Lewis Acid and Photochemically Mediated Cyclization of Olefinic β-Keto Esters[1]

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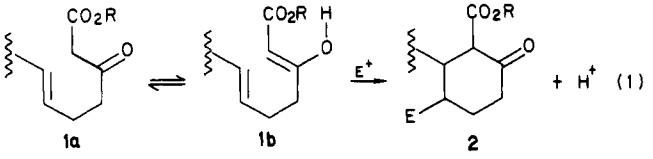
Olefinic β-keto esters **8**, **17**, and **20**, prepared by either carbomethoxylation of the parent ketone or alkylation of the dianion of methyl acetoacetate with the allylic bromide, underwent cyclization with stannic chloride in dichloromethane to give mono- and bicyclic keto esters **10** and **18**, respectively. The latter was transformed via ketone **24** to $\Delta^{8(14)}$-podocarpen-13-one (**27**) and to keto acid **29**, an intermediate in the synthesis of ambreinolide. Keto ester **46**, prepared by condensation of the dianion of methyl acetoacetate with β-cyclocitral, gave **56** as the major product upon irradiation in neutral solution but, in the presence of sodium methoxide, a mixture (ca. 1:1) of **45** and **65** was produced in 66% yield. Enol derivatives **52**, **53**, and **54** of **46** underwent 1,5-hydrogen migration upon photolysis to give **55**, **58**, and **59**. The dark transformation of **56** to **47** with triethylamine revealed a pathway to this pyranoid structure unrecognized in previous photochemical studies of β-ionone, and the conversion of **47** to **45** and **65** upon irradiation in the presence of sodium methoxide suggests a mechanistic hypothesis for these light-induced reactions involving a manifold of equilibrating enolates which terminate at **45**.

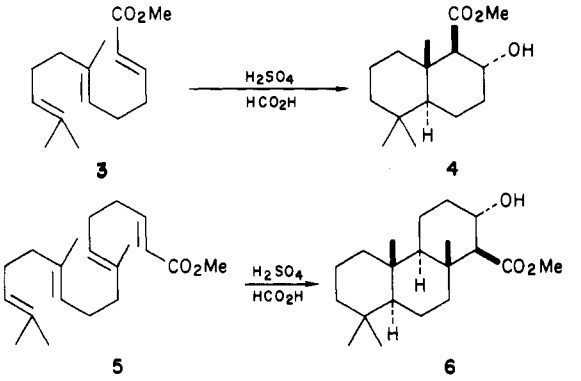
The synthesis of carbocyclic structures by electrophilic cyclization of 1,5-dienes, originally inspired by the Ruzicka isoprene hypothesis,[3] was first reduced to practical terms through the elegant studies of Eschenmoser[4] and Stork.[5] Numerous elaborations have been woven around the fabric of this reaction, including biomimetic variations which the Stanford school, in particular, have exploited with conspicuous success.[6] As a result of these developments, polyolefin cyclizations can now afford a dramatically efficient as well as aesthetically pleasing route to the skeleta of higher terpenoids and steroids.[7]

A contributing factor to progress in this area has been the recognition that careful attention must be paid to the initiation of olefin cyclization, and it is now clear that the selection of the electrophile, reaction conditions, and substrate functionality for inducing ring closure are critically important. Limited consideration has been given to the cyclization terminator unit although this, in principle, can lend greatly increased versatility to olefin cyclization. In seeking to broaden the basis underlying the Eschenmoser–Stork strategem, we were attracted to olefinic β-keto esters (**1a**) as cyclization substrates in the belief that enol tautomer **1b** would represent a good candidate for the electrophile-mediated ring closure depicted in eq 1. In addition, the residual β-keto ester moiety in **2** would afford a convenient seat for the annexation of additional structure, including rings not readily accessible via direct cyclization. This appeared to be particularly significant in view of the observation that, while the acid-catalyzed cyclization of triene **3** gave **4** in 70% yield,[8] the homologous tetraene **5** provided **6** in only 5–10% yield.[9]



(1)

We describe herein the synthesis of certain olefinic β-keto esters which undergo efficient cyclization in the presence of stannic chloride.[10] In addition, we describe the synthesis of a conjugated dienone ester, the enolate of which upon irradiation undergoes a sequence of discrete reactions leading ultimately to cyclization.[11] This process afforded an unsaturated variant of the carbocycle obtained from Lewis acid-catalyzed cyclization.



Results

ϵ-Alkenyl β-keto esters of type **1a** are accessible, in principle, via alkylation of the dianion of a keto ester[12] with an allylic halide. Although Casey and Marten reported that alkylation of the dianion of methyl acetoacetate with 1-bromo-3-methylbut-2-ene (**7**) affords **8**,[13] it was found more convenient to prepare this substrate by carbomethoxylation of the anion of 6-methylhept-5-en-2-one (**9**) with dimethyl carbonate. This route, which led to **8** in 65% yield, avoids the lachrymatory bromide **7**. After considerable experimentation, it was found that the optimum conditions for cyclization of **8** to **10** entailed exposure of the former to 1.5 equiv of stannic chloride in dichloromethane, initially at 0 °C and then at room temperature for several hours. This protocol gave the cyclohexanone derivative **10** in 73% yield after chromatography. Sum and

(1) Abstracted from the Ph.D. thesis of R.W.S., Oregon State University, 1979.
(2) National Institutes of Health Postdoctoral Fellow, 1974–1975.
(3) Ruzicka, L. *Angew. Chem.* **1938**, *51*, 5.
(4) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890.
(5) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068.
(6) Johnson, W. S. *Acc. Chem. Res.* **1968**, *1*, 1. van Tamelen, E. E. *Ibid.* **1968**, *1*, 111.
(7) An interesting retrospective view can be found in Fleming, I. "Selected Organic Syntheses: A Guidebook for Organic Chemists"; Wiley: London, 1973; pp 156–164.
(8) Stadler, P. A.; Nechvatal, P. A.; Frey, A. J.; Eschenmoser, A. *Helv. Chim. Acta* **1957**, *40*, 1373.
(9) Eschenmoser, A.; Felix D.; Gut, M.; Meier, J.; Stadler, P. A. In "The Ciba Foundation Symposium on the Biosynthesis of Terpenes and Sterols"; Wolstenholme, G.E.W., O'Connor, M., Eds.; J. and A. Churchill: London, 1959; pp 217–227.
(10) Skeean, R. W.; Trammell, G. L.; White, J. D. *Tetrahedron Lett.* **1976**, 525. See also: van Tamelen, E. E.; Hwu, J. R.; Leiden, T. M. *J. Chem. Soc., Chem. Commun.* **1983**, 62.
(11) White, J. D.; Skeean, R. W. *J. Am. Chem. Soc.* **1978**, *100*, 6296.
(12) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.
(13) Casey, C. P.; Marten, D. F. *Synth. Commun.* **1973**, 321.

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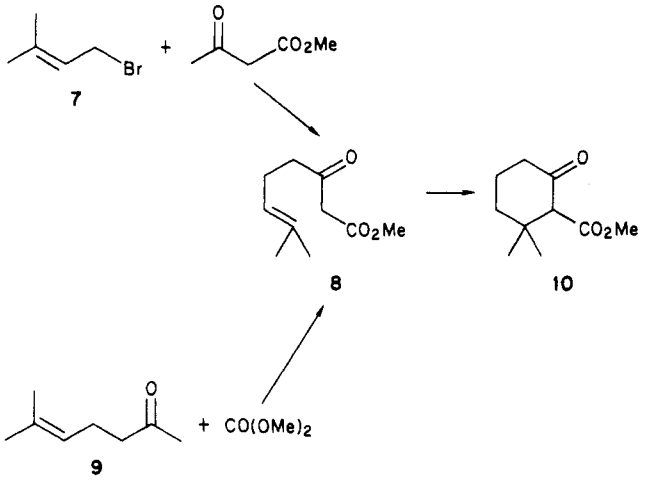
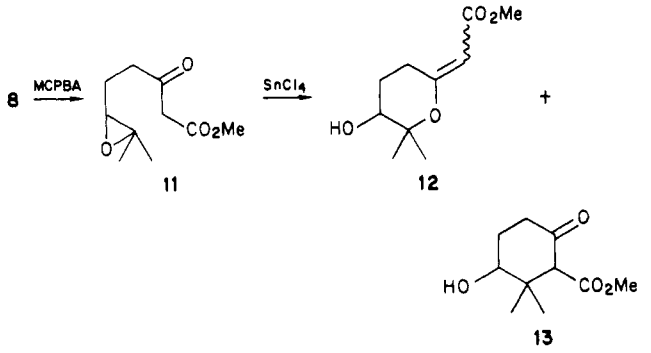
Weiler have also reported the transformation of 8 to 10 by a similar procedure.[14]

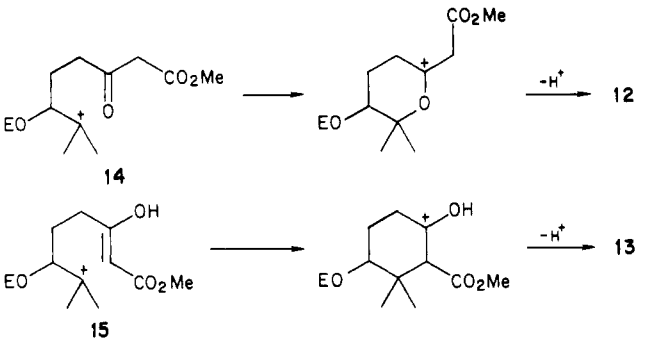


In an attempt to extend this cyclization to the preparation of a cyclohexanone bearing a hydroxyl substituent at the "biogenetic" site adjacent to the geminal methyl groups, the epoxide 11 was prepared by treatment of 8 with

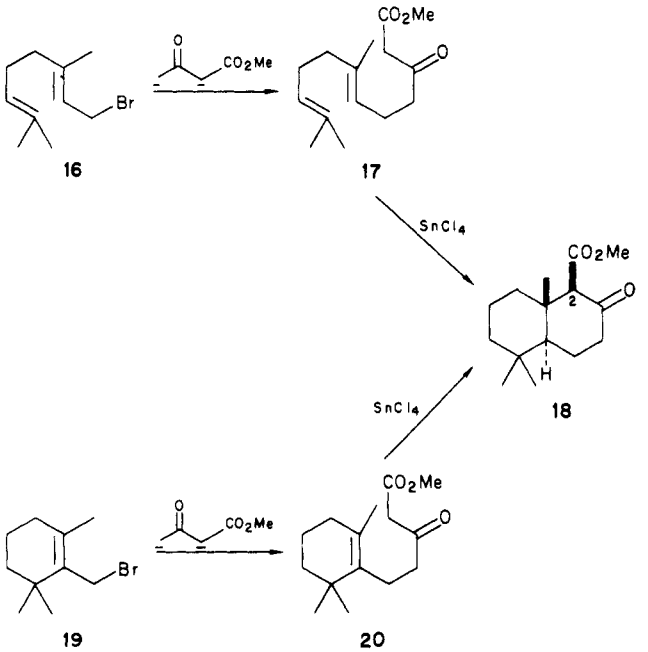


m-chloroperbenzoic acid. In contrast to the clean transformation of 8 to 10, exposure of 11 to stannic chloride in dichloromethane gave a complex mixture, from which the tetrahydropyran 12 was separated as the major product (45%) by chromatography. The carbocycle 13 was obtained in only 18% yield as an inseparable mixture of cis and trans isomers. That fundamentally different mechanisms were operating in the cyclization of 8 and 11 was apparent from the fact that the latter was consumed rapidly at −70 °C with only a catalytic quantity of the Lewis acid. Moreover, the reaction of 11 was relatively insensitive to the acid catalyst employed, since zinc chloride, *p*-toluenesulfonic acid, and even residual *m*-chlorobenzoic acid from the epoxidation of 8 gave similar ratios of 12:13. It was demonstrated that 12 and 13 were not interconverted under the reaction conditions, and it is tempting to speculate that these two products arise from closure of keto and enol tautomers of the intermediate carbocations 14 and 15, respectively. The absence of a heterocycle analogous to 12 from cyclization of 8 with stannic chloride, together with the requirement of >1 equiv of Lewis acid for this reaction, suggests that a tin(IV) enol complex may be the effective nucleophile which closes upon the carbocationic intermediate in this case. Mechanistic evidence bearing on this point will be disclosed subsequently.

The carbocycle synthesis expressed in the conversion of 8 to 10 would obviously have broader utility if it could be extended to the prenyl homologue 18 of 10. This was



accomplished by two routes. In the first, the dianion of methyl acetoacetate was alkylated with geranyl bromide (16)[15] to provide keto ester 17 which, upon treatment with stannic chloride in dichloromethane, gave the crystalline bicyclic product 18 in 53% yield. This substance possessed spectral properties identical with those reported for the product obtained by esterification and oxidation of 4,[16] confirming the trans ring fusion and equatorial orientation of the ester substituent. A second route to 18 was opened from the monocyclic precursor 20, prepared by alkylation of the dianion of methyl acetoacetate with cyclogeranyl bromide (19).[17] Cyclization of 20 with stannic chloride in dichloromethane gave 18 in 70% yield in a reaction that was less contaminated with polymeric byproducts than in the case of 17. The formation of trans-fused decalin 18 from 20 implies that cyclization is not concerted. However, no evidence of products of cationic rearrangement was seen.



The facile acquisition of 18 makes this bicyclic keto ester an attractive platform from which to launch syntheses of higher terpenoids. Initially, attempts were made to introduce additional structure into 18 by alkylation of the enolate of the β-keto ester, but this was foiled by the severe steric hindrance at C-2 of the enolate. An alternative plan which was more successful involved conversion of 18 to the *exo*-methylene ketone 24 by a sequence similar to that

(14) Sum, F. W.; Weiler, L. *Tetrahedron Lett.* **1979**, 707.

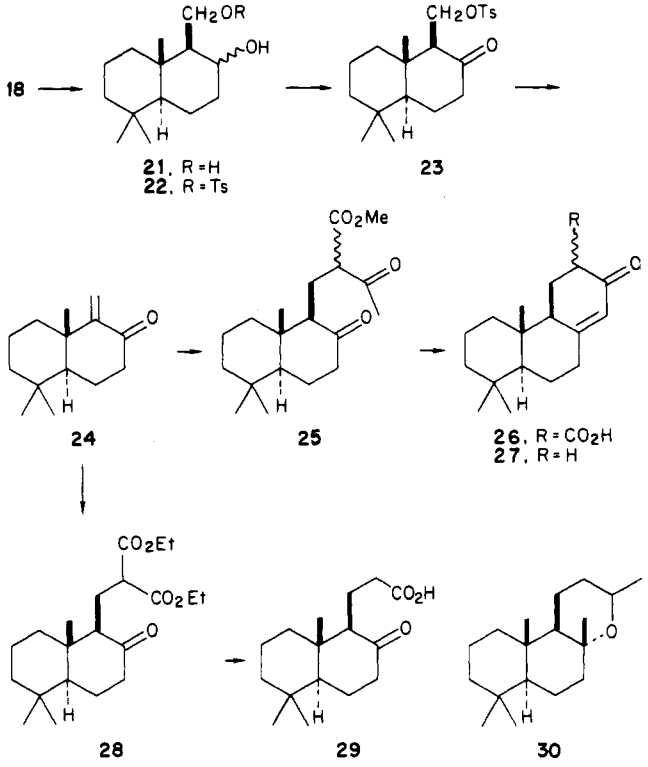
(15) Corey, E. J.; Kim, C. U.; Takeda, M. *Tetrahedron Lett.* **1972**, 4339.

(16) Romann, E.; Frey, A. J.; Stadler, P. A.; Eschenmoser, A. *Helv. Chim. Acta* **1957**, *40*, 1900.

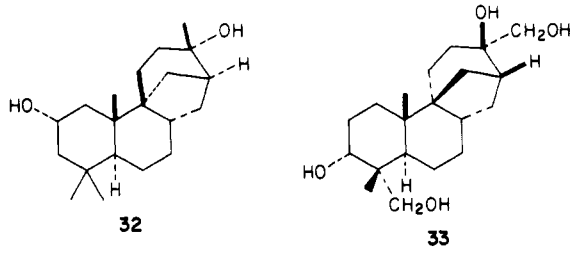
(17) Büchi, G.; White, J. D. *J. Am. Chem. Soc.* **1964**, *86*, 2884.

employed by Eschenmoser et al.[9] Thus, **18** was reduced to **21** with lithium aluminum hydride and this diol was selectively transformed to the primary monotosylate **22**. Oxidation of **22** with Jones' reagent gave ketone **23**, which underwent smooth elimination with 1,5-diazabicyclo-[5.4.0]undec-5-ene to yield **24**. This ketone, which decomposed over several days of 0 °C, proved to be a receptive partner in a Michael reaction with methyl acetoacetate, affording diketo ester **25** (as a mixture of epimers) in good yield. Treatment of **25** with 5 N sodium hydroxide effected intramolecular aldolization, dehydration, and saponification of the ester to furnish the tricyclic keto acid **26**. Decarboxylation of this material at 80 °C gave crystalline $\Delta^{8(14)}$-podocarpen-13-one (**27**), a substance which has been prepared by other, lengthier routes,[18] and which has been a focal intermediate in numerous diterpene syntheses, including labdanolic acid,[19] phyllocladene,[20] and hibaone.[21]

The Michael reaction of **24** with diethyl malonate proceeded efficiently to **28**, which was saponified and decarboxylated at 140 °C to furnish **29** in 73% yield from **24**. This keto acid can also be obtained from the ozonolysis and oxidation of **27** and has previously been employed in the synthesis of ambreinolide (**30**) and related diterpenoids.[22]



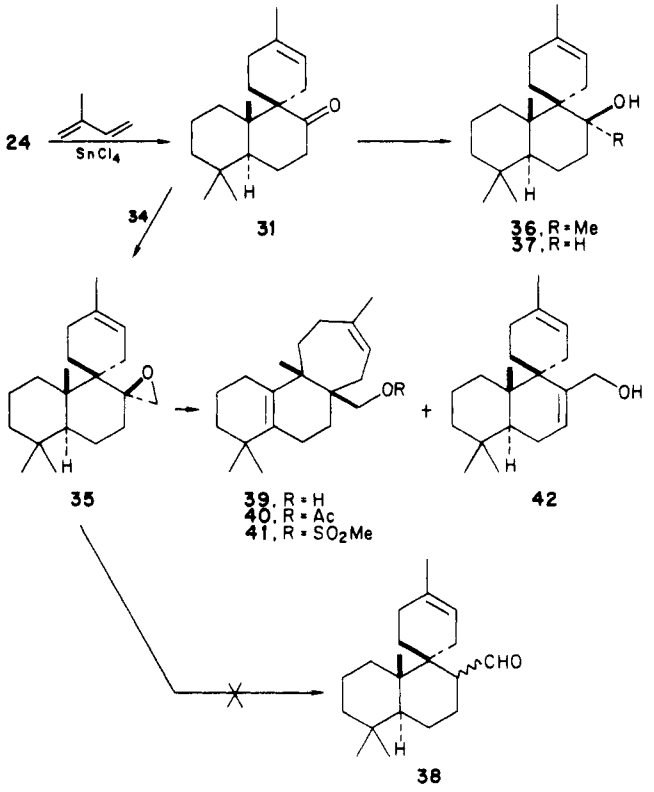
Finally, utilization of **24** as the dienophile in a stannic chloride catalyzed Diels–Alder reaction with isoprene was found to give a single crystalline adduct **31**. The high regioselectivity of this process is consonant with substituent directing effects in cycloadditions of this type,[23] and the stereoselectivity is clearly derived from the more ready access of isoprene to the face of the dienophile opposite the two axial methyl groups. It was hoped that the spirotricyclic structure **31** would afford an entry to the diterpenoid skeleton present in stemodin (**32**)[24] and/or aphidicolin (**33**)[25] and, to this end, attempts were made to append a functionalized one-carbon unit to the carbonyl group. The sterically encumbered environment of this ketone, not surprisingly, nullified all efforts at methylenation, and even the phosphide Ph_2P^-CHOMe—a reagent purportedly effective for conversion of sterically hindered ketones to aldehydes[26]—failed to react with **31**. Likewise, an attempt to prepare the epoxide **35** with the sulfurane $Me_2S^+CH_2^-$ (**34**) in Me_2SO returned **31** unchanged.[27] However, the same reagent in a THF–HMPA cosolvent led rapidly and almost quantiatively to **35**. The configuration of this epoxide was confirmed through its reduction with lithium aluminum hydride to the axial alcohol **36**, in which there was a pronounced downfield shift of the signal for the angular methyl substituent in the ^1H NMR spectrum. A similar downfield shift of this methyl signal was observed in the ^1H NMR spectrum of **37**. Equatorial delivery of hydride to **31** follows the generally observed pattern for a substituted ketone of this type,[28] and the configuration of epoxide **35** similarly reflects attack by **34** from the less hindered direction. Evidently, the steric barrier presented by the two axial methyl groups of **31** reverses the normal axial addition of this sulfurane.[27]



Exposure of epoxide **35** to a variety of Lewis acids, in an attempt to promote its conversion to aldehyde **38**, led instead to a primary alcohol, in which it was clear that a deep-seated skeletal rearrangement had taken place. Spectral data, especially the chemical shifts of the methyl substituents, are in agreement with structure **39** for this alcohol, which arises from a stereoelectronically favorable expansion of the spiro cyclohexene ring and subsequent angular methyl migration in concert with epoxide opening. Steric compression around the spiro center of **35**, which is relieved in **39**, provides obvious impetus to this rearrangement. Alcohol **39** furnished a primary acetate **40** upon esterification with acetic anhydride in pyridine, and treatment of **39** with methanesulfonyl chloride in pyridine afforded mesylate **41** quantitatively. A second product, isolated in minor amount when **35** was treated with dilute perchloric acid, was shown from its ^1H NMR spectrum to be the allylic alcohol **42**.

With the feasibility of constructing **18** from either a monocyclic or acyclic precursor firmly established, our attention was turned to modification of this scheme to permit incorporation of unsaturation into the keto ester ring. The introduction of this functionality was considered desirable because it could afford access to terpenoids, e.g., drimanes,[29] possessing a broad array of structural com-

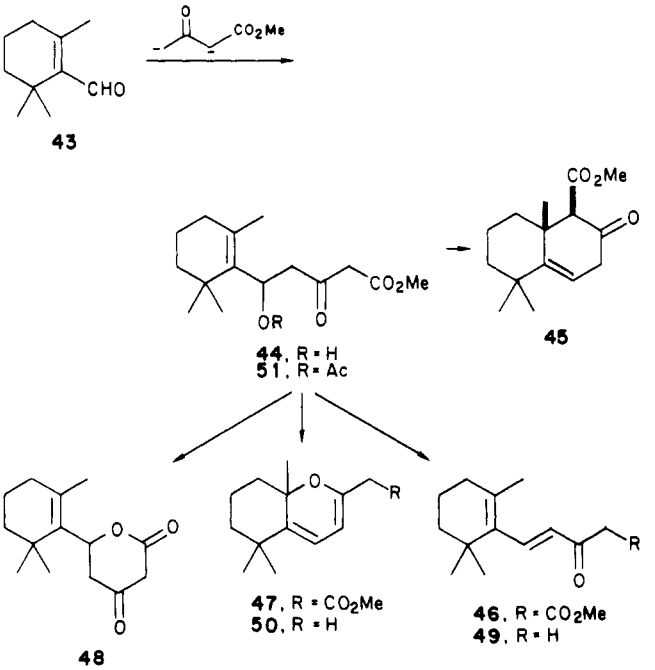
(18) (a) Barltrop, J. A.; Rogers, N. A. J. *J. Chem. Soc.* **1958**, 2566. (b) Church, R. F.; Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1966**, *31*, 2526.
(19) Bigley, D. B.; Rogers, N. A. J.; Barltrop, J. A. *J. Chem. Soc.* **1960**, 4613.
(20) Do Khac Manh Duc, D.; Fetizon, M.; Lazare, S. *J. Chem. Soc., Chem. Commun.* **1975**, 282.
(21) Do Khac Manh Duc, D. Fetizon, M.; Flament, J. P. *Tetrahedron* **1975**, *31*, 1897.
(22) Henrick, C. A.; Jefferies, P. R. *Tetrahedron* **1965**, *21*, 1175.
(23) Houk, K. N.; Strozier, R. W. *J. Am. Chem. Soc.* **1973**, *95*, 4094.
(24) White, J. D.; Manchand, P. S. *Biorg. Chem. Suppl.* **1978**, *2*, 349. Manchand, P. S.; White, J. D.; Wright, H.; Clardy, J. *J. Am. Chem. Soc.* **1973**, *95*, 2705.
(25) Dalziel, W.; Hesp, B.; Stevenson, K. M.; Jarvis, J. A. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2841.
(26) Corey, E. J.; Tius, M. A. *Tetrahedron Lett.* **1980**, *21*, 3535.
(27) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
(28) Lansbury, P. T.; MacLeay, R. E. *J. Org. Chem.* **1963**, *28*, 1940.



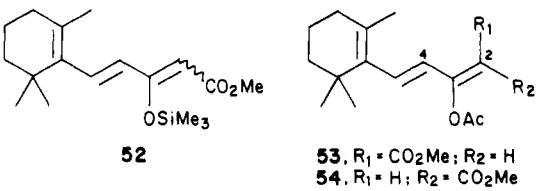
ponents in the B ring. In searching for a cyclization substrate which could be adapted to this end, our first plan was patterned upon methodology developed by Johnson,[30] in which an allylic alcohol initiates Lewis acid catalyzed olefin cyclization. We chose **44** as our candidate and were gratified to find that this alcohol was available in 75% yield by reaction of the dianion of methyl acetoacetate with β-cyclocitral (**43**).[17] However, upon exposure to stannic chloride, **44** gave, in addition to much polymeric material, three products in low yield. These were the desired bicyclic keto ester **45** (11%), the dienone **46** (13%) from dehydration of **44**, and the pyran **47** (16%), which perhaps arises by internal capture of the allylic cation from **44** by the enol tautomer of the ketone. Treatment of **44** with several other acidic catalysts gave similar results, whereas contact of the alcohol with *p*-toluenesulfonic acid produced δ-lactone **48** as the only isolable product.

In spite of the disappointing outcome of our attempted cyclization of **44**, it was felt that access to **45** might be gained from **46** via an electrocyclization pathway, provided (a) a trans-to-cis isomerization of the disubstituted double bond could be effected and (b) closure of the resulting *Z* dienone to pyran **47** could be suppressed. The well-known conversion of β-ionone (**49**) to pyran **50** upon irradiation[31] provided a strong photochemical precedent for the former, and it was surmised that an enol (or enloate) derivative of keto ester **46** might satisfy the latter. Accordingly, an efficient method for synthesis of **46** was sought, and this was achieved by two independent routes. First, **44** was transformed to **51** with acetyl chloride in dichloromethane–pyridine and the acetate was heated in toluene containing triethylamine to effect elimination (quantitative) to **46**, which was obtained exclusively as its *E* isomer. Later, it was discovered that the enolate of **49**, prepared with sodium hydride, could be acylated with excellent selectivity at the methyl group with dimethyl carbonate,[32] thus affording direct access to **46** from β-ionone. The ^{1}H NMR spectrum of **46** revealed that it was a mixture of keto and enol tautomers (ca. 85:15 respectively), with *E* and *Z* geometries at the enol double bond present.

Both the enol trimethylsilyl ether and enol acetate of **46** were prepared for study of their photochemical reactivity. The silyl derivative **52** was obtained as a mixture of 2-*E* and 2-*Z* isomers which proved to be too labile for chromatographic separation. In contrast, the 2-*E* (**53**) and 2-*Z* (**54**) isomers of the enol acetate, obtained in a ratio of 3:2, respectively, were readily separated chromatographically. Marked differences in the ^{1}H NMR spectra of **53** and **54**, particularly the downfield shifted H-4 signal in the *E* isomer (δ 7.40) due to deshielding by the carbomethoxy group, facilitated stereochemical assignment.



Irradiation of **52**, **53**, and **54** was carried out in pentane with either a General Electric sunlamp (250-W) or a Hanovia medium-pressure mercury lamp (450-W) through Pyrex glass. The results were qualitatively the same with



both sources except that conversions were more rapid with the latter. Silyl ether **52** produced two closely related irradiation products, (*E*)- and (*Z*)-**55**, in quantitative yield which, after hydrolysis with dilute acid, gave a single keto ester **56**. The unmistakeable presence of an *exo*-methylene group in **56**, together with other spectral characteristics, affirmed the fact that the exclusive photochemical pathway from **52** entails a 1,5-hydrogen migration. On the supposition that this transformation could be reversed by base-catalyzed isomerization of the diene into conjugation with the ketone, **56** was treated with triethylamine. To

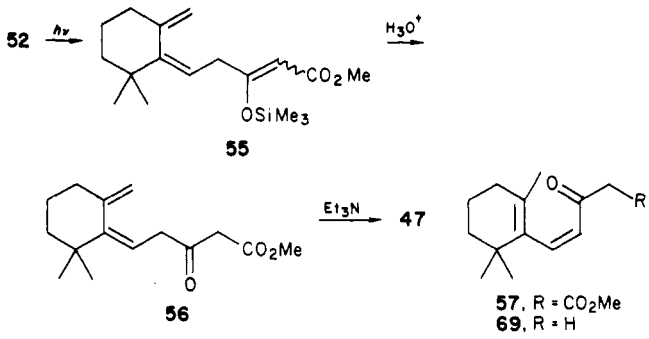
(29) Heathcock, C. H. "The Total Synthesis of Natural Products"; ApSimon, J. W., Ed.; Wiley-Interscience: New York, 1973; Vol 2, pp 338–353. Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. "The Total Synthesis of Natural Products"; ApSimon, J. W., ed.; Wiley: New York, 1983; Vol 5, pp 169–179.

(30) Johnson, W. S.; Lunn, W. H.; Fitzi, K. *J. Am. Chem. Soc.* **1964**, *86*, 1972.

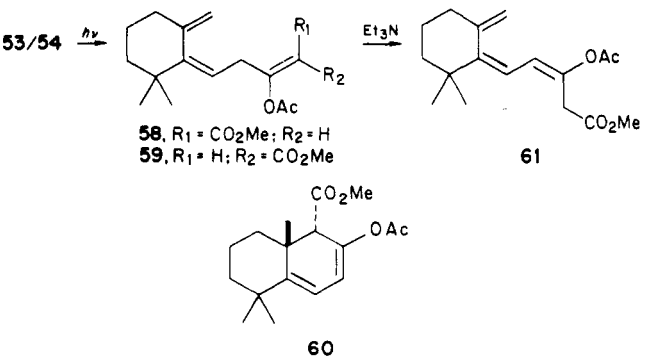
(31) Büchi, G.; Yang, N.-C. *J. Am. Chem. Soc.* **1957**, *79*, 2318.

(32) Green, N.; LaForge, F. B. *J. Am. Chem. Soc.* **1948**, *70*, 2287.

our surprise, a rapid, quantitative conversion to **47** occurred. The precise pathway followed by this intriguing reaction remains in doubt, but it was established that **46** is not involved since this substance was unresponsive to triethylamine. The question of whether the *Z* isomer **57** is an intermediate in the transformation **56** → **47** is addressed below. It was further shown that the formation of **47** from **56** with triethylamine occurs rapidly in the dark and takes place slowly even in the absence of a base.

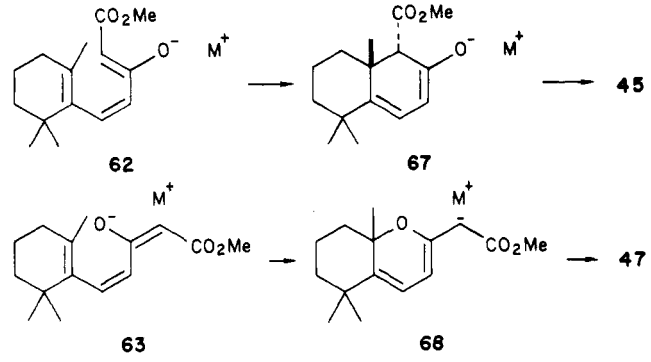


Irradiation of **53** or **54** in pentane produced in each case a mixture of **58** (51%) and **59** (31%). These products, which again result from a 1,5-hydrogen migration, were separated chromatographically and their configurations were assigned primarily from the chemical shift of the C-4 methylene protons. The pertinent signal in **58** was deshielded (δ 3.75) relative to **59** (δ 3.14) by the cisoid carbomethoxy function in the former. This result is at variance with that of Isoe, who has claimed that irradiation of **54** leads via its 4,5-*Z* isomer to **60**.[33] No trace of **60** could be found among our photochemical products from either **53** or **54**. Base-catalyzed treatment of **58** and **59** again led to an unexpected outcome, returning not **53** and **54** but instead an isomeric conjugated triene **61**. This substance, whose configuration could not be assigned with certainty, was generated rapidly and in high yield (95%) from **58** with triethylamine in ether. By contrast, **61** was produced much more slowly from **59** and required a refluxing toluene solution of base to effect complete isomerization. Preservation of the hetero diene moiety of **58** and **59** in their equilibration to **61** implies that this structure is thermodynamically preferred over the more extensively conjugated triene system present in **53** or **54**. A possible rationale can be found in steric compression arising from the enforced planarity of substituents at the cyclohexene double bond of **53** and **54**; this strain can be relieved by twisting about the cyclohexane bond between the diene system of **61**.



Since irradiation of the enol derivatives **52**, **53**, and **54** of **46** had failed to yield products of carbocyclization, the photochemistry of **46** itself was next examined with the initial objective of reversing the configuration of the 4,5-*E* double bond. Solutions of **46** in tetrahydrofuran or methanol underwent a rapid photochemical reaction (<2 h) giving, after chromatography, the deconjugated system **56** as the major photoproduct (60%). Small quantities of **45** (8%) and **47** (7%) were also isolated. Longer irradiation gave increasing amounts of **47**, which was produced at the expense of **56**, together with much polymeric material. The formation of pyran **47** was greatly enhanced when irradiation of **46** was carried out in pentane–dichloromethane solution, and addition of triethylamine to the photochemical reaction gave **47** in virtually quantitative yield.

From these results, it was apparent that photochemical pathways from **46** and its enol derivatives were likely to be dominated by 1,5-hydrogen migration, and that a direct trans → cis isomerization and cyclization to **45** was probably not feasible from these substrates. However, it has been noted that the light-initiated behavior of ketone enolates can diverge markedly from that of their enols.[34] Accordingly, the photochemistry of **46** was examined in the presence of bases which were expected to convert this keto ester partially or completely to its enolate. An admittedly speculative rationale for this approach was drawn from considerations of enolate geometry. Specifically, it was felt that an enolate **62** possessing 2-*Z*,4-*Z* configuration would be more likely to undergo electrocyclization to **45** than enolate **63** with 2-*E* configuration. The latter would be a logical precursor of the pyran **47**. Analogy with the stannic chloride mediated cyclization of **20** suggested metal ion complexation as a means for steering enolate geometry toward **62**.

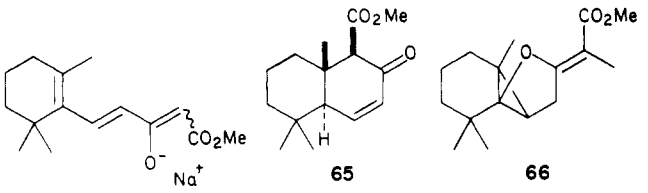


Not surprisingly, complete conversion of **46** to its enolate with one equivalent of sodium hydride afforded a species **64**, which was photochemically inert. Enolate formation here is accompanied by a change in the ultraviolet spectrum from λ_{max} 323 nm (ε ~26 000) to a broad and very diffuse absorption (ε <3000) in the 300–400-nm range, and the photochemical 1,5-hydrogen shift observed in **46** and its enol derivatives is consequently suppressed in **64**. However, when a methanol solution of **46** containing sodium methoxide was irradiated, a marked change in product distribution from that observed in the neutral reaction was noted. Increasing quantities of **45** and its conjugated isomer **65** were produced as the proportion of methoxide was increased up to 2 equiv, at which point the isolated yields of conjugated and nonconjugated enones were 30% and 36%, respectively. That this mixture represents the position of thermodynamic equilibrium in this system was shown by treating each ketone with sodium methoxide to give the same ratio of **45**:**65**. Thus, the methoxide-mediated photochemical carbocyclization of **46**,

(33) Isoe, S. *Int. Congr. Pure Appl. Chem.* [*Proc.*] **1977**, *26th*, 1108.

(34) van Tamelen, E. E.; Schwartz, J.; Brauman, J. I. *J. Am. Chem. Soc.* **1970**, *92*, 5798.

which must lead initially to **45**, is reasonably efficient, the major contaminant being polymeric material arising from subsequent photochemistry involving **65**. Amounts of sodium methoxide in excess of 2 equiv, in addition to retarding the photochemical reaction, led to an increase in decomposition products. Less than 1 equiv of base—for example, irradiation of **46** in tetrahydrofuran containing 0.5 equiv of sodium hydride—gave **47** and **56**, as well as lesser amounts of **45** and **65**. In an independent investigation of the photochemistry of **46**, Isoe noted the formation of **65** (but not **45**) when irradiation was carried out in the presence of sodium methoxide[33] and, in a recent study, he has reported that irradiation of 2-alkyl derivatives of **46** leads not only to a pyran and a diene exactly analogous to our photoproducts **47** and **56** but to a novel of tricyclic ether **66** as well.[35]

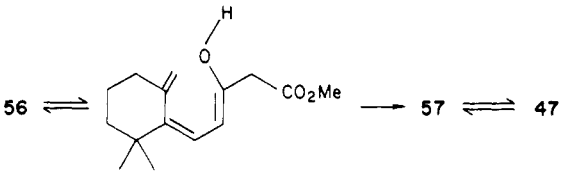


64 65 66

The facile geometrical inversion of the C-2,3 double bond of enol acetates **53** and **54** in the course of their photochemical transformation to **58** and **59** raised the issue of whether such a photoequilibration might be induced between enolates **62** and **63**. Indeed, it seemed conceivable that the entire array encompassing these and the derived bicyclic enolates **67** and **68** could involve a manifold of equilibrating species, with **45** at the terminus by virtue of its diminished ultraviolet absorption. Accordingly, **47** was irradiated in methanol containing sodium methoxide and, in a gratifying confirmation of our prediction, **45** and **65** were produced in virtually the same ratio as was obtained with **46** under similar conditions. As expected, no reaction of **47** took place with sodium methoxide in the dark.

Although this experiment clarifies the role of enolate geometry in the partition between photochemical routes from **46** to **45** and **47**, it leaves unanswered key questions regarding the photochemistry of **46** in neutral solution. Foremost among these is the matter of whether the 4-*Z* dienone **57** is an intermediate in the genesis of **56** and/or **47**. Analogy with the photochemical production of **55** from **52** and of **58** and **59** from **53** and **54** suggests that **46** may undergo 1,5-hydrogen migration to **56** without the prior isomerization to **57** assumed by Isoe.[35] On the other hand, Marvell et al. have established that **50**, obtained upon photolysis of trans β-ionone (**49**),[31] is in thermal equilibrium with *cis*-ionone **69** at 40 °C.[36] This finding may be relevant to the issue of how pyran **47** is generated (a) from the photochemical reaction of **46** and (b) from the dark reaction of **56** (slowly in the absence of base but rapidly in the presence of triethylamine) by a process which does not return to **46**.

Thus, a possible explanation may be found in the enol tautomer **70** of **56**. If this intermediate undergoes a 1,7-hydrogen shift to the 4-*Z* isomer **57**, the latter would be



70

in thermal equilibrium with **47** which, as with the ionone system, lies heavily to the side of the pyran. Our results do not exclude a mechanism for the photochemical pathway from **46** to **47** via a direct $E \rightarrow Z$ isomerization to **57** followed by electrocyclization. However, they do suggest that a pathway through **56**, previously unrecognized in β-ionone photochemistry, exists for this transformation.

Experimental Section

General Methods. Melting points were determined on a Kofler hot-stage melting point apparatus and are corrected. Infrared (IR) spectra were obtained with a Perkin-Elmer Model 137 or 727B spectrophotometer by using polystyrene film (1601 cm^{-1}) for calibration. Nuclear magnetic resonance (NMR) spectra were obtained with a Varian Associates Model EM-360, EM-360A, or HA-100 spectrometer and are reported in δ units with tetramethylsilane as standard. Coupling constants (*J*) are given in Hertz, with the following abbreviations denoting the signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Elemental analyses were carried out by Micro-Tech Laboratories, Inc., Skokie, IL. Exact mass determinations were made with a CEC-110B spectrometer at an ionizing potential of 70 eV. Thin-layer chromatography (TLC) was performed on Merck precoated silica plates. Unless otherwise specified, column chromatography was performed with a 30:1 ratio of activity II silica gel to compound. Triethylamine, pyridine, and diisopropylamine were dried by distillation from barium oxide. Methanol used in the photolysis experiments was dried by distillation from magnesium methoxide. Ether and tetrahydrofuran were dried by distillation from sodium benzophenone. Methylene chloride and pentane were washed with sulfuric acid followed by water, then distilled from phosphorus pentoxide. Unless otherwise noted, organic solutions from extraction of reaction mixtures were dried by stirring briefly over anhydrous magnesium sulfate and filtering.

Methyl 3-Oxo-7-methyloct-6-enoate (8). A 50% mineral oil suspension of sodium hydride (5.30 g, 0.11 mol) was placed in a flame-dried, three-neck flask equipped with a reflux condenser. The flask was flushed with nitrogen and the hydride was rinsed twice with 50-mL portions of pentane to remove mineral oil. A solution of dimethyl carbonate (12.00 g, 0.10 mol) in 15 mL of dry ether was added, and the suspension was stirred magnetically and heated to reflux. 6-Methylhept-5-en-2-one (**9**, 6.30 g, 0.05 mol) was added dropwise until ca. 2 mL had been added, at which point addition was stopped until steady hydrogen evolution was observed. The remaining **9** was added slowly (ca. 3 h). The reaction mixture was refluxed for 2 h after addition was complete and allowed to stand overnight at room temperature. The solid mass was cooled in an ice bath, and a solution of methanol (10 mL) in ether (50 mL) was added. The reaction mixture was broken up carefully with a stirring rod and then stirred magnetically for 2 h. The resultant suspension was poured onto a mixture of ice (80 g) and concentrated hydrochloric acid (20 mL). The aqueous layer was extracted twice with ether and the combined layers were washed with saturated aqueous sodium bicarbonate, dried, and evaporated. The residue was distilled to give 6.00 g (65%) of **8**: bp 55–70 °C (1.5 torr); IR (film) 2970, 2930, 1750, 1720, 1650, 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (3 H, s), 1.65 (3 H, s), 1.8–2.8 (4 H, m), 3.45 (2 H, s), 3.75 (3 H, s), 4.95 (1 H, m). This material was identical with **8** prepared by the method of Casey and Marten.[13]

2-Carbomethoxy-3,3-dimethylcyclohexanone (10). Stannic chloride (0.95 mL, 2.10 g, 8.10 mmol) was added to a cooled (ice bath), stirred solution of **8** (1.01 g, 5.4 mmol) in methylene chloride (35 mL). After addition was complete, the cooling bath was removed and the solution was stirred for 12 h at room temperature.

(35) Kim, T. H.; Hayase, Y.; Isoe, S. *Chem. Lett.* **1983**, 651. Reference 6 of this publication infers that our study of the photochemistry of **46** in the presence of sodium methoxide is derived from earlier work by Isoe. This is incorrect. Our results were well in hand, although not complete, when the brief report from Professor Isoe appeared (ref 33). Furthermore, we had already uncovered many of the novel photochemical aspects of the work reported in ref 11 before Isoe disclosed his findings.

(36) Marvell, E. N.; Chadwick, T.; Caple G.; Gosink, T.; Zimmer, G. *J. Org. Chem.* **1972**, *37*, 2992.

The solution was diluted with twice its volume of ether, washed four times with 50-mL portions of 5% hydrochloric acid and once with water, dried, and evaporated. The residue was chromatographed (5% ether in pentane) to give 0.73 g (73%) of **10** as an oil: IR (film) 2960, 1750, 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.0 (3 H, s), 1.1 (3 H, s), 1.2–3.1 (6 H, m), 3.2 (1 H, s), 3.65 (3 H, s); mass spectrum, m/z 184 (M^+). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.88; H, 8.71.

Methyl 3-Oxo-7-methyl-6,7-epoxyoctanoate (11). To a stirred solution of **8** (1.00 g, 5.4 mmol) in methylene chloride (40 mL) was added *m*-chloroperbenzoic acid (1.28 g, 85% purity, 6.4 mmol). After a few minutes a precipitate of *m*-chlorobenzoic acid began to form and TLC indicated that reaction was complete after 1 h. The solution was diluted with ether (100 mL) and extracted twice with 80-mL portions of 10% aqueous sodium carbonate. The organic layer was dried and evaporated to give 1.09 g (100%) of virtually pure **11**: IR (film) 1740, 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.3 (6 H, s), 1.75 (2 H, m), 2.5–2.9 (3 H, m), 3.5 (2 H, s), 3.7 (3 H, s); mass spectrum, m/z 200 (M^+).

Reaction of 11 with Stannic Chloride. A solution of **11** (1.00 g, 5.0 mmol) in methylene chloride (60 mL) was cooled in a dry ice–acetone bath to −70 °C and stannic chloride (15 μL, 33 mg, 0.13 mmol) was added. The mixture was stirred for 1 h, after which it was diluted with ether (100 mL) and washed twice with 5% hydrochloric acid and then once with water. After drying and evaporation of the solvent, the residue was chromatographed (1:1 ether–petroleum ether) to give 177 mg (18%) of **13**: IR (film) 3450, 2970, 1735 cm^{-1}; NMR ($CDCl_3$) (major isomer) δ 1.10 (3 H, s), 1.22 (3 H, s), 2.05 (4 H, m), 2.75 (1 H, broad s), 2.82 (1 H, s), 3.68 (3 H, s), 3.88 (1 H, m); mass spectrum, m/z 200 (M^+). **12**: 448 mg (45%); IR (film) 3500, 1730, 1680 cm^{-1}; NMR ($CDCl_3$) δ 1.20 (3 H, s), 1.34 (3 H, s), 1.84–2.20 (2 H, m), 2.58 (1 H, broad s), 2.7–3.4 (2 H, m), 3.68 (3 H, s), 4.27 (1 H, m), 5.36 (1 H, t, J = 1 Hz); mass spectrum, m/z 200 (M^+).

Methyl 3-Oxo-7,11-dimethyldodeca-6,10-dienoate (17). A suspension of sodium hydride (2.70 g of a 50% mineral oil dispersion, 56.3 mmol) in dry tetrahydrofuran (120 mL) was stirred in an ice-bath as methyl acetoacetate (5.88 g, 50.5 mmol) was added dropwise. The mixture was stirred for 10 min after addition was complete and butyllithium (23 mL of a 2.4M solution, 55 mmol) was slowly added. The resultant solution was stirred in the ice-bath for an additional 10 min, geranyl bromide (**16**, 12.10 g, 55.7 mmol) was added in one portion, and the mixture was then stirred at room temperature for 20 min. A solution of concentrated hydrochloric acid (10 mL) in water (25 mL) was added carefully, followed by ether (50 mL). The organic layer was separated and washed with three 50-mL portions of water, dried, and evaporated to leave an oil. Distillation afforded 8.60 g (61%) of **17**: bp 140–144 °C (0.6 torr); IR (film), 2925, 2850, 1748, 1642, 1628, 1450, 1440, 1405, 1372, 1316, 1236, 1150 cm^{-1}; NMR ($CDCl_3$) δ 1.60 (6 H, s), 1.67 (3 H, s), 2.0 (4 H, m), 2.4 (4 H, m), 3.44 (2 H, s), 3.74 (3 H, s), 5.1 (2 H, m); mass spectrum, m/z 252.172 (M^+, calcd for $C_{15}H_{24}O_3$ 252.173).

Methyl 3-Oxo-5-(2,6,6-trimethylcyclohexen-1-yl)pentanoate (20). Keto ester **20** was prepared from **19** by the procedure used for **17**: bp 118–125 °C (0.3 torr); IR (film) 1745, 1710, 1650 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (6 H, s), 1.57 (3 H, s), 2.2–2.75 (4 H, m), 3.32 (2 H, s), 3.73 (3 H, s); mass spectrum, m/z 252.171 (M^+, calcd for $C_{15}H_{24}O_3$ 252.173).

Methyl 2-Oxo-5,5,8a-trimethyldecahydronaphthalene-1-carboxylate (18). To a solution of **17** (1.00 g, 3.96 mmol) in water-saturated methylene chloride (35 mL) cooled by stirring in an ice-bath under argon was added anhydrous stannic chloride (5.20 g, 20.0 mmol). The solution was stirred for 30 min at 0 °C and then for 20 h at room temperature. The mixture was diluted with three 20-mL portions of 5% aqueous hydrochloric acid and 50 mL of ether. The organic phase was washed with three 10-mL portions of 5% aqueous hydrochloric acid, water, and brine and dried. Concentration gave an orange oil that was chromatographed (gradient 10–50% ether in petroleum ether) to give 0.53 g (53%) of **18**: mp 83–84.5 °C (lit.[8] mp 83.5–84 °C); IR (Nujol) 1754, 1715 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (3 H, s), 0.97 (3 H, s), 1.15 (3 H, s), 1.2–2.3 (9 H, m), 2.43 (2 H, m), 3.22 (1 H, s), 3.70 (3 H, s); mass spectrum, m/z 252.171 (M^+, calcd for $C_{15}H_{24}O_3$ 252.173). When **20** was subjected to the same conditions, a 70% yield of **18** was obtained.

2-Hydroxy-5,5,8a-trimethyldecahydronaphthalene-1-methanol (21). To a stirred solution of **18** (2.21 g, 8.74 mmol) in dry ether (50 mL) cooled in an ice-bath was added lithium aluminum hydride (0.312 g, 8.23 mmol). After 1 h at 0 °C and 2 h at room temperature, the reaction mixture was quenched by addition of saturated, aqueous potassium sodium tartrate and filtered. The residue was suspended in tetrahydrofuran and the suspension was refluxed and filtered. The filtrates were combined and evaporated to give 1.92 g (97%) of **21**: IR (Nujol) 3200 cm^{-1}; NMR ($CDCl_3$) δ 0.9 (9 H, m), 1.7 (12 H, m), 2.72 (2 H, m), 3.9 (3 H, m). This material was used without further purification.

1-[[(*p*-Tolylsulfonyl)oxy]methyl]-2-hydroxy-5,5,8a-trimethyldecahydronaphthalene (22). A solution of **21** (3.83 g, 17 mmol) in pyridine (60 mL) was cooled in an ice-bath and *p*-toluenesulfonyl chloride (3.5 g, 10 mmol) was added with stirring. The solution was kept at 0 °C for 18 h, after which it was poured over ice (100 g). The aqueous slurry was extracted with two 75-mL portions of ether and the combined extracts were washed repeatedly with 5% aqueous copper sulfate until the washings remained light blue. The extract was dried and evaporated to give 5.30 g (82%) of **22**: IR (film) 3484, 3335, 1597 cm^{-1}; NMR ($CDCl_3$) δ 0.9 (9 H, m), 1.6 (12 H, m), 2.4 (3 H, s), 4.1 (3 H, m), 4.9 (1 H, broad s), 7.5 (4 H, m). This material was used without further purification.

1-Methylene-5,5,8a-trimethyl-2-oxodecahydronaphthalene (24). A solution of **22** (5.30 g, 14 mmol) in acetone (100 mL) was treated with Jones' reagent until an orange color persisted and then was stirred for 30 min. The acetone was removed in vacuo and water (50 mL) was added. The resulting suspension was extracted with three 40-mL portions of ether and the combined extracts were dried and evaporated to give 5.41 g of crude **23**: IR (film) 1709, 1595 cm^{-1}. To a solution of this material in benzene (100 mL) was added 1,5-diazabicyclo[5.4.0]undec-5-ene (2.20 g, 14.5 mmol) and the mixture was left at room temperature for 17 h. The solution was washed with three 50-mL portions of water, dried, and evaporated, and the residue was chromatographed on Florisil. Elution with benzene gave 2.15 g (76% from **22**) of pure **24**: IR (film) 1700, 1620 cm^{-1}; NMR (CCl_4) δ 0.9 (3 H, s), 0.95 (3 H, s), 1.0 (3 H, s), 1.1–2.8 (11 H, m), 4.9 (1 H, d), 5.4 (1 H, d); mass spectrum, m/z 206.166 (M^+, calcd for $C_{14}H_{22}O$ 206.167).

Diketo Ester 25. A solution of **24** (100 mg, 0.48 mmol) in methanol (0.5 mL) was added dropwise over 3 h to a stirred solution of methyl acetoacetate (60 μL, 64 mg, 0.55 mmol) in 0.1 N methanolic sodium methoxide (1 mL). The mixture was left at room temperature for 5 h, then neutralized by the addition of 5% aqueous ammonium chloride (3 mL). Most of the methanol was removed in vacuo and the aqueous suspension was extracted with two 5-mL portions of ether. The combined ether extracts were dried and evaporated, and the residue was chromatographed (20% ether in petroleum ether) to give 110 mg (70%) of **25** as a mixture of epimers: IR (film) 1750, 1710 cm^{-1}; NMR (CCl_4) δ 0.75 (3 H, s), 0.88 (3 H, s), 0.98 (3 H, s), 2.10, 2.23 (3 H, two s), 3.4 (1 H, m), 3.65, 3.70 (3 H, two s); mass spectrum, m/z 322.214 (M^+, calcd for $C_{19}H_{30}O_4$ 322.214).

$\Delta^{8(14)}$-Podocarpen-13-one (27). To a solution of **25** (110 mg, 0.34 mmol) in methanol (0.5 mL) was added 5 N aqueous sodium hydroxide (0.25 mL) and the mixture was stirred for 1.5 h at room temperature. Most of the methanol was removed and water (5 mL) was added. The mixture was extracted with ether (5 mL), cooled to 0 °C, and acidified with 5 N hydrochloric acid to pH 1. The suspension was extracted with two 5-mL portions of ethyl acetate, which were combined, dried, and concentrated. The semicrystalline residue of **26** was converted to **27** by heating to 80 °C at 0.1 torr for 2.5 h. The crude product was chromatographed (10% ether in petroleum ether) to give 60 mg (50%) of **27**: mp 90.5–91.5 °C (lit.[18b] mp 92.5–93.5 °C); IR (Nujol) 1680, 1630 cm^{-1}; NMR ($CDCl_3$) δ 0.80 (3 H, s), 0.90 (3 H, s), 0.95 (3 H, s), 1.2–1.7 (16 H, m), 5.85 (1 H, broad m); mass spectrum, m/z 246.199 (M^+, calcd for $C_{17}H_{26}O$ 246.198).

3-(5,5,8a-Trimethyl-2-oxodecahydronaphthyl)propanoic Acid (29). A solution of **24** (110 mg, 0.53 mmol) in ethanol (1 mL) was added dropwise during 2 h to a solution of diethyl malonate (90 μL, 95 mg, 0.59 mmol) in 0.1 N ethanolic sodium ethoxide (1 mL). After standing for 14 h, the solution was treated with 6 N sodium hydroxide (0.25 mL) and stirred for 6 h. The mixture was diluted with water (5 mL) and extracted with two

5-mL portions of ether. The aqueous solution was acidified with concentrated hydrochloric acid and extracted with two 5-mL portions of ethyl acetate. The combined extracts were dried and evaporated, leaving a glass. This was heated at 140–150 °C under a nitrogen atmosphere for 1 h and the residue was crystallized from ether–hexane to give 110 mg (75%) of **29**: mp 130–132 °C; IR (film) 2750 (broad), 1715, 1458, 1440, 1408, 1381, 1374, 1361, 1310, 1299, 1270, 1263, 1231, 1217, 1180, 1120, 1102, 1072 cm^{-1}; NMR ($CDCl_3$) δ 0.70 (3 H, s), 0.85 (3 H, s), 0.96 (3 H, s), 1.0–2.8 (16 H, m), 10.5 (1 H, broad s); mass spectrum, m/z 266.187 (M^+, calcd for $C_{16}H_{26}O_3$ 266.188).

Spiro Ketone 31. A solution containing **24** (458 mg, 2.22 mmol) and stannic chloride pentahydrate (1.1 g, 3.1 mmol) in 10 mL of isoprene and 2 mL of acetonitrile was allowed to stand for 24 h at room temperature. Ether (30 mL) was added and the mixture was washed with two 10-mL portions of 5% aqueous hydrochloric acid and with saturated aqueous sodium chloride. The organic solution was dried and evaporated, and the residue was chromatographed on Florisil (20 g, benzene) to give 405 mg (67%) of **31**: IR (CCl_4) 1704 cm^{-1}; NMR ($CDCl_3$) δ 0.85 (6 H, s), 0.95 (3 H, s), 1.45 (11 H), 1.57 (3 H, s), 2.0 (4 H, m), 2.48 (2 H, m), 5.27 (1 H, m); mass spectrum, m/z 274.229 (M^+, calcd for $C_{19}H_{30}O$ 274.230).

Epoxide 35. To a stirred solution of trimethylsulfonium iodide (407 mg, 1.99 mmol) in 4 mL of tetrahydrofuran and 5 mL of hexamethylphosphoramide cooled in an ice–salt bath was added *n*-butyllithium (1.0 mL of a 2 M solution, 2.0 mmol). The solution turned yellow and after 1 min **31** (179 mg, 0.65 mmol) was added. A brown color appeared immediately and after 1.5 h the cooling bath was removed and the mixture was stirred at room temperature for 19 h. Water (20 mL) was added and the mixture was extracted with two 15-mL portions of ether. The combined ether extract was dried and concentrated to give 175 mg (93%) of virtually pure **35**: IR (CCl_4) 2960, 1543, 1453, 1435, 1377, 1228, 1114, 1065 cm^{-1}; NMR (CCl_4) δ 0.89 (6 H, s), 1.00 (3 H, s), 1.62 (3 H, s), 1.2–2.0 (15 H), 2.03 (1 H, d, J = 4 Hz), 2.53 (1 H, d, J = 4 Hz), 5.33 (1 H, m); mass spectrum, m/z 288.245 (M^+, calcd for $C_{20}H_{32}O$ 288.245).

Alcohol 36. To a solution of **35** (29.5 mg, 0.10 mmol) in 3 mL of tetrahydrofuran was added lithium aluminum hydride (12 mg, 0.14 mmol) and the mixture was stirred at room temperature for 22 h. The mixture was treated with saturated aqueous potassium sodium tartrate (25 mL) and extracted with ether (15 mL). The ethereal extract was washed with brine, dried, and evaporated to give 30 mg (99%) of virtually pure **36**: IR (neat) 3430 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (6 H, s), 1.11 (3 H, s), 1.17 (3 H, s), 1.64 (3 H, s), 1.90 (4 H, m), 5.32 (1 H, s); mass spectrum, m/z 290.260 (M^+, calcd for $C_{20}H_{34}O$ 290.261).

Alcohol 37. To a solution of **31** (17.1 mg, 0.062 mmol) in 2 mL of tetrahydrofuran was added lithium aluminum hydride (3 mg, 0.07 mmol) and the mixture was stirred at room temperature for 1 h. The mixture was treated with potassium sodium tartrate (10 mL) and extracted with three 10-mL portions of ether. The ether extracts were combined, dried, and evaporated, and the residue was chromatographed (benzene) to give 13.8 mg (81%) of **37**: IR (CCl_4) 3610, 3333 cm^{-1}; NMR (CCl_4) δ 0.87 (3 H, s), 0.89 (3 H, s), 1.21 (3 H, s), 1.62 (3 H, s), 1.2–1.5 (8 H), 1.5–1.8 (3 H, m), 1.8–2.2 (5 H), 3.88 (1 H, m), 5.20 (1 H, m); mass spectrum, m/z 276.243 (M^+, calcd for $C_{19}H_{32}O$ 276.245).

Acid-Catalyzed Rearrangement of 35. To a solution of **35** (40.0 mg, 0.139 mmol) in tetrahydrofuran (2 mL) was added 3% aqueous perchloric acid (1 mL) and the mixture was stirred at room temperature for 24 h. The mixture was diluted with ether (10 mL) and washed with water and brine. After drying the solution, the solvent was evaporated to leave a pale yellow oil which was purified by HPLC (μ-Porisil, elution with hexane–ethyl acetate, 8:1). This affored 15.7 mg (39%) of **39**: IR (CCl_4) 3448 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, s), 0.99 (3 H, s), 1.00 (3 H, s), 1.71 (3 H, bs), 2.38 (1 H, dd, J = 6, 14 Hz), 3.45 (1 H, d, J = 11 Hz), 3.63 (1 H, d, J = 11 Hz), 5.39 (1 H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 20.2, 21.4, 22.5, 24.7, 25.9, 27.2, 28.2, 28.9, 29.8, 30.5, 32.4, 34.5, 39.9, 40.0, 44.0, 67.4, 121.4, 132.8, 135.8, 142.7; mass spectrum, m/z 288.244 (M^+, 62%, calcd for $C_{20}H_{32}O$ 288.245), 273 (16%), 257 (100%).

Further elution of the chromatogram gave 6.6 mg (17%) of **42**: ^1H NMR ($CDCl_3$) δ 0.88 (3 H, s), 0.91 (3 H, s), 0.93 (3 H, s), 1.66 (3 H, bs), 2.29 (1 H, bd, J = 16 Hz), 4.06 (2 H, bs), 5.41 (1 H, m), 5.73 (1 H, m); ^{13}C NMR δ 16.1, 19.0, 22.3, 23.4, 24.0, 24.9, 29.4, 33.2, 33.4, 33.8, 40.8, 42.0, 43.3, 65.8, 122.0, 125.1, 133.8, 144.6; mass spectrum, m/z 288.246 (M^+, calcd for $C_{20}H_{32}O$ 288.246).

A solution of **39** (9.0 mg, 0.031 mmol), acetic anhydride (16 mg, 0.16 mmol), and pyridine (13 mg, 0.16 mmol) in methylene chloride (2 mL) containing a crystal of 4-(*N*,*N*-dimethylamino)pyridine was stirred at room temperature for 4 h. The mixture was evaporated in vacuo and the residue was taken up in ether (10 mL). The ethereal solution was washed with two 10-mL portions of water and brine and dried. Evaporation of the solvent gave 10 mg (100%) of **40**: IR (film) 1728 cm^{-1}; NMR ($CDCl_3$) δ 0.79 (3 H, s), 0.84 (3 H, s), 0.89 (3 H, s), 1.64 (3 H, s), 2.02 (3 H, s), 2.18 (2 H, broad s), 3.68 (1 H, d, J = 11 Hz), 3.90 (1 H, d, J = 11 Hz), 5.25 (1 H, broad t).

A mixture of **39** (28 mg, 0.097 mmol) and methanesulfonyl chloride (22 mg, 0.19 mmol) in pyridine was allowed to stand overnight at 0 °C. Water (20 mL) was added and the mixture was extracted with three 10-mL portions of ether. The combined ether extract was washed with five 10-mL portions of 5% aqueous hydrochloric acid and one 10-mL portion of brine, dried, and evaporated to give 35.1 mg (98%) of **41**: NMR (CCl_4) δ 0.87 (9 H, s), 1.65 (3 H, s), 1.8–2.4 (6 H), 2.87 (3 H, s), 3.82 (2 H, s), 5.20 (1 H, m).

Methyl 5-Hydroxy-3-oxo-5-(2,6,6-trimethylcyclohexen-1-yl)pentanoate (44). To a stirred suspension of sodium hydride (1.06 g of a 50% mineral oil dispersion, 22 mmol) in dry tetrahydrofuran (60 mL) at 0 °C under nitrogen was added dropwise methyl acetoacetate (2.60 g, 22 mmol), and the reaction mixture was stirred for 10 min. Butyllithium (9.2 mL of a 2.4 M solution, 22 mmol) was added slowly via syringe, and the resultant solution was stirred for 10 min. To this solution was added β-cyclocitral (3.40 g, 22 mmol) in one portion, after which the mixture was stirred at room temperature for 1 h. Excess 10% aqueous ammonium chloride was added and the aqueous layer was separated and extracted twice with an equal volume of ether. The combined organic layers were dried and evaporated, leaving a yellow oil, which was chromatographed (1:1 ether–petroleum ether) to give 4.40 g (75%) of **44** as a low-melting solid: IR (film) 3550, 1750, 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.94 (3 H, s), 1.1 (3 H, s), 1.1–2.1 (6 H, m), 1.84 (3 H, s), 2.55 (1 H, broad s, exchanged with D_2O), 2.5–3.5 (2 H, m), 3.54 (2 H, m), 3.54 (2 H, s), 3.74 (3 H, s), 4.75–4.90 (1 H, broad d, changes to d of d after treatment with D_2O); mass spectrum, m/z 250.155 ($M^+ - H_2O$, calcd for $C_{15}H_{22}O_3$ 250.157).

Reaction of 44 with Stannic Chloride. To a solution of **44** (135 mg, 5 mmol) in methylene chloride (3 mL) at 0 °C was added stannic chloride (60 μL, 130 mg, 5 mmol), which produced a dark brown color. After 5 min, the brown solution was treated with 2 mL of 1 N hydrochloric acid. Ether (5 mL) was added and the mixture was stirred for 10 min, after which the aqueous layer was separated and extracted repeatedly with ether. The ether layers were combined and washed with three 5-mL portions of 1 N hydrochloric acid, followed by water, then dried, and evaporated. The residue was chromatographed (gradient 10–100% ether–petroleum ether) to yield 16 mg (13%) of **46**: UV (ethanol) λ_{max} 285 nm (ϵ 5800); IR (film) 1750, 1715, 1655, 1635, 1590, 1450, 1395, 1235, 1150 cm^{-1}; NMR ($CDCl_3$) δ 1.07 (6 H, s), 1.1–1.8 (4 H, m), 1.76 (3 H, s), 2.04 (2 H, m), 3.58 (2 H, s), 3.72 (3 H, s), 6.14 (1 H, d, J = 16 Hz), 7.32 (1 H, d, J = 16 Hz), mass spectrum, m/z 250.156 (M^+, calcd for $C_{15}H_{22}O_3$ 250.157). **47**: 20 mg (16%); UV (methanol) λ_{max} 323 nm (ϵ 26 500); IR (film) 1740, 1660, 1595, 1440, 1210, 1120 cm^{-1}; NMR ($CDCl_3$) δ 1.06 (3 H, s), 1.11 (3 H, s), 1.36 (3 H, s), 1.2–2.3 (6 H, m), 3.10 (2 H, s), 3.70 (3 H, s), 5.20 (1 H, d, J = 6 Hz), 5.73 (1 H, d, J = 6 Hz); mass spectrum, m/z 250.158 (M^+, calcd for $C_{15}H_{22}O_3$ 250.157). **45**: 13.2 mg (11%); IR (film) 1755, 1675, 1475, 1435, 1340, 1265, 1195, 1015, 910, 730 cm^{-1}; NMR ($CDCl_3$) δ 1.17 (3 H, s), 1.20 (3 H, s), 1.35 (3 H, s), 1.2–2.0 (6 H, m), 2.98 (2 H, m), 3.52 (1 H, s), 3.75 (3 H, s), 6.65 (1 H, t); mass spectrum, m/z 250 (M^+).

Reaction of 44 with *p*-Toluenesulfonic Acid. To a stirred solution of **44** (153 mg, 0.57 mmol) in 15 mL of dry methylene chloride was added *p*-toluenesulfonic acid (2 mg) and the mixture was stirred for 1 h at room temperature. The solution was diluted with 30 mL of ether and washed twice with 30-mL portions of water. The organic solution was dried and evaporated to give 104 mg of crude product which partially crystallized after standing

overnight. Trituration with ether left 80 mg (55%) of pure **48**: IR (Nujol) 1660, 1650, 1580, 1455, 1370, 1290 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (3 H, s), 1.12 (3 H, s), 1.2–1.7 (4 H, m), 1.75 (3 H, s), 2.05 (2 H, broad t), 2.5–3.8 (4 H, m), 5.2 (1 H, dd); mass spectrum, m/z 236.140 (M^+, calcd for $C_{14}H_{20}O_3$ 236.141).

Methyl 5-Acetoxy-3-oxo-5-(2,6,6-trimethylcyclohexen-1-yl)pentanoate (51). To a solution of **44** (281 mg, 1.05 mmol) in methylene chloride (5 mL) at 0 °C was added pyridine (100 μL, 100 mg, 1.2 mmol), followed by acetyl chloride (78 μL, 87 mg, 1.1 mmol). A precipitate was formed which gradually dissolved when the reaction mixture was stirred for 24 h at room temperature. The solution was diluted with ether (10 mL), washed twice with water, dried, and evaporated, and the residue was chromatographed to give 260 mg (80%) of **51**: NMR ($CDCl_3$) δ 1.02 (3 H, s), 1.16 (3 H, s), 1.78 (3 H, s), 2.0 (3 H, s), 1.3–2.4 (6 H, broad m), 2.7–3.3 (2 H, m), 3.52 (2 H, s), 3.76 (3 H, s), 5.92 (1 H, dd).

***trans*-Methyl 3-Oxo-5-(2,6,6-trimethylcyclohexen-1-yl)-pent-4-enoate (46). A. From 51.** The acetate **51** (79 mg, 0.25 mmol) was dissolved in toluene (3 mL) containing triethylamine (29 mg, 0.29 mmol) and the solution was refluxed under nitrogen for 1.5 h. The solution was cooled to 0 °C, diluted with ether, washed with water, dried, and evaporated to give 63 mg (100%) of **46**, identical with the material obtained from **44**.

B. From β-Ionone (49). Sodium hydride (10.50 g, 0.23 mol of a 50% mineral oil suspension) was rinsed under nitrogen with pentane to remove mineral oil, and dimethyl carbonate (24 g, 0.27 mol) was added. The stirred suspension was heated to gentle reflux. From a dropping funnel containing β-ionone (**49**, 20.00 g, 0.1 mol) 3 mL was added dropwise to the suspension. As hydrogen began to evolve, the remaining **49** was added slowly (3 h) and stirring was continued until the reaction mixture solidified. After addition was complete, heating was continued for 2 h. The mixture was allowed to stand for 3.5 h at room temperature, then 5 mL of methanol in benzene was added and the mixture was stirred for 45 min. The mixture was poured on to 50 g of ice and 10 mL of concentrated hydrochloric acid was added, followed by ether (200 mL). The mixture was agitated and a further quantity of hydrochloric acid was added to make the aqueous layer acidic to litmus. The ether layer was separated, washed with water and saturated sodium bicarbonate, dried, and evaporated. The residue was chromatographed (ether–petroleum ether 1:1) to give 20.0 g (80%) of **46**, identical with the material prepared by method A.

Methyl (2*EZ*,4*E*)-3-(Trimethylsiloxy)-5-(2,6,6-trimethylcyclohexen-1-yl)penta-2,4-dienoate (52). To a solution of **46** (100 mg, 0.4 mmol) in 5 mL of dry ether was added a solution of chlorotrimethylsilane (222 mg, 2 mmol) in 15 mL of dry ether containing triethylamine (202 mg, 2 mmol). The resultant slurry was stirred in a sealed flask for 2 h, the solvent was removed in vacuo, and the product was separated from triethylamine hydrochloride by extraction with pentane. The pentane extract was filtered and evaporated to give 130 mg (100%) of **52**: NMR (CCl_4) δ 0.2 (9 H, two s), 1.3 (6 H, two s), 1.2–1.7 (4 H, two s), 1.7 (3 H, two s), 2.0 (2 H, broad d), 3.55 (3 H, s), 4.95 (1 H, d), 5.6–7.4 (2 H, m); mass spectrum, m/z 322.195 (M^+, calcd for $C_{18}H_{30}O_3Si$ 322.196).

Irradiation of 52. A solution of **52** (125 mg, 0.38 mmol) in pentane (20 mL) in a Pyrex flask equipped with reflux condenser and nitrogen inlet was irradiated with a 250-W General Electric sunlamp for 22 h. The solution was allowed to reflux, thus maintaining a temperature of 35 °C. The pentane was evaporated to give 125 mg (100%) of **55** as a mixture of isomers: NMR (CCl_4) δ 0.3 (9 H, two s), 1.1 (6 H, two s), 1.2–1.9 (4 H, m), 2.3 (2 H, broad t), 3.0–3.8 (2 H, m), 3.7 (3 H, two s), 4.7–5.5 (4 H, m).

Methyl (2*E*,4*E*)-3-Acetoxy-3-(2,6,6-trimethylcyclohexen-1-yl)penta-2,4-dienoate (53) and Methyl (2*Z*,4*E*)-3-Acetoxy-3-(2,6,6-trimethylcyclohexen-1-yl)penta-2,4-dienoate (54). To a solution of **46** (1.00 g, 4 mmol) in pyridine (15 mL) was added acetic anhydride (2.60 g, 25 mmol). The mixture was stirred for 18 h and poured over ice (75 g) and concentrated hydrochloric acid (16 mL). The resulting suspension was extracted twice with 50-mL portions of ether and the combined ether extracts were washed with 1 N hydrochloric acid (25 mL), water (25 mL), and 3 times with saturated sodium bicarbonate, then dried, and evaporated. The residue was chromatographed (10% ether–petroleum ether) to give 620 mg (53%) of **53**: NMR ($CDCl_3$) δ 1.06 (6 H, s), 1.78 (3 H, s), 2.25 (3 H, s), 1.2–2.2 (6 H, m), 3.74 (3 H, s), 5.55 (1 H, s), 6.60 (1 H, broad d, J = 16 Hz), 7.40 (1 H, d, J = 16 Hz). **54**: 420 mg (36%); NMR ($CDCl_3$) δ 1.01 (6 H, s), 1.72 (3 H, s), 2.36 (3 H, s), 1.2–2.2 (6 H, m), 3.74 (3 H, s), 5.64 (1 H, s), 6.0 (1 H, d, J = 16 Hz), 6.2 (1 H, d, J = 16 Hz); mass spectrum, m/z 292.167 (M^+, calcd for $C_{17}H_{24}O_4$ 292.167).

Irradiation of 53 and 54. Solutions of **53** (620 mg, 2.12 mmol) and **54** (420 mg, 1.44 mmol) in 180 mL of pentane were irradiated separately for 1 h with a Hanovia 450-W mercury lamp through a Pyrex filter. TLC indicated that a similar mixture resulted from each reaction. The mixtures from the two reactions were combined, the pentane was evaporated, and the residue was chromatographed (10% ether–petroleum ether) to give 528 mg (51%) of **58**: IR (film) 1770, 1730, 1660, 1435, 1370, 1355, 1200, 1105, 1080, 1030, 900 cm^{-1}; NMR ($CDCl_3$) δ 1.03 (6 H, s), 1.34–1.82 (4 H, m), 2.16 (3 H, s), 2.19 (2 H, broad t), 3.73 (3 H, s), 3.75 (2 H, d), 4.61 (1 H, d), 5.04 (1 H, m), 5.17 (1 H, t, J = 7 Hz), 5.68 (1 H, s); mass spectrum, m/z 292.168 (M^+, calcd for $C_{17}H_{24}O_4$ 292.167). **59**: 323 mg (31%); IR (film) 1775, 1730, 1670, 1570, 1415, 1280, 1165, 1110, 1030 cm^{-1}; NMR ($CDCl_3$) δ 1.06 (6 H, s), 1.1–1.82 (4 H, m), 2.18 (2 H, broad t), 2.25 (3 H, s), 3.14 (2 H, d, J = 2 Hz), 3.69 (3 H, s), 4.63 (1 H, d, J = 3 Hz), 5.01 (1 H, m), 5.25 (1 H, t, J = 7 Hz), 5.58 (1 H, t, J = 2 Hz); mass spectrum, m/z 292.168 (M^+, calcd for $C_{17}H_{24}O_4$ 292.167).

Methyl 3-Acetoxy-5-(2-methylene-6,6-dimethylcyclohex-1-ylidene)pent-3-enoate (61). A. From 58. A solution of **58** (100 mg, 0.40 mmol) in ether (1 mL) containing triethylamine (14 mg, 0.14 mmol) was stirred for 21 h at room temperature. Evaporation of the solvent and triethylamine in vacuo afforded a solid residue which was crystallized from hexane to give 60 mg (60%) of **61** as colorless needles: mp 80–82.5 °C; IR (film) 1760, 1740, 1375, 1215, 1110 cm^{-1}; NMR ($CDCl_3$) δ 1.06 (6 H, s), 1.25–2.85 (4 H, m), 2.24 (2 H, broad t), 3.33 (2 H, s), 3.72 (3 H, s), 4.72 (1 H, d, J = 3 Hz), 5.08 (1 H, m), 5.92 (1 H, d, J = 10 Hz), 6.23 (1 H, d, J = 10 Hz); mass spectrum, m/z 292.168 (M^+, calcd for $C_{17}H_{24}O_4$ 292.167).

B. From 59. A solution of **59** (100 mg, 0.40 mmol) in toluene containing triethylamine (14 mg, 0.14 mmol) was refluxed for 60 min. Workup as described above gave 60 mg (60%) of **61**, which was identical with material obtained from **58**.

Methyl 2-(5,5,8a-Trimethyl-5,6,7,8-tetrahydro-1(8a*H*)-benzopyranyl)acetate (47). A solution of **46** (500 mg, 2.0 mmol) and triethylamine (103 mg, 2 mmol) in 180 mL of pentane–methylene chloride (4:1) was irradiated for 1 h with a 450-W Hanovia lamp through a Pyrex filter. The solvent and triethylamine were removed by evaporation to give 500 mg (100%) of virtually pure **47**, identical with the material obtained from **44** with stannic chloride.

Methyl 3-Oxo-5-(2-methylene-6,6-dimethylcyclohex-1-ylidene)pentanoate (56). A solution of **46** (500 mg, 2.0 mmol) in dry methanol (180 mL) was irradiated for 1 h with a 450-W Hanovia lamp through Pyrex. The solvent was removed and the residual oil was chromatographed (10% ether-petroleum ether) to give 300 mg (60%) of **56**: IR (film) 1750, 1720, 1660, 1630, 1440 cm^{-1}; NMR ($CDCl_3$) δ 1.06 (6 H, s), 1.1–1.9 (4 H, m), 2.18 (2 H, broad t), 3.41 (2 H, d, J = 7 Hz), 3.48 (2 H, s), 3.76 (3 H, s), 4.55 (1 H, d, J = 3 Hz), 5.02 (1 H, m), 5.38 (1 H, t, J = 7 Hz); mass spectrum, m/z 250.157 (M^+, calcd for $C_{15}H_{22}O_3$ 250.157).

***cis*-Methyl 2-Oxo-5,5,8a-trimethyl-1,2,3,5,6,7,8,8a-octahydronaphthalenecarboxylate (45) and *cis,trans*-Methyl 2-Oxo-5,5,8a-trimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalenecarboxylate (65).** To a solution of sodium methoxide, prepared from freshly cut sodium (70 mg, 3 mmol) and 50 mL of dry methanol, was added a solution of **46** (500 mg, 2.0 mmol) in 130 mL of methanol. This solution was irradiated for 4 h through a Pyrex filter with a 450-W Hanovia lamp. Ammonium chloride was added to neutralize the sodium methoxide and the methanol was removed by evaporation. Ether, followed by water, was added and the ether layer was separated, washed with water, dried, and evaporated. The residual oil was chromatographed (10–50% ether–petroleum ether) to give 180 mg (36%) of **65**: mp 111–113 °C; IR (Nujol) 1745, 1675, 1150 cm^{-1}; NMR ($CDCl_3$) δ 0.99 (3 H, s), 1.07 (3 H, s), 1.24 (3 H, s), 1.0–1.9 (6 H, m), 2.23 (1 H, t, J = 3 Hz), 3.30 (1 H, s), 3.72 (3 H, s), 6.16 (1 H, dd, J = 3 Hz, 7 Hz), 7.04 (1 H, dd, J = 3 Hz, 7 Hz); mass spectrum,

m/z 250.157 (M^+, calcd for $C_{15}H_{22}O_3$ 250.157). **45**: 150 mg (30%); identical with material obtained from **44** with stannic chloride.

Irradiation of 47 in Methanol–Sodium Methoxide. To a solution of sodium methoxide, prepared from sodium hydride (50 mg of 50% mineral oil dispersion, 1 mmol) and dry methanol (180 mL) was added **47** (283 mg, 1.1 mmol) and the mixture was irradiated for 4 h with a Hanovia 450-W mercury lamp through a Pyrex filter. The mixture was worked up as for irradiation of **46** to give 263 mg of a semicrystalline material. This was a mixture of **45** and **65** as determined by TLC and NMR spectroscopy in a ratio of 1:1. During the same time period, a similar solution of **47** in methanolic sodium methoxide which was kept in the dark underwent no significant changes.

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Supplementary Material Available: Elemental analyses data (1 page). Ordering information is given on any current masthead page.

Synthesis of Methylated Benzo[*b*]fluoranthenes and Benzo[*k*]fluoranthenes[1,2]

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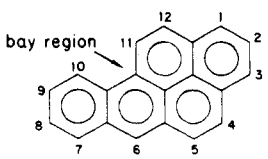
A series of monomethyl and dimethyl derivatives of benzo[*b*]fluoranthene (BbF) and benzo[*k*]fluoranthene (BkF) were synthesized in order to investigate the environmental occurrence and structural requirements for carcinogenicity of methylated nonalternant polycyclic aromatic hydrocarbons. 9-Methyl-BbF (**5**), 12-methyl-BbF (**6**), and 1-methyl-BbF (**7**) were prepared from the appropriate oxotetrahydro-BbF's (**17–19**). 8-Methyl-BbF (**8**) was synthesized from 1-methyl-3-oxo-1,2,3,10b-tetrahydrofluoranthene (**20**) in 11 steps. 3-Methyl-BbF (**9**) and 1,3-dimethyl-BbF (**10**) were prepared from 3-methyl-1-oxo-1,2,3,3a-tetrahydrobenzo[*b*]fluoranthene (**31**), which was synthesized from methyl 11*H*-benzo[*b*]fluorene-11-carboxylate (**28**). 7-Methyl-BbF (**11**) was obtained by condensation of 1-methylfluorene (**33**) with *o*-bromobenzaldehyde, followed by treatment with KOH and quinoline. 5,6-Dimethyl-BbF (**12**) was synthesized by reaction of 2,3-dimethylbutadiene with acephenanthrylene (**38**) followed by aromatization. 8-Methyl-BkF (**13**) was synthesized from 8-oxo-8,9,10,11-tetrahydro-BkF. 9-Methyl-BkF (**14**) was prepared by Friedel–Crafts reaction of 2-methylsuccinic anhydride with fluoranthene, followed by Wolff–Kishner reduction, cyclization, $LiAlH_4$ reduction, dehydration, and aromatization. 2-Methyl-BkF (**16**) was synthesized by an analogous sequence, beginning with 2-methylfluoranthene and succinic anhydride. 7,12-Dimethyl-BkF (**15**) was prepared by a two-step reduction of 7,12-dicyano-BkF (**51**).

Methyl substitution influences the carcinogenicity and tumor initiating activity of polycyclic aromatic hydrocarbons (PAH). For example, 6-, 7-, 8-, 9-, and 10-methylbenzo[*a*]pyrene, as well as 7,10-dimethylbenzo[*a*]pyrene, are less active as tumor initiators on mouse skin than is benzo[*a*]pyrene (**1**) whereas 11-methylbenzo[*a*]pyrene is a stronger tumor initiator than is **1**.[3,4] Chrysene (**2**) is a weak tumor initiator, but 5-methylchrysene is a powerful tumor initiator and carcinogen.[5,6] The other monomethylchrysenes are only weakly active or inactive.[5] Many other examples are available[7] and, among the alternant PAH, the structural requirements favoring tumorigenicity are the presence of a bay region methyl group and a free peri position, both adjacent to an unsubstituted angular ring.[8]



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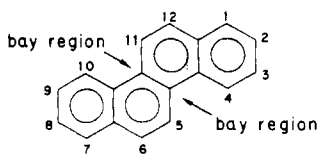

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It is not known, however, whether similar effects on carcinogenicity would occur upon methyl substitution of nonalternant PAH such as benzo[*b*]fluoranthene (BbF, **3**)

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