Synthesis of Sesquiterpene Antitumor Lactones. 6.[1] *cis*-8a-Vinyloctahydro-3*H*-2-benzopyran-3,7-dione, a Precursor to Vernolepin

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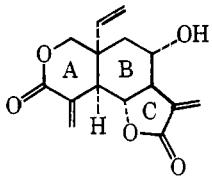
Received March 24, 1976

An efficient six-stage synthesis of bicyclic keto lactone **5**, a valuable intermediate for conversion into analogues of the sesquiterpene antitumor lactone vernolepin, has been developed.

The sesquiterpene antitumor lactone vernolepin (**1**)[2] and its congener vernomenin (**2**) have elicited considerable synthetic attention. Several groups have reported interesting syntheses of the prototype α-methylenevalerolactone **3**,[3-6] which has been shown to possess mildly cytotoxic properties,[4b] and we have applied the Norton cyclocarbonylation process[7] to a synthesis of the prototype α-methylenebutyrolactone **4**.[1]



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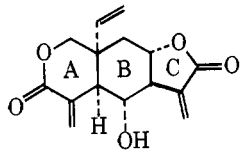

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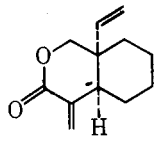

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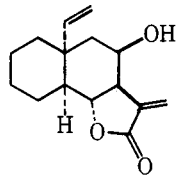

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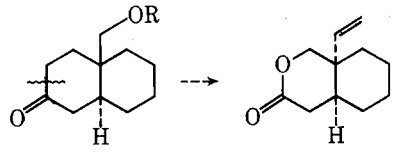
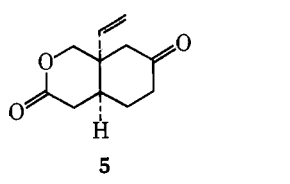
Grieco[8] and Danishefsky[9] have recently reported total syntheses which yield vernolepin and vernomenin in ratios of 3:1 and 2:1, respectively.

To date, most of the synthetic approaches have involved elaboration of the cis-fused δ-valerolactone system by scission of the C_2–C_3 bond of an angularly functionalized *trans*-bicyclo[4.4.0]decane. In this paper, we report a completely different approach to this problem in the synthesis of keto lactone **5**, a promising intermediate for further elaboration into





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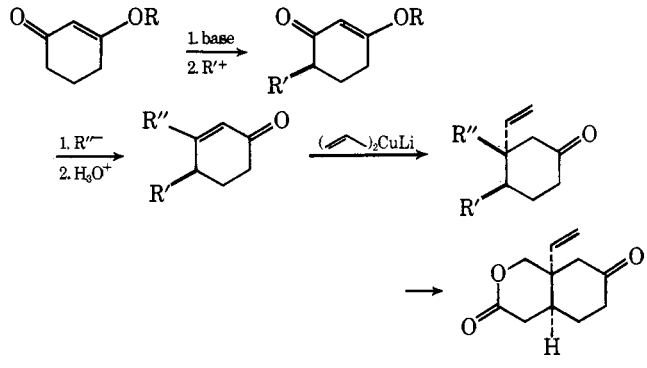
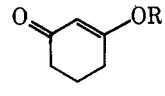
natural products **1** and **2**, as well as analogues of these interesting compounds.

Our basic synthetic plan is outlined below, where R′ is a synthon for an acetic acid unit, $-CH_2COOH$, and R″ is a synthon for a hydroxymethyl unit, $-CH_2OH$. In our plan, R′ would be added as an electrophile and R″ as a nucleophile.

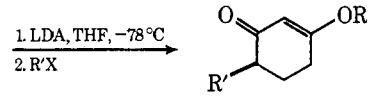
As a starting material for our work, we have used the 1,3-cyclohexanedione enol ethers **6**[10] and **7**.[11] Alkylation of the



kinetic enolate, following the procedure of Danheiser and Stork,[12] with a variety of alkyl halides affords compounds **8**–**12**



6, R = CH_2CH_3
7, R = $CH_2CH(CH_3)_2$



8, R = $CH_2CH(CH_3)_2$; R′ = $CH_2CO_2C_2H_5$
9, R = CH_2CH_3; R′ = $CH_2CO_2C(CH_3)_3$
10, R = $CH_2CH(CH_3)_2$; R′ = $CH_2CH{=}CH_2$
11, R = CH_2CH_3; R′ = $CH_2CH{=}CHCH_3$
12, R = CH_2CH_3; R′ = $CH_2CH{=}C(CH_3)_2$

in yields of 55, 99, 98,[12] 81, and 90%, respectively. Each of the R′ groups are, in principle, convertible to acetic acid side chains by either hydrolysis or oxidation.

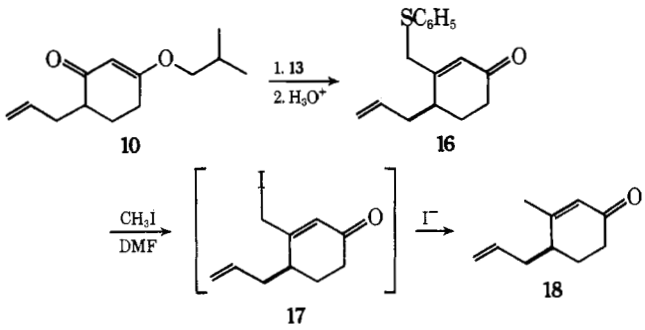
As masked hydroxymethyl groups, we initially explored the use of phenylthiomethyllithium (**13**),[13] methylthiomethyllithium (**14**),[14] and methoxymethylmagnesium chloride (**15**).[15]

$C_6H_5SCH_2Li$	CH_3SCH_2Li	CH_3OCH_2MgCl
13	**14**	**15**

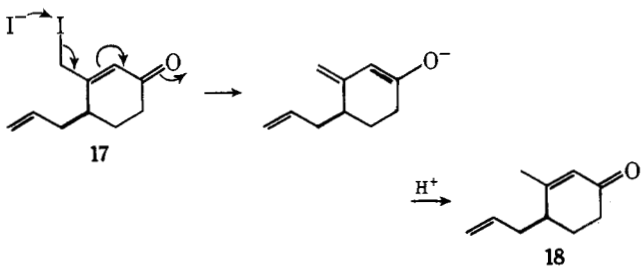
We soon discovered that organometallic reagents **13**–**15** are not suitable for the introduction of a one-carbon unit into compounds **8** or **9**. For example, treatment of keto ester **8** with lithium reagent **13** gave only recovered starting material, even under conditions which have been used for the reaction of compound **13** with other esters and ketones.[13b] It may be that keto ester **8** undergoes exclusive enolization, due to the inductive effect of the second carbonyl group. On the other hand, Grignard reagents such as **15** react indiscriminately at both carbonyl groups, even with *tert*-butyl ester **9**.

Therefore, we turned our attention to allylated enol ether **10**. This material reacts smoothly with phenylthiomethyllithium (**13**) to give sulfide **16**, after hydrolysis of the initial adduct with dilute aqueous acid. However, an attempt to re-

place the phenylthio group by iodo, following Corey's procedure (CH_3I, NaI in DMF or DMA),[16] gave enone **18** in nearly

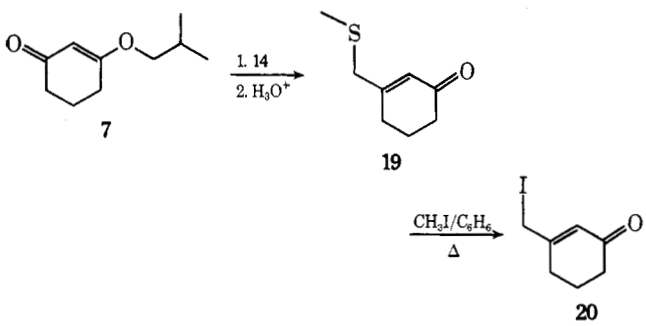


quantitative yield. Presumably, iodide **17** is an intermediate in the conversion of **16** to **18**. It is probably deiodinated by iodide ion by the following process:

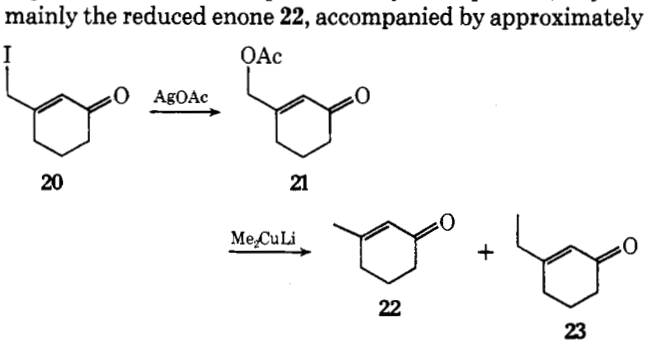


However, even the iodide produced in the initial methylation reaction is sufficient to reduce **17**, for the same result is obtained when sodium iodide is omitted from the reaction mixture.

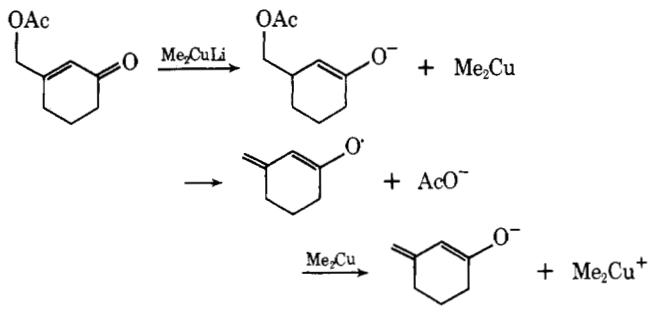
We reasoned that if we could cause the conversion of **16** to **17** to occur more rapidly, relative to the annoying reduction of **17**, we might realize the selective synthesis of this compound. Since the rate-limiting step in the conversion of **16** to **17** is probably methylation of the sulfur, we turned to the more basic methylthio group. As a model, enol ether **7** was allowed to react with methylthiomethyllithium (**14**) to obtain sulfide **19**. Our anticipation was realized when we found that iodide **20** is produced in yields of up to 90% by refluxing sulfide **19** in a 1:1 mixture of methyl iodide and benzene for 20 h.



Treatment of iodide **20** with silver acetate yields acetate **21**. Unfortunately, this material reacts with lithium dimethylcuprate (a model for our planned vinylation process) to yield mainly the reduced enone **22**, accompanied by approximately

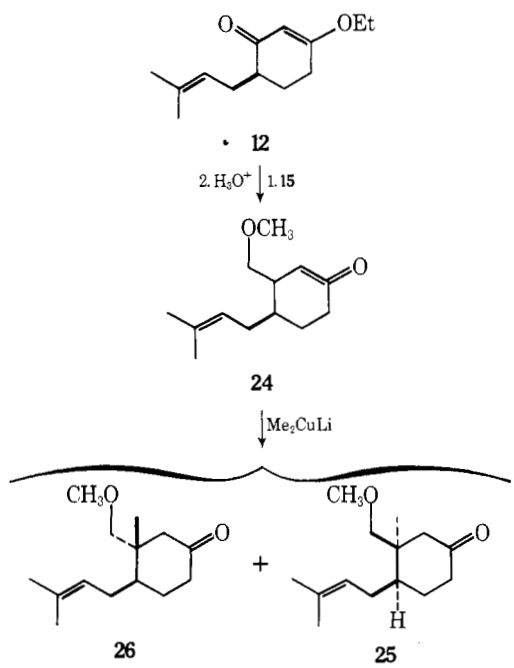


15% of enone **23**. Reductive removal of the acetoxy group in this reaction is not surprising, since such a good leaving group should be expelled rather readily from the radical anion supposed to be an intermediate in this reaction:[17]



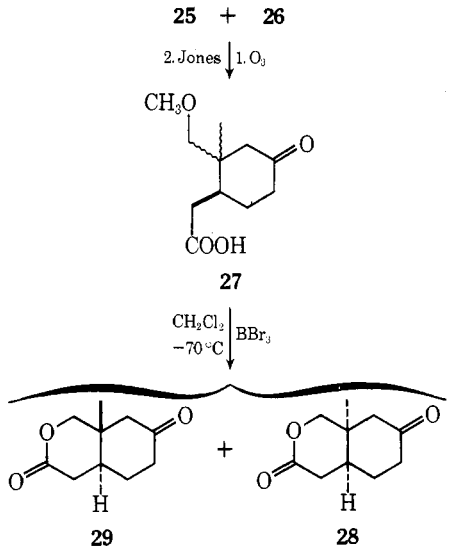
Similar reductions have subsequently been reported.[18]

It seemed that replacing the acetoxy group by a poorer leaving group, such as alkoxy, might alleviate this problem. However, because of the delicate nature of the desulfurization reaction and low yields encountered in displacements of the allylic iodide **20**, we turned to a more direct method of introducing the desired alkoxymethyl group. Methoxymethylmagnesium chloride proved to be admirably suited for this purpose. Treatment of compound **12** with this reagent in methylal for several hours at room temperature, followed by hydrolysis with dilute acid, affords enone ether **24** in 80% yield.

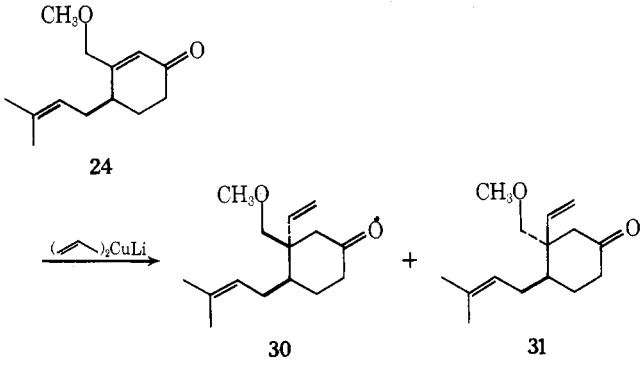


Enone **24** does indeed react smoothly with lithium dimethylcuprate, giving a 92:8 ratio of ketones **25** and **26** in 94% yield; no reductive removal of the methoxy group is observed.[19] The stereoselectivity observed in the addition of lithium dimethylcuprate to **24** was expected on the basis of analogy to the reaction of 3,4-dimethylcyclohex-2-en-1-one with lithium divinylcuprate, which affords the adduct with the vinyl trans to the C-3 methyl in greater than 95% yield.[21]

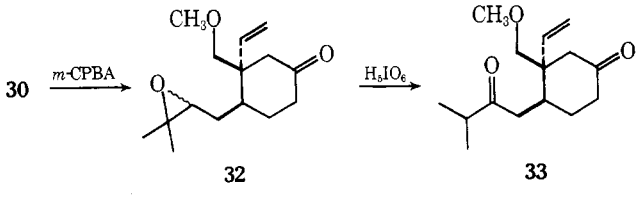
Compounds **25** and **26** provided us with an excellent opportunity to test our proposed elaboration of the two functionalized side chains into the desired δ-lactone. Treatment of the diastereomeric mixture with ozone in methylene chloride at −78 °C followed by Jones oxidation[22] of the ozonide affords a mixture of diastereomeric acids (**27**) in 55% yield. Treatment of the crude acid mixture with boron tribromide in methylene chloride at −70 °C affords lactones **28** and **29** (86:14 ratio) in 90% yield.



With a method for construction of the δ-lactone in hand, we turned to introduction of the potential angular vinyl group. Enone **24** reacts smoothly with lithium divinylcuprate, affording adducts **30** and **31** in a ratio of 94:6 (76% yield).

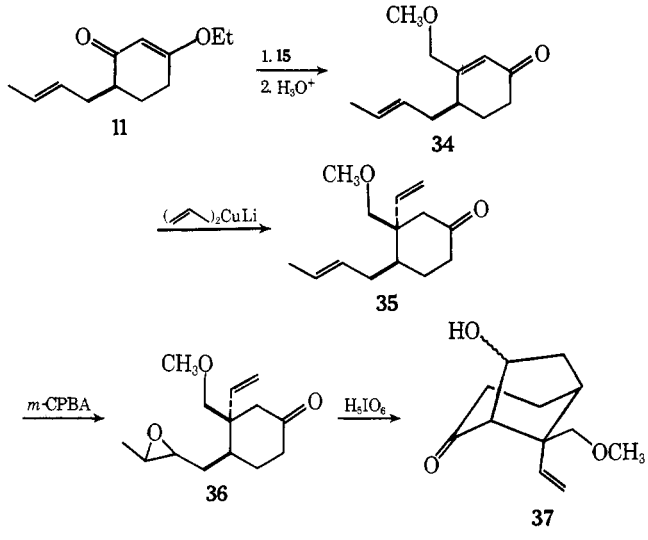


However, numerous attempts to achieve selective fission of the trisubstituted double bond in this attractive intermediate were unsuccessful. For example, selective ozonization could not be achieved. Compound **30** does react selectively with *m*-chloroperoxybenzoic acid to yield oxirane **32** (a diastereomeric mixture), but attempts at cleavage to an aldehyde met with failure, due to the propensity of **32** to rearrange to the isomeric isopropyl ketone **33**.

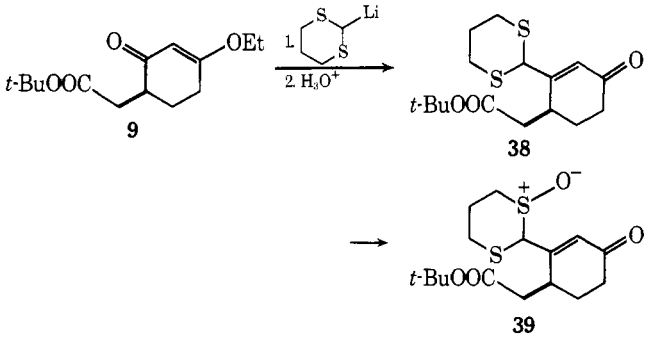


In an attempt to thwart this annoying rearrangement, we prepared oxirane **36**, via intermediates **34** and **35**. This oxirane does undergo the desired periodic acid cleavage, but the only product which may be isolated from the reaction is the bicyclic aldol **37**.

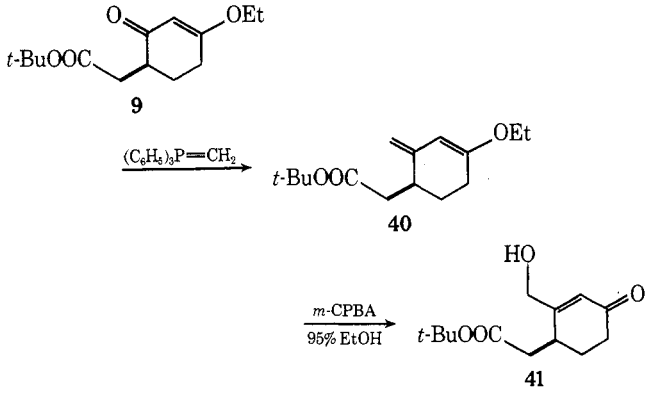
Because of these unexpected problems with conversion of the allyl side chains to the desired acetic acid side chain, we again turned our attention to precursors **8** and **9**, in which the carboxy group is already present. Continuing our search for a functionalized one-carbon nucleophile which would add selectively to the ketone carbonyl of one of these keto esters, we examined the reaction of *tert*-butyl ester **9** with 2-lithio-1,3-dithiane.[23] We were gratified to find that selective addition does occur, affording dithiane **38** in 51% yield after acidic hydrolysis and chromatographic purification. However, we



were unable to hydrolyze dithiane **38** or the monosulfoxide **39** under a variety of conditions.[24]



The hydroxymethyl problem was eventually solved in a most straightforward and elegant manner when we found that keto ester **9** reacts with methylenetriphenylphosphorane cleanly and in high yield to afford dienyl ether **40**. Furthermore, we were pleased to find that this material is readily oxidized by *m*-chloroperoxybenzoic acid in 95% ethanol[25,26] to give the desired hydroxymethyl derivative **41**. The overall yield for the two-stage conversion of **9** to **41** is 65–77%.



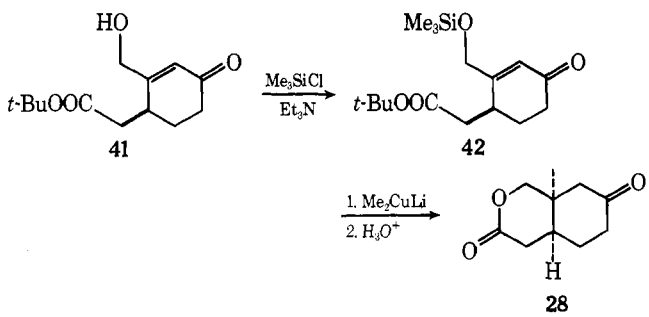
With the hydroxymethyl group in place and the acetic acid side chain protected as the *tert*-butyl ester, it remained only to introduce the angular vinyl group and close the δ-lactone to achieve our goal of keto lactone **5**. After a few unsuccessful attempts to carry out cuprate additions on the unprotected alcohol, it became clear that the hydroxy group must be temporarily blocked. Because of our earlier experience in the reaction of enone ester **21** with cuprates, we decided to protect this function as the trimethylsilyl ether. This is easily accomplished by treatment of compound **41** with trimethylsilyl

Table I. ^{1}H NMR Parameters of Keto Lactone 5

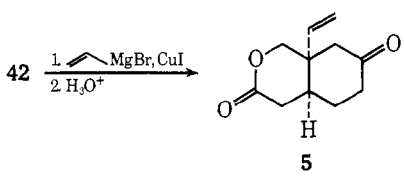
δ, ppm	Assignment	Multiplicity	J, Hz
1.78[a]	H_6	Multiplet (AB of ABXYZ)	$J_{6,7}$ = 14.2, $J_{6,9}$ = 9, $J_{6,5}$ = 9, $J_{6,8}$ = 5.3
2.095[a]	H_7		$J_{7,9}$ = 5.3, $J_{7,5}$ = 5.3, $J_{7,8}$ = 6.5
2.26–2.46	H_5, H_8, H_9	Multiplet	
2.48[b]	H_{10}, H_{11}	AB Δν = 18.2[c]	$J_{10,11}$ = 15.4
2.54[a], 2.82[a]	H_3, H_4	AB of ABX	$J_{3,4}$ = 17.5, $J_{3,5}$ = 7.1, $J_{4,5}$ = 6.5
4.11[b]	H_1, H_2	AB Δν = 75.2[c]	$J_{1,2}$ = 11.9
5.25[a]	H_{14}	ABC	$J_{12,13}$ = 11, $J_{12,14}$ = 18, $J_{13,14}$ = 0
5.29[a]	H_{13}		
5.72[a]	H_{12}		

[a] Center of multiplet, not chemical shift. [b] Geometric center of the AB pattern. [c] Δν is the difference between the chemical shifts of A and B in hertz.

chloride and triethylamine in ether. In one preliminary experiment, enone **42** was treated with lithium dimethylcuprate

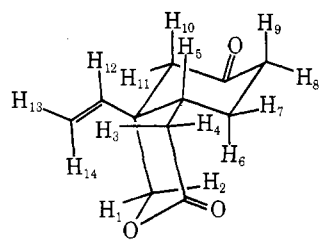


in ether. After hydrolysis of the crude product with sulfuric acid in aqueous 1,2-dimethoxyethane and chromatographic purification, lactone **28** was obtained in 22% yield. This angularly methylated keto lactone was spectrally identical with a specimen prepared earlier by a different route (vide supra). Treatment of enone **42** with vinylmagnesium bromide in the presence of 50 mol % CuI, followed by acidic hydrolysis of the crude product, affords the angularly vinylated keto lactone **5** in 60–85% yield from silyl ether **42**. The stereoselectivity



observed in the cuprate additions to **42** is impressive. High-resolution ^{1}H NMR analysis of compound **5** reveals that it contains at most 2.5% of the trans isomer.

An analysis of the coupling constants obtained from the 360-MHz ^{1}H NMR spectrum of **5** reveals that it exists predominantly in the "nonsteroid" conformation. The spectral parameters are summarized in Table I. The most enlightening



values are the nearly equal values of $J_{3,5}$ and $J_{4,5}$. In the steroid conformation, one of these couplings would be diaxial and the other axial–equatorial.

In summary, we have achieved a viable synthesis of bicyclic keto lactone **5**, an attractive intermediate for conversion to the natural products vernolepin and vernomenin and analogues thereof. The synthetic route developed is short (six steps from the readily available keto ether **6**) and efficient (about 40% overall yield). Furthermore, the reactions involved are easily adaptable to large-scale work (we have prepared approximately 100 g of keto lactone **5**).

Experimental Section

Melting points and boiling points are uncorrected. The ^{1}H NMR spectra were determined on a Varian T-60 NMR spectrometer or on a Bruker HXS-360 (Stanford Magnetic Resonance Laboratory). Infrared spectra were determined on a Perkin-Elmer 137 infrared spectrophotometer. Analytical and preparative gas–liquid phase chromatography was performed using 0.125-in. stainless steel columns (5 ft, 5% SE-30, and 10 ft, 10% FFAP). Low-resolution mass spectra were obtained on a AEI MS-12 mass spectrometer, and high-resolution mass spectra on a CEC 21-110 mass spectrometer. Microanalyses were performed by the University of California Microanalytical Laboratory.

***tert*-Butyl 2-(4-Ethoxy-2-oxocyclohex-3-enyl)acetate (9).** A solution of enol ether **6** (140 g, 1.0 mol) in THF (250 ml) was added dropwise to a −70 °C solution of LDA (1.2 mol) in THF (100 ml) over 30 min. The resulting solution was stirred for 45 min and a solution of *tert*-butyl bromoacetate (205 g, 1.05 mol) in THF (100 ml) was added over 30 min. The solution was allowed to warm to room temperature and water (5 ml) was added. The mixture was evaporated and the residue was taken into ether, washed with water and brine, dried, and evaporated to 252 g (99%) of light yellow powder. This material was sufficiently pure for use in the next reaction (NMR identical with that of purified material; one spot on TLC, R_f 0.6, ether). Further purification may be effected by recrystallization at −78 °C from petroleum ether: mp 68.5–70.5 °C; ir ($CDCl_3$) 1733, 1664, 1613, 1190 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 3 H), 1.53 (s, 9 H), 3.96 (quartet, 2 H), 5.38 (s, 1 H).

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.14; H, 8.51.

***tert*-Butyl 2-(2-Methylene-4-ethoxycyclohex-3-enyl)acetate (40).** Methyltriphenylphosphonium bromide (53.5 g, 150 mmol) was added to a solution of sodium dimsylate (from 150 mmol of sodium hydride) in 150 ml of dimethyl sulfoxide. The mixture was stirred for several minutes, followed by addition of enol ether **9** (25.4 g, 100 mmol) in dimethyl sulfoxide (25 ml). After 3 h at room temperature, the reaction was quenched by addition of water (300 ml) and petroleum ether (300 ml). After filtration, the aqueous phase was extracted with petroleum ether and the combined organic layers were washed with water and brine, dried, and evaporated to 22.0 g (85%) of **40** as a colorless liquid: ir (film) 1733, 1639, 1186, 1143 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.12 (t, 3 H), 1.44 (s, 9 H), 1.73 (m, 2 H), 3.77 (quartet, 2 H), 4.53 (s, 2 H), 5.18 (s, 1 H); mass spectrum *m/e* (rel intensity) 252 (31), 196 (52), 195 (29), 151 (100), 123 (59), 57 (68); exact mass 252.1731 (calcd for $C_{15}H_{24}O_3$, 252.1725).

***tert*-Butyl 2-(2-(Hydroxymethyl)-4-oxocyclohex-2-enyl)-acetate (41).** A solution of enol ether **40** (32.0 g, 127 mmol) in 95% ethanol (225 ml) was added at once to a stirred solution of *m*-chloroperbenzoic acid (198 mmol) in 95% ethanol (700 ml). The temperature of the mixture increased to 38 °C, then the mixture was stirred for 2 h at ambient temperature. Sodium thiosulfate (35.0 g) and sodium bicarbonate (25.0 g) in water (125 ml) were added and the mixture was stirred for 45 min. Most of the solvent (800 ml) was evaporated at reduced pressure and the residue was taken into water (1000 ml) and extracted with ether (3 × 300 ml). The ether was washed with brine, dried, and evaporated to 27.5 g (90.2%) of alcohol **41** as a light yellow oil. This material was somewhat unstable and was used without further purification: ir (film) 3676, 1727, 1675, 1149 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9 H), 4.27 (s, 2 H), 4.53 (s, 1 H), 6.13 (s, 1 H); mass spectrum *m/e* 226.

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.06; H, 8.35.

***tert*-Butyl 2-(2-(Trimethylsiloxymethyl)-4-oxocyclohex-2-enyl)acetate (42).** Triethylamine (34.9 g, 343 mmol) and trimethylsilyl chloride (37.0 g, 343 mmol) were added to a solution of alcohol **41** (46.0 g, 191.6 mmol) in ether (250 ml). After 2 h at room temperature, the mixture was filtered and evaporated. The residue was taken

into petroleum ether, filtered again, and evaporated to 54.0 g (90.8%) of silyl ether **42**, a colorless oil. Owing to its hydrolytic instability, this material was used without further purification: ir (film) 1730, 1678, 1248, 1148 cm^{-1}; ^1H NMR (CCl_4) δ 0.24 (s, 9 H), 1.55 (s, 9 H), 4.38 (s, 2 H), 6.08 (s, 1 H).

***cis*-8a-Vinyloctahydro-3*H*-2-benzopyran-3,7-dione (5).** A solution of vinylmagnesium bromide was prepared from magnesium (8.3 g, 342 mmol) and vinyl bromide (40.2 g, 376 mmol) in THF (650 ml) and cooled to −5 °C. Cuprous iodide (32.5 g, 171 mmol) was added and the resulting jet-black solution was stirred at −5 °C for 3 min, then rapidly cooled to −70 °C. A solution of enone **42** (33.3 g, 107 mmol) in THF (100 ml) was added slowly and the mixture was stirred for 1 h at −70 °C, then allowed to warm to 0 °C. Sulfuric acid (13 ml) and water (40 ml) were cautiously added and the mixture was suction filtered. The filtrate was evaporated and the residue was extracted with chloroform. The combined extracts were evaporated and the residue was dissolved in glyme (500 ml) and 10% sulfuric acid (300 ml). This solution was refluxed for 4 h and the glyme was removed by rotary evaporation. The aqueous residue was extracted with chloroform and the combined extracts were washed with 5% sodium bicarbonate and brine, then dried ($MgSO_4$). The chloroform was evaporated to yield 17.8 g (85.8%) of keto lactone **5** as tan crystals. Recrystallization from ethyl acetate gave an analytical sample: mp 104–105 °C; ir ($CDCl_3$) 1739, 1718, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.48 (AB quartet, J = 15.4 Hz, 2 H), 4.11 (AB quartet, J = 12 Hz, 2 H), 5.25–5.72 (ABC pattern, 3 H), see Table I for complete spectral data; mass spectrum *m/e* (rel intensity) 194 (6), 165 (6), 164 (39), 162 (9), 147 (11), 136 (14), 122 (79), 94 (38), 80 (50), 79 (100); exact mass 194.0943 (calcd for $C_{11}H_{14}O_3$, 194.0939).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.88; H, 7.01.

Acknowledgments. This work was supported by the U.S. Public Health Service (Grant CA-12617). We thank Dr. Woodrow Conover of the Stanford Magnetic Resonance Laboratory for instructing us in the use of the HXS-360 spectrometer, and Mr. Sam L. Woo for technical assistance.

Registry No.—**5,** 59711-44-3; **6,** 5323-87-5; **7,** 29941-87-5; **8,** 58775-58-9; **9,** 58775-59-0; **10,** 40649-34-1; **11,** 59711-45-4; **12,** 58775-55-6; **13,** 13307-75-0; **14,** 10415-47-1; **15,** 107-30-2; **16,** 58775-62-5; **18,** 58775-63-6; **19,** 58775-64-7; **20,** 58775-65-8; **21,** 50557-37-4; **24,** 59711-46-5; **25,** 59711-47-6; **26,** 59711-48-7; **27** (isomer A), 59711-49-8; **27** (isomer B), 59711-50-1; **28,** 59711-51-2; **29,** 59711-52-3; **30,** 59711-53-4; **31,** 59711-54-5; **32** (isomer A), 59711-55-6; **32** (isomer B), 59751-85-8; **33,** 59711-56-7; **34,** 59711-57-8; **35,** 59711-58-9; **36,** 59711-59-0; **38,** 59711-60-3; **39,** 59711-61-4; **40,** 59711-62-5; **41,** 59711-63-6; **42,** 59711-64-7; *tert*-butyl bromoacetate, 5292-43-3; methyltriphenylphosphonium bromide, 1779-49-3; trimethylsilyl chloride, 75-77-4; vinyl bromide, 593-60-2; ethyl bromoacetate, 105-36-2; 1-bromo-2-butene, 4784-77-4; prenyl bromide, 870-63-3; lithium dimethylcuprate, 15681-48-8; lithium divinylcuprate, 22903-99-7; periodic acid, 27803-33-4; 1,3-dithiane, 505-23-7.

Supplementary Material Available. The following experimental procedures: (1) ethyl 2-(4-isobutoxy-2-oxocyclohex-2-enyl)acetate (**8**); (2) 3-ethoxy-6-(2-butenyl)cyclohex-2-en-1-one (**11**); (3) 3-ethoxy-6-(3-methyl-2-butenyl)cyclohex-2-en-1-one (**12**); (4) 3-phenylthiomethyl-4-(2-propenyl)cyclohex-2-en-1-one (**16**); (5) 3-methyl-2-(2-propenyl)cyclohex-2-en-1-one (**18**); (6) 3-methylthiomethylcyclohex-2-en-1-one (**19**); (7) 3-acetoxymethylcyclohex-2-en-1-one (**21**); (8) reaction of **21** with lithium dimethylcuprate; (9) 3-methoxymethyl-4-(3-methyl-2-butenyl)cyclohex-2-en-1-one (**24**); (10) *cis*-3-methoxymethyl-4-(3-methyl-2-butenyl)-3-methylcyclohexanone (**25**); (11) 2-methoxymethyl-2-methylcyclohexan-4-onylacetic acid (**27**); (12) *cis*-8a-methyloctahydro-3*H*-2-benzopyran-3,7-dione (**28**); (13) *cis*-3-methoxymethyl-4-(3-methyl-2-butenyl)-3-vinylcyclohexanone (**30**); (14) *cis*-3-methoxymethyl-4-(3-methyl-2,3-oxidobutyl)-3-vinylcyclohexanone (**32**); (15) reaction of **32** with periodic acid; (16) 3-methoxymethyl-4-(2-butenyl)cyclohex-2-en-1-one (**34**); (17) *cis*-3-methoxymethyl-4-(2-butenyl)-3-vinylcyclohexanone (**35**); (18) *cis*-3-methoxymethyl-4-(2,3-oxidobutyl)-3-vinylcyclohexanone (**36**); (19) reaction of **36** with periodic acid; (20) *tert*-butyl 2-[2-(2,6-dithianyl)-4-oxocyclohex-2-enyl]acetate (**38**); (21) *tert*-butyl 2-[2-(2-oxo-2,6-dithianyl)-4-oxocyclohex-2-enyl]acetate (**39**).

References and Notes

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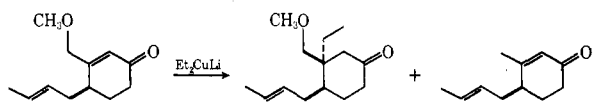

i ii iii

reduced product iii in a ratio of 3:2. An identical product mixture is obtained in the CuI-catalyzed addition of ethylmagnesium bromide to enone i. A similar result is obtained from the reaction of enone sulfide iv with lithium divinylcuprate. Adduct v and enone vi are obtained in a ratio of 3:1.[20]

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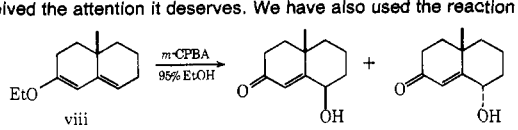

viii viii ix

high-yield conversion of dienyl ether vii to γ-hydroxy enones viii and ix.[27]
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