(37) Manufactured by Waters Associates, Milford, Mass.
(38) R. Smith and C. Tanford, *Proc. Natl. Acad. Sci. U.S.A.*, **70**, 289 (1973).
(39) Reference 3, pp 50–51.
(40) M. F. Czarniecki and E. R. Thornton, to be published.
(41) An error in the legend of Figure 1 of ref 1a should be noted. The sample size for this baseline separation was smaller. It was in fact 25 μL of a solution ca. 4 mM in each acid, or 1 μmol of each.
(42) G. P. Cartoni and I. Ferretti, *J. Chromatogr.*, **122**, 287 (1976).
(43) F. M. Slasinski, J. M. Tustin, F. J. Sweeney, A. M. Armstrong, Q. A. Ahmed, and J. P. Lorand, *J. Org. Chem.*, **41**, 2693 (1976).

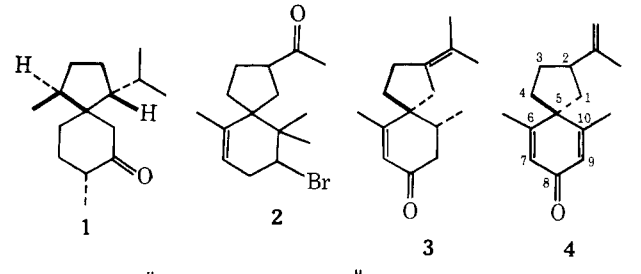
A General Method of Preparing Functionalized Spirocycles. Synthesis of Spirovetivane Sesquiterpenes[1,2]

William G. Dauben* and David J. Hart

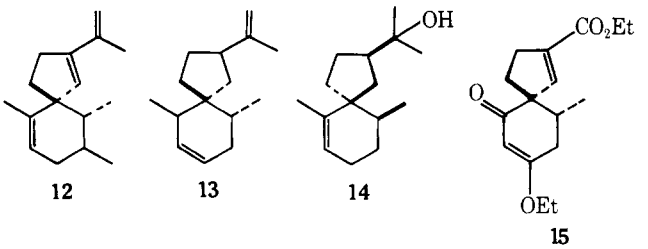
Contribution from the Department of Chemistry, University of California, Berkeley, California 94720. *Received March 17, 1977*

Abstract: The reaction between the sodium salts of α-formylcycloalkanones and 1-carbethoxycyclopropyltriphenylphosphonium tetrafluoroborate has been found to produce moderate yields of spirocycles. The application of this reaction to the total synthesis of the sesquiterpenes (±)-β-vetivone, (±)-hinesol, (±)-β-vetispirene, and (±)-α-vetispirene via a common intermediate is discussed.

A large number of sesquiterpenes possessing a spiro[4.5]decane carbon skeleton have been characterized during the past 20 years.[3] These natural products can be divided into four classes based upon the location of alkyl substituents on the spiro[4.5]decane nucleus. The acoranes and the enantiomerically related alaskanes constitute the largest class of naturally occurring spir[4.5]decanes (e.g. acorone (**1**)).[3] Spirolaurenone (**2**), a halogenated sesquiterpene recently isolated from the marine plant *Laurencia glandulifera*, is the sole member of a second type of spiro[4.5]decane sesquiterpene.[4] The spirovetivanes, a third class of these sesquiterpenes, have been isolated from a variety of sources such as the essential oil of the Indian grass *Vetiveria zizanioides* (e.g., β-vetivone (**3**)).[3] Recently, anhydro-β-rotunol (**4**),[5] lubimin (**5**),[6a-c] oxylubimin (**6**),[6a,7] and solavetivone (**7**),[5] have been isolated as stress metabolites from potato tubers infected with the blight fungus *Phytophoria infestans*.[8] It has been demonstrated that lubimin possesses antifungal properties and it, as well as the other spirovetivanes produced by these potatoes, may be involved in the defense mechanism of the potato against various pathenogens. Also, an interest has been expressed in assaying these metabolites for their mammalian toxicity.[9] Finally, spiranes **8–10**, known as the spiroaxanes, were recently isolated from the marine sponge *Axinella cannabina*.[10]

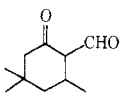
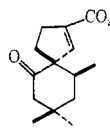
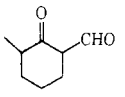
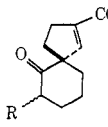
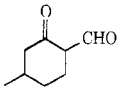
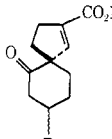
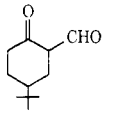
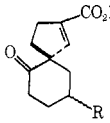
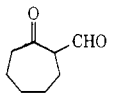
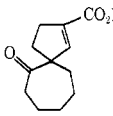
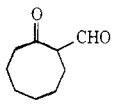
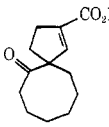


The spirovetivanes, spiroaxanes, and spirolaurenone are related in the respect that they all have alkyl substituents attached to C-2 of the spiranyl moiety. Many approaches to spiro[4.5]decanes of this type have been evaluated, a number of which culminated in successful syntheses of one or more natural products.[3,11] Owing to the increasing occurrence of spiro[4.5]decanes possessing interesting biological activity, the development of efficient routes to such spirocycles has been actively pursued. In this laboratory the investigation of the reaction between α-formylcycloalkanones and 1-carbethoxycyclopropyltriphenylphosphonium tetrafluoroborate (**11**)[12] has led to the development of a new route to a variety of 2-substituted spiro[4.5]decanes. This reaction has also been used in rapid, stereospecific syntheses of the spirovetivanes α-vetispirene (**12**),[11b,13] β-vetispirene (**13**),[13,14] β-vetivone (**3**),[15] and hinesol (**14**),[16] via the pivotal intermediate **15**.[17]

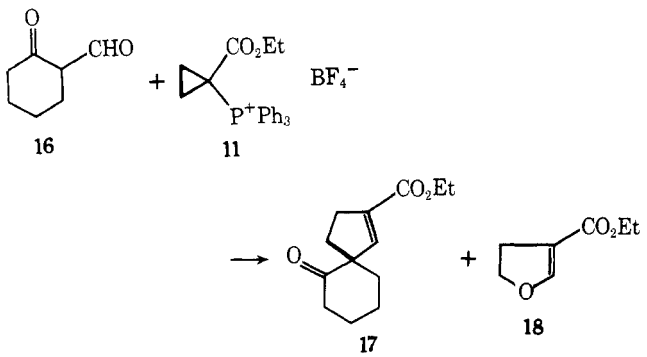


It had been reported that when enolates of β-keto esters and symmetrical β-diketones were allowed to react with **11**, excellent yields of cyclopent-1-enecarboxylates were obtained.[12] Since it has been established that stabilized phosphoranes exhibit greater reactivity toward aldehydic than toward ketonic carbonyl groups,[18] it was anticipated that α-formylketone enolates might react with **11** to produce spiranyl vinylogous β-keto esters.[19] It was found that when the sodium salt of α-formylcyclohexanone (**16**) and **11** were allowed to react in HMPT, spiro keto ester **17** was produced as the major isolable non-phosphorus-containing compound. This reaction presumably involves nucleophilic attack of the enolate on the geminally activated cyclopropane to produce a stabilized phosphorus ylide which then undergoes a regiospecific intramolecular Wittig reaction at the aldehyde carbonyl group. No products arising from closure at the ketone carbonyl group were detected. In addition to **17**, small amounts of cyclohexanone and 4-carbethoxy-2,3-dihydrofuran (**18**) were ob-

Table I. Reaction of 11 with α-Formylcycloalkanones

α-Formylcycloalkanone[22-25]	Products[a-d]			% yield[e]
		19	(6.30)	10
		20 21	R = —Me (6.42) R = —Me (6.70)	35[f]
		22 23	R = —Me (6.48) R = —Me (6.66)	36[g]
		24 25	R = —t-Bu (6.46) R = —t-Bu (6.78)	30[h]
		26	(6.60)	44
		27	(6.39)	44

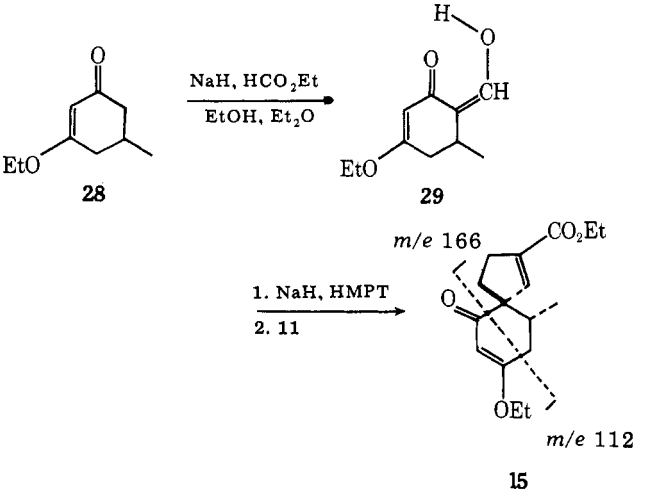
[a] In most reactions, 18 was isolated in yields of no greater than 5%. On some occasions also small amounts of starting formylketone and deformylated starting material were obtained. Ph_3PO was always formed. [b] Isomers were easily separated by preparative thin layer chromatography over silica gel. [c] Numbers in parentheses represent chemical shift of vinyl proton (δ, CCl_4). [d] Stereochemical assignments are discussed in the text. [e] Isolated yields. [f] **20:21**, 3:2. [g] **22:23**, 2:1. [h] **24:25**, 3:1.



16 **11** **17** **18**

tained. The former presumably arose from deformylation of **16**. It was established that the dihydrofuran **18** came from a reaction between the other deformylation product, sodium formate, and salt **11**. The details of this reaction have been reported elsewhere.[20] The generality of the above method for preparing functionalized spirocycles was demonstrated by treating **11** with a variety of α-formylcycloalkanones. The results are given in Table I. The stereochemical assignments depicted in the table will be the subject of the latter portion of this report.

Although the yields of spiranes were only moderate, it is evident that this reaction was specially suited for the synthesis of 2-alkyl spiro[4.5]decane sesquiterpenes. Thus, attention was turned to the synthesis of **15**, a molecule bearing functionality in both rings suitable for conversion into the various structural units found among the spirovetivanes. The required formyl ketone **29** was prepared from enol ether **28**[21] in a 61% yield by



28 **29** **15**

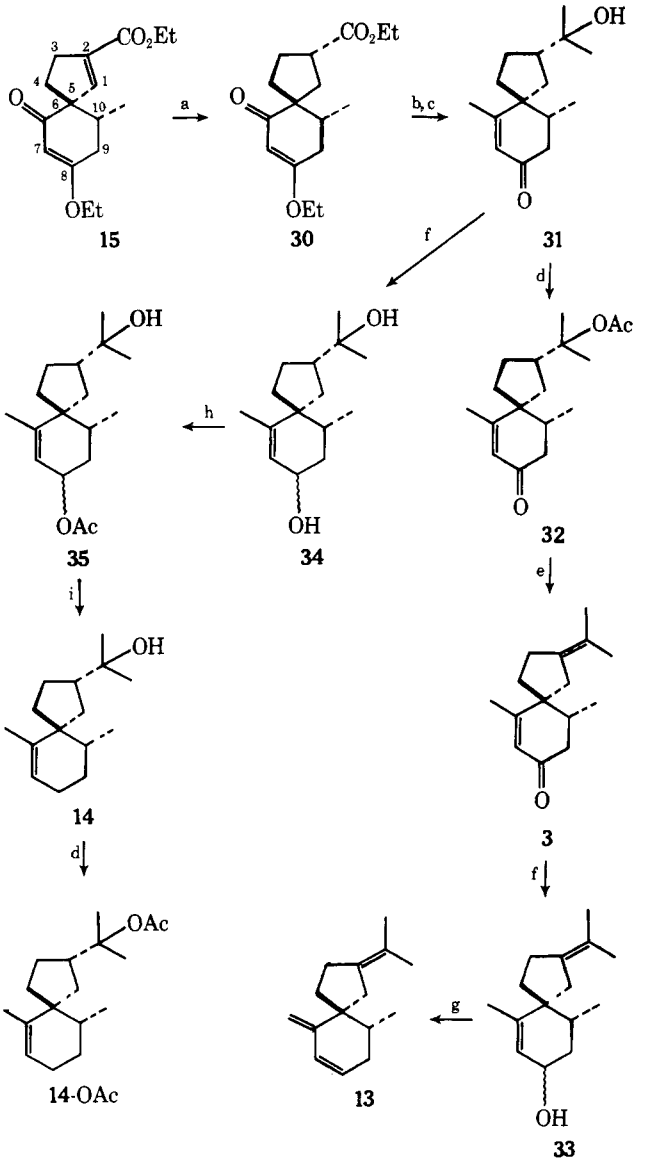
direct formylation with ethyl formate. Formyl ketone **29** underwent clean spiroannelation upon treatment with **11** to produce a single crystalline spiro keto ester in 25–38% yield after chromatography over silica gel and recrystallization from hexane. The spectral and analytical data of this material were consistent with those expected for the desired intermediate **15**. The infrared spectrum of **15** exhibited strong signals at 1720, 1668, and 1617 cm^{-1}, consistent with the presence of an α,β-unsaturated ester, a cyclohexenone, and a polarized double bond. In addition to showing a parent ion and fragments for loss of methyl and ethoxy groups, the mass spectrum of **15** displayed significant peaks at *m/e* 166 and 112, corresponding to retro-Diels–Alder fragments. The 220-MHz ^1H NMR spectrum of **15** consisted of a methyl doublet at δ 1.00 ($-CHCH_3$), methyl triplets at δ 1.30 and 1.38 ($-OCH_2CH_3$), methylene quartets at δ 3.90 and 4.12 ($-OCH_2CH_3$), and vinyl protons at δ 5.19 (−COC*H*=COEt) and 6.33 (−C*H*=C COOEt) in addition to a seven-proton multiplet at δ 1.6–2.8.

The ultimate proof of structure and stereochemistry of **15** was provided by the conversion of this material into a variety of spirovetivanes as outlined in Schemes I and II. The key intermediate **15** upon hydrogenation over palladium on charcoal in ethanol produced keto ester **30** in a regiospecific, stereospecific manner. The stereochemistry of the C-2 substituent was proven by subsequent conversion of **30** into hinesol (**14**). Successive treatment of **30** with excess methyllithium and 1.2 N HCl gave crystalline ketol **31** in a 60% yield from **15**. Since one optical antipode of **31** has been previously converted to anhydro-β-rotunol (**4**)[26], this reaction sequency represents a formal synthesis of this naturally occurring cross-conjugated spirodienone. Acetylation of **31** followed by treatment of the resulting tertiary acetate **32** with boron trifluoride etherate, according to established procedures,[27] afforded a 50% yield of (±)-β-vetivone (**3**), spectrally[28] and chromatographically identical with an authentic sample.[29]

Lithium aluminum hydride reduction of **3** gave allylic alcohol **33**. Dehydration of **33** with 10-camphorsulfonic acid in benzene gave (±)-β-vetispirene (**13**) in an 86% overall yield.

Lithium aluminum hydride reduction of **31** followed by selective acetylation of the resulting diol **34** produced a mixture of hydroxyacetates **35** in an 81% yield. Reduction of the mixture of acetates with lithium in ethylamine[30] afforded a 75% yield of a 9:1 mixture of two compounds. The major component was shown to be (±)-hinesol (**14**), spectrally and chromato-

Scheme I



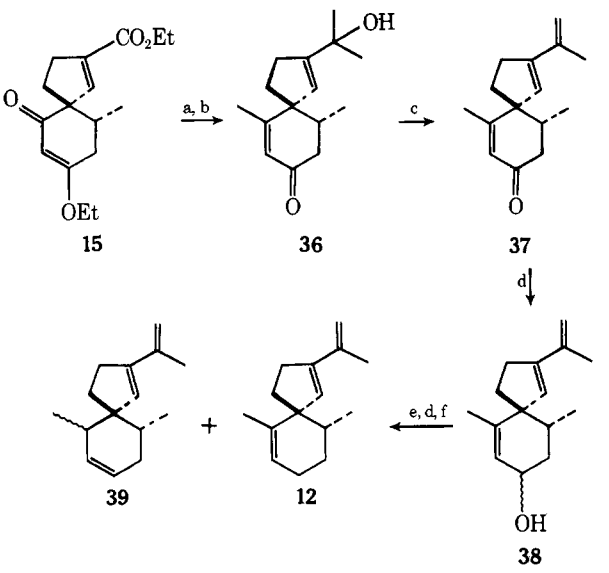
(a) H_2, Pd/C, EtOH (b) MeLi (c) H_3O^+ (d) Ac_2O, NaOAc (e) $BF_3 \cdot Et_2O$ (f) $LiAlH_4$ (g) 10-CSA (h) Ac_2O, pyridine (i) Li, $EtNH_2$

graphically identical with an authentic sample.[29] Further identification was made by converting this material to hinesol acetate (**14-QAc**) and comparing it with the acetate prepared from an authentic sample of **14**.

The presence of the C-1,2 double bond in **15** added to the versatility of this material as a synthetic source of spirosesquiterpenes, and the utilization of this unsaturation permitted the conversion of **15** to α-vetispirene (**12**) by the sequence of reactions outlined in Scheme II. Successive treatment of **15** with methyllithium and 1.2 N HCl–ether yielded ketol **36** which was dehydrated with 10-camphorsulfonic acid to give trienone **37** in an overall yield of 78%. Reduction of **37** with lithium aluminum hydride gave a mixture of isomeric alcohols **38** in a quantitative yield. Deoxygenation of **38** was effected without appreciable allylic rearrangement by successively treating the alcohol with *n*-butyllithium, pyridine–sulfur trioxide complex, and lithium aluminum hydride.[31] In this manner, an 80% yield of a separable 8:1 mixture of (±)-α-vetispirene (**12**) and **39**, respectively, was produced.[32]

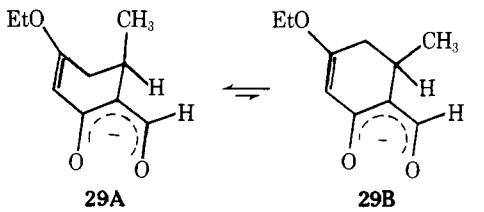
Several of the preceding reactions merit further discussion. The first is the reaction between formyl ketone **29** and phosphonium salt **11** to produce **15** in a stereospecific manner.

Scheme II



(a) MeLi (b) H_3O^+ (c) 10-CSA (d) $LiAlH_4$ (e) *n*-BuLi (f) Pyr·SO_3

Applying Johnson and Malhotra's concept of $A^{1,3}$-strain[33] to conformations of the intermediate enolate provides one explanation of why such specificity is observed. The most stable conformation of the enolate of **29** can be represented by **29A**, in which the C-5 methyl group is axially disposed. This eliminates severe A-1,3 interactions present in the alternate conformation **29B**. If **29A** is attacked by the electrophilic cyclo-

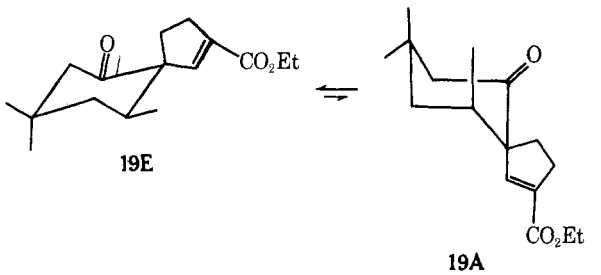


29A **29B**

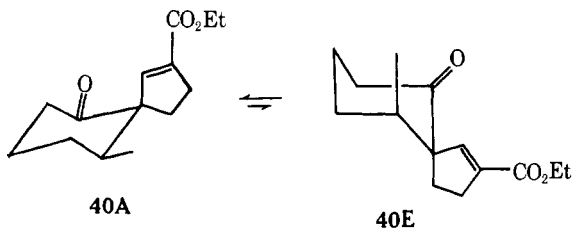
propane **11** in an irreversible manner from the face opposite the axially disposed methyl group, formation of **15** necessarily results. This explanation, of course, is only valid if $\Delta G^{\ddagger}$ for this mode of attack is equal to or less than $\Delta G^{\ddagger}$ for the other three possible modes of attack of **11** on the enolate.

The second is the stereospecificity and regiospecificity observed during the hydrogenation of **15** to **30**. Perhaps solvation of the highly polarized carbonyl group of the β-ethoxyenone moiety creates a steric barrier to catalyst binding from that face of the cyclopentene double bond.[34] It was possible to demonstrate a definite solvent effect on the course of the hydrogenation. When **15** was hydrogenated over palladium on charcoal in ethyl acetate several products, none of which was isolated in pure form, were obtained. An NMR analysis of the mixture, however, indicated that indiscriminate reduction of both double bonds has occurred.

Since the stereochemistry of **15** had been clearly established, this compound became a useful molecule in the assignment of stereochemistry to the keto esters obtained from the reactions of **11** with α-formylcyclohexanones. The stereochemistry of compounds **19–25** was assigned from the chemical shifts of their vinyl protons in the following manner. It was assumed that the predominant conformation in compounds **19–25** was that conformation placing the maximum number of substituents in equatorial sites on the cyclohexane ring.[35] Thus, the chemical shift of the vinyl protons in spiranes **19–25** should depend on whether they are in a predominantly axial or equatorial environment as illustrated in **19E** and **19A**. A suitable model for a vinyl proton on an axially disposed carbon



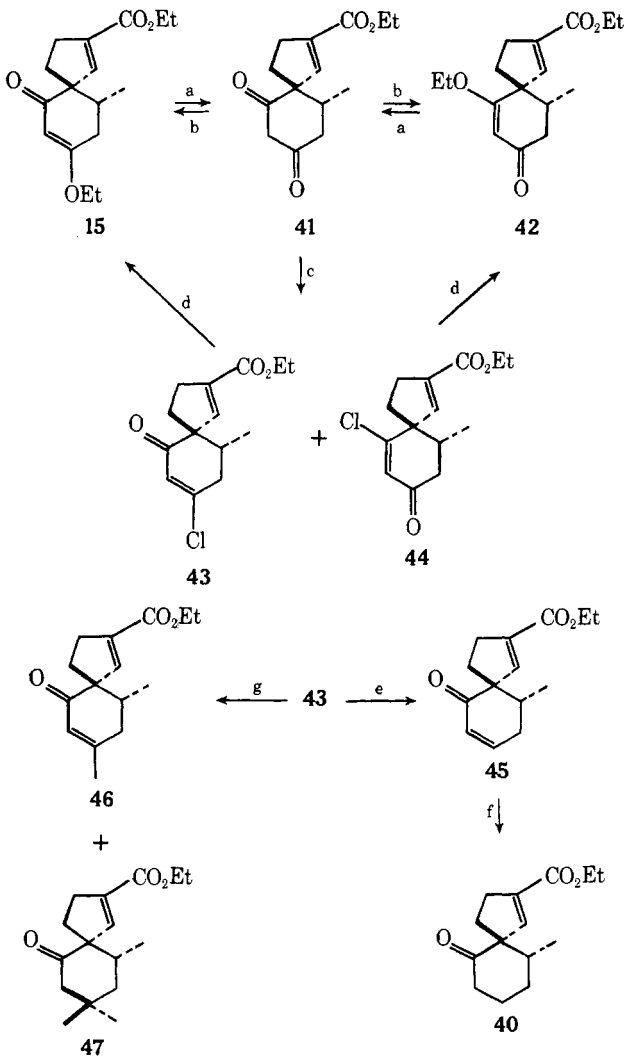
19E 19A



40A 40E

is keto ester **40** which, according to the assumption made above, should prefer conformation **40A** over conformation **40E**.[36] Spirane **40** was prepared from **15**, whose stereochemistry was clearly defined, as outlined in Scheme III. Two-phase

Scheme III



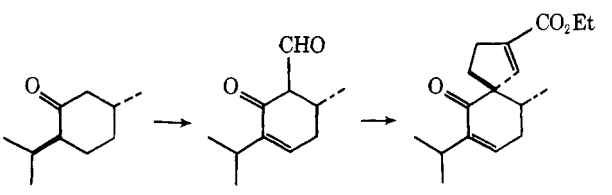
(a) HCl, H_2O, Et_2O (b) PTS, EtOH (c) $Cl(CO)_2Cl$ (d) NaOEt (e) Zn(Ag), MeOH (f) H_2, Pd/C, EtOH (g) Me_2CuLi

acid hydrolysis of **15** afforded crystalline diketo ester **41** in an 86% yield. Etherification of **41** produced an 87:13 mixture of enol ethers **15** and **42**, respectively, in a 98% yield. The high selectivity in enol ether formation encouraged us to prepare an enol derivative in which the β substituent could be removed. Treatment of dione **41** with oxalyl chloride[37] gave a 76% yield of a 12:1 mixture of enol chlorides **43** and **44**, respectively. The isomeric chlorides were easily separated by chromatography over silica gel. The structures were assigned on the basis of spectral data. Of particular use in assigning the correct structures to the isomeric enol chlorides were the strong retro-Diels–Alder peaks in their mass spectra. In addition, treatment of halides **43** and **44** with sodium ethoxide afforded enol ethers **15** and **42**, respectively. These results confirmed the structural assignments and also established that no epimerization at C-5 had taken place during enol chloride formation from **41**. Pure **43** was reduced with zinc–silver couple to enone **45** in an 83% yield.[38] Catalytic reduction of **45** afforded an 80% yield of the desired model compound, spiro keto ester **40**, which exhibited a single vinyl triplet at δ 6.60 in its NMR spectru. Although a suitable model for an equatorially disposed vinyl proton was not readily available, the NMR spectrum of **40** suggested that the upfield resonances (δ 6.33–6.48) for **19–25** should be assigned to equatorially disposed vinyl protons and the downfield resonances (δ 6.66–6.78) to those oriented axially. Thus, the stereochemistry of molecules **19–25** was assigned as shown in the table.

Since the chemical shift of the vinyl proton in **40** was only slightly downfield when placed in the continuum of vinyl proton shifts present in **19–25**, further confirmation of the stereochemical assignments was sought. Treatment of **43**, whose stereochemistry at C-5 and C-10 was firmly established, with lithium dimethylcuprate gave a 40% yield of keto ester **47** accompanied by a 15% yield of enone **46**. Ketone **47** exhibited a single vinyl proton at δ 6.67 in its NMR spectrum and was clearly nonidentical, but isomeric to **19** (δ_{vinyl} 6.33). This result strongly supports the stereochemical assignments made above.

The stereochemical outcome of the reactions between α-formylcyclohexanones and phosphonium salt **11** suggests that the major spiro[4.5]decane product is always that product derived from axial attack of the cyclopropane on the thermodynamically most stable conformation of the enolate ion. This approach has been used to explain the stereochemical course of a variety of Robinson annelations[39] and at least one α-formylcyclohexanone alkylation.[40] It is interesting that this stereochemical model correctly predicts the formation of **15** and **19** from their respective formyl ketone precursors. In one case, axial attack is trans to the incipient C-10 methyl group while in the other case, axial attack is cis to the methyl group.

The potential of this spiroannelation reaction in the area of spiro[4.5]decane sesquiterpene synthesis was underscored by applying it to the preparation of a chiral spiro keto ester possessing the carbon skeleton of the spiroaxanes. The absolute configuration of these sesquiterpenes has yet to be established.[10] *l*-Menthone (**48**) was converted to α-formyl ketone **49** using a straightforward bromination–dehydrobromination–formylation reaction sequence. Successive treatment of **49** with sodium hydride and **11** afforded a 20% yield of a single spiro keto ester which was assigned structure **50** on the basis



48 49 50

of spectral evidence. It follows from the preceding discussion that the relative stereochemistry at C-5 and C-10 in **50** should be that observed in the spiroaxanes.

Experimental Section

General. Solvents were dried and distilled prior to use: diethyl ether, tetrahydrofuran (from Na metal); hexamethylphosphoric triamide (from CaH_n2); chloroform (from P_2O_5). Dry nitrogen was used in reactions requiring an inert atmosphere. Analytical and preparative vapor phase chromatography were carried out predominantly on Hewlett-Packard 402 and Varian Aerograph A-90-P instruments, respectively. Bulb to bulb distillations were performed in a Büchi Kugelrohrapparat. All melting points were determined on a Mel-Temp Laboratory Device and are uncorrected, as are boiling points. Proton magnetic resonance spectra (60 MHz) were recorded on Varian T-60 or Perkin-Elmer R-24A instruments. Chemical shifts are reported in units of δ from internal tetramethylsilane. ^{13}C magnetic resonance spectra (25 MHz) were recorded on an NTC-TT-23 spectrometer (Nicolet) and are reported in parts per million from internal tetramethylsilane. Owing to the presence of a crystal filter on the spectrometer, carbons resonating below 175 ppm were not observed. Infrared spectra were taken on Perkin-Elmer 137, 237, and 71A spectrometers and ultraviolet spectra on a Perkin-Elmer Model 202 instrument. Mass spectral data were collected on AEI-MS-12 and CEC-21-110B instruments. Combustion analyses were carried out by the University of California Microanalytical Laboratory.

General Procedure for Reaction between α-Formylcycloalkanones and Phosphonium Salt 11. To a suspension of 1.13 equiv of sodium hydride (as a 57% oil dispersion) in HMPT (5 mL mequiv^{-1}) was added 1.0 equiv of the α-formylcycloalkanone. The mixture was stirred until it became homogeneous, and 1.2 equiv of solid **11** was added.[12] The solution was stirred under nitrogen for 24–60 h, poured into water, and extracted several times with hexane. The extracts were washed with water, dried (Na_2SO_4 or $MgSO_4$), and concentrated in vacuo. The residue was chromatographed over silica gel (5–10 g mequiv^{-1} and eluted with benzene followed by ether) to give the desired spiro keto ester. In the general study, the reaction was run on a 1–2-mmol scale.

2-Carbethoxyspiro[4.5]dec-1-en-6-one (17). To a suspension of 95 mg (2.25 mmol) of a 57% sodium hydride oil dispersion in 10 mL of HMPT was added 252 mg (2.0 mmol) of α-formylcyclohexanone (**16**). The solution was stirred for 20 min, and 1.15 g (2.5 mmol) of solid **11** was added. The homogeneous solution was stirred at ambient temperature for 18 h, poured into 100 mL of water, and extracted with two 150-mL portions of hexane. The combined extracts were washed with 200 mL of water, dried ($MgSO_4$), and concentrated. The residue was filtered through 5–10 g of silica gel (eluted with benzene followed by ether) to afford 180 mg (40%) of keto ester **17** as the major, nonphosphorus-containing compound: UV max (MeOH) 233 nm(ϵ 7700); IR (neat) 1718 cm^{-1}; NMR (CCl_4) 1.30 (t, 3, J = 7 Hz), 1.6–2.8 (m, 12), 4.12 (q, 2, J = 7 Hz), 6.64 (t, 1, J = 1 Hz); MS (70 eV) *m/e* 222 (M^+), 77 (base).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.02; H, 8.37.

2-Carbethoxy-8,8,10*t*-trimethyl-(5*r*C^1)-spiro[4.5]dec-1-en-6-one (19)[41] was prepared in 10% yield from 2-formyl-3,5,5-trimethylcyclohexanone:[22] UV max (MeOH) 225 nm (ϵ 5400); IR (neat) 1725, 1710, 1645 cm^{-1}; NMR (CCl_4) δ 0.85 (d, 3, J = 6 Hz), 0.90 (s, 3), 1.03 (s, 3), 1.29 (t, 3, J = 7 Hz), 1.6–2.8 (m, 9), 4.07 (q, 2, J = 7 Hz), 6.30 (t, 1, J = 1 Hz); MS (70 eV) *m/e* 265 (M^+), 179 (base).

2-Carbethoxy-7-methylspiro[4.5]dec-1-en-6-ones 20 and 21 were prepared in 35% yield from 2-formyl-6-methylcyclohexanone.[23] These isomers were separated by thin layer chromatography over silica gel (two elutions with benzene) to give **20** [R_f 0.28; NMR (CCl_4) δ 1.00 (d, 3, J = 7 Hz), 1.32 (t, 3, J = 7 Hz), 1.6–2.8 (m, 11), 4.10 (q, 2, J = 7 Hz), 6.42 (t, 1, J = 1 Hz); MS (70 eV) *m/e* 236 (M^+)] and **21** [R_f 0.46; NMR (CCl_4) 1.00 (d, 3, J = 7 Hz), 1.32 (t, 3, J = 7 Hz), 1.6–2.8 (m, 11), 4.10 (q, 2, J = 7 Hz), 6.70 (s, 1, J = 1 Hz); MS (70 eV) *m/e* 236 (M^+)] A 3:2 mixture of **20**:**21** exhibited the following properties: UV max (MeOH) 230 nm (ϵ 6000); IR (neat) 1710, 1630 cm^{-1}.

Anal. ($C_{14}H_{20}O_3$) C, H.

2-Carbethoxy-8-methylspiro[4.5]dec-1-en-6-ones 22 and 23 were prepared in 36% yield from 2-formyl-5-methylcyclohexanone.[24] An analytically pure sample of a 2:1 mixture of **22** and **23**, respectively, exhibited the following spectral properties: UV max (MeOH) 234 nm (ϵ 6600); IR (neat) 1720, 1636 cm^{-1}; NMR (CCl_4) δ 1.07 (m, 3), 1.28 (t, 3, J = 7 Hz), 1.6–2.7 (m, 11), 4.12 (q, 2, J = 7 Hz), 6.48 (t, 0.67, J = 1.5 Hz), 6.66 (t, 0.33, J = 1.5 Hz); MS (70 eV) *m/e* 236 (M^+), 208, 193, 192, 191, 163, 29 (base).

Anal. ($C_{14}H_{20}O_3$) C, H.

9-*tert*-Butyl-2-carbethoxyspiro[4.5]dec-1-en-6-ones 24 and 25. A 3:1 mixture of **24** and **25**, respectively, prepared in a 30% yield from 4-*tert*-butyl-2-formylcyclohexanone, exhibited the following spectral properties: UV max (MeOH) 225 nm (ϵ 9000); IR ($CHCl_3$) 1705 cm^{-1}; NMR (CCl_4) δ 0.93 (s, 9), 1.30 (t, 3, J = 7 Hz), 1.3–2.9 (m, 11), 4.13 (q, 2, J = 7 Hz), 6.46 (t, 0.75, J = 1 Hz), 6.75 (t, 0.25, J = 1 Hz); MS (70 eV) *m/e* 278 (M^+), 57, 41 (base). The isomers were separated by preparative thin layer chromatography over silica gel (eluted twice with benzene) to give pure **24** (R_f 0.22) and **25** (R_f 0.43). An analytically pure sample of **24** melted at 72–73 °C.

Anal. For **24** ($C_{17}H_{26}O_4$) C, H.

2-Carbethoxyspiro[4.6]undec-1-en-6-one (26) was prepared in 44% yield from 2-formylcycloheptanone:[25] UV max (MeOH) 230 nm (ϵ 7500); IR (neat) 1720, 1651 cm^{-1}; NMR (CCl_4) 1.25 (t, 3, J = 7 Hz), 1.5–2.8 (m, 14), 4.02 (q, 2, J = 7 Hz), 6.60 (t, 1, J = 1 Hz); MS (70 eV) *m/e* 236 (M^+), 208, 165, 77 (base).

Anal. ($C_{14}H_{20}O_3$) C, H.

2-Carbethoxyspiro[4.7]dodec-1-en-6-one (27) was prepared in 44% yield from 2-formylcyclooctanone:[25] UV max (MeOH) 232 nm (ϵ 7000); IR (neat) 1720, 1635 cm^{-1}; NMR (CCl_4) δ 1.25 (t, 3, J = 7 Hz), 1.4–2.8 (m, 16), 4.05 (q, 2, J = 7 Hz), 6.39 (t, 3, J = 1 Hz); MS (70 eV) *m/e* 250 (M^+), 152 (base).

Anal. ($C_{15}H_{22}O_3$) C, H.

3-Ethoxy-6-formyl-5-methylcyclohex-2-en-6-one (29). To a suspension of 4.79 g (0.1 mol) of a 57% sodium hydride oil dispersion in 200 mL of ether and 0.5 mL of ethanol at 0 °C was added a mixture of 15.4 g (0.1 mol) of 3-ethoxy-5-methylcyclohex-3-en-1-one (**28**)[21] and 12.6 g (0.15 mol) of ethyl formate over a 45-min period. The mixture was warmed under reflux for 4 h and stirred for an additional 16 h at room temperature. To the resulting mixture was added 50 mL of water. The aqueous layer was washed with 250 mL of ether, acidified to pH 2–3 with 6 N hydrochloric acid, and extracted with 100 mL of methylene chloride. The organic solution was dried ($MgSO_4$) and concentrated, and the residue was distilled to yield 11.1 g (61%) of analytically pure **29** as a yellow liquid: bp 107–108 °C (0.3 mm); UV max (MeOH) 258, 300 nm (ϵ 9800, 8650); IR (neat) 1645, 1610, 1592 cm^{-1}; NMR (CCl_4) 1.16 (d, 3, J = 7 Hz), 1.40 (t, 3, J = 7 Hz), 2.2–3.0 (m, 3), 3,93 (Q= 2= J = 7 Hz), 5.23 (s, 1), 7.18 (broad s, 1), 13.90 (very broad s, 1); MS (70 eV) *m/e* 182 (M^+), 167, 154, 139, 111 (base).

Anal. ($C_{10}H_{14}O_3$) C, H.

2-Carbethoxy-8-ethoxy-10*c*-methyl-(5*r*C^1)-spiro[4.5]deca-1,7-dien-6-one (15). To 4.41 g (0.105 mol) of a 57% sodium hydride oil dispersion in 400 mL of HMPT was added 18.4 g (0.100 mol) of α-formyl ketone **29**. The solution was stirred for 45 min and 50.8 g (0.110 mol) of solid **11** was added. The mixture was stirred under nitrogen for 40 h, poured into 300 mL of water, and extracted with four 1-L portions of hexane. The combined extracts were dried (Na_2SO_4) and concentrated, and the residue was chromatographed over 200 g of silica gel (eluted sequentially with benzene and ether). The resulting crude material was recrystallized from hexane to give 6.5 g (24%) of analytically pure keto ester **15**. On smaller scales, yields of up to 38% were obtained: mp 82–84 °C; UV max (MeOH) 254 nm (ϵ 21 000); ^1H NMR (CCl_4) δ 1.00 (d, 3, J = 7H), 1.30 (t, 3, J = 7 Hz), 1.38 (t, 3, J = 7 Hz), 1.6–2.8 (m, 7), 3.90 (q, 2, J = 7 Hz), 4.12 (q, 2, J = 7 Hz), 5.19 (s, 1), 6.33 (t, 1, J = 1 Hz); ^{13}C NMR ($CDCl_3$) 13.8 (q), 13,9 (q), 16.1 (q), 29.0 (t), 31.1 (t), 34.9 (t), 36.4 (d), 59.9 (t), 64.0 (t), 64.4 (t), 100.8 (d), 139.4 (s), 140.5 (d), 164.2 (s), 174.9 ppm (s); MS (70 eV) *m/e* 278 (M^+), 233, 166, 112, 91 (base).

Anal. ($C_{16}H_{22}O_4$) C, H.

2-Carbethoxy-8-ethoxy-10*c*-methyl-(5*r*C^1)-spiro[4.5]dec-7-en-6-one (30) and 2-(2-Hydroxyprop-2-yl)-6,10*c*-dimethyl-(5*r*C^1)-spiro[4.5]dec-6-en-8-one (31). A solution of 2.27 g (8.2 mmol) of α,β-unsaturated ester **15** was hydrogenated at room temperature and 1 atm over 300 mg of 5% palladium on charcoal until 204 mL (1 equiv) of hydrogen uptake had occurred. The solution was filtered through Celite and concentrated at reduced pressure to give crude ester **30** as a colorless liquid. A purified sample exhibited the following spectral properties: UV max (MeOH) 251 nm (ϵ 18 900); IR (neat) 1730, 1653, 1613 cm^{-1}; NMR (CCl_4) δ 1.00 (d, 3, J = 7 Hz), 1.27 (t, 3, J = 7 Hz), 1.37 (t, 3, J = 7 Hz), 1.6–2.8 (m, 10), 3.88 (q, 2, J = 7 Hz), 4.07 (q, 2, J = 7 Hz), 5.09 (s, 1); MS (70 eV) *m/e* 280 (M^+), 235, 207, 167 (base), 112.

Exact mass. Calcd for $C_{16}H_{24}O_4$: 280.1673. Found: 280.1625.

To the crude **30** in 125 mL of ether was added 16 mL (27.2 mmol)

of 1.7 M ethereal methyllithium via syringe at 0 °C. The mixture was stirred for 1 h and quenched with 10 mL of saturated aqueous ammonium chloride. The ether layer was separated and concentrated. The residual oil was stirred for 1 h with 75 mL of ether and 75 mL of 1 N aqueous hydrochloric acid. The mixture was extracted with ether and the extracts were dried ($MgSO_4$) and concentrated. The residual solid was recrystallized from carbon tetrachloride to give 1.17 g (60%) of analytically pure ketol **31**:[26] mp 116–119 °C; UV max (MeOH) 424 nm (ϵ 12 700); IR (KBr) 3400, 1650 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (d, 3, J = 7 Hz), 1.25 (s, 6), 1.6–2.6 (m, 14, with d, J = 1 Hz, at 1.95), 5.72 (q, 1, J = 1 Hz); MS (70 eV) *m/e* 221, 219, 218, 203, 176, 161, 59 (base).

Anal. ($C_{15}H_{24}O_2$) C, H.

2-(2-Acetoxyprop-2-yl)-6,10c-dimethyl-(5rC^1)-spiro[4.5]dec-6-en-8-one (32) and (±)-β-Vetivone (3). A mixture of 390 mg (1.65 mmol) of ketol **31** and 315 mg (3.3 mmol) of anhydrous sodium acetate in 3.5 mL of acetic anhydride was warmed at 140 °C under nitrogen for 2 h. The mixture was added to 100 mL of saturated aqueous sodium bicarbonate by pipet. The resulting solution was extracted with 50 mL of methylene chloride and the extract was dried ($MgSO_4$) and concentrated. The residue was chromatographed over 10 g of silica gel (eluted with ether) to give 350 mg (75%) of acetate **32**:[15a] IR (CCl_4) 2950, 1733, 1675, 1616, 1374, 1361, 1250, 1222, 1205, 1134, 1015, 943 cm^{-1}; NMR (CCl_4) 1.01 (d, 3, J = 6 Hz), 1.48 (s, 6), 1.7–2.5 (m, 16 with s's at 1.91 and 1.93), 4.50 (q, 1, J = 1 Hz).

To a solution of 360 mg (1.26 mmol) of keto acetate **32** in 1.2 mL of ether was added 1.2 mL of boron trifluoride etherate. The mixture was stirred at room temperature for 60 min. The resulting dark mixture was poured into 50 mL of cold aqueous 5% sodium hydroxide and extracted with two 50-mL portions of ether. The combined extracts were dried ($MgSO_4$) and concentrated, and the residual oil was chromatographed over 10 g of silica gel (eluted with benzene–ether, 1:1) to give 195 mg (71%) of (±)-β-vetivone (**3**). This material was chromatographically identical with an authentic sample of (±)-β-vetivone.[29] A portion of this material was crystallized from pentane as described elsewhere[15a] to give a crystalline sample which melted at 43.5–47.0 °C (lit.[15a] 43.5–46.0 °C). The isopropylidene methyl groups of this material were cleanly resolved in its 220-MHz ^1H NMR spectrum: IR (CCl_4) 2924, 1667, 1610, 1431, 1370, 1333, 1299, 1188, 891 cm^{-1}; NMR (CCl_4) 0.97 (d, 3, J = 6 Hz), 1.67 (broad s, 6), 1.8–2.6 (m, 12, with s at 1.89), 5.69 (broad s, 1); MS (70 eV) *m/e* 218 (M^+).

8-Hydroxy-2-isopropylidene-6,10c-dimethyl-(5rC^1)-spiro[4.5]-dec-6-ene (33) and (±)-β-Vetispirene (13). To a stirred suspension of 7.6 mg (0.2 mmol) of lithium aluminum hydride in 4.0 mL of ether was added 95 mg (0.43 mmol) of (±)-β-vetivone (**3**) in 25 mL of ether. The mixture was stirred for 60 min and wet ether was added to destroy the remaining hydride. The solution was filtered, dried ($MgSO_4$), and concentrated to give 96 mg (100%) of crude alcohol **33** that was suitable for use directly in the next reaction: IR (neat) 3350, 1661 cm^{-1}; NMR (CCl_4) δ 0.89 (d, 3, J = 6 Hz), 1.4–2.6 (m, 18), 2.90 (broad s, 1), 4.00 (broad s, 1), 5.23 (broad s, 1).

The crude alcohol **33** was stirred with 10 mg of 10-camphorsulfonic acid in 10 mL of benzene under nitrogen for 20 h. The reaction mixture was chromatographed directly on 10 g of silica gel (eluted with benzene) to give 75 mg (85%) of (±)-β-vetispirene (**13**), greater than 90% pure by VPC (10 ft × 0.25 in. 10% SE-30 on Chromosorb W, 170 °C). A VPC-purified sample had spectral characteristics similar to those reported for natural β-vetispirene:[13a] UV max (MeOH) 232 nm (ϵ 12 000); IR (neat) 3075, 3030, 2970, 1785, 1640, 1601, 1377, 890, 779 cm^{-}; NMR (CCl_4) δ 0.83 (d, 3, J = 6 Hz), 1.4–2.8 (m, 15, with sharp peaks at 1.63, 1.69), 4.75 (m, 2), 5.59 (m, 1), 5.95 (m, 1); MS (70 eV) *m/e* 202 (M^+).

8-Hydroxy-2-(2-hydroxyprop-2-yl)-6,10c-dimethyl-(5rC^1)-spiro-[4.5]dec-6-ene (34) and 8-Acetoxy-2-(2-hydroxyprop-2-yl)-6,10c-dimethyl-(5rC^1)-spiro[4.5]dec-6-ene (35). To a solution of 114 mg (3.0 mmol) of lithium aluminum hydride in 15 mL of ether was added a solution of 206 mg (0.88 mmol) of ketol **31** in 35 mL of ether over a 20-min period. The mixture was stirred for 20 h and 0.1 mL of water, 0.1 mL of 15% aqueous sodium hydroxide, and 0.3 mL of water were added, sequentially. The solution was filtered, dried ($MgSO_4$), and concentrated to give 200 mg (97%) of crude diol **34** as a colorless oil. This material was homogeneous by thin layer chromatography over silica gel (eluted with ether) and was used directly in the next reaction without further purification: IR (neat) 3350, 1650 cm^{-1}; NMR ($CDCl_3$) δ 0.97 (d, 3, J = 6 Hz), 1.20 (s, 6), 1.75 (s, 3), 4.10 (broad s, 1), 5.23 (broad s, 1); MS (70 eV) *m/e* 220, 202, 187, 97 (base).

A solution of 200 mg (0.86 mmol) of crude **34** in 1.0 mL of acetic anhydride and 1.5 mL of pyridine was warmed at 70 °C for 90 min and was stirred at ambient temperature for 4 h. The mixture was poured into saturated aqueous sodium bicarbonate and extracted with chloroform. The organic extract was washed with dilute aqueous hydrochloric acid, dried (Na_2SO_4), and concentrated to give 250 mg of a residual oil. This oil was chromatographed over silica gel (eluted with benzene followed by ether) to afford 200 mg (81%) of hydroxy acetate **35** as a mixture of crystalline isomers: mp 45–55 °C; IR (neat) 3350, 1725, 1650, 1240 cm^{-1}; NMR ($CDCl_3$) δ 0.97 (d, 3, J = 6 Hz), 1.22 (s, 6), 1.3–2.1 (m, 17, with s's at 1.75 and 2.03), 5.20 (m, 2); MS (high resolution) *m/e* 262.1928 ($C_{17}H_{26}O_2$, M − H_2O), 220.1794 ($C_{15}H_{24}O$, M − HOAc), 202.1728 ($C_{15}H_2$, M − HOAc − H_2O).

(±)-Hinesol (14). To a solution of 100 mg (0.36 mmol) of allylic acetate **35** in 5 mL of anhydrous ethylamine in a tightly stoppered flask was added 55 mg of lithium metal. The mixture was shaken at room temperature until a deep blue color persisted for 5–10 min. The solution was decanted from the excess lithium into 75 mL of water. The resulting aqueous solution was extracted with two 75-mL portions of ether and the combined extracts were dried ($MgSO_4$) and concentrated. The residue was chromatographed over 3 g of silica gel (eluted with increasing increments of ether in benzene) to give 60 mg (75%) of (±)-hinesol (**14**) which was 90% pure by VPC (6 ft × 1/8 in. 6% SE-30, 130 °C). This material was chromatographically and spectrally identical with an authentic sample of (±)-hinesol:[29] IR (neat) 3350, 1450, 1390, 930 cm^{-1}; NMR (CCl_4) δ 0.90 (d, 3, J = 6 Hz), 1.15 (s, 6), 1.4–2.2 (m, 16, with d at 1.63), 5.18 (m, 1, $W_{1/2}$ = 9 Hz); MS (high resolution) *m/e* 204.1898 ($C_{15}H_{18}$), 162.1368 ($C_{12}H_{18}$), 147.1144 ($C_{11}H_{15}$). The impurity in the hinesol, prepared as described above, exhibited vinyl proton absorption at δ 5.35 in the NMR spectrum of the product mixture and may be due to the presence of the $\Delta^{7,8}$ isomer of **14**.

(±)-Hinesol Acetate (14-OAc).[16] This material was prepared according to an established procedure. A mixture of 35 mg (0.16 mmol) of (±)-hinesol (**14**) and 35 mg of anhydrous sodium acetate in 1.0 mL of acetic anhydride was warmed at 140 °C for 120 min. The mixture was cast into 20 mL of saturated aqueous sodium bicarbonate and extracted with methylene chloride. The extract was dried (Na_2SO_4), concentrated, and warmed under high vacuum to remove traces of acetic anhydride. The residue was thin layer chromatographed over silica gel (eluted with ether–benzene, 5:7) to yield 30 mg (71%) of (±)-hinesol acetate (**14**-OAc)[16] which was 90% pure by VPC (6 ft × 1/8 in. 5% FFAP on Chromosorb W, 150 °C). This material was spectrally and chromatographically identical with a sample of **14**-OAc prepared from an authentic sample of (±)-hinesol.[29]

2-(2-Hydroxyprop-2-yl)-6,10c-dimethyl-(5rC^1)-spiro[4.5]deca-1,6-dien-8-one (36) and 2-Isopropenyl-6,10c-dimethyl-(5rC^1)-spiro[4.5]deca-1,6-dien-8-one (37). To a solution of 4.0 g (14.4 mmol) of keto ester **15** in 200 mL of ether at 0 °C was added 34 mL)58.0 mmol) of 1.7 M ethereal methyllithium over a 10-min period. The mixture was stirred with concurrent warming to room temperature over a 45-min period and 25 mL of saturated aqueous ammonium chloride and 25 mL of water were added. The organic layer was dried ($MgSO_4$) and concentrated to afford 3.4 g of crude ketol **36** suitable for use directly in the next reaction: UV max (MeOH) 240 nm (ϵ 13 300); IR (neat) 3350, 1665, 1614 cm^{-1}; NMR (CCl_4) δ 0.92 (d, 3, J = 6 Hz), 1.35 (s, 6), 1.85 (d, 3, J = 1 Hz), 1.85–2.6 (m, 7), 3.00 (broad s, 1), 5.33 (t, 1, J = 1 Hz), 5.67 (q, 1, J = 1 Hz); MS (70 eV) *m/e* 234 (M^+), 219, 216, 43 (base).

Exact mass. Calcd for $C_{15}H_{22}O_2$: 234.1619. Found: 234.1618.

A solution of the crude **36** in 100 mL of benzene was warmed with 75 mg of 10-camphorsulfonic acid at 45 °C for 48 h and concentrated, and the residue chromatographed over 80 g of silica gel (eluted with ether–benzene, 1:3) to give 2.44 g (78%) of trienone **37**: UV max (MeOH) 242 nm (ϵ 33 000); IR (CCl_4) 1671, 1616, 892 cm^{-1}; NMR (CCl_4) 0.97 (d, 3, J = 6 Hz), 1.83 (d, 3, J = 1 Hz), 1.95 (broad s, 3), 1.8–2.8 (m, 7), 4.90 (broad s, 2), 5.58 (broad s, 1), 5.68 (q, 1, J = 1 Hz); MS (70 eV) *m/e* 216 (M^+), 131 (base).

Exact mass. Calcd for $C_{15}H_{20}O$: 216.1503. Found: 216.1475.

8-Hydroxy-2-isopropenyl-6,10c-dimethyl-(5rC^1)-spiro[4.5]-deca-1,6-diene (38). To a suspension of 50 mg (1.35 mmol) of lithium aluminum hydride in 15 mL of ether at 0 °C was added a solution of 432 mg (2.0 mmol) of trienone **37** in 10 mL of ether. The solution was stirred for 18 h and 0.1 mL of water 0.1 mL of 15% aqueous sodium hydroxide, and 0.3 mL of water were added successively. The mixture

was filtered, dried ($MgSO_4$), and concentrated to give 440 mg (100%) of analytically pure alcohol **38**: mp 51–62 °C; IR (CCl_4) 3400, 1652, 1628, 1595, 889 cm^{-1}; NMR (CCl_4) δ 0.85 (d, 3, J = 6 Hz), 1.60 (d, 3, J = 1 Hz), 1.89 (s, 3), 2.48 (m, 2), 4.15 (m, 1), 4.85 (s, 2), 5.38 (m, 2); MS (70 eV) *m/e* 218 (M^+), 200, 185, 91.

Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.19; H, 10.00.

(±)-α-Vetispirene (12). To a solution of 109 mg (0.5 mmol) of allylic alcohol **38** in 4.0 mL of tetrahydrofuran was added 0.33 mL (0.5 mmol) of 1.5 M ethereal methyllithium at 0–3 °C under nitrogen. The solution was stirred for 5 min and 159 mg (1.0 mmol) of pyridine–sulfur trioxide complex was added in one portion. The resulting orange-yellow solution was stirred in the cold for 120 min and 148 mg (4.0 mmol) of lithium aluminum hydride in 8 mL of tetrahydrofuran was added. The mxiture was stirred for 16 h at room temperature and water, 15% aqueous sodium hydroxide, water, and anhydrous magnesium sulfate were added. The solution was filtered and concentrated, and residue was chromatographed over silica gel to give 80 mg (80%) of an 8:1 mixture of (±)-α-vetispirene and triene **39**, respectively. Pure samples of each hydrocarbon were obtained by preparative VPC (10 ft × ¼ in. 10% SE-30, 190 °C, 60 mL He min^{-1}). Pure **39** exhibited the following properties: UV max (MeOH) 243 nm (ϵ 31 000); NMR (CCl_4) δ 0.89 (m, 6), 1.4–2.6 (m, 11, with s at 1.90), 4.77 (broad s, 2), 5.33 (m, 3).

Exact mass. Calcd for $C_{15}H_{22}$: 202.1721. Found: 202.1701.

Pure (±)-α-vetispirene exhibited spectral data in agreement with those reported for the natural product:[13a] UV max (MeOH) 242 nm (ϵ 28 000); IR (neat) 3100, 3070, 2985, 1780, 1665, 1637, 1601, 1370, 1200, 1075, 881, 843, 795 cm^{-1}; NMR (CCl_4) δ 0.84 (d, 3, J = 6 Hz), 1.4–2.2 (m, 13, with d at 1.53 and s at 1.88), 2.42 (m, 2), 4.75 (broad s, 2), 5.20 (m, 1), 5.33 (m, 1); MS (70 eV) *m/e* 202 (M^+).

Anal. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 88.55; H, 10.88.

2-Carbethoxy-10c-methyl-(5rC^1)-spiro[4.5]dec-1-ene-6,8-dione (41). A two-phase mixture of 800 mg (2.88 mmol) of keto ester **15** in 10 mL of 2.4 N hydrochloric acid and 5 mL of ether was stirred for 48 h at ambient temperature. Methylene chloride was added, the organic phase was dried (Na_2SO_4) and concentrated, and the residue was recrystallized from methylene chloride–hexane to give 620 mg (86%) of analytically pure **41**: mp 135–137 °C; UV max (MeOH) 261 nm (ϵ 9 500); IR ($CHCl_3$) 3500–3400 (broad), 1735 (shoulder), 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (d, 3, J = 6 Hz), 1.27 (t, 3, J = 7 Hz), 1.6–2.8 (m, 7), 3.43, 5.16, 5.33, 8.53 (s's, 2), 5.10 (overlapping q's, 2, J = 7 Hz), 6.38, 6.55, (t's, 1, J = 1 Hz); MS (70 eV) *m/e* 250 (M^+), 222, 186, 166, 137, 121, 105, 91 (base), 71.

Anal. ($C_{14}H_{18}O_4$): C, H.

2-Carbethoxy-6-ethoxy-10c-methyl-(5rC^1)-spiro[4.5]deca-1,6-dien-8-one (42). A solution of 650 mg (2.6 mmol) of dione **41** in 20 mL of benzene–ethanol (20:1) was warmed under reflux with 5 mg of *p*-toluenesulfonic acid for 16 h with concomitant removal of water using a Dean-Stark trap filled with Linde 4A molecular sieves. The mixture was concentrated under reduced pressure and the residue was chromatographed over silica gel (eluted with ether) to give 600 mg (84%) of crystalline **15** and 108 mg (14%) of **42** as a colorless oil: UV max (MeOH) 257 nm (ϵ 28 000); IR (neat) 1725, 1668, 1603 cm^{-1}; NMR (CCl_4) δ 1.00 (d, 3, J = 6 Hz), 1.30 (t, 3, J = 7 Hz), 1.35 (t, 3, J = 7 Hz), 1.8–2.8 (m, 7), 3.90 (q, 2, J = 7 Hz), 4.17 (q, 2, J = 7 Hz), 5.15 (s, 1), 6.47 (t, 1, J = 1 Hz); MS (70 eV) *m/e* 278 (M^+), 236 (base).

Exact mass. Calcd for $C_{16}H_{22}O_4$: 278.1473. Found: 278.1512.

2-Carbethoxy-8-chloro-10c-methyl-(5rC^1)-spiro[4.5]deca-1,7-dien-6-one (43) and 2-Carbethoxy-6-chloro-10c-methyl-(5rC^1)-spiro[4.5]deca-1,6-dien-8-one (44). A solution of 500 mg (2.0 mmol) of dione **41** and 638 mg (0.43 mL, 5.02 mmol) of oxalyl chloride in 3.0 mL of chloroform was warmed under reflux in a nitrogen atmosphere for 60 min. The mixture was concentrated, allowed to stand at room temperature for 6 h, and chromatographed over 15 g of silica gel (eluted with benzene–ether, 22:3) to afford 368 mg of analytically pure crystalline enol chloride **43** and 52 mg of a mixture of **43** and **44**. The mixture of isomeric enol chlorides was subjected to preparative thin layer chromatography over silica gel (20 cm× 20 cm × 1 mm; eluted with benzene–ether, 5:1) to give an additional 13 mg (70.5% overall) of **43** and 31 mg (5.8%) of **44**. Enol chloride **43** exhibited the following properties: mp 56–62 °C; IR (CCl_4) 1725, 1690, 1625 cm^{-1}; NMR (CCl_4) δ 1.05 (d, 3, J = 7 Hz), 1.30 (t, 3, J = 7 Hz), 1.6–2.9 (m, 7), 4.12 (q, 2, J = 7 Hz), 6.13 (q, 1, J = 1 Hz), 6.35 (t, 1, J = 1 Hz); MS (70 eV) *m/e* 270, 268 (M^+), 225, 224, 223, 222, 212, 116 (base), 104, 102.

Anal. Calcd for $C_{14}H_{17}ClO_3$: C, 62.57; H, 6.38; Cl, 13.19. Found: C, 62.21; H, 6.43; Cl, 13.30.

Enol chloride **44** exhibited the following properties: UV max (MeOH) 244 nm (ϵ 17 000); IR (CCl_4) 1735, 1698, 1605 cm^{-1}; NMR (CCl_4) δ 1.07 (d, 3, J = 6 Hz), 1.33 (t, 3, J = 7 Hz), 2.0–3.0 (m, 7), 4.20 (q, 2, J = 7 Hz), 6.13 (s, 1), 6.48 (t, 1, J = 1 Hz); MS (70 eV) *m/e* 270, 268 (M^+), 228, 226 (base).

Exact mass. Calcd for $C_{14}H_{17}{}^{35}ClO_3$: 268.0865. Found: 268.0855.

Conversion of Enol Chloride 43 to Enol Ether 15. A solution of 25 mg (0.09 mmol) of enol chloride **43** in 1.0 mL of 2% ethanolic sodium ethoxide was allowed to stand at room temperature for 15 min. The mixture was chromatographed directly over 10 g of silica gel (eluted with ether) to afford 16 mg (67%) of **15** which crystallized on standing, mp 75–82 °C.

Conversion of Enol Chloride 44 to Enol Ether 42. A solution of 23 mg (0.085 mmol) of enol chloride **44** in 0.7 mL of 2% ethanolic sodium ethoxide was allowed to stand at room temperature for several hours. The solution was directly chromatographed over 10 g of silica gel (eluted with ether) to give 20 mg (80%) of pure **42**.

Hydrolysis of Enol Ether 42. A mixture of 15 mg (0.054 mmol) of **42** in a two-phase mixture of 0.5 mL of ether and 0.5 mL of 2.4 N aqueous hydrochloric acid was stirred at room temperature for 24 h. Chloroform was added, and the organic phase was dried (Na_2SO_4) and concentrated. The residual oil was crystallized from methylene chloride–hexane to give 9.5 mg (65%) of dione **41**, mp 134–135 °C.

2-Carbethoxy-10c-methyl-(5rC^1)-spiro[4.5]deca-1,7-dien-6-one (45). To 0.5 g of freshly prepared zinc–silver couple[37] suspended in 2.5 mL of methanol was added 100 mg (0.372 mmol) of enol chloride **43** in 1.0 mL of methanol. The mixture was stirred at room temperature for 7 h and filtered, and the residual zinc was washed with 10 mL of methanol. The methanol was removed at reduced pressure and the residue was chromatographed over silica gel (eluted with benzene) to give 72 mg (83%) of enone **45** which was 93% pure by VPC (10 ft × ¼ in. SE-30; 200 °C; 60 mL He min^{-1}). The minor component (7%) of the mixture was probably the corresponding methyl ester of **45** (singlet in NMR spectrum of mixture at δ 3.72). An analytically pure sample of **45** was obtained by bulb to bulb distillation: bp 110 °C (0.3 mm); UV max (MeOH) 233 nm (ϵ 10 000); IR (CCl_4) 1719, 1680, 1628 cm^{-1}; NMR (CCl_4) δ 1.02 (d, 3, J = 6 Hz), 1.30 (t, 3, J = 7 Hz), 1.5–3.0 (m, 7), 4.17 (q, 2, J = 7 Hz), 5.99 (d, 1, J = 10 Hz), 6.45 (t, 1, J = 1 Hz), 6.85 (m, 1, which collapses to d, J = 10 Hz, upon irradiation at 2.65); MS (70 eV) *m/e* 234 (M^+), 166 (base).

Anal. ($C_{14}H_{18}O_3$) C, H.

2-Carbethoxy-10c-methyl-(5rC^1)-spiro[4.5]dec-1-en-6-one (40). A solution of 36 mg (0.154 mmol) of enone **45** (93% pure) in 2.0 mL of absolute ethanol was hydrogenated at room temperature and 1 atm over 5 mg of 5% palladium on charcoal for 20 min. The solution was filtered through Celite and concentrated, and the residue was bulb to bulb distilled to give 29 mg (80%) of analytically pure keto ester **40**. This material contained about 7% of a contaminant by VPC (5 ft × ⅛ in. 3% SE-30, 170 °C). A pure sample of **40** was obtained by preparative VPC (10 ft × ¼ in. 5% SE-30, 200 °C, 60 mL He min^{-1}): IR (CCl_4) 1725 (shoulder), 1715, 1635 cm^{-1}; NMR (CCl_4) δ 0.93 (m, 3), 1.28 (t, 3, J = 7 Hz), 1.5–2.9 (m, 11), 4.12 (q, 2, J = 7 Hz), 6.60 (t, 1, J = 1 Hz); MS (high resolution) *m/e* 236.1438 (M^+), 91.0529 (base, C_7H_7).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.74; H, 8.56.

2-Carbethoxy-8,10c-dimethyl-(5rC^1)-spiro[4.5]deca-1,7-dien-6-one (46) and 2-Carbethoxy-8,8,10c-trimethyl-(5rC^1)-spiro[4.5]dec-1-en-6-one (47). To a suspension of 190.5 mg (1.0 mmol) of cuprous iodide in 3 mL of ether at 0 °C was added 1.28 mL (2.0 mmol) of 1.56 M ethereal methyllithium. The solution was stirred for 5 min and 134 mg (0.5 mmol) of enol chloride **43** in 3 mL of ether was added over a 7-min period. The resulting dark mixture was stirred at 0 °C for an additional 30 min and was added dropwide to a vigorously stirred solution of 15 mL of 1.2 N aqueous hydrochloric acid. The mixture was extracted with 75 mL of ether and the extract was dried ($MgSO_4$) and concentrated. The residual oil was preparative thin layer chromatographed over silica gel (eluted with benzene) to give 61 mg of a 3:1 mixture of keto ester **47** and enol chloride **43** and 17 mg (15%) of pure enone **46**: bp (bulb to bulb) 110 °C (0.4 mm); IR (neat) 1715,

1670 cm^{-1}; NMR (CCl_4) δ 1.00 (d, 3, J = 7 Hz), 1.38 (t, 3, J = 7 Hz), 1.5–2.9 (m, 10, with s at 1.96), 4.15 (q, 2, J = 7 Hz), 5.81 (broad s, 1), 6.36 (broad s, 1); MS (high resolution) m/e 166.1004 (base, $C_{10}H_{14}O_2$).

Exact mass. Calcd for $C_{15}H_{20}O_3$: 248.1411. Found: 248.1393.

The mixture of **43** and **47** was again subjected to thin layer chromatography to afford 36 mg of a mixture of **43** and **47** and 20 mg of pure **47**: IR (neat) 1720, 1630 cm^{-1}; NMR (CCl_4) δ 0.90 (s, 3), 0.92 (d, 3, J = 7 Hz), 1.10 (s, 3), 1.28 (t, 3, J = 7 Hz), 1.2–3.0 (m, 9), 4.12 (q, 2, J = 7 Hz), 6.53 (t, 1, J = 1 Hz); MS (high resolution) 179.1094 (base, $C_{11}H_{15}O_2$).

Exact mass. Calcd for $C_{16}H_{24}O_3$: 265.1728. Found: 264.1687.

(−)-2-Isopropyl-5-methylcyclohex-2-en-1-one.[42] To a solution of 40 g (0.26 mol) of (−)-menthone in 500 mL of dry tetrahydrofuran was added a solution of 94 g of phenyltrimethylammonium bromide perbromide in 250 mL of tetrahydrofuran over a 2.5-h period. The mixture was stirred for an additional 0.5 h and poured into 1 L of saturated aqueous sodium bicarbonate solution, and the solution was extracted with 1 L of ether. The organic layer was washed with aqueous sodium bicarbonate solution and water and dried ($MgSO_4$), and the solvent was evaporated.

The residual liquid was dissolved in 130 mL of dimethylformamide and this solution was added to a suspension of 55.7 g (0.52 mol) of lithium bromide and 57.5 g (0.78 mol) of lithium carbonate in 260 mL of dimethylformamide at 110 °C over a period of 60 min. The mixture was heated for an additional 60 min and poured into 1 L of water, and the mixture was extracted with ether. The ethereal extract was washed with 15% aqueous sodium hydroxide and water and dried ($MgSO_4$), and the solvent was rotary evaporated. The residue was distilled, bp 73–75 °C (5 mm), to yield 12.9 g (33%), $[\alpha]_D$ −57.5°.

2-Isopropyl-5-methyl-6-formylcyclohex-2-en-1-one (49). To a slurry of 4.1 g of a 56% suspension of sodium hydride in mineral oil in 150 mL of dry ether and 0.15 mL of dry ethanol was added, over a 40-min period, a solution of 12.0 g (79 mmol) of (−)-2-isopropyl-5-methylcyclohex-2-en-1-one (**48**) in 8.9 g (0.12 mol) of ethyl formate. The mixture was warmed under gentle reflux for 60 min and stirred for 7 h at room temperature. The mixture was poured into 75 mL of water, and the aqueous layer was extracted with 150 mL of ether and acidified at 0 °C with 6 N hydrochloric acid. The resulting oil was dissolved in 75 mL of methylene chloride, the solution dried ($MgSO_4$), and the solvent rotary evaporated and the residual oil distilled to yield 9.05 g (64%) of product: bp 55–59 °C (0.2 mm); IR (CCl_4) 1650 cm^{-1}; NMR (CCl_4) δ 1.08 (d, 3, J = 4 Hz), 1.15 (d, 6, J = 6 Hz); MS (70 eV) m/e 180 (M^+), 165, 123 (base).

Anal. ($C_{11}H_{16}O_2$) C, H.

2-Carbethoxy-7-isopropyl-10c-methyl-(5rC^1)-spiro[4.5]deca-1,7-dien-6-one (50) was prepared in 17% yield from **49**: IR (CCl_4) 1712, 1668 cm^{-1}; NMR (C_6D_6) δ 0.67 (d, 3, J = 6 Hz), 0.96 (d, 3, J = 6 Hz), 0.97 (t, 3, J = 7 Hz), 0.99 (d, 3, J = 6 Hz), 1.1–1.9 (m), 2.5–3.3 (m), 3.95 (q, 2, J = 7 Hz), 6.05 (m, 1), 6.66 (m, 1).

Anal. ($C_{17}H_{24}O_3$) C, H.

References and Notes

(1) This work was supported by National Science Foundation Grant MPS 73-04662.
(2) For a preliminary account of a portion of this work see W. G. Dauben, and D. J. Hart, *J. Am. Chem. Soc.*, **97**, 1622 (1975).
(3) For an excellent review on these sesquiterpenes see J. A. Marshall, S. F. Brady, and N. H. Anderson, *Fortschr. Chem. Org. Naturst.*, **31**, 283 (1974).
(4) M. Suzuki, I. Kurosawa, and T. Irie, *Tetrahedron Lett.*, 4995 (1970).
(5) (a) D. T. Coxon, K. R. Price, B. Howard, S. F. Osman, E. B. Kalan, and R. M. Zacharium, *Tetrahedron Lett.*, 2921 (1974); (b) D. L. Hughes and D. T. Coxon, *J. Chem. Soc., Chem. Commun.*, 822 (1974).
(6) (a) N. Katsui, A. Matsunaga, and T. Masamune, *Tetrahedron Lett.*, 4483 (1974); (b) A Stoessl, J. B. Stothers, and E. W. B. Ward, *Can. J. Chem.*, **53**, 3351 (1975); (c) *J. Chem. Soc., Chem. Commun.*, 709 (1974).
(7) A. Stoessl, J. B. Stothers, and E. W. B. Ward, *J. Chem. Soc., Chem. Commun.*, 431 (1975).
(8) Lubimin and oxylubimin have also been isolated from eggplants infected with various fungi.[6b,c,7]
(9) For a discussion of the properties of these fungal metabolites see J. Kuc, W. Currier, and G. E. Wood In "Mycotoxins and Other Fungal Related Food Problems", *Adv. Chem. Ser.*, **No. 149**, 356, 369 (1976).
(10) B. DiBlasio, E. Fattorusso, S. Magno, L. Mayol, C. Pedone, C. Santacroce, and D. Sica, *Tetrahedron*, **32**, 473 (1976).
(11) The following recent studies are not reported in ref 3: (a) For a recent approach to hinesol from a chiral starting material see D. Buddhsukh and P. Magnus, *J. Chem. Soc., Chem. Commun.*, 952 (1975); (b) For a recent synthesis of **12** see D. Caine, A. A. Boucugnani, S. T. Chao, J. B. Dawson, and P. F. Ingwalson, *J. Org. Chem.*, **41**, 1539 (1976); (c) For a recent synthesis of (−)-agarospirol, a close relative of hinesol, and (−)-β-vetivone see R. Ramage, M. Deighton, and C. R. Hughes, *J. Chem. Soc., Chem. Commun.*, 662 (1975); for a novel synthesis of β-vetivone see G. Buchi, D. Berthet, R. Decorzant, A. Grieder, and A. Hauser, *J. Org. Chem.*, **41**, 3208 (1976).
(12) P. L. Fuchs, *J. Am. Chem. Soc.*, **96**, 1607 (1974).
(13) For the structure of this substance see N. H. Anderson, M. S. Falcone, and D. D. Syrdal, *Tetrahedron Lett.*, 1759 (1970).
(14) For the first total synthesis of this material see P. M. McCurry and R. K. Singh, *Tetrahedron Lett.*, 3325 (1973).
(15) (a) For the structure and first total synthesis of this substance see J. A. Marshall and P. C. Johnson, *J. Org. Chem.*, **35**, 192 (1970); (b) for a recent efficient synthesis see G. Stork, R. L. Danheiser, and B. Ganem, *J. Am. Chem. Soc.*, **95**, 3414 (1973).
(16) For the structure and first total synthesis of this substance see J. A. Marshall and S. F. Brady, *J. Org. Chem.*, **35**, 4068 (1970).
(17) For an alternate general approach to a number of spirovetivanes via a common intermediate see K. Yamada, H. Nagase, Y. Hayakawa, K. Aoki, and Y. Hirata, *Tetrahedron Lett.*, 4963, 4967 (1973).
(18) For examples of intermolecular reactions of stabilized phosphoranes with an α-formylcycloalkanone see P. F. Beal III, J. C. Babcock, and F. H. Lincoln, *J. Am. Chem. Soc.*, **88**, 3131 (1966).
(19) For reviews on the synthesis of spiro compounds see A. P. Krapcho, *Synthesis*, 383 (1974); 425 (1976). For other methods of preparing spiro compounds from α-formylcycloalkanones see V. Dave and J. S. Whitehurst, *Tetrahedron*, **30**, 745 (1974); A. de Groot and B. J. M. Jansen, *Tetrahedron Lett.*, 2709 (1976).
(20) W. G. Dauben and D. J. Hart, *Tetrahedron Lett.*, 4353 (1975).
(21) H. L. Goering, *J. Am. Chem. Soc.*, **73**, 5863 (1951).
(22) L. Ruzicka, C. F. Seidel, and H. Schinz, *Helv. Chim. Acta*, **23**, 935 (1940).
(23) L. Ruzicka, C. F. Seidel, H. Schinz, and M. Pfeiffer, *Helv. Chim. Acta*, **31**, 422 (1948).
(24) V. A. Petrow, *J. Chem. Soc.*, 693 (1942).
(25) V. Prelog, L. Ruzicka, and O. Metzler, *Helv. Chim. Acta*, **30**, 1883 (1947).
(26) H. Hikino, K. Aota, D. Kuwano, and T. Takemoto, *Tetrahedron*, **27**, 4831 (1971). For a relay synthesis from nootkatone see D. Caine and C. Chu, *Tetrahedron Lett.*, 703 (1974).
(27) I. Yosioka and T. Kimura, *Chem. Pharm. Bull.*, **13**, 1430 (1965).
(28) A comparison of the 220-MHz ^{1}H NMR spectrum of **3** with those reported for **3** and 10-*epi*-**3** established the relative stereochemistry of C-10 and C-5: P. M. McCurry, R. K. Singh, and S. Link, *Tetrahedron Lett.*, 1155 (1973).
(29) We wish to thank Professor J. A. Marshall for kindly supplying us with samples of (±)-**3**, (±)-**14**, and (−)-**14**.
(30) A. S. Hallsworth, H. B. Henbest, and T. I. Wrigley, *J. Chem. Soc.*, 1969 (1957).
(31) E. J. Corey and K. Achiwa, *J. Org. Chem.*, **34**, 3667 (1969).
(32) This deoxygenation sequence is substantially better than the route described in ref 2.
(33) F. Johnson and S. K. Malhotra, *J. Am. Chem. Soc.*, **87**, 5492 (1965).
(34) For a relevent study dealing with solvent effects on the stereochemistry of a heterogeneous catalytic hydrogenation see H. W. Thompson, E. McPherson, and B. L. Leuces, *J. Org. Chem.*, **41**, 2903 (1976).
(35) For a discussion of conformations of cyclohexanones see E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill New York, N.Y., 1962, pp 239–246, 430–431.
(36) An analysis of the solution conformations of **15** and **37** has been performed using ^{1}H NMR techniques. In both molecules, an appreciable amount of the conformer in which the C-10 methyl group occupies an equatorial site appears to be present: W. G. Dauben and D. J. Hart, unpublished results.
(37) R. D. Clark and C. H. Heathcock, *Synthesis*, 47 (1974).
(38) R. D. Clark and C. H. Heathcock, *J. Org. Chem.*, **38**, 3658 (1973); **41**, 636 (1976).
(39) C. H. Heathcock in "The Total Synthesis of Natural Products", Vol. II, J. ApSimon, Ed., Wiley, New York, N.Y., 1974, p 286.
(40) M. Pesaro, G. Bozzato, and P. Schudel, *Chem. Commun.*, 1152 (1968).
(41) For an explanation of the nomenclature used here see footnote 16 in ref 15a.
(42) W. Treibs and H. Albrecht, *J. Prakt. Chem.*, **13**, 291 (1961).