Supplementary Material Available. (1) The final atomic positions and temperature factors for isotetrahydroanemonin (**15**), and the final atomic positions and temperature factors for di-α-methyleneanemonin (**4b**) (Tables 1–4); (2) supplements to Tables I, II, VII, and VIII, which list the bond lengths and angles involving hydrogen atoms in **15** and **4b**; (3) Tables IV, V, VI, VII, VIII, X, XI, XII, and XIII, which are mentioned in the text; and (4) Figures 2, 4, 5, and 6 mentioned in the text (15 pages). Ordering information is given on any current masthead page.

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Synthesis of ω-Bromo Ketones[1]

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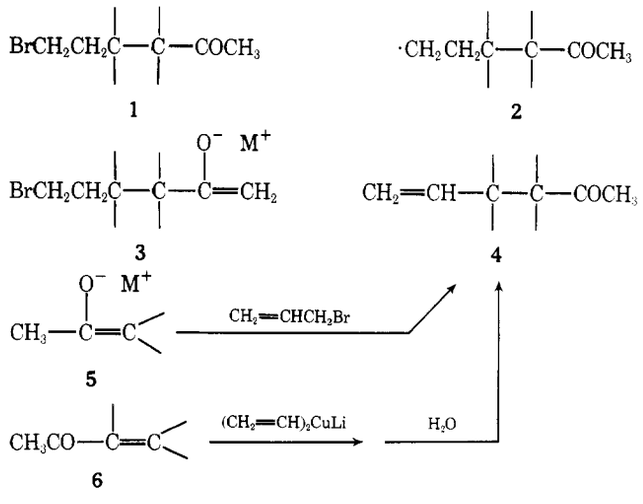
Various methyl ketones **8**, **9**, **21**, **24**, **26**, **27**, **34**, and **54** containing terminal vinyl groups have been synthesized by regiospecific alkylations of metal enolates with allyl bromide, by the conjugate addition of $(CH_2{=}CH)_2CuLi$ or $CH_2{=}CHMgBr$ with Me_2SCuBr as a catalyst to enones, and by other procedures. The light-catalyzed radical-chain addition of HBr in pentane solution to these olefinic ketones constituted an efficient method for the synthesis of ω-bromo ketones **40–47** and **55**.

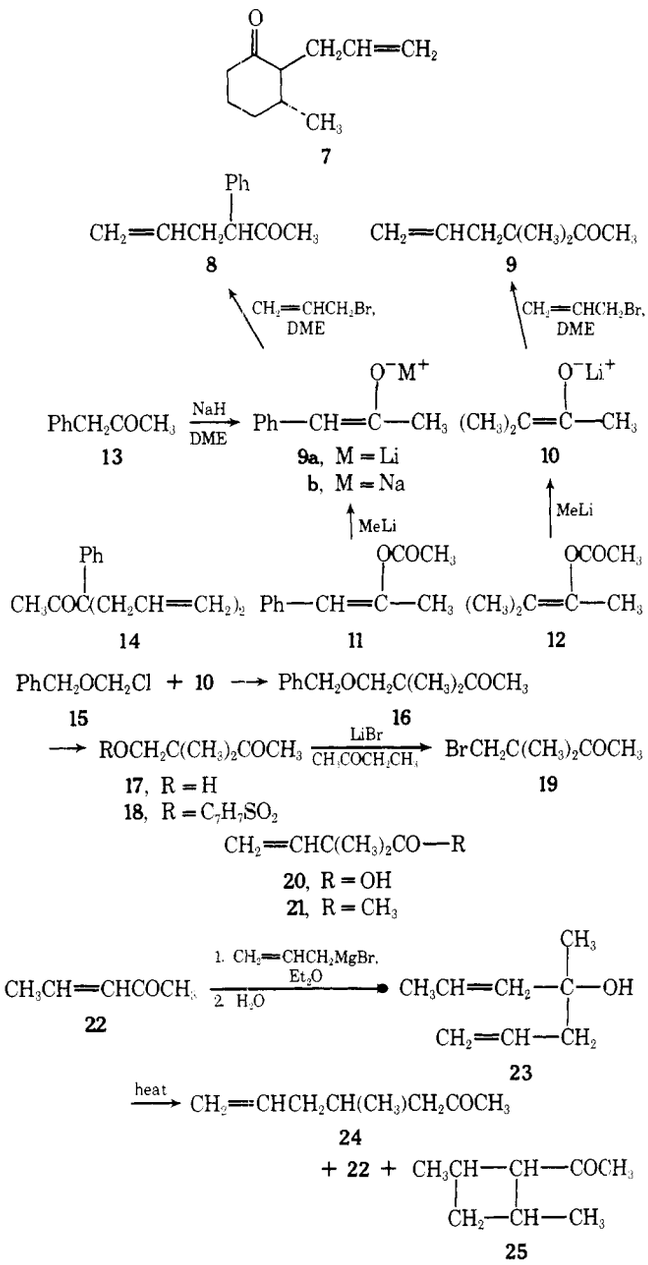
We were interested in preparing a group of ω-bromo ketones of the type **1** as substrates for use in studying the behavior of the related carbon radicals **2** and the enolate anions **3** (Scheme I). The vinyl ketones **4** appeared to be particularly attractive precursors for such bromo ketones **1** since these olefinic intermediates **4** were readily accessible either by regiospecific alkylation of a preformed lithium enolate **5** with an allyl halide[2] or by the conjugate addition of lithium divinylcuprate (or its equivalent) to an enone **6**.[3,4]

Scheme I

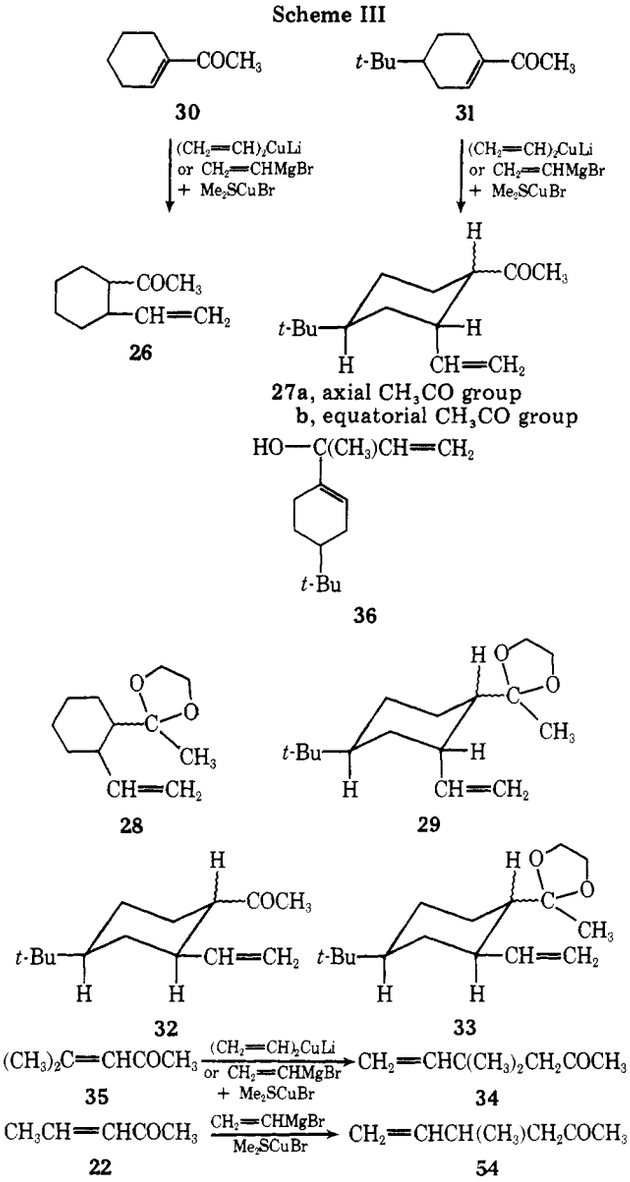


Preparation of the Olefinic Ketones. In the present study we utilized the ketone **7**, from a previously described[2a] regiospecific alkylation, and prepared the α-allyl ketones **8** and **9** by allylation of the enolates **9** and **10** (Scheme II). We also utilized a regiospecific alkylation of the enolate **10** to obtain precursors **16–18** of the bromo ketone **19**, a lower homologue of the bromo ketone system **1**. The precursor **21** for a second lower homologue of the bromo ketone **1** was obtained by the previously described[5] reaction of the acid **20** with MeLi. To obtain a precursor for a higher homologue of the

Scheme II



Scheme III



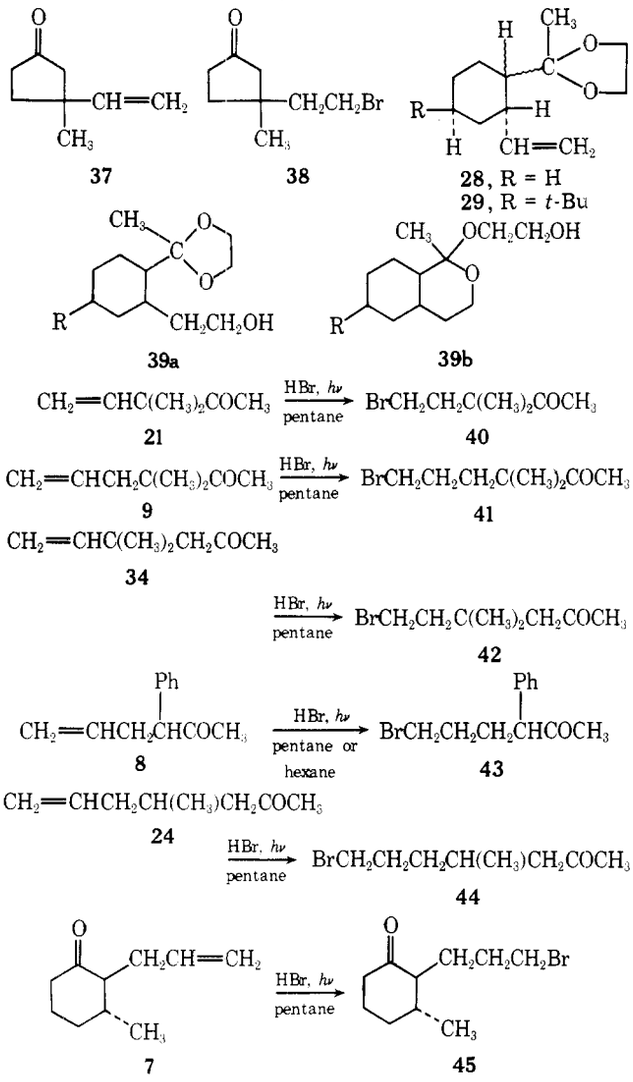
bromo ketone **1**, the known dienol **23**[6] was subjected to an oxy-Cope rearrangement[7] to obtain the unsaturated ketone **24**.

In a previous study[3h] the unsaturated ketones **26** and **27** (Scheme III), also characterized as their ketals **28** and **29**, had been obtained by the conjugate addition of $(CH_2{=}CH)_2CuLi$ to the enones **30** and **31**. The same procedure had been used[3a] to obtain the ketone **34** from the enone **35**.

During the course of this work, the commercial solutions of $CH_2{=}CHLi$ in THF were removed from the market leading us to explore the use of the more easily prepared $CH_2{=}CHMgBr$ with a copper(I) catalyst[4] in place of $(CH_2{=}CH)_2CuLi$. We found the use of a THF solution of $CH_2{=}CHMgBr$ with the complex, Me_2S–CuBr,[3h] as a catalyst to be an effective substitute for $(CH_2{=}CH)_2CuLi$ in the preparation of ketones **26, 27, 34,** and **54** *provided that the temperature of the reaction solution was maintained at −30 to −40 °C* so that the vinylcopper derivative did not undergo thermal decomposition[3g,h,8] before reaction with the enone could occur.

Preparation of the ω-Bromo Ketones. In an earlier study,[3e] the unsaturated ketone **37** (Scheme IV) had been converted to the bromo ketone **38** by the reaction sequence unsaturated ketone **37** → unsaturated ketal → alkylborane → primary alcohol → mesylate → primary alkyl bromide **38**. In exploring an analogous sequence with the ketals **28** and **29**, we were plagued by the tendency of the hydroboration–oxidation product **39a** to undergo trans ketalization forming ketal **39b** and related materials. For this reason, we concluded that a more efficient route for the conversion, $RCH{=}CH_2$ → RCH_2CH_2Br, was clearly required. Accordingly, we were led to consider the addition of anhydrous HBr in a free-radical chain process. Although this reaction seems only rarely to have been applied to molecules containing both a terminal $CH{=}CH_2$ group and a second functional group,[9] it was not apparent that a ketone function would interfere with this reaction if conditions were chosen that would minimize the tendency for the ketone to be present in equilibrium with its enol form. This expectation has proved to be correct. When anhydrous HBr gas was passed through pentane solutions of the various unsaturated ketones **7, 8, 9, 21, 24,** and **34** and the mixtures were irradiated with light from a medium pressure Hg lamp, the addition reactions were complete within 5–10 min and practically quantitative yields of the crude bromo ketones **40–45** were obtained. After purification by distillation or column chromatography, the pure bromo ketones **40–45** were obtained. Neither ^1H NMR nor ^{13}C NMR measurements gave any indication that these products were contaminated

Scheme IV

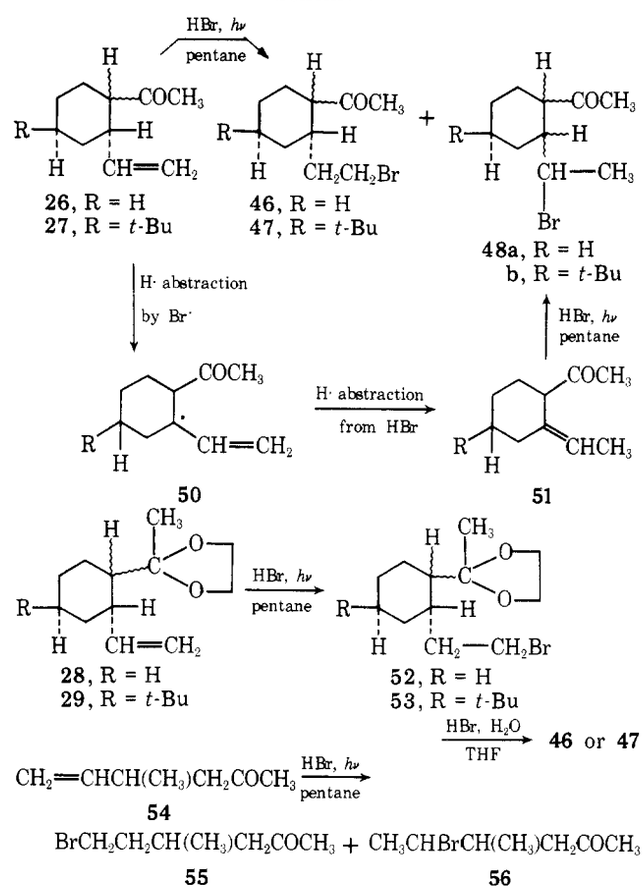


with the isomeric secondary alkyl bromides (the products expected from addition in the Markownikoff sense).

In our initial studies of this free-radical addition where hexane was employed as the reaction solvent, we were constantly troubled by the instability of the crude bromo ketone products. The crude products rapidly turned black when warmed or allowed to stand at 25 °C. We were able to demonstrate that this rapid decomposition was not attributable to an inherent instability of the bromo ketones but rather to minor impurity formed in the reaction from an impurity in the hexane. Although our identification of this reactive impurity is tentative, we believe that it may be $PhCH_2Br$ formed from the small amounts of $PhCH_3$ impurity in the hexane solvent.

When the reaction conditions used successfully for HBr addition to form bromo ketones **40–45** were applied to the unsaturated ketones **26** and **27** (Scheme V) we were puzzled to find that the crude bromo ketone products **46** and **47** were again unstable and rapidly darkened on storage or distillation. The ^1H NMR spectra of each of these crude products contained two sets of extraneous signals, a doublet at δ 1.66–1.68 (J = 7 Hz, CH_3) and a multiplet at δ 4.23–4.26, an appropriate location for a >CHBr grouping. A product with the same NMR spectrum as this contaminant was obtained when the unsaturated ketone **26** was allowed to react with aqueous 48% HBr. Thus, we conclude that the contaminants formed along with the bromo ketones **46** and **47** are the secondary bromides **48** (ca. 5% of the product from ketone **26** and ca. 20–30% of the product from ketone **27**). These same minor contaminants **48**

Scheme V



were also present in bromo ketones **46** and **47** formed by the light-catalyzed addition of HBr in pentane to the ketals **28** and **29** followed by hydrolysis of the ketals **52** and **53**. Consequently, the presence of a ketone function is not responsible for the formation of the by-products **48**. A variety of additional experiments in which special care was taken to ensure anhydrous reactants and in which small amounts of H_2O were deliberately added had little influence on the amount of the by-product **48** that was formed. Therefore, we concluded that the by-products **48** were also being formed by a free-radical process.

Since the unsaturated ketones **26** and **27** differed from the other ketones studied (**8, 9, 21, 24, 34**) in containing a tertiary allylic CH grouping, we were prompted to consider the possibility that reaction of the ketones **26** and **27** with a Br atom resulted not only in addition of this radical to form precursors of the primary bromides **46** and **47** but also in H atom abstraction to form the allylic radicals **50**. Further reaction of these allylic radicals **50** to abstract an H atom from the excess HBr could form the isomeric olefins **51** that would yield the secondary bromides **48** upon addition of HBr in a radical chain process. There are reported examples[10] of just this type of isomerization in other studies of the free-radical addition of HBr to terminal olefins.

To provide additional evidence that the presence of tertiary allylic CH bonds in ketones (which would enhance the stability of the allylic radicals **50**) favor this side reaction leading to secondary bromide by-products, we also examined the addition of HBr to the ketone **54** (Scheme V), an acyclic system that also contains this structural feature. Upon light-catalyzed addition of HBr, the expected bromo ketone product **55** again contained ca. 5% of a contaminant believed to be the secondary bromide **56**. In these cases, the small amounts of secondary bromide impurities **48** and **56** could be readily separated from the desired primary bromides by chromatography on silica gel.

Experimental Section[11]

Preparation of the Ketone 34. A. With $(Vinyl)_2CuLi$.[12] To a cold (−35 °C) solution of $(vinyl)_2CuLi$, prepared by the addition (dropwise with stirring at −50 to −65 °C during 15 min) of 270 mL of a THF solution containing 0.433 mol of vinyllithium (Alfa Inorganics) to a solution of 45.2 g (0.220 mol) of Me_2SCuBr in 100 mL of Me_2S and 100 mL of Et_2O, was added, dropwise with stirring during 20 min, a solution of 20.0 g (0.200 mol) of ketone **35** in 20 mL of Et_2O while the temperature of the reaction mixture was maintained at −20 to −35 °C. The resulting mixture was stirred for 1 h while it was allowed to warm to room temperature and then the mixture was filtered and partitioned between Et_2O and an aqueous solution (pH 8) of NH_3 and NH_4Cl. The organic solution was washed successively with aqueous NH_3 and with aqueous NaCl and then dried and concentrated. Fractional distillation of the residual yellow liquid (63.4 g) separated 18.06 g (72%) of the ketone **34**, bp 55–62 °C (13 mm), n^{25}_D 1.4307 [lit. bp 45–50 °C (30 mm),[13a] 69–71 °C (45 mm),[13b] n^{20}_D 1.4375,[13a] n^{20}_D 1.4305[13b]] that contained (GLC, silicone SE-30 on Chromosorb P) the ketone **34** (retention time 4.0 min) accompanied by a small amount (<2%) of the starting enone **35** (2.8 min).

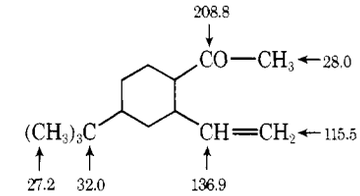
B. With Vinyl-MgBr and Me_2SCuBr.[4] A solution of vinyl-MgBr was prepared by addition of 116 g (1.08 mol) of CH_2=CHBr in 150 mL of THF to 24 g (0.99 g-atom) of Mg in 200 mL of THF containing 0.1 g of $BrCH_2CH_2Br$ as an initiator. The solution of CH_2=CHMgBr was cooled to −30 °C, 2.0 g (11 mol, 1.1 mol %) of Me_2SCuBr was added, and then a solution of 55.0 g (0.561 mol) of the ketone **35** in 100 mL of THF was added, dropwise and with stirring during 50 min while the temperature was maintained at −30 to −33 °C. The resulting dark colored reaction mixture was stirred for 40 min while it was allowed to warm to 5 °C and then it was poured onto 500 g of ice and the resulting mixture was partitioned between H_2O and Et_2O. The ethereal solution, which contained (GLC) the ketone **34** (ca. 99%) and the enone **35** (ca. 1%), was dried and fractionally distilled to separate 48.07 g of the ketone **34**, bp 58–60 °C (22 mm), n^{25}_D 1.4301. The aqueous phase (containing suspended solids) from the original extraction was acidified (HCl) and again extracted with Et_2O. After this extract had been washed with aqueous $NaHCO_3$ and dried, fractional distillation separated an additional 12.17 g of the ketone **34** as a pale yellow liquid: bp 58–65 °C (22 mm); n^{25}_D 1.4322 (total yield 60.24 g or 85%); IR (CCl_4) 1720, 1710 (C=O), 1635 (C=C), and 915 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 5.4–6.2, 4.7–5.1 (total 3 H, m, vinyl CH), 2.33 (2 H, s, CH_2CO), 1.99 (3 H, s, CH_3CO), and 1.08 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 126 (M^+, 3), 111 (8), 83 (12), 69 (31), 55 (19), 43 (100), and 41 (37).

After considerable experimentation the following procedure was found to be the most satisfactory for the copper-catalyzed conjugate addition of vinyl-MgBr to enones **30**, **31**, and **35**. A solution of 514 mg (2.5 mmol, 10 mol % based on the enone) of Me_2SCuBr in 5.2 mL of Me_2S was diluted with 25 mL of THF and then cooled to −55 °C. Then a solution of 25 mmol of the enone in 25 mL of THF was added and the reaction mixture was maintained at −50 to −55 °C while 37 mL of a THF solution containing 30 mmol of vinyl-MgBr was added, dropwise and with stirring during 30 min. During this process it was important to immerse the entire reaction flask in the cooling bath so that any vinyl-Cu reagent splashed on the walls of the flask did not undergo thermal decomposition. The reaction solution, which successively changed from red to purple to green-black in color, was stirred at −45 to −50 °C for an additional 30 min and then siphoned into cold, vigorously stirred aqueous 2 M HCl. In this procedure it was important to keep the reaction temperature below −40 °C and to hydrolyze the product by *addition of the reaction mixture to aqueous acid*. The resulting mixture was extracted with Et_2O or pentane and the organic extract was washed with aqueous $NaHCO_3$, dried, concentrated, and distilled to separate the olefinic ketone product.

Preparation of the Ketone 27. Following the previously described optimum procedure, a cold (−50 to −55 °C) solution (containing some suspended Me_2SCuBr that separated as the solution was cooled) from 990 mg (4.8 mmol) of Me_2SCuBr in 10 mL of Me_2S and 100 mL of THF and 9.00 g (50 mmol) of the enone **31** in 50 mL of THF was treated with 110 mL of a THF solution containing the vinyl-MgBr from 104 mg-atoms of Mg. During this addition the reaction mixture turned from colorless to red to green-black in color. After the reaction mixture had been stirred for an additional 30 min at −35 to −50 °C, it was added to cold, aqueous NH_4Cl, then acidified with aqueous 2 M HCl, treated with excess solid $NaHCO_3$, and extracted with Et_2O. The crude product from this extract (10.29g of yellow liquid) contained (NMR analysis and GLC analysis, silicone XE-60 on Chromosorb P) ca. 6% of the alcohol **36** (retention time 4.3 min) accompanied by ca. 94% of the ketones **27** and **32** [mainly the stereoisomers **27a** (7.8 min) and **27b** (11.0 min) accompanied by minor amounts of the stereoisomeric ketone **32** (8.8 min) and the starting enone **31** (9.6 min)]. Distillation afforded 4.61 g of pure ketone **27**, bp 98.5–99 °C (1.3 mm), n^{25}_D 1.4720 (lit.[3h] n^{25}_D 1.4728), accompanied by 3.53 g (total yield 8.14 g or 81%) of less pure fractions [bp 94–98.5 °C (1.3 mm)] all of which could be used for the subsequently described fractional crystallization.

In a similar experiment where the order of addition was changed so that the vinyl-MgBr from 10.4 mg-atoms of Mg was treated with 0.4 mmol of Me_2SCuBr followed by 5.0 mmol of the enone **31**, the crude product contained (NMR analysis) ca. 25% of the alcohol **36** and ca. 75% of the ketones **27** and **32**. Employing this same order of addition with 30 mol % (based on the enone **31**) of the Me_2SCuBr catalyst, the crude product contained ca. 10% alcohol **36** and ca. 90% of the ketones **27** and **32**. Further increases in the mol % Me_2SCuBr used diminished the content of alcohol **36** in the crude product but increased the amount of enone **31** recovered. Standardization[14] of various THF solutions of vinyl-MgBr indicated that the typical yield in this Grignard reagent preparation was 80–85% based on the Mg used. Using standardized vinyl-MgBr reagent and the optimim inverse addition procedure, the molar proportions 1.0 mol of enone **31**, 0.1 mol of Me_2SCuBr, and 1.2 mol of vinyl-MgBr gave the ketones **27** and **32** in 81% yield.

When a solution of 10.4 g of the mixture of ketones **27** (major) and **32** (minor) in 15 mL of pentane was slowly cooled to −15 to −20 °C, the isomer **27b** separated as white needles that were collected at −25 °C and washed with cold (−78 °C) pentane. The crystalline product, mp 17–18 °C, amounted to 6.75g (65% recovery) and contained (GLC and NMR analyses) 85–90% of ketone **27b** and 10–15% of ketone **27a** with <1% of the stereoisomers **32**. Recrystallization from pentane separated the pure ketone **27b** as needles, mp 17.5–18 °C; this product was identified with the previously described[3h] sample by comparison of NMR spectra and GLC retention times. As noted previously,[3h] treatment of mixtures of **27a** and **27b** with a catalytic amount of NaOMe in refluxing MeOH produced mixtures of the two epimers containing (NMR and GLC analyses) ca. 30% of **27a** and ca. 70% of **27b**. The natural abundance ^{13}C NMR spectrum ($CDCl_3$ solution) of the ketone **27b** is summarized in the following formula; the indicated assignments are consistent with off-resonance decoupling measurements.



(CH groups at 54.2, 41.2, and 40.7 ppm and CH_2 groups at 33.7, 26.3, and 22.8 ppm).

An alternative method for separating the ketone **27b** from the mixture of ketones **27** and **32** involved reaction of the crude ketones with 2,4-dinitrophenylhydrazine to form a mixture of 2,4-dinitrophenylhydrazones. Fractional recrystallization from an EtOH-EtOAc mixture separated the 2,4-dinitrophenylhydrazone of ketone **27b** as orange needles: mp 145.5–147 °C; NMR ($CDCl_3$) δ 11.0 (1 H, broad, NH), 9.07 (1 H, d, J = 2.5 Hz, aryl CH), 8.27 (1 H, d of d, J = 2.5 and 9.5 Hz, aryl CH), 7.90 (1 H, d, J = 9.5 Hz, aryl CH), 4.8–6.3 (3 H, m, vinyl CH), 2.3–3.1 (2 H, m, allylic CH and CHC=N), 2.00 (3 H, s, CH_3C=N), 1.0–2.0 (7 H, m, aliphatic CH), and 0.87 (9 H, s, *t*-Bu). Reaction of this solid derivative with a mixture of levulinic acid and aqueous 1 M HCl as previously described[15] afforded a sample of the pure ketone **27b** (NMR analysis).

Reaction of the ketone **27b** with $HOCH_2CH_2OH$ and TsOH in refluxing PhH as previously described[3h] afforded the ketal **29** (a mixture of epimers), bp 100.5–102 °C (0.4 mm), n^{25}_D 1.4789 (lit.[3h] n^{25}_D 1.4790), in 85% yield.

Preparation of the Alcohol 36. To 10 mL of a cold (0 °C) THF solution containing the vinyl-MgBr from 20.8 mg-atoms of Mg was added, dropwise with stirring over 25 min, a solution of 2.50 g (13.9 mmol) of the enone **31** in 6 mL of THF. After the resulting solution had been stirred at 25 °C for 35 min, it was partitioned between aqueous NH_4Cl and Et_2O. The ethereal solution was dried and concentrated to leave the crude product as a yellow liquid containing (NMR analysis) ca. 73% of the alcohol **36**, ca. 21% of the ketones **27** and **32**, and ca. 6% of the enone **31**. A portion of the crude product was subjected to preparative liquid chromatography on a Merck silica gel column with Et_2O–PhH (1:49 v/v) as the eluent. After separation of the early fractions containing ketones **27** and **31**, the crude alcohol **36**

was collected and further purified by short-path distillation at 0.5 mm. The alcohol **36** was collected as a colorless liquid that solidified on standing: mp 30.5–32 °C; IR (CCl_4) 3590 (OH) and 915 cm^{-1} ($CH{=}CH_2$); NMR (CCl_4) δ 4.8–6.3 (4 H, m, vinyl CH), 1.5–2.4 (7 H, m, aliphatic CH), 1.31 (3 H, s, CH_3CO), 1.18 (1 H, broad, OH), and 0.87 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 208 (M^+, 7), 190 (39), 133 (100), 106 (60), 105 (53), 91 (94), 57 (80), 55 (38), 43 (37), and 41 (70).

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.62; H, 11.64.

Preparation of Ketone 26. The previously described procedure was employed with 990 mg (4.8 mmol) of Me_2SCuBr, 10 mL of Me_2S, 6.20 g (50 mmol) of the enone **30**, 150 mL of THF, and 74. 1 mL of a THF solution containing 60 mmol of vinyl-MgBr. The reaction solution, which successively turned red, dark purple, and then orange during the addition of the Grignard reagent, was warmed to −30 °C during 30 min accompanied by a further color change from orange to brown-black. After the reaction mixture had been hydrolyzed (aqueous NH_4Cl and HCl), made basic with solid $NaHCO_3$, and extracted with pentane, distillation of the crude organic product (7.42 g of yellow liquid) separated 6.21 g (82%) of the ketone **26** (a mixture of epimers) as a colorless liquid, bp 53–56 °C (1.2 mm), $n^{25}D$ 1.4694 [lit.[3h] bp 80–95 °C (20 mm), $n^{25}D$ 1.4691–1.4706]. The IR and NMR spectra of this product corresponded to those previously reported and the product contained (GLC, silicone XE-60 on Chromosorb P) ca. 88% of the cis epimer of ketone **26** (retention time 12.4 min) and ca. 12% of the trans epimer (13.6 min).

Reaction of the ketones **26** with $HOCH_2CH_2OH$ and TsOH in refluxing PhH afforded the ketal **28** (a mixture of epimers) as a colorless liquid, bp 76–84 °C (1.3 mm), $n^{25}D$ 1.4786 (lit.[3h] $n^{25}D$ 1.4773 for trans epimer and 1.4791 for cis epimer), in 87% yield. The IR and NMR spectra of the product corresponded to those previously described.[3h]

Preparation of the Ketones 16 and 17. Conversion of 3-methyl-2-butanone to its enol acetate **12** is described elsewhere.[16] A previously described procedure[17] was used to prepare the chloromethyl ether **15**: bp 68–68.5 °C (2 mm); $n^{25}D$ 1.5257 [lit.[17] bp 53–56 °C (1.5 mm); $n^{20}D$ 1.5268–1.5279]; NMR (CCl_4) δ 7.30 (5 H, s, aryl CH), 5.42 (2 H, s, CH_2Cl), and 4.68 (2 H, s, aryl CH_2); mass spectrum *m/e* (rel intensity) 158 (M^+, 5), 156 (M^+, 11), 128 (4), 126 (11), 91 (100), 65 (10), and 39 (8).

To a cold (−20 °C) solution of the enolate **10**, prepared in the usual manner[18] from 9.8 g (76 mmol) of the enol acetate **12** in 120 mL of DME and 160 mmol of MeLi in 64 mL of Et_2O, was added rapidly with stirring 25 g (160 mmol) of freshly distilled chloromethyl ether **15**. The reaction mixture, whose temperature rose to 15 °C, was cooled to −5 °C, stirred for 2 min, and then partitioned between pentane and aqueous $NaHCO_3$. After the organic solution had been dried over Na_2SO_4 and concentrated, fractional distillation separated 7.2 g (46%) of the ketone **16** as a colorless liquid, bp 109–110 °C (1.4 mm), $n^{25}D$ 1.4956. In some runs a higher boiling fraction was isolated containing $(PhCH_2O)_2CH_2$: bp 110.5–111 °C (0.22 mm); $n^{25}D$ 1.5420 [lit.[19] bp 173–175 °C (11 mm)]; NMR (CCl_4) δ 7.25 (10 H, s, aryl CH) 4.71 (2 H, s, OCH_2O), and 4.56 (4 H, s, aryl CH_2); mass spectrum *m/e* (rel intensity) 137 (2), 107 (21), 92 (100), 91 (89), 79 (9), and 65 (11). Mixtures of these components could be analyzed by GLC (silicone SE-30 on Chromosorb P) using peaks for the ketone **16** (retention time 9.8 min) and $(PhCH_2O)_2CH_2$ (17.2 min). The spectroscopic properties of ketone **16** follow: IR (CCl_4), 1708 cm^{-1} (C=O); UV (*n*-heptane), intense end absorption (ε 5460 at 209 nm) with a series of weak maxima (ε 111–201) in the region 248–269 nm; NMR (CCl_4) δ 7.27 (5 H, s, aryl CH), 4.48 (2 H, s, aryl CH_2), 3.40 (2 H, s, CH_2O), 2.06 (3 H, s, $COCH_3$), and 1.09 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 108 (17), 107 (10), 92 (12), 91 (100), 85 (21), 65 (10), and 43 (39).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.65; H, 8.82.

A solution of 5.0 g (24 mmol) of the benzyloxy ketone **16** in 10 mL of MeOH was hydrogenated at 25 °C and 2–3 atm pressure over 400 mg of a 5% Pd on C catalyst. When the H_2 uptake ceased, the mixture was filtered, the filtrate was concentrated at 25 °C under reduced pressure, and the residual liquid was distilled *rapidly* in a short-path still to separate 2.17 g (78%) of the hydroxy ketone **17** as a colorless liquid: bp 79–80 °C (5 mm); $n^{25}D$ 1.4372 [lit.[20] 78–79 °C (14 mm)]; IR ($CHCl_3$) 3610, 3530 (OH), and 1695 cm^{-1} (C=O); NMR (CCl_4) δ 3.24 (1 H, s, OH), 3.50 (2 H, s, CH_2O), 2.13 (3 H, s, $COCH_3$), and 1.08 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 116 (M^+, <1), 86 (18), 71 (17), 56 (80), 55 (29), 43 (100), and 41 (34).

Preparation of the Bromo Ketone 19. Following the general procedures described previously,[20] 1.9 g (16 mmol) of the hydroxy ketone **17** was converted with 5.7 g (32 mmol) of TsCl in 25 mL of pyridine at 0 °C for 24 h to 4.1 g (95%) of the tosyl ketone **18** as colorless needles: mp 53.5–54 °C (lit.[20] mp 56 °C); IR (CCl_4) 1712 cm^{-1} (C=O); NMR (CCl_4) δ 7.2–7.9 (4 H, m, aryl CH), 3.95 (2 H, s, CH_2O), 2.46 (3 H, s, aryl CH_3), 2.05 (3 H, s, $COCH_3$), and 1.11 (6 H, s, CH_3). Reaction of 2.0 g (7.4 mmol) of the tosyl ketone **18** with 3.9 g (45 mmol) of anhydrous LiBr in 50 mL of refluxing 2-butanone for 48 h yielded 0.92 g (70%) of the bromo ketone **19** as a colorless liquid: bp 61–63 °C (8 mm); $n^{25}D$ 1.4628 [lit.[20] bp 79 °C (18 mm)]; IR (CCl_4) 1710 cm^{-1} (C=O); NMR (CCl_4) δ 3.47 (2 H, s, CH_2Br), 2.15 (3 H, s, $COCH_3$), and 1.25 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 180 (M^+, 3), 178 (M^+, 3), 56 (80), 55 (19), 43 (100), and 41 (23).

Preparation of Ketone 9.[21] To a cold (4 °C) solution of the enolate **10**, from 4.03 g (31.4 mmol) of the enol acetate **12**, and 66.2 mmol of MeLi in 70 mL of DME, was added rapidly 7.99 g (66 mmol) of allyl bromide. The reaction mixture, whose temperature rose from 4 to 19 °C, was stirred for 45 min in an ice bath and then for 30 min at 25 °C. After the mixture had been partitioned between aqueous $NaHCO_3$ and pentane, the aqueous phase was saturated with NaCl and extracted with additional pentane. The combined organic solutions were dried, concentrated, and fractionally distilled to separate early fractions containing DME and 3-methyl-2-butanone followed by 0.34 g of fractions, bp 25–28 °C (20 mm), containing (GLC, silicone OV-17 on Porosil) the ketone **9** (ca. 79%, retention time 11.2 min) accompanied by lesser amounts of 3-methyl-2-butanone (3.6 min) and the enol acetate **12** (4.6 min). The subsequent distillation fraction, 1.46 g (37%) of colorless liquid, bp 55 °C (19 mm), contained (GLC) ca. 95% of the desired ketone **9**. A pure sample of this ketone **9** was collected (GLC) for characterization: $n^{25}D$ 1.4263;[22] IR (CCl_4) 1710 (C=O), 1640 (C=C), and 920 cm^{-1} ($CH{=}CH_2$); UV max (95% EtOH) 284 nm (ε 29); NMR (CCl_4) δ 4.7–6.0 (3 H, m, $CH{=}CH_2$), 2.23 (2 H, d, J = 7 Hz, further partially resolved splitting also apparent, allylic CH_2), 2.03 (3 H, s, CH_3CO), and 1.07 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 126 (M^+, 6), 111 (9), 108 (9), 83 (40), 55 (100), 43 (52), and 41 (38).

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.22; H, 11.21.

The electrochemical reduction[21] of solutions containing 5.6–7.9 × 10^{-3} M ketone **9** and 0.5 M n-Bu_4NBF_4 in DMF were examined by standard polarographic procedures.[23] Although the polarographic reduction wave for the ketone **9** was not well resolved from the background current, from the difference between the two curves we estimated the $E_{1/2}$ value for ketone **9** to be −2.96 V vs. SCE. A solution of 406 mg (3.22 mmol) of ketone **9** in 10 mL of EtOH was hydrogenated[21] at 25 °C and 1 atm pressure over 37 mg of 5% Pd on C catalyst. After the H_2 uptake ceased (5 h), the solution was filtered and concentrated to leave 278 mg of pale yellow liquid. The pure ketone, $CH_3CH_2CH_2C(CH_3)_2COCH_3$, was collected (GLC, silicone OV-17 on Porosil) as a colorless liquid: $n^{25}D$ 1.4144 [lit.[24] bp 151–152 °C, $n^{20}D$ 1.4175]; IR (CCl_4) 1710 cm^{-1} (C=O); NMR (CCl_4) δ 2.03 (3 H, s, $COCH_3$) and 0.8–1.7 (13 H, m, aliphatic CH including a CH_3 singlet at 1.07); mass spectrum *m/e* (rel intensity) 86 (65), 85 (78), 57 (37), 43 (100), 41 (65), and 39 (27).

A solution of 390 mg (3.1 mmol) of 6-methyl-5-hepten-2-one (Aldrich Chemical Co., Inc.) in 15 mL of EtOH was hydrogenated at 25 °C and 1 atm pressure over 40 mg of 5% Pd on C catalyst. After the H_2 uptake ceased (75 min), the mixture was filtered and concentrated to leave 294 mg of liquid that contained (GLC, silicone OV-17 on Porosil) the ketone $(CH_3)_2CH(CH_2)_3COCH_3$ accompanied by several minor unidentified impurities. A collected (GLC) sample of the pure ketone $(CH_3)_2CH(CH_2)_3COCH_3$ was obtained as a colorless liquid: $n^{25}D$ 1.4115 [lit.[25] bp 163–164 °C, $n^{20}D$ 1.4151]; IR (CCl_4) 1720 cm^{-1} (C=O); NMR (CCl_4) δ 2.33 (2 H, t, J = 7 Hz, CH_2CO), 2.01 (3 H, s, CH_3CO), and 0.8–1.9 (11 H, m, aliphatic CH including a CH_3 doublet, J = 6 Hz, at 0.89); mass spectrum *m/e* (rel intensity) 128 (M^+, 4), 110 (13), 95 (17), 71 (31), 70 (17), 58 (58), 43 (100), 42 (17), 41 (25), and 39 (19).

The unsaturated ketone **21**, obtained from the acid **20** by a previously described procedure,[5] was isolated in 70% yield as a colorless liquid, bp 53–55 °C (55 mm), $n^{25}D$ 1.4210 [lit.[5] bp 52–55 °C (55 mm), $n^{25}D$ 1.4221], with IR and NMR spectra corresponding to those previously described.[5]

Preparation of the Ketone 8. A. From Enol Acetate 11. The enol acetate **11**, bp 55–65 °C (0.05 mm), $n^{25}D$ 1.5321, was prepared as previously described.[26] After reaction of 210 mmol of MeLi in 199 mL of DME containing 10 mg of 2,2-bipyridyl (an indicator) with 17.60 g (100 mmol) of the enol acetate **11** by the usual procedure,[2b] the resulting solution of the enolate **9a** was treated with 25.4 g (210 mmol) of allyl bromide. The reaction mixture, which warmed to 15–19 °C, was stirred for 30 min at this temperature and then partitioned between aqueous $NaHCO_3$ and pentane. The organic phase was dried

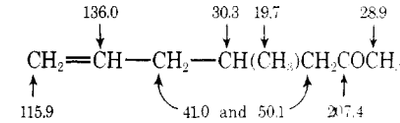
and concentrated to leave 15.8 g of yellow liquid. Fractional distillation afforded 12.9 g (74%) of the ketone **8** as a colorless liquid: bp 64.5–69 °C (0.5 mm); n^{25}_D 1.5130 [lit.[27] bp 119–121 °C (14–15 mm), n^{20}_D 1.5158]; IR (CCl_4) 1720 (C=O), 1640 (C=C), and 920 cm^{-1} ($CH=CH_2$); UV (95% EtOH) a series of weak maxima (ϵ 180–288) in the region 250–270 nm with a maximum at 287.5 nm (ϵ 273) and end absorption with ϵ 7900 at 210 nm; NMR (CCl_4) δ 7.0–7.3 (5 H, m, aryl CH), 4.7–6.0 (3 H, m, $CH=CH_2$), 3.63 (1 H, t, J = 7.5 Hz, benzylic CH), 2.0–3.1 (2 H, m, allylic CH_2), and 1.92 (3 H, s, CH_3CO); mass spectrum m/e (rel intensity) 174 (M^+, 3), 131 (100), 91 (71), 77 (25), 51 (23), 43 (100), and 39 (23). The higher boiling fractions from this distillation [1.3 g bp 95–104 °C (0.5 mm)] contained (GLC) mixtures of the monoalkylated (**8**) and dialkylated (**14**) ketones.

The course of this alkylation reaction could be followed by GLC (silicone SE-30 on Chromosorb P), employing aliquots removed from the reaction mixture, partitioned between H_2O, and hexane, and then dried and concentrated. The GLC retention times of the various ketones follow: **13**, 2.2 min; **8**, 3.1 min; and **14**, 6.6 min. A collected (GLC) sample of the dialkylated ketone **14** was obtained as a colorless liquid: n^{25}_D 1.5250 [lit.[28] bp 138–141 °C (18 mm), n^{25}_D 1.5269]; IR (CCl_4) 1710 (C=O), 1640 (C=C), and 920 cm^{-1} ($CH=CH_2$); UV (95% EtOH) series of weak maxima (ϵ 250–317) in the region 247–266 nm with a maximum at 289 nm (ϵ 276) and end absorption, ϵ 8400 at 210 nm; NMR (CCl_4) δ 7.0–7.5 (5 H, m, aryl CH), 4.7–5.9 (6 H, m, vinyl CH), 2.71 (4 H, d, J = 6 Hz, allylic CH_2), and 1.81 (3 H, s, $COCH_3$); mass spectrum m/e (rel intensity) 214 (M^+, 4), 171 (20), 129 (51), 117 (34), 115 (22), 91 (87), 67 (26), 43 (100), 41 (23), and 39 (20).

B. From Ketone 13. A solution of the enolate **9b**, prepared[26] from 25.2 g (1.05 mol) of NaH (prewashed with hexane), 500 mL of DME, and 123.1 g (0.92 mol) of ketone **13**, was cooled to 5 °C and 127.2 g (91 mL, 1.05 mol) of allyl bromide was added, dropwise and with stirring during 15 min while the temperature of the mixture was maintained at 30–35 °C. The resulting mixture was partitioned between hexane and aqueous NH_4Cl and the organic layer was washed with H_2O, dried, and concentrated. Fractional distillation of the crude product, 173.2 g of yellow oil, separated the following fractions: (1) 3.62 g of colorless liquid, bp 79–83 °C (1.3 mm), n^{25}_D 1.5131, containing (GLC) a mixture of ketones **13** (ca. 15%) and **8** (ca. 85%); (2) 140.34 g (88%) of the ketone **8**, bp 84–89.5 °C (1.3 mm), n^{25}_D 1.5137–1.5138; and (3) 1.82 g of colorless liquid, bp 93–105 °C (1.3 mm), containing mixtures of the ketones **8** (ca. 40%) and **14** (ca. 60%).

Preparation of Ketone 24. To 468 ml of a cold (3 °C) ethereal solution containing[14] 328 mmol of $CH_2=CHCH_2MgBr$ was added, dropwise with stirring and cooling during 38 min, a solution of 22.95 g (273 mmol) of the enone **22** in 10 mL of Et_2O. During this addition the temperature of the reaction mixture was maintained at 15–17 °C. After the addition was complete, the mixture was stirred at 25 °C for 1 h and then partitioned between Et_2O and aqueous NH_4Cl. The ethereal layer was washed with aqueous NaCl, dried over molecular sieves (no. 4A), concentrated, and distilled to separate 28.52 g (83%) of the alcohol **23** as fractions of colorless liquid: bp 48–53 °C (5.5 mm); n^{25}_D 1.4520–1.4533 [lit. bp 44–46 °C (5–6 mm),[29] 52–53 °C (7 mm),[30] n^{23}_D 1.4528–1.4536[29]]; IR (CCl_4) 3590, 3560, 3460 (OH), 1640 (C=C), 975, and 925 cm^{-1} (trans CH=CH and $CH=CH_2$); UV (95% EtOH) end absorption with ϵ 972 at 210 nm; NMR (CCl_4) δ 4.8–6.1 (5 H, m, vinyl CH), 2.22 (2 H, d, J = 7 Hz, allylic CH_2), 1.6–1.8 (4 H, m, OH and allylic CH_3), and 1.17 (3 H, s, CH_3); mass spectrum m/e (rel intensity) 108 (3), 85 (100), 69 (18), 67 (43), 43 (66), 41 (32), and 39 (18).

A solution of 9.54 g (75.7 mmol) of the alcohol **23** in 60 mL of pentane was added dropwise to the top of a column packed with glass beads and surrounded by a furnace heated to 440 °C; the pyrolysis products were swept from the heated column in a stream of N_2 and collected in a cold trap. The mixture of pyrolysis products contained (GLC, UCON 50HB 280X on Chromosorb P) the enone **22** (retention time 2.3 min), the ketone **25** (4.4 min), the ketone **24** (4.9 min), and the starting alcohol **23** (6.5 min), as well as several rapidly eluted unidentified components. The rate of addition of the alcohol **23** in pentane and the flow rate of N_2 were adjusted for the most efficient conversion of the alcohol **23** to the desired ketone **24**. After removal of the pentane, the crude pyrolysis product (6.61 g of colorless liquid) contained 27% of **22**, 14% of **25**, 34% of **24**, and 25% of **23**. Fractional distillation through an 18-cm spinning-band column separated 959 mg of the enone **22** [bp 38–52 °C (29–31 mm), n^{25}_D 1.4346], 215 mg of a fraction, bp 53–57 °C (29 mm), containing (GLC) mainly the ketone **25**, and 4.69 g of fractions, bp 57–66 °C (29–30 mm), containing various mixtures of **23**, **24**, and **25**. This latter mixture was chromatographed on silica gel with hexane–Et_2O mixtures as the eluent to separate a mixture of ketones **24** and **25** in the early fractions and 1.740 g of unchanged alcohol **23** in the later fractions. The mixture of ketones **24** and **25** was rechromatographed on a column packed with silica gel coated with $AgNO_3$ (5% by weight) and eluted with hexane–Et_2O mixtures. The early fractions contained (GLC) the pure ketone **25** and the later fractions contained 924 mg (9.7% yield based on the starting alcohol **23**) of the desired ketone **24**, n^{25}_D 1.4256. Combined samples from this product from several runs were distilled to separate the pure ketone **24** as a colorless liquid: bp 85 °C (56 mm); n^{25}_D 1.4251–1.4254; IR (CCl_4) 1720 (C=O), 1642 (C=C), and 922 cm^{-1} ($CH=CH_2$); NMR (CCl_4) δ 4.8–6.1 (3 H, m, vinyl CH), 1.8–2.4 (8 H, m, aliphatic CH including a CH_3CO singlet at 2.04), and 0.8–1.1 (3 H, m, CH_3); mass spectrum m/e (rel intensity) 126 (M^+, 1), 111 (8), 68 (42), 58 (14), 43 (100), 41 (22), and 39 (13). The ^{13}C NMR spectrum of the ketone **24** ($CDCl_3$) is summarized in the following structure;



the assignments are consistent with off-resonance decoupling measurements.

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.16; H, 11.21.

From chromatographic fractions rich in the ketone **25**, a pure sample of the ketone **25**[31] was collected (GLC, TCEP on Chromosorb P) as a colorless liquid: n^{25}_D 1.4296; IR (CCl_4) 1708 cm^{-1} (C=O); UV max (95% EtOH) 285 nm (ϵ 45); NMR (CCl_4) δ 2.5–3.0 (3 H, m, aliphatic CH), 1.96 (3 H, s, CH_3CO), 1.5–1.8 (2 H, m, CH_2), and 0.9–1.2 (6 H, two overlapping doublets, J = 6 and 7 Hz, CH_3); mass spectrum m/e (rel intensity) 126 (M^+, 5), 111 (31), 85 (83), 83 (25), 69 (100), 55 (70), 43 (81), 41 (47), and 39 (26); calcd for $C_8H_{14}O$, 126.1045; found, 126.1022. The natural abundance ^{13}C NMR spectrum of the ketone **25** ($CDCl_3$) exhibited a C=O peak at 207.6 ppm, three CH_3 peaks at 16.4, 20.7, and 56.3 ppm, and four additional strong peaks at 27.3, 29.1, 29.5, and 32.9 ppm whose off-resonance decoupling patterns were obscured by the presence of additional small peaks attributable to a second stereoisomer.

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.21; H, 11.19.

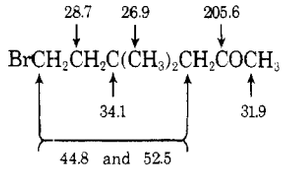
Preparation of Ketone 54. To a cold (−50 to −55 °C) mixture, prepared from 205 mg (1.0 mmol) of Me_2SCuBr, 10 mL of Me_2S, and 20 mmol of $CH_2=CHMgBr$ in 65 mL of THF, was added, dropwise and with stirring during 30 min, a solution of 103 mg (0.50 mmol) of Me_2SCuBr, 5 mL of Me_2S, and 840 mg (10 mmol) of the enone **22** in 10 mL of THF. The resulting solution was stirred at −40 to −50 °C for 45 min, hydrolyzed in the usual manner (NH_4Cl and HCl), made basic with $NaHCO_3$, and extracted with Et_2O. After the ethereal extract had been washed with aqueous 2 M HCl and with aqueous $NaHCO_3$, it was dried, concentrated, and distilled to separate 0.70 g (63%) of the ketone **54** as a colorless liquid: bp 62–63.5 °C (50 mm); n^{25}_D 1.4213–1.4216 [lit.[32] bp 137–138 °C, n^{25}_D 1.4193]; IR (CCl_4) 1720 (C=O), 1640 (C=C), and 925 cm^{-1} ($CH=CH_2$); NMR (CCl_4) δ 4.7–6.1 (3 H, m, vinyl CH), 2.3–3.1 (3 H, m, aliphatic CH), 2.03 (3 H, s, CH_3CO), and 1.00 (3 H, d, J = 6.5 Hz, CH_3); mass spectrum m/e (rel intensity) 112 (3), 97 (15), 69 (11), 55 (18), 43 (100), and 41 (20).

Preparation of Bromo Ketones. A. General Procedure. The pentane used as a solvent in these reactions was purified by stirring over concentrated H_2SO_4 for several days followed by washing with H_2O, drying over $MgSO_4$, and distillation from CaH_2. In a typical preparation a solution of 10 mmol of the unsaturated ketone in 300 mL of purified pentane was placed in a quartz photochemical reaction vessel and flushed with N_2. Then gaseous HBr [passed through anhydrous $Mg(ClO_4)_2$] was passed through the solution for 4 min while the solution was irradiated with the light from a Hanovia 450-W medium-pressure Hg lamp. The resulting colorless pentane solution was flushed with N_2 to remove most of the HBr and then washed repeatedly with saturated aqueous $Na_2S_2O_3$. The resulting organic solution was then dried and concentrated under reduced pressure to leave the crude bromo ketone.

B. Bromo Ketone 42. The light-catalyzed addition of HBr to a solution of 1.90 g (15 mmol) of the ketone **34** in 300 mL of pentane yielded 2.82 g (91%) of the crude bromo ketone **42** as a pale yellow liquid that darkened on standing. Distillation separated 2.35 g (76%) of the pure bromo ketone **42** as a colorless liquid: bp 56.5–57.5 °C (0.45 mm); n^{25}_D 1.4717–1.4720; IR (CCl_4) 1720 cm^{-1} (C=O); NMR (CCl_4) δ 3.1–3.5 (2 H, m, CH_2Br), 2.34 (2 H, s, CH_2CO), 2.08 (3 H, s, CH_3CO), 1.8–2.0 (2 H, m, CH_2), and 1.02 (6 H, s, CH_3); mass spectrum m/e (rel intensity) 126 (12), 125 (12), 110 (73), 83 (15), 69 (26), 55 (23), 43 (100), and 41 (26).

Anal. Calcd for $C_8H_{15}BrO$: C, 46.40; H, 7.25; Br, 38.62. Found: C, 46.44; H, 7.30; Br, 38.45.

The natural abundance ^{13}C NMR spectrum ($CDCl_3$) of the bromo ketone **42** is summarized in the following formula; the indicated assignments are consistent with off-resonance decoupling measure-

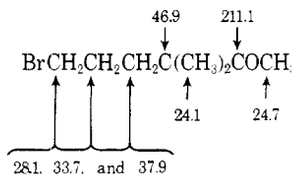


ments. The product exhibited a single GLC peak (silicone XE-60 on Chromosorb P); however, a collected sample of the material eluted from this GLC column had IR absorption (3035 and 1670 cm^{-1}) different from that of the ketone **42** suggesting that the bromo ketone **42** may have been converted to an enol ether in the GLC apparatus.

C. Bromo Ketone 41. The comparable addition of HBr to a pentane solution of 1.26 g (10 mmol) of the ketone **9** yielded 1.98 (96%) of the crude bromo ketone **41** as a colorless liquid. Distillation separated 1.90 g (92%) of the pure bromo ketone **41**: bp 81–82 °C (1.2 mm), $n^{25}D$ 1.4703; IR (CCl_4) 1708 cm^{-1} (C=O); NMR (CCl_4) δ 3.2–3.5 (2 H, m, CH_2Br), 2.07 (3 H, s, CH_3CO), 1.4–1.9 (4 H, m, CH_2), and 1.10 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 165 (29), 163 (30), 127 (40), 83 (75), 55 (59), 43 (100), and 41 (44).

Anal. Calcd for $C_8H_{15}BrO$: C, 46.40; H, 7.25; Br, 38.62. Found: C, 46.35; H, 7.32; Br, 38.51.

The natural abundance ^{13}C NMR spectrum ($CDCl_3$) of the bromo ketone **41** is summarized in the following formula; the indicated as-

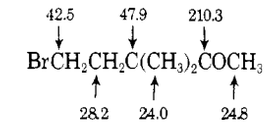


signments are consistent with off-resonance decoupling measurements.

D. Bromo Ketone 40. Addition of HBr to 1.12 g (10 mmol) of the ketone **21** gave 1.90 g (98%) of the crude bromo ketone **40** as a colorless liquid. Distillation gave 1.66 g (86%) of the pure bromo ketone **40**: bp 67–68 °C (1.3 mm); $n^{25}D$ 1.4705; IR (CCl_4) 1710 cm^{-1} (C=O); NMR (CCl_4) δ 3.0–3.5 (2 H, m, CH_2Br), 1.8–2.3 (5 H, m, CH_2 and a CH_3CO singlet at 2.10), and 1.17 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 151 (1), 149 (1), 112 (25), 97 (59), 82 (28), 80 (29), 69 (45), 55 (38), 43 (100), 41 (86), and 39 (26).

Anal. Calcd for $C_7H_{13}BrO$: C, 43.55; H, 6.74; Br, 41.42. Found: C, 43.67; H, 6.82; Br, 41.22.

The natural abundance ^{13}C NMR spectrum ($CDCl_3$) of the bromo ketone **40** is summarized in the following formula; the indicated as-



signments are consistent with off-resonance decoupling measurements.

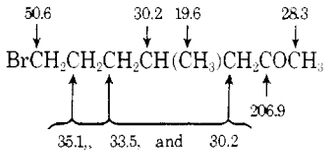
E. Bromo Ketone 45. A sample of the unsaturated ketone **7**, bp 90–91 °C (4 mm), $n^{25}D$ 1.4685 [lit.[2a] bp 99–102 °C (12 mm), $n^{25}D$ 1.4680–1.4683], containing (NMR analysis) ca. 67% of the trans epimer and ca. 33% of the cis epimer, was obtained by a previously described procedure.[2a] Addition of HBr to 2.00 g (13.2 mmol) of this ketone **7** in 300 mL of pentane yielded 2.97 g (97%) of the crude bromo ketone **45** as a colorless liquid. Distillation gave 2.85 g (93%) of the pure bromo ketone **45**: bp 81–82 °C (0.03 mm); $n^{25}D$ 1.4990; IR (CCl_4) 1712 cm^{-1} (C=O); NMR (CCl_4) δ 3.2–3.6 (2 H, m, CH_2Br), 1.3–2.7 (12 H, m, aliphatic CH), 1.0–1.2 (ca. 68% of 3 H, m, CH_3 of trans epimer), and 0.84 (ca. 34% of 3 H, d, J = 7 Hz, CH_3 of cis epimer); mass spectrum *m/e* (rel intensity) 219 (2), 217 (2), 153 (83), 137 (64), 109 (22), 97 (21), 95 (22), 83 (25), 81 (35), 71 (27), 69 (54), 67 (28), 56 (20), 55 (100), 43 (32), 41 (62), and 39 (28).

Anal. Calcd for $C_{10}H_{17}BrO$: C, 51.52; H, 7.30; Br, 34.31. Found: C, 51.70; H, 7.38; Br, 34.13.

F. Bromo Ketone 43. A solution of 5.00 g (29 mmol) of ketone **8** in 260 mL of reagent hexane was irradiated for 15 min while a stream of gaseous HBr was passed through the solution. After following the usual isolation procedure, the crude product (7.03 g of red-brown liquid) was chromatographed on silica gel with hexane–Et_2O mixtures as eluents. The fractions eluted with 1:4 (v/v) Et_2O–hexane contained 4.13 g (57%) of the bromo ketone **43** as a pale yellow liquid: $n^{25}D$ 1.5392 [lit.[28] bp 123–125 °C (0.5 mm), $n^{20}D$ 1.5412]; IR (CCl_4) 1720 cm^{-1} (C=O); UV (95% EtOH) a series of weak maxima (ε 360–400) in the region 247–264 nm with a maximum at 284 nm (ε 320) and end absorption, ε 7200 at 210 nm; NMR (CCl_4) δ 7.0–7.5 (5 H, m, aryl CH), 3.63 (1 H, t, J = 7 Hz, benzylic CH), 3.31 (2 H, m, CH_2Br), and 1.4–2.5 (7 H, m, aliphatic CH including a $COch_3$ singlet at 1.91); mass spectrum *m/e* (rel intensity) 256 (M^+, 1), 254 (M^+, 1), 213 (16), 211 (17), 131 (33), 104 (12), 103 (11), 92 (21), 91 (100), and 43 (56).

Anal. Calcd for $C_{12}H_{15}BrO$: C, 56.48; H, 5.93; Br, 31.32. Found: C, 56.49; H, 5.96; Br, 31.15.

G. Bromo Ketone 44. Addition of HBr to 754 mg (5.98 mmol) of the ketone **24** in 300 mL of pentane gave 1.285 g of the crude bromo ketone **44** as a pale yellow liquid containing (TLC, silica gel, Et_2O–hexane eluent, 3:7 v/v) the bromo ketone **44** (R_f 0.33) and one minor impurity (R_f 0.58). Chromatography on silica gel with Et_2O–hexane mixtures as eluents separated 1.18 g (96%) of the bromo ketone which was distilled to give the pure bromo ketone **44** as a colorless liquid: bp 59.5–60.5 °C (0.27 mm); $n^{25}D$ 1.4672; IR (CCl_4) 1720 cm^{-1} (C=O); UV max (95% EtOH) 278 nm (ε 33); NMR (CCl_4) δ 3.36 (2 H, t, J = 7 Hz, CH_2Br), 1.1–2.5 (10 H, m, aliphatic CH including a CH_3CO singlet at 2.04), and 0.93 (3 H, d, J = 6.5 Hz, CH_3); mass spectrum *m/e* (rel intensity) 208 (M^+, <1), 206 (M^+, <1), 127 (8), 111 (9), 69 (13), 68 (21), 58 (61), 43 (100), and 41 (23). The natural abundance ^{13}C NMR spectrum ($CDCl_3$) is summarized in the following structure;



the indicated assignments are consistent with off-resonance decoupling measurements.

Anal. Calcd for $C_8H_{15}BrO$: C, 46.39; H, 7.30; Br, 38.58. Found: C, 46.42; H, 7.32; Br, 38.63.

H. Bromo Ketone 46. The light-catalyzed addition of HBr to a solution of 2.00 g (10.2 mmol) of the ketal **28** (a mixture of epimers) in 300 mL of pentane was effected in 5 min taking special care to protect the reaction mixture from H_2O. The crude bromo ketal product **52** amounted to 2.78 g (98%) of colorless liquid, $n^{25}D$ 1.4971. Distillation afforded 2.54 g (90%) of the bromo ketal **52**, bp 130–134 °C (0.45 mm), $n^{25}D$ 1.4978, that contained ca. 10–15% of the bromo ketone **46**: IR (CCl_4) 1710 cm^{-1} (weak, C=O of bromo ketone **46**); NMR (CCl_4) δ 3.8–4.0 (4 H, m, CH_2O), 3.2–3.7 (2 H, m, CH_2Br), and 0.8–2.6 [15 H, m, aliphatic CH including a weak CH_3CO singlet at 2.08 (bromo ketone impurity) and CH_3 singlets at 1.26 (minor) and 1.19 (major) attributable to the cis and trans epimers of the ketal **52**]; mass spectrum *m/e* (rel intensity) 278 (M^+, 0.2), 276 (M^+, 0.2), 153 (22), 109 (30), 67 (27), 43 (100), and 41 (24).

A solution of 690 mg (2.5 mmol) of the bromo ketal **52** and 6 mL of aqueous 1 M HBr in 14 mL of THF was stirred at 25 °C for 1 h and then partitioned between Et_2O and aqueous $NaHCO_3$. After the ethereal layer had been dried and concentrated, the residual crude bromo ketone **46** (560 mg or 97% of colorless liquid, $n^{25}D$ 1.4972) was distilled to separate 497 mg (86%) of the bromo ketone **46**: bp 105–107 °C (0.3 mm); $n^{25}D$ 1.4970; IR (CCl_4) 1712 cm^{-1} (C=O); NMR (CCl_4) δ 3.2–3.6 (2 H, m, CH_2Br) and 0.9–2.4 [15 H, m, aliphatic CH including CH_3CO singlets at 2.17 (minor) and 2.08 (major)]; mass spectrum *m/e* (rel intensity) 234 (M^+, <1), 232 (M^+, <1), 153 (16), 137 (17), 109 (34), 81 (19), 67 (31), 55 (15), 43 (100), 41 (22), and 39 (14).

Anal. Calcd for $C_{10}H_{17}BrO$: C, 51.52; H, 7.30; Br, 34.31. Found: C, 51.62; H, 7.36; Br, 34.18.

When a comparable HBr addition was performed with 1.52 g (10 mmol) of the unsaturated ketone **26** in either pentane or hexane, the crude bromo ketone **46** (2.21 g or 96% of initially colorless liquid, $n^{25}D$ 1.4931) rapidly darkened on standing. After distillation, the resulting bromo ketone **46** (1.72 g or 74%), bp 78–81 °C (0.45 mm), $n^{25}D$ 1.4962, exhibited NMR absorption corresponding to the bromo ketone **46** accompanied by at least two additional weak signals, a quartet (J = 7 Hz, additional partially resolved splitting was also apparent) at δ 4.23 (CHBr) and a doublet (J = 7 Hz) at δ 1.66 (CH_3). These extra NMR signals, suggesting the presence of 5–10% of the impurity **48a**, were just barely discernible in the sample of bromo ketone **46** obtained by hydrolysis of the bromo ketal **52**.

Several additional experiments were performed in an effort to learn the origin of the impurity **48a**. After a mixture of 500 mg of the ketone **26** and 5 mL of aqueous 48% HBr had been stirred at 25 °C for 1 h, it

was warmed in a steam bath for 15 min and then cooled and partitioned between Et_2O and aqueous $NaHCO_3$. After the Et_2O solution had been dried and concentrated, short-path distillation of the dark-colored residual liquid at 0.03 mm separated a crude sample of the bromo ketone **48a** as an initially colorless liquid that rapidly turned yellow on standing: IR (CCl_4) 1710 cm^{-1} (C=O); NMR (CCl_4) δ 4.24 (1 H, q, J = 7 Hz, further partially resolved splitting apparent, CHBr) and 0.8–3.0 [16 H, m, aliphatic CH including a CH_3CO singlet at 2.14 and a CH_3 doublet (J = 7 Hz) at 1.67]. Appropriate decoupling experiments demonstrated that the signals at δ 4.24 and 1.67 were coupled to one another.

A solution of 0.50 g (3.3 mmol) of the ketone **26** in 300 mL of purified pentane was flushed with N_2 and then saturated with anhydrous HBr and allowed to stand at 25 °C for 2 h while being protected from light and from O_2. The solution was then concentrated to leave 0.62 g of colorless liquid, $n^{25}D$ 1.4712, that contained (NMR analysis) approximately equal amounts of the starting unsaturated ketone **26** and the bromo ketone **46**. None of the bromo ketone **48a** was detected by NMR analysis.

I. Bromo Ketone 47. The addition of HBr to a solution of 1.00 g (3.9 mmol) of the unsaturated ketal **29** in 300 mL of pentane yielded, after distillation, 1.1 g (84%) of the crude bromo ketal **53**, bp 108–109 °C (0.3 mm), $n^{25}D$ 1.4972. The spectra of this product indicated the presence of 5–10% of the bromo ketone **47**; IR (CCl_4) 1710 cm^{-1} (weak, C=O of ketone **47**); NMR (CCl_4) δ 3.8–4.0 (4 H, m, CH_2O), 3.1–3.6 (2 H, m, CH_2Br), 1.0–2.4 [14 H, m, aliphatic CH including CH_3 singlets at 1.25 (major) and 1.17 (minor)], and two singlets at 0.82 and 0.86 (total 9 H, t-Bu groups of two epimers); mass spectrum m/e (rel intensity) 319 (2), 317 (2), 109 (7), 87 (100), 57 (13), 43 (28), and 41 (9).

A solution of 300 mg of this crude bromo ketal **53** and 3 mL of aqueous 1 M HBr in 7 mL of THF was stirred at 25 °C for 1 h and then subjected to the previously described isolation procedure. The crude bromo ketone **47** (0.25 g or 81%) was distilled to separate the pure bromo ketone **47** as a colorless liquid: bp 91–93 °C (0.01 mm); $n^{25}D$ 1.4960; IR (CCl_4) 1711 cm^{-1} (C=O); NMR (CCl_4) δ 3.2–3.7 (2 H, m, CH_2Br), 1.0–2.8 [14 H, m, aliphatic CH including CH_3 singlets at 2.13 (minor) and 2.08 (major)], and two singlets at 0.85 and 0.89 (total 9 H, t-Bu groups of two epimers); mass spectrum m/e (rel intensity) 290 (M^+, 0.4), 288 (M^+, 0.5), 209 (23), 109 (40), 57 (69), 43 (100), and 41 (34).

Anal. Calcd for $C_{14}H_{25}BrO$: C, 58.13; H, 8.71; Br, 27.62. Found: C, 58.25; H, 8.73; Br, 27.58.

The light-catalyzed addition of HBr to a solution of 1.04 g (5.0 mmol) of the ketone **27b** in 300 mL of pentane gave 1.43 g (99%) of the crude bromo ketone **47** as a pale yellow liquid. Short-path distillation (0.03 mm and an 85 °C bath) separated 1.21 g (84%) of the crude bromo ketone **47** as a colorless liquid: $n^{25}D$ 1.4956; IR (CCl_4) 1710 cm^{-1} (C=O); NMR (CCl_4) δ 3.2–3.6 (2 H, m, CH_2Br), 1.0–2.8 (14 H, m, aliphatic CH including CH_3 singlets at 2.15 and 2.10), and two singlets at 0.85 and 0.89 (total 9 H, t-Bu signals of epimers). The NMR spectrum also exhibits small peaks attributable to the impurity **48b** (ca. 20–30% of the mixture). A 380-mg aliquot of a comparable sample of the crude bromo ketone **47**, containing (NMR, TLC, silica gel with an Et_2O–hexane eluent, 1:9 v/v) some starting olefin **27b** (R_f 0.33), the secondary bromide **48b** (R_f 0.40), and the desired bromo ketone **47** (R_f 0.20), was chromatographed on silica gel with Et_2O–hexane mixtures as the eluent to separate 55 mg (15% of the mixture) of the crude bromo ketone **48b** in the early fractions: IR (CCl_4) 1708 cm^{-1} (C=O); NMR (CCl_4) δ 4.24 (1 H, q of d, J = 7 and 2 Hz, CHBr), 2.16 (3 H, s, $COCH_3$), 1.68 (3 H, d, J = 7 Hz, CH_3), and 0.89 (9 H, s, t-Bu). Later fractions from the chromatograph contained increasing amounts of the olefin **27b** and the desired bromo ketone **47**.

J. Bromo Ketone 55. Addition of HBr to 300 mg (2.68 mmol) of the ketone **54** in pentane gave 530 mg of the crude bromo ketone **55** as a pale yellow oil that rapidly darkened on standing. The NMR spectrum of the crude product exhibited weak absorption not present in the pure bromo ketone **55** in the regions δ 4.0–4.6 and 1.5–1.7. This absorption may be attributable to the bromo ketone **56** since stirring 137 mg of the unsaturated ketone **54** with 1.5 mL of aqueous 48% HBr for 10 min on a steam bath and then for 90 min at room temperature yielded, after distillation, a crude sample of the bromo ketone **56** as a yellow liquid with distinctive NMR absorption (CCl_4) at δ 3.9–4.4 (m, CHBr), 2.05 (s, $COCH_3$), and 1.62 and 1.64 (two overlapping doublets, J = 7 Hz, CH_3). Chromatography of the crude bromo ketone **55** on silica gel with an Et_2O–hexane eluent (1:9 v/v) separated 318 mg (61.5%) of the bromo ketone **55** from a faster and a slower moving component, neither of which contained a C=O function (IR analysis). Distillation afforded the pure bromo ketone **55** as a colorless liquid: bp 60.5–61.5 °C (0.75 mm); $n^{25}D$ 1.4672–1.4680; IR (CCl_4) 1720 cm^{-1} (C=O); NMR (CCl_4) δ 3.35 (2 H, t, J = 7 Hz, CH_2Br), 1.5–2.4 (8 H, m, aliphatic CH including a CH_3 singlet at 2.05), and 0.9–1.1 (3 H, m, CH_3); mass spectrum m/e (rel intensity) 113 (14), 112 (16), 97 (48), 69 (21), 43 (100), 41 (25), and 39 (11).

Anal. Calcd for $C_7H_{13}BrO$: C, 43.53; H, 6.80; Br, 41.38. Found: C, 43.72; H, 6.81; Br, 41.18.

Registry No.—*cis*-**7**, 61674-93-9; *trans*-**7**, 61674-94-0; **8**, 26965-15-1; **9**, 26118-94-5; **9a**, 55977-36-1; **9b**, 61674-95-1; **10**, 57918-72-6; **13**, 103-79-7; **14**, 33523-78-3; **15**, 3587-60-8; **16**, 61674-96-2; **17**, 1823-90-1; **18**, 24706-89-2; **19**, 19961-40-1; **21**, 4181-07-1; **22**, 625-33-2; **23**, 919-98-2; **24**, 35194-34-4; **25**, 61674-97-3; *cis*-**26**, 54678-08-9; *trans*-**26**, 54678-07-8; **27a**, 54678-12-5; **27b**, 54678-11-4; **27b** DNP, 61674-98-4; *cis*-**28**, 54678-10-3; *trans*-**28**, 54678-09-0; **29** (α-H), 54678-16-9; **30**, 932-66-1; **31**, 37881-09-7; **34**, 1753-37-3; **35**, 141-79-7; **36**, 61674-99-5; **40**, 61689-48-3; **41**, 61675-00-1; **42**, 61675-01-2; **43**, 36307-12-7; **44**, 61675-02-3; **45**, 61675-03-4; **46** (α-H), 61675-04-5; **46** (β-H), 61675-05-6; **47**-(α-H), 61675-06-7; **47** (β-H), 61675-07-8; **48a**, 61675-08-9; **48b**, 61675-09-0; **52** (α-H), 61675-10-3; **52** (β-H), 61675-11-4; **29** (β-H), 54678-15-8; **53** (α-H), 61675-12-5; **53** (β-H), 61675-13-6; **54**, 61675-14-7; **55**, 30610-07-2; **56**, 61675-15-8; $CH_3CH_2CH_2C(CH_3)_2COCH_3$, 26118-38-7; 6-methyl-5-hepten-2-one, 110-93-0; $(CH_3)_2CH(CH_2)_3COCH_3$, 928-68-7.

References and Notes

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(11) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated $MgSO_4$ was employed as a drying agent. The IR spectra were determined with a Perkin-Elmer Model 257 infrared recording spectrophotometer fitted with a grating. The UV spectra were determined with a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The ^1H NMR spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60-A NMR spectrometer and the ^{13}C NMR spectra were determined at 25 MHz with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shift values are expressed in δ values (ppm) relative to a Me_4Si internal standard. The mass spectra were obtained with an Hitachi (Perkin-Elmer) Model RMU-7 or a Varian Model M-66 mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.

(12) This procedure for the preparation and use of $(vinyl)_2CuLi$ was described previously in ref 3h. The preparation of this same cuprate reagent from $(n\text{-}Bu_3P\text{-}CuI)_4$ and its addition to ketone **35** has been described in ref 3a.

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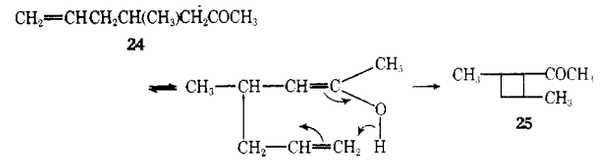
(31) Since the amount of this ketone **25** in the pyrolysis product increased at higher temperatures or when the residence time of the mixture in the pyrolysis tube increased, we presume that this ketone **25** is formed from ketone **24** by the following thermal reorganization. Reported examples of



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Total Synthesis of (+)-Costunolide

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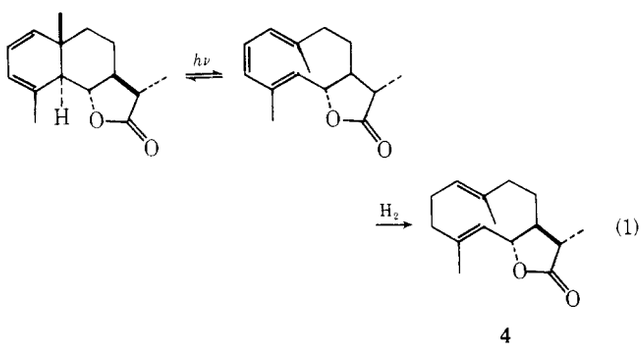
The total synthesis of the germacranolide costunolide (**2**) is described which employs the Cope rearrangement of synthetic dehydrosaussurea lactone (**1**) for generation of the ten-membered carbocyclic cyclodecadiene unit. In addition the synthesis of saussurea lactone (**3**) and its conversion to dihydrocostunolide (**4**) is recorded. The synthesis demonstrates the potential of the Shapiro olefin forming reaction in the presence of a reactive carbonyl and the usefulness of selenium in organic synthesis.

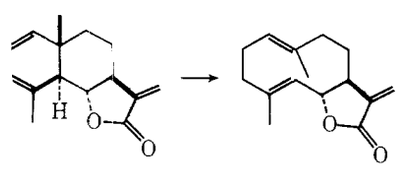
Costunolide (**2**)[1] is a member of the germacrane class of sesquiterpenes. Over the years the cyclodecane ring system of germacranolides has received little attention from synthetic chemists. This is primarily due to the primitive state of conformational analysis of ten-membered rings and the lack of methods for elaboration of the ten-membered carbocyclic framework. To date there has been no recorded total synthesis of costunolide. The only synthesis of a germacranolide is that of dihydrocostunolide (**4**) which employs a photolytic cleavage of a hexahydronaphthalene derivative for construction of the cyclodecane ring system (cf. eq 1).[2]



(1)

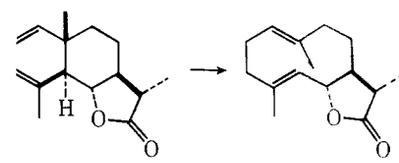
4

We describe herein the total synthesis of costunolide (**2**) via synthetic dehydrosaussurea lactone (**1**) utilizing the Cope



(2)

1 **2**

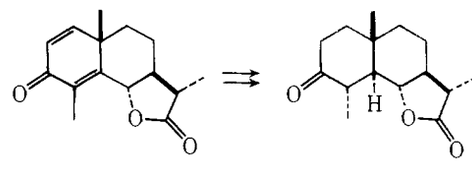


(3)

3 **4**

rearrangement[3,4] for construction of the ten-membered carbocyclic unit (eq 2). In addition we record the synthesis of saussurea lactone (**3**)[5] and its conversion to dihydrocostunolide (**4**) (eq 3).

The starting point of our synthesis (Chart I) was the keto lactone **6**, which was prepared from santonin (**5**) by the known two-step procedure involving hydrogenation and epimerization at C-4.[6] Treatment of the keto lactone **6** with tosylhydrazine provided the corresponding hydrazone which when treated with excess lithium diisopropylamide in dry tetrahydrofuran at 0 °C gave a 65% isolated yield (overall) of the crystalline olefin **7**, mp 142–143 °C. The use of lithium diisopropylamide in the Shapiro olefin-forming reaction[7] allows for the presence within the same molecule of a reactive carbonyl function as evidenced by the conversion of **6** → **7**. The lactone enolate undoubtedly acts as a protecting group for the lactone moiety. Lithium dialkylamides have recently been employed in the Shapiro olefin-forming reaction; however, no reactive carbonyl groups were present.[8] Sodium bis(tri-



5 **6**