Reaction of Copper Enolates of Esters with Propargylic Systems. Facile Preparation of 3,4-Dienoic Esters, Stereoselective Rearrangement to (2*E*,4*Z*)- and (2*E*,4*E*)-Dienoic Esters, and Stereoselective Synthesis of a Fragrance from the Bartlett Pear

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Received August 6, 1977

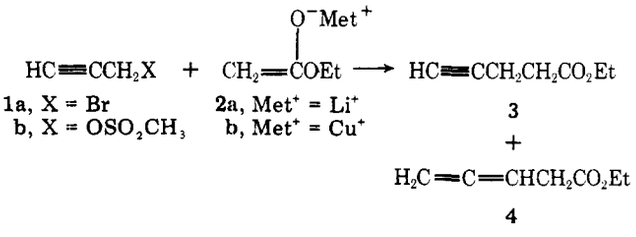
A copper enolate species derived by treatment of the lithium enolate of ethyl acetate with cuprous iodide has been found to react with propargyl bromide cleanly in an S_N2' manner to give ethyl 3,4-pentadienoate, a β-allenic ester. Under the same conditions, the lithium enolate gives only ethyl 4-pentynoate, the corresponding β-acetylenic ester, resulting from direct S_N2 displacement. The reaction of propargylic methanesulfonates having an alkyl group at the propargylic position shows the same remarkable effect of enolate counterion; with the copper enolate, higher homologues of the β-allenic esters can be synthesized efficiently. Copper can act in a catalytic fashion, as the reaction proceeds satisfactorily with only 0.2 equiv. Yields of β-allenic esters from reactions using the copper enolate derived from methyl propionate are lower. Extension of the reaction to a γ alkylation of a vinylogous copper enolate to produce a δ-allenic α,β-unsaturated ester succeeded in the case of 3,3-dimethylacrylic acid, but not with crotonic acid. When exposed to sodium ethoxide in ethanol, the β-allenic esters undergo rapid reconjugation to the 2,4-dienoates in excellent yield. The 2*E*,4*Z* isomer is the principal product upon reconjugation, and the reconjugation mixture can be equilibrated to predominantly the 2*E*,4*E* isomer by heating with thiophenol and 2,2′-azobis(isobutyronitrile). These reactions were used for the stereoselective preparation of ethyl (2*E*,4*Z*)-decadienoate, a component of the odoriferous principle of Bartlett pears.

It is well documented that the reaction of organometallic agents with propargylic electrophiles can lead to products having acetylenic as well as allenic structures (from S_N2 and S_N2' displacements, respectively).[1,2] Reaction with group 1 or 2 organometallic compounds generally produces mixtures of these products;[1] however, selective formation of allenic products is generally observed in reactions of organocopper reagents[2] and reactions catalyzed by ferric salts.[3] The reaction of propargylic electrophiles with stabilized anions such as enolates has not been reported, however.

We recently noted that in the reaction of allylic electrophiles with copper dienolates derived from the dianions of α,β-unsaturated acids, there appears to be an electronic preference for the allylic species to undergo transposition (S_N2' displacement).[4] In this report, we describe that certain propargylic bromides and methanesulfonates undergo S_N2' displacement in their reaction with copper enolates to produce exclusively β-allenic esters, while none of these products are found in reactions of the corresponding lithium enolates. Furthermore, these β-allenic esters provide convenient precursors for the selective preparation of either the 2*E*,4*Z* isomer (by base-catalyzed reconjugation) or the 2*E*,4*E* isomer of 2,4-dienoic esters (by reconjugation followed by radical-catalyzed equilibration). These reactions have been used in a stereoselective synthesis of ethyl (2*E*,4*Z*)-decadienoate, a component of the odoriferous principle of the Bartlett pear.[5]

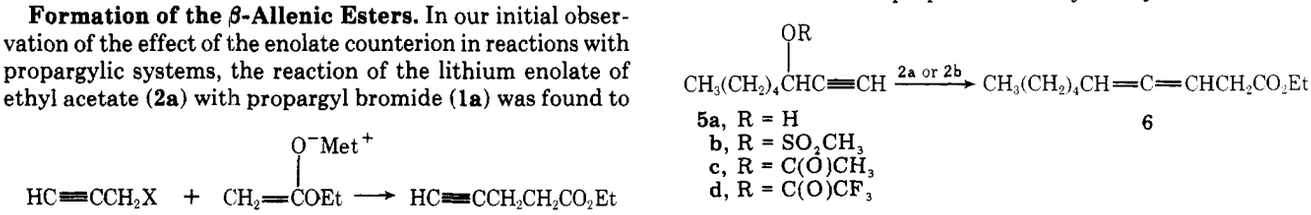
Results and Discussion

Formation of the β-Allenic Esters. In our initial observation of the effect of the enolate counterion in reactions with propargylic systems, the reaction of the lithium enolate of ethyl acetate (**2a**) with propargyl bromide (**1a**) was found to afford ethyl 4-pentynoate (**3**) (12% isolated yield); none of the allene product ethyl 3,4-pentadienoate (**4**) was produced, as indicated by both gas chromatography and infrared analysis of the crude reaction product. In contrast, reaction of propargyl bromide with the copper enolate **2b** provided only trace amounts of the acetylene product; essentially only a single volatile product characterized as the β-allenic ester **4** was formed in a 45% yield (39% isolated).



The reported use of sulfonate esters[2j,k] as leaving groups in propargylic rearrangements prompted us to prepare the methanesulfonate of propargyl alcohol (**1b**) as a substrate. Reaction of **1b** with the lithium enolate **2a** was very sluggish even when warmed to 0 °C. Small amounts of the acetylene product were formed, but the percent conversion was too low to permit a valid assessment of the yield. In contrast, the copper enolate reaction was complete within 15 min at −78 °C, affording **4** as essentially the only volatile product in a 34% yield (26% isolated). This material was identical with that obtained in the bromide reaction and only trace amounts of the acetylene were observed.

Extension of the reaction to higher homologues required the preparation of acetylenic carbinol derivatives substituted with alkyl groups in the propargylic position. These were prepared by the addition of an aldehyde to the acetylenic Grignard reagent at 0 °C. The methanesulfonate was formed in high yield with methanesulfonyl chloride in triethylamine–dichloromethane. Based on the use of propargylic acetates in reaction with organocuprates by Crabbe,[2d-h] the acetate **5c** was also prepared in 90% yield by reaction of **5a**



with acetic anhydride in pyridine. Attempted reaction of **5c** with the copper enolate **2b**, however, gave essentially no conversion of starting material, even after 16 h at room temperature. Use of a better leaving group, trifluoroacetate **5d**, gave complete consumption of starting material but afforded

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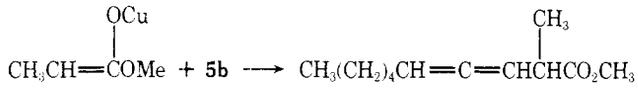
only the starting alcohol **5a,** presumably by a nucleophilic attack at the ester function.

Reaction of the copper enolate **2b** with methanesulfonate **5b** proceeds very cleanly to produce allene **6** in a 76% isolated yield. The reaction is complete within 15 min at −78 °C and affords only a single volatile product, with no evidence of the undesired acetylene product. In contrast, the lithium enolate **2a** gave poor conversion of starting material even after 1 h at 0 °C. Small amounts of allene **6** were detected, estimated at 1–2% of the volatile product; the presence of the acetylene product could not be confirmed without an authentic sample, but no peaks were present with the expected gas chromatographic retention time. Scale-up of the reaction for preparation of gram quantities of the allenes presents no difficulties. Multigram quantities of the alcohol **5a** were converted to the allene **6,** in 76% yield, without purification of the intermediate methanesulfonate. In summary, this reaction, combined with the high yield formation of the acetylenic carbinol, allows the net conversion of an aldehyde to a β-allenic ester having an alkyl chain four carbons longer. The process requires three steps and proceeds in good overall yield.

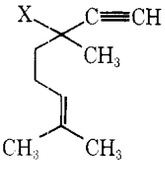
Having demonstrated the utility of the reaction for straight chain compounds, efforts were directed toward preparation of substituted derivatives. The preliminary results obtained thus far have not been encouraging. Branching at the C-2 carbon requires the use of esters other than acetates. However, reaction of the copper enolate of methyl propionate (**7**) with



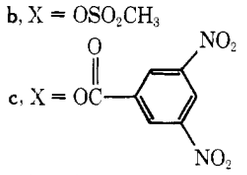
7 **8**

5b gave a disappointing yield of 13% for the corresponding allene **8.** Reaction was rapid (15 min) at −78 °C, but the crude product gave a multitude of peaks on gas chromatography and showed only a weak allene absorption in the infrared. Purification of **8** was difficult, as several unidentified products had very similar polarities.

Branching at the C-5 carbon requires the preparation of a tertiary acetylenic carbinol, conveniently made by reaction of ethynylmagnesium bromide with a ketone. Thus 6-methyl-5-hepten-2-one gives **9a** in high yield. Formation of



9a, X = OH
b, X = OSO_2CH_3

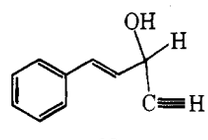


c, X = OC

d, X = Br

the methanesulfonate **9b** was unsuccessful, as the product underwent a vigorous decomposition upon attempted isolation, presumably due to its tertiary and propargylic nature. This is somewhat surprising since secondary, propargylic methansulfonates, such as **5b,** can be purified by a bulb-to-bulb distillation at reduced pressure. The 3,5-dinitrobenzoate derivative **9c** was successfully formed in 94% yield. However, reaction of this substrate with the copper enolate **2b** afforded a dark purple product having no allene peak in the infrared. Reduction of the nitro groups by the organocopper may have been responsible for the formation of the intensely colored product and the resulting failure of the reaction. Preparation of the bromide derivative **9d** using triphenylphosphine dibromide[6] was unsuccessful.

As might be anticipated from the preceding discussion, problems with electrophile stability were also encountered with the extension to unsaturated aldehydes and ketones, substrates that would provide access to triene esters. In these cases, the potential leaving group is both propargylic and allylic and is either secondary or tertiary depending on the choice of an aldehyde or a ketone. Attempted bromination of **10** using the triphenylphosphine dibromide failed to give any



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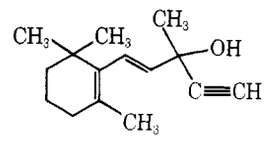
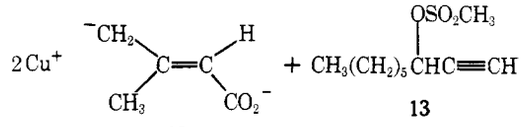


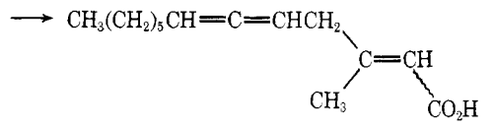
11

product that possessed an acetylene function, as indicated by both ^1H NMR and infrared spectra. Likewise, the methanesulfonate derived from **11** was too unstable for isolation, presumably undergoing facile elimination reactions.

The other access to triene esters, namely the reaction of vinylogous copper enolates with a methanesulfonate such as **5b,** has met with mixed success. The copper dianion of 3,3-dimethylacrylic acid (**12**) reacts with the methanesulfonate



12 **13**



14

13 at the γ position[4] to give allene **14,** isomeric at the α,β bond, in a 36% yield. However, reaction of **13** with the copper enolates derived from both crotonic acid and its ethyl ester failed to give the desired allene.

Mechanistic Considerations. Throughout this discussion, the reactive species has been termed a "copper enolate", but in fact the actual character of the organometallic has not been elucidated in detail. The copper species is generated by the addition of 1 equiv of cuprous iodide to the lithium enolate, preformed by the addition of the ester to lithium diisopropylamide (LDA) in tetrahydrofuran at −78 °C. The mixture is stirred for 1 h at −78 °C to ensure ample time for formation of the reactive species; at this point, it is a pale yellow heterogeneous mixture. If this material is allowed to warm to −30 °C, it becomes nearly homogeneous, but turns dark brown. Reaction of this brown species with the propargylic derivatives is not as clean as with the reagent prepared and used at −78 °C. This procedure for generating copper enolates has been modified somewhat from a literature method[7] (LDA addition to the ester in the presence of cuprous iodide at −110 °C), but it was felt the same species should be generated in each case. Despite the uncertainty as to the precise nature of the "copper enolate", it is obvious that copper is participating in the reaction, judging by the dramatic change in reaction course in going from a lithium enolate to the copper species. Some insights into the species present and the mechanism involved may be obtained from the following studies.

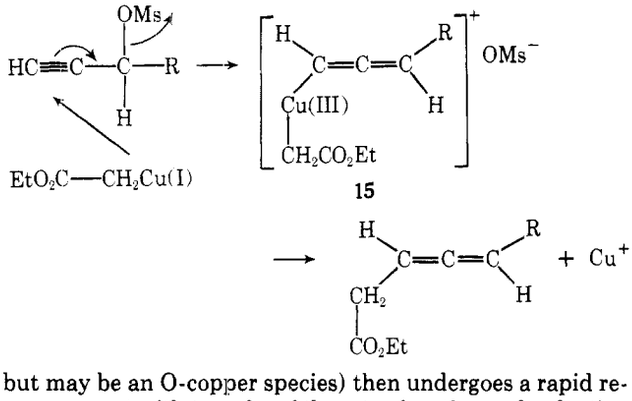
The oxidative dimerization of organocoppers using molecular oxygen is a well-recognized process,[8] and Kuwajima and Doi[7] were able to demonstrate that their copper species,

designated ethoxycarbonylmethylcopper, did in fact undergo oxidative dimerization to give diethyl succinate. Although our reactant (**2b**) was generated in a slightly different manner, introduction of molecular oxygen at −50 °C to the organocopper yielded diethyl succinate, although in lower yield (29% isolated) than that reported in the literature (73%).[7] This result would substantiate the claim that the reactive species is some type of organocopper derivative.

It was also determined that the copper can function in a catalytic role. When **5b** was reacted with the lithium enolate of ethyl acetate in the presence of 0.2, 0.5 and 1.0 equiv of cuprous iodide, the isolated yields of allene were 77, 77, and 76%, respectively. The 0.2 equiv of cuprous iodide may be approaching the lower limit, as small amounts of starting material persisted in the reaction mixture, but the reaction rate is not detectably slower (still complete within 15 min at −78 °C). This result also demands that any mechanism which proposes changes in the oxidation state of the copper must, in the end, return the metal to the Cu(I) state. It might also be mentioned that product isolation from reactions using catalytic amounts of cuprous iodide is much simpler because smaller amounts of insoluble salts remain after the reaction mixture is quenched.

The major mechanistic question which needs to be addressed is the difference in reactivity of the lithium and copper enolates. A possible explanation may be based on differences in the mode of reaction; the lithium enolates undoubtedly react via a nucleophilic attack on the substrate whereas cuprates,[9] and potentially other organocoppers, are generally thought to react by an electron transfer mechanism. Such reactions occur by an initial transfer of a single electron, followed by a coupling of the resulting radical ions.

Following the prevailing view of the involvement of copper(III) intermediates in conjugate addition and coupling reactions, we propose the following mechanism, which is analogous to one proposed by Brandsma[2j] for copper-catalyzed Grignard additions to propargylic electrophiles. The postulated copper enolate species **2b** attacks at the terminal acetylenic carbon leading to a propargylic rearrangement with loss of the methanesulfonate anion. The intermediate copper(III) species **15** (which is formulated as a C-copper enolate,



but may be an O-copper species) then undergoes a rapid rearrangement with transfer of the ester function and reduction of the copper(III) to the cuprous oxidation state, yielding the allene product.

The major departure of this mechanism from those proposed by Crabbe[2g] and Brandsma[2j] is the rapid transfer of the ester group in **15** to give the product. Both of these workers reported that in the reaction of organocopper reagents with propargylic systems, the unsubstituted allene (the hydrolysis product of the copper(III) intermediate analogous to **15**) was isolated if a protic quench was carried out at low temperatures. It is not surprising that in our case the ester group, with its greater capacity to bear negative charge, appears to undergo more rapid rearrangement to give the alkylated product.

Table I. Isomer Ratios Obtained after Reconjugation of β-Allenic Esters[a]

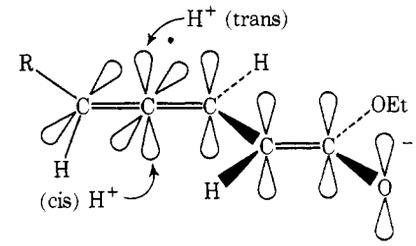
Allene	Conditions	Diene ester[b] 2Z,4Z	2Z,4E	2E,4Z	2E,4E
4	(NaOEt)			100	
6	(NaOEt)		6	63	31
6	(PhSH,AIBN)		(——16——)[c]		84

[a] Reconjugation was effected by NaOEt in EtOH; equilibration, by PhSH and AIBN subsequent to NaOEt (see text). [b] Isomer ratios determined by GLC analysis. [c] The isomers were not sufficiently well resolved to allow for an accurate determination of quantities formed. Fourth isomer (2Z,4Z) not formed in the reconjugation step is now present in small amounts.

Formation of the Diene Esters. The reconjugation of a variety of β-allenic carbonyl compounds has been studied, including ketones,[10] aldehydes,[11] amides,[12] and esters.[13] In most cases, base catalysis was used to accomplish the formation of the fully conjugated system. Table I presents the isomer ratios obtained by reconjugation of the β-allenic esters **4** and **6** with sodium ethoxide in ethanol at 0 °C. Treatment with base was at least 30 min in duration in each case, frequently longer. Variation in reaction times did not appear to substantially affect the product ratios.

$$\mathbf{6} \xrightarrow[\text{EtOH}]{\text{NaOEt}} \underset{\mathbf{16}}{CH_3(CH_2)_4CH{=}CHCH{=}CHCO_2Et}$$

As can be seen from the data, the predominant geometry at the α,β double bond in **16** after reconjugation is the expected *E* configuration. However, the unexpected *Z* geometry predominates at the γ,δ double bond, standing in a 2:1 ratio over the 4*E* geometry. Such a result can be rationalized by visualizing the enolate **17**, presumed to be the intermediate

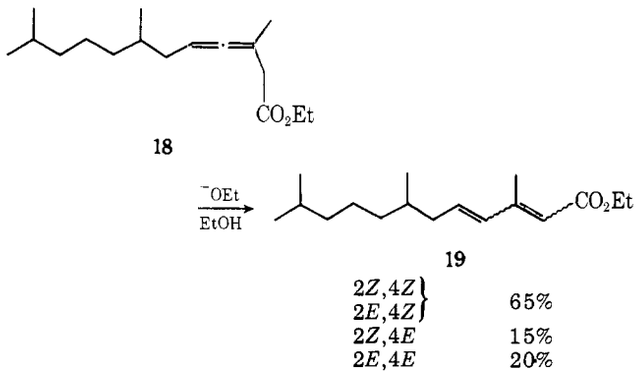


17

in the reconjugation. Approach of the proton to the digonal carbon of the allene would be expected to occur from the less hindered side (cis), attacking the π lobe opposite the bulky R group. The net result is the *Z* geometry at the γ,δ bond. The configuration of the other double bond is determined by the more stable rotamer of the α,β bond in the extended enolate. The conformation having the bulky groups trans to one another (s-trans) is more stable and affords the *E* geometry.

The formation of the 2*E*,4*Z* isomer (**16**) (the major isomer upon reconjugation) represents the synthesis of a natural product, a component of the odoriferous principle of Bartlett pears.[5] The desired isomer was separated from the 2*Z*,4*E* and 2*E*,4*E* isomers by means of preparative thin layer chromatography. Multiple developments using a low polarity solvent were required to achieve the separation.

It should be noted that Henrick and co-workers[13] observed but provided no explanation for this same propensity for 4*Z* isomer formation in their reconjugation studies on more highly substituted dienoates. In their case reconjugation of the β-allenic ester **18** gave the isomeric dienoates **19** in the ratios noted. The lowered stereoselectivity at the α,β site presumably results from the fact that the methyl substituent at C-3 makes the s-cis and s-trans conformers (about the C-2–C-3 bond of



the corresponding enolate intermediate: cf. **17**) of more comparable energy.

Equilibration of the Diene Esters. The predominance of the 2*E*,4*Z* isomer of **16** in the reconjugation of **6** and the stability of the product ratios indicate that the reconjugation is a kinetically controlled process, sodium ethoxide not being a sufficiently strong base to lead to any equilibration of the dienoates formed. Since the 2*E*,4*E* isomer is expected to be thermodynamically most stable, it should be possible to increase the proportion of this isomer by equilibration of the reconjugation mixture.

The use of catalytic amounts of thiophenol and 2,2′-azobis(isobutyronitrile) (AIBN) has been reported to give equilibration of dienoate isomers.[13,14] Presumably the isomerization occurs by a reversible addition of a benzenethiyl radical to the dienoate system. No thiol adducts were isolated, nor was there any tendency toward polymerization.[14] Thus, treatment of the reconjugation isomer mixtures of **16** with 5 mol % of thiophenol and 1 mol % of AIBN gave isomer equilibration to predominantly the *E*,*E* compound (see Table I). The 2*E*,4*E* isomer of **16** was separated in isomerically pure form by preparative thin layer chromatography.

Both the reconjugation and equilibration steps proceed in high yield, allowing an effective conversion of β-allenic esters to the dienoates. The reconjugation of allene **6** affords the diene ester isomer mixture in a 93% yield after purification by silica gel chromatography. Further equilibration of the crude reconjugation product proceeds in an 86% isolated yield (overall for the two steps).

Conclusion

The reaction of copper enolates derived from esters with propargylic electrophiles provides a convenient route to β-allenic esters. In contrast, the lithium enolates under the same conditions are either unreactive or react sluggishly to give mainly the acetylenic products. The copper enolate route to β-allenic esters parallels and complements another method for preparation of such systems, the Claisen rearrangement of propargylic orthoesters.[13,15] While our method works on easily prepared methanesulfonate derivatives, the orthoester rearrangement operates successfully on tertiary propargylic systems whose corresponding methanesulfonates are very unstable.

The rearrangement of the β-allenic esters to 2,4-dienoates is also of synthetic value, particularly with the recognition that the 2*E*,4*Z* isomer is favored under kinetic conditions and the 2*E*,4*E* isomer under equilibrating conditions. While many other methods for the preparation of dienoates are known,[16] few of these offer control over the stereochemistry of the double bond in the γ,δ position.

Experimental Section

General. Analytical thin layer chromatography was performed using 0.25 mm silica gel glass-backed plates with F-254 indicator (Merck). Visualization was by ultraviolet light, iodine, or phosphomolybdic acid. Preparative plates were from Merck or were prepared using Merck Silica Gel 60 PF-254 + 366.

Analytical gas chromatography (GLC) utilized a Hewlett-Packard 5750 instrument equipped with flame ionization detectors and using a 20 ft × 0.125 in. SE-30, 5% on Gas-Chromosorb Q, 80/100 column (to establish isomer compositions) and a 5 ft × 0.125 in. OV-17, 3% on Supelcoport, 100/120 (to follow reactions), with nitrogen (30 mL/min) as carrier gas. Determinations were made in either an isothermal mode or using programmed runs at 15 °C/min with a 2 min postinjection delay. Peak areas, where determined, were obtained by planimetry based on the average of three consecutive runs.

Proton magnetic resonance (^{1}H NMR) spectra were recorded on Varian Associates spectrometers, Models T-60, A-60, EM-390, and HR-220; chemical shifts are reported in ppm downfield from a tetramethylsilane internal standard (δ scale). The ^{1}H NMR data are presented in the form: δ value of signal (peak multiplicity, coupling constant (if any), integrated number of protons). Infrared spectra were recorded on either a Perkin-Elmer Model 137 spectrometer or a Beckman Model IR-12 instrument. Unless otherwise noted, spectra were obtained on neat compounds held between sodium chloride plates. Data are presented in cm^{-1} and only the important diagnostic bands are reported.

Mass spectra were obtained from a Varian MAT CH-5 spectrometer and were at 70 eV ionization voltage unless otherwise indicated. Data are presented in the form: *m/e* (intensity relative to base peak). Elemental analyses were provided by the microanalytical service laboratory of the University of Illinois.

Chemicals were obtained from the following sources: Aldrich Chemical Co.: hexanal, β-ionone, benzophenone, tetrahydrofuran, triethylamine, diisopropylamine, propargyl alcohol, propargyl bromide, thiophenol, methyl propionate, 3,3-dimethylacrylic acid, crotonic acid, methanesulfonyl chloride, trifluoroacetic anhydride, 2,2′-azobis(isobutyronitrile). Fisher Scientific Co.: cuprous iodide, dichloromethane. J. T. Baker Chemical Co.: ethyl bromide. Fluka: 6-methyl-5-hepten-2-one. Linde: acetylene. Mallinckrodt: ethyl acetate, diethyl ether, acetic anhydride, magnesium metal. Ventron: *n*-butyllithium.

The acetylene gas was passed through an alumina scrubbing tower, a dry ice–acetone trap, concentrated sulfuric acid, and finally a tube containing sodium carbonate. Tetrahydrofuran was distilled from sodium–benzophenone by use of a recirculating still, maintaining a deep blue coloration at all times. Diisopropylamine and triethylamine were refluxed over calcium hydride and then distilled to ensure dryness. Ethyl acetate was dried by distillation from phosphorus pentoxide. The hexanal was distilled from anhydrous sodium sulfate, discarding the initial forerun.

The organolithium reagent was titrated periodically to determine the organic base present, using either the double titration method[17] or the single titration method[18] with 1,10-phenanthroline as an indicator. All values used were the average of at least three separate determinations.

Glassware for all reactions involving moisture-sensitive compounds was dried for a minimum of 2 h at 120 °C. Such reactions were run under a positive pressure nitrogen atmosphere, predried by use of a Drierite drying tower. Transfers involving moisture- or air-sensitive liquids were performed using hypodermic syringes, added via rubber septa on the side arm of the reaction flask.

Reaction products were dried over anhydrous magnesium sulfate unless otherwise stated. All yields reported are isolated products after purification unless indicated otherwise. Silica gel chromatography was performed using 0.05–0.2 mm silica gel with weight ratios usually in the range 30:1 to 50:1 silica gel/crude product. Close separations required ratios as high as 200:1. Elution solvent mixtures are given as volume percentages.

1-Octyn-3-ol (5a). Magnesium metal turnings, 2.67 g (0.11 mol), were added to a hot, dry three-necked flask equipped with addition funnel and reflux condensor. The entire system was flushed with dry nitrogen, and 50 mL of dry tetrahydrofuran was added. A solution of 11.99 g (0.11 mol) of ethyl bromide in 5 mL of solvent was added over a 1-h period, while the temperature was maintained at 25–30 °C by means of a water bath. The dark mixture was stirred for 1 h following the addition to ensure complete formation of the ethylmagnesium bromide. A small amount of magnesium metal remained.

A second flask, equipped with a side arm and addition funnel, was filled with 50 mL of dry tetrahydrofuran and purified acetylene was bubbled through for 5 min. The above Grignard solution was then transferred slowly through Teflon tubing under nitrogen pressure. The addition required 45 min and the temperature was held at 15–20 °C. A constant stream of acetylene was maintained during the addition and for 5 min afterwards.

After cooling to 0 °C, the hexanal, 10.02 g (0.1 mol), in 5 mL of solvent was added dropwise. The cooling produced some precipitate, presumably the Grignard reagent, but it did not interfere with the reaction. Following the addition, the mixture was stirred 30 min at 0 °C and a similar length of time at room temperature. The reaction was quenched with saturated ammonium chloride (with cooling), the solvent was removed under reduced pressure, and the product was extracted with ether and dried. Silica gel chromatography (20% ether/hexane) gave 10.71 g (85%) of pure product: ^{1}H NMR (CCl_4) δ 4.10–4.40 (m, 1 H), 2.92 (broad s, 1 H, D_2O exchangeable), 2.30 (d, J = 2 Hz, 1 H), 1.15–1.85 (m, 8 H), and 0.70–1.15 (m, 2 H); IR 3360 (OH), 3310 (C≡CH), and 2120 (C≡C) cm^{-1}; mass spectrum (10 eV) m/e (rel intensity) 125 (0.8), 111 (1.3), 97 (13), 93 (27), 83 (32), 79 (35), and 43 (100). Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.35; H, 11.20.

Methanesulfonate of 1-Octyn-3-ol (5b). Acetylenic carbinol **5a,** 5.05 g (40 mmol), was added to 50 mL of dichloromethane, followed by 6.07 g (60 mmol) of triethylamine. After cooling to 0 °C, 5.73 g (50 mmol) of methanesulfonyl chloride was added dropwise. The resulting yellow reaction mixture was stirred at 0 °C for 3 h. A white precipitate formed soon after the addition was complete. After dilution with ether, the mixture was washed with half-saturated brine containing 20 mL of 3 N hydrochloric acid and with saturated sodium bicarbonate. The product was dried and chromatographed on silica gel (25% ether/hexane) to give 7.63 g (93%) of product: ^{1}H NMR (CCl_4) δ 5.03 (dt, J = 2, 6 Hz, 1 H), 3.01 (s, 3 H), 2.67 (d, J = 2 Hz, 1 H), 1.75–2.20 (m, 2 H), 1.20–1.75 (m, 6 H), and 0.75–1.20 (m, 3 H). Anal. Calcd for $C_9H_{16}O_3S$: C, 52.92; H, 7.89; S, 15.70. Found: C, 53.05; H, 8.10; S, 15.92.

The homologous methanesulfonate **13** was prepared in an analogous fashion starting from heptanal.

Methanesulfonate of Propargyl Alcohol (1b). The above precedure was followed using 3.36 g (60 mmol) of propargyl alcohol, 7.56 g (66 mmol) of methanesulfonyl chloride, and 7.08 g (70 mmol) of triethylamine. Purification by silica gel chromatography (50% ether/hexane) afforded 6.98 g (87%) of product: ^{1}H NMR (CCl_4) δ 4.80 (d, J = 2 Hz, 2 H), 3.10 (s, 3 H), and 2.70 (t, J = 2 Hz, 1 H). Anal. Calcd for $C_4H_6O_3S$: C, 35.81; H, 4.51; S, 23.90. Found: C, 35.86; H, 4.55; S, 24.06.

Ethyl 3,4-Decadienoate (6). Diisopropylamine, 0.51 g (5 mmol), was added to 20 mL of dry tetrahydrofuran and cooled to −10 °C. n-Butyllithium, 2.13 mL of a 2.35 M solution (5 mmol), was then added. After stirring 10 min at −10 °C, the mixture was cooled to −78 °C and 0.44 g (5 mmol) of ethyl acetate in 3 mL of solvent was added. Stirring was continued for 30 min at −78 °C to ensure complete formation of the enolate. Cuprous iodide, 0.95 g (5 mmol), was added and stirred for 1 h at −78 °C. The mixture never became homogeneous but did assume a pale yellow-tan coloration. Methanesulfonate **5b,** 1.02 g (5 mmol), in 2 mL of solvent was added dropwise at −78 °C. The mixture turned green during the addition but reverted to the yellow-tan color after the addition was complete. TLC indicated the reaction was complete within 15 min at −78 °C. Saturated ammonium chloride was used to quench the reaction, and the solvent was removed under reduced pressure. The product was extracted with ether and dried. Silica gel chromatography (5% ether/hexane) gave 0.74 g (76%) of product: ^{1}H NMR (CCl_4) δ 4.90–5.30 (m, 2 H), 4.07 (q, J = 7 Hz, 2 H), 2.89 (dd, J = 6, 3 Hz, 2 H), 1.75–2.20 (m, 2 H), 1.10–1.75 (m, 6 H), 1.24 (t, J = 7 Hz, 3 H), and 0.70–1.10 (m, 3 H); IR 1970 (C=C=C), 1745 (C=O), and 1170 (C–O) cm^{-1}; mass spectrum m/e (rel intensity) 196 (M$^+$, 9.7), 167 (6), 151 (5), 140 (16), 139 (10), 123 (3), 112 (23), 111 (20), 108 (13), 98 (11), 93 (12), 83 (53), and 67 (100). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.34; H, 10.20.

Reactions run using a catalytic amount of cuprous iodide were conducted in the same manner, with 0.2 and 0.5 equiv of cuprous iodide both giving 77% isolated yields. A larger scale reaction using 5.11 g (25 mmol) of methanesulfonate **5b** (used without purification) and comparable amounts of all other reagents gave a 76% isolated yield. Reactions run with the lithium enolate were conducted in a similar manner, omitting the use of cuprous iodide. Warming to 0 °C was required to observe reaction with these enolates and even then reaction was slow and gave several products.

Ethyl 2,4-Pentadienoate (4). The above procedure was followed using 1.34 g (10 mmol) of methanesulfonate **1b** and the corresponding amounts of all other reagents. GLC yield of the product (internal standard) was 34% and silica gel chromatography (10% ether/hexane) gave 323 mg (26%) of product. Only trace amounts of the acetylene product **3** were evident in the GLC trace: ^{1}H NMR (CCl_4) δ 5.20 (p, J = 7 Hz, 1 H), 4.69 (td, J = 3, 7 Hz, 2 H), 4.07 (q, J = 7 Hz, 2 H), 2.94 (td, J = 3, 7 Hz, 2 H), and 1.23 (t, J = 7 Hz, 3 H); IR 1960 (C=C=C), 1745 (C=O), and 1165 (C–O) cm^{-1}; mass spectrum (10 eV) m/e (rel intensity) 126 (M$^+$, 1.18), 125 (1), 124 (3), 98 (100), 81 (18), 70 (62), 55 (15), and 53 (50). Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.85; H, 8.01.

Reaction under similar conditions with propargyl bromide **1a** gave a GLC yield of 45% for **4,** with 488 mg (39%) isolated after purification by silica gel chromatography. Again only trace amounts of the acetylenic product **3** were detected in the GLC trace.

Methyl 3-Methyl-2,5,6-tridecatrienoate (Methyl Ester of 14). The above procedure was followed using 2 equiv of lithium diisopropylamide and cuprous iodide for each equivalent of 3,3-dimethylacrylic acid and methanesulfonate **13.** The mixture was stirred for 3 h at −78 °C before quenching with saturated ammonium chloride. The solvent was removed, followed by acidification of the aqueous layer with 3 N hydrochloric acid and extraction with ether. After drying the product, silica gel chromatography (1% HOAc/15% ether/84% hexane) gave 160 mg (36%) of a viscous yellow oil.

The above product was esterified by the addition of 138 mg of the acid to 10 mL of HMPA, followed by 1 mL of 20% sodium hydroxide. After stirring 1 h, 0.75 mL of methyl iodide was added and the mixture was stirred 16 h at room temperature. The product was poured into dilute hydrochloric acid and then extracted with ether, washing the extracts with brine to remove the HMPA. After drying, the product was purified by silica gel chromatography (5% ether/hexane): ^{1}H NMR (CCl_4) δ 5.50–5.65 (m, 1 H), 4.80–5.15 (m, 2 H), 3.60 (s, 3 H), 3.15–3.30 and 2.60–2.80 (m, 2 H, E and Z isomers), 2.12 and 1.85 (d, J = 1.5 Hz, 3 H, E and Z isomers), 1.75–2.10 (m, 2 H), 1.10–1.60 (m, 8 H), and 0.70–1.10 (m, 3 H); IR 1960 (C=C=C), 1720 (C=O) and 1645 (C=C) cm^{-1}; mass spectrum m/e (rel intensity) 236 (M$^+$, 10.9), 221 (4), 205 (6), 177 (34), 166 (15), 165 (25), 152 (41), 151 (28), 138 (21), 137 (10), and 93 (100). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 75.94; H, 10.00.

Ethyl 4-Pentynoate (3). Diisopropylamine, 1.52 g (15 mmol), was added to 30 mL of dry tetrahydrofuran and cooled to −10 °C. n-Butyllithium, 6.09 mL of a 2.46 M solution (15 mmol), was then added, and after stirring for 10 min, the mixture was cooled to −78 °C. Ethyl acetate, 1.32 g (15 mmol), was then added dropwise to form the enolate. After 30 min at −78 °C, 1.78 g (15 mmol) of propargyl bromide was added dropwise. Following 1 h at −78 °C, the mixture was warmed to 0 °C for 2 h. The yellow solution was quenched with saturated ammonium chloride, the solvent was removed under reduced pressure, and the product was extracted with ether and dried. Silica gel chromatographic separation (10% ether/hexane) of the most mobile component afforded 0.22 g (12%) of product. GLC and infrared analysis showed no evidence of allene **4;** ^{1}H NMR (CCl_4) δ 4.09 (q, J = 7 Hz, 2 H), 2.45 (d, J = 2 Hz, 4 H), 1.80–1.90 (m, 1 H), and 1.24 (t, J = 7 Hz, 3 H); IR 3300 (HC≡C), 2120 (C≡C), 1740 (C=O), and 1175 (C–O) cm^{-1}; mass spectrum m/e (rel intensity) 126 (M$^+$, 4.5), 98 (75), 97 (18), 81 (87), 70 (39), and 53 (100). Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.47; H, 7.96.

The use of methanesulfonate **1b** in this reaction led to a very slow consumption of starting material, even at 0 °C, and gave a mixture of products of which starting material was the major component. Both the acetylene (**3**) and the allene (**4**) products appeared to be present in this case, but no attempt was made to determine yields as the percent conversion of the methanesulfonate was very low.

Ethyl 2,4-Decadienoate (16). Allene **6,** 1.50 g (7.64 mmol), was added to 40 mL of absolute ethanol and cooled to 0 °C. Sodium ethoxide solution, 2.29 mL of a 1 M solution in ethanol (2.29 mmol), was added to give a brownish-yellow solution. After stirring for 30–40 min at 0 °C, the mixture was quenched with 3 N hydrochloric acid by adding the acid until the color faded to a pale yellow. The ethanol was removed under reduced pressure, and the product was extracted and dried. GLC analysis of the product indicated an isomer ratio of 6:63:31 for the 2Z,4E/2E,4Z/2E,4E isomers of **16,** respectively, in order of elution of the products.

This mixture was equilibrated by the addition of 42 mg (0.38 mmol) of thiophenol and 13 mg (0.076 mmol) of 2,2′-azobis(isobutyronitrile) to the above crude product. No solvent was used, and the mixture was heated at 80 °C for 2 h under a nitrogen atmosphere. After cooling, the product was diluted with ether, washed with 3 N sodium hydroxide, and then dried. Silica gel chromatography (5% ether/hexane) gave 1.29 g (86%) of purified isomer mixture. GLC analysis now showed the 2E,4E isomer constituted 84% of the mixture, with the other three isomers contained in the remaining 16%. These isomers were not sufficiently well resolved on GLC analysis to allow determination of their relative quantities.

The 2E,4Z and 2E,4E isomers were separated from the reconjugation and equilibration products respectively by means of preparative TLC. Eight developments using 3% ether/97% hexane were required to achieve a separation, taking in each case only a portion of

the band to ensure purity. Each plate was spotted with 40 mg of product and a total of 34 mg of 2*E*,4*Z* and 26 mg of 2*E*,4*E* was obtained. A silver nitrate (20% by weight) coated silica gel column failed to produce any separation of the isomers. 2*E*,4*Z* isomer: ^{1}H NMR (CCl_4) δ 7.43 (dd, J = 10, 15 Hz, 1 H), 6.03 (t, J = 10 Hz, 1 H), 5.55–5.95 (m, 1 H), 5.71 (d, J = 15 Hz, 1 H), 4.12 (q, J = 7 Hz, 2 H), 2.15–2.50 (m, 2H), 1.10–1.70 (m, 6 H), 1.24 (t, J = 7 Hz, 3 H), and 0.75–1.10 (m, 3 H). 2*E*,4*E* isomer: ^{1}H NMR (CCl_4) δ 7.10 (ddd, J = 15, 6, 3 Hz, 1 H), 5.95–6.20 (m, 2 H), 5.62 (d, J = 15 Hz, 1 H), 4.09 (q, J = 7 Hz, 2 H), 1.95–2.30 (m, 2 H), 1.10–1.65 (m, 6 H), 1.24 (t, J = 7 Hz, 3 H), and 0.70–1.10 (m, 3 H).

Ethyl (*E*)-2,4-Pentadienoate. Reconjugation of allene 4 under the same conditions as described above gave essentially a single product as indicated by GLC analysis. Although TLC did give a very faint indication of a higher R_f spot, no other product could be isolated. The reduced yield (50%) resulted from the volatility of the product: ^{1}H NMR (CCl_4) δ 7.14 (dd, J = 15, 11 Hz, 1 H), 6.39 (dt, J = 17, 10 Hz, 1 H), 5.10–5.95 (m, 3 H), 4.10 (q, J = 7 Hz, 2 H), and 1.27 (t, J = 7 Hz, 3 H); IR 1720 (C=O), 1647, 1605, 1010, and 925 (C=C) cm^{-1}; mass spectrum *m/e* (rel intensity) 126 (M^+, 17), 111 (2), 98 (20), 97 (12), 81 (100), 70 (8), 53 (58), and 43 (10). Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.77; H, 8.05.

Acknowledgments. Support for this research through grants from the National Institutes of Health (PHS GM 17061) and the National Science Foundation (NSF MPS 73-08691 and 76-10037) is gratefully acknowledged. J.A.K. is a Camille and Henry Dreyfus Teacher-Scholar and R.A.A. was supported by fellowships from the University of Illinois, Procter and Gamble, Eli Lilly, and Johnson and Johnson.

Registry No.—**1a,** 106-96-7; **1b,** 16156-58-4; **2a,** 56579-97-6; **2b,** 64706-02-1; **3,** 63093-41-4; **4,** 30332-99-1; **5a,** 818-72-4; **5b,** 64706-03-2; **6,** 36186-28-4; **12,** 64714-94-9; **13,** 64706-04-3; *E*-14 Methyl ester, 64706-05-4; *Z*-14 Methyl ester, 64706-06-5; (2*E*,4*Z*)-**16,** 3025-30-7; (2*E*,4*E*)-**16,** 7328-34-9; (2*Z*,4*E*)-**16,** 3025-31-8; ethyl bromide, 74-96-4; hexanal, 66-25-1; methanesulfonyl chloride, 124-63-0; propargyl alcohol, 107-19-7; ethyl (*E*)-2,4-pentadienoate, 13369-23-8.

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An Efficient Synthesis of γ-Methylene-γ-butyrolactone (α′-Angelicalactone). Application to the Synthesis of Deoxyobtusilactone and Deoxyisoobtusilactone

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Received August 16, 1977

The mercury(II)-catalyzed cyclization of 4-pentynoic acid proceeds efficiently to give γ-methylene-γ-butyrolactone (α′-angelicalactone). The enolate of this lactone reacts with 11-dodecenal producing separable diastereomeric β-hydroxylactones. The corresponding methanesulfonate derivatives undergo partially selective elimination to afford deoxyobtusilactone and deoxyisoobtusilactone.

Introduction

γ-Methylene-γ-butyrolactone or α′-angelicalactone (**1**) forms the basic ring structure of two newly described classes of natural products, the obtusilactones (**2a–f**)[1] and the fimbrolides (**3**).[2,3] Obtusilactone (**2a**) was the first-discovered member of a series of cytotoxic natural products (**2b–f**) isolated from the plant *Lindera obtusiloba* by Yamamura and co-workers.[1] The fimbrolides are marine natural products with antimicrobial (including antifungal) activity that have been isolated from the red alga *Delisea fimbriata* by Wells[2] and Sims.[3] Because of the demonstrated biological activity of these compounds, the synthesis of γ-methylene-γ-butyrolactones is of interest. In this report, we describe a method for the facile synthesis of γ-methylene-γ-butyrolactone and the application of this method to the preparation of the deoxy analogs of obtusilactone (**2a**) and isoobtusilactone (**2b**).

0022-3263/78/1943-0560$01.00/0