Preparation, Stereochemistry, and Nuclear Magnetic Resonance Spectroscopy of 4-Hydroxy(acetoxy)bicyclo[5.1.0]octanes. Synthesis of (-)- and (±)-8,8-Dimethylbicyclo[5.1.0]oct-2-en-4-one

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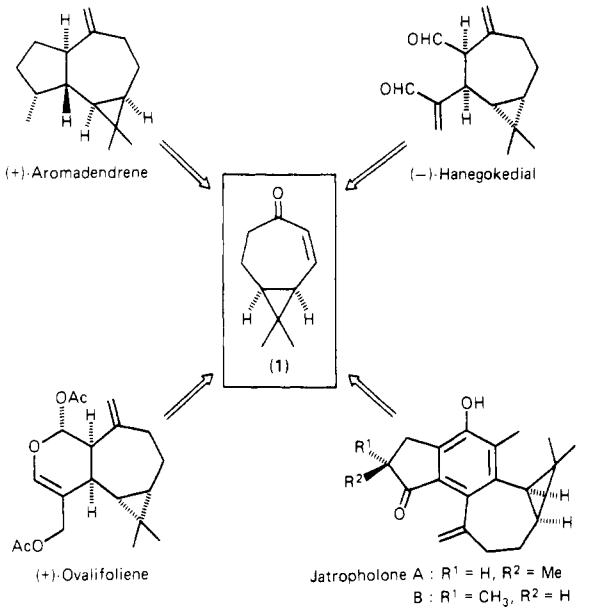
A potentially versatile intermediate for the synthesis of natural products containing the bicyclo[5.1.0]octane ring system is 8,8-dimethylbicyclo[5.1.0]oct-2-en-4-one (1). This intermediate was prepared efficiently in racemic form from 5-acetoxycycloheptene and in chiral form (1*R*,7*S*) from (-)-2-carene, via separate synthetic strageties. In addition, a number of 4-hydroxy(acetoxy)bicyclo[5.1.0]octanes (3, 4, and 6) were also prepared and their stereochemistry established rigorously by NMR spectroscopy and chemical correlation to 3t, the structure of which was determined by X-ray crystallographic analysis.

Introduction and Background

Recently a portion of our ongoing effort directed toward the total synthesis of natural products has focused on the preparation of targets that contain the bicyclo[5.1.0]octane ring system. This substructure is common to several groups of naturally occurring sesquiterpenes including the aromadendranes[2] and secoaromadendranes,[3] members of which have long been used in folk medicines.[2b,4] Of particular interest here are the diterpenoid jatropholones,[5] which contain the bicyclo[5.1.0]octane as part of a tetracyclic array and which are believed to be biogenetically related to the antitumor diterpene, jatrophone.[6] Examination of possible synthetic approaches to these compounds led us to consider bicyclic enone 1 as a common versatile intermediate, which could potentially be elaborated to a number of individual members of these classes of natural products.

In this paper we describe the successful preparation of 1 in both racemic and chiral forms (1*R*,7*S*) via separate synthetic strategies. Of considerable significance in this effort is the development of a novel cycloheptenone synthesis based, in part, on the Lewis acid promoted intramolecular condensation of acetals with enol silyl ethers, a reaction first introduced by Mukaiyama.[7] Finally, we have also prepared and defined rigorously the stereochemistry of several 4-hydroxy(acetoxy)bicyclo[5.1.0]octanes as well as analyzed their nuclear magnetic resonance spectra as they relate to stereochemistry.



Results and Discussion

(1) Synthesis of (±)-8,8-Dimethylbicyclo[5.1.0]oct-2-en-4-one ((±)-1). Our first approach to enone 1 employed a cycloheptene precursor to which the cyclopropane ring was appended with use of dibromocarbene. The starting material for this approach, 5-acetoxycycloheptene (2), was prepared according to the method of Scheiner[8] from 4-cycloheptenecarboxylic acid.[9] Treatment of 2 with dibromocarbene in a two-phase system afforded an equimolar mixture of cis and trans bicyclooctanes 3, as illustrated in Scheme I. A similar reaction performed under homogeneous conditions produced an identical mixture but in considerably lower yield. This mixture could be carried forward without separation, although for characterization purposes the components were isolated as white crystalline compounds via careful chromatography. Unfortunately, an unambiguous assignment of stereochemistry could not be made based solely on NMR spectroscopy. A striking difference was, however, noticed in the chemical shift and coupling pattern observed for the C-4 methine proton. For the isomer that eluted first, this signal was observed at δ 4.60 as a closely defined triplet of triplets (Table I). X-ray

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Scheme I

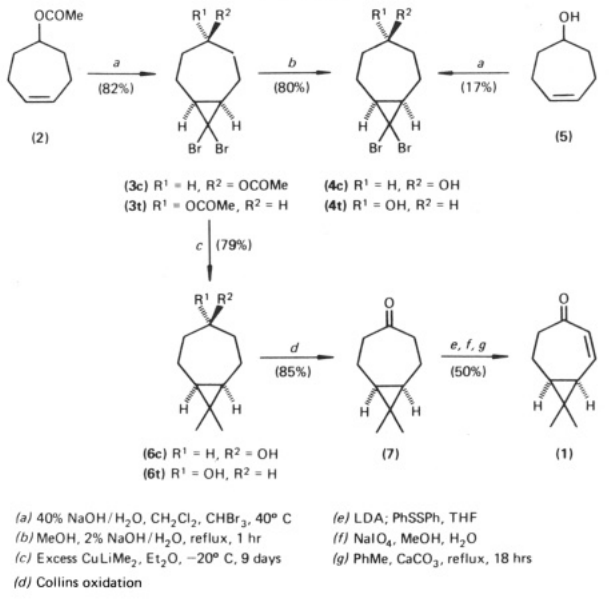


Table I. ^{1}H NMR Data for Diastereomers 3, 4, and 6

	C-4 methine chemical shift, δ		
compd	cis	trans	Δ(cis–trans)
3	5.20 (br s)	4.60 (tt, J = 10.8, 3.7 Hz)	0.60
4	4.26 (br s)	3.48 (tt, J = 10.8, 3.7 Hz)	0.78
6	4.22 (br s)	3.44 (tt, J = 10.8, 3.7 Hz)	0.78

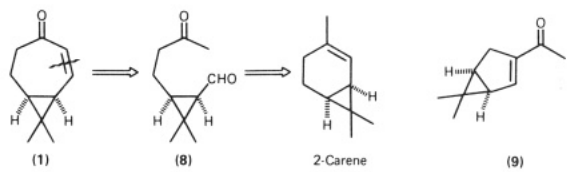
crystallographic analysis[10] defined this isomer to be the trans derivative **3t**. The other isomer possessing the cis configuration displayed the C-4 methine as a broad singlet at δ 5.20, downfield relative to **3t**. With the stereochemistry of **3c** and **3t** secure, the spectroscopic observations are consistent with both isomers existing in chairlike conformation.[11] In **3c** the C-4 methine proton occupies a pseudoequatorial position and from Dreiding models has a dihedral angle of approximately 90° relative to one of the adjacent methylene protons; thus one would expect a simpler coupling pattern. In **3t** the corresponding proton is pseudoaxial, and the dihedral angles to the adjacent methylene protons are approximately 40° and 155°, again consistent with the observed pattern of coupling. The relative chemical shifts of the C-4 methine proton in **3c** and **3t** are also consistent with this chairlike model when compared to the axial vs. equatorial proton chemical shifts found in cyclohexanols.[12]

While no selectivity in the addition of dibromocarbene to **2** was observed, considerable selectivity was observed in the addition to 5-cycloheptenol **5**, prepared by saponification of **2**. Under homogeneous conditions, the alcohols **4c** and **4t**, were obtained in low yield (ca. 21%) in a ratio of 1:9. Lower but still significant was the selectivity observed under biphasic conditions when 1:2 mixture was obtained, again with the trans isomer predominating. The stereochemistry of **4c** and **4t** could readily be ascertained by inspection of their NMR spectra, which were closely analogous to that observed for **3c** and **3t**. Confirmation of these assignments was achieved by hydrolysis of **3c** to **4c** and **3t** to **4t**, respectively.

Treatment of an equimolar mixture of **3c** and **3t** with excess lithium dimethylcuprate[13] afforded the isomeric bicyclic alcohols **6** in 79% yield, which could easily be separated chromatographically. The now characteristic pattern for the C-4 methine was again observed in the NMR spectra of **6c** and **6t**, allowing ready assignment of their stereochemistry. Conversion of pure samples of **3c** and **3t** to **6c** and **6t**, respectively, confirmed these assignments. Finally oxidation of this mixture using Collins[14] conditions produced a single ketone **7** in 85% yield. Alternatively, separate oxidation of isomerically pure samples of **6c** and **6t** gave **7** in similar yields (ca. 85%).

With the preparation of racemic ketone **7** secure, conversion to the desired enone **1** appeared straightforward. This, however, was not the case. For example, use of the Reich–Sharpless procedure[15] involving selenenylation followed by oxidative–elimination gave variable but consistently low yields of **1**. This result is consistent with the poor yield of cycloheptenone obtained by Reich from cycloheptanone.[15] Similarly unsuccessful was an attempt to oxidize the enol silyl ether derived from **1** with dichlorodicyanoquinone.[16] The most satisfactory procedure for the conversion of **7** to **1** proved to be the three-step protocol of Trost,[17] involving sulfenylation with diphenyl disulfide, oxidation, and thermal elimination of the resulting sulfoxide. In this way a reproducible 50% yield of enone **1** was obtained from **7**.

(2) Synthesis of (−)-8,8-Dimethylbicyclo[5.1.0]oct-2-en-4-one ((−)-1). Our second approach to enone **1**, designed to afford chiral material, derived from the deceptively simple analysis illustrated below. Dissection of the



enone double bond via a retro-aldol condensation leads to the keto aldehyde **8**, which in turn may be obtained upon ozonolysis of 2-carene, a naturally occurring monoterpene. Although 2-carene is found in the dextrorotatory form in many essential oils,[18] it is not available commerically. Nevertheless, it is an attractive chiral starting material since it is readily prepared in large quantities in *either optical series* from D- or L-carvone.[19] Immediately obvious, however, is the problem of controlling the regiochemistry in the aldol condensation to afford **1** rather than

(10) Unpublished results of Dr. P. Carroll, Department of Chemistry, University of Pennsylvania. The trans stereochemistry and chair conformation of **3t** are clearly shown in the ORTEP plot shown below:

(11) This terminology is used by analogy to known conformations of cycloheptene: Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, C. A. "Conformational Analysis"; Interscience: New York, 1965; p 209.

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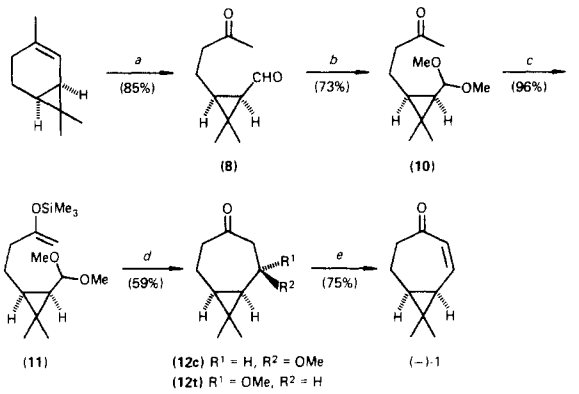
(19) This conversion was accomplished in overall yields of 40–45% by the following: (1) lithium bronze conjugate reduction, Mueller, R. H.; Gillick, J. G. *J. Org. Chem.* **1978**, *43*, 4647. (2) Hydrochlorination–cyclization: Huffman, J. W.; Swain, W. E.; Jacobus, J.; McPhail, A. T. *J. Org. Chem.* **1980**, *45*, 3088. (3) Shapiro reaction, Brunetti, P.; Fringnelli, F.; Taticchi, A. *Gazz. Chim. Ital.* **1977**, *107*, 433.

Scheme II

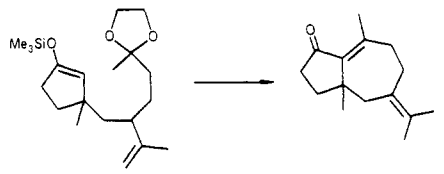


(a) O_3, MeOH, −78° C; MeSMe, −78 to 25° C
(b) MeOH, $(MeO)_3CH$, $CeCl_3$
(c) LDA, THF; TMSCl
(d) $ZnCl_2$, Et_2O, CH_2Cl_2, 25° C
(e) KO^{t}Bu, THF

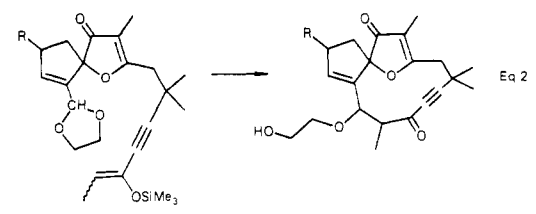
the thermodynamically favored five-membered-ring product **9**. Indeed, controlling the regiochemistry of this reaction is the central element of our strategy.

In the event, ozonolysis of (−)-2-carene in methanol followed by treatment with dimethyl sulfide afforded **8** in 85% yield (Scheme II), which upon treatment with dilute aqueous sodium hydroxide in methanol produced a single condensation product. The NMR spectrum of this product was consistent with the presence of a methyl ketone and a single olefinic proton, thus allowing identification of this compound as **9**. Attempts to form **1** from **8** via an aluminum enolate employing diisobutylaluminum phenoxide, the latter reported to give specifically enolates derived from methyl ketones,[20] also produced **9** along with considerable destruction of **8**.

At this point we turned to the titanium(IV) chloride catalyzed crossed-aldol strategy introduced by Mukaiyama. To date, use of this protocol *in the intramolecular case* has only two precedents. The first is the formation of an azulene ring system reported by Posner[23] (eq 1), the second, macrocyclization (eleven-membered ring) accomplished by Smith[24] in the total synthesis of normethyljatrophone, jatrophone, and epijatrophone (eq 2).



Eq 1



Eq 2

A central prerequisite for the intramolecular Mukaiyama strategy is the ready availability of acetal **10**. Toward this end, selective acetalization of the aldehyde could be effected in methanol under cerium catalysis[21] to afford **10** in good yield (ca. 73%), accompanied by production of small amounts of the bis ketal, the latter easily removed by chromatography. Subsequent formation of the kinetic enolate with lithium diisopropylamide followed by capture with chlorotrimethylsilane took place in near quantitative yield to afford **11**. The alternative enol ether, derived from deprotonation at the α-methylene carbon, was not detected.

Initial attempts to effect cyclization of **10** employing titanium(IV) chloride catalyst led only to poor yield (<-10%) of the desired ethers **12**, as an approximately equimolar mixture of the cis and trans isomers as determined by the ^1H NMR spectrum of the mixture. The bulk of the starting material was destroyed under these conditions (CH_2Cl_2, $TiCl_4$, −78 °C). Extensive experimentation eventually led to the use of zinc chloride catalyst in ether–dichloromethane to effect ring closure. With use of these conditions the reaction proceeded rapidly at room temperature to afford a 59% yield of a 12:1 mixture of isomers.

The predominant isomer was assigned the trans stereochemistry (**12t**) on the basis of the results of a series of nuclear Overhauser enhancement (NOE) difference experiments.[25] In particular, irradiation of the upfield methyl signal of the major isomer elicited a significant (8%) enhancement of the methine proton at C-2, bearing the methoxyl substituent. Alternatively, irradiation of either of the two geminal methyl groups of the minor isomer produced no enhancement of the C-2 methine. Dreiding models of **12c** and **12t** reveal the C-2 methine proton to be proximal to one of the geminal methyl groups in the trans derivative only. This observation remains true regardless of the specific conformation examined.

Elimination of the β-methyl ether substituent was subsequently accomplished under basic catalysis to afford the levorotatory enone **1** in 75% isolated yield. This material was identical in all respects, except optical rotation, to **1** prepared as described previously from 5-acetoxycycloheptene. The overall yield of (−)-**1** from (−)-2-carene was 27%.

Exploitation of (−)-**1** in the synthesis of various natural products as well as exploration of the generality of the zinc chloride mediated ring closure for the preparation of medium-size rings are currently under active investigation in our laboratories.

Experimental Section

Materials and Equipment. Infrared spectra (IR) were obtained for CCl_4 solutions on a Perkin-Elmer Model 337 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained for deuteriochloroform solutions on a Bruker, WP-250-FT (^1H, 250 MHz; ^{13}C, 62.9 MHz) spectrometer with Me_4Si as an internal standard. Melting points were obtained with a Thomas-Hoover melting-point apparatus and are uncorrected. Ether and tetrahydrofuran were distilled prior to use from sodium and benzophenone. Other liquid reagents or solvents indicated as dry were distilled under argon from CaH_2 unless otherwise stated. Organic extracts were dried over $MgSO_4$. Flash chromatography refers to the method described by Still and co-workers.[26]

4-Acetoxy-8,8-dibromobicyclo[5.1.0]octane (3). A 1-L three-necked flask equipped with a water condensor and ther-

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mometer was charged with a solution of 10.0 g (64.8 mmol) of acetate **2**, in 250 mL of methylene chloride. To this was added 500 mL of 40% aqueous sodium hydroxide, followed by 1.5 mL of tri-*n*-butylamine and 40 mL (116 g, 0.47 mol) of bromoform. The reaction mixture was vigorously stirred at 40–45 °C for 24 h. The resulting dark-brown solution was cooled to room temperature and then poured into 1 L of ice–water. The solution was filtered through glass wool and extracted twice with 500 mL of chloroform followed by washing with brine. Drying and evaporation of the solvent afforded a black oil, which was dissolved in 1 volume of 5% ether in hexane. Flash chromatography (5% ether in hexane) gave a tan solid, 17.2 g (81.5%). Recrystallization from 45 mL of hexane produced tan crystals, 15.9 g (75.2%), suitable for use in subsequent reactions.

Careful flash chromatography of this mixture using 5% ether in pentane resulted in separation of two white crystalline bromo acetates **3c** (mp 134–135 °C) and **3t** (mp 107–108 °C). The trans stereochemistry was assigned to **3t** after X-ray crystallographic analysis.[10]

The first compound eluted was **3t**: R_f 0.28, 10% ether in pentane; IR 1730 (s) cm^{-1}; NMR δ 1.20 (m, 2 H), 1.54 (, 2 H), 1.74 (m, 2 H), 2.02 (s, 3 H), 2.02 (m, 2 H), 2.22 (m, 2 H), 4.60 (tt, J = 10.8, 3.7 Hz, 1 H).

Anal. Calcd for $C_{10}H_{14}O_2Br_2$: C, 36.84; H, 4.33. Found: C, 37.08; H, 4.41.

The second compound eluted was **3c**: R_f 0.22, 10% ether in pentane; IR 1730 (s) cm^{-1}; NMR δ 1.67 (m, 6 H), 2.04 (m, 4 H), 2.06 (s, 3 H), 5.20 (br s, 1 H).

Anal. Calcd for $C_{10}H_{14}O_2Br_2$: C, 36.84; H, 4.33. Found: C, 36.87; H, 4.52.

8,8-Dibromobicyclo[5.1.0]octan-4-ol (4). A solution of 7.0 g (21.5 mmol) of the dibromo acetates **3** in 75 mL of 95% ethanol was treated with 75 mL of 2% aqueous sodium hydroxide and the mixture heated at reflux for 1 h. After the mixture cooled to room temperature, the ethanol was evaporated and the aqueous solution extracted with ether. The extracts were combined, dried, and evaporated. The residue was subjected to flash chromatography on silica (50% ether in hexane) to yield as the first component 2.35 g (8.33 mmol, 39.2%) of **4c** followed by 2.52 g (8.93 mmol, 41.3%) of **4t**, both as white needles. **4c**: mp 121.5–122 °C; IR 3620 (m), 3650–3150 (m), 2940 (s) cm^{-1}; NMR δ 4.26 (br s, 1 H), 1.98 (m, 3 H), 1.72 (m, 6 H), 1.39 (m, 2 H); mass spectrum, m/e 283.9214 (M^+, calcd for $C_8H_{12}OBr_2$ 283.9235). **4t**: mp 126–127.5 °C; IR 3615 (m), 3650–3150 (b), 2935 (s) cm^{-1}; NMR δ 4.20 (tt, J = 10.8, 3.7 Hz, 1 H), 2.16 (m, 2 H), 2.04 (m, 2 H), 1.75 (m, 3 H), 1.46 (m, 2 H); 1.15 (m, 2 H); mass spectrum, m/e 283.9230 (M^+, calcd for $C_8H_{12}OBr_2$ 283.9235).

Anal. Calcd for $C_8H_{12}OBr_2$ (**7t**): C, 33.83; H, 4.26. Found: C, 34.14; H, 4.29.

Preparation of 4c and 4t from Cyclohept-4-en-1-ol. (A) A solution of 1.0 g (8.9 mmol) of cycloheptenol **5** was treated with 80 mL of 40% aqueous sodium hydroxide, 0.25 mL of tri-*n*-butylamine, and 5 mL of bromoform. The mixture was vigorously stirred at 40 °C for 24 h, cooled to room temperature, and poured into 150 mL of ice–water. After filtration through a glass wool plug, the mixture was extracted with chloroform. The organic extracts were dried and evaporated, and the dark-brown residue was subjected to flash chromatography on silica (25% ether in pentane) to yield 0.13 g (5.4%) of **4c**, followed by 0.29 g (12%) of **4t**, both as off-white needles.

(B) A suspension of 0.50 g (4.45 mmol, 2.5 equiv) of potassium *tert*-butoxide in 15 mL of dry pentane was treated with a solution of 0.20 g (1.78 mmol) of **5** in 5 mL of dry pentane. The reaction mixture was cooled to 0–5 °C and charged with 0.62 mL (7.0 mmol) of bromoform. After 10 min the reaction was quenched with water (25 mL) and extracted with ether. The ether extracts were washed with brine, dried, and concentrated to a dark oil, which was subjected to flash chromatography on silica (25% ether in pentane) to yield 12 mg (2.2%) of **4c** and 95 mg (19%) of **4t** as off-white needles.

4-Hydroxy-8,8-dimethylbicyclo[5.1.0]octane (6). A flame-dried, 1-L two-necked flask was equipped with a graduated 250-mL addition funnel. The flask was flushed with argon and 18 g (95 mmol, 6.8 eq) of dry cuprous iodide was added followed by 400 mL of dry ether. The mixture was cooled to −15 °C (dry ice–ethylene glycol) and 140 mL of 1.68 M (17.4 equiv) methyllithium was then transferred via canula to the addition funnel and added dropwise to the stirred mixture. Following the addition, the mixture was stirred 15 min and then a solution of the dibromoacetates **3** (4.5 g, 13.8 mmol) in 30 mL of dry ether was added dropwise by syringe. The reaction with bath was stored at −20 °C for 9 days. The solution was stirred 2 h at 0 °C and then quenched with excess saturated ammonium chloride solution. The mixture was filtered, the cake was washed with 50 mL of ether, and the layers were separated. The organic fraction was washed with brine, dried, and concentrated to yield 2.1 g of a tan oil. Flash chromatography on silica gel (3:1 pentane–ether) produced 0.85 g of **6c**: R_f 0.36, 50% ether in pentane; mp 56–58 °C; IR: 3620 (m), 3600–3100 (m), 2850 (s), 1075 (m), 1040 (m), 990 (m), 910 (m), cm^{-1}; NMR δ 0.56 (m, 2 H), 1.00 (s, 3 H), 1.04 (s, 3 H), 1.34–1.80 (m, 6 H), 1.80–1.98 (m, 2 H), 4.22 (br s, 1 h); mass spectrum, m/e 154.1350 (M^+, calcd for $C_{10}H_{18}O$ 154.1358).

Also isolated was 0.82 g of **6t**: R_f 0.22, 50% ether in pentane; mp <10 °C; IR 3620 (m), 3600–3100 (m), 3850 (s), 1450 (m), 1055 (s), 1000 (m), 980 (m), 920 (m) cm^{-1}; NMR δ 0.56 (m, 2 H), 0.86 (m, 2 H), 0.98 (s, 3 H), 1.00 (s, 3 H), 1.42 (m, 2 H), 1.82 (m, 2 H), 2.0 (m, 2 H), 2.18 (s, 1 H), 3.44 (tt, J = 10.8, 3.7 Hz, 1 H); mass spectrum, m/e 154.1369 (M^+, calcd for $C_{10}H_{18}O$ 154.1358). The combined yield of **6** was 1.67 g (78.5%).

8,8-Dimethylbicyclo[5.1.0]octan-4-one (7). A solution of 20.6 mL (0.26 mol) of pyridine in 500 mL of methylene chloride was treated with 19.4 g (0.127 mol) of chromium trioxide and the mixture stirred 15 min. The mixture of alcohols **6** (3.27 g, 21.2 mmol) was dissolved in 3 mL of methylene chloride and added to the reaction mixture in a single portion. After being stirred for 25 min, the black mixture was decanted. The black residue was washed with ether (3 × 40 mL). The decanted fraction was combined with the washings, filtered, and then washed sequentially with 10% aqueous sodium hyroxide, 1 N hydrochloric acid, saturated sodium bicarbonate, and brine. The solution was dried over potassium carbonate and concentrated to yield 2.45 g (85%) of the ketone **7** as a clear oil: IR 2940 (s), 1690 (s), 1460 (m), 1330 (m), 1150 (s) cm^{-1}; NMR δ 0.80 (m, 2 H), 0.98 (s, 3 H), 1.06 (s, 3 H), 1.12 (m, 2 H), 2.02 (m, 2 H), 2.48 (m, 4 H); mass spectrum, m/e 152.1193 (M^+, calcd for $C_{10}H_{16}O$ 152.1201).

(±)-8,8-Dimethylbicyclo[5.1.0]oct-2-en-4-one ((±)-1). A solution of 0.53 g (3.5 mmol) of **7** in 5 mL of tetrahydrofuran was cooled to −78 °C under argon and then 2 equiv of lithium diisopropylamide was added dropwise. After being stirred for 30 min, the enolate solution was transferred via syringe to a solution of 0.91 g (4.2 mmol) of diphenyl disulfide in 5 mL of dry hexamethylphosphoramide at room temperature. The resulting solution was stirred at room temperature 1.5 h. The solution was concentrated under reduced pressure and the residue subjected to flash chromatography on silica (15% ether in pentane) to produce a mixture of cis and trans sulfides, 0.66 g (73%), which was used without further purification.

The crude mixture of sulfides (0.31 g, 1.2 mmol) was dissolved in 5 mL of absolute methanol and treated at 0 °C with 0.25 g (1.2 mmol) of sodium metaperiodate dissolved in a minimum of water. Thin-layer chromatography revealed complete consumption of starting material after stirring 24 h at room temperature. The mixture was diluted with 5 mL of methanol and vacuum filtered. The filter cake was washed with an additional 15–20 mL of methanol. The combined filtrate and washings were concentrated under reduced pressure. The residue was partitioned between water and ether. The layers were separated, and the ether extract was washed with brine, dried, and evaporated to yield 0.30 g (91%) of a mixture of sulfoxides as a pale-yellow oil, used in the following step without further purification.

The crude mixture of sulfoxides (0.30 g, 1.1 mmol) was dissolved in 5 mL of dry toluene, followed by the addition of 0.5 g (5 mmol) of calcium carbonate. The mixture was heated at reflux under a drying tube ($CaSO_4$) for 24 h. The mixture was cooled to room temperature and vacuum filtered and the filter cake was washed with several portions of ether. The solvent was removed under reduced pressure and the residue was purified by careful flash chromatography (50% ether in pentane) to yield 0.12 g (75%) of (±)-1 as a colorless oil. Overall yield for the three steps was 50%. (±)-1: IR 2940 (s), 1660 (s) cm^{-1}; NMR δ 6.41 (d, J = 13.0 Hz, 1 H), 5.83 (d, J = 13.0 Hz, 1 H), 2.64 (m, 2 H), 2.05 (m, 1 H), 1.52 (m, 1 H), 1.25 (m, 1 H), 1.17 (s, 3 H), 1.04 (s, 3 H), 0.84 (m,

1 H); spectrum, m/e 150.1034 (M^+, calcd for $C_{10}H_{14}O$ 150.1044).

(−)-*cis*-3-(3-Oxobutyl)-2,2-dimethylcyclopropanecarboxaldehyde (8). A stirred solution of 5.17 g (37.9 mmol) of (−)-2-carene $[\alpha]^{25}$ (neat) −83.9 (lit.[27] +76.36 for the enantiomer) in 50 mL of methanol at −78 °C was treated with ozone until a faint-green color was observed. Dimethyl sulfide (30 mL) was then added and the solution stirred for 2 h while the temperature slowly rose to room temperature. The solvents were evaporated, and the residue was subjected to flash chromatography on silica, using hexane–10% ethyl acetate as the eluant, to afford 5.40 g (32.1 mmol, 85%) of aldehyde **8** as a colorless liquid. This compound underwent considerable decomposition when stored at 0 °C under argon for 24 h and was thus best prepared immediately prior to use: IR 2950 (m), 1715 (s), 1690 (s) cm^{-1}; NMR δ 9.54 (d, J = 7.0 Hz, 1 H), 2.46 (t, J = 9.0 Hz, 2 H), 2.12 (s, 3 H), 2.04 (m, 1 H), 1.93 (m, 1 H), 1.61 (dd, J = 9.0, 5.5 Hz, 1 H), 1.42 (t, 7.0 Hz, 1 H), 1.32 (s, 3 H), 1.16 (s, 3 H); mass spectrum, m/e 168.1106 (M^+, calcd for $C_{10}H_{16}O_2$ 168.1106); $[\alpha]^{25}_D$ −41.1° ($CHCl_3$, 0.335).

6,6-Dimethyl-3-(1-oxoethyl)bicyclo[3.1.0]hex-2-ene (9). A solution of 113 mg (0.672 mmol) of keto aldehyde **8** in 5 mL of methanol was treated with 6 drops of 10% sodium hydroxide aqueous and stirred for 15 min. The solution was concentrated in vacuo and the residue partitioned between ether and water, and the layers were separated. The aqueous fraction was extracted twice with ether, and the organic extracts were combined, dried, and evaporated to yield 74 mg (74%) of **9** as a clear liquid. The analytical sample was obtained by flash chromatography on silica (10% ethyl acetate in pentane): IR 2950 (m), 2920 (m), 1655 (s), 1360 (s); NMR δ 6.60 (s, 1 H), 2.55 (dd, J = 18, 8 Hz, 1 H), 2.32 (d, J = 16 Hz, 1 H) 2.18 (s, 3 H), 1.74 (m, 1 H), 1.46 (m, 1 H), 1.06 (s, 3 H), 0.73 (s, 3 H); mass spectrum, m/e 150.1049 (M^+, calcd for $C_{10}H_{14}O$ 150.1044; $[\alpha]^{25}_D$ −49.5° ($CHCl_3$, 0.041).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.33. Found: C, 79.78; H, 9.39.

(−)-*cis*-1-(Dimethoxymethyl)-2,2-dimethyl-3-(3-oxobutyl)cyclopropane (10). A solution of 968 mg (2.60 mmol) of cerium(III) chloride heptahydrate in 2.0 mL (18.3 mmol) of trimethyl orthoformate and 6.5 mL of methanol was added to 437 mg (2.60 mmol) of aldehyde **8**. The mixture was stirred under argon at room temperature for 20 min. The reaction was quenched by the addition of 40 mL of 5% sodium bicarbonate solution and extracted with hexane. The organic extracts were combined, dried, and evaporated to afford 512 mg of acetal **10**, which was 80% pure by ^1H NMR analysis (yield 73%), as a colorless liquid. For characterization purposes a pure sample of **10** was obtained by high-pressure liquid chromatography (Waters Prepack 500; hexane–10% acetone); however, the crude acetal was generally used in subsequent reactions without further purification: IR 1720 (s), 1360 (s), 1100 (s), 1050 (s) cm^{-1}; NMR δ 4.23 (d, J = 8 Hz, 1 H), 3.37 (s, 3 H), 3.34 (s, 3 H), 2.56 (m, 2 H), 2.21 (s, 3 H), 1.67 (m, 2 H), 1.12 (s, 3 H), 1.06 (s, 3 H), 0.95 (t, 8 Hz, 1 H), 0.68 (dd, J = 13, 8 Hz, 1 H); mass spectrum, m/e 215.1621 (M + 1, calcd for $C_{12}H_{23}O_3$ 215.1647); $[\alpha]^{26}_D$ −7.46° ($CHCl_3$, 0.028).

(−)-*cis*-1-(Dimethoxymethyl)-2,2-dimethyl-3-[3-[(trimethylsilyl)oxy]-3-butenyl]cyclopropane (11). To an argon-flushed, flame-dried 50-mL round-bottom flask cooled to −78 °C was added 0.49 mL (3.50 mmol) of dry diisopropylamine followed by 5 mL of tetrahydrofuran and 1 equiv of *n*-butyllithium in hexane (2.23 mL, 1.58 M). The mixture was warmed to 0 °C for 10 min and then recooled to −78 °C. A solution of 581 mg (2.71 mmol) of acetal **10** in 3 mL of tetrahydrofuran was added dropwise over 2 min, and the mixture was stirred at −78 °C for 30 min. Chlorotrimethylsilane, 1.80 mL (14.2 mmol), was then added and the mixture stirred 1 h while the temperature warmed slowly to room temperature. The solvent was removed in vacuo and dry pentane added to the residue. The pentane extract was filtered through a pad of Celite and then evaporated to afford 748 mg (2.61 mmol, 96%) of silyl enol ether **11** as a pale-yellow liquid: IR 2495 (s), 1110 (m), 1065 (s), 850 (b) cm^{-1}; NMR δ 4.28 (d, J = 8.3 Hz, 1 H), 4.18 and 4.16 (unresolved singlets, 2 H), 3.47 (s, 3 H), 3.43 (s, 3 H), 2.20 (m, 2 H), 1.63 (m, 2 H), 1.19 (s, 3 H), 1.15 (s, 3 H), 0.98 (t, J = 8.5 Hz, 1 H), 0.82 (dd, 13.0, 8.3 Hz, 1 H), 0.33 (s, 9 H).

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(+)-*cis*- and (−)-*trans*-8,8-Dimethyl-2-methoxybicyclo[5.1.0]octan-1-one (12c and 12t). To a flame-dried 50-mL round-bottom flask under argon was added 127 mg (0.932 mmol) of anhydrous zinc chloride followed by 2 mL of dry ether and 5 mL of dichloromethane. The mixture was stirred at room temperature until the zinc chloride had dissolved and then a solution of 265 mg (0.928 mmol) of silyl enol ether **11** in 2 mL of dichloromethane was added dropwise via cannula over 1 min. The mixture was stirred for 0.5 h and then quenched by the addition of 10 mL of a saturated sodium bicarbonate solution. Ether (30 mL) was added and the organic layer separated. The aqueous layer was extracted with ether, and the combined extracts were washed with brine, dried, and evaporated. The residue was subjected to flash chromatography on silica (pentane–9% ethyl acetate) to afford 8 mg (0.044 mmol, 5%) of the minor ketone **12c** as a colorless oil, followed by 92 mg (0.51 mmol, 54%) of the major ketone **12t** as a white solid, which recrystallized from pentane (−10 °C) as colorless prisms, mp 71–72 °C.

Minor ketone: IR 2760 (s), 1710 (s), 1460 (m), 1110 (s) cm^{-1}; NMR δ 3.96 (ddd, J = 10.6, 6.2, 4.5 Hz, 1 H), 3.32 (s, 3 H), 2.90 (t, J = 10.8 Hz, 1 H), 2.50 (dd, J = 9.4, 5.7 Hz, 1 H), 2.44 (dd, J = 7.7, 4.0 Hz, 1 H), 2.36 (td, J = 16.6, 4.0 Hz, 1 H), 2.09 (m, 1 H), 1.68 (m, 1 H), 1.22 (s, 3 H), 1.11 (s, 3 H), 0.92 (m, 1 H), 0.80 (dd, J = 16.6, 9.1 Hz, 1 H); ^{13}C NMR δ 209.3 (s), 73.5 (d), 55.6 (q), 53.0 (t), 43.8 (t), 31.6 (d), 27.9 (q), 24.9 (d), 19.4 (t), 18.3 (s), 15.6 (q); mass spectrum, m/e 182.1306 (M^+, calcd for $C_{11}H_{18}O_2$ 182.1306); $[\alpha]^{25}_D$ +42.3° ($CHCl_3$, 0.0678).

Major ketone: IR 2945 (s), 1705 (s), 1455 (m), 1120 (s) cm^{-1}; NMR 3.24 (s, 3 H), 3.14 (ddd, J = 10.3, 8.6, 2.6 Hz, 1 H), 2.78 (t, J = 11.9 Hz, 1 H), 2.71 (tdd, J = 11.9, 2.6, 2.3 Hz, 1 H), 2.42 (m, 2 H), 1.96 (m, 1 H), 1.07 (s, 3 H), 1.02 (s, 3 H), 0.88 (td, J = 9.4, 5.6 Hz, 1 H), 0.71 (t, J = 9.4 Hz, 1 H); ^{13}C NMR δ 210.4 (s), 76.0 (d), 56.3 (q), 47.3 (t), 43.6 (t), 30.0 (t), 28.8 (d), 26.8 (d), 21.0 (q), 19.6 (q), 16.4 (q); mass spectrum, m/e 182.1295 (M^+, calcd for $C_{11}H_{18}O_2$ 182.1306); $[\alpha]^{25}_D$ −26.1° ($CHCl_3$, 0.0466).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.47; H, 9.97. Found: C, 72.36; H, 9.85.

(−)-8,8-Dimethylbicyclo[5.1.0]oct-2-en-3-one ((−)-1). To a solution of 92 mg (0.51 mmol) of ketones **12** in 15 mL of ether and under argon was added about 20 mg of potassium *tert*-butoxide. The mixture was stirred for 20 min and then quenched by the addition of 10 mL of brine and extracted with hexane. The extracts were combined, dried, and evaporated. The residue was subjected to flash chromatography on silica (pentane–20% ether) to afford 57 mg (0.38 mmol, 75%) of enone **1** as a colorless oil. The IR and NMR spectra of this material were identical with (±)-**1** previously prepared: mass spectrum, m/e 150.1032 (M^+, calcd for $C_{10}H_{16}O$ 150.1044); $[\alpha]^{25}_D$ −564° ($CHCl_3$, 0.0125).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.94; H, 9.41. Found: C, 80.06; H, 9.32.

NOE Difference Experiments. Spectra at 250 MHz were obtained with 16K data points over 3000 Hz, giving acquisition times of 2.7 s and pulse width of 1.6 μs (30°). Irradiating frequency power level was adjusted to maximize selectivity. Details for obtaining NOE difference spectra can be found in ref 25. The samples, in deuteriochloroform, were degassed by five freeze–thaw cycles at $\leq 10^{-3}$ mmHg and then sealed under vacuum.

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Registry No. (±)-**1**, 82768-64-7; (−)-**1**, 82691-87-0; **2**, 82706-18-1; **3c**, 82691-88-1; **3t**, 82730-77-6; **4c**, 82691-89-2; **4t**, 82730-78-7; **5**, 38607-27-1; **6c**, 82691-90-5; **6t**, 82730-79-8; **7**, 82691-91-6; **7** *cis*-3-(phenylthio), 82691-95-0; **7** *trans*-3-(phenylthio), 82730-83-4; **7** *cis*-3-(phenylsulfinyl), 82691-96-1; **7** *trans*-3-(phenylsulfinyl), 82730-84-5; **8**, 82730-80-1; **9**, 82730-81-2; **10**, 82691-92-7; **11**, 82691-93-8; **12c**, 82691-94-9; **12t**, 82730-82-3; bromoform, 75-25-2; (−)-2-carene, 65878-59-3; trimethyl orthoformate, 149-73-5.