A New Preparation of Acetylenic Ketones and Application to the Synthesis of *exo*-Brevicomin, the Pheromone from *Dendroctonus brevicomis*[1]

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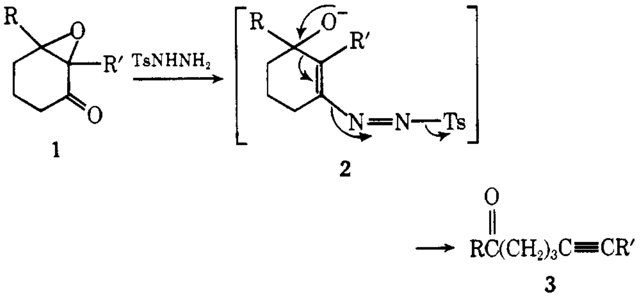
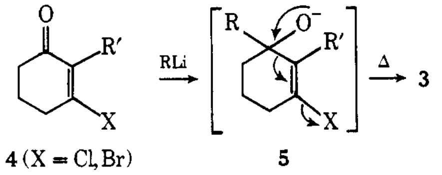
A new synthesis of acetylenic ketones has been developed. This involves addition of alkyllithium reagents to the carbonyl group of β-halo-α,β-unsaturated ketones and thermal cleavage of the intermediate alkoxides to give good yields of acetylenic ketones. This method provides a straightforward, versatile synthesis of several acetylenic ketones. An application of this method is given to the synthesis of *exo*-brevicomin (**19**), the pheromone from *Dendroctonus brevicomis.* The addition of lithium dimethylcuprates to β-halo-α,β-unsaturated ketones is shown.

In 1967 Eschenmoser[2] and Tanabe[3] and their co-workers developed a method for converting α,β-epoxy ketones to acetylenic ketones or aldehydes[4] by reaction of epoxy ketones such as **1** with tosylhydrazine to give intermediate **2** which spontaneously cleaves to the final ketone **3.** In some systems this method has the disadvantage of low yields or difficulty of preparing the starting material **1.**



$$\xrightarrow{} \mathrm{R\overset{O}{\overset{\|}{C}}(CH_2)_3C{\equiv}CR'}$$

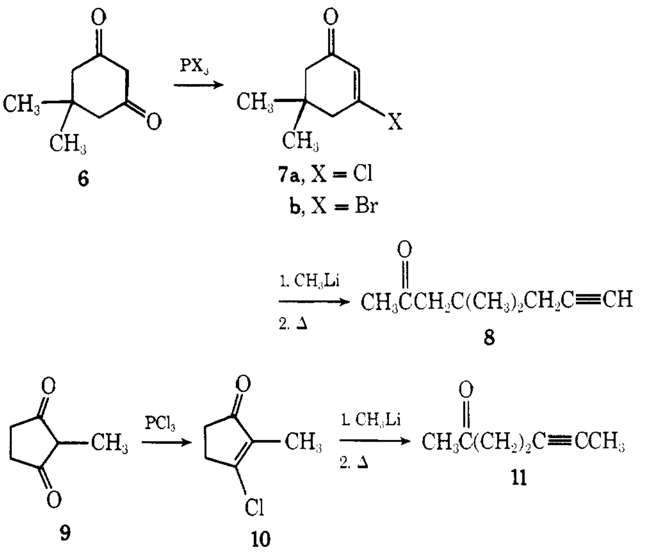
We have developed an alternate scheme for the preparation of compounds like **3.** Our method is based on the construction of an intermediate similar to **2,** i.e., an allylic alkoxide with a vinyl leaving group in the proper position to allow cleavage of the carbon–carbon bond. This scheme can be illustrated by the reaction of β-halo-α,β-unsaturated ketone **4** with an alkyllithium reagent to generate intermediate **5** which is then pyrolyzed to give acetylenic ketone **3.**



Among the variables which make this method versatile is the ability to vary each of the two R groups. Another variable is the ring size which in turn controls the number of methylene groups separating the ketone and acetylene groups in the final product. It should be noted that the cleavage reactions of intermediates **2** and **5** are examples of a very general kind of elimination–cleavage reaction, other types of which have been reviewed.[5]

Exploratory work is shown in Chart I. Dimedone was converted to the corresponding vinyl chloride **7a** and vinyl bromide **7b,** both of which were found to give good yields (70–75%) of the acetylenic ketone **8** upon reaction with methyllithium followed by pyrolysis of the intermediate alkoxide. There were some impurities in the crude pyrolysis product which we have not yet identified but it is interesting to note that similar impurities seem to be absent in other examples when the alkyllithium reagent is used in hexane solution. Chloride **7a** is the preferred reagent because it is cheaper to prepare and gives as good a yield as the bromide. Similarly, 2-methyl-1,3-cyclopentanedione (**9**) was converted to the corresponding vinyl chloride **10,** reacted with methyllithium, and the intermediate alkoxide was subjected to pyrolysis to give acetylenic ketone **11** in 32% yield.[6]

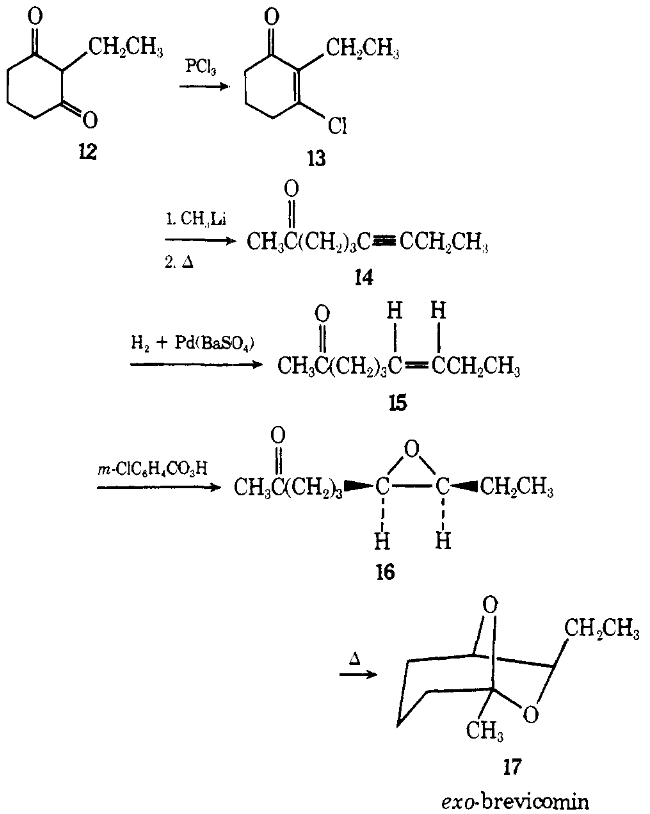
Chart I



Acetylenic ketones are useful intermediates in the synthesis of several insect pheromones as exemplified by the synthesis of brevicomin (Chart II). Preparation of the necessary diketone involved alkylation of dihydroresorcinol[7] with ethyl iodide and base to give 2-ethyl-1,3-cyclohexanedione (**12**).[8] Compound **12** was treated with phosphorus trichloride to give chloride **13,** which was allowed to react with methyllithium. The resulting alkoxide was subjected to pyrolysis to give 6-nonyn-2-one (**14**).[9] The acetylenic ketone **14** was reduced to the corresponding cis olefin **15,**[10] which was converted to epoxide **16**[10] using *m*-chloroperbenzoic acid. *exo*-Brevicomin, the pheromone from *Dendroctonus brevicomis,* was formed by simple thermolysis of epoxide **16** by the procedure of Wasserman and Barber,[10] giving a mixture of about 90% *exo*-brevicomin (**17**) and 10% *endo*-brevicomin. A sample of the *exo*-brevicomin, isolated by gas chromatography, was identical with an authentic sample.[11] Brevicomin has been synthesized by a number of methods,[9,10,12,13] including one synthesis of optically active material.[14]

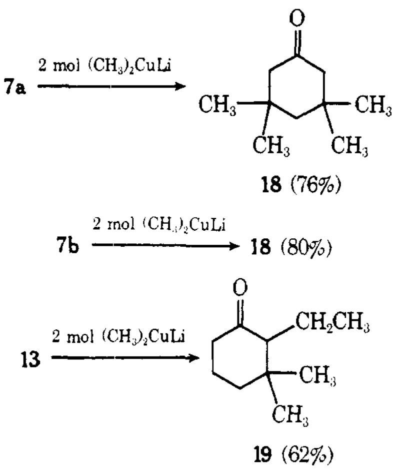
Structures involving a β-halo-α,β-unsaturated ketone are bifunctional and should be capable of adding electrophiles at the carbonyl carbon (above) or at the β position as shown by the addition of cuprates to similar compounds having β substituents such as sulfides[15] or acetoxy groups.[16] On the basis of work by House and Umen[17] and the known σ_p constants of

Chart II



halides[18] one can predict that structures such as 4 should add dialkyl cuprates and we have observed this (Chart III). On reaction with 2 mol of lithium dimethylcuprate compounds 7a and 7b give good yields of 18 and compound 13 gives 19. Since the initial report of our work,[1] there have appeared two other accounts of this type of reaction[19] showing its general usefulness.

Chart III



Experimental Section[20]

Preparation of 1,3-Diketones. Dimedone (6) was purchased from Aldrich Chemical Co. and 2-methyl-1,3-cyclopentanedione (9) was prepared according to the procedure of Schick and Lehman.[21]

2-Ethyl-1,3-cyclohexanedione (12). Compound 12 was prepared in 35% yield by the method of Schick and Lehmann[21] but a better method was the following. Dihydroresorcinol (7, 11 g, 0.1 mol) was added to a solution of 24 mL of water, 7 mL of dioxane, and 4 g (0.1 mol) of sodium hydroxide. A total of 15 g (0.1 mol) of ethyl iodide was added and the mixture was stirred at reflux for 6 h. An additional 4 g of ethyl iodide was added and heating was continued for 12 h. The solution was basified with 4 g of sodium hydroxide, cooled in ice, extracted with ether, and acidified to Congo red. The yellow solid which formed was collected and recrystallized from water (using charcoal) to give 5 g (36%) of 2-ethyl-1,3-cyclohexanedione, mp 174–176 °C (lit.[8] mp 178 °C).

Preparation of β-Halo-α,β-unsaturated Ketones. The general procedure used was that of Crossley and LeSueur[22] with minor modifications. A mixture of 0.1 mol of diketone, 0.3 mol of phosphorus tribromide or trichloride, and 500 mL of chloroform was heated at reflux with stirring for 3 h and was then cooled and poured over ice. The chloroform layer was separated and the water layer was extracted with chloroform. The chloroform solutions were combined, washed with 10% sodium bicarbonate and water, and dried and evaporated. Distillation of the residue gave the β-halo-α,β-unsaturated ketone.

3-Chloro-5,5-dimethyl-2-cyclohexen-1-one (7a). The procedure, using 56 g (0.4 mol) of dimedone (6), gave 50 g (79%) of 7a, bp 98 °C (14 mm), n^{25}D 1.5168 [lit.[23] bp 105 °C (20 mm), n^{20}D 1.4942].

3-Bromo-5,5-dimethyl-2-cyclohexen-1-one (7b). The above procedure using 14 g (0.1 mol) of dimedone (6) gave 15.5 g (76%) of 7b, bp 92–95 °C (7 mm), n^{25}D 1.4912 [lit.[22] bp 129 °C (25 mm)].

3-Chloro-2-methyl-2-cyclopenten-1-one (10). The above procedure using 22.4 g (0.2 mol) of 9 gave 9.7 g (37%) of 10, bp 67–68 °C (6 mm) [lit.[19b] bp 43 °C (1.6 mm)].

3-Chloro-2-ethyl-2-cyclohexen-1-one (13). The above procedure using 14 g (0.1 mol) of 12 gave 11.1 g (76%) of 13, bp 100 °C (15 mm), n^{25}D 1.5083.

Anal. Calcd for $C_8H_{11}ClO$: C, 60.57; H, 6.99; Cl, 22.35. Found: C, 60.18; H, 7.03; Cl, 22.18.

Reaction of β-Halo-α,β-unsaturated Ketones with Methyllithium and Pyrolysis to Give Acetylenic Ketones.[24] The general procedure for this cleavage reaction was as follows. A solution of 0.07 mol of β-substituted α,β-unsaturated ketone in 50 mL of dry ether was cooled to −20 °C under nitrogen. A total of 0.1 mol of methyllithium in ether was added slowly and the solution was stirred for 10 min. The resulting solution was then slowly introduced into a Pyrex pyrolysis tube at 200 °C under 15 mm of nitrogen pressure. The distillate was collected at −78 °C and the solvent was removed under vacuum. Distillation of the residue gave the acetylenic ketones.

4,4-Dimethyl-6-heptyn-2-one (8). By the above procedure compound 8 was formed in 70% yield from 15.8 g (0.1 mol) of chloride 7a and in 75% yield from 20.3 g (0.1 mol) of bromide 7b.[25] Compound 8 was purified by distillation, bp 80 °C (6 mm), n^{25}D 1.4408.

Anal. Calcd for $C_9H_{14}O$: C, 78.26; H, 10.14. Found: C, 78.23; H, 10.15.

5-Heptyn-2-one (11). By the above procedure, except that pyrolysis was carried out in a round-bottom flask,[6] compound 11 was formed in 32% yield from 2.6 g (0.02 mol) of chloride 10. Compound 11 was purified by distillation in a Kugelrohr, bp 60 °C (10 mm), 2,4-DNP derivative mp 121 °C [lit.[26] bp 58–60 °C (10 mm), 2,4-DNP derivative mp 122–122.5 °C].

6-Nonyn-2-one (14).[27] By the above procedure compound 14 was formed in 60% yield[25] from 11 g (0.07 mol) of chloride 13. Compound 14 was purified by distillation to give 4.2 g (44% isolated yield), bp 98 °C (6 mm), n^{25}D 1.4595 [lit.[9] bp 50–51 °C (0.5 mm)].

***cis*-6-Nonen-2-one (15).** A solution of 1.39 g (1 mmol) of 6-nonyn-2-one (14) in 10 mL of methanol containing 3 drops of quinoline was hydrogenated with 50 mg of 10% palladium on barium sulfate, at atmospheric pressure, until 1 mmol of hydrogen had been absorbed (40 min). The mixture was filtered and evaporated under vacuum and the residue was distilled in a Kugelrohr to give 1.2 g (86%) of *cis*-6-nonen-2-one (15), bp 56 °C (6 mm), having spectral properties identical with those of an authentic sample[10,11] [lit.[10] bp 92–92 °C (20 mm)].

***cis*-6,7-Epoxynonan-2-one (16).** The procedure of Wasserman and Barber was used.[10] A solution of 2 g (14.3 mmol) of 15 in 12 mL of methylene chloride was added to a stirred solution of 5.69 g (28.6 mmol) of 87% *m*-chloroperbenzoic acid in 60 mL of methylene chloride at 0 °C. The mixture was maintained at 0 °C for 3 h and was then filtered and washed with sodium bisulfite and water. The solution was dried and evaporated and the residue was distilled in a Kugelrohr to give 1.7 g (76%) of epoxide 16, bp 45–46 °C (0.1 mm), identical with an authentic sample[10,11] [lit.[10] bp 45–46 °C (0.1 mm)].

***exo*-Brevicomin (17).**[10] Pyrolysis of 100 mg (0.64 mmol) of epoxide 16 in a base-washed Pyrex tube for 48 h at 210 °C gave 90 mg of brevicomin which by gas chromatography was found to be 10% *endo*-brevicomin and 90% *exo*-brevicomin. A pure sample of *exo*-brevicomin[10,11] (shorter retention time) was collected by preparative gas chromatography on a 10% Carbowax 20M on Chromosorb column.

Lithium Dimethylcuprate Addition to β-Halo-α,β-unsaturated Ketones. The general procedure used was to add 1 equiv of the unsaturated ketone in ether to a stirred solution of 3 equiv of lithium dimethylcuprate[28] in ether at 0 °C. The mixture was stirred for 2 h at 0 °C and was then poured over ice containing 2 N hydrochloric acid (4 equiv). The product was then extracted into ether. The ether solution was dried and evaporated under vacuum, and the product was distilled.

3,3,5,5-Tetramethylcyclohexanone (18). By the above procedure compound **18** was formed in 76% yield from 16 g (0.1 mol) of chloride **7a** and in 80% yield from 20 g (0.1 mol) of bromide **8b**. Compound **18** was purified by distillation, bp 82–83 °C (9 mm), $n^{20}\text{D}$ 1.4521 [lit.[29] bp 59–61 °C (5.5 mm), $n^{20}\text{D}$ 1.4520].

2-Ethyl-3,3-dimethylcyclohexanone (19). By the above procedure compound **19** was formed in 62% yield from 4 g (0.026 mol) of chloride **13** and was purified by distillation, bp 86 °C (6 mm), $n^{25}\text{D}$ 1.4556.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.92; H, 11.69. Found: C, 78.17; H, 11.87.

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Registry No.—**7a,** 17530-69-7; **7b,** 13271-49-3; **8,** 17520-15-9; **10,** 35173-23-0; **11,** 22592-18-3; **13,** 61426-12-8; **14,** 57237-89-5; **15,** 34019-86-8; **16,** 57238-62-7; **17,** 60018-04-4; **18,** 14376-79-5; **19,** 61426-13-9.

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(24) The pyrolysis tube was a simple Pyrex tube (1 × 24 in.) with ground glass joints at each end. The tube was wound with a heating coil and was insulated. *The temperature was measured by an ordinary thermometer mounted* next to the glass tubing (under the insulation) and heating was controlled by a Variac. The tube was mounted at a slight downward angle with an addition funnel attached directly onto the pyrolysis tube at the upper end. Solution to be pyrolyzed was added by way of the addition funnel and a vacuum and nitrogen flow were maintained inside the pyrolysis tube. Products were trapped in a cold trap. We found that this type of pyrolysis tube always gave higher yields than pyrolysis from a round-bottom flask.

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Selective Reductive Cleavage of the Propargyl Oxygen Bond of Acetylenic Epoxides. A General Synthesis of 2-Ethynylcycloalkanones

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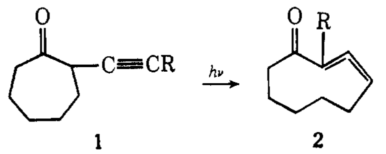
The reduction of the acetylenic epoxides **9** with lithium in liquid ammonia leads to the selective cleavage of the propargyl oxygen bond and produces a mixture of *cis*- and *trans*-2-ethynylcycloalkanols. The 2-ethynylcycloalkanols can be oxidized to 2-ethynylcycloalkanones which are useful substrates for photochemical ring expansions.

2-Alkynylcycloalkanones, e.g., **1**, on photolysis undergo a novel two-atom ring expansion to produce the interesting cyclic allenones **2**.[1,2] Although the cyclopentyl, cyclohexyl, and cycloheptyl analogues of **1** are readily prepared by reaction of acetylide anion or a substituted acetylide anion with the corresponding cycloalkene oxide and careful oxidation of the resulting alcohol,[1,2] this method fails with higher homologues because of the inertness of the cycloalkene oxides to carbon nucleophiles. Consequently, we sought a general method for the preparation of 2-ethynylcycloalkanones which would be applicable to a variety of ring sizes and which would use the readily available cyclic ketones as starting materials. Fur-



1 **2**