spectrometers and accessories.

Registry No. 1, 73368-16-8; 2, 73368-17-9; 3, 22527-23-7; 5, 73368-18-0; farnesane, 3891-98-3; 4-phenyl-1,2,4-triazoline-3,5-dione, 4233-33-4.

Conversion of Methyl Ketones into Terminal Acetylenes and (*E*)-Trisubstituted Olefins of Terpenoid Origin

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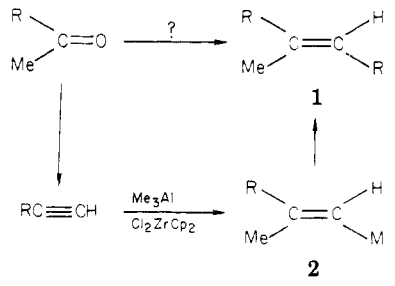
Received December 5, 1979

Carbonyl olefination reactions, such as the Wittig reaction, represent one of the most commonly used methods for the synthesis of olefins. Although the stereoselectivity of the conversion of aldehydes into olefins can be ≥95%, that of the ketone-to-olefin conversion has usually been disappointingly low[2] and hence represents an important synthetic problem to be solved. Although it appears difficult to provide a direct and generally applicable solution to this problem, there can be an indirect solution at least in a very important case of converting methyl ketones into methyl-substituted trisubstituted olefins (**1**) including various terpenes. Since we have recently developed a highly stereo- and regioselective Zr-catalyzed carbometallation procedure for converting terminal acetylenes into (*E*)-2-methyl-1-alkenylmetals (**2**)[3] as well as various reactions for converting **2** into trisubstituted olefins **1**,[4] we hoped to develop a convenient and widely applicable carbonyl olefination sequence such as that represented by Scheme I. As the isolation of **2** is not usually required, such a sequence would amount to a two-step but highly stereoselective alternative to conventional carbonyl olefination reactions.

In order to demonstrate the practicality of such a procedure, we decided to synthesize monocyclofarnesol (**3**)[5] from β-ionone (**4**) (see Scheme II). Unfortunately, however, our attempts to convert dihydro-β-ionone (**5**), obtained in quantitative yield by reducing **4** with $LiAlH_4$ and CuI,[6] into the required intermediate **6** by various known procedures[7] were disappointing. Even the best of those examined, which was developed by Craig and Moyle,[7f] yielded **6** only in <50% yield, which was contaminated with at least two isomeric products.

Clean conversion of **5** into **6** via enol derivatives would result if the "kinetic" enol phosphate **7** forms cleanly and β eliminates regioselectively. We have therefore tested several highly basic and sterically hindered amide bases

Scheme I



M = $AlMe_2$ and/or $ZrCp_2Cl$

Scheme II

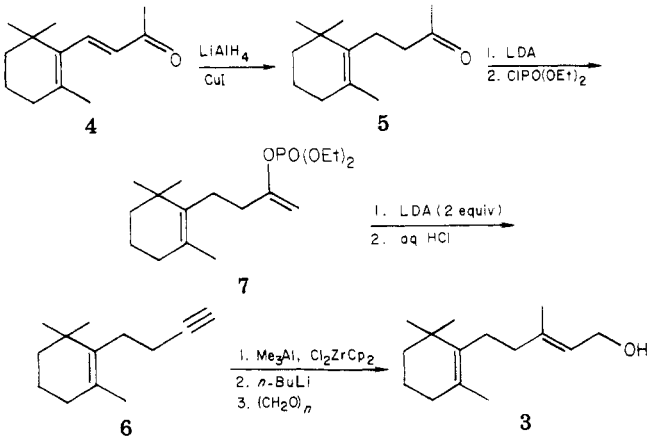


Table I. Conversion of Methyl Ketones into Terminal Acetylenes via Enol Phosphates

ketone	base	yield of acetylene, % GLC	yield of acetylene, % isolated
β-ionone (4)	LDA	95	85
dihydro-β-ionone (5)	LDA	90	85
acetophenone	LDA	85	80
pinacolone	LDA	90	78
cyclohexyl methyl ketone	LDA	85	80
2-octanone	LDA	23	
2-octanone	LTMP	75	
6-methyl-5-hepten-2-one	LDA	25	
6-methyl-5-hepten-2-one	LTMP	75	61

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(2) For reviews of various methods for the synthesis of olefins including carbonyl olefination reactions, see (a) D. J. Faulkner, *Synthesis*, 175 (1971); (b) J. Reucroft and P. G. Sammes, *Q. Rev., Chem. Soc.*, **25**, 135 (1971).

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(5) S. Kanno, T. Kato, and Y. Kitahara, *Chem. Commun.*, 1257 (1967).

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(7) We note that essentially all of the highly successful examples of the methyl ketone-to-acetylene conversion reported previously involve those methyl ketones which do not contain α-methylene or α-methine hydrogens. In cases where methyl ketones contain α-methylene or α-methine hydrogens, the yields of the desired acetylenes are either low or unspecified, frequent major products being isomeric allenes. Various reagent combinations for the conversion of methyl ketones into terminal acetylenes that we have tested include the following: (a) PCl_5 in benzene, then $NaNH_2$ in NH_3 [R. S. Sweet and C. S. Marvel, *J. Am. Chem. Soc.*, **54**, 1184 (1932)]; (b) PCl_5 and 2,6-lutidine, then $NaNH_2$ in NH_3 [E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, *J. Am. Chem. Soc.*, **89**, 4245 (1967)]; (c) $POCl_3$ in DMF, then NaOH [M. Rosenblum, N. Brawn, J. Papenmeier, and M. Applebaum, *J. Organomet. Chem.*, **6**, 173 (1966)]; (d) $(CF_3SO_2)_2O$, CCl_4, pyridine, then heat [R. J. Hargrove and P. J. Stang, *J. Org. Chem.*, **39**, 581 (1974)]; (e) NH_2NH_2 in Et_3N, and I_2 and Et_3N in THF, and finally methanolic KOH [A. M. Krubiner, N. Gottfried, and E. P. Oliveto, *J. Org. Chem.*, **34**, 3502 (1969)]; (f) NaOEt, then $ClPO(OEt)_2$, and finally $NaNH_2$ in NH_3 [J. C. Craig and M. Moyle, *J. Chem. Soc.*, 3713 (1963)].

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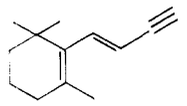
and found that sequential but "one-pot" treatment of **5** with 1.05 equiv of LDA (−78 °C), 1.1 equiv of diethyl chlorophosphate (−78 to 25 °C), and 2.25 equiv of LDA (−78 °C) followed by acidification (3 N HCl) and the usual workup produces **6** in 85% isolated yield (90% by GLC). No difficulty was encountered in applying our recent procedure[4b] for converting terminal acetylenes into (*E*)-3-methyl-2-alken-1-ols via carboalumination to the conversion of **6** into monocyclofarnesol (**3**) (71% isolated yield), which was ≥98% *E* by GLC as well as by ^{1}H and ^{13}C NMR spectroscopy.

β-Ionone itself was also cleanly converted into the corresponding terminal acetylene **8** in 85% isolated yield. As



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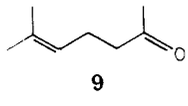

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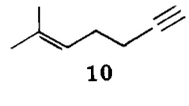

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might be expected, this procedure was quite satisfactory in a few other simpler cases where no isomer formation was possible (Table I).

Our expectation that the procedure might be very general with respect to the R groups of methyl ketones was shattered, however, when it was applied to 2-octanone and 6-methyl-5-hepten-2-one (**9**), both of which gave the desired acetylenes in only 20–25% yields. Since both ketones are cleanly and regioselectively converted into the corresponding enol phosphates as judged by ^{1}H NMR, the difficulty must lie in the β-elimination step. Although we did not clarify the exact course of this step, GLC, NMR, and IR examination of each of these reaction mixtures indicate the formation of an allenic byproduct in a significant amount. Since the difference between the case of **9** and those of **4** and **5** was thought to be largely steric, we tested lithium tetramethylpiperidide,[8] a di-*tert*-alkylamide which presumably is sterically more demanding than LDA, a di-*sec*-alkylamide. We indeed observed that both of these ketones were converted cleanly and in high yields into the corresponding terminal acetylenes (Table I). The enyne **10** has previously been converted into stereochemically pure geraniol.[4b]

Although it may seem somewhat surprising, we believe that the presently reported method provides, for the first time, a reasonably general and highly selective procedure for converting methyl ketones into the corresponding terminal acetylenes,[7] thereby making the "two-pot" but highly stereoselective carbonyl olefination sequence shown in Scheme I a viable synthetic operation, potentially applicable to the synthesis of various terpenes.

Experimental Section

All reactions were carried out under a nitrogen atmosphere. All commercial reagents except THF were used without purification; THF was purified by distillation from $LiAlH_4$.

4-(2,6,6-Trimethyl-1-cyclohexyl)-2-butanone (5). The following procedure is based on that reported by Ashby, Lin, and Kovar.[6] To cuprous iodide (38.1 g, 200 mmol) placed in a three-necked flask were added 400 mL of dry THF and a THF solution of $LiAlH_4$ (1.35 M, 37 mL, 50 mmol) at 0 °C. A dark brown suspension was obtained within 15 min at 0 °C. To this was added dropwise β-ionone (9.62 g, 10.3 mL, 50 mmol) at 0 °C. After the reaction mixture was stirred for 3 h at 0 °C, ca. 10 mL of water was added to destroy the residual hydride. The organic compounds were thoroughly extracted with *n*-hexane, and the extract was washed with aqueous $NaHCO_3$, aqueous $Na_2S_2O_3$, and then water, dried over $MgSO_4$, and distilled to produce 8.05 g (83%) of **5**: bp 60–64 °C (0.2 mmHg); n^{26}_D1.4804 (lit.[9] n^{20}_D1.4819); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.98 (s, 6 H), 1.57 (s, 3 H), and 2.12 (s, 3 H). In a separate small-scale run, a quenched aliquot of the reaction mixture was analyzed by GLC, which indicated the formation of **5** in ca. 100% yield as an essentially single product.

1-(3-Butynyl)-2,6,6-trimethyl-1-cyclohexene (6). The following is representative of the LDA procedure for the conversion of methyl ketones into terminal acetylenes. To a solution of LDA prepared at 0 °C from diisopropylamine (10.6 g, 105 mmol) and *n*-butyllithium in hexane (2.3 M, 45.6 mL, 105 mmol) in 200 mL of dry THF is added dropwise dihydro-β-ionone (**5**) (19.4 g, 100 mmol) in 20 mL of THF at −78 °C. After the solution was stirred for 1 h, diethyl chlorophosphate (19.0 g, 15.9 mL, 110 mmol) was added at this temperature. After the reaction mixture was gradually warmed to room temperature, it was added dropwise to a solution of LDA in THF (225 mmol) prepared at −78 °C as described above. The resultant mixture was warmed to room temperature over 3 h and quenched with water. The organic compounds were extracted with pentane, washed with 1 N HCl, water, and aqueous $NaHCO_3$, dried over $MgSO_4$, and distilled to give 15.0 g (85%) of **6**: bp 69–71 °C (1.8 mmHg); n^{27}_D1.4833; ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.00 (s, 6 H), 1.15–2.35 (m with peaks at 1.28, 1.64, 1.95, and 2.27, 14 H); IR (neat) 3310 (s), 2110 (w) cm^{-1}.

1-(*trans*-1-Buten-3-ynyl)-2,6,6-trimethyl-1-cyclohexene (8), Phenylethyne, 3,3-Dimethyl-1-butyne, and Cyclohexylethyne. These compounds were prepared in a manner similar to that described above for the preparation of **6**. Their yields are indicated in Table I, and their identification was established by GLC co-injection with authentic samples except for **8** which exhibited the following physical properties: n^{24}_D 1.5130; ^{1}H NMR (CCl_4, Me_4Si) δ 1.01 (s, 6 H), 1.22–1.83 (m, 7 H), 1.83–2.26 (m, 2 H), 2.76 (d, J = 2 Hz, 1 H), 5.32 (dd, J = 17 and 2 Hz, 1 H), 6.56 (d, J = 17 Hz, 1 H); IR (neat) 3220 (s), 2080 (m), 954 (s), 785 (s), 761 (s) cm^{-1}; high-resolution mass spectrum, calcd for $C_{13}H_{18}$ 174.141, found 174.142.

1-Octyne and 2-Methyl-2-hepten-6-yne[10] (10). These terminal acetylenes were prepared from 2-octanone and 6-methyl-5-hepten-2-one (**9**), respectively, in a manner similar to that described above for the preparation of **6**, except that lithium 2,2,6,6-tetramethylpiperidide (LTMP) was used as a base in place of LDA. 1-Octyne and **10** obtained in this manner were contaminated with a minor amount of *n*-octane present in the *n*-butyllithium solution. *n*-Octane was removed by column chromatography. LTMP was prepared by treating 2,2,6,6-tetramethylpiperidine with 1 equiv of *n*-butyllithium at 0 °C. LDA can be used in the formation of lithium enolates. It is necessary, however, to evaporate diisopropylamine at ca. 50 °C (0.5 mmHg) prior to treatment of the enol phosphates with LTMP. When this evaporation was omitted, the terminal acetylene product in each case was contaminated with a few minor unidentified byproducts with longer retention times (SE-30). These terminal acetylenes were identified by GLC co-injection with authentic samples.

5-(2,6,6-Trimethyl-1-cyclohexenyl)-3-methyl-2-penten-1-ol (3). This procedure is based on that reported by us recently.[3b] To a slurry of Cl_2ZrCp_2 (5.85 g, 20 mmol) in 80 mL of 1,2-dichloroethane was added trimethylalane (2.88 g, 40 mmol) at 0 °C. To the lemon yellow solution thus obtained was added dropwise **6** (3.53 g, 20 mmol) in 20 mL of 1,2-dichloroethane at room temperature. After the mixture was stirred for 2–3 h, volatile compounds were evaporated at reduced pressure (maximum 50 °C, 0.3 mmHg). The organic compounds were extracted with *n*-hexane, and the extract was transferred into another flask via a double-tipped needle. To this was added *n*-BuLi in hexane (12.5 mL, 1.6 M, 20 mmol). THF was added to dissolve the precipitate, and the resultant solution was added to a suspension of paraformaldehyde (1.80 g, 60 mmol) in THF. The reaction mixture was stirred for several hours, quenched with 3 N HCl, and extracted with ether. The extract was washed with aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated. Examination of the crude product by ^{1}H NMR with benzene as a standard indicated the formation of **3** in 75% yield as judged by the peak areas for the

(8) Other highly basic reagents which did not give satisfactory results include: (a) lithium cyclohexylisopropylamide, (b) *tert*-butyllithium, (c) potassium 3-aminopropylamide, and (d) potassium bis(trimethylsilyl)-amide. All these reagents produced **10** in ≤40%.

(9) L. Ruzicka and W. Fischer, *Helv. Chim. Acta*, **17**, 633 (1934).
(10) K. Sato, S. Inoue, and S. Ota, *J. Org. Chem.*, **35**, 565 (1970).

alkenyl and hydroxymethyl protons. After a simple column chromatographic purification (silica gel) **3**[5] was isolated in 71% yield (3.16 g): n^{27}_D 1.4984; IR (neat) 3300 cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 1.00 (s, 6 H), 1.2–2.4 (m with peaks at 1.61, 1.71, and 2.08, 17 H), 4.15 (d, J = 7 Hz, 2 H), 5.41 (t, J = 7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.90, 17.23, 17.42, 25.19, 26.27 (2C), 30.46, 32.64, 37.59, 37.78, 56.68, 120.81, 124.75, 134.56, 137.43. The stereoisomeric purity based on the ^{13}C NMR spectrum was ≥98%.

Acknowledgments are made to the National Science Foundation, the National Institutes of Health, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We thank Professor P. A. Bartlett, University of California, Berkeley, and Professor M. Koreeda, University of Michigan, for helpful discussions, Drs. N. Okukado, M. Kobayashi, and M. J. Idacavage for their experimental assistance, and Dr. T. Yoshida of International Flavors and Fragrances for a gift of 6-methyl-5-hepten-2-one.

Registry No. **3**, 18665-81-1; **4**, 79-77-6; **5**, 17283-81-7; **6**, 36772-04-0; **8**, 73395-75-2; **9**, 110-93-0; **10**, 22842-10-0; phenylethyne, 536-74-3; 3,3-dimethyl-1-butyne, 917-92-0; cyclohexylethyne, 931-48-6; 1-octyne, 629-05-0; 2-octanone, 111-13-7; acetophenone, 98-86-2; pinacolone, 75-97-8; cyclohexyl methyl ketone, 823-76-7.

Stereochemical Course of the Catalytic Reduction and of the Acidic Isomerization of 14β Steroids. Synthesis of Δ^8-14β and 8α,9α,14β Steroids

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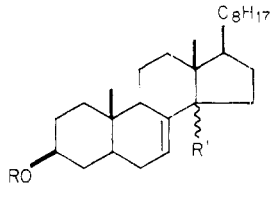
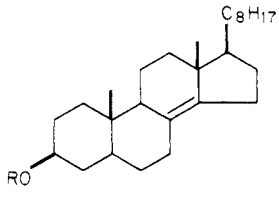
Received December 17, 1979

It is well-known[1b] that the Δ^7 double bond in the normal steroid series is isomerized either under hydrogenation conditions or by acid to the 8(14) position. Indeed, treatment of 3β-(acetyloxy)-5α-cholest-7-ene (**1a**) with

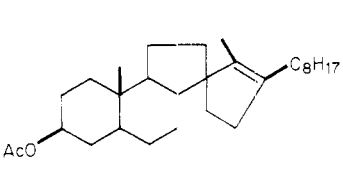


1a, R = Ac; R′ = α-H
b, R = H; R′ = α-H
c, R = H; R′ = β-H
d, R = Ac; R′ = β-H



2a, R = Ac
b, R = H

BF_3·OEt_2 or toluene-4-sulfonic acid produces at first 3β-(acetyloxy)-5α-cholest-8(14)-ene (**2a**) and as the final product the backbone-rearranged steroid 3β-(acetyloxy)-12,14α-cyclo-12,13-seco-5α-cholest-13(17)-ene (**3**).[2]



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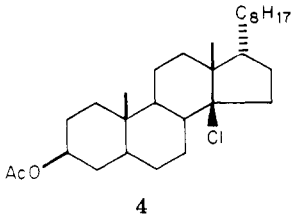

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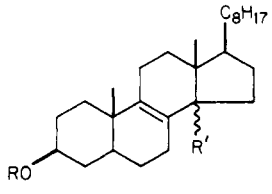
Table I. ^{13}C NMR Chemical Shifts[a] for 3β-(Acetyloxy)-5α,14β-cholest-7- and -8-ene (1d and 5d) and 5α,8β,14β-Cholestan-3β-ol (6b)

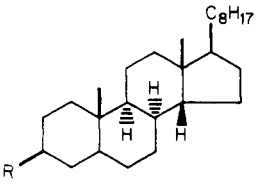
carbon	1d	5d	6b
1	36.5	35.4[b]	38.0
2	27.0[b]	27.4	30.9
3	73.4	73.5	71.3
4	32.7	33.9	38.0
5	39.8	41.3	44.9
6	30.0	30.2	28.0
7	120.6	30.2	30.1
8	139.1	130.5	37.6
9	45.2	134.9	45.6
10	34.0	36.1	36.7
11	21.5	20.7	22.5
12	33.7	35.6[b]	36.4
13	42.6	41.3	42.8
14	55.7	51.0	47.9[b]
15	22.6	25.4	25.3
16	27.5[b]	28.3	27.8
17	56.5	54.0	53.6[b]
18	20.8	23.5	20.2
19	12.4	17.3	15.1
20	34.1	33.5	33.4
21	20.0	19.8	19.8
22	33.8	34.3	34.8
23	25.0	24.5	24.2
24	39.6	39.5	39.5
25	28.0	27.9	27.8
26	22.6	22.5	22.8
27	22.7	22.7	22.8
CH_3 (Ac)	21.5	21.4	
C=O (Ac)	170.4	170.3	

[a] In parts per million relative to Me_4Si. [b] These values can be reversed in any vertical column.

The action of hydrogen chloride at −60 °C on **1a** affords 3β-(acetyloxy)-14-chloro-5α,14β,17β*H*-cholestane (**4**) probably[3,4] via **3**. On the other hand 5α-cholest-7-en-3β-ol (**1b**) is reversibly isomerized to 5α-cholest-8-en-3β-ol (**5b**)



5a, R = Ac; R′ = α-H
b, R = H; R′ = α-H
c, R = H; R′ = β-H
d, R = Ac; R′ = β-H



6a, R = H
b, R = OH
c, R = OAc
d, R = OTos

by rat liver microsomal enzymes,[5] the equilibrium being almost completely shifted to the Δ^7 isomer. Recently we synthesized[6] 5α,14β-cholest-7-en-3β-ol (**1c**) and demonstrated[7] that it was isomerized by rat liver enzymes into 5α-cholest-8(14)-en-3β-ol (**2b**). This result indicates that inversion of the configuration at C-14 alters the course of the enzyme-catalyzed isomerization of a Δ^7 sterol. In

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