMR (CCl_4) δ 0.98 (t, 3 H, J = 7.5), 1.05 (s, 3 H), 1.2–2.4 (m), 3.8 (t, 2 H, J = 7.5), 3.94 (s, 4 H), and 5.35 (t, 1 H, J = 4); IR (neat) 3030, 1640 and 1080 cm^{-1}.

(±)-[1α(*Z*),4aβ]-1-(3-Chloro-2-pentenyl)-3,4,4a,5,6,7-hexahydro-1,4a-dimethyl-2(1*H*)-naphthalenone (7). In a dry flask, was placed 13 mmol of NaH (547 mg of 57% in oil), washed twice with hexanes. The washed powder was dried with a flame under nitrogen, and allowed to react with 20 mL of Me_2SO at 65 °C for 1 h. The resulting solution was cooled to room temperature and enone 3 (1.78 g, 10 mmol) in 20 mL of Me_2SO was added. The reaction mixture was stirred at 40–50 °C for 2 h and cooled to room temperature. A solution of 2.2 g (12 mmol) of 1-bromo-3-chloro-2-pentene in 10 mL of Me_2SO was introduced and the reaction mixture was stirred at room temperature for 7.5 h, poured into 50 mL of saturated NH_4Cl, and extracted with 4 × 30 mL of ether. The combined ether extracts were washed with 2 × 30 mL of water, 30 mL of saturated NaCl, and dried over $MgSO_4$. Removal of solvent left 3.14 g of crude oil which was purified by HPLC (19% ether:hexanes) to give the C-alkylated product 7 (1.79 g, 64%): ^1H NMR (CCl_4) δ 1.0 (s, 3 H), 1.12 (t, 3 H, J = 7 Hz), 1.18 (s, 3 H), 5.20 (t, 1 H, J = 7), and 5.54 (t, 1 H, J = 3); IR (neat) 3030, 1710, and 1660 cm^{-1}.

(±)-[1α(*Z*),4aβ]-1-(3-Chloro-2-butenyl)-3,4,4a,5,6,7-hexahydro-1,4a-dimethyl-2(1*H*)-naphthalenone (11). In a dry flask was placed 65 mmol of NaH (2.74 g of 57% in oil), washed twice with hexanes. The washed solid was dried with a flame under nitrogen, and allowed to react with 150 mL of Me_2SO at 65 °C for 1 h. To the cooled solution was added 8.9 g (50 mmol) of compound 3 in 20 mL of Me_2SO. The reaction mixture was stirred at 45–50 °C for 1.75 h and cooled to room temperature. A solution of 8.13 g (65 mmol) of 1,3-dichloro-2-butene in 20 mL of Me_2SO was added and the solution was stirred at room temperature for 8 h, poured into 200 mL of saturated NH_4Cl, and extracted with 4 × 100 mL of ether. The combined ether extracts were washed with 2 × 100 mL of water and 100 mL of saturated NaCl, and dried over $MgSO_4$. Removal of the solvent left 14.3 g of crude oil which was purified by HPLC (8% ether:hexanes) to give the C-alkylated product 11 (8.54 g, 64%): ^1H NMR (CCl_4) δ 0.92 (s, 3 H), 1.1 (s, 3 H), 1.3–2.1 (m), 2.0 (broad s), 2.2–2.6 (m), 5.17 (t, 1 H, J = 8), and 5.5 (t, 1 H, J = 4); IR (neat) 3050, 1710, 1660, and 1640 cm^{-1}. Anal. Calcd for $C_{16}H_{23}OCl$: C, 72.02; H, 8.69; Cl, 13.29. Found: C, 71.86; H, 8.55; Cl, 13.03.

(±)-*trans*-3,4,4a,5,6,7-Hexahydro-1,4a-dimethyl-1-(3-oxopentyl)-2(1*H*)-naphthalenone (8). To a rapidly stirring solution of 6.38 g (20 mmol) of mercuric acetate and compound 7 (2.88 g, 10.2 mmol) in 100 mL of glacial acetic acid, was added dropwise 2.84 g (20 mmol) of boron trifluoride etherate. The resulting clear yellow solution was stirred at room temperature for 1.75 h, poured into 150 mL of saturated brine, and extracted with 4 × 50 mL of 1:1 ether–petroleum ether. The combined organic layers were washed with 2 × 50 mL of ether, 2 × 50 mL of 10% Na_2CO_3 solution, 50 mL of saturated brine, and dried over $MgSO_4$. Removal of solvent left 3.34 g of a crude oil which was used for the next step without purification: ^1H NMR (CCl_4) δ 1.0 (s, 3 H), 1.01 (t, 3 H), 1.14 (s, 3 H), 1.4–2.6 (m), and 5.5 (t, 1 H, J = 4); IR (neat) 1710 and 1645 cm^{-1}.

(±)-*cis*-4,4a,6,7,8,8a,9,10-Octahydro-1,4a,8a-trimethyl-2-(3*H*)-phenanthrenone (9). (a) The crude diketone 8 (3.34 g) was suspended in 30 mL of a 1:1 mixture of 10% aqueous KOH and methanol, and the reaction mixture was heated at gentle reflux for 2.5 h. The heterogeneous mixture was cooled to room temperature, acidified with 10% HCl (about 9 mL), diluted with 20 mL of saturated brine, and extracted with 3 × 30 mL of ether. The combined ether extracts were washed with 30 mL of water, 2 × 30 mL of saturated $NaHCO_3$, and 30 mL of saturated brine, and dried over $MgSO_4$. Removal of solvent left 2.64 g of red-brown oil which was purified by HPLC (1:3 ether/hexanes) to give 1.5 g (61% from compound 7) of the tricyclic enone 9: ^1H NMR (CCl_4) δ 1.36 (s, 3 H), 1.40 (s, 3 H), 1.74 (s, 3 H), 1.1–2.6 (m), and 5.5 (t, 1 H, J = 4); IR (neat) 3050, 1670, and 1610 cm^{-1}.

(b) A mixture of 95.3 g of 2-methylcyclohexanone (0.85 mol) and 157.9 g of 1-chloro-3-pentanone (1.31 mol) was taken up in 600 mL of dry benzene. This solution was charged with 9.5 g of anhydrous 2-naphthalenesulfonic acid and was heated at reflux under a nitrogen atmosphere. A large volume of gas was evolved during the first few hours. After refluxing for 3 $^3/_4$ days, the mixture was concentrated with a rotary evaporator to a thick orange residue, which was taken up in 400 mL of 20% aqueous KOH and 400 mL of methanol. The reaction mixture was heated at reflux for 7 h, then cooled, and concentrated with a rotary evaporator. The residue was partitioned between 1 L of water and 200 mL of ether, and the aqueous layer was extracted with three 200-mL portions of ether. The combined organic portions were extracted with 200 mL of brine, were dried ($MgSO_4$), and concentrated to give 172.9 g of orange liquid. Distillation of the crude product gave 97.4 g (64%) of octalone 3 as a clear liquid, bp 78 °C (0.2 torr), 5.6 g (4%) of slightly impure octalone 3, and 37.3 g (18%) of dienone 9 as a viscous yellow oil, bp 140–145 °C (0.25 torr), which crystallized on standing for several days.

To a solution of 5.54 g of prewashed NaH (0.23 mol) in 700 mL of dry THF and 70 mL of dry Me_2SO containing 0.475 mL of methanol was added 42 g of octalone 3 (0.236 mol). The resulting solution was heated at reflux under nitrogen for 4.5 h and was then cooled to −20 °C. A solution of 32.7 g of 1-chloro-3-pentanone in 100 mL of THF was added with vigorous stirring over a 30-min period, and the reaction mixture was stirred for 1 h at −20 °C and allowed to warm to room temperature over a 4-h period. The resulting tan suspension was concentrated with a rotary evaporator to 300 mL of oil, which was taken up in 300 mL of methanol and 300 mL of 20% aqueous KOH. The reaction mixture was heated at reflux for 7.5 h and was then cooled and concentrated with a rotary evaporator. The residue was taken up in 2 L of water and the aqueous solution was extracted with 4 × 350 mL of methylene chloride. The combined organic portions were extracted with 400 mL of brine, dried ($MgSO_4$), and concentrated to give 58.4 g of orange oil. Distillation of the crude product gave 17.15 g of starting octalone 3 (41%), contaminated with a trace of 9. The remaining 36.28 g of orange oil was predominately the desired dienone 9 (65%) contaminated with traces of other products. The material was used directly for further transformations.

(±)-*cis*-4,4a,6,7,8,8a,9,10-Octahydro-4a,8a-dimethyl-2-(3*H*)-phenanthrenone (13). To a rapidly stirring solution of 3.2 g (10 mmol) of mercuric acetate and 1.33 g (5 mmol) of compound 11 in 50 mL of glacial acetic acid was added 1.42 g (10 mmol) of boron trifluoride etherate. The resulting yellow solution was stirred at room temperature for 1.5 h, poured into 100 mL of saturated brine, and extracted with 3 × 30 mL of ether. The combined ether extracts were washed with 2 × 50 mL of half-saturated brine and saturated $NaHCO_3$ and dried over sodium

sulfate. Removal of the solvent left 1.4 g of diketone **12** as a viscous oil which was used for the next step without purification.

The crude diketone was suspended in 10 mL of a 1:1 mixture of 10% aqueous KOH and methanol and the resulting mixture was refluxed for 2 h, cooled to room temperature, and acidified with 10% aqueous HCl. The mixture was extracted with 3 × 10 mL of ether, and the combined ether extracts were washed with water, saturated $NaHCO_3$, and saturated brine and dried over $MgSO_4$. Removal of solvent yielded 1 g of an orange oil which was purified by HPLC (1:3 ether/petroleum ether) to give 0.45 g (45%) of the tricyclic enone **13**, along with small amounts of the precursor **3**: ^1H NMR (CCl_4) δ 1.35 (s, 3 H), 1.40 (s, 3 H), 5.48 (t, 1 H, J = 4), and 5.56 (s, 1 H); IR (neat) 3050, 1675, 1640, and 1612 cm^{-1}. The analytical sample, mp 91.5–92.5 °C, was obtained by crystallization from ether–hexanes. Anal. Calcd for $C_{12}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.64; H, 9.39.

(±)-*cis*-3′,4′,4′a,6′,7′,8′,8′a,9′-Octahydro-4′a,8′a-dimethylspiro[1,3-dioxolane-2,2′(1′*H*)-phenanthrene] (17). The tricyclic enone **13** (400 mg) was mixed with 2 mL of ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid in 20 mL of benzene, and the reaction mixture was refluxed under a Dean–Stark water separator for 16 h. The cooled reaction mixture was treated with a small amount of sodium bicarbonate, washed with 2 × 10 mL of saturated $NaHCO_3$ and 10 mL of saturated brine, and dried over Na_2CO_3. Removal of solvent left 440 mg of pale yellow oil which was homogeneous by TLC. This material was purified by passage through a short column of 8 g of basic alumina (grade III, eluted with 1:9 ether/hexanes) to give 390 mg (82%) of ketal **17**: ^1H NMR (CCl_4) δ 1.14 (s, 3 H), 1.21 (s, 3 H), 1.4–2.6 (m), 3.8 (s, 4 H), 5.22 (broad m, 1 H), and 5.43 (t, 1 H, J = 4); IR (neat) 3040, 1670, and 1090 cm^{-1}.

(±)-*cis*-4,4a,6,7,8,8a-Hexahydro-1,4a,8a-trimethyl-2(3*H*)-phenanthrenone (22). To a solution of 1.22 g (5 mmol) of the tricyclic dienone **9** and 1.48 g (10 mmol) of triethyl orthoformate in 10 mL of benzene was added 100 mg of *p*-toluenesulfonic acid, and the resulting red-brown solution was refluxed for 3 h. The solution was cooled, diluted with 30 mL of ether, and washed with 20 mL of 5% aqueous NaOH, water, and saturated brine. The aqueous solution was extracted with 10 mL of ether, and the combined ether extracts were dried over $MgSO_4$. Bulb-to-bulb distillation of the crude concentrated product gave 1.18 g (87%) of the ethyl enol ether **20** as a pale yellow oil: bp 100–110 °C (bath temp) (0.03 torr); ^1H NMR (CCl_4) δ 1.12 (s, 3 H), 1.23 (s, 3 H), 1.27 (t, 3 H, J = 7), 1.7 (s, 3 H), 3.74 (q, 2 H, J = 7), 5.4 (m, 2 H).

To a solution of 1.36 g (5 mmol) of enol ether **20** in 50 mL of a 5:95 water/acetone mixture was added a solution of 1.14 g (5 mmol) of DDQ in 10 mL of 5:95 water/acetone, dropwise. After 2 min, the red solution was passed through a column of 50 g of neutral alumina (Grade 1), which was washed with acetone until the color reached the base of the column. Removal of the solvent under reduced pressure afforded 1.4 g of a yellow oil which was chromatographed on a column of 35 g of silica gel (eluted with 1:9 ether/hexanes) to give 1 g (80%) of the tricyclic trienone **22**: IR (CH_2Cl_2) 1660, 1620, and 1575 cm^{-1}; ^1H NMR (CCl_4) δ 1.34 (s, 3 H), 1.37 (s, 3 H), 1.78 (s, 3 H), 5.44 (t, 1 H, J = 3), 5.85 (d, 1 H, J = 10), and 6.28 (d, 1 H, J = 10); mass spectrum 242 (M^+, 5.09), 227 (6.65), 199 (4.20), 171 (2.80); HRMS, found for $C_{17}H_{22}O$ 242.1664, calcd 242.1671.

(±)-*cis*-4,4a,8,8a,9,10-Hexahydro-1,4a,8a-trimethyl-2,6-(3*H*,7*H*)-phenanthrenedione (27). To a solution of 10.2 g (41 mmol) of dienone **9** in 200 mL of glacial acetic acid containing 5% of acetic anhydride was added 16.0 g of finely pulverized chromium trioxide (160 mmol). The temperature was maintained at about 25–35 °C with a water bath, and stirring was continued for 1.5 h. The resulting mixture was poured into 1 L of water and the whole was extracted with 4 × 150 mL of methylene chloride. The combined extracts were washed with 3 × 300 mL of ether and 2 × 300 mL of saturated, aqueous $NaHCO_3$. The methylene chloride solution was dried ($MgSO_4$) and evaporated under reduced pressure to obtain 8.56 g of diketone **27**, as a yellow oil. Although this material is pure enough for the subsequent ketalization step, it may be further purified by chromatography on silica gel, eluting with 2:1 hexanes/ethyl acetate. The analytical sample was a white solid: mp 137–139 °C; IR ($CHCl_3$) 2970, 2925, 2865, 1660, 1610, 1595, 1455, 1330, 1310, 1265, 1020, 825 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (s, 6 H), 1.77 (s, 3 H), 1.5–2.2 (m, 4 H), 2.5 (m, 6 H), 5.89 (s, 1 H). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.88; H, 8.43.

(±)-(1′α,4′aβ,8′aβ)-4′,4′a,7′,8′,8′a,9′-Hexahydro-1′,4′a,8′a-trimethylspiro[1,3-dioxolane-2,2′(1*H*)-phenanthren]-6′(3′*H*)-one (30). A solution of 2.77 g (10.7 mmol) of dienedione **27** in 200 mL of dry benzene was charged with 35 mL of ethylene glycol and 0.42 g of anhydrous 2-naphthalenesulfonic acid, and this mixture was heated at reflux through a Soxhlet apparatus containing a thimble filled with CaH_2. The thimble was recharged with fresh CaH_2 twice over a period of 5 days of reflux. The reaction mixture was cooled, charged with 1.0 mL of triethylamine, and was stirred for 2 h. The mixture was poured into 150 mL of water, the layers were separated, and the aqueous layer was extracted with three 100-mL portions of methylene chloride. The combined organic portions were extracted with 150 mL of brine, were dried ($MgSO_4$), and concentrated to give 3.82 g of the mixture of bisketal isomers **28** and **29** (103%) as an orange semisolid; IR ($CHCl_3$) 2980, 2940, 2880, 1655, 1595, 1450, 1350, 1265, 1240, 1170, 1070, 1010, 905 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (d, 3 H, J = 7), 1.14 (s, 3 H), 1.29 (s, 3 H), 1.5–1.9 (m, 8 H), 1.9–2.1 (m, 2 H), 2.7 (m, 1 H), 3.9 (m, 8 H), 5.45 (s, 1 H), 5.48 (m, 1 H).

To a solution of 3.82 g of crude bisketals in 300 mL of methylene chloride was added 16 g of silica and 3.8 mL of water. The reaction mixture was heated at reflux for 2 days, then cooled, and diluted with 200 mL of ethyl acetate. The resulting solution was dried ($MgSO_4$) and vacuum filtered through Celite with an additional 300 mL of ethyl acetate. The filtrate was concentrated to give 3.59 g of orange oil, which was chromatographed (150 g silica, 1:6 ethyl acetate/hexane, with increasing ethyl acetate) to yield 0.35 g (13%) of starting dienedione, 0.46 g (10%) of a mixed fraction, and 2.48 g (77%) of enone ketal **30** as a pale yellow solid, mp 98–104 °C. Recrystallization from ether gave colorless leaflets: mp 109–111 °C; IR (film) 2925, 1670, 1655, 1600, 1450, 1350, 1265, 1180, 1010, 905, 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (d, 3 H, J = 6), 1.28 (s, 3 H), 1.33 (s, 3 H), 1.5–2.9 (m, 6 H), 1.9–2.1 (m, 2 H), 2.35 (m, 2 H), 2.65 (m, 1 H), 3.83 (m, 4 H), 5.45 (dq, 1, J = 2, 4.5), 5.96 (s, 1 H). Anal. Calcd for $C_{19}H_{28}O_3$: C, 75.46; H, 8.67. Found: C, 75.51, H, 8.52.

(±)-(1′α,4a′β,4′bα,8′aβ)-4′,4′a,4′b,5′,7′,8′,8′a,9′-Octahydro-1′,4′a,8′a-trimethylspiro[1,3-dioxolane-2,2′(1′*H*)-phenanthren]-6′(3′*H*)-one (31). Into a 1-L, three-necked flask was distilled from sodium 500 mL of ammonia. Lithium wire (181 mg, 25.8 mmol) was cut from a spool and the pieces added rapidly to the ammonia, followed by 1.4 mL (17.2 mmol) of *tert*-butyl alcohol, which was added dropwise over a 5-min period. The unsaturated ketone **30** (2.53 g, 8.3 mmol) was dissolved in 100 mL of THF and added to the lithium/ammonia solution from a dropping funnel over a 10-min period. After 20 min, the blue color had discharged and a further 20.3 mg (2.9 mmols) of lithium was added. After a total reaction time of 30 min, methanol was added dropwise to discharge the remaining blue color and the ammonia was allowed to evaporate at room temperature overnight. At this point, 150 mL of water was added and the mixture was extracted with 3 × 150 mL of methylene chloride. The combined organic extracts were washed with 2 × 150 mL of water, dried ($MgSO_4$), and evaporated to obtain 2.4 g (97%) of ketone **31** as a clear oil, pure enough for use in the subsequent reaction. If desired, the material may be purified by chromatography on silica (eluting with 1:6 ethyl acetate/hexane): IR (film) 2965, 2940, 2880, 1710, 1455, 1390, 1345, 1240, 1190, 1010, 920, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (d, 3 H, J = 7), 1.05 (s, 3 H), 1.15 (s, 3 H), 1.5–1.9 (m, 7 H), 1.9–2.1 (m, 2 H), 2.1–2.5 (m, 4 H), 2.70 (m, 1 H), 3.92 (m, 4 H), 5.42 (m, 1 H).

Methyl (±)-(1′α,4′aβ,4′bα,8′aβ)-3′,4′,4′a,4′b,5′,6′,7′,8′,8′a,9′-Decahydro-1′,4′a,8′a-trimethyl-6′-oxospiro[1,3-dioxolane-2,2′(1′*H*)-phenanthrene]-7′-carboxylate (32). Ketone **31** (1.297 g, 4.26 mmol) was dissolved in 10 mL of a 2 M solution of methoxymagnesium methyl carbonate in dry DMF (Stiles reagent)[38] in a 50-mL pear-shaped flask. The resulting solution was heated at 110 °C for 6 h while a slow stream of nitrogen was bubbled through the mixture with a pipette. The reaction mixture, including semisolids, was treated with 100 mL of chilled 2.5% aqueous HCl and 50 mL of methylene chloride. The layers were separated and the aqueous layer was extracted with two 50-mL portions of methylene chloride and 50 mL of ethyl acetate. The

combined organic layers were concentrated to 50 mL, and this residue was treated with excess ethereal diazomethane for 20 min. The organic solution was dried ($MgSO_4$) and concentrated to give 1.61 g of yellow solid. The crude product was chromatographed (30 g silica, 1:9 ethyl acetate/hexane) to yield 1.38 g of keto ester **32** (90%) as a white solid, mp 49–61 °C. The material was recrystallized from ether/hexane to give cubes: mp 134–139 °C; IR ($CHCl_3$) 3600–3000, 2975, 2950, 2880, 1735, 1710, 1655, 1615, 1440, 1350, 1295, 1275 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92, 1.01, 1.03, 1.06, 1.11, 1.17 (singlets, total 9 H), 1.70 (m, 4 H), 1.9–2.1 (m, 4 H), 2.1–2.5 (m, 4 H), 2.73 (m, 1 H), 3.75 (s, 3 H), 3.95 (m, 4 H), 5.42 (s, 1 H). Anal. Calcd for $C_{21}H_{30}O_5$: C, 69.59; H, 8.34. Found: C, 69.76; H, 8.17.

Methyl (±)-(1′α,4′aβ,4′bα,8′aβ)-3′,4′,4′a,4′b,5′,6′,8′a,9′-Octahydro-1′,4′a,8′a-trimethyl-6′-oxospiro[1,3-dioxolane-2,2′-(1′*H*)-phenanthrene]-7′-carboxylate (33). A solution of 972.2 mg (2.68 mmol) of keto ester **32** in 7 mL of dry THF was added to a suspension of 91.7 mg (3.82 mmol) of prewashed NaH, and the mixture was stirred at room temperature for 30 min and then cooled to 0 °C. The pale yellow enolate solution was charged slowly with a solution of 542.8 mg (2.83 mmol) of phenylselenenyl chloride in 4 mL of THF. The resulting mixture was stirred at 0 °C for 20 min and then warmed to room temperature over a 20-min period. The volatiles were removed under reduced pressure to leave a yellow residue, which was taken up in 45 mL of methylene chloride and 15 mL of pH 7 phosphate buffer. The reaction mixture was treated with 0.3 mL of dry pyridine, was chilled to 0 °C, and was charged with 0.85 mL of 30% aqueous hydrogen peroxide (8.32 mmol). After 20 min at 0 °C, the mixture was warmed to room temperature and stirred for another 19 h. Reaction was quenched by the addition of 30 mL of pH 7 phosphate buffer and 0.9 g of $NaHSO_3$. The resulting mixture was stirred for 20 min and the layers were separated. The aqueous layer was extracted with two 40-mL portions of methylene chloride and 40 mL of ethyl acetate. The combined organic layers were extracted with 70 mL of 5% aqueous NaOH and with 70 mL of brine, were dried ($MgSO_4$), and concentrated to give 962.7 mg of yellow solid. The crude product was chromatographed (50 g of silica, 1:3 ethyl acetate/hexane) to yield 39.6 mg (4%) of **32** and 807.9 mg (84%) of unsaturated keto ester **33** as a white solid, mp 148–151 °C. The product was recrystallized from ether to give tiny needles: mp 152–155 °C; IR ($CHCl_3$) 2990, 2960, 2890, 1710, 1690, 1620, 1460, 1440, 1370, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (d, 3 H, J = 7), 1.22 (s, 3 H), 1.29 (s, 3 H), 1.5–1.9 (m, 4 H), 1.9–2.3 (m, 3 H), 2.3–2.6 (m, 2 H), 2.7 (m, 1 H), 3.84 (s, 3 H), 3.95 (m, 4 H), 5.4 (m, 1 H), 7.37 (s, 1 H). Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83. Found: 69.76; H, 7.77.

1,1-Dimethylethyl (±)-(1′α,4′aβ,4′bα,8′α,8′aβ)-3′,4′,4′a,4′b,5′,6′,7′,8′,8′a,9′-Decahydro-7′-(methoxycarbonyl)-1,4′a,8′a-trimethyl-6′-oxaspiro[1,3-dioxolane-2,2′-(1′*H*)-phenanthrene]-8′-acetate (39). A mixture of 2.51 g (6.97 mmols) of unsaturated keto ester **33** and 5.06 g (20 mmol) of ketene acetal **35**[41] in 50 mL of dry acetonitrile was subjected to 5.2 kbar pressure at 25 °C for eight days. After depressurization, TLC showed complete disappearance of starting **33**. The solvent was removed at reduced pressure and the residual yellow oil was dissolved in 250 mL of THF. A solution of 4.73 g (81.6 mmol) of KF in 50 mL of water was added and the resulting solution was stirred at room temperature for 7 h. The reaction mixture was partitioned between 300 mL of saturated brine and 150 mL of ethyl acetate and the layers were separated. The aqueous layer was further extracted with 2 × 150 mL of ethyl acetate. The combined extracts were dried over $MgSO_4$ and evaporated under reduced pressure to obtain a yellow, oily residue. This material was chromatographed (120 g of silica, 5:7 ethyl acetate/hexane) to obtain 3.17 g (95%) of **39** as a white solid. Recrystallization from methanol furnished the analytical sample as white needles: mp 156–157 °C; ^1H NMR ($CDCl_3$) δ 0.97 (s, 3 H), 1.01 (d, 3 H, J = 6), 1.14 (s, 3 H), 1.44 (s, 9 H), 1.6–2.0 (m, 5 H), 2.1 (m, 2 H), 2.2–2.6 (m, 4 H), 2.75 (m, 1 H), 2.89 (dd, 1 H, J = 3, 7.5), 3.75 (s, 3 H), 3.94 (m, 4 H), 5.42 (m, 1 H); IR (CH_2Cl_2) 2980, 2950, 2880, 1725, 1665, 1620, 1440, 1360, 1290, 1220, 1150, 920 cm^{-1}. Anal. Calcd for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 67.81; H, 8.33.

(±)-(4′α,4′a*S,5′aβ,6′aβ,10′aα,10′bβ)-Octahydro-4′,6′a,10′b-trimethylspiro[1,3-dioxolane-2,3′(4′*H*)-[2*H*]phenanthro-[8a,9-*b*]oxiren]-9′(5′a*H*)-one (42) and (±)-(4′α,4′a*R**,5′aα,6′aβ,10′aα,10′bβ)-Octahydro-4′,6′a,10′b-trimethylspiro[1,3-dioxolane-2,3′(4′*H*)-[2*H*]phenanthro[8a,9-*b*]oxiren]-9′(5′a*H*)-one (43).** (a) A solution of 403.6 mg (1.33 mmol) of unsaturated ketone **31** in 30 mL of dry methylene chloride was charged with 0.36 g of $NaHCO_3$ and cooled to 0 °C under a Drierite tube. To this solution was added 325.8 mg of 85% *m*-chloroperoxybenzoic acid (1.60 mmol). The reaction mixture was stirred at 0 °C for 21 h, and was then stirred vigorously for 45 min with 25 mL of 2.5% aqueous NaOH and 0.25 g of $NaHSO_3$. The mixture was diluted with 25 mL of water, and the layers were separated. The aqueous layer was extracted with 30 mL of methylene chloride and 30 mL of ethyl acetate. The combined organic layers were extracted with 25 mL of brine, dried ($MgSO_4$), and concentrated to give 398.2 mg of off-white semisolid. The crude product was chromatographed (40 g of silica, 1:4 ethyl acetate/hexane, increasing to 1:1) to yield five fractions: 23.5 mg (6%) of returned **31** as a pale yellow oil, 28.2 mg (7%) of a Baeyer–Villiger product, 80.5 mg (18%) of a product of Baeyer–Villiger oxidation and epoxidation, 31.2 mg (7%) of keto epoxide **43** as a pale yellow oil, and 220.3 mg (52%) of keto epoxide **42** as a white solid, mp 131–137 °C. Recrystallization of **42** from methylene chloride gave prisms, mp 149–151 °C.

Isomer 42: IR ($CHCl_3$): 2950, 1710, 1655, 1440, 1390, 1280 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.72 (d, 3 H, J = 6.7), 1.13 (s, 3 H), 1.17 (s, 3 H), 1.4–2.1 (m, 9 H), 2.2–2.5 (m, 5 H), 3.09 (dd, 1 H, J = 1.1, 3.3), 3.9 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 6.0, 16.2, 23.3, 29.8, 30.4, 31.4, 36.2, 37.1, 37.6, 37.7, 38.9, 43.6, 44.4, 53.2, 64.3, 65.0, 65.8, 110.3, 211.3. Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.34; H, 8.68.

Isomer 43: IR ($CHCl_3$) 2940, 2880, 1715, 1435, 1385, 1280 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.69 (d, 3 H, J = 7), 1.02 (s, 3 H), 1.1–1.8 (m, 7 H), 1.32 (s, 3 H), 1.8–2.5 (m, 7 H), 3.32 (s, 1 H), 3.93 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 5.4, 17.4, 19.1, 31.3, 32.3, 34.7, 36.6, 37.2, 38.4, 39.5, 39.8, 43.4, 49.8, 56.4, 63.3, 64.1, 65.5, 110.9, 211.1.

(b) A solution of 38.9 mg (0.199 mmol) of 1,1,3,3-tetrachloroacetone in 0.1 mL of 30% aqueous hydrogen peroxide (0.979 mmol) was stirred at room temperature for 15 min. The solution was charged with 29.1 mg (0.109 mmol) of $Na_2HPO_4 \cdot 7H_2O$ and then with 57.9 mg of unsaturated ketone **31** in 0.4 mL of chloroform. The reaction mixture was stirred at room temperature for 2.5 days and was then poured into 10 mL of methylene chloride and 10 mL of water containing 0.5 g $NaHSO_3$. After the mixture was shaken briefly, 8 mL of 5 M aqueous NaOH was added and the layers were separated. The aqueous layer was extracted with three 8-mL portions of methylene chloride and the combined organic portions were extracted with 15 mL of 5 M aqueous NaOH, 15 mL of water, and 15 mL of brine. The organic solution was dried ($MgSO_4$) and concentrated to give 53.1 mg of white solid. The crude product was chromatographed (5 g of silica, 1:4 ethyl acetate/hexane, then 1:1 ethyl acetate/hexane) to yield 19.0 mg (33%) of starting material as a pale yellow oil and 33.5 mg (55%) of **42** as a white solid. No trace of isomer **43** was detected by TLC or ^1H NMR spectroscopy.

Methyl (±)-(4′α,4′a*S,5′aβ,6′aβ,10′aα,10′bβ)-Decahydro-4′,6′a,10′b-trimethyl-9′-oxospiro[1,3-dioxolane-2,3′(4′*H*)-[2*H*]phenanthro[8a,9-*b*]oxirene]-8′-carboxylate (44).** A solution of 330.5 g (1.03 mmol) of epoxy ketone **42** in 8 mL of 2 M methoxymagnesium methyl carbonate in DMF in a pear-shaped flask was diluted with 4 mL of dry DMF and heated to 115 °C. A slow stream of nitrogen was bubbled through the solution with a pipette. After 8 h, the reaction mixture was cooled and poured into a mixture of 100 mL of chilled 2.5% aqueous HCl and 75 mL of methylene chloride. The resulting mixture was stirred vigorously for 5 min, and the layers were separated. The aqueous layer was extracted with 50-mL and 25-mL portions of methylene chloride and 25 mL of ethyl acetate. The combined organic layers were extracted with 50 mL of brine and concentrated to 10 mL, and the residue was treated with excess ethereal diazomethane. The ether solution was diluted with 150 mL of ethyl acetate, was dried ($MgSO_4$) and concentrated to give 393.6 mg of orange solid. The crude product was chromatographed (20 g of silica, 1:4 ethyl acetate/hexane) to yield 262.5 mg (67%) of **44** as a pale yellow solid: IR ($CHCl_3$) 3600–3000, 2980, 2945, 2885, 1715, 1650, 1610, 1435, 1355, 1280 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.72 (d, 3 H, J = 7), 0.93 (s, 3 H), 1.12 (s, 3 H), 1.2–2.5 (m, 14 H), 3.06 (s, 1 H), 3.74 (s, 3 H), 3.95 (m, 4 H).

Methyl (±)-(4′α,4′aS*,5′aβ,6′aβ,10′aα,10′bβ)-1′,5′a,6′,6′a,9′,10′,10′a,10′b-Octahydro-4′,6′a,10′b-trimethyl-9′-oxospiro[1,3-dioxolane-2,3′(4′H)-[2H]phenanthro[8a,9-b]oxirene]-8′-carboxylate (45). A suspension of 10.7 mg of prewashed NaH (0.446 mmol) in 1.0 mL of dry THF was charged with a solution of 117.0 mg (0.309 mmol) of keto ester **44** in 1.5 mL of THF. The resulting solution was stirred at room temperature for 30 min and was then cooled to 0 °C. The cold solution was treated with a solution of 62.2 mg of phenylselenenyl chloride in 1.5 mL of THF. The reaction mixture was stirred at 0 °C for 45 min, and the volatiles were removed under reduced pressure. The yellow residue was taken up in 12 mL of methylene chloride and 4 mL of pH 7 phosphate buffer. The solution was chilled to 0 °C and treated with 0.03 mL of pyridine and 0.10 mL of 30% aqueous hydrogen peroxide (0.979 mmol). The reaction mixture was stirred at 0 °C for 45 min, then warmed to room temperature, and stirred for 14 h. The mixture was charged with 25 mL of buffer, 10 mL of methylene chloride, and 66.0 mg of $NaHSO_3$. The layers were separated, and the aqueous layer was extracted with two 20-mL portions of methylene chloride and 20 mL of ethyl acetate. The combined organic layers were extracted with two 20-mL portions of chilled 2.5% aqueous NaOH and 40 mL of brine. The organic solution was dried ($MgSO_4$) and concentrated to give 103.9 mg of white solid. The crude product was chromatographed to yield 15.5 mg (13%) of returned **44** as a yellow solid and 77.9 mg (67%) of **45** as a white solid. Recrystallization from ether gave white needles: mp 171–176 °C; IR ($CHCl_3$) 3660, 3600–3000, 3030, 2985, 2955, 2890, 1725, 1680, 1615, 1435, 1365, 1295 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.73 (d, 3 H, J = 7.5), 1.21 (s, 6 H), 1.55 (m, 2 H), 1.80 (m, 2 H), 2.02 (m, 2 H), 2.37 (m, 4 H), 3.16 (s, 1 H), 3.80 (s, 3 H), 3.90 (m, 4 H), 7.20 (s, 1 H).

1,1-Dimethylethyl (±)-(4′α,4′aS*,5′aβ,6′aβ,7′aα,10′aα,10′bβ)-Decahydro-8′-(methoxycarbonyl)-4′,6′a,10′b-trimethyl-9′-oxospiro[1,3-dioxolane-2,3′(4′H)-[2H]phenanthro[8a,9-b]oxirene]-7′-acetate (46). (a) A solution of 50 mg (0.31 mmol) of unsaturated keto ester **45** and 100.5 mg of 1-(*tert*-butoxy)-1-(*tert*-butyldimethylsilyl)oxy]ethylene in 1 mL of acetonitrile was compressed at 15 kbar for 24 h. Concentration gave 115.8 mg of pale yellow oil. This residue was dissolved in 5 mL of THF and treated with a solution of 100 mg of KF in 1 mL of water. The reaction mixture was stirred at room temperature for 7 h and was then partitioned between 15 mL of brine and 10 mL of ethyl acetate. The aqueous layer was extracted with two 10-mL portions of ethyl acetate. The combined organic portions were dried ($MgSO_4$) and concentrated to give a yellow oil, which was purified by preparative TLC (1:1 ethyl acetate/petroleum ether) to yield 2.9 mg (6%) of returned **45** and 52.5 mg (81%) of **46** as a white solid, mp 162–176 °C. The analytical sample was obtained as small white crystals, mp 185–188 °C, by recrystallization from methanol: IR (CH_2Cl_2) 3030, 2960, 2950, 2880, 1720, 1650, 1615, 1440, 1360, 1290, 1210, 1145, 1090, 1045, 950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.72 (d, 3 H, J = 6.7), 1.03 (s, 3 H), 1.15 (s, 3 H), 1.44 (s, 9 H), 1.55 (m, 2 H), 1.80 (m, 3 H), 1.9–2.2 (m, 5 H), 2.43 (m, 2 H), 2.58 (t, 1 H, J = 3.5), 3.05 (d, 1 H, J = 3.7), 3.08 (s, 2 H), 3.70 (s, 3 H), 3.99 (m, 4 H). Anal. Calcd for $C_{27}H_{40}O_8$: C, 65.99; H, 8.26. Found: C, 65.83; H, 8.18.

(b) A solution of 506 mg of compound **39** and 233 mg of 85% *m*-chloroperoxybenzoic acid (1.1 mmol) in 3 mL of methylene chloride was stirred at room temperature for 5 min. Reaction was quenched by vigorous shaking of the methylene chloride solution with 10 mL of 10% aqueous sodium carbonate. After drying over $MgSO_4$, the solvent was removed under reduced pressure to obtain 460 mg (88%) of epoxide **46** as a white solid. Recrystallization from methanol gave white crystals, mp 185–188 °C, identical in all respects with the material prepared as in part a.

1,1-Dimethylethyl (±)-(4′α,4′aS*,5′aβ,6′aβ,7′α,8′β,10′aα,-10′bβ)-Decahydro-8′-hydroxy-8′-(methoxycarbonyl)-4′,6-a,10′b-trimethyl-9′-oxospiro[1,3-dioxolane-2,3′(4′H)-[2H]-phenanthro[8a,9-b]oxirene]-7′-acetate (47). (a) A solution of 51.1 mg (0.1 mmol) of **39** and 91.2 mg of 85% *m*-chloroperoxybenzoic acid (0.3 mmol) in 0.3 mL of methylene chloride was stirred at room temperature for 3 h. The reaction mixture was extracted with 3 × 5 mL of 10% aqueous sodium carbonate, dried ($MgSO_4$), and evaporated under reduced pressure to obtain 52.3 mg (98%) of **47** as a white solid. Recrystallization from methanol gave white crystals: mp 186–190 °C; IR (CH_2Cl_2) 3450, 2950, 2900, 1760, 1730, 1460, 1390, 1370, 1240, 1160, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.23 (s, 1 H), 3.8–4.1 (m, 4 H), 3.72 (s, 3 H), 3.05 (t, 1 H, J = 1), 2.90 (dd, 1 H, J = 8, 3), 0.8–2.55 (m, 10 H), 1.40 (s, 9 H), 1.20 (s, 3 H), 0.68 (d, 3, J = 7). Anal. Calcd for $C_{27}H_{40}O_9$: C, 63.76; H, 7.92. Found: C, 63.48; H, 7.77.

(±)-(4aα,4bβ,8aα,10β)-4,4a,4b,7,8,8a,9,10-Octahydro-10-hydroxy-1,4a,8a-trimethylphenanthrene-2,6(3H,5H)-dione (49). Lithium diethylamide was prepared by adding 0.105 mL (73.5 mg, 1.0 mmol) of diethylamine (freshly distilled from calcium hydride) to a solution of 0.76 mL of 1.5 M *n*-butyllithium (1.12 mmol) in 0.6 mL of dry ether at 0 °C. After 10 min, a solution of 66 mg (0.22 mmol) of epoxide **42** in 0.4 mL of ether was added and the reaction mixture was heated at reflux for 1 h. Reaction was quenched by addition of 1 mL of 5% aqueous HCl and the mixture was stirred for 1 h at room temperature with 2 mL of THF. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 5 mL). The combined organic phases were washed with brine (2 × 5 mL), dried, and evaporated. The resulting yellow oil was chromatographed on 3 g of silica, yielding 13.3 mg (24%) of white crystals: mp 193–196 °C; ^1H NMR ($CDCl_3$) δ 4.88 (dd, 1 H, J = 9, 5.1), 2.4 (m, 6 H), 2.05 (s, 3 H), 1.33 (s, 3 H), 1.19 (s, 3 H), 2.0–0.9 (m, 7 H); IR (CH_2Cl_2) 3600, 3500, 2980, 2920, 1710, 1660, 1300, 1290, 1190, 1150, 1110 cm^{-1}; MS (70 eV) 276 (parent), 55 (base); HRMS calcd for $C_{17}H_{24}O_3$, M^+ 276.1726, found 276.1717.

(±)-(1′α,4′aβ,4′bα,8′aβ,10′β,10′aα)-Decahydro-10′a-hydroxy-1′,4′a,8′a-trimethyl-10′-(phenylseleno)spiro[1,3-dioxolane-2,2′(1′H)-phenanthren]-6′(3′H)-one (50). Epoxide **42** (198 mg, 0.62 mmol) was taken up in a solution made up with diphenyl diselenide (577 mg, 1.85 mmol), $NaBH_4$ (281.2 mg, 7.3 mmol), and ethanol (2 mL, anhydrous commercial absolute ethanol was distilled from magnesium ethoxide before use). The reaction mixture was heated at reflux for 1.5 h. After cooling, the solvent was removed, yielding a sticky yellow residue, which was taken up in 5 mL of methylene chloride and extracted with 5% HCl (3 × 5 mL) and water (5 mL). Drying and removal of the solvent furnished a yellow residue which was chromatographed (8 g of silica, 5:7 ethyl acetate/hexane) to afford 233 mg (77%) of white crystals: mp 161–162 °C (MeOH); ^1H NMR ($CDCl_3$) δ 7.5 (m, 2 H), 7.2 (m, 3 H), 4.15 (s, 1 H), 3.95 (m, 4 H), 3.4 (dd, 1 H, J = 2.5, 5.5), 2.7 (q, 1 H, J = 6), 2.5–2.2 (m, 6 H), 1.9 (dd, 1 H, J = 15, 3), 1.7–1.2 (m, 6 H), 1.6 (s, 3 H), 1.2 (s, 3 H), 1.0 (d, 3 H, J = 6); IR (CH_2Cl_2) 3500, 2960, 2900, 1705, 1560, 1460, 1440, 1350, 1300, 1200, 1140, 950 cm^{-1}. Anal. Calcd for $C_{25}H_{34}O_4Se$: C, 62.88; H, 7.17. Found: C, 62.71; H, 7.06.

(±)-(1′α,4′aβ,4′bα,8′aβ,10′aα)-4′,4′a,4′b,5′,7′,8′,8′a,10′a-Octahydro-10′a-hydroxy-1′,4′a,8′a-trimethylspiro[1,3-dioxolane-2,2′(1′H)-phenanthren]-6′(3′H)-one (51). A solution of 230 mg (0.48 mmol) of selenide **50** in 3.5 mL of methylene chloride was treated with 194 mg of 85% *m*-chloroperoxybenzoic acid (0.96 mmol) at −78 °C. The mixture was stirred for 1 h at −78 °C and 15 mL of 10% aqueous sodium carbonate was added all at once as the mixture was vigorously stirred. The layers were separated and the organic layer was washed with a further 10 mL of 10% sodium carbonate solution, dried, and evaporated. The resulting clear oil was triturated with petroleum ether to obtain 153 mg (95%) of white crystals: mp 159–160 °C; IR (CH_2Cl_2) 3500, 2950, 2900, 1700, 1460, 1400, 1360, 1190, 1170, 1140, 1100, 1040, 960, 940 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.78 (s, 1 H, J = 10), 5.63 (d, 1 H, J = 10), 3.95 (m, 5 H), 2.7 (dd, 1 H, J = 6, 19), 2.1–2.5 (m, 5 H), 1.45–1.75 (m, 5 H), 1.25 (m, 1 H), 1.12 (s, 3 H), 1.01 (d, 3 H, J = 6), 0.92 (s, 3 H). Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.21; H, 8.91. Found: C, 71.03; H, 8.90.

(±)-(4aα,4bβ,8aα)-4,4a,4b,7,8,8a-Hexahydro-1,4a,8a-trimethyl-2,6(3H,5H)-phenanthrenedione (52). Allylic alcohol **51** (20.2 mg, 0.063 mmol) was dissolved in 0.6 mL of THF and 0.5 mL of 5% HCl was added. Stirring was continued for 15 h at room temperature. Neutralization was then effected by addition of 10 mL of saturated $NaHCO_3$. Extraction with methylene chloride (3 × 5 mL), drying, and evaporation afforded diketone **52** as a pale yellow solid (15.2 mg, 93%). Crystallization from methylene chloride/hexane gave white needles: mp 139–140 °C; ^1H NMR ($CDCl_3$) δ 6.48 (d, 1 H, J = 10), 6.10 (d, 1 H, J = 10), 2.5 (m, 6 H), 1.87 (s, 3 H), 1.45 (s, 3 H), 1.13 (s, 3 H), 2.0–1.2 (m, 5 H); IR (CH_2Cl_2) 3040, 2980, 2940, 1710, 1650, 1620, 1420, 1240

cm^{-1}. Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.02; H, 8.53.

1,1-Dimethylethyl (±)-(1′α,4′aβ,4′bα,8′α,8′aβ,10′β,10′aα)-Dodecahydro-10a′-hydroxy-7′-(methoxycarbonyl)-1′,4′a,8′a-trimethyl-6′-oxo-10′-(phenylseleno)spiro[1,3-dioxolane-2,2′-(1′H)-phenanthrene]-8′-acetate (53). Epoxide **46** (503 mg, 1.02 mmol) was taken up in a solution of 949 mg (3.04 mmol) of diphenyl diselenide and 460 mg (11.3 mmol) of sodium borohydride in 3 mL of absolute ethanol. The mixture was refluxed for 1.5 h and the solvent was then evaporated under reduced pressure. The yellow residue was taken up in 10 mL of methylene chloride and extracted with 3 × 5 mL of 5% aqueous HCl and then with 5 mL of water. The methylene chloride solution was dried over $MgSO_4$ and then treated with a solution of diazomethane in ether (prepared from the reaction of 7.5 g of *N*-(nitrosomethyl)urea with 9 g of KOH in 23 mL of water and 75 mL of ether). After a few minutes, the excess diazomethane was destroyed by the dropwise addition of acetic acid. Evaporation of the solvent gave a yellow oil, which was chromatographed (30 g of silica, 5:7 ethyl acetate/hexane) to yield 376 mg (57%) of allylic alcohol **53**, as a white solid. Crystallization from ethanol gave white crystals: mp 163–164 °C; IR (CH_2Cl_2) 3500, 2950, 2880, 1720, 1650, 1620, 1440, 1360, 1280, 1220, 1140, 1110, 1060, 1050, 950, 920 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.50 (m, 2 H), 7.30 (m, 3 H), 4.00 (s, 1 H), 3.95 (m, 4 H), 3.70 (s, 3 H), 3.38 (dd, 1 H, *J* = 1.5, 5), 2.4–2.8 (m, 3 H), 2.15 (br s, 3 H), 0.8–2.0 (m, 6 H), 1.40 (s, 3 H), 1.35 (s, 9 H), 1.20 (s, 3 H), 0.95 (d, 3 H, *J* = 7). Anal. Calcd for $C_{33}H_{46}O_8Se$: C, 61.01; H, 7.13. Found: C, 60.86; H, 7.13.

In addition, the foregoing chromatographic purification gave 130 mg of unchanged epoxide **46**. Thus, the yield of hydroxy selenide **53**, based on unrecovered epoxide, is 78%.

1,1-Dimethylethyl (±)-(1′α,4′aβ,4′bα,8′α,8aβ,10′aα)-3′,4′,4′a,4′b,5′,6′,7′,8′,8′a,10′a-Decahydro-10′a-hydroxy-7′-(methoxycarbonyl)-1′,4′a,8′a-trimethyl-6′-oxospiro[1,3-dioxolane-2,2′(1′H)-phenanthrene]-8′-acetate (40). To a solution of 213 mg (0.43 mmol) of selenide **53** in 3.5 mL of methylene chloride at −78 °C was added 194 mg of 85% *m*-chloroperoxybenzoic acid (0.96 mmol). The mixture was stirred at −78 °C for 1 h and 10 mL of 10% aqueous sodium carbonate was added with vigorous stirring. The mixture was allowed to warm to room temperature, and the phases were separated. The organic layer was extracted with a second 10-mL portion of 10% sodium carbonate solution. After drying over $MgSO_4$, the solvent was removed under reduced pressure to afford 159 mg of **40** as a clear oil that solidified upon standing. Crystallization from methylene chloride–petroleum ether furnished white crystals: mp 166–170 °C; IR (CH_2Cl_2) 3500, 2950, 2900, 1720, 1640, 1610, 1440, 1420, 1220, 1140, 950, 850 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.82 (d, 1 H, *J* = 10), 5.58 (d, 1 H, *J* = 10), 3.95 (m, 4 H), 3.78 (s, 1 H), 3.70 (s, 3 H), 2.45–2.75 (m, 3 H), 2.00–2.20 (m, 4 H), 1.2–1.8 (m, 3 H), 1.42 (s, 9 H), 1.02 (s, 3 H), 0.98 (d, 3 H, *J* = 7), 0.94 (s, 3 H). Anal. Calcd for $C_{27}H_{40}O_8$: C, 65.83; H, 8.18. Found: C, 65.54; H, 8.07.

1,1-Dimethylethyl (±)-(1α,4aα,4bβ,10aβ)-1,2,3,4,4a,4b,5,6,7,10a-Decahydro-2-(methoxycarbonyl)-4b,8,10a-trimethyl-3,7-dioxo-1-phenanthreneacetate (54) and (+)-(1α,4aβ,4bβ,10aβ)-1,2,3,4,4a,4b,5,6,7,10a-Decahydro-2-(methoxycarbonyl)-4b,8,10a-trimethyl-3,7-dioxo-1-phenanthreneacetic Acid (55). (a) A solution of 45.8 mg (0.093 mmol) of allylic alcohol **40** and 3 mL of 10% aqueous HCl in 5 mL of THF was stirred for 4 h at 25 °C. The reaction mixture was partitioned between 20 mL of saturated brine and 20 mL of ethyl acetate. The layers were separated and the organic phase was dried and evaporated to obtain a yellow oil. Chromatography of this material (10 g of silica, 9:1 ethyl acetate/methanol) gave 12.8 mg (39%) of ester **54** and 5.3 mg (14%) of acid **55**, both as white solids. An identical experiment, except that a reaction time of 72 h was employed, gave 38% of **54** and 17% of **55**.

Ester 54. The analytical sample, mp 145–147 °C, was obtained by recrystallization from methylene chloride–petroleum ether: IR (CH_2Cl_2) 2980, 1720, 1655, 1645, 1610, 1350, 1210, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.50 (d, 1 H, *J* = 8.5), 6.08 (d, 1 H, *J* = 8.5), 3.78 (s, 3 H), 3.04 (dd, 1 H, *J* = 4.5, 3), 1.3–2.7 (m, 10 H), 1.87 (s, 3 H), 1.47 (s, 9 H), 1.22 (s, 3 H), 1.16 (s, 3 H). Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.53; H, 7.87.

Acid 55. The analytical sample was obtained as a white powder, mp 225–230 °C, by crystallization from chloroform–hexane: IR (CH_2Cl_2) 2700–3700, 1730, 1710, 1650, 1620, 1440, 1260, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.53 (d, 1 H, *J* = 10), 6.08 (d, 1 H, *J* = 10), 3.76 (s, 3 H), 2.94 (dd, 2 H, *J* = 4.5, 4), 2.1–2.7 (m, 10 H), 1.85 (s, 3 H), 1.24 (s, 3 H), 1.16 (s, 3 H); MS (70 eV) 374 (M$^+$, 0.04), 3.42 (0.1), 314 (1.37), 1.88 (2.4), 145 (2.7), 44 (base); HRMS, calcd for $C_{21}H_{26}O_6$ 374.1729, found 374.1733.

(b) A solution of 49.7 mg (0.1 mmol) of allylic alcohol **40** and 2 mg of anhydrous 2-naphthalenesulfonic acid in 1 mL of toluene was refluxed for 3 h and was then cooled and washed with 2 × 5 mL of aqueous sodium bicarbonate. After evaporation of solvent, the residue was chromatographed (10 g silica, 9:1 ethyl acetate/methanol) to obtain 14.3 mg (38%) of crystalline acid **55** and 6 mg of a mixture of less polar material, containing some lactone **41**, as evidenced by its characteristic ^{1}H NMR signals (vide infra).

Methyl (±)-(13β)-3,3-(1,2-Ethanediyldioxy)-12,16-dioxopicras-5-en-21-oate (41) and 1,1-Dimethylethyl (±)-(1′α,4′aβ,4′bα,8′α,8′aβ)-3′,4′,4′a,4′b,5′,6′,7′,8′,8′a,9-Decahydro-7′-(methoxycarbonyl)-1′,4′a,8′a-trimethyl-6′,9′-dioxospiro-[1,3-dioxolane-2,2′(1′H)-phenanthrene]-8′-acetate (57). Pyridinium chlorochromate (103.2 mg, 0.4 mmol) was added to a solution of 50.1 mg (0.1 mmol) of alcohol **40** in 1 mL of methylene chloride. After 2 h at 25 °C, 20 mL of diethyl ether was added, and the resulting turbid solution was filtered through a short plug of $MgSO_4$. Evaporation of solvent and chromatography of the residue (2.5 g of silica, 2:1 ethyl acetate/petroleum ether) yielded 5 mg (10%) of starting material, 24.0 mg (56%) of lactone **41**, and 6.8 mg (14%) of enone **57**.

Lactone 41: white needles: mp 225–230 °C dec (obtained from ether or from ethyl acetate–hexane); IR (CH_2Cl_2) 3060, 2960, 2890, 1730, 1660, 1440, 1220, 1070, 1010, 910 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.62 (dd, 1 H, *J* = 7, 2), 4.60 (dd, 1 H, *J* = 7, 1.8), 3.90 (m, 4 H), 3.80 (m, 4 H), 1.0–2.9 (m, 12 H), 1.20 (s, 3 H), 1.05 (d, 3 H, *J* = 8), 1.00 (s, 3 H). Anal. Calcd for $C_{27}H_{30}O_7$: C, 66.01; H, 7.22. Found: C, 66.25; H, 7.21.

Enone 57. The analytical sample, mp 136–138 °C, was obtained by recrystallization from ethyl acetate–hexane: IR (CH_2Cl_2) 3050, 2980, 2940, 1720, 1660, 1620, 1440, 1360, 1220, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.92 (d, 1 H, *J* = 1.8), 3.95 (m, 4 H), 3.78 (s, 3 H), 3.39 (dd, 1 H, *J* = 6.5, 4.5), 1.85 (br q, 1 H, *J* = 7), 2.45 (m, 4 H), 1.2–2.1 (m, 6 H), 1.60 (s, 3 H), 1.40 (s, 9 H), 1.15 (s, 3 H), 1.10 (d, 3 H, *J* = 7). Anal. Calcd for $C_{27}H_{38}O_8$: C, 66.10; H, 7.81. Found: C, 66.00; H, 7.79.

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Registry No. **3**, 54832-12-1; **4**, 13652-02-3; **5**, 91191-66-1; **6**, 91191-67-2; **7**, 91191-68-3; **8**, 91201-25-1; **9**, 91237-33-1; **10**, 10075-38-4; **11**, 91191-69-4; **12**, 91201-37-5; **13**, 91191-70-7; **14**, 32830-97-0; **17**, 91191-71-8; **20**, 91191-72-9; **22**, 91191-73-0; **27**, 91191-74-1; **28**, 91191-75-2; **29**, 91191-76-3; **30**, 91191-77-4; **31**, 91191-78-5; **32**, 91191-79-6; **33**, 89337-65-5; **35**, 74786-02-0; **39**, 91191-80-9; **40**, 91191-81-0; **41**, 91278-63-6; **42**, 91191-82-1; **43**, 91237-34-2; **44**, 91201-38-6; **45**, 91191-83-2; **46**, 91191-84-3; **47**, 91191-85-4; **49**, 91208-69-4; **50**, 91191-86-5; **51**, 91191-87-6; **52**, 91191-88-7; **53**, 91191-89-8; **54**, 91191-90-1; **55**, 91191-91-2; **57**, 91191-92-3; 2-pentyn-1-ol, 6261-22-9; 3-chloro-2-penten-1-ol, 91201-39-7; propionyl chloride, 79-03-8; ethylene, 74-85-1; 2-methylcyclohexanone, 583-60-8.

Supplementary Material Available: Experimental procedure for the X-ray structure, table of atomic coordinates, general temperature factor expressions, bond distances, bond angles, torsion angles, and notes on the structure (14 pages). Ordering information is given on any current masthead page.