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(20) All computations were carried out on the CDC Cyber 74 system. Standard programs utilized included: Germain, Main, and Woolfsons' MULTAN, Zalkin's FORDAP, Iber's NUCLS modification of Busing, Martin, and Levy's least-squares program, Busing and Levy's ORFFE, and Johnson's ORTEP. Scattering factors were taken from Cromer and Waber's tabulation[21] for carbon and oxygen; Stewart's hydrogen atom scattering factors[22] were used. Anomalous dispersion factors employed were those given by Cromer.[23]
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Total Synthesis of (±)-Acorone

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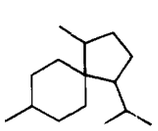
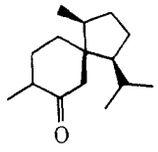
(±)-Acorone (**3**) has been synthesized by an efficient sequence beginning with 4-methyl-3-cyclohexenecarboxaldehyde (**5**). The imine of the aldehyde was alkylated with trimethylsilylpropargyl bromide. The acetylene moiety was hydrated with dilute acid and mercuric sulfate which also removed the trimethylsilyl group to give 1-(2-oxopropyl)-4-methyl-3-cyclohexenecarboxaldehyde which was cyclized with base to 8-methylspiro[4.5]deca-1,7-dien-3-one (**4**). Base-induced condensation of **4** with ethyl formate followed by acetic anhydride yielded 1-(*anti*-acetoxymethylene)-8-methylspiro[4.5]deca-3,7-dien-2-one (**14**). Two successive treatments of **14** with lithium dimethylcuprate followed by hydroboration and oxidation afforded a mixture consisting almost entirely of (±)-acorone and (±)-isoacorone (**21**) from which pure (±)-acorone could be isolated by crystallization.

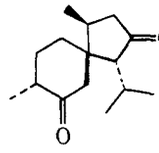
The acorane skeleton (**1**) has recently been subjected to intense synthetic scrutiny.[1] Notable results have been achieved, especially with acorenone B (**2**).[2] Acorone (**3**), itself, has been approached less successfully. The synthesis of Pinder et al.[3a] failed in the penultimate step, while Marx and Norman[3b] were successful in producing the enantiomer of natural (+)-acorone.



1

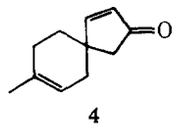


2



3

Spirocyclopentenone (**4**) appeared to be a very attractive intermediate. Indeed, we have synthesized crystalline (±)-acorone via **4** without a single chromatographic separation. A problem in preparing **4** is that most methods of cyclopentenone construction are not sufficiently versatile to incorporate the quaternary carbon necessary for a spiro skeleton.[4] Regiospecific hydration of an acetylenic carbonyl compound to generate the 1,4-dicarbonyl precursor avoids this problem. Alkylation of the appropriate enolate anion with a propargyl halide should provide the quaternary carbon readily. A communication by Stork and Borch[5a] appeared in 1964 describing the regiospecific hydration of acetylenic ketones. Both 1,4 and 1,5 diketones were prepared, and a synthesis of *cis*-jasmone was delineated.[5b] We have begun an extended study of this reaction, with special regard for its synthetic utility.[6]

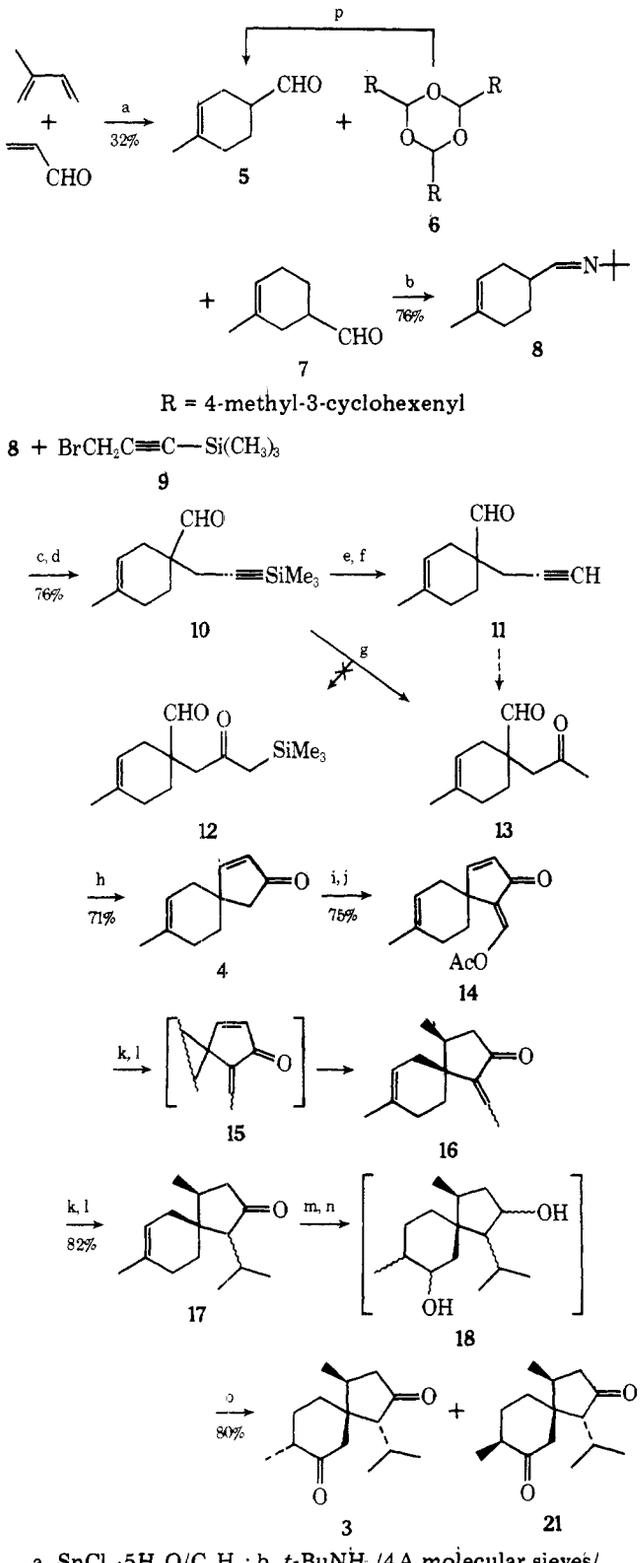


4

The synthesis (Scheme I) was begun with 4-methyl-3-cyclohexene-1-carboxaldehyde (**5**).[7a,b] Lewis acid catalyzed Diels–Alder reaction of isoprene and acrolein gave **5**, accompanied by the symmetrical trioxane (**6**) which was pyrolyzed in the presence of acid to regenerate **5**. The poor yield obtained at our hands (32%) was mitigated by the ready availability of the starting materials. As reported earlier,[7b] the expected 3-methyl isomer (**7**) could not be separated by GLC nor was it distinguishable by NMR, and was assumed to comprise ≤5% of the product.

The *tert*-butyl imine (**8**) was generated in 76% yield without incident. Alkylation was accomplished using the imine alkylation procedure of House.[8,9] Treatment of imine **8** with *n*-butyllithium in dimethoxyethane (DME) to form the anion followed by addition of 3-bromo-1-trimethylsilyl-1-propyne (**9**)[10] and then by acid hydrolysis gave the alkylated aldehyde **10** (76%).

Scheme I



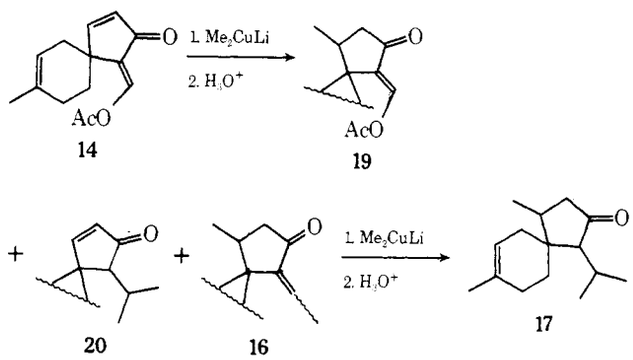
a, $SnCl_4 \cdot 5H_2O/C_6H_6$; b, *t*-$BuNH_2$/4A molecular sieves/pentane; c, *n*-BuLi/DME; d, HCl/H_2O; e, $AgNO_3$/EtOH/H_2O; f, 2 M HCN; g, $HgSO_4/H_2SO_4$/aq THF; h, NaOEt/EtOH; i, NaOMe/ethyl formate; j, Ac_2O; k, Me_2CuLi; l, H_3O^+; m, $BH_3 \cdot SMe_2$; n, H_2O_2/OH^-; o, Jones reagent; p, $TsOH/\Delta/C_6H_6$

Our first thoughts were to remove the trimethylsilyl protecting group, then to hydrate the acetylene generating the required keto aldehyde. Compound **10** was treated with 1.1 equiv of ethanolic $AgNO_3$, followed by aqueous KCN.[11] GLC analysis of the product mixture revealed one major peak (about 85% of the total) corresponding to the propynylaldehyde **11** and several minor unidentified compounds. Rather than attempting to optimize this reaction, we hoped that mercuric ion might play the same role as silver ion in the release of the trimethylsilyl group. However, we did not expect the mercuric complex to precipitate from the reaction as did the silver acetylide. In this case, hydration could conceivably occur generating the keto aldehyde **13** in a single step. At worst we expected to obtain the α-trimethylsilyl ketone **12**, which would not be disastrous. Compound **10** was treated with 0.06 equiv of $HgSO_4$ and a trace of H_2SO_4 in aqueous THF, which cleanly gave **13** (≥93% pure by GLC). The unstable oil was immediately cyclized with 1 M NaOEt/EtOH to produce 8-methylspiro[4.5]deca-1,7-dien-3-one (**4**) in 71% distilled yield from **10**. Deprotection and hydration of the acetylene were accomplished in a single, very clean reaction.

Realizing the difficulties attendant to direct isopropylation, we proceeded to treat **4** with ethyl formate and NaOMe, then with excess acetic anhydride.[2b] This produced crystalline 1-(*anti*-acetoxymethylene)-8-methylspiro[4.5]deca-3,7-dien-2-one (**14**) in 75% yield after sublimation (mp 116–119 °C). The anti stereochemical assignment was based on the downfield position of the C-11 vinyl proton (δ 8.10), in agreement with other workers.[2b] We found no evidence (NMR, GLC) of the syn isomer.

A priori, treatment of **14** with excess lithium dimethylcuprate could be expected to produce a number of 1,4-addition products (**16, 19, 20**) following workup (Scheme II). Further

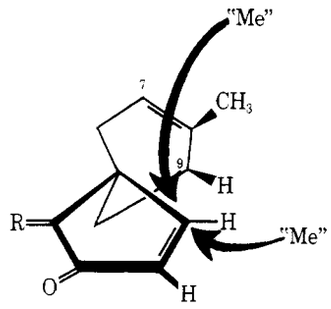
Scheme II



treatment of **16, 19,** and **20** with lithium dimethylcuprate should give the thrice-alkylated compound **17**. We hoped to titrate the reaction mixture containing the enolate anions of **16, 19,** and **20** with 1 equiv of AcOH, add lithium dimethylcuprate, and obtain **17** in a one-pot procedure.

This sequence generates two chiral centers with the attendant possibilities for complication. Examination of molecular models suggested that the required stereochemistry at C-4 should be favored. The active methyl transfer agent was expected to approach past the Δ^7 double bond giving the desired stereochemistry. Approach past C-9 to the opposite face of the five-membered ring is subject to a skew butane type interaction and, hence, is not as favorable. The required configuration at C-1 is known to be much the more stable.[12] The epimerizable center thus posed no problems. In the event, treatment of **14** with 6 equiv of lithium dimethylcuprate produced two major compounds in a ratio of 7:1, ≥98% pure by GLC. These proved to be the *Z* and *E* isomers of **16**, respectively. Only one of the C-4 epimers was present by NMR. The absorption arising from the C-4 methyl group was a sharp doublet (δ 0.88, J = 7 Hz) with no indication of a second doublet for the other epimer. That this was the desired diastereomer was confirmed by conversion to acorone.

It appears that the first equivalent of lithium dimethylcuprate adds to **14** at C-11, followed by elimination of acetate to give intermediate **15**. At this point, the second equivalent



15

adds to the endo double bond rather than the exo double bond. Using the method of House,[13] the difference in reduction potentials of the two possible α,β-unsaturated carbonyl systems may be estimated. We calculate the endocyclic system to be ~0.1 V more positive than the exocyclic system, hence the more reactive as confirmed by isolation of **16** as the major product.

All attempts at a one-pot reaction sequence failed. The only major compound produced was **16**. Instead, crude **16** was treated with 3 equiv more of lithium dimethylcuprate to give **17** as a clear oil, 98% pure by GLC, as a mixture of C-1 epimers (82% from **14**).

With acorone almost in hand, we elected not to purify **17**, but treated it with borane–dimethyl sulfide complex to give, after oxidative workup, a compound presumed to be diol **18**, which was not characterized. The crude oil was oxidized with Jones reagent to produce an oil containing (±)-acorone and (±)-isoacorone (96%), and one unidentified component (4%) by GLC in a total yield of 80% from **17**.[3b] The oil was taken up in hexane/chloroform and stored overnight at −5 °C, yielding a crystalline material (mp 101.5–103.5 °C) which proved identical with an authentic sample of (+)-acorone[14] by NMR, IR, and GLC after sublimation and recrystallization.

Experimental Section

General. Melting points were determined on a Koefler hot stage and are uncorrected. Infrared spectra were run on Beckman IR-7 or IR-10 instruments as CCl_4 solutions. NMR spectra were run on Varian HA-100 or XL-100-15 spectrometers as solutions in $CDCl_3$. Chemical shifts are reported in δ units downfield of internal reference Me_4Si. Mass spectra and elemental analysis were performed by Dr. R. Wielesek of the University of Oregon Microanalytical Laboratory.

All reactions were performed under an atmosphere of dry nitrogen and were routinely followed by GLC of small aliquots. All GLC analyses were run on an F & M Model 700 equipped with a thermal conductivity detector and a 6 ft × 0.25 in. 20% DC 410, Chromosorb W AW column unless otherwise noted.

4-Methyl-3-cyclohexene-1-carboxaldehyde (5).[7] In a 500-mL round-bottom flask were placed 19 g (0.054 mol) of $SnCl_4 \cdot 5H_2O$ and 150 mL of benzene. To the rapidly stirred suspension was added 67 mL (1.0 mol) of acrolein (bp 53 °C) at which time the $SnCl_4$ dissolved to give a clear solution. The temperature was reduced to −8 °C on a NaCl/ice bath and isoprene (100 mL, 1.0 mol) was added at a rate of ≤1 drop/s. More rapid rates lead to a temperature rise and attendant polymerization. After 5.5 h, the resulting pale yellow slush was poured onto 200 mL of H_2O. The emulsion which formed proved completely intractable. The material was vacuum filtered to yield a white solid which proved to be trioxane **6**. The two-phase filtrate (benzene/H_2O) was separated, and the benzene layer was washed with brine and dried (Na_2SO_4). The white solid was dissolved in benzene with a trace of acid and heated to 120–130 °C (5 mm), which distilled over a clear liquid. The combined organics were distilled on a tantalum spiral column to yield 40.0 g (32.4%) of **5**, ≥99% pure by GLC:[15] bp 64–65 °C (10 mm); IR 2715, 1730, 1435 cm^{-1}; NMR δ 1.66 (br s, 3 H, vinyl $-CH_3$), 1.80–2.60 (complex, 7 H), 5.43 (br s, 1 H, vinyl H), 9.68 (s, 1 H, –CHO); 2,4-DNP, mp 178.5–180 °C (lit. 176.4–177.5 °C).

Recrystallization of a sample of the solid (ethanol/pentane, 4:1) produced short, fluffy crystals (mp 162–164 °C). The very simple NMR spectrum showed no evidence of an aldehyde. The IR showed no carbonyl absorbtion: IR 3030, 1440, 1135 cm^{-1}; NMR δ 1.65 (br s, 3 H, vinyl $-CH_3$), 1.70–2.40 (complex, 7 H), 4.65 (d, J = 5 Hz, 1 H, acetal H), 5.38 (br s, 1 H, vinyl H). A possible parent ion at m/e 248 in the mass spectrum was appropriate for a dimer. However, the peak at m/e 249 (M + 1) was 60% of m/e 248, too large for natural ^{13}C abundance. This evidence suggested that the compound was in fact the symmetric trimer. Pyrolysis of a sample in an NMR tube at 220 °C produced **5**.

***N-tert*-Butyl-4-methyl-3-cyclohexene-1-carboxaldehyde Imine (8).** A 500-mL round-bottom flask was charged with 100 g of 4A molecular sieves, 25.4 mL (0.242 mol) of dry *tert*-butylamine (distilled from KOH), and 100 mL of pentane. Aldehyde **5** (30.0 g, 0.242 mol) in 150 mL of pentane was added dropwise at a rate sufficient to maintain reflux. The mixture was held at reflux for 4 h, filtered, and distilled to yield 33.4 g (77%) of **8** (>99% pure by GLC): bp 90–91 °C (16 mm); IR 3035, 1668 cm^{-1}; NMR δ 1.16 (s, 9 H, $-CH_3$), 1.65 (br s, 3 H, vinyl $-CH_3$), 1.70–2.50 (complex, 7 H), 5.40 (br s, 1 H, vinyl H), 7.50 (d, J = 5 Hz, 1 H, N=CH).

1-(3-Trimethylsilyl-2-propynyl)-4-methyl-3-cyclohexene-1-carboxaldehyde (10).[10] Lithium diisopropylamide was generated by adding *n*-butyllithium (0.167 mol) to 23.6 mL (0.167 mol) of diisopropylamine (KOH) and 60 mg of phenanthroline in 100 mL of DME (distilled from Na/benzophenone) at −30 °C. After 30 min **8** (30 g, 0.167 mol) was added dropwise, then stirred for 1.25 h as the temperature rose to 20 °C. 3-Bromo-1-trimethylsilyl-1-propyne (**9**, 30.3 g, 0.159 mol) was added dropwise to the red-brown solution. The temperature was kept below 20 °C with judicious application of an ice bath. After 21 h the pale yellow slurry was quenched with 200 mL of 10% HCl and refluxed for 4 h. The mixture was saturated with NaCl and extracted with 3 × 100 mL of ether. The combined organics were washed with brine, dried ($MgSO_4$), and distilled to yield 24.3 g (68.5%) of **10**: >95% pure by GLC; bp 102–107 °C (0.85 mm); IR 2710, 2160, 1730, 1435, 1245 cm^{-1}; NMR δ 0.14 (s, 9 H, $-CH_3$), 1.66 (br s, 3 H, vinyl $-CH_3$), 1.70–2.60 (complex, 6 H), 2.38 (s, 2 H, propargylic H), 5.41 (br s, 1 H, vinyl H), 9.60 (s, 1 H, –CHO); mol wt (calcd for $C_{14}H_{22}OSi$, 234.144), 234.144.

1-(2-Propynyl)-4-methyl-3-cyclohexene-1-carboxaldehyde (11).[11] A 50-mL round-bottom flask was equipped with a magnetic stirrer and addition funnel to which was added 234 mg (1.0 mmol) of **10** in 5 mL of absolute EtOH. $AgNO_3$ (187 mg, 1.1 mmol) in 3 mL of 70% EtOH was added dropwise, precipitating a white material; 0.5 h later 2 mL of 2 M KCN was added to dissolve all the precipitate. The mixture was extracted with 2 × 10 mL of pentane and dried ($MgSO_4$). After the solvent was removed (distillation), GLC analysis showed a complex mixture of products. Preparative GLC of the major peak (85%) provided an analytical sample: NMR δ 1.67 (br s, 3 H, vinyl $-CH_3$), 2.01 (t, J = 2.25 Hz, 1 H, acetylenic H), 2.37 (d, J = 2.25 Hz, 2 H, propargylic H), 1.70–2.50 (complex, 6 H), 5.40 (br s, 1 H, vinylic H), 9.61 (s, 1 H, –CHO); mol wt (calcd for $C_{11}H_{14}O$, 162.104), 162.102.

8-Methylspiro[4.5]deca-1,7-dien-3-one (4). $HgSO_4$ (891 mg, 3.0 mmol), concentrated H_2SO_4 (300 mg), H_2O (12 mL), and THF (60 mL) were placed in a 250-mL round-bottom flask and stirred. Compound **10** (11.7 g, 0.050 mol) was added to the yellow suspension and stirred for 1 h during which time the mixture became homogeneous. The solution was poured onto 50 mL of H_2O and extracted with 2 × 50 mL of CH_2Cl_2. The aqueous phase was saturated with NaCl and extracted with 2 × 25 mL of CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), and stripped of solvent under vacuum to yield 1-(2-oxopropyl)-4-methyl-3-cyclohexene-1-carboxaldehyde (**13**). An analytical sample was purified by GLC: NMR δ 1.66 (br s, 3 H, vinyl $-CH_3$), 2.12 (s, 3 H, O=CCH_3), 1.70–2.60 (complex, 6 H), 2.77 (d, J = 2 Hz, O=CCH_2), 5.40 (br s, 1 H, vinylic H), 9.70 (s, 1 H, –CHO); mol wt (calcd for $C_{11}H_{16}O_2$, 180.115), 180.115. No detectable amounts of dialdehyde were observed (≤5%).

Crude **13** was dissolved in 100 mL of absolute EtOH in a 250-mL round-bottom flask. To the stirred solution was added 50 mL of 1 M NaOEt/EtOH (0.05 mol). The reaction mixture was stirred for 1 h. The red-brown solution was neutralized with 2 N H_2SO_4, the color changing to pale yellow. The mixture was worked up as above yielding 5.75 g (71%) of **4** (94% pure by GLC) after distillation: bp 59–60 °C (0.15 mm); IR 1720, 1590, 1450, 1440 cm^{-1}; NMR δ 1.72 (br s, 3 H, vinyl $-CH_3$), 2.19 (s, 2 H, O=CCH_2), 1.60–2.40 (complex, 6 H), 5.42 (br s, 1 H, vinylic H), 6.07 (d, J = 6 Hz, C-2 H), 7.57 (d, J = 6 Hz, C-1 H); mol wt (calcd for $C_{11}H_{14}O$, 162.104), 162.102.

1-(*anti*-Acetoxymethylene)-8-methylspiro[4.5]deca-3,7-dien-2-one (14).[26] In a flamed 100-mL round-bottom flask equipped with a mechanical stirrer was placed 1.94 g (36 mmol) of commercial NaOMe (Mallinckrodt) in 50 mL of dry ether (distilled from $LiAlH_4$). Ethyl formate (7.25 mL, 90 mmol) was syringed into the cold (−7 °C) slurry, followed by dropwise addition of **4** (2.92 g, 18 mmol) in 5 mL of dry ether. After 4 h the reaction was quenched with 15 mL of acetic

anhydride (distilled from Mg) to give a yellow suspension. After 1 h of stirring, the mixture was poured onto 50 mL of H_2O, neutralized with solid NH_4Cl, and extracted with 3 × 25 mL of ether. The combined organics were washed with brine and dried (Na_2SO_4). Solvent was removed under aspirator pressure to give crude yellow crystals. The solid was recrystallized twice from hexane and sublimed (80–90 °C bath temperature, 0.01 mm) to yield 2.387 g. The mother liquors were concentrated and chilled (−5 °C) to give a second crop of solid that was recrystallized and sublimed as above and combined with the first crop to yield 3.137 g (75%) of **14**. An analytical sample recrystallized from ether melted at 116–119 °C; IR 1785, 1720, 1660, 1450 cm^{-1}; NMR δ 1.77 (br s, 3 H, vinyl $-CH_3$), 2.14 (s, 3 H, $-O_2CCH_3$), 1.80–3.00 (complex, 6 H), 5.48 (br s, 1 H, vinylic H), 6.25 (d, $J \approx 6$ Hz, 1 H, C-3 H), 7.66 (d, $J \approx 6$ Hz, 1 H, C-4 H), 8.10 (s, 1 H, C-11 H). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.06; H, 7.12.

1-Ethylidene-4,8-dimethylspiro[4.5]dec-7-one (16).[2b] In a 100-mL round-bottom flask was placed 5.71 g (30.0 mmol) of anhydrous CuI (Fischer) in 20 mL of ether (distilled from $LiAlH_4$). The mechanically stirred slurry was cooled to −70 °C in a dry ice/2-propanol bath and MeLi (64.5 mL, 59.5 mmol) was added via syringe. After 0.5 h **14** (1.14 g, 5.0 mmol) in 25 mL of ether was added over 5 min giving an orange slurry. The mixture was quenched 1 h later by addition of 5% HCl and poured onto 50 mL of H_2O, and the organic layer separated. The aqueous layer was extracted with 4 × 40 mL of ether. The combined organics were washed with saturated $Na_2S_2O_3$ (100 mL) and brine, dried (Na_2SO_4), and distilled to remove solvent yielding a gold-brown oil, shown by GLC to be two major components (95%) in a ratio of 7:1. Preparative GLC of the major peak provided an analytical sample [NMR δ 0.88 (d, J = 7 Hz, 3 H, C-4 methyl), 1.65 (br s, 3 H, vinyl $-CH_3$), 2.05 (d, J = 7 Hz, 3 H, ethylidene $-CH_3$), 1.96–2.10 (complex, 8 H), 2.66 (dd, J = 8, 18 Hz, 1 H, C-3 H), 5.47 (br s, 1 H, vinylic H), 6.00 (q, J = 7 Hz, 1 H, C-11 H)] interpreted as the Z isomer.[2b] The minor peak was identified as the E isomer having the ethylidene resonances at δ 1.85 (d, J = 7 Hz, 3 H, ethylidene $-CH_3$) and 6.77 (q, J = 7 Hz, 1 H, ethylidene H).

1-Isopropyl-4,8-dimethylspiro[4.5]dec-7-en-2-one (17).[16] As above, 15 mmol of lithium dimethylcuprate was prepared at 0 °C. The crude oil **15** in 5 mL of ether was added dropwise and the reaction mixture stirred for 1 h. After an identical workup 9.25 mg of oil was obtained, 98% pure by GLC (82.5% yield): IR 1740, 1467, 2452 cm^{-1}; NMR δ 0.88 (dd, J = 2, 7 Hz, 6 H, isopropyl CH_3), 1.09 (d, J = 7 Hz, 3 H, C-4 $-CH_3$), 1.63 (br s, 3 H, vinyl $-CH_3$), 1.70–2.70 (complex, 11 H), 5.38 (br s, 1 H, vinylic H); mol wt (calcd for $C_{15}H_{24}O$, 220.183), 220.184.

(±)-Acorone (3). In a flamed 25-mL round-bottom flask was placed 500 mg (2.28 mmol) of **17** in 10 mL of THF (Na/benzophenone). $BH_3{\cdot}SMe_2$ (Aldrich, 150 μL, 1.61 mmol) was added via a septum inlet and the solution stirred for 2 h. One milliliter of 3 N NaOH followed by 1 mL of 30% H_2O_2 were added and the reaction mixture stirred for an additional 1 h. The solution was poured onto 15 mL of H_2O and the organic layer separated. The aqueous layer was extracted with 2 × 5 mL of ether, saturated with NaCl, and reextracted with 2 × 5 mL of ether. The combined organics were washed with brine, dried (Na_2SO_4), and stripped of volatiles under vacuum to yield 519 mg of pale yellow oil. No starting material was present by GLC and NMR.

The crude oil was dissolved in 15 mL of acetone and treated dropwise with Jones reagent until a faint red color persisted.[3b] Water (15 mL) was added and the mixture extracted with 4 × 5 mL of CH_2Cl_2. The combined organics were washed with brine, dried (Na_2SO_4), and stripped of solvent to yield 447 mg of yellow oil (80%). GLC analysis (15 ft × 0.125 in., 20% Carbowax 20M on Chromosorb W AW, 200 °C, FID detector) indicated the oil to be a mixture of acorone (55%) and isoacorone (45%) accounting for 96% of the total (identical with authentic samples[14]) and 4% of an unidentified component. The oil was dissolved in hexane/$CHCl_3$ and placed in a freezer overnight. Crystals were deposited which were recrystallized from hexane/$CHCl_3$ and sublimed (80 °C bath temperature, 0.1 mm) to yield 47 mg, mp 98–102 °C. Crystals (10.2 mg) were dissolved in heptane with a trace of ether and chilled. The crystals which were deposited were recrystallized from heptane to yield 6.7 mg of long needles, mp 101.5–103.5 °C, identical with authentic (+)-acorone (mp 96.0–97.5 °C)[3b] by NMR, IR, and GLC. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.26; H, 9.89. Found: C, 76.14; H, 9.97.

Registry No.—**3**, 61475-94-3; **4**, 61426-14-0; **5**, 61426-17-3; **6**, 6739-07-7; **8**, 61426-15-1; **9**, 38002-45-8; **10**, 61426-16-2; **11**, 61426-18-4; **13**, 61426-19-5; **14**, 61426-20-8; **15** isomer A, 61426-21-9; **15** isomer B, 61426-22-0; (*Z*)-**16**, 61426-23-1; (*E*)-**16**, 61475-95-4; **17** isomer A, 61426-24-2; **17** isomer B, 61475-96-5; **21**, 61475-97-6; acrolein, 107-02-8; isoprene, 78-79-5; *tert*-butylamine, 75-64-9; ethyl formate, 109-94-4; lithium dimethylcuprate, 15681-48-8.

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Purine *N*-Oxides. 66. Synthesis of 9-Hydroxyadenine[1]

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The synthesis of 9-hydroxyadenine, by a variation of the Shaw purine synthesis, involved the condensation of ethyl *N*-(dicyanomethyl)formimidate tosylate (**2**) with benzyloxyamine to a cyanoimidazole derivative **3** which was then ring closed to the purine derivative. This is the third adenine *N*-oxide isomer available for carcinogenicity testing.

The biological studies on the oncogenicity of purine *N*-oxides have demonstrated that adenine 1-*N*-oxide[2] is a mild oncogen with respect to the strong oncogen, 3-hydroxyxanthine,[3] whereas adenine 3-*N*-oxide is not oncogenic.[4] 9-Hy-