Stereoselective Total Synthesis of (±)-Trichodiene: Biogenetic Precursor of the Trichothecane Sesquiterpenoids

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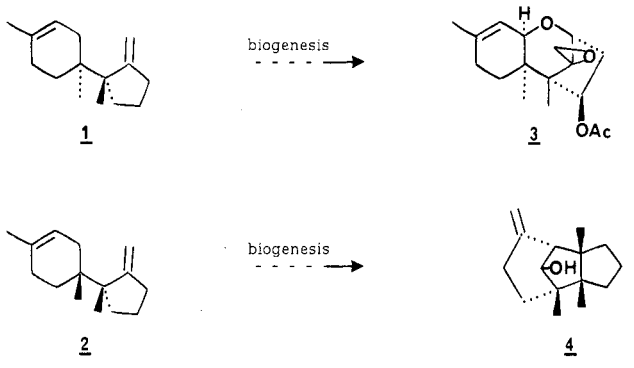
Received April 10, 1980

Two approaches to the total synthesis of (±)-trichodiene (1) are reported from cis-fused lactone **10**. Sequential alkylation of lactone **10** was observed to be highly stereoselective as established by the construction of diastereomeric lactone esters **12** and **14**. Lactone ester **12** was utilized to prepare (±)-trichodiene (1) with a high degree of regioselectivity. All attempts to synthesize (±)-bazzanene (**2**), the diastereomer of (±)-trichodiene (1), from lactone **13** were found to be unsuccessful in the last stage of the synthetic scheme.

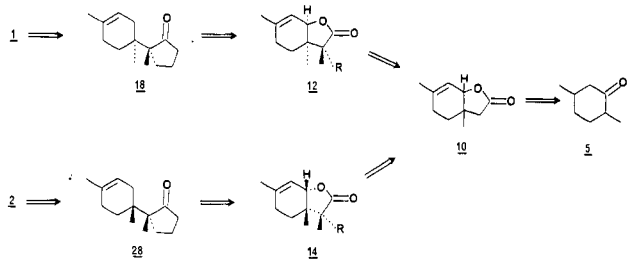
The sesquiterpene hydrocarbon (±)-trichodiene (1, Scheme I) was isolated from the extract of mycelium of the fungus *Trichothecium roseum* Link. The structure of trichodiene (1) was determined by Nozoe and Machida in 1970 via degradation and spectroscopy.[1] Trichodiene (1) was found to arise, biogenetically, from all *trans*-farnesyl pyrophosphate via *Trichothecium roseum*.[2] Trichodiene (1) has also been shown to be the biogenetic precursor of the trichothecane family of sesquiterpenoids as characterized by the cytotoxic fungal metabolite (−)-trichodermin (**3**).[2-4] The structure and absolute stereochemistry of (−)-trichodermin (**3**) were elucidated by X-ray diffraction, and, therefore, the structure and absolute stereochemistry of trichodiene (1) are now firmly established.[5] The trichothecane family of sesquiterpenoids contains a wide variety of biologically active antifungal, antitumor, cytotoxic, and phytotoxic molecules.[6,7] The natural products are potent inhibitors of protein and DNA syntheses in eukaryotic cells. The mode of action of the trichothecanes is thought to occur by binding to eukaryotic polysomes and ribosomes followed by inactivation of the ribosomal cycle.[8]

In 1969 Matsuo and co-workers isolated (+)-bazzanene (**2**, Scheme I) from leafy liverworts *Bazzania pompeana* (*Hepaticae*).[9] However, Andersen and co-workers in 1977 revised the original structural assignment to that represented by structure **2** on the basis of spectroscopic data and biogenetic considerations.[10] Concurrently, Matsuo and Hayashi also revised their original structural assignment and absolute configuration to conform to structure **2** for (+)-bazzanene on the basis of further degradation and spectroscopy.[11] Bazzanene (**2**) is thought to be the biogenetic precursor of another family of cyclotrichothecanes, one member of which is (+)-gymnomitrol (**4**).[12] Trichodiene (1) and bazzanene (**2**) are diastereomers. We wish to report, herein, the full details of our successful stereo-

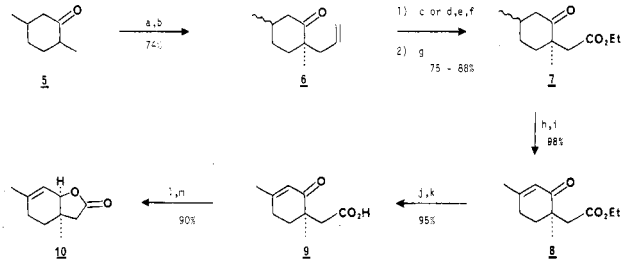
Scheme I



Scheme II. Retrosynthetic Plan



Scheme III. Preparation of Lactone 10[a]



[a] (a) NaH, DME. (b) $BrCH_2CH{=}CH_2$. (c) $RuCl_3$ (catalyst), $NaIO_4$, H_2O, *t*-BuOH. (d) O_3, CH_2Cl_2, −78 °C. (e) Zn, HOAc. (f) H_2CrO_4, acetone. (g) EtI, K_2CO_3, acetone. (h) Br_2, HOAc. (i) $CaCO_3$, DMA. (j) KOH/EtOH/H_2O. (k) H_3O^+. (l) 2× *i*-Bu_2AlH, C_6H_6, CH_2Cl_2. (m) 10% H_2SO_4.

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(12) See ref 1–4 in the following paper.

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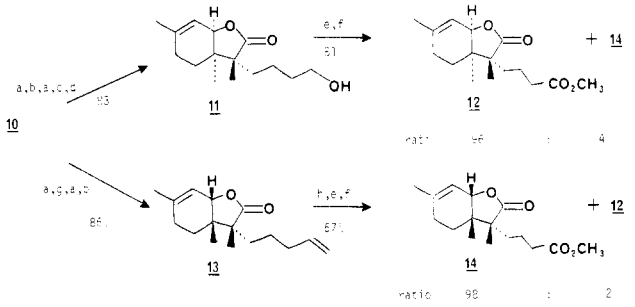
selective total synthesis of (±)-trichodiene (1) and our attempts to construct (±)-bazzanene (2) via a common synthetic intermediate.[13,14]

One of the most difficult tasks that beset the synthetic organic chemist is the construction of two adjacent chiral quaternary centers with a high degree of stereoselectivity. This objective becomes a real dilemma when the two adjacent chiral quaternary centers are free to rotate about a common carbon–carbon single bond as in the diastereomers trichodiene (1) and bazzanene (2). One excellent method which has been utilized to solve this type of stereochemical enigma is to direct sequential alkylation reactions in a cis-fused bicyclic carbonyl compound from the less hindered convex side of the molecule. In a retrosynthetic plan (Scheme II) it should be possible to construct trichodiene (1) and bazzanene (2) from the respective cyclopentanones **18** and **28** by some type of carbonyl-to-methylene transfer reagent or process. Ketones **18** and **28** could be prepared from diastereomerically pure lactones **12** and **14** [R = $(CH_2)_3CO_2Me$], respectively. The stereoselective synthesis of lactones **12** and **14** from cis-fused lactone **10** might be realized, hopefully, by sequential methylation and alkylation [R = $(CH_2)_4OTHP$] or the reverse alkylation [R = $(CH_2)_3CH{=}CH_2$] and methylation, followed by appropriate chemical manipulation. It is in this latter stage of these syntheses that the stereochemical problems associated with trichodiene (1) and bazzanene (2) need to be solved. Finally, in a retrosynthetic sense, lactone **10** should be readily available from 2,5-dimethylcyclohexanone (**5**) in a limited number of synthetic steps. Thus the synthesis begins with ketone **5**.

Ketone **5** (Scheme III) is alkylated regioselectivity in the following manner. The thermodynamically more stable $\Delta^{1,2}$ enolate anion is generated with sodium hydride in 1,2-dimethoxyethane. Conia reports that selective generation of the $\Delta^{1,2}$ enolate anion is reinforced by both methyl substitutents at positions 2 and 5.[15] Carefully controlled quenching of this enolate anion with allyl bromide at 0 °C affords ketoalkene **6** in 74% yield after fractional distillation. Two methods of oxidative cleavage of alkene **6** were explored. Ozonolysis[16] of alkene **6** in dichloromethane at −78 °C followed by reduction with zinc powder in acetic acid, oxidation with Jones reagent,[17] and esterification[18] with ethyl iodide in the presence of anhydrous potassium carbonate in acetone affords keto ester **7** in 75% overall yield. Alternatively, oxidation of alkene **6** with sodium metaperiodate in aqueous *tert*-butyl alcohol in the presence of a catalytic amount of ruthenium trichloride followed by esterification gives keto ester **7** in 88% overall yield.[19] Bromination of keto ester **7** followed by dehydrobromination of the crude bromo ketone with anhydrous calcium carbonate in refluxing *N,N*-dimethylacetamide (DMA) produces enone **8** in 88% yield.[20] Saponification of enone ester **8** with potassium hydroxide in aqueous ethanol gives keto acid **9** in 95% yield after acidification. Reductive lactonization of keto acid **9** to lactone **10**[13a,b,14] in 90% yield was smoothly accomplished by sequential treatment of keto acid **9** with 2 equiv of diisobutylaluminum hydride[21] in benzene–dichloromethane at 0 °C followed by quenching the 10% sulfuric acid at 0 °C. This lactonization presumably proceeds via intramolecular attack of the carboxylic acid group on an intermediate allylic carbonium ion. Examination of a Dreiding stereomodel for this lactonization intermediate suggests that this cyclization should be highly regioselective and should produce the desired cis-fused γ-lactone **10**. This stereochemical outcome is confirmed by NMR spectroscopy. The dihedral angle subtended by the allylic oxymethine proton and the vinyl proton is approximately 40°. The predicted coupling constant, based upon the Karplus equation,[22] would be between 4 and 5 Hz. The observed coupling constant for the allylic oxymethine doublet at δ 4.24 is 4 Hz. The respective dihedral angle for a trans-fused lactone is about 90° which is associated with a vicinal coupling constant near zero according to the Karplus equation.[22] These data are fully consistent with a cis-fused γ-lactone for structure **10**, and no trans-fused γ-lactone was observed or isolated. Lactone **10** also was prepared by Raphael and co-workers[13a,b] in their synthesis of (−)-trichodermin (**3**).

Methylation of lactone **10** (Scheme IV) by generating the enolate anion with lithium diisopropylamide (LDA) in DME followed by the addition of methyl iodide gives

Scheme IV. Alkylation of Lactone 10[a]



[a] (a) LDA, DME. (b) CH_3I. (c) $Br(CH_2)_4OTHP$, HMPA. (d) *p*-TsOH, CH_3OH. (e) H_2CrO_4, acetone. (f) CH_2N_2, Et_2O. (g) $Br(CH_2)_3CH{=}CH_2$, HMPA. (h) OsO_4 (catalyst), $NaIO_4$, H_2O, *t*-BuOH.

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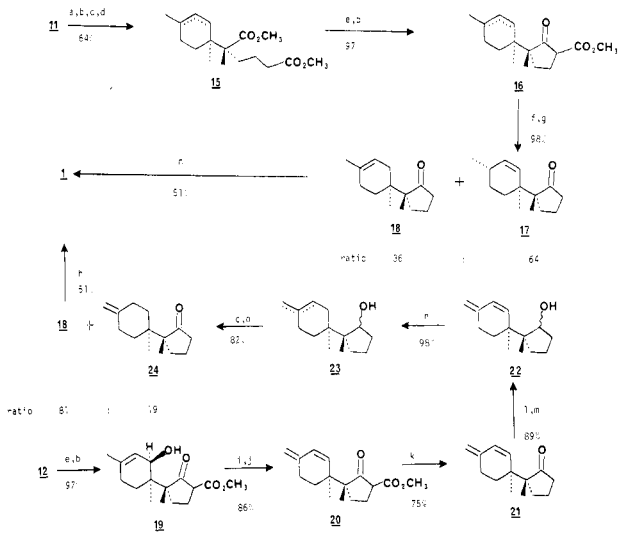
Scheme V. Synthesis of (±)-Trichodiene (1)[a]



[a] (a) Ca, NH_3, THF, HMPA, −33 °C. (b) H_3O^+. (c) H_2CrO_4, acetone. (d) CH_2N_2, Et_2O. (e) $NaN(SiMe_3)_2$, DME. (f) DBU, xylene, Δ. (g) Chromatography on 15% $AgNO_3$-silica gel 60 using 2.5% Et_2O-97.5% petroleum ether (bp 30-60 °C) as an eluant. (h) $Ph_3P{=}CH_2$, Me_2SO, Δ. (i) HCl(g), CH_2Cl_2, −20 °C. (j) 2,4,6-Collidine, Δ. (k) DBU, 2,4,5-collidine, Δ. (l) $LiAlH_4$, Et_2O. (m) 15% NaOH, H_2O. (n) Li, NH_3, Et_2O, EtOH. (o) Chromatography on 15% $AgNO_3$-silica gel 60 using 25% Et_2O-75% petroleum ether (bp 30-60 °C) as an eluant.

the corresponding monomethyl lactone, **10A**,[13a,23] in quantitative yield. Alkylation of methyl lactone **10A** by generation of the enolate anion with LDA in DME followed by quenching with 4-bromobutyl tetrahydropyranyl ether[24] dissolved in hexamethylphosphoric triamide (HMPA) and subsequent methanolysis in the presence of *p*-toluenesulfonic acid affords lactone alcohol **11** in 83% overall yield. This alkylation appears to be highly stereoselective. It is expected that this alkylation should take place from the less hindered convex side of the cis-fused bicyclic enolate anion. Oxidation of alcohol **11** with excess Jones reagent[17] in acetone and esterification of the resulting acid with an ethereal solution of diazomethane produces a mixture of lactone esters **12** and **14** in 81% yield as a 96:4 ratio of diastereomers, respectively. These two isomers are readily distinguishable by GLC, LC, NMR, and melting point. The reverse alkylation sequence to that mentioned above resulted in incomplete methylation and poor stereoselectivity in the second stage. However, alkylation of lactone **10** with 5-bromo-1-pentene in HMPA followed by methylation under similar conditions to those utilized earlier gives lactone **13** in 86% overall yield. Oxidative cleavage of alkene **13** with sodium metaperiodate in aqueous *tert*-butyl alcohol in the presence of a catalytic amount of osmium tetraoxide produces an intermediate aldehyde.[25] Oxidation of this aldehyde with Jones reagent[17] in acetone followed by esterification with an ethereal solution of diazomethane affords a mixture of lactone esters **12** and **14** in 67% overall yield as a 2:98 ratio of diastereomers, respectively. Thus the stereochemical problems associated with the syntheses of diastereomers trichodiene (**1**) and bazzanene (**2**) are resolved with a reasonably high degree of stereoselectivity.[26]

Hydrogenolysis of the allylic carbon–oxygen bond of lactone alcohol **11** (Scheme V) is smoothly effected by calcium metal in liquid ammonia–HMPA–tetrahydrofuran (THF) at −33 °C.[27] Acidification affords a carboxylic acid alcohol which when oxidized with Jones reagent[17] in acetone followed by esterification with an ethereal solution of diazomethane gives diester **15** in 64% overall yield as a 36:64 ratio of tri- to disubstituted alkenes, respectively. Other metals (Li, Na, K, or Zn) and conditions proved to be much less efficient in terms of the regioselectivity of the desired trisubstituted alkene isomer. Dieckmann condensation[28] of diester **15** with 4 equiv of sodium bis(trimethylsilyl)amide[29] in DME followed by quenching with 5% HCl at 0 °C produces β-keto ester **16** in 97% yield. Decarboxylation of β-keto ester **16** with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU)[30] in refluxing xylene for 16 h produces enones **17** and **18** in 98% yield in a 64:36 ratio, respectively. These enones were separated by high-pressure LC on 15% silver nitrate impregnated silica gel 60[31] with 2.5% ether–97.5% petroleum ether (bp 30–60 °C) as an eluant. Trichoenone (**18**) was converted into (±)-trichodiene (**1**) in 51% yield with 10 equiv of methylenetriphenylphosphorane Wittig reagent[32] in scrupulously dried dimethyl sulfoxide, despite the fact that previous reports[1,13f,25] indicated that this reaction was unsuccessful. The IR, NMR (60 and 100 MHz), and mass spectral data for synthetic (±)-trichodiene (**1**) and the corresponding mono- as well as the diepoxide[11] of **1** were identical with the respective data reported[1-3,11] for the natural substance. Because of the poor regioselectivity in the construction of trichoenone **18** by the aforementioned route, an alternative synthesis of enone **18** was devised and explored.

Dieckmann condensation[28] of lactone ester **12** (Scheme V) with 3.5 equiv of sodium bis(trimethylsilyl)amide[29] in DME followed by quenching with 10% HCl at 0 °C produces β-keto ester **19** in 97% yield. All attempts to hydrolyze and decarboxylate β-keto ester **19** under acid, base, or neutral conditions gave only the lactone carboxylic acid corresponding to lactone ester **12**. The hydroxyl function of compound **5** could not be esterified under ordinary conditions (Ac_2O, pyridine; Ac_2O, HOAc, $HClO_4$; MsCl, Et_3N, CH_2Cl_2; *p*-TsCl, pyridine). However, treatment of allylic alcohol **19** with anhydrous hydrogen chloride gas in dichloromethane at −20 °C affords an unstable *tertiary* allylic chloride, presumably by S_N2' rearrangement. Dehydrochlorination of this intermediate chloride by heating it in 2,4,6-collidine at 180–185 °C for 25 min produces diene **20** in 86% overall yield from alcohol **19**. Decarboxylation of β-keto ester **20** with DBU[30] in 2,4,6-

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(26) Shortly after preliminary communication of our successful syntheses of (±)-trichodiene (**1**) we received a personal communication from Professor W. Kreiser, University of Braunschweig. Professor W. Kreiser and M. Scholtz (Ph.D. Dissertation, 1976) have prepared lactone **12** [R = $(CH_2)_3I$, Scheme II] and characterized this compound by X-ray diffraction in conjunction with Professor U. Thewalt. Professor W. Kreiser and M. Scholtz also have synthesized lactone **12** [R = $(CH_2)_3CO_2Me$] as well as structures **15** and **17–19** independently. We thank Professor W. Kreiser for providing us with this information.

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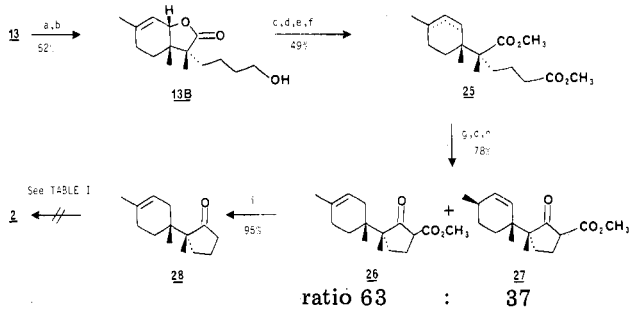
Scheme VI. Synthesis of (±)-Bazzanenone (28)[a]

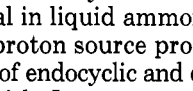


[a] (a) OsO_4 (catalyst), $NaIO_4$, H_2O, *t*-BuOH. (b) $NaBH_4$, EtOH, 0 °C. (c) Ca, NH_3, TMEDA, EtOH, −33 °C. (d) H_3O^+. (e) H_2CrO_4, acetone. (f) CH_2N_2, Et_2O. (g) $NaN(SiMe_3)_2$, DME. (h) Chromatography on silica gel-60 using 10% Et_2O-90% petroleum ether (bp 30–60 °C) as an eluant. (i) DBU, 2,4,5-collidine, Δ.

collidine at 180–185 °C for 2.5 h gives dienone **21** in 75% yield. Reduction of dienone **21** with lithium aluminum hydride in ether followed by a workup using 15% sodium hydroxide solution affords dienol **22** as a mixture of diastereomers in 89% yield. Reduction of dienol **22** with lithium metal in liquid ammonia–ether[33] with 100% ethanol as the proton source produces enol **23** in 98% yield as a mixture of endocyclic and exocyclic alkenes. Oxidation of enol **23** with Jones reagent[17] in acetone followed by chromatography of the resulting mixture of enones on 15% silver nitrate impregnated silica gel 60[31] with 25% ether–75% petroleum ether (bp 30–60 °C) as an eluant gives enones **18** and **24** in 82% yield in a 81:9 ratio, respectively. Synthetic trichoenone (**18**) was then converted into (±)-trichodiene (**1**) by the Wittig reaction[32] described above.

Our approach to the synthesis of (±)-bazzanene (**2**) begins with lactone **13** (Scheme VI). Selective oxidative cleavage of the monosubstituted alkene with sodium metaperiodate with a catalytic amount of osmium tetraoxide[25] in aqueous *tert*-butyl alcohol affords an intermediate aldehyde. Reduction of this aldehyde with a solution of sodium borohydride in 100% ethanol at 0 °C gives lactone alcohol **13B** in 52% overall yield from alkene **13**. Hydrogenolysis[27] of the allylic carbon–oxygen bond with calcium metal in liquid ammonia–tetramethylethylenediamine (TMEDA) at −33 °C followed by acidification gives an intermediate acid alcohol. Oxidation of this acid alcohol with Jones reagent[17] in acetone followed by esterification of the resulting diacid with an ethereal solution of diazomethane produces diester **25** in 49% overall yield from **13B** as a 63:37 ratio of tri- to disubstituted alkenes, respectively. Interestingly enough, this ratio is nearly the inverse to that observed upon hydrogenolysis of lactone alcohol **11** to diester **15** (Scheme V). Dieckmann condensation of diester **25** with 3 equiv of sodium bis(trimethylsilyl)amide[29] in DME followed by quenching with 10% hydrochloric acid solution at 0 °C and chromatography on silica gel 60 with a solution of 10% ether–90% petroleum ether (bp 30–60 °C) as an eluant gives β-keto esters **26** and **27** in 78% overall yield as a 63:37 ratio of tri- to disubstituted alkene isomers. Decarboxylation of β-keto ester **26** to bazzanenone **28** is smoothly accomplished in 95% yield by treatment of **26** with DBU[30] in 2,4,6-collidine at 180 ± 5 °C for 3 h. A Wittig reaction[32] on synthetic bazzanenone (**28**) under identical conditions with those utilized for (±)-trichoenone (**18**) showed only about 5% conversion to a product containing an exocyclic methylene moiety as indicated by NMR spectra of the crude reaction material. This result could not be improved even after repeated attempts to do so. Both synthetic trichoenone (**18**) and bazzanenone (**28**) were treated with a variety of reagents under different conditions listed in Table I in attempts to effect the conversion of the cyclopentanones to exocyclic methylenes. Synthetic bazzanenone (**28**) failed to undergo reaction with all but three of the entries listed in Table I, even though appropriate ex-

Table I

reagents and conditions[e]	(±)-trichoenone (18)	(±)-bazzanenone (28)	ref
$(C_6H_5)_3P{=}CH_2$, Me_2SO	+[a]	−[b]	32
CH_3Li, Et_2O or THF −75 °C to rt	−	−	
CH_3MgX, THF, X = Cl or Br		−	
CH_2I_2, Mg(Hg), Et_2O, rt	−		34
$C_6H_5SCH_2Li$, Et_2O, 0 °C to rt	−		35
$C_6H_5SCH_2Li$, THF, TMEDA		−	35
Me_3SiCH_2MgCl, THF, 67 °C	−		36
Me_3SiCH_2Li, Et_2O, 5 °C	−		36
$(EtO)_2POCHLiSO_2CH_3$, DMF or THF		−	37
$(EtO_2)POCHLiSCH_3$		−	37
$Me_2S{=}CH_2$, Me_2SO		−	38
$Me_2SO{=}CH_2$, Me_2SO		−	38
		±[c]	39
p-$TsCH_2NC$, KO-*t*-Bu, *t*-BuOH		−	40
p-$TsCH_2NC$, $NaCH_2SOCH_3$, Me_2SO		±[c]	40
$EtOC{\equiv}CLi$, THF, −78 °C to rt		−	41
$EtOC{\equiv}CMgBr$, THF, rt		−	41
$(C_6H_5)_3P$, Me_3SiCH_2Cl		−[d]	42
p-$TsNHNH_2$, EtOH, HCl		−	43
CH_3NO_2, piperidine, C_6H_6		−	44

[a] + indicates successful reaction, 51% yield. [b] − indicates no reaction. [c] ± indicates resulted in an unidentifiable mixture of products. [d] The trimethylsilyl enol ether of **28** was obtained. [e] rt = room temperature.

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ternal control reactions with either camphor or estrone methyl ether were found to be successful.

Experimental Section

Materials and Techniques. Melting points were determined on a Büchi melting point apparatus and are uncorrected. All boiling points were measured external to the bulb-to-bulb distillation pot in an Aldrich Kugelrohr apparatus (catalog No. Z10, 046-3) and are uncorrected. IR spectra were recorded on either a Perkin-Elmer Model 700 or 237B spectrometer using 0.10-mm NaCl solution cells or as thin films between NaCl plates. NMR spectra were measured on either a Varian Associates Model T-60 or XL-100 spectrometer. High-resolution mass spectra were measured on a Du Pont Flash CEC 21-110B spectrometer at 70 eV, and low-resolution mass spectra were recorded on a Hewlett-Packard Model 5930A with a gas chromatograph (Model 5710) and data system (Model 5933A) at 70 eV. All gas chromatographic analyses were carried out on a Varian Aerograph Series Model 1400 gas chromatograph equipped with a flame-ionization detector with helium as the carrier gas (flow rate 15 mL/min at ambient temperature) and using 6 ft × $^1/_8$ in. stainless-steel columns packed with either (a) 3% SE-30 on Varaport 30, 100/120 mesh, (b) 5% OV-17 on Varaport 30, 80/100 mesh, or (c) 5% FFAP on Varaport 30, 80/100 mesh. Silica gel 60 (F-254, E. Merck No. 5765 and E. Merck No. 7734, 70–230 mesh) were used for thin-layer and column chromatography, respectively. Silica gel 60 (E. Merck No. 9385, 230–400 mesh) impregnated with 15% $AgNO_3$ (w/w)[31] packed in a $^3/_4$ in. × 27 in. stainless-steel column with a $^3/_8$ in. × 12 in. precolumn (170-mL total column volume) in a Waters Associates Model 201 liquid chromatograph equipped with a Model M-6000 pump was used to separate alkene products. All elution solutions were prepared by volume. Ether (Et_2O), tetrahydrofuran (THF), and 1,2-dimethoxyethane (DME) were purified by fresh distillation of anhydrous commercial solvents from $LiAlH_4$ under N_2 immediately before use in all reactions. Pentane and CH_2Cl_2 were distilled from P_2O_5. Diisopropylamine, bis(trimethylsilyl)amine, 2,4,6-collidine, tetramethylethylenediamine (TMEDA), and benzene were distilled from CaH_2 (-40 mesh) under N_2. Hexamethylphosphoric triamide (HMPA) was vacuum distilled from CaH_2 (-40 mesh) onto freshly activated molecular sieves of type 13X. Dimethyl sulfoxide was vacuum distilled (3×) from 95% CaH_2 (-40 mesh)–5% $NaNH_2$ with the last distillation onto freshly activated molecular sieves of type 4A. For all anhydrous reactions performed under an atmosphere of dry N_2 or Ar the equipment was dried in an oven at 120 °C for several hours and then allowed to cool in an atmosphere of dry N_2 or Ar. All liquid transfers were made with N_2- or Ar-filled syringes. The term petroleum ether refers to the Baker "Analyzed Reagent", bp 30–60 °C. The usual workup procedure consisted of extraction of the organic product from an aqueous layer with Et_2O (3–6×). The combined ethereal extracts were then washed with saturated NaCl solution (once), dried over anhydrous $MgSO_4$ (powder) or Na_2SO_4 (granular), filtered through anhydrous $MgSO_4$, and concentrated in vacuo. All microanalyses were performed by Spang Microanalytical Laboratory. The nomenclature utilized is that preferred by Chemical Abstracts.[45]

2,5-Dimethyl-2-(3-propenyl)cyclohexanone (6). To sodium hydride (1.34 g, 31.9 mmol, 57% in mineral oil, washed 3× with 8 mL of dry DME) in DME (70 mL) were added ketone **5** (4.0 g, 31.7 mmol freshly distilled) dissolved in dry DME (10 mL) and 100% EtOH (1 drop) under N_2. The resultant mixture was heated just below reflux for 14.5 h. The resulting suspension of sodium enolate anion was then cooled to 0 °C (ice bath) and allyl bromide (3.83 g, 31.7 mmol, freshly distilled) was added. The reaction mixture was allowed to stir an additional 15 min at 0 °C, and then it was poured into a slurry of ice and saturated NH_4Cl solution and worked up in the usual way. Careful fractional distillation gave 3.89 g (74%) of ketone 6 as a colorless liquid: bp 60–61 °C (0.125 mmHg); IR (film) 3080 ($CH{=}CH_2$), 2930 (CH_3), 1705 (C=O), 1635 (C=C), 920 cm^{-1} ($CH{=}CH_2$); NMR (CCl_4) δ 0.95 (s, 3, CH_3), 1.00 (d, J = 6 Hz, 3 CH_3CH), 4.67–5.94 (m, 3, $CH{=}CH_2$).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.20; H, 10.84.

Ethyl 1,4-Dimethyl-2-oxo-1-cyclohexaneacetate (7). Method A. To a solution of $NaIO_4$ (126.5 g, 592 mmol) in H_2O (2.2 L) was added ketoalkene **6** (16.4 g, 98.6 mmol) and sufficient *tert*-butyl alcohol (~500 mL) to attain a homogenous solution. A catalytic amount of ruthenium trichloride (77 mg) was added, and the resulting clear, yellow solution was allowed to stand at room temperature over a period of 102 h during which time a precipitate of $NaIO_3$ formed. An additional 1.0 L of H_2O was added to dissolve the precipitate, and the reaction mixture was allowed to stand at room temperature for an additional 62 h. The reaction mixture was extracted with Et_2O (10 × 400 mL). The combined ethereal extracts were washed with 10% NaOH solution (5 × 10 mL). The combined basic extracts were washed with Et_2O (5 × 50 mL) to remove neutral side products, acidified with concentrated HCl, and worked up in the usual way to give 16.9 g (93%) of keto acid **7A** as a viscous oil which crystallized on standing. Recrystallization (3×) from Et_2O/hexane resulted in analytically pure keto acid **7A**: mp 108–109 °C; IR (CCl_4) 3650–2400 (CO_2H), 2930 (CH_3), 1800–1730 (CO_2H), 1700 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.98 (d, J = 6 Hz, 3, CH_3CH), 1.16 (s, 3, CH_3), 8.84 (s, 1, CO_2H).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.15; H, 8.86.

Method B. Ketone **6** (43 g, 0.26 mol) dissolved in CH_2Cl_2 (650 mL) was treated with O_3 (Welsbach Ozonizer) at -78 °C (dry ice/*i*-PrOH bath) until a blue color developed. A stream of N_2 was passed through the solution to remove the excess O_3, and the cold bath was removed. To this rigorously stirred cold solution was added 50% HOAc solution (260 mL) followed by Zn metal dust (26 g) in small portions in order to maintain the reduction reaction at gentle reflux. The resulting gray mixture was allowed to stir at room temperature for 45 min. The mixture was diluted with H_2O and filtered through Celite, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (4 × 100 mL). The combined organic extracts were worked up in the usual way to give 41.4 g (95%) of crude keto alkehyde **7B**. The crude keto aldehyde **7B** was dissolved in reagent acetone (1.2 L), and Jones reagent[17] (105 mL, 2.67 M, 0.28 mmol) was added dropwise at 0–15 °C (ice bath) with vigorous stirring. The reaction was then allowed to warm up to room temperature over a period of 30 min. The excess oxidant was quenched with *i*-PrOH, and H_2O (1.5 L) was added to dissolve the green precipitate. The mixture was extracted with Et_2O (5 × 150 mL). The combined ethereal extracts were washed with 10% NaOH solution (3 × 100 mL). The combined basic washes were cooled in an ice bath and acidified with concentrated HCl. The resulting mixture was worked up in the usual way to afford 37.8 g (79%) of viscous colorless keto acid **7A**.

A mixture of the above keto acid **7A** (35 g, 0.19 mol), reagent acetone (1 L, dried over Na_2SO_4), anhydrous K_2CO_3 (39 g, 0.293 mol), and ethyl iodide (147 g, 0.95 mol) was stirred under N_2 at reflux for 2 h. The reaction mixture was cooled to room temperature and filtered, and the acetone was removed in vacuo. Water was added to the residual oil containing precipitated KI, and the mixture was worked up in the usual way to give 38.6 g (96%) of crude ester **7**. Distillation gave 38.2 g (95%) of pure ester **7**: bp 74–75 °C (0.15 mmHg); IR (film) 2940 (CH_3), 1735 (CO_2Et), 1710 (C=O), 1200 cm^{-1} (CO_2Et); NMR ($CDCl_3$) δ 1.00 (d, J = 4 Hz, 3, CH_3CH), 1.14 (s, 3, CH_3), 1.22 (*t*, J = 6 Hz, 3, CH_2CH_3), 4.14 (q, J = 6 Hz, 2, OCH_2CH_3).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.95; H, 9.34.

Ethyl 1,4-Dimethyl-2-oxo-3-cyclohexeneacetate (8). A solution of keto ester **7** (37.5 g, 0.18 mol) in glacial HOAc (250 mL) was cooled to 17 °C (ice water). To this stirred and cooled solution was added a solution of Br_2 in HOAc (41 mL, 4.36 M Br_2 in HOAc) under N_2. The reaction mixture was allowed to warm to room temperature with stirring over a period of 6.5 h. The reaction mixture was then poured into a mixture of Et_2O (330 mL) and H_2O (400 mL). The separated ethereal layer was washed with 10% Na_2SO_3 solution (50 mL), saturated $NaHCO_3$ solution (5 × 100 mL), H_2O (3 × 50 mL), and saturated NaCl solution, dried (Na_2SO_4), and concentrated in vacuo to give 50.1 g (97%) of crude α-bromo ester **8A** as a white crystalline material. Re-

(45) Loening, K. L. Nomenclature Director, Chemical Abstracts Service, P. O. Box 3012, Columbus, OH 43210

crystallization of a small sample from pentane (2×) gave analytically pure bromo ester **8A**: mp 68–72 °C; IR (CCl_4) 2935 (CH_3), 1735 (CO_2Et), 1720 cm^{-1} (α-Br, C=O); NMR (CCl_4) δ 1.22 (s, 3, CH_3), 4.00 (q, J = 7 Hz, 2, OCH_2CH_3), 4.47 (d, J = 9 Hz, 1, CHBrCO).

Anal. Calcd for $C_{12}H_{19}BrO_3$: C, 49.49; H, 6.58; Br, 27.45. Found: C, 49.57; H, 6.59; Br, 27.39.

A solution of this crude α-bromo keto ester **8A** (149.8 g, 0.515 mol) and anhydrous $CaCO_3$ (110 g, 1.10 mol) in *N,N*-dimethylacetamide (1.5 L) was heated at reflux for 45 min under N_2. The reaction mixture was cooled to room temperature and poured into H_2O (3.0 L) and extracted with EtOAc (3 × 400 mL). The combined organic extracts were washed with H_2O (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. Distillation gave 98.0 g (91%) of pure enone ester **8** as a colorless liquid: bp 75–76 °C (0.05 mmHg); IR (CCl_4) 3050 (C=CH), 2986 (CH_3), 1730 (CO_2Et), 1670 (enone), 1640 cm^{-1} (C=C); NMR (CCl_4) δ 1.10 (s, 3, CH_3), 1.21 (t, J = 6 Hz, 3, CH_2CH_3), 1.93 (s, 3, $C=CCH_3$), 2.34 (AB, J_{AB} = 14 Hz, 2, CH_2CO), 4.02 (q, J = 6 Hz, 2, OCH_2CH_3), 5.67 (m, 1, C=CH).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.30; H, 8.74.

1,4-Dimethyl-2-oxo-3-cyclohexeneacetic Acid (9). To enone ester **8** (32.3 g, 153.5 mmol) was added a solution of KOH (86 g, 1.30 mol) in water (500 mL). Enough 100% EtOH was added to the turbid, two-phase mixture to attain homogeneity. The reaction was then allowed to stir at room temperature for 15.5 h. The solution was poured into a mixture of H_2O (500 mL) and Et_2O (200 mL), and saturated NaCl solution (100 mL) was added. The aqueous layer was separated and extracted with Et_2O (5 × 100 mL) to remove neutral products, and then the aqueous layer was acidified with concentrated HCl. This acidified aqueous layer was worked up in the usual way to give 26.6 g (95%) of enone acid **9** as a yellow oil which crystallized on standing. The analytical sample was prepared by recrystallization from Et_2O/hexane to give analytically pure enone acid **9**: mp 89.5–90.5 °C; IR ($CHCl_3$) 3600–2400 (CO_2H), 1800–1705 (CO_2H), 1660 (C=O), 1640 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.20 (s, 3, CH_3), 1.98 (br s, 3, $C=CH_3$), 2.57 (AB, J_{AB} = 14 Hz, 2, CH_2CO), 5.86 (m, 1, C—CH), 10.51 (br s, 1, CO_2H).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.71; H, 7.84.

(3a-*cis*)-3a,4,5,7a-Tetrahydro-3a,6-dimethyl-2(3*H*)-benzofuranone (10). Enone acid **9** (20.0 g, 0.110 mol) was dissolved in dry CH_2Cl_2 (1 L), and the solution was cooled to 0 °C (ice bath) under N_2. Diisobutylaluminum hydride in benzene (151 mL, 1.47 M, 0.222 mmol) was added dropwise, the resulting mixture was allowed to stir for 15 min, and the ice bath was removed. The reaction mixture was stirred an additional 45 min at room temperature and then recooled to 0 °C (ice bath). To this cooled solution was added 20% H_2SO_4 solution (1 L) dropwise at first and then rapidly toward the end of the addition. The resulting reaction mixture was stirred for 30 min, and then the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic solutions were washed with H_2O (2 × 100 mL), saturated $NaHCO_3$ solution (2 × 100 mL), H_2O (100 mL), and saturated NaCl solution (150 mL), dried ($MgSO_4$), filtered ($MgSO_4$), and concentrated in vacuo to give 19 g of crude lactone **10**. Distillation (80 °C, 0.05 mmHg) gave 16.5 g (90%) of analytically pure lactone **10**: mp 48–48.5 °C (lit.[13a] mp 47–48 °C); IR (CCl_4) 1775 (C=O), 1670 cm^{-1} (C=C); NMR (CCl_4) δ 1.14 (s, 3, CH_3), 1.75 (br s, 3, $C=CCH_3$), 2.22 (s, 2, CH_2CO_2), 4.24 (d, J = 4 Hz, 1, CHO), 5.44 (m, 1, C=CH).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.76; H, 8.49. Found: C, 72.32; H, 8.52.

(3aα,3aα,7aα)-3a,4,5,7a-Tetrahydro-3,3a,6-trimethyl-2-(3*H*)-benzofuranone (10A). An ethereal solution of methyllithium (15.6 mL, 2.12 M, 33.1 mmol) was added to anhydrous DME (120 mL) containing a few crystals of 2,2′-bipyridine at −50 °C (dry ice/acetone bath) under N_2. Diisopropylamine (4.62 mL, 33 mmol) was added slowly over a period of 10 min, and the resulting solution was allowed to stir at −50 °C until the evolution of CH_4 ceased. To this dark red solution was added lactone **10** (4.98 g, 30.0 mmol) dissolved in DME (10 mL) at −30 °C over a period of 10 min. The reaction was then allowed to stir for 20 min at room temperature. Iodomethane (8.94 g, 3.91 mL, 63.0 mmol, freshly distilled from P_2O_5) was added, and the resulting reaction mixture was allowed to stir at room temperature for 6 h. The reaction mixture was poured into ice cold 5% HCl solution (100 mL) and worked up in the usual way to give 6 g of methylated lactone **10A**. Distillation gave 5.40 g (100%) of lactone **10A**: bp 75–78 °C (0.4 mmHg) [lit.[13a] bp 104 °C (1 mmHg)]; IR (film) 1770 (C=O), 1670 cm^{-1} (C=C); NMR (CCl_4) δ 1.02 (s, 3, CH_3), 1.03 (d, J = 8 Hz, 3, $CHCH_3$), 1.75 (br s, 3, C=CH), 2.40 (q, J = 7 Hz, 1, $CHCH_3$), 4.37 (m, 1, CHO), 5.40 (m, 1, C=CH).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.77, 73.24; H, 9.01, 9.04.

(3aα,3aα,7aα)-3a,4,5,7a-Tetrahydro-3,3a,6-trimethyl-3-(4-hydroxybutyl)-2(3*H*)-benzofuranone (11). An etheral solution of methyllithium (14.7 mL, 2.16 M, 31.8 mmol) was added to DME (100 mL) containing a few crystals of 2,2′-bipyridine at −50 °C (dry ice/acetone bath) under N_2. Diisopropylamine (3.2 g, 4.4 mL, 31.8 mmol) was added slowly over a period of 15 min, and the reaction was stirred at −50 °C until the evolution of CH_4 ceased. To this dark red solution was added the above methylated lactone **10A** (5.20 g, 28.9 mmol) dissolved in DME (20 mL) over a period of 15 min at −30 °C. The reaction was then allowed to warm to room temperature over a period of 20 min. To the resulting light pink solution was added rapidly HMPA (40 mL) followed by 4-bromobutyl tetrahydropyranyl ether[24] (8.2 g, 34.7 mmol, freshly chromatographed on silica gel and vacuum distilled). The reaction mixture was then heated at 80 °C for 20 h. During this time the color of the reaction mixture changed to a light yellow. The reaction mixture was cooled to room temperature, quenched with ice cold saturated $NaHCO_3$ solution, and extracted with Et_2O (3 × 100 mL). The combined ethereal extracts were washed with H_2O (2 × 25 mL), 10% HCl solution (50 mL), saturated $NaHCO_3$ solution (25 mL), H_2O (50 mL), and saturated NaCl solution (50 mL), dried ($MgSO_4$), filtered ($MgSO_4$), and concentrated in vacuo to give 10 g of crude alkylated lactone **10B**. Chromatography on silica gel (1 kg) using 50% Et_2O/50% petroleum ether as an eluant gave 9.04 g (83%) of analytically pure lactone **10B**: bp 152 °C (0.01 mmHg); IR (CCl_4) 1770 (C=O), 1670 cm^{-1} (C=C); NMR (CCl_4) δ 0.88 (s, 3, CH_3), 0.98 (s, 3, CH_3), 1.77 (br s, 3, $C=CCH_3$), 3.47 (m, 4, CH_2O, OCH_2), 4.27 (br d, J = 5 Hz, 1, CHO), 4.45 (br s, 1, CHO), 5.50 (m, 1, C=CH).

Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.13; H, 9.79.

Alkylated lactone **10B** (9.04 g, 23.9 mmol) was dissolved in absolute CH_3OH (100 mL) containing a few crystals of *p*-TsOH (0.1 g), and the resulting solution was allowed to stir at room temperature for 24 h. The CH_3OH was then removed in vacuo, and the residue was dissolved in Et_2O (200 mL). The ethereal solution was washed with saturated $NaHCO_3$ solution (50 mL), H_2O (2 × 25 mL), and saturated NaCl solution (50 mL), dried ($MgSO_4$), filtered ($MgSO_4$), and concentrated in vacuo to give crude alcohol **11**. Distillation gave 7.25 g (100%) of pure alcohol **11**, bp 145–150 °C (0.5 mmHg), which crystallized upon standing. Recrystallization from Et_2O/pentane gave analytically pure alcohol **11**: mp 76.5–77.5 °C; IR (CCl_4) 3450 (OH), 1760 (C=O), 1670 cm^{-1} (C=C); NMR (CCl_4) δ 0.97 (s, 3, CH_3), 1.02 (s, 3, CH_3), 1.77 (br, s, 3, $C=CCH_3$), 3.50 (m, 3, CH_2OH), 4.42 (br d, J = 5 Hz, 1 CHO), 5.58 (m, 1, C=CH).

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.95. Found: C, 71.28; H, 9.54.

Methyl (3aα,3aα,7aα)-2,3,3a,4,5,7a-Hexahydro-3,3a,6-trimethyl-2-oxo-3-benzofuranbutanoate (12). To a stirred solution of alcohol **11** (5.00 g, 19.8 mmol) in reagent grade acetone (50 mL) at 15 °C (ice bath) was added Jones reagent[17] (7.9 mL, 2.67 M, 21 mmol) slowly until the orange color persisted. The reaction mixture was stirred an additional 30 min and then quenched with *i*-PrOH. The reaction mixture was diluted with H_2O (200 mL), and the resulting solution was extracted with Et_2O (3 × 50 mL). The combined ethereal extracts were washed with 5% NaOH solution (3 × 25 mL). The combined basic extracts were washed with Et_2O (25 mL), acidified with 5% HCl solution with cooling (ice bath), and extracted with Et_2O (3 × 50 mL). The combined ethereal extracts were washed with H_2O (2 × 25 mL) and saturated NaCl solution (50 mL), dried ($MgSO_4$) and filtered ($MgSO_4$). An ethereal solution of CH_2N_2 was added until there was no further evolution of N_2. The excess CH_2N_2 was quenched by adding glacial HOAc dropwise. The solvent was removed in

vacuo to give 4.9 g of crude lactone ester **12** which crystallized upon standing. GLC analysis on column b (column temperature 280 °C) shows two peaks at 4.7 and 6.2 min in a 4:96 ratio, respectively, for lactones **14** and **12**. Recrystallization from Et_2O/petroleum ether gave 4.5 g (81%) of pure lactone ester **12**: mp 75–76.5 °C; IR (CCl_4) 1740 (CO_2Me), 1765 (C=O), 1675 cm^{-1} (C=C); NMR (CCl_4) 0.91 (s, 3, CH_3), 1.00 (s, 3, CH_3), 1.77 (s, 3, $C{=}CCH_3$), 3.63 (s, 3, CO_2CH_3), 4.33 (d, J = 5 Hz, 1 CHO), 5.56 (m, 1, C=CH).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.52; H, 8.59.

(3β,3aβ,7aβ)-3a,4,5,7a-Tetrahydro-3,3a,6-trimethyl-3-(5-pentenyl)-2(3*H*)-benzofuranone (13). An ethereal solution of methyllithium (27.8 mL, 1.8 M, 50 mmol) was added to DME (150 mL) containing a few crystals of 2,2′-bipyridine at −50 °C (dry ice/acetone) under N_2. Diisopropylamine (7.12 mL, 5.06 g, 50 mmol) was added slowly, and the resulting solution was stirred at −50 °C until the evolution of CH_4 ceased (~30 min). To this dark red solution was added lactone **10** (8.11 g, 8.83 mmol) dissolved in DME (30 mL) slowly over a period of 20 min at −30 °C. The resulting solution was allowed to warm to room temperature over a period of 20 min, and then HMPA (20 mL) and 5-bromo-1-pentene (8.94 g, 60 mmol, Columbia Organic Chemicals) were added. The reaction mixture was then heated at 52–55 °C for 20 h, cooled to room temperature, quenched with ice cold 5% HCl solution, and worked up in the usual way to give 11 g of crude alkylated lactone **10C**. Distillation gave 10.4 g (91%) of lactone **10C**: bp 110–115 °C (0.2 mmHg); IR (CCl_4) 1770 (C=O), 1640, 1670 (C=C), 910, 985 cm^{-1} ($CH{=}CH_2$); NMR (CCl_4) δ 1.00, 1.10 (2 s, 3, CH_3), 1.77 (br s, 3, $C{=}CCH_3$), 4.03, 4.10, 4.27 (3 br s, 1, CHO), 4.7–6.16 (m, 4, $CH{=}CH_2$, C=CH), integration of the NMR spectrum indicates **10C** is a 2/3 ratio of α/β diastereomers.

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.83; H, 9.49.

An ethereal solution of methyllithium (26.5 mL, 1.7 M, 45 mmol) was added to DME (150 mL) containing a few crystals of 2,2′-bipyridine at −50 °C (dry ice/acetone bath) under N_2. Diisopropylamine (6.33 mL, 4.55 g, 45 mmol) was added slowly at −50 °C, and then the mixture was allowed to stir until the evolution of CH_4 ceased (~30 min). To this dark red solution was added the above lactone **10C** (10.4 g, 44.5 mmol) dissolved in DME (30 mL) slowly over a period of 20 min at −30 °C. After the mixture was stirred an additional 10 min at −30 °C, HMPA (20 mL) and iodomethane (5.60 mL, 12.8 g, 90.1 mmol) were added sequentially and rapidly. The reaction mixture was allowed to stir at room temperature for 20 h, quenched with ice cold 10% HCl solution (500 mL), and extracted with Et_2O (3 × 100 mL). The combined ethereal extracts were washed with saturated $Na_2S_2O_3$ solution (2 × 25 mL), H_2O (3 × 25 mL), and saturated NaCl solution (50 mL), dried ($MgSO_4$), filtered ($MgSO_4$), and concentrated in vacuo to give 11 g of crude lactone **13**. Distillation gave 10.4 g (94%) of pure lactone **13**: bp 110–115 °C (0.2 mmHg); IR (CCl_4) 1770 (C=O), 1640, 1675 (C=C), 920, 980 cm^{-1} ($CH{=}CH_2$); NMR δ 0.93 (s, 3, CH_3), 1.13 (s, 3, CH_3), 1.77 (s, 3, $C{=}CCH_3$), 4.17 (d, J = 5 Hz, 1, CHO), 4.73–6.32 (m, 4, $CH{=}CH_2$, C=CH).

Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.76. Found: C, 77.45; H, 9.86.

(3β,3aβ,7aβ)-3a,4,5,7a-Tetrahydro-3,3a,6-trimethyl-3-(4-hydroxybutyl)-2(3*H*)-benzofuranone (13B). A solution of $NaIO_4$ (30.2 g, 141 mmol), lactone **13** (10.4 g, 41.9 mmol), H_2O (500 mL), *tert*-butyl alcohol (500 mL), and OsO_4 (20 mL, 6 mg/mL in H_2O) was stirred at room temperature for 30 h. During this time a precipitate of $NaIO_3$ formed. The reaction was monitored by GLC using column b [column temperature 250 °C; R_t (alkene) = 5.8 min; R_t (aldehyde) = 10.9 min]. After being stirred for 30 h at room temperature, the reaction mixture was diluted with H_2O (4 L) and worked up in the usual way to give 10.5 g (100%) of crude aldehyde **13A**. This crude aldehyde **13A** was dissolved in 100% EtOH (100 mL) and cooled to 0 °C (ice bath), and a solution of $NaBH_4$ (0.77 g, 80 mmol) in 100% EtOH (50 mL) was added over a period of 10 min. The reaction mixture was allowed to stir an additional 20 min at 0 °C and then allowed to warm to room temperature over a period of 3 h. Excess $NaBH_4$ was quenched by adding methanol (25 mL) and H_2O (500 mL). The reaction was then worked up in the usual way to give 8 g of crude alcohol **13B**. Distillation gave 5.5 g (52%) of alcohol **13B**: bp 130–135 °C (0.2 mmHg); IR (CCl_4) 3360–3420 (OH), 1765 (C=O), 1675 cm^{-1} (C=C); NMR (CCl_4) δ 0.93 (s, 3, CH_3), 1.15 (s, 3, CH_3), 1.75 (br s, 3, $C{=}CCH_3$), 3.52 (m, 2, $-CH_2OH$), 4.13 (d, J = 5 Hz, 1, CHO), 5.53 (m, 1, C=CH).

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.38; H, 9.58.

Methyl (3β,3aβ,7aβ)-2,3,3a,4,5,7a-Hexahydro-3,3a,6-trimethyl-2-oxo-3-benzofuranbutanoate (14). To a stirred solution of the above crude aldehyde **13A** (8.00 g, 32.0 mmol) in reagent grade acetone (100 mL) at 0 °C (ice bath) was added Jones reagent[17] (12.4 mL, 2.67 M, 33.1 mmol) slowly over a period of 20 min. The resulting orange mixture was then allowed to stir at room temperature for 1 h. The reaction was then quenched with *i*-PrOH and diluted with H_2O (400 mL). The aqueous mixture was extracted with Et_2O (3 × 100 mL), and the combined ethereal extracts were washed with 10% NaOH solution (3 × 50 mL). The combined basic washes were extracted with Et_2O (25 mL) and then acidified with 10% HCl solution with cooling (ice bath). The solution was then worked up in the usual way to afford 7.2 g (85%) of crude acid **13C**. Recrystallization of a small amount of this product from Et_2O/petroleum ether gave analytically pure lactone acid **13C**: mp 132–134 °C; IR ($CDCl_3$) 2400–3400 (br, CO_2H), 1775 (C=O), 1715 cm^{-1} (CO_2H); NMR ($CDCl_3$) δ 0.97 (s, 3, CH_3), 1.23 (s, 3, CH_3), 1.77 (s, 3, CH_3), 4.30 (d, J = 4 Hz, 1, CHO), 5.59 (m, 1, C=CH), 10.3 (br s, 1, CO_2H).

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.59; H, 8.38.

This crude acid **13C** was dissolved in Et_2O (50 mL) and esterified with an ethereal solution of CH_2N_2. The excess CH_2N_2 was quenched with glacial HOAc, and the solvent was removed in vacuo to give 7.2 g (80%) of crude lactone ester **14**. GLC analysis on column b (column temperature 280 °C) shows two peaks at 4.7 and 6.2 min in a ratio of 98:2, respectively, for lactones **14** and **12**. Recrystallization from 25% Et_2O–75% petroleum ether gave 6.01 g (67%) of pure lactone ester **14**: mp 58.5–59.5 °C; IR (CCl_4) 1730 (CO_2Me), 1760 (C=O), 1670 cm^{-1} (C=C); NMR (CCl_4) δ 0.97 (s, 3, CH_3), 1.20 (s, 3, CH_3), 1.78 (br, s, 3, $C{=}CCH_3$), 3.67 (s, 3, CO_2CH_3), 4.18 (d, J = 5 Hz, 1, CHO), 5.57 (m, 1, C=CH).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.62; H, 8.64.

Dimethyl 2-[1,4-Dimethyl-2(or 3)-cyclohexen-1-yl]-2-methylhexanedioate (15). Calcium metal (0.72 g, 18 mmol) was added in small portions to anhydrous liquid NH_3 (50 mL) over a period of 10 min. After the mixture was stirred at −33 °C for an additional 10 min, a solution of THF/HMPA (10 and 5 mL, respectively) was added. To the resulting deep blue solution was added lactone alcohol **11** (0.910 g, 3.61 mmol) dissolved in THF/HMPA (10 and 5 mL, respectively). After a period of 5 min, the blue reaction mixture was quenched with 100% EtOH (1.0 mL), and after 10 min the blue color faded. The liquid NH_3 was evaporated, and the residue was diluted with H_2O (50 mL). The aqueous solution was washed with Et_2O (3 × 50 mL) to remove neutral side products. The aqueous layer was then acidified with 10% HCl solution and worked up in the usual way to give 0.904 g (98%) of crude acid alcohol **11A**. Crude acid alcohol **11A** (0.842 g, 3.31 mmol) was dissolved in reagent grade acetone (20 mL) and cooled to 15 °C (ice bath), and Jones reagent[17] (3.0 mL, 2.67 M, 8.0 mmol) was added dropwise until the orange color persisted. The reaction mixture was allowed to stir at room temperature for 30 min, quenched with *i*-PrOH, diluted with H_2O (100 mL), and worked up in the usual way to give 0.85 g of crude diacid **11B**. Crude diacid **11B** was dissolved in Et_2O (10 mL) and esterified with an ethereal solution of CH_2N_2. Excess CH_2N_2 was quenched by the dropwise addition of glacial HOAc. The solvent was removed in vacuo, and the resulting crude diester **15** was chromatographed on silica gel (100 g) with a solution of 25% Et_2O–75% petroleum ether as an eluant to obtain 0.640 g (65%) of diester **15**: bp 103–105 °C (0.4 mmHg); IR (CCl_4) 1745, 1725 cm^{-1} (2 CO_2CH_3); NMR δ 3.63 (s, 6, 2 CO_2CH_3), 5.43 (m, 1.5, C=CH, CH=CH); low-resolution mass spectrum, m/z (relative intensity) 296 (m^+, 0.2), 265 (4), 237 (13), 187 (60), 155 (24), 128 (52), 109 (100).

Anal. Calcd for $C_{17}H_{28}O_4$: mol wt 296.1987. Found: mol wt (mass spectrum) 296.1980, 2.4-ppm error by high-resolution mass spectroscopy. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 69.02; H, 9.71.

Methyl 3-[1,4-Dimethyl-2(or 3)-cyclohexen-1-yl]-3-methyl-2-oxocyclopentanecarboxylate (16). A mixture of $NaNH_2$ (0.312 g, 8.00 mmol) and bis(trimethylsilyl)amine[29] (1.61 g, 10.0 mmol) was stirred at reflux in benzene (1.69 mL) under N_2 for 2.5 h. The suspended impurities were removed by filtration under N_2, and the solvent was removed in vacuo. To the resulting sodium bis(trimethylsilyl)amide was added DME (20 mL), and the solution was cooled to 0 °C (ice bath). Diester **15** (0.600 g, 2.02 mmol) dissolved in DME (5 mL) was added slowly, and the resulting solution was stirred at room temperature for 16 h. The reaction mixture was cooled to 0 °C (ice bath), quenched with cold 5% HCl solution, and then worked up in the usual way to give 0.54 g of crude β-keto ester **16**. Distillation gave 0.520 g (97%) of pure β-keto ester **16**: bp 100–104 °C (0.3 mmHg); IR (CCl_4) 1725 (CO_2CH_3), 1750 (C=O), 1610, 1660 cm^{-1} (C=C); NMR (CCl_4) δ 0.90, 1.00, 1.08, 1.11 (4 s, 6, two isomeric CH_3), 3.73 (s, 3, CO_2CH_3), 5.04–5.88 (m, 1.6, C=CH, CH=CH).

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.71; H, 9.15.

2-(1α,4α-Dimethyl-2-cyclohexen-1-yl)-2-methylcyclopentanone (17) and 2-(1,4-Dimethyl-3-cyclohexen-1-yl)-2-methylcyclopentanone or Trichoenone (18). A solution of β-keto ester **16** (0.380 g, 1.44 mmol) and DBU (1.10 g, 72.4 mmol) in reagent grade xylene (20 mL) was heated at reflux for 16 h under N_2. The reaction mixture was cooled to room temperature, diluted with cold 10% HCl solution (50 mL) and then worked up in the usual way to give 0.294 g (98%) of a mixture of enones **17** and **18** in a ratio of 64:36, respectively (GLC column a, column temperature 170 °C). These two isomeric enones were separated by chromotography on a column of 15% $AgNO_3$/silica gel with 2.5% Et_2O–97.5% petroleum ether as an eluant at a flow rate of 1.2 mL/min for 24 h at 250 lb/sq in. pressure on the recycle mode. After the sample was recycled for 24 h, 25-mL fractions were collected at a flow rate of 2.5 mL/min. The purity of each fraction was monitored by GLC using column a (column temperature 170 °C) where enone **17** has a R_t = 3.0 min and enone **18** has a R_t = 4.1 min. Trichoenone (**18**) (0.10 g, 35%) eluted from the high-pressure LC column before enone **17** (0.188 g, 63%).

The spectral data for trichoeneone (**18**) are as follows: bp 60–65 °C (0.2 mmHg); IR (CCl_4) 1730 (C—O), 3020, 860 cm^{-1} (C=CH); NMR (CCl_4, 100 MHz) δ 0.88 (s, 3, CH_3), 0.98 (s, 3, CH_3), 1.61 (br s, 3, $C=CCH_3$), 5.20 (m, 1, C=CH).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.40; H, 10.75.

The spectral data for enone **17** are as follows: bp 60–65 °C (0.2 mmHg); NMR ($CDCl_3$, 100 MHz) 0.92 (d, J = 7 Hz, 3, CH_3CH), 1.00 (s, 6, 2 CH_3), 5.56 (AB of an ABX, J_{AB} = 10.3 Hz, 2, CH=CH).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.53; H, 10.79.

Trichodiene (1). Sodium hydride (0.215 g, 5.1 mmol, 57% dispersion) was washed (3×) under N_2 with distilled pentane, dried, and flushed with N_2. Anhydrous Me_2SO (3.0 mL) was added, and the mixture was stirred at 80 ± 2 °C for 30 min under N_2. The solution was cooled to room temperature and vacuum dried, and $Ph^3{}^+PCH_3Br^-$ (1.79 g, 5.01 mmol) dissolved in hot Me_2SO (5.0 mL) was added. After the mixture was warmed to 80 °C over a period of 15 min, trichoenone **18** (0.100 g, 0.485 mmol) dissolved in Me_2SO (2.0 mL) was added. The resulting dark orange reaction mixture was heated at 80 ± 2 °C under N_2 for 60 h. The resulting dark red reaction mixture was cooled to room temperature, quenched with cold H_2O (50 mL), and worked up in the usual way. The crude product was chromatographed on silica gel (10 g) with petroleum ether to elute the column to give 0.55 g (51%) of trichodiene (**1**): bp 65–70 °C (0.5 mmHg); IR (CCl_4) 3060 ($C=CH_2$), 3000 (C=CH), 1640 (C=C), 890 cm^{-1} ($C=CH_2$); NMR (CCl_4, 100 MHz) δ 0.84 (s, 3, CH_3), 1.03 (s, 3, CH_3), 1.63 (s, 3, $C=CCH_3$), 4.69, 4.90 (2 br s, 2, $C=CH_2$), 5.21 (m, 1, C=CH); low-resolution mass spectrum, m/z (relative intensity) 204 (M^+, 1.7), 189 (1.0), 161 (0.6), 147 (0.8), 133 (2), 121 (4), 119 (3), 109 (100), 96 (10), 93 (35), 81 (19), 79 (25), 77 (21), 67 (35).

Anal. Calcd for $C_{15}H_{24}$: mol wt 204.1878. Found: mol wt (mass spectrum) 204.1867, 5.1-ppm error by high-resolution mass spectroscopy. Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.36; H, 11.71.

Methyl ((1α,2α)-2-Hydroxy-1,4-dimethyl-3-cyclohexen-1-yl)-3-methyl-2-oxocyclopentanecarboxylate (19). To a stirred suspension of $NaNH_2$ (2.60 g, 66.6 mmol) in benzene (50 mL) under N_2 was added bis(trimethylsilyl)amine[29] (15.3 mL, 11.8 g, 73.5 mmol). The resulting mixture was stirred at reflux for 2.5 h under N_2, cooled to room temperature, and filtered under N_2, and the solvent was removed in vacuo. The resulting sodium bis(trimethylsilyl)amide was dissolved in DME (75 mL) and cooled to 0 °C (ice bath), and lactone ester **12** (5.30 g, 18.9 mmol) dissolved in DME (25 mL) was added over a period of 10 min. The reaction mixture was stirred for 18 h at room temperature under N_2. The resulting milky white reaction mixture was then poured into ice cold 10% HCl solution and worked up in the usual way to give 5.4 g of crude product. Distillation gave 5.15 g (97%) of pure β-keto ester **19**: bp 140–142 °C (0.05 mmHg); IR (CCl_4) 3490, 3570 (OH), 1720 (CO_2CH_3), 1750 (C=O), 1675 cm^{-1} (C=C); NMR (CCl_4) δ 0.78, 0.82 (2 s, 3, CH_3), 0.90, 0.93 (2 s, 3, CH_3), 1.70 (br s, 3, $C=CCH_3$), 3.65, 3.70 (2 s, 3, CO_2CH_3), 3.87 (br d, J = 4 Hz, 1, CHO), 5.45 (m, 1, C=CH).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.62; H, 8.71.

Methyl 3-Methyl-3-(1-methyl-4-methylene-2-cyclohexenyl)-2-oxocyclopentanecarboxylate (20). To a stirred solution of β-keto ester **19** (0.700 g, 2.50 mmol) in CH_2Cl_2 (50 mL) at −20 °C (dry ice/*i*-PrOH bath) was added HCl gas slowly for 20 min. The resulting solution was stirred for an additional 15 min at −20 °C and then filtered through anhydrous $MgSO_4$, and the solvent was removed in vacuo to obtain 0.75 g of crude tertiary chloride. This crude product was immediately dissolved in 2,4,5-collidine (10 mL), and this solution was heated at 180–185 °C in a preheated oil bath for 25 min. The reaction was then cooled to room temperature, diluted with ice cold 10% HCl solution (100 mL), and worked up in the usual way to give 0.666 g of crude product. Distillation gave 0.570 g (86%) of pure β-keto ester **20**: bp 110–115 °C (0.5 mmHg); IR (CCl_4) 3070 ($C=CH_2$), 3020 (CH=CH), 1730 (CO_2CH_3), 1755 (C=O), 1660, 1620 (C=C), 880 cm^{-1} ($C=CH_2$); NMR (CCl_4) δ 1.17 (s, 3, CH_3), 1.18 (s, 3, CH_3), 3.77 (s, 3, CO_2CH_3), 4.70 (br s, 2, $C=CH_2$), 6.00 (br s, 2, CH=CH).

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.21; H, 8.58.

2-Methyl-2-(1-methyl-4-methylene-2-cyclohexen-1-yl)-cyclopentanone (21). A solution of β-keto ester **20** (0.390 g, 1.49 mmol) and DBU (1.14 g, 7.50 mmol) in 2,4,6-collidine (5.0 mL) was stirred at 180–185 °C for 2.5 h under N_2. The reaction mixture was cooled to room temperature, diluted with cold 10% HCl solution (50 mL), and worked up in the usual way to give 0.32 g of crude product. Chromatography on silica gel (5.0 g) with a solution of 10% Et_2O–90% petroleum ether as an eluant gave after distillation 0.228 g (75%) of dienone **21**: bp 75–80 °C (0.5 mmHg); IR (CCl_4) 3040 ($C=CH_2$), 3000 (CH=CH), 1730 (C=O), 1625, 1585 (C=C), 870, 855 cm^{-1} ($C=CH_2$); NMR (CCl_4) δ 1.04 (s, 3, CH_3), 1.10 (s, 3, CH_3), 4.70 (d, J = 2 Hz, 2, $C=CH_2$), 6.03 (s, 2, CH=CH).

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.25; H, 9.94.

2-Methyl-2-(1-methyl-4-methylene-2-cyclohexen-1-yl)-cyclopentanol (22). A solution of dienone **21** (0.110 g, 0.538 mmol) in Et_2O (3.0 mL) was added to a stirred suspension of $LiAlH_4$ (0.04 g, 1 mmol) in Et_2O (5.0 mL) at 0 °C (ice bath) under N_2. After being stirred at 0 °C for 2 h, the reaction was quenched by the addition of H_2O (0.04 mL), 15% NaOH solution (0.04 mL), and H_2O (0.12 mL). The resulting granular precipitate was filtered and washed with Et_2O (25 mL) through $MgSO_4$. The filtrate was concentrated in vacuo to give after distillation 0.099 g (89%) of dienol **22**: bp 75–80 °C (0.5 mmHg); IR (CCl_4) 3550, 3400 (OH), 3060 ($C=CH_2$), 3010 (CH=CH), 1635, 1590 (C=C), 880, 860 cm^{-1} ($C=CH_2$); NMR (CCl_4) δ 0.87 (s, 3, CH_3), 1.10 (s, 3, CH_3), 3.90 (br s, 1, CHO), 4.73 (br s, 2, $C=CH_2$), 6.06 (m, 2, CH=CH).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.48; H, 10.81.

2-(1,4-Dimethyl-3-cyclohexen-1-yl)-2-methylcyclopentanol and 2-Methyl-2-(1-methyl-4-methylenecyclohex-1-yl)cyclopentanol (23). Lithium wire (0.014 g, 2.0 mmol) was added in three pieces to anhydrous liquid NH_3 (15 mL) and the mixture allowed to stir at −33 °C for 5 min. To this deep blue solution was added dienol **22** (0.065 g, 0.315 mmol) dissolved in Et_2O (3.0

mL) containing 100% EtOH (0.1 mL). After about 3 min the blue solution faded to colorless, and the NH_3 was allowed to evaporate. The residue was dissolved in H_2O (25 mL) and Et_2O (25 mL) and worked up in the usual way to give 0.070 g of crude product. Chromatography on silica gel (10 g) with a solution of 25% Et_2O–75% petroleum ether as an eluant gave 0.064 g (98%) of pure enols **23**: bp 70–80 °C (0.5 mmHg); IR (film) 3400 (OH), 3000, 760, 780 cm^{-1} (C=CH); NMR (CCl_4) δ 0.67 (s, 5, CH_3), 0.95 (s, 3, CH_3), 3.80 (br d, J = 5 Hz, 1, CHO), 5.17 (m, 1, C=CH).

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.80; H, 11.70.

2-(1,4-Dimethyl-3-cyclohexen-1-yl)-2-methylcyclopentanone (Trichoenone 18) and 2-Methyl-2-(1-methyl-4-methylenecyclohex-1-yl)cyclopentanone (24). To a solution of enols **23** (0.160 g, 0.769 mmol) in reagent grade acetone (5.0 mL) was added Jones reagent[17] (0.30 mL, 2.67 M, 0.80 mmol) dropwise with stirring at 0 °C (ice bath) until the orange color persisted. After the mixture was stirred an additional 30 min, the reaction was quenched with *i*-PrOH (0.1 mL) and H_2O (20 mL), and the resulting green solution was worked up in the usual way to give 0.16 g of crude product. Distillation gave 0.131 g (81%) of a mixture of enones **18** and **24**, bp 70–75 °C (0.5 mmHg). Chromatography on 15% $AgNO_3$/silica gel (25 g) with a solution of 25% Et_2O–75% petroleum ether as an eluant gave 0.106 g (80.8%) of trichoenone (**18**), the physical data of which were identical with those reported above, and 0.0251 g (19.2%) of enone **24**: bp 70–75 °C (0.5 mmHg); IR (CCl_4) 3060, 880 (C=CH_2), 1730 cm^{-1} (C=O); NMR (CCl_4) δ 0.97 (s, 3, CH_3), 1.07 (s, 3, CH_3), 4.50 (br, s, 3, C=CH_2).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.45; H, 10.65.

Dimethyl 2-[1,4-Dimethyl-2(or 3)-cyclohexen-1-yl]-2-methylhexanedioate (25). A solution of lactone alcohol **13B** (4.15 g, 16.4 mmol) in TMEDA (15 mL) was added to anhydrous liquid NH_3 (150 mL). Freshly cut Ca metal (3.57 g, 89.1 mmol) was added in five pieces, and the resulting blue solution was allowed to stir at −33 °C for 10 min. The residue was diluted with H_2O (100 mL), acidified with 10% HCl solution, and worked up in the usual way to give a crude acid. This crude acid was dissolved in Et_2O (25 mL) and esterified with ethereal CH_2N_2. The excess CH_2N_2 was quenched with glacial HOAc, and the solvent was removed in vacuo to give after distillation 4.35 g (90%) of ester alcohol **13C**: bp 95–105 °C (0.5 mmHg); IR (CCl_4) 3300–3500 (OH), 1725 cm^{-1} (CO_2CH_3); NMR (CCl_4) δ 0.85, 0.97, 1.03, 110 (4 s, 6, 2 CH_3), 1.63 (br s, 3 C=CCH_3), 3.53 (t, J = 6 Hz, 2, CH_2OH), 3.63 (s, 3, CO_2CH_3), 5.10–5.76 (m, 1.5, C=CH).

Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.64; H, 10.56.

Ester alcohol **13C** (4.00 g, 14.9 mmol) was dissolved in reagent grade acetone (100 mL), and Jones reagent[17] (15 mL, 2.67 M, 40 mmol) was added dropwise with stirring at 0 °C (ice bath) until the reaction mixture remained orange. The reaction was stirred for an additional 30 min at room temperature and then quenched with *i*-PrOH. The green mixture was diluted with H_2O (400 mL) and extracted with Et_2O. The combined ethereal extracts were washed with cold 10% NaOH solution (2 × 50 mL). The combined basic extracts were acidified with 10% HCl solution at 0 °C (ice bath) and worked up in the usual way to give a crude ester acid. This crude ester acid was dissolved in Et_2O (25 mL) and esterified with an ethereal solution of CH_2N_2. The excess CH_2N_2 was quenched with glacial HOAc, and the solvent was removed in vacuo to give 3 g of crude diester. Chromatography on silica gel (300 g) with a solution of 25% Et_2O–75% petroleum ether as an eluant gave after distillation 2.18 g (49%) of diester **25**: bp 110–115 °C (0.3 mmHg); IR (CCl_4) 1730 cm^{-1} (CO_2CH_3); NMR (CCl_4) δ 0.86 (s, 3, CH_3), 1.13 (s, 3, CH_3), 1.63 (br s, ~3, C=CCH_3), 3.65 (s, 6, 2 CO_2CH_3), 5.05–5.87 (m, 1.4, C=CH).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.96; H, 9.55. Calcd for $C_{17}H_{28}O_4$: mol wt 296.1987. Found: mol wt (mass spectrum) 296.1980, 2.4-ppm error by high-resolution mass spectroscopy.

Methyl 3-(1,4-Dimethyl-3-cyclohexen-1-yl)-3β-methyl-2-oxocyclopentanecarboxylate (26) and Methyl 3-(1,4-Dimethyl-2-cyclohexen-1-yl)-3β-methyl-2-oxocyclopentanecarboxylate (27). To a solution of bis(trimethylsilyl)amide[29] (3.32 g, 18.1 mmol, prepared as above) in DME (50 mL) was added a solution of diester **25** (1.79 g, 6.03 mmol) in DME (20 mL) slowly over a period of 10 min at 0 °C (ice bath) under N_2. The resulting solution was allowed to stir at room temperature for 20 h. The reaction was quenched at 0 °C (ice bath) with cold 10% HCl solution (200 mL) and worked up in the usual way to give 1.8 g of crude product. Distillation gave 1.24 g (78%) of a mixture of β-keto esters **26** and **27**: bp 110–120 °C (0.5 mmHg); IR (CCl_4) 1760 (C=O), 1730 (CO_2CH_3), 1665, 1620 cm^{-1} (C=C); NMR (CCl_4) δ 0.88, 1.05, 1.11 (3 s, 6, 2 CH_3), 3.72 (s, 3, CO_2CH_3), 5.27–5.40 (2 br s, 1.3, C=CH). This isomeric mixture (1.20 g) was chromatographed on silica gel (150 g) with a solution of 10% Et_2O–90% petroleum ether as an eluant.

Fractions 3–7 gave after distillation 0.444 g (37%) of β-keto ester **27**: bp 105–110 °C (0.4 mmHg); IR (CCl_4) 3000, 860 (C-H=CH), 1760 (C=O), 1730 (CO_2CH_3), 1665, 1625 (C=C); NMR (CCl_4) δ 0.96 (d, J = 7 Hz, 3, $CHCH_3$), 1.07 (s, 3, CH_3), 1.13 (s, 3, CH_3), 3.73 (s, 3, CO_2CH_3), 5.25 (AB of an ABX, J_{AB} = 10 Hz, 2, CH=CH).

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.63; H, 9.30.

Fractions 9–12 gave after distillation 0.756 g (63%) of β-keto ester **26**: bp 100–110 °C (0.4 mmHg); IR (CCl_4) 1755 (C=O), 1725 (CO_2CH_3), 1664, 1620 cm^{-1} (C=C); NMR (CCl_4) δ 0.90 (s, 3, CH_3), 1.07 (s, 3, CH_3), 1.63 (br s, 3, C=CCH_3), 3.73 (s, 3, CO_2CH_3), 5.23 (br m, 1, C=CH).

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.65; H, 9.18.

2-(1β,4-Dimethyl-3-cyclohexen-1-yl)-2β-methylcyclopentanone (Bazzanenone, 28). A solution of β-keto ester **26** (0.440 g, 1.66 mmol) and DBU (1.26 g, 8.28 mmol) in 2,4,6-collidine (10 mL) was heated at 180 ± 5 °C for 3 h under N_2. The resulting dark red reaction mixture was cooled to room temperature, diluted with 10% HCl solution (100 mL), and extracted with Et_2O (3 × 50 mL). The combined ethereal extracts were washed with cold 5% HCl solution (2 × 25 mL) and worked up in the usual way to give 0.35 g of crude product. Distillation gave 0.326 g (95%) of (±)-bazzanenone (**28**): bp 70–75 °C (0.3 mmHg); IR (CCl_4) 3000, 860 (C=CH), 1730 cm^{-1} (C=O); NMR (CCl_4) δ 0.87 (s, 3, CH_3), 0.97 (s, 3, CH_3), 1.63 (br s, 3, C=CCH_3), 5.23 (br m, 1, C=CH).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.94; H, 10.64.

Acknowledgment. We thank the Research Corp (Grant No. S-733), the National Institute of General Medicine (Grant No. 1Ro1 GM18759), and the Robert A. Welch Foundation (Grant No. E-518) for support of this research program. We also thank The National Science Foundation (Grant No. MPS 75-06162) for the funds to purchase a departmental Varian XL-100 NMR spectrometer. We are also grateful to Professor S. Nozoe (University of Tokyo) for copies of his NMR and IR spectra of natural trichodiene, trichoenone, and trichodiene monoepoxide, to Professor J. Hanson (University of Sussex) for a copy of his mass spectrum of natural trichodiene, and to Professor A. Matsuo (Hiroshima University) for copies of his NMR and IR spectra of natural bazzanene and bazzanene diepoxide.

Registry No. 1, 61505-17-7; 5, 932-51-4; 6, 37720-04-0; 7, 37720-06-2; 7A, 37720-05-1; 7B, 74592-60-2; 8, 37720-07-3; 8A, 74592-37-3; 9, 37720-03-9; 10, 33722-72-4; 10A, 61476-32-2; 10B, 61431-49-0; 10C (isomer 1), 74592-38-4; 10C (isomer 2), 74592-39-5; 11, 74592-40-8; 11A (isomer 1), 74592-41-9; 11A (isomer 2), 74592-42-0; 11B (isomer 1), 74592-43-1; 11B (isomer 2), 74592-44-2; 12, 62140-77-6; 13, 74592-45-3; 13A, 74592-46-4; 13B, 74592-47-5; 13C, 74592-48-6; 13D (isomer 1), 74592-49-7; 13D (isomer 2), 74592-50-0; 14, 74592-51-1; 15 (isomer 1), 74592-52-2; 15 (isomer 2), 74592-53-3; 16 (isomer 1), 74592-54-4; 16 (isomer 2), 74592-55-5; 17, 61431-50-3; 18, 61375-52-8; 19, 62096-97-3; 20, 62096-98-4; 21, 62096-99-5; 22 (isomer 1), 74643-97-3; 22 (isomer 2), 74643-98-4; 23 (isomer 1), 74592-56-6; 23 (isomer 2), 74592-57-7; 24, 62097-01-2; 25 (isomer 1), 74592-58-8; 26, 74643-99-5; 27, 74644-00-1; 28, 74592-59-9; allyl bromide, 106-95-6; 4-bromobutyl tetrahydropyranyl ether, 31608-22-7; 5-bromo-1-pentene, 1119-51-3.