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Stereochemistry and Mechanism of the Reaction of $LiCu(CH_3)_2$ with β-Cyclopropyl α,β-Unsaturated Ketones

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Abstract: 1,6-Dimethylbicyclo[4.1.0]-4-hepten-3-one-*exo*-7-d_1 (**9**-d_1) was stereospecifically synthesized in seven steps from *o*-xylene. The reaction of $LiCu(CH_3)_2$ with **9**-d_1 gave a 48:52 mixture of the normal conjugate addition product *exo*-1,5,6-trimethylbicyclo[4.1.0]heptan-3-one-*exo*-7-d_1 (**19**-d_1) and of the cyclopropane ring opened product 5-(ethyl-*1*-d_1)-4,5-dimethyl-3-cyclohexenone (**12**-d_1). The stereochemistry of the ring-opened product **12**-d_1 was determined by 270-MHz ^1H NMR. The ratio of the diastereotopic methylene protons of the ethyl group of **12**-d_1, which appear at δ 1.48 and 1.33, was found to be 0.053 ± 0.02:1.0. The high stereospecificity of the ring-opening reaction provides evidence against radical anion intermediates in this reaction and is interpreted in terms of a direct nucleophilic attack of cuprate at the cyclopropyl carbon atom.

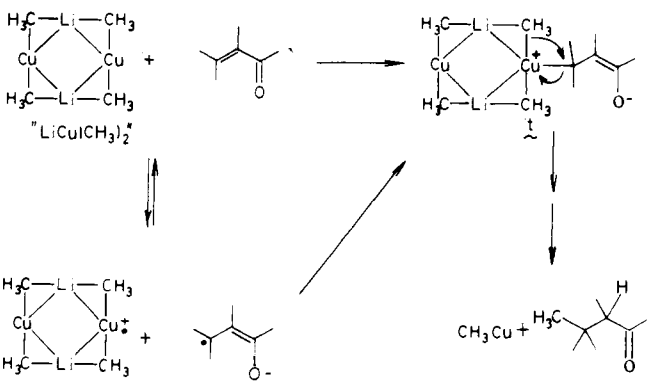
Introduction

While the conjugate addition of lithium diorganocuprates to α,β-unsaturated carbonyl compounds has proved to be extremely valuable in organic synthesis, its mechanism remains incompletely defined.[1] At one point, a six-centered transition state was considered, but this possibility was eliminated by the observation that lithium dimethylcuprate adds to *trans*-3-penten-2-one to give 69% of the trans enolate.[2] The absence of free radicals in the conjugate addition reaction has been demonstrated by several experiments: (1) reaction of lithium *tert*-butyl(*endo*-2-norbornyl)cuprate with mesityl oxide yields the conjugate adduct, 4-methyl-4-(*endo*-2-norbornyl)pentan-2-one, with no detectable exo isomer;[3] (2) reaction of either lithium di-*cis*- or di-*trans*-1-propenylcuprate with 2-cyclohexenone occurs with retention of stereochemistry at the propenyl group;[4] (3) isoprene does not interfere with the conjugate addition reactions of organocuprates.[5]

The conjugate addition of lithium dimethylcuprate, $LiCu(CH_3)_2$,[6] to unsaturated ketones is now thought to proceed either by an electron-transfer mechanism[7] or by a nucleophilic addition mechanism (Scheme I).[8] Both mechanisms are viewed as proceeding via an oxidative addition to give a Cu(III) adduct,[9] **1**, which subsequently undergoes reductive elimination of the observed enolate; however, there is no direct evidence for a Cu(III) intermediate, and direct transfer of an alkyl group cannot be excluded. The two mechanisms differ in the way in which the oxidative addition is accomplished. In the electron-transfer mechanism, $LiCu(CH_3)_2$ transfers an electron to the enone to produce the radical anion of the enone and a radical cation of the cuprate; subsequent combination produces **1**. Alternatively, $LiCu(CH_3)_2$ can act as a nucleophile and add to the β carbon of the enone without the intervention of odd-electron species.

The nucleophilic addition mechanism is similar to the familiar Michael addition reaction. The ability of organocuprates to act as nucleophiles has been demonstrated in substitution

Scheme I



reactions[10] with alkyl halides,[6a,11] tosylates,[8] and epoxides,[9a] all of which proceed with inversion of stereochemistry.

House has cited several experiments that support his proposed electron-transfer mechanism. First, the susceptibility of unsaturated carbonyl compounds to conjugate addition of organocuprates was found to correlate strongly with the one-electron polarographic reduction potentials of the unsaturated carbonyl compounds.[7,12] This implies that organocuprates can act as one-electron reducing agents;[13] however, one-electron electrochemical oxidation of organocuprates has not been observed polarographically.[7] Johnson has suggested that the reduction potential measures the affinity of the substrate for electrons and that correlation with either an electron-transfer process or a nucleophilic addition process might be expected.[8] In a rejoinder, House has pointed out that no obvious correlation exists between reduction potentials of unsaturated carbonyl compounds and their reactivity in the Michael reaction, and that steric effects of β-alkyl groups play a dominant role in the Michael reaction.[7a]

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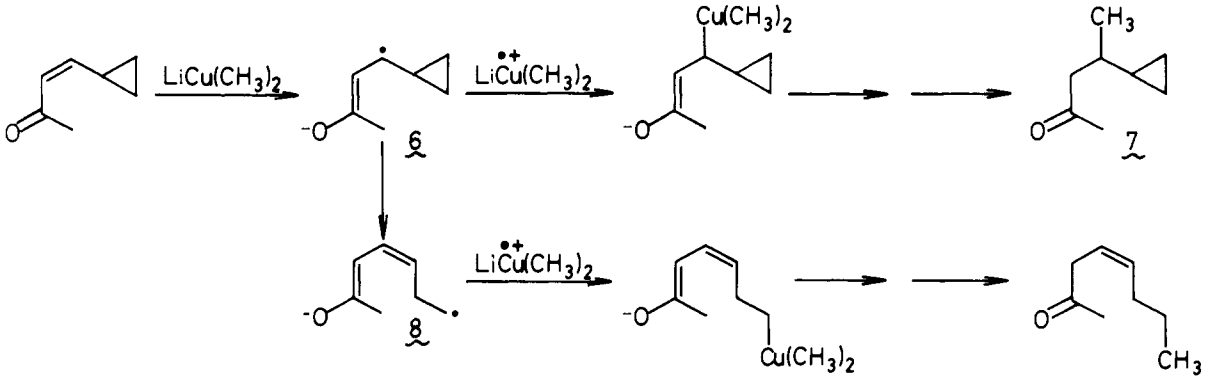
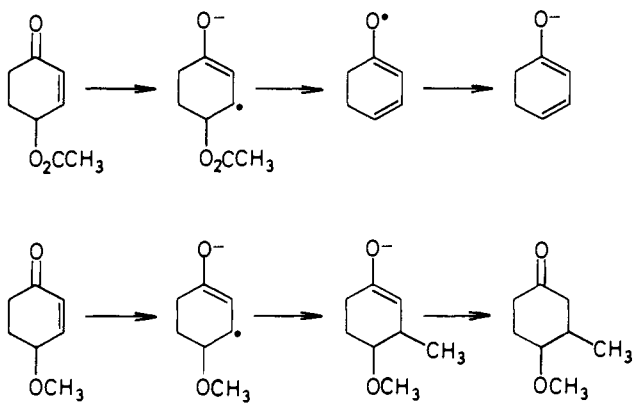
Scheme II

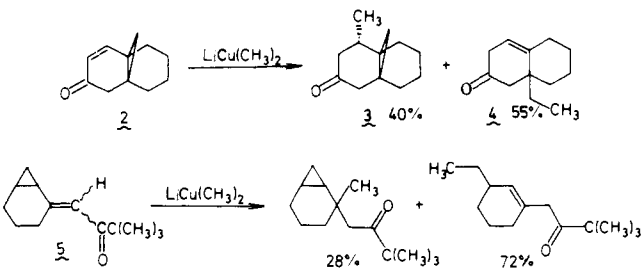


A second observation cited in support of an electron-transfer mechanism is the cis-trans isomerization of *cis*-2,2-dimethyl-5-phenyl-4-penten-3-one, which occurs concomitant with the addition of $LiCu(CH_3)_2$.[14] This isomerization has been proposed to occur via the enone radical anion, which would be formed by electron transfer from $LiCu(CH_3)_2$. Electron transfer between the enone and the enone radical anion gives rise to a chain reaction which catalytically isomerizes the enone. However, it is not clear whether the isomerization is a side reaction unrelated to the conjugate addition of cuprate or whether the enone radical anion is an intermediate in the conjugate addition.

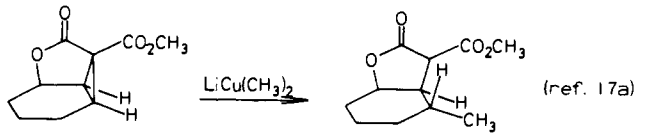


Third, the observation that 4-acetoxy-2-cyclohexenone is reduced by $LiCu(CH_3)_2$ has been interpreted in terms of elimination of acetate from an intermediate radical anion.[33] In contrast, 4-methoxy-2-cyclohexenone undergoes conjugate addition of $LiCu(CH_3)_2$, presumably because methoxide is eliminated more slowly from an intermediate anion radical.

Finally, the alkylative ring opening of β-cyclopropyl α,β-unsaturated ketones which accompanies the conjugate addition of $LiCu(CH_3)_2$ has been attributed to ring opening of an intermediate radical anion. Marshall and Ruden observed that **2** reacts with $LiCu(CH_3)_2$ to give both the normal conjugate addition product **3** and the ring-opened adduct **4**.[15] Similarly, House and Snoble found ring-opened products in the reaction of **5** with $LiCu(CH_3)_2$.[16] House has interpreted these results (Scheme II) as arising from electron transfer to give an enone radical anion, **6**. This radical anion can either give normal addition products, **7**, or undergo ring opening of the cyclopropylcarbinyl system, **6**, to give a butenyl radical, **8**, which is subsequently alkylated.



However, the ring-opened products can also be explained by direct nucleophilic attack of the cuprate on a cyclopropyl carbon. Nucleophilic ring opening of cyclopropyl esters[17a-d] and ketones[17e,f] by cuprates have been reported. Electron transfer is unlikely for these difficult to reduce compounds.



(ref. 17a)

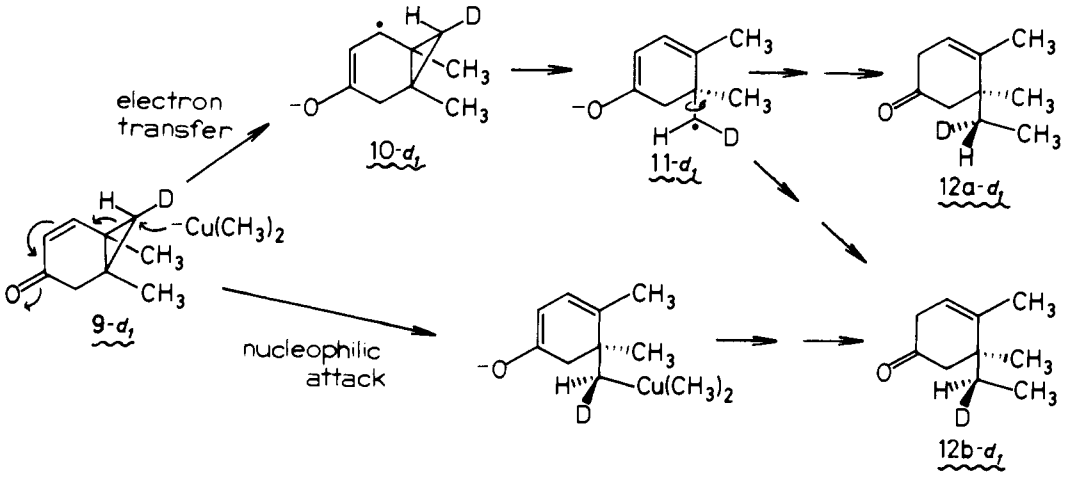
To determine the mechanism of the ring opening of cyclopropyl enones, we have studied the stereochemistry of the ring opening of the deuterium-labeled cyclopropyl enone **9**-d_1 (Scheme III). If ring opening proceeds via a radical anion intermediate, **10**, the alkyl radical generated, **11**, would be able to undergo rapid bond rotation and loss of stereochemistry. On the other hand, backside nucleophilic attack of cuprate at the cyclopropyl carbon atom would lead to stereospecific ring opening with inversion. The stereochemistry of the ring opening can be determined from the ^1H NMR spectrum since the methylene protons of the ethyl group are diastereotopic.

Results

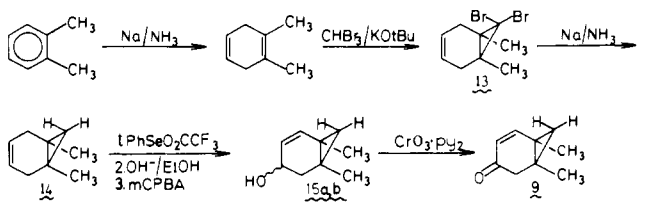
Synthesis of 1,6-Dimethylbicyclo[4.1.0]-4-hepten-3-one (9). To determine whether the diastereotopic methylene protons of the ethyl group of the undeuterated ring-opened product, **12**, were resolvable by ^1H NMR, the undeuterated cyclopropyl ketone, **9**, was synthesized and reacted with $LiCu(CH_3)_2$. The synthesis of **9** is outlined in Scheme IV. Dibromocarbene addition to 1,2-dimethyl-1,4-cyclohexadiene occurred only at the tetrasubstituted double bond.[18] Reduction of the *gem*-dibromocyclopropane **13** with sodium in liquid ammonia[18] gave the cyclopropyl alkene **14**.

Allylic oxidation with double-bond shift was accomplished using a new organoselenium reagent developed by Reich.[19] Reaction of benzene selenenotrifluoroacetate, prepared from benzeneselenenyl chloride and silver trifluoroacetate, with **14** resulted in a trans addition of benzene selenenotrifluoroacetate across the double bond to form the trans adducts **16a** and **16b**. The trans addition has been proposed to occur via the intermediacy of a bridging selenonium ion. Treatment of the mixture of trifluoroacetates **16a** and **16b** yielded a mixture of selenenyl alcohols, **17a** and **17b**. Oxidation of this mixture of selenides to the selenoxides with *m*-chloroperbenzoic acid (MCPBA),[20] followed by thermal selenoxide elimination,[21] yielded the allylic alcohol mixture **15a** and **15b** in 75% overall

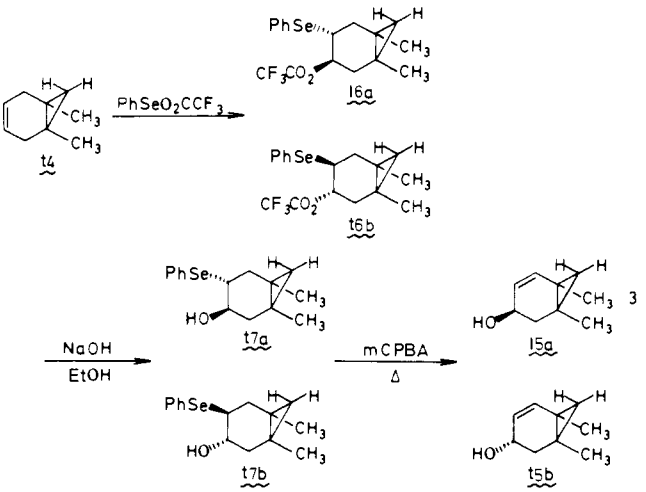
Scheme III



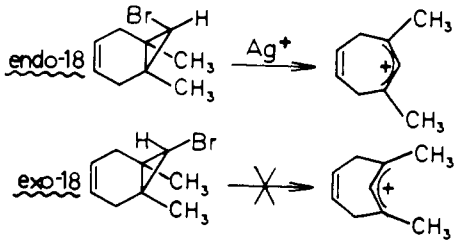
Scheme IV



yield from **14**. Finally, Collins oxidation of the mixture of allylic alcohols yielded the β-cyclopropyl enone **9** in 50% yield.



Synthesis of 1,6-Dimethylbicyclo[4.1.0]-4-hepten-3-one-*exo*-7-d_1 (9-d_1). Reduction of **13** with 1 equiv of triphenyltin hydride[22] gave a 4:1 mixture of exo:endo monobromocyclopropanes, *exo*-**18** and *endo*-**18**, in 90% yield. The stereochemistry of the monobromides was assigned on the basis of their reactivity toward silver nitrate. Silver nitrate selectively



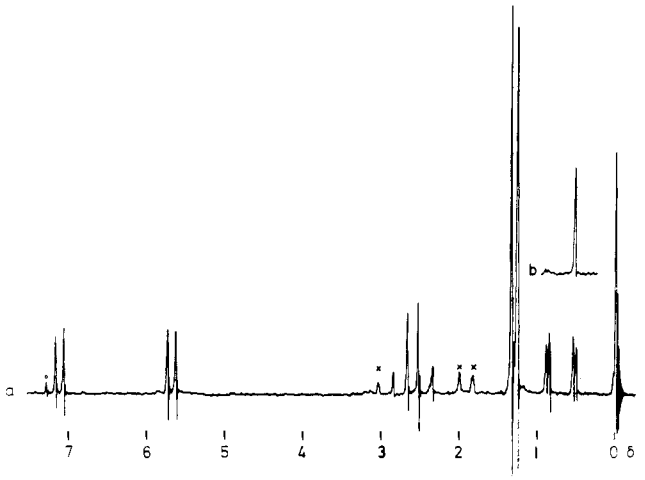
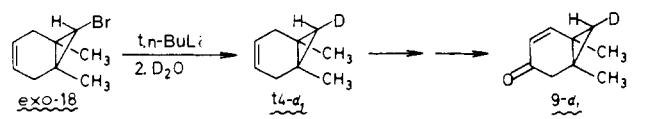


Figure 1. (a) 100-MHz ^{1}H NMR spectrum ($CDCl_3$) of 1,6-dimethylbicyclo[4.1.0]-4-hepten-3-one (**9**). (b) Cyclopropyl region of the spectrum of **9**-d_1, O = $CHCl_3$; x = impurity.

solvolyzes the endo isomer to a mixture of dimethylcycloheptatrienes and allowed the isolation of pure *exo*-**18** from the mixture of monobromides.[23a] This proved particularly useful since the exo-endo mixture could not be separated by distillation, gas chromatography, thin layer chromatography, or crystallization. The disrotatory solvolytic ring opening of cyclopropyl halides is known to take place with "backside orbital assistance" and concerted formation of allylic cations,[23b-e] Solvolysis of *endo*-**18** produces a stable allylic cation, whereas solvolysis of *exo*-**18** would produce a highly strained cation.

Stereospecific replacement of the bromine atom in *exo*-**18** by deuterium was accomplished by metal halogen exchange with *n*-BuLi in hexane-THF at −20°C and quenching with D_2O. The bicyclic monodeuterated alkene **14**-d_1 was obtained in 22% yield by this procedure. The exo assignment of deuterium in **14**-d_1 is based on the known stereochemistry of metal-halogen exchanges in cyclopropyl halides.[23a,24] The ^{1}H NMR spectrum of **14**-d_1 showed the presence of a single isomer of d_1 material (singlet at δ 0.81, C_6D_6) and 6 ± 2% of d_0 material, **14** (1:1 doublet at δ −0.04).

Conversion of the monodeuterated alkene **14**-d_1 to mono-



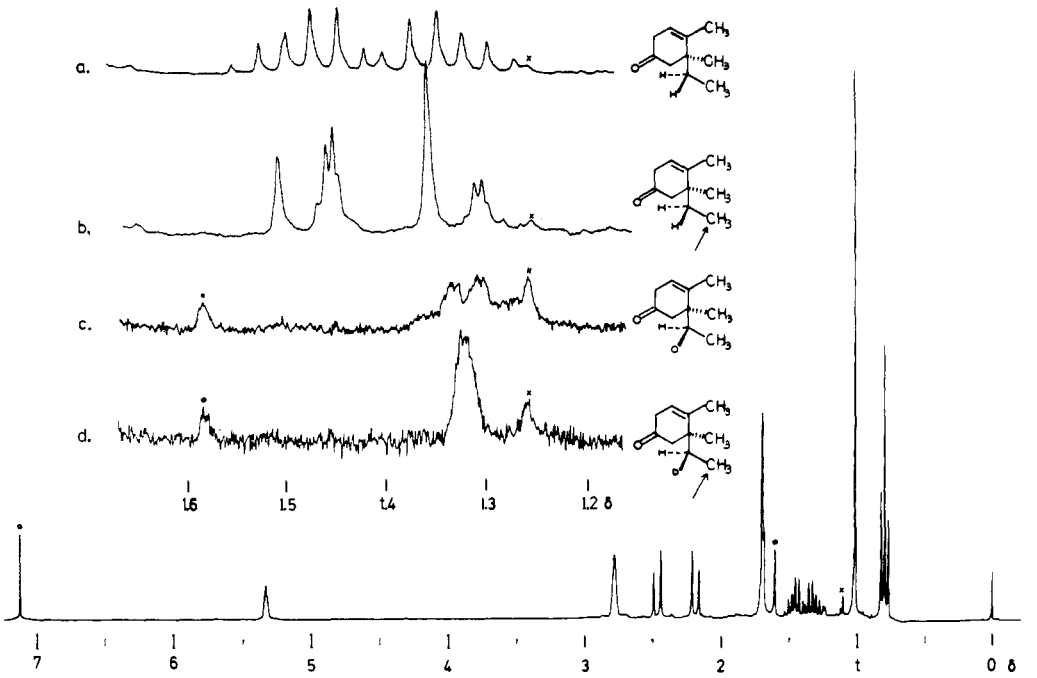
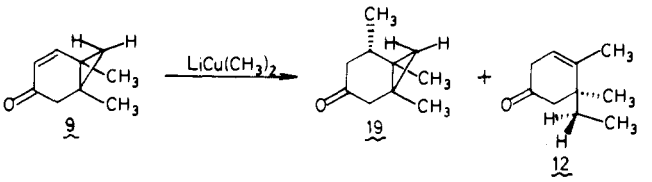


Figure 2. 270-MHz ^1H NMR spectrum ($CDCl_3$) of 5-ethyl-4,5-dimethyl-3-cyclohexenone (**12**). (a) Methylene region of ethyl group of **12**. (b) Methylene region of ethyl group of **12**, methyl of ethyl group (δ 0.81) decoupled. (c) Methylene region of ethyl group of 5-(ethyl-1-d_1)-4,5-dimethyl-3-cyclohexenone (**12**-d_1). (d) Methylene region of ethyl group of **12**-d_1, methyl of ethyl group (δ 0.81) decoupled. ○ = $CHCl_3$; ● = H_2O; x = impurity.

deuterated enone **9**-d_1 was accomplished by the same allylic oxidation–Collins oxidation procedure employed for the undeuterated material. The ^1H NMR of **9**-d_1 (Figure 1) showed 94 ± 2% of a single monodeuterated compound and 6 ± 2% of undeuterated material, **9**.

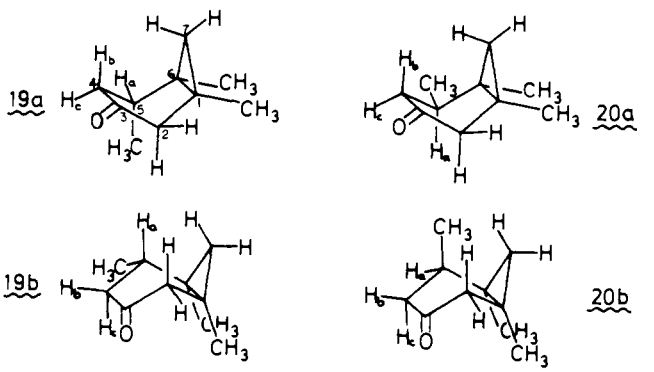
Reaction of Undeuterated Enone 9 with $LiCu(CH_3)_2$. The reaction of a 5% excess of $LiCu(CH_3)_2$, prepared from halide-free CH_3Li and $[(n\text{-}C_4H_9)_2S]_2CuI$,[25] with undeuterated enone **9** in diethyl ether at −78 °C gave a 48:52 mixture of 1,5-*exo*-6-trimethylbicyclo[4.1.0]heptan-3-one (**19**) and 4,5-dimethyl-5-ethyl-3-cyclohexenone (**12**), which were isolated by preparative gas chromatography.



The structure of **12** was assigned on the basis of IR and NMR spectra. The infrared spectrum indicated the presence of unconjugated ketone (1724 cm^{-1}, strong) and carbon–carbon double bond (1683 cm^{-1}, weak). The 270-MHz ^1H NMR spectrum (Figure 2) was fully consistent with the assigned structure. A single proton at δ 5.43 confirmed the presence of a trisubstituted alkene. The methylene protons of the ethyl group are diastereotopic and appear as the AB portion of an ABM_3 system: an AB quartet ($J_{H_aH_b}$ = 14.1 Hz) of quartets ($J_{H_a\text{-}CH_3} = J_{H_b\text{-}CH_3}$ = 7.2 Hz) was observed between δ 1.6 and 1.2 (a, Figure 2). The chemical shift difference between H_a and H_b was 0.14 ppm (38 Hz at 270 MHz). Proton decoupling of the methyl pseudotriplet of the ethyl group at δ 0.81 collapses the methylene pattern to nearly an AB quartet (b, Figure 2). The incomplete collapse of the pattern was due to the fact that the ethyl group, an ABM_3 system, is not quite first order at 270 MHz. The resolution of the diastereotopic protons of **12** in the 270-MHz NMR spectrum made it possible to determine the stereochemistry of the ring opening of the deuterated enone **9**-d_1 (vide infra).

The assignment of the structure of **19** was also based on IR and NMR spectra. The infrared spectrum shows the presence of a ketone carbonyl stretch at 1713 cm^{-1} and of a cyclopropyl C–H stretch at 3060 cm^{-1}. In the 270-MHz ^1H NMR spectrum of **19**, the cyclopropyl methyl groups appear as singlets at δ 1.17 and 1.11. The cyclopropyl protons appear as a doublet (J = 5.5 Hz) at δ 0.72 and a finely split doublet (J = 5.5, J' = 1.1 Hz) at δ 0.15. The protons attached to carbon C-2, joining the cyclopropane and ketone groups, appear as an AB quartet (δ 2.53, 2.42, J = 18.8 Hz). The C-5 methyl group β to the ketone appears as a finely split doublet (J = 6.6, J' = 0.8 Hz) at δ 1.05. The tertiary hydrogen on C-5 at δ 2.17 is a multiplet ($J_{H\text{-}CH_3}$ = 6.6, J' = 5.8, J'' = 2.6 Hz). The methylene protons on C-4 appear as doublets of doublets at δ 2.30 (J = 17.8, J' = 5.8 Hz) and 2.09 (J = 17.8, J' = 2.6 Hz).

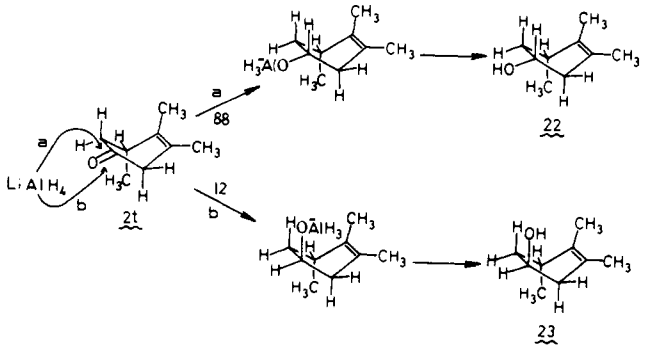
A distinction between the exo methyl isomer **19** and the endo methyl isomer **20** can be made on the basis of the NMR spectrum. Analysis of Dreiding models of **20** indicate that **20a** will be the principal conformation; conformation **20b** has a destabilizing eclipsing interaction between the C-5 methyl group and the cyclopropane ring. Analysis of Dreiding models of **19** indicate that either **19a** or **19b** might be the more stable



conformation. The observation of two small coupling constants (J' = 5.8, J'' = 2.6 Hz) from the C-5 methine proton to the C-4 methylene protons of the conjugate addition product estab-

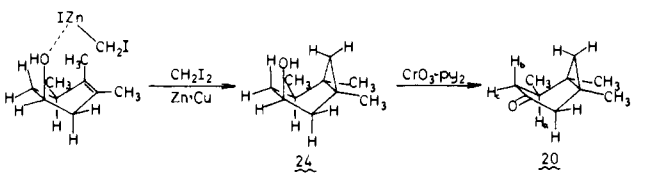
lishes the equatorial orientation of the C-5 methine proton. Consequently, structure **20a** can be excluded, and by the process of elimination structure **19** is established. Moreover, the conformation of **19** must be **19a**, in which the C-5 proton is equatorial and the C-5 methyl group is axial. In conformation **19a** the C-5 methyl group is nearly perfectly staggered with respect to the neighboring methyl and cyclopropyl groups. The observation that the normal conjugate addition product results from attack of cuprate from the side opposite the cyclopropane ring is similar to Marshall's finding for addition of $LiCu(CH_3)_2$ to **2**.[15]

The structural assignment of **19** is also supported by the independent stereospecific synthesis of **20** and by the demonstration that this material was different from the conjugate addition product **19**. Lithium aluminum hydride reduction of 3,4,5-trimethyl-3-cyclohexenone (**21**) gave an 88:12 mixture of *cis*- and *trans*-3,4,5-trimethyl-3-cyclohexenol (**22** and **23**).



The stereochemistry of cis alcohol **22** was established from the 270-MHz ^1H NMR spectrum (see Experimental Section). The principal conformation of ketone **21** has the C-5 methyl group is an axial orientation as determined by 270-MHz ^1H NMR (see Experimental Section); the conformation with the C-5 methyl in an equatorial position is destabilized by an eclipsing of the C-4 and C-5 methyl groups. The cis alcohol **22** is the product derived from attack of $LiAlH_4$ on ketone **21** from the side opposite the axial C-5 methyl group.[26]

The Simmons–Smith reaction on cis alcohol **22** led stereospecifically to the formation of a single cyclopropyl alcohol **24**.



The known directing effect of hydroxyl groups in the Simmons–Smith reaction[27] allows a confident assignment of the stereochemistry of **24** in which the hydroxyl group, the cyclopropane ring, and the C-5 methyl group are all on the same face of the cyclohexane ring. Oxidation of **24** gave **20**, which was different from the conjugate product **19**. The NMR spectrum of **20** indicated that the C-5 methyl group was equatorial as expected (see above); the C-5 methine proton was axial, since coupling constants of 11.2 and 5.5 Hz to the C-4 methylene protons were observed.

Reaction of Deuterated Enone 9-d_1 with $LiCu(CH_3)_2$. Reaction of $LiCu(CH_3)_2$ with deuterated enone **9**-d_1 gave the same 48:52 ratio of normal conjugate addition product **19**-d_1 and ring-opened product **12**-d_1 as obtained from the undeuterated ketone **9**. The ring-opened product **12**-d_1 was isolated by preparative gas chromatography.

The 270-MHz spectrum of **12**-d_1 (c and d, Figure 2) indicates that the ring-opening reaction is stereospecific within experimental error. Specifically, in spectrum d, in which the methyl protons of the ethyl group are decoupled, only the diastereotopic proton at δ 1.32 is observed, and no resonance due to the diastereotopic proton at δ 1.48 is visible. Careful integration showed the ratio of protons at δ 1.48:1.33 to be 0.053 ± 0.02:1.00; this corresponds to a mixture of 95 ± 2% stereospecifically labeled **13**-d_1 and 5 ± 2% undeuterated material **12**. Since the cyclopropyl enone **9**-d_1 was a mixture of 94 ± 2% stereospecifically labeled material and 6 ± 2% unlabeled material, the ring-opening reaction is stereospecific within experimental error.

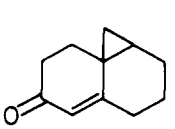
The assignment of the chemical shifts of the diastereotopic protons of the ethyl group of **12** has not been possible. Consequently, we do not know whether the ring-opening reaction occurred with complete retention or complete inversion of stereochemistry.

Discussion

The high stereospecificity observed in the ring opening of **9**-d_1 provides firm evidence that a ring-opened radical anion **11**-d_1 is not an intermediate in formation of ring-opened product **12**-d_1. A further implication is that the radical anion of the enone, **10**, is also not involved in the ring-opening reaction. The stereochemistry of the ring-opened product is not known; however, backside nucleophilic ring opening of the cyclopropane most readily explains the stereospecificity of the process and leads to **12b**-d_1.

Previously, the ring opening of cyclopropyl enones was attributed to a rearrangement of a radical anion intermediate and was cited as a major piece of evidence for a radical anion intermediate in the conjugate addition of organocuprates to enones.[7,14,16] The results reported here demonstrate that at least the ring-opening reaction involves a stereospecific nucleophilic attack and not a radical anion. Our experiment provides no direct information concerning the presence or absence of radical anion intermediates in the normal conjugate addition reactions. However, it should be pointed out that, if cuprates are capable of attacking the cyclopropane ring of a cyclopropyl enone, they should also be able to add nucleophilically to the normally more reactive enone functionality. On the other hand, if the addition to the enone proceeds via a radical anion intermediate one is forced to accept the following reactivity sequence: addition to enone via radical anion ≈ nucleophilic cyclopropane opening ≫ nucleophilic addition to enone.

House has found that the lifetime of the electrochemically generated radical anion of enone **25**, in which the cyclopropyl



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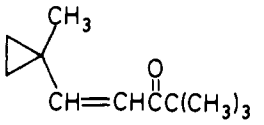

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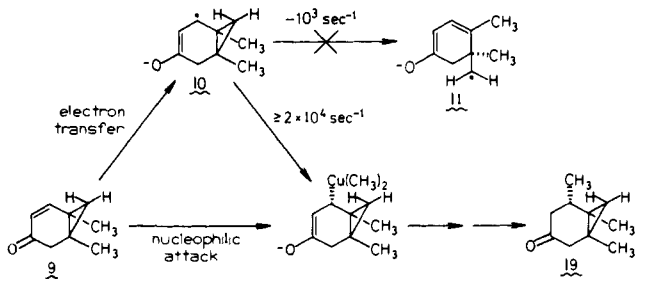
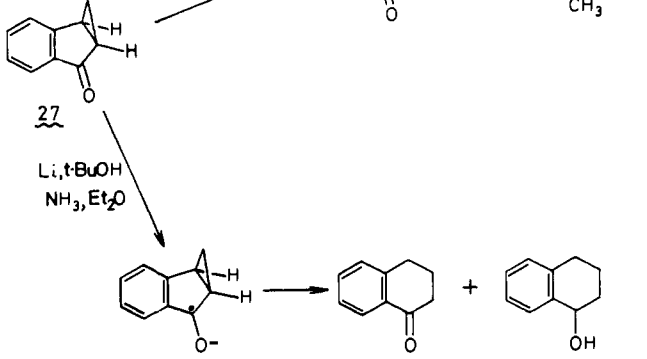
ring is held in a conformation favorable for ring opening, is substantially shorter than that of enone **26** in which the cyclopropyl group is not constrained.[7a,14] The short ($\sim 10^{-3}$ s) lifetime of the radical anion of enone **25** is probably due to opening of the cyclopropane ring. The lifetime of the radical anion of **9** should be similar to that of **25**, both because of their structural similarity and because of the similarity of their reactivity with $LiCu(CH_3)_2$. While we cannot say whether the radical anion **10** is involved in reaction of **9** to give the normal conjugate addition product **19**, we do know from our experiment that, if radical anion **10** is formed, it must react with cuprate at least 20 times faster than ring opening occurs. This implies that an enone radical anion can be an intermediate in the normal conjugate addition reaction only if it reacts with the cuprate at a rate greater than $\sim 2 \times 10^4$ s^{-1}.

In related work, House has found that cyclopropyl ketone **27** reacts with $LiCu(CH_3)_2$ to give some ring opened pro-



duct.[17f] The ring-opened product cannot arise from a radical anion intermediate since this intermediate was generated from **27** by Li–NH_3 reduction and was shown to rearrange by cleavage of a different cyclopropane bond.



At this point, no enone radical anion rearrangement exists which is fast enough to intercept the postulated radical anion intermediate.[34] If faster radical anion rearrangements are discovered, they should be employed to test for radical anions in normal conjugate addition reactions of cuprates.

Experimental Section

General. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Methylene chloride was distilled from P_2O_5. Benzene was stirred over H_2SO_4, neutralized with $NaHCO_3$, and distilled from CaH_2 onto Linde 4A molecular sieves. All other solvents were used as purchased without further purification. All reactions involving organolithium or organocopper reagents were carried out under an atmosphere of dry nitrogen in flame-dried glassware. Lithium reagents were standardized using a double-titration procedure using 1,2-dibromoethane and standard aqueous acid.[28]

Analytical gas chromatography was carried out on a Hewlett-Packard 5700A instrument with flame ionization detector, coupled with a Hewlett-Packard 3380A electronic integrator. Preparative gas chromatographic separations were carried out on a Varian 90P instrument. Preparative thin layer chromatography was done using Merck PF-254 silica gel.

NMR spectra were recorded on JEOL MH-100 (100 MHz) and Bruker WH-270 spectrometers. All chemical shifts are reported in parts per million δ relative to internal $(CH_3)_4Si$. Infrared spectra were recorded on a Perkin-Elmer 267 grating infrared spectrophotometer or on a Digilab FTS-20 Fourier transform spectrophotometer. Ultraviolet-visible spectra were recorded on a Cary 118 spectrophotometer. Mass spectra were recorded on an AE-1-MS903 spectrometer at 70 eV. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

1,2-Dimethyl-1,4-cyclohexadiene. Following a procedure of Vogel,[18] *o*-xylene (106.5 g, 1.0 mol) was reacted with sodium (57.5 g, 2.5 g-atoms) in liquid ammonia at −78 °C to yield a clear, colorless liquid, bp 44–45 °C (20 mm) [lit.[18] 57–58 °C (40 mm)]. Integration of the ^1H NMR spectrum of the liquid indicated a 70:30 mixture of 1,2-dimethyl-1,4-cyclohexadiene-*o*-xylene (70% yield of diene). NMR ($CDCl_3$): δ 7.05 (s, 4 H, *o*-xylene aromatic H), 5.65 (m, 2 H, diene vinylic H), 2.56 (s, 4 H, diene allylic H), 2.20 (s, 6 H, *o*-xylene-CH_3), 1.6 (s, 6 H, diene-CH_3). The product was carried out without further purification.

7,7-Dibromo-1,6-dimethylbicyclo[4.1.0]-3-heptene (13). Following a procedure of Vogel,[18] 1,2-dimethyl-1,4-cyclohexadiene (70% in *o*-xylene, 72.1 g, 0.50 mol) was reacted with bromoform (126.4 g, 0.50 mol) and $KOC(CH_3)_3$ (61.7 g, 0.55 mol) to yield 7,7-dibromo-1,6-dimethylbicyclo[4.1.0]-3-heptene (**13**) as a white, crystalline solid (84.2 g, 60%), mp 107–108 °C (lit.[18] 107–108 °C). NMR ($CDCl_3$): δ 5.5 (bs, 2 H, vinylic H), 2.3 (s, 4 H, allylic H), 1.31 (s, 6 H, $-CH_3$).

1,6-Dimethylbicyclo[4.1.0]-3-heptene (14). An adaptation of the procedure of Vogel et al. was used.[18] **13** (18.5 g, 66.2 mmol) was reacted with sodium (9.7 g, 0.42 g-atom) in liquid ammonia to yield 1,6-dimethylbicyclo[4.1.0]-3-heptene (**14**, 5.7 g, 70%) as a clear, colorless liquid, bp 40–42 °C (20 mm) [lit.[18] 55–56 °C (40 mm)]. NMR ($CDCl_3$): δ 5.48 (m, 2 H, vinylic H), 2.16 (m, 4 H, allylic H), 1.12 (s, 6 H, $-CH_3$), 0.65 (d, J = 3.7 Hz, cyclopropyl H), −0.04 (d, J = 3.7 Hz, cyclopropyl H).

1,6-Dimethylbicyclo[4.1.0]-4-hepten-3-ol (15a,b). An allylic oxidation procedure developed by Reich was employed.[19,20] Silver trifluoroacetate (10.3 g, 46.6 mmol) was added to a deep red solution of benzeneselenenyl chloride (8.9 g, 46.6 mmol) in 120 mL of benzene. The resultant light orange mixture, containing suspended AgCl, was stirred for 15 min at room temperature. **14** (5.7 g, 46.6 mmol) was added, the reaction mixture was stirred for 10 min, and 85 mL of saturated aqueous $NaCl$-Na_2CO_3 solution was added. The reaction mixture was filtered through Celite, and the organic layer was added to a solution of NaOH (1.9 g, 47.5 mmol) in 40 mL of ethanol to hydrolyze the trifluoroacetate ester intermediate, **16a,b**. The orange reaction mixture was stirred for 15 min, and 120 mL of 0.5 N aqueous HCl was added. The layers were separated, and the aqueous layer was extracted with 50 mL of Et_2O. The combined organic layers were concentrated on a rotary evaporator to yield a mixture of isomeric *trans*-1,6-dimethyl-3-(benzeneselenено)bicyclo[4.1.0]-4-heptanols (**17a,b**) as an amber oil (13.0 g, 95%). NMR of mixture (acetone-d_6, 270 MHz) follows. **17a**: δ 7.54 (m, 2 H, phenyl), 7.24 (m, 3 H, phenyl), 3.61 (broad m, ~1 H, -OH), 3.51 (td, J = 11, 7 Hz, 1 H, C-3 or C-4 methine), 3.04 (td, J = 11, 5 Hz, 1 H, C-3 or C-4 methine), 2.24 (dd, J = 14, 5 Hz, 1 H, C-2 or C-5), 2.06 (dd, J = 16, 7 Hz, 1 H, C-2 or C-5), 2.05 (m, ~1 H, C-2 or C-5), 1.72 (dd, J = 14, 2 Hz, 1 H, C-2 or C-5), 1.06 (s, 3 H, $-CH_3$), 1.02 (s, 3 H, $-CH_3$), 0.53 (d, J = 4 Hz, cyclopropyl), 0.06 (d, J = 4 Hz, cyclopropyl). **17b** (some peaks obscured by overlap with peaks from major isomer): δ 7.54 (m, 2 H, phenyl), 7.24 (m, 3 H, phenyl), 3.61 (broad m, -OH), 3.37 (td, J = 11, 4 Hz, 1 H, C-3 or C-4 methine), 3.13 (td, J = 11.5, 6 Hz, 1 H, C-3 or C-4 methine), 2.14 (m, ~1 H, obscured, C-2 or C-5), 1.87 (dd, J = 15, 11 Hz, 1 H, C-2 or C-5), 1.69 (dd, J = 14, 4 Hz, 1 H, C-2 or C-5), 1.55 (dd, J = 14, 11 Hz, C-2 or C-5), 1.08 (s, 3 H, $-CH_3$), 1.02 (s, 3 H, $-CH_3$), 0.30 (d, J = 4 Hz, cyclopropyl). Measurement of peak heights of the 270-MHz NMR spectrum of **17a,b** indicated a 3:1 isomer ratio of **17a:17b**.

m-Chloroperoxybenzoic acid (85%, 9.46 g, 46.6 mmol) was added to a solution of **17a,b** (13.0 g, 44.3 mmol) in 75 mL of CH_2Cl_2 at −10 °C. The reaction mixture was stirred at −10 °C for 30 min, during which time a precipitate of *m*-chlorobenzoic acid formed. The resulting solution was filtered and diethylamine (3.75 g, 51.3 mmol) in 500 mL of CCl_4 was added. The solution was refluxed for 3 h to carry out selenoxide elimination. Evaporation of solvent gave a red oil which was stirred with 50 mL of 15% aqueous H_2O_2 and pyridine (4.05 g, 51.3 mmol) in 60 mL of $CHCl_3$ for 1 h to oxidize selenium compounds to water-soluble derivatives ($PhSeO_2H$).

The layers were separated, and the organic layer was washed with saturated aqueous $NaHCO_3$ solution and saturated aqueous NaCl solution and dried ($MgSO_4$). The solvent was removed on a rotary evaporator to yield a mixture of isomeric 1,6-dimethylbicyclo[4.1.0]-4-hepten-3-ols (**15a,b**) as a dark amber oil (7.44 g). The NMR spectrum indicated a 65% purity for the oil; the impurities were a mixture of phenylselenium compounds (δ 8.0–7.0). This represents a 75% yield of **15**. A small amount of the crude amber oil was purified by preparative TLC (20:80 Et_2O–hexane, R_f 0.25) to give a pale yellow liquid mixture of **15a** and **15b**. NMR ($CDCl_3$, mixture, 270 MHz) follows. **15a**: δ 6.06 (d, J = 10 Hz, 1 H, C-5 vinylic H), 5.50 (dd, J = 10, 5.5 Hz, 1 H, C-4 vinylic H), 4.0 (td, J = 5.5, 2.0 Hz, 1 H, carbinol methine), 2.07 (dd, J = 15, 2.0 Hz, 1 H, C-2), 1.65 (dd, J = 15, 5.5 Hz, 1 H, C-2), 1.19 (s, 3 H, $-CH_3$), 1.16 (s, 3 H, $-CH_3$),

0.91 (d, J = 4.0 Hz, 1 H, cyclopropyl), 0.52 (d, J = 4.0 Hz, cyclopropyl). **15b**: δ 5.73 (m, 1 H, C-4 vinylic), 5.35 (d, J = 10 Hz, 1 H, C-5 vinylic), 4.03 (broad t, J = 7 Hz, carbinol methine), 2.22 (m, 1 H, C-2), 1.78 (m, 1 H, C-2), 1.13 (s, 3 H, $-CH_3$), 1.10 (s, 3 H, $-CH_3$), 0.80 (d, J = 4.0 Hz, cyclopropyl), 0.66 (d, J = 4.0 Hz, cyclopropyl). Measurement of peak heights of the cyclopropyl resonances in the 270-MHz spectrum indicated that the ratio of **15a**:**15b** was 3:1. The crude product was carried on without further purification.

1,6-Dimethylbicyclo[4.1.0]-4-hepten-3-one (9). Anhydrous CrO_3 (17.5 g, 0.175 mol) was added to a solution of pyridine (27.6 g, 0.350 mol) in 150 mL of CH_2Cl_2. The mixture was stirred for 1 h at room temperature. The **15a** and **15b** mixture (7.44 g, 65%, 35.0 mmol) was added slowly with rapid stirring, and the reaction mixture was stirred for 90 min at room temperature. The solution was filtered, and the flask and filter cake were washed with 20 mL of Et_2O. The combined filtrate was washed with 5% aqueous NaOH solution, 10% aqueous H_2SO_4 solution, saturated aqueous $NaHCO_3$ solution, and saturated aqueous NaCl solution and dried ($MgSO_4$). The solvents were removed on a rotary evaporator, and the crude yellow oil was distilled at reduced pressure using a short-path cold finger apparatus to yield 1,6-dimethylbicyclo[4.1.0]-4-hepten-3-one (**9**) as a pale yellow oil, bp 35–40 °C (0.02 mm), 2.6 g, 95% purity by NMR integration (Figure 1), 50%. NMR ($CDCl_3$): δ 7.11 (d, J = 10 Hz, 1 H, C-5 vinylic H), 6.68 (d, J = 10 Hz, 1 H, C-4 vinylic H), 2.58 (AB quartet, J = 20 Hz, 2 H, C-2), 1.32 (s, 3 H, $-CH_3$), 1.24 (s, 3 H, $-CH_3$), 0.86 (d, J = 4 Hz, 1 H, cyclopropyl), 0.45 (d, J = 4 Hz, 1 H, cyclopropyl). IR (CCl_4): 3040, 2995, 2980, 2960, 2880, 1745, 1640 cm^{-1}. UV (EtOH): λ_{max} 268 nm, ϵ 3850. MS: calcd for $C_9H_{12}O$, 136.088 81; found, 136.0889.

7-Bromo-1,6-dimethylbicyclo[4.1.0]-3-heptene (18). Triphenyltin hydride[22] (84%, 24.8 g, 59.2 mmol) was added to a solution of **13** (16.6 g, 59.2 mmol) in 200 mL of Et_2O, and the mixture was stirred for 36 h at room temperature. The volume of the reaction mixture was reduced to 30 mL on a rotary evaporator, and the reaction mixture was filtered. The filtrate was distilled at reduced pressure to yield a mixture of *exo*- and *endo*-7-bromo-1,6-dimethylbicyclo[4.1.0]-3-heptenes (**18**) as a clear, colorless oil, bp 40–45 °C (0.15 mm), 10.7 g, 90%. The ratio exo:endo was determined to be 4:1 by integration of the cyclopropyl resonances in the ^1H NMR spectrum. NMR ($CDCl_3$): δ 5.5 (m, 2 H, vinyl), 3.20 (s, *exo*-**18** cyclopropyl), 2.74 (s, *endo*-**18** cyclopropyl), 2.4–2.0 (m, 4 H, allylic), 1.18 (s, *endo*-**18** $-CH_3$'s), 1.15 (s, *exo*-**18** $-CH_3$'s).

Silver-Catalyzed Solvolysis of *exo*-18 in *endo*-18–*exo*-18 Mixture. A modification of the procedure of Warner and Lu was employed.[23a] Silver nitrate (6.92 g, 40 mmol) was added to a solution of *exo*- and *endo*-**18** (4:1 *exo*-**18**–*endo*-**18**, 10.7 g, 53.2 mmol) in 250 mL of 90% aqueous acetone, and the mixture was stirred for 16 h at room temperature. AgBr was removed, and the solution was concentrated on a rotary evaporator. The liquid was extracted with pentane and dried ($MgSO_4$) to yield a yellow oil (9.8 g). A small amount of this oil was separated by preparative gas chromatography (10 ft × $^3/_8$ in. 20% Carbowax 20M on 60/80 Chromosorb W, A/W DMCS, 110 °C, 100 mL/min). Two peaks, A (retention time 9.5 min, relative area 1.0) and B (retention time 37.8 min, relative area 4.0), were collected. Peak A was a mixture of 1,3-dimethyl-1,3,5-cycloheptatriene, 1,6-dimethyl-1,3,5-cycloheptatriene, and 2,4-dimethyl-1,3,5-cycloheptatriene, relative abundances 67:32:1, respectively, as determined by measurement of 270-MHz ^1H NMR peak heights. NMR of mixture ($CDCl_3$, 270 MHz) follows. 1,3-Dimethyl: δ 6.25 (broadened d, J = 5.7 Hz, 1 H, C-4), 6.03 (dd, J = 9.4, 5.7 Hz, 1 H, C-5), 5.82 (broadened s, 1 H, C-2), 5.31 (dt, J = 9.4, 6.8 Hz, 1 H, C-6), 2.30 (d, J = 6.8 Hz, 2 H, C-7), 1.97 (narrow m, 6 H, $-CH_3$'s). 1,6-Dimethyl: δ 6.38–5.92 (m, AA'BB', 4 H, C-2, C-3, C-4, C-5), 2.27 (s, 2 H, C-7), 2.01 (s, 6 H, $-CH_3$'s). 2,4-Dimethyl (partial): δ 5.39 (dt, J = 10.0, 6.2 Hz, 1 H, C-6), 5.04 (t, J = 6.2 Hz, 1 H, C-1). IR (CCl_4): 3010, 2960, 2910, 2870, 2840, 1632, 1550, 1540, 1445, 1435, 1372, 1326, 1290, 1245 cm^{-1}. Peak B was pure *exo*-**18**. NMR ($CDCl_3$, 270 MHz): δ 5.49 (m 2 H, vinyl), 3.22 (s, 1 H, cyclopropyl), 2.23 (broadened AB quartet, J_{AB} = 16 Hz, allylic), 1.17 (s, 6 H, $-CH_3$). IR (CCl_4): 3040–2820 (broad), 1660, 1630, 1430, 1380, 1320, 1210, 1180, 1140, 1130, 1025, 995, 945, 920, 910, 880 cm^{-1}. MS: calcd for $C_9H_{13}{}^{79}Br$, 200.020 11; found, 200.0205. The crude product oil was distilled at reduced pressure to yield *exo*-**18** as a clear, colorless oil, bp 40–45 °C (0.15 mm), 8.0 g, 75% based on total **18**, 94% based on starting *exo*-**18**. There was no detectable *endo*-**18** or other impurities in the ^1H NMR spectra of distilled *exo*-**18**.

1,6-Dimethylbicyclo[4.1.0]-3-heptene-*exo*-7-d_1 (14-d_1). An adaptation of the procedure of Walborsky and Impastato[24a] was employed. *exo*-**18** (7.5 g, 37.3 mmol) was added by syringe to a mixture of *n*-BuLi (1.5 M in hexane, 24.7 mL, 37.3 mmol) and 2.0 mL of THF at −20 °C, and the reaction mixture was stirred for 90 min. D_2O (99.8 atom % D, 3 mL) was added, and the reaction mixture was allowed to warm slowly to room temperature. The layers were separated, and the aqueous layer was extracted with 5 mL of pentane. The combined organic layers were dried ($MgSO_4$), and the solvent was removed by distillation at atmospheric pressure. The crude yellow oil was subjected to preparative gas chromatography (8 ft × $^1/_4$ in. 20% SE-30 on 60/80 mesh Chromosorb P, HMDS treated, 130 °C, flow rate 80 mL/min). 1,6-Dimethylbicyclo[4.1.0]-3-heptene-*exo*-7-d_1 (**14**-d_1) was collected as a clear, colorless liquid, retention time 7.0 min, 1.0 g, 22% yield. ^1H NMR (C_6D_6): δ 5.49 (m, 2 H, vinyl), 2.18 (m, 4 H, allylic), 1.08 (s, 6 H, $-CH_3$), 0.81 (s, 1 H, endo cyclopropyl H), 0.02 (d, trace, **14** exo cyclopropyl H). The deuterium incorporation of **14**-d_1 was determined both by measurement of the peak heights and by planimetry integration of the cyclopropyl proton resonances of the 270-MHz NMR spectrum. Both methods gave values of 94 ± 2% d_1, 6 ± 2% d_0.

1,6-Dimethylbicyclo[4.1.0]-4-hepten-3-ol-*exo*-7-d_1 (15-d_1). Using the procedure described above for the preparation of **15**, **14**-d_1 (1.0 g, 8.1 mmol) was converted into a 3:1 mixture of 1,6-dimethylbicyclo[4.1.0]-4-hepten-3-ols-*exo*-7-d_1, **15a**-d_1 and **15b**-d_1, as a yellow oil (1.4 g, 67% purity by NMR integration, 80% yield). NMR ($CDCl_3$): δ 6.2–5.2 (m, 2 H, vinyls), 4.4–4.0 (m, 1 H, carbinol methine H), 2.9–1.5 (m, 3 H), 1.19 (s, $-CH_3$, **15a**-d_1), 1.16 (s, $-CH_3$, **15a**-d_1), 1.13 (s, $-CH_3$ **15b**-d_1), 1.10 (s, $-CH_3$, **15b**-d_1), 0.91 (s, **15a**-d_1, endo cyclopropyl H), 0.66 (s, **15b**-d_1 endo cyclopropyl H). The crude product oil was carried on without further purification.

1,6-Dimethylbicyclo[4.1.0]-4-hepten-3-one-*exo*-7-d_1 (9-d_1). Using the procedure described above for the preparation of **9**, the **15**-d_1 mixture (1.4 g, 67% purity, 6.48 mmol) was converted to 1,6-dimethylbicyclo[4.1.0]-3-one-*exo*-7-d_1 (**9**-d_1) as a pale yellow oil (520 mg, 85% purity by NMR, GC, 50% yield). Purity was determined by gas chromatography (5 ft × $^1/_8$ in. 20% SE-30 on 60/80 mesh Chromosorb P, 85 °C, flow rate 20 mL/min, retention time 31 min) to be 85%. Deuterium incorporation was determined by measurement of peak heights of the cyclopropyl region of the NMR spectrum to be 94 ± 2% d_1, 6 ± 2% d_0.

Lithium Dimethylcuprate. A modification of the procedures of Casey and Marten[25a] and of House and Fischer[25b,c] was employed. CH_3Li (1.23 M in Et_2O, 1.30 mL, 1.60 mmol) was added by syringe to a solution of $(n\text{-}Bu_2S)_2CuI$ (0.797 g, 1.65 mmol) in 10 mL of Et_2O at −78 °C, forming CH_3Cu as a bright yellow precipitate. The suspension was centrifuged at low temperature, and the supernatant solution removed by cannula from the precipitate. The precipitate was washed with four 10-mL portions of cold (0° C) Et_2O. Et_2O (10 mL) was added, followed by CH_3Li (1.20 mL, 1.48 mmol) at −78 °C. The mixture was stirred at −78 °C until all the CH_3Cu redissolved, forming a colorless, clear solution of lithium dimethylcuprate, $LiCu(CH_3)_2$ (1.48 mmol), in Et_2O.

Reaction of 9 with $LiCu(CH_3)_2$. A solution of $LiCu(CH_3)_2$ in Et_2O (1.48 mmol) was added at −78 °C to a solution of **9** (190 mg, 1.40 mmol) in 5 mL of Et_2O. Formation of a yellow precipitate began immediately. The reaction mixture was warmed to −10 °C and stirred for 1 h, then poured into 25 mL of saturated aqueous NH_4Cl solution. The mixture was stirred for 15 min, the layers were separated, and the aqueous layer was extracted with 25 mL of Et_2O. The combined organic layers were dried ($MgSO_4$) and the solvent was removed on a rotary evaporator to leave 200 mg of a yellow oil. The gas chromatogram of the product mixture (6 ft × $^1/_8$ in. 10% Carbowax 20M on 80/100 mesh Chromosorb W, AW DMCS, 95 °C, 20 mL/min) showed complete disappearance of starting material and appearance of two products, *exo*-1,5,6-trimethylbicyclo[4.1.0]heptan-3-one (**19**, retention time 33.9 min) and 5-ethyl-4,5-dimethyl-3-cyclohexenone (**12**, retention time 42.4 min). The GC ratio of **19** to **12** was 48:52. Purification of small samples of **19** and **12**, both clear, colorless liquids, was achieved by preparative gas chromatography (10 ft × $^3/_8$ in. 20% Carbowax 20M on 60/80 mesh Chromosorb W, AW DMCS, 120 °C, 100 mL/min), where the retention times for **19** and **12** were 48.5 and 57.2 min, respectively. For **19**: NMR ($CDCl_3$, 270 MHz) δ 2.53, 2.42 (AB quartet, J = 18.8 Hz, 2 H, C-2; the upfield half of the AB quartet is further split into two doublets, J = 1.0 Hz), 2.30 (dd, J = 17.8, 5.8 Hz, 1 H, C-4), 2.17 (m, J = 6.6, 2.6 Hz, 1 H, C-5 equatorial H), 2.09

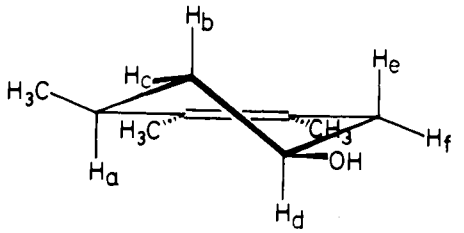
(dd, J = 17.8, 2.6 Hz, 1 H, C-4), 1.17 (s, 3 H, cyclopropyl $-CH_3$), 1.11 (s, 3 H, cyclopropyl $-CH_3$), 1.05 (dd, J = 6.6, 0.8 Hz, 3 H, C-5 axial $-CH_3$), 0.72 (d, J = 5.5 Hz, endo cyclopropyl H), 0.15 (dd, J = 5.5, 1.1 Hz, exo cyclopropyl H); IR (CCl_4) 3060, 2980, 2970, 2954, 2878, 1713, 1664, 1460, 1120, 910 cm^{-1}; MS 152.1201 (calcd for $C_{10}H_{16}O$, 152.120 11). For **12**, NMR ($CDCl_3$, 270 MHz) 5.43 (m, 1 H, C-3 vinylic), 2.83 (m, 2 H, C-2), 2.35 (AB quartet, J = 24 Hz, 2 H, C-6), 1.72 (m, 3 H, C-4 $-CH_3$), 1.6–1.2 (12-line pattern, AB portion of ABM_3, J = 14.1, 7.2 Hz, diastereotopic methylene protons of ethyl group), 1.03 (s, 3 H, C-5 $-CH_3$), 0.81 (t, J = 7.3 Hz, 3 H, methyl protons of ethyl group); {^{1}H at δ 0.81} 1.6–1.2 (m, broadened AB quartet, J = 14.1 Hz); IR (CCl_4) 2970, 2942, 2922, 2880, 1724, 1683, 1460, 1380, 1060, 1050 cm^{-1}; MS 152.1203 (calcd for $C_{10}H_{16}O$, 152.120 11).

Reaction of 9-d_1 with $LiCu(CH_3)_2$. Using the same procedure as that carried out for conversion of **9** to **19** and **12**, **9-d_1** (230 mg, 85% purity, 1.44 mmol) was reacted with $LiCu(CH_3)_2$ (1.70 mmol) to yield 200 mg of an amber oil. Analytical gas chromatography of the product oil (5 ft × $^1/_8$ in. 20% SE-30 on 60/80 Chromosorb P, 85 °C, flow rate 20 mL/min) showed complete disappearance of starting material (retention time 31 min) and appearance of two peaks, A and B, retention times 35.6 and 41.9 min, relative areas 52:48. A small sample of **12-d_1**, peak B, was isolated by preparative gas chromatography (10 ft × $^3/_8$ in. 20% Carbowax 20M on 60/80 mesh Chromosorb W, AW DMCS, 120 °C, flow rate 80 mL/min). NMR ($CDCl_3$, 270 MHz): δ 5.43 (m, 1 H, C-3 vinylic H), 2.83 (m, 2 H, C-2), 2.35 (AB quartet, J = 24 Hz, 2 H, C-6), 1.72 (m, 3 H, C-4 $-CH_3$), 1.48 (m, trace), 1.33 (quartet of 1:1:1 triplets, J = 7.3, 2.1 Hz, 1 H, single diastereotopic ethyl methylene H split by H–D geminal coupling), 1.03 (s, 3 H, C-4 $-CH_3$), 0.81 (d, J = 7.3 Hz, ethyl $-CH_3$). {^{1}H at 0.81 δ}: 1.33 (broad s, 1 H); no δ 1.48 signal observable. Planimetry integration of the methylene region of the NMR spectrum (Figure 2) indicated that the ratio of protons at δ 1.48 to 1.33 is 0.053 ± 0.02:1.00, corresponding to a mixture of 95 ± 2% **12-d_1**, stereospecifically labeled, and 5 ± 2% **12**.

1-Methoxy-3,4,5-trimethyl-1,4-cyclohexadiene. Following the procedure reported by Dastur,[29] 3,4,5-trimethylanisole[30] (12.25 g, 81.5 mmol) was reacted with lithium wire (5.2 g, 0.75 g-atom) in liquid ammonia to yield 1-methoxy-3,4,5-trimethyl-1,4-cyclohexadiene as a colorless oil (11.1 g, 85%), bp 38–40 °C (0.2 mm) (lit.[29] 65–68 °C (17 mm)). NMR ($CDCl_3$): δ 4.58 (m, 1 H, C-2), 3.54 (s, 3 H, $-OCH_3$), 2.9–2.1 (m, 3 H, C-3, C-6), 1.65 (broad s, 6 H, C-4, C-5 $-CH_3$'s), 1.07 (d, J = 7 Hz, 3 H, C-3 $-CH_3$).

3,4,5-Trimethyl-3-cyclohexenone (21). An adaptation of the procedure of Clarke and Bergman[31] was used. 1-Methoxy-3,4,5-trimethyl-1,4-cyclohexadiene (5.4 g, 35.8 mmol) was added dropwise over 5 min to a solution of oxalic acid (4.15 g, 46.2 mmol) in 80 mL of CH_3OH and 4 mL of H_2O. The solution was stirred for 1 h at room temperature. $NaHCO_3$ (3.48 g, 41.4 mmol) was added slowly, and the reaction mixture was stirred for 15 min. The reaction mixture was then poured into a mixture of 75 mL of pentane and 150 mL of H_2O. The aqueous layer was extracted with three 75-mL portions of pentane, and the combined organic layers were dried (Na_2SO_4). The solvent was removed by rotary evaporator to give 4.6 g of a colorless oil. Analytical vapor phase chromatography (5 ft × $^1/_8$ in. 10% Carbowax 20M on 80/100 mesh Chromosorb W, AW DMCS, 110 °C, 20 mL/min) of the oil showed the major peak, retention time 15.8 min, to be 89% of the product. A small sample of this compound was purified by preparative gas chromatography (5 ft × $^1/_4$ in. 3% EGS on 60/80 mesh Chromosorb P, 80 °C, 80 mL/min, retention time 8.5 min), to give 3,4,5-trimethyl-3-cyclohexenone (**21**) as a colorless liquid. NMR ($CDCl_3$, 270 MHz): δ 2.76 (AB quartet, J = 22 Hz, 2 H, C-2), 2.65 (dd, J = 13.4, 6.3 Hz, 1 H, C-6), 2.53 (broad quintet, J = 7 Hz, 1 H, C-5 methine H), 2.27 (dd, J = 13.4, 2.8 Hz, 1 H, C-6), 1.74 (broad s, 3 H, C-4 $-CH_3$), 1.65 (broad s, 3 H, C-3 $-CH_3$), 1.00 (d, J = 7.1 Hz, 3 H, C-5 $-CH_3$). IR (CCl_4): 2960, 2915, 2860, 1716, 1638, 1500, 1374, 1350, 1312, 1253, 1247, 1200, 1142, 1085, 850 cm^{-1}. MS: calcd for $C_9H_{14}O$, 138.104 60; found, 138.1045. The crude **21** was carried on without further purification (4.6 g, 89% purity by GC, 83% yield of **21**).

***cis*- and *trans*-3,4,5-Trimethyl-3-cyclohexenols (22, 23).** A solution of **21** (1.52 g, 89%, 9.7 mmol) in 10 mL of dry Et_2O was added slowly to a suspension of $LiAlH_4$ (776 mg, 20.5 mmol) in 15 mL of dry Et_2O, and the reaction mixture was stirred at reflux for 8 h. The reaction mixture was cooled to room temperature, and 776 μL of H_2O, 776 μL of 15% aqueous NaOH solution, and 2.32 mL of H_2O were added in that order. The granular precipitate was removed by filtration, and the organic layer was dried over $MgSO_4$ and concentrated on a rotary evaporator to yield 1.45 g of a light yellow-green oil. Preparative gas chromatography (10 ft × $^3/_8$ in. 20% Carbowax 20M on 60/80 mesh Chromosorb W, 100 °C, 80 mL/min) of a small sample of the product oil showed two peaks, A and B, of retention times 125 and 135 min, respectively, and area ratio 12:88. Peak B was *cis*-3,4,5-trimethyl-3-cyclohexenol (**22**). ^{1}H NMR ($CDCl_3$, 270 MHz): δ 3.81 (13-line pattern, dddd, J = 11.5, 9.3, 5.6, 3.7 Hz, 1 H, H_d), 2.18 (m, 2 H, H_a, H_f), 1.97 (m, 2 H, H_c, H_e), 1.59 (broad s, 3 H, vinylic $-CH_3$), 1.56 (m, 3 H, vinylic $-CH_3$), 1.45 (broad s, 1 H, $-OH$), 1.20 (dt, J = 11.5, 10.5 Hz, 1 H, H_b), 1.01 (d, J = 7.0 Hz, C-5 $-CH_3$). Single frequency decoupling {δ 3.81}: 2.18 (broad d, J = 15.75 Hz), 1.97 (some simplification), 1.20 (t, J = 11 Hz). {δ 2.18}: 3.81 (ddd, width 19 Hz, J = 11.5, 9.3, 3.7 Hz), 1.97 (broad d, J = 7 Hz), 1.20 (t, J = 11 Hz), 1.01 (s). {δ 1.97}: 3.81 (dd, J = 11, 5.3 Hz), 2.18 (simplification), 1.20 (t, J = 11 Hz). {δ 1.20}: 3.81 (ddd, J = 9.3, 5.5, 3.7 Hz), 1.97 (simplified), 2.18 (simplified). On the basis of the decoupling experiments and the multiplicity and coupling constants of the δ 3.81 (H_d) and 1.20 (H_b) multiplets, the structure of **22** was deduced as shown below. The



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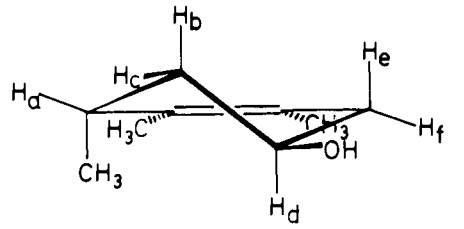
coupling constants as determined for the decoupling experiments are as follows: J_{ab} = 11.5 or 10.5, J_{bc} = 11.5 or 10.5, J_{bd} = 11.5, J_{cd} = 3.7, J_{ed} = 9.3, J_{df} = 5.6, $J_{a\text{-}CH_3}$ = 7.0, J_{ef} = 15.75 Hz. IR (CCl_4): 3340, 2975, 2958, 2920, 2872, 2860, 1660, 1455, 1440, 1370, 1120, 1040 cm^{-1}. MS: calcd for $C_9H_{16}O$, 140.120 03; found, 140.1201.

Peak A was *trans*-3,4,5-trimethyl-3-cyclohexenol (**23**), a clear, colorless liquid. NMR ($CDCl_3$, 270 MHz): δ 3.99 (13-line multiplet, dddd, J = 9.2, 7.8, 5.3, 3.9 Hz, 1 H), 2.23 (m, J = 5, 16.5 Hz, 2 H, H_a, H_f), 1.90 (broadened dd, J = 16.6, 7.4 Hz, 1 H, H_e), 1.65 (m, partially obscured by singlet at δ 1.59, 2 H, H_b, H_c), 1.59 (broad s, 6 H, vinylic $-CH_3$'s), 1.43 (s, 1 H, $-OH$), 1.02 (d, J = 7.2 Hz, C-5 $-CH_3$). Single frequency decoupling {δ 3.99}: 2.23 (broad d, J = 17 Hz, overlapping a multiplet), 1.90 (broad d, J = 17 Hz), 1.65 (some simplification). {δ 2.23}: 3.99 (ddd, J = 9, 7.5, 3.8 Hz), 1.90 (d, J = 7 Hz), 1.65 (some simplification), 1.02 (s). {δ 1.90}: 3.99 (ddd, J = 9, 7.5, 5.3 Hz), 2.23 (some simplification). IR (CCl_4): 3500–3200, 3063, 3035, 2978, 1670, 1455, 1370, 1128, 1090, 1040, 958 cm^{-1}. MS: calcd for $C_9H_{16}O$, 140.120 03; found, 140.1203. Although a structure for **23** could not



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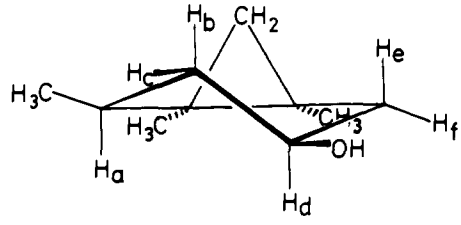
be assigned on the basis of its NMR spectrum alone, comparison of its NMR spectrum to that of the more completely analyzable isomer **22**, along with analysis of the splitting pattern of **23** for the H_d carbinol methine proton and the decoupling experiments, allowed for the stereochemical assignment shown. The coupling constants determined from the decoupling experiments are J_{bd} = 9.2, J_{cd} = 3.9, J_{de} = 7.8, J_{df} = 5.3, J_{ef} = 16.6, $J_{a\text{-}CH_3}$ = 7.0 Hz.

The cis alcohol, **22**, was purified by five successive recrystallizations of the crude product from Et_2O at −78 °C to yield a white, crystalline solid, mp 29 °C (0.68 g, 50% yield). Gas chromatographic analysis of recrystallized **22** (6 ft × $^1/_8$ in. 10% Carbowax 20M on 80/100 mesh Chromosorb W, AW, DMCS, 75 °C, 20 mL/min) indicated 98.9% purity.

***cis*-1,5,6-Trimethylbicyclo[4.1.0]heptan-3-ol (24).** A mixture of

CH_2I_2 (1.82 g, 6.79 mmol) and **22** (680 mg, 4.85 mmol) in 3 mL of Et_2O was added dropwise over 5 min to a stirred suspension of zinc-copper couple.[32] The reaction mixture was stirred at reflux for 5 days. The reaction mixture was filtered, and the solid was washed with 20 mL of Et_2O. The combined organic liquid was washed with saturated aqueous $NaHSO_3$ solution, saturated aqueous NH_4Cl solution, and saturated aqueous NaCl solution and dried ($MgSO_4$). Concentration on a rotary evaporator afforded a clear yellow oil, which was purified by thin layer chromatography on silica gel (20% Et_2O–80% hexane eluent, single band at R_f 0.25) to yield *cis*-1,5,6-trimethylbicyclo[4.1.0]heptan-3-ol (**24**) as a clear, colorless oil (300 mg, 40%).



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NMR ($CDCl_3$, 270 MHz): δ 3.52 (dddd, J = 11.6, 10.9, 6.4, 3.2 Hz, 1 H, H_d), 1.94 (ddd, J = 13.4, 6.4, 3.2 Hz, 1 H, H_f), 1.75 (seven-line pattern, d of quartets of d, J = 12.8, 6.4, 6.4 Hz, 1 H, H_a), 1.57 (dddd, J = 12.4, 6.4, 3.2, 2.2 Hz, 1 H, H_c), 1.41 (dd, J = 13.2, 10.8 Hz, 1 H, H_e), 1.07 (s, 3 H, cyclopropyl -CH_3), 1.02 (s, 3 H, cyclopropyl -CH_3), 0.94 (d, J = 6.4 Hz, 3 H, C-5 -CH_3), 0.70 (four-line pattern, ddd, all $J \approx$ 12 Hz, 1 H, H_b), 0.27 (d, J = 4.4 Hz, 1 H, cyclopropyl H), −0.03 (d, J = 4.4 Hz, 1 H, cyclopropyl H). IR (CCl_4): 3050, 2985, 2960, 2932, 2872, 1562, 1472, 1200, 1150, 1120 cm^{-1}. MS: calcd for $C_{10}H_{16}O$, 154.1360; found 154.1359. The coupling constants are as follows: J_{ab} = 12.8, J_{ac} = 6.4, $J_{a\text{-}CH_3}$ = 6.4, J_{bc} = 12.4, J_{bd} = 11.6, J_{cd} = 3.2, J_{cf} = 2.2 ("w" coupling), J_{de} = 10.8, J_{df} = 6.4, J_{ef} = 13.2, $J_{cyclopropyl}$ = 4.4 Hz.

***endo*-1,5,6-Trimethylbicyclo[4.1.0]heptan-3-one (20).** Anhydrous CrO_3 (0.97 g, 9.7 mmol) was added to a solution of dry pyridine (1.54 g, 19.4 mmol) in 25 mL of CH_2Cl_2, and the mixture was stirred for 30 min, until all the CrO_3 dissolved. **24** (300 g, 1.94 mmol) was added, and the reaction mixture was stirred vigorously for 30 min. The reaction mixture was filtered, and the filtrate was washed with 5% aqueous NaOH solution, 10% aqueous H_2SO_4, saturated aqueous $NaHCO_3$ solution, and saturated aqueous NaCl solution. The organic layer was dried ($MgSO_4$), concentrated on a rotary evaporator, and purified by preparative thin layer chromatography (1:1 Et_2O–hexane eluent, R_f 0.5) to yield *endo*-1,5,6-trimethylbicyclo[4.1.0]heptan-3-one (**24**) as a colorless oil (250 mg, 85% yield). NMR ($CDCl_3$, 270 MHz): δ 2.46 (AB quartet, J = 18.6 Hz, 2 H, C-2), 2.19 (complex m, 2 H), 1.73 (complex m, 1 H), 1.11 (s, 3 H, cyclopropyl -CH_3), 1.10 (s, 3 H, cyclopropyl -CH_3), 0.98 (d, J = 6.2 Hz, 3 H, C-5 -CH_3), 0.56 (d, J = 5.6 Hz, 1 H, cyclopropyl), 0.03 (d, J = 5.6 Hz, 1 H, cyclopropyl). The multiplets at δ 2.19 and 1.73 were simplified in the presence of 10 mol % tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium: δ 2.19 (dd, J = 16.8, 5.5 Hz, C-4 equatorial H, and d of quartets of d, J = 11.2, 6.2, 5.5 Hz, axial C-5 methine H), 1.73 (dd, J = 16.8, 11.2 Hz, C-4 axial H). IR (CCl_4): 3055, 2978, 2960, 2925, 2900, 2870, 1716, 1605 (w), 1570 (w), 1452 cm^{-1}. MS: calcd for $C_{10}H_{16}O$, 152.1200; found, 152.1198.

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