Synthesis of (−)-Acorone and Related Spirocyclic Sesquiterpenes[1]

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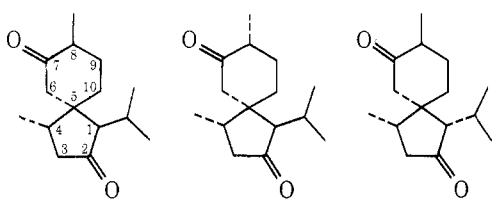
Total syntheses for four acorane sesquiterpenes, β-acoradiene (4), δ-acoradiene (5), and the enantiomers (27 and 28) of acorone (1) and isoacorone (2), are described. The synthetic route involves conversion of (*R*)-pulegone (11) into 3-methyl-2-carbethoxycyclopentanone (8) by improvement of literature procedures, then conversion of this into (*R*)-3-methyl-2-methylenecyclopentanone (17) by the sequence ketalization, reduction, deketalization, and dehydration. A Diels–Alder reaction between 17 and isoprene gave four adducts 18–21. The para:meta ratio in this reaction was improved from 2:1 to 24:1 by the use of $SnCl_4$ catalysis, which gave a ratio of products of 69:27:3:1. Structures were assigned to the various isomers on the basis of the known steric and electronic requirements in the Diels–Alder reaction. The major ketones 18 and 19 were purified by preparative high-pressure liquid chromatography. Treatment of 18 with isopropyllithium and then $SOCl_2$ gave γ-acoradiene (4) and its endocyclic isomer 23, whereas 19 led to δ-acoradiene (5) and its isomer 25. Hydroboration of 25 followed by Jones oxidation gave an equilibrium mixture of (−)-acorone (27), the enantiomer of natural acorone (1), and (+)-isoacorone (28), the enantiomer of natural isoacorone (2).

Acorone (1), isolated from the oil of Sweet Flag, *Acorus calamus L.*, is the best known member of a small group of spirocyclic sesquiterpenes having the acorane skeleton.[3] Other members include isoacorone (2), cryptoacorone (3), and acorenone from the same source,[3] as well as acorenone B from *Bothriochoa intermedia*,[4] two unnamed dienes from *Vetiveria zizanoides*,[5] and α-acorenol, β-acorenol, α-acoradiene, β-acoradiene, γ-acoradiene (4), and δ-acoradiene (5) from *Juniperus rigida*.[5] α-Alaskene, isolated from alaska cedar, *Chamecyparis nootkatensis*, was shown to be identical with γ-acoradiene, but β-alaskene from the same source was shown to be enantiomeric to δ-acoradiene.[6]



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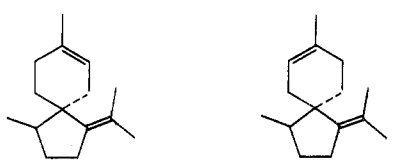

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The absolute stereochemistry of acorone was assigned on the basis of ORD studies and X-ray of a derivative,[8] whereas that of γ-acoradiene follows[6,7] from its acid-catalyzed cyclization to α-edrene, whose absolute stereochemistry has been determined independently. Stereochemical assignments of other compounds in the series rest on chemical interconversions and on an X-ray study of acorenone B.

Successful syntheses of several members of the acorane class have been reported recently. An intermediate in a biogenetic-like synthesis of racemic α-cedrene by Crandall and Lawton[9] has the structure later assigned to α-acorenol.[6] A total synthesis of an unnamed diene by Kaiser and Naegeli[5] was reported as part of its structure proof. Total synthesis of optically active α-acorenol and β-acorenol has been accomplished.[10] Several other types of synthetic entries into this class have been reported,[11–13] though some[12,13] have not led to any natural products. Pinder's[12] attempted synthesis of acorone failed only at the penultimate step.

We report here full details of formal total syntheses of optically active β-acoradiene (4) and δ-acoradiene (5),[1] as well as syntheses of the enantiomeric forms of acorone (1) and isoacorone (2) from the same precursors. Since the acoradienes have the opposite absolute stereochemistry from the acorones, using the C-4 methyl as the point of reference, both natural series cannot be derived from the same precursors. The present synthesis uses a Diels–Alder reaction as the key step to generate the spirocyclic center and to establish the relative stereochemistry at C-4 and C-5. Since our starting material is pulegone (11), with absolute stereochemistry at the methyl known to be *R*,[14] the synthesis also establishes the absolute stereochemistry at C-4 and C-5 and collaborates the previous stereochemical assignments for both the acoradienes and the acorones.

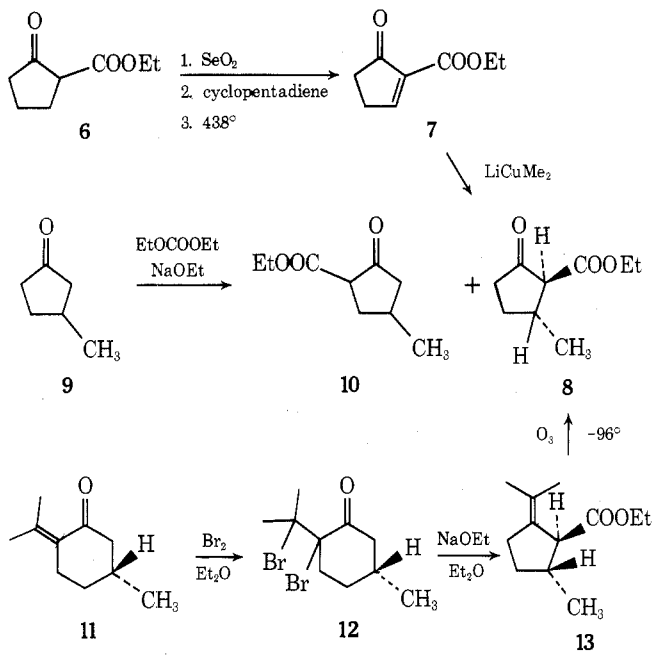
The starting material chosen was 3-methyl-2-carbethoxycyclopentanone (8). Although the compound has been synthesized from pulegone (11),[15] the overall reported yield was ca. 5% and some rather difficult separations were required; so we initially turned to other potential routes to the compound.

Selenium dioxide oxidation of 2-carbethoxycyclopentanone (see Chart I) gave up to 50% yields of 2-carbethoxycyclopent-2-enone (7).[16] However, evidently because of the great polarity of the chromophore in the molecule, it polymerized too rapidly for purification, and so was purified by trapping as a mixture of Diels–Alder adducts with cyclopentadiene and regenerating by pyrolysis.[16] The pure compound, which is also a potentially valuable intermediate for other syntheses, reacted smoothly with lithium dimethylcopper at −80° to give racemic 3-methyl-2-carbethoxycyclopentanone (8). However, this route to 8 was judged impractical for its use as starting material in a total synthesis.

Another approach investigated briefly was to condense 3-methylcyclopentanone (9) with diethyl carbonate. This gave, as expected, both 8 and 10 in the ratio 40:60.[16] While the two could be separated by VPC, no method applicable to large-scale work could be found for this separation.

We then turned to improving the yield of 8 from pulegone (11). Bromination of pulegone at −10° in ether gave mostly the dibromide 12, although the product was always contaminated with some unreacted pulegone and doubtlessly products of further bromination. The crude product was added to NaOEt in ether at 25°, giving, after simple distillation, a mixture of 85% ethyl pulegenate (13) and 15% unreacted pulegone. Wolinsky[17] reports similar yields, following a very careful distillation. In our hands, spinning band distillation was unsatisfactory for the separation, but

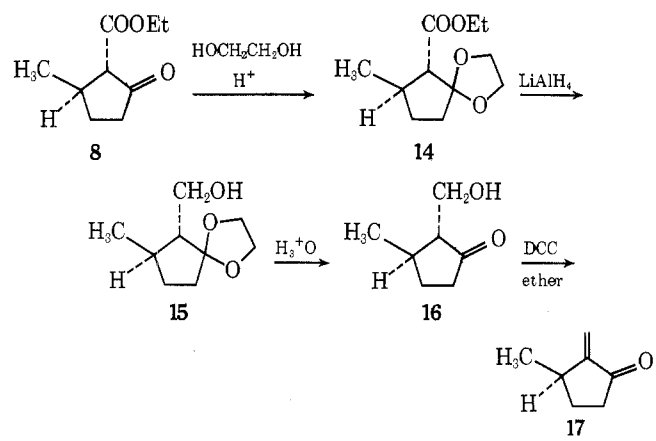
Chart I



selectively converting pulegone into its semicarbazone and extraction with pentane gave ethyl pulegenate (**13**) with no detectable impurities. Ozonolysis at −90° in ethyl acetate then gave the desired 3-methyl-2-carbethoxycyclopentanone (**8**) in 85% yield. The overall yield from pulegone was 57%.

3-Methyl-2-carbethoxycyclopentanone was converted into its ethylene ketal **14** (Chart II) by standard procedures

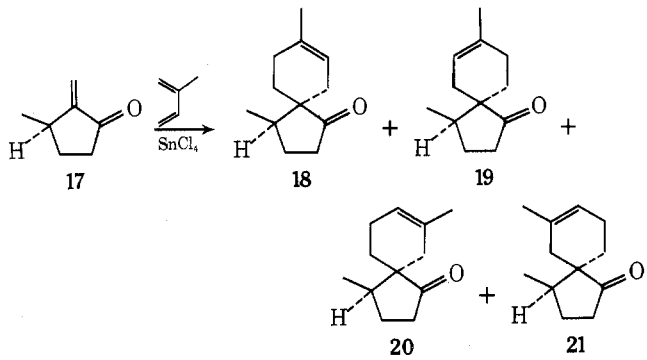
Chart II



(87%). This compound was then reduced smoothly by $LiAlH_4$ to the corresponding alcohol **15** (86%). The ketal group could then be removed by treatment of **15** with 3 *N* HCl for 2 min at 25° to give the keto alcohol **16** (96%). Dehydration of this with dicyclohexylcarbodiimide (DCC)[18] gave the rather easily polymerized (*R*)-3-methyl-2-methylenecyclopentanone (**17**, 67%). Other reaction sequences to convert **15** into **17**, including combined deketalization and dehydration by acid and elimination sequences on the derived tosylate, all gave very low yields of **17** because of polymerization which occurred under the acidic or basic conditions used.

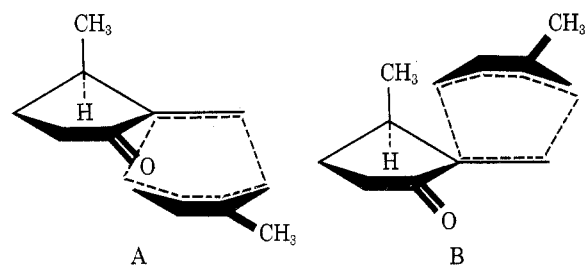
Heating **17** and an excess of isoprene in a sealed tube at 100° for 1 hr gave a mixture of four adducts in a 45:25:20:10 ratio. These are assigned the structures **18**, **19**, **20**, and **21** (Chart III), respectively, on the basis of the following considerations.

Chart III



When the reaction was run in the presence of 0.2 equiv of $SnCl_4$, the reaction proceeded at room temperature and the same four products were found in a ratio of 69:27:3:1. Thus, the first two products must be products of "para" orientation in the addition of isoprene to **17** and the last two must be products of "meta" orientation, since such orientation is controlled by electronic factors, with "para" orientation favored,[19] and Lewis acid catalysis increases this selectivity.[20-22] In the present case, the ratio of "para" to "meta" products was enhanced from 2:1 to 24:1 by the use of the $SnCl_4$.

Consideration of the transition states A and B for the Diels–Alder reaction which determine the stereochemistry

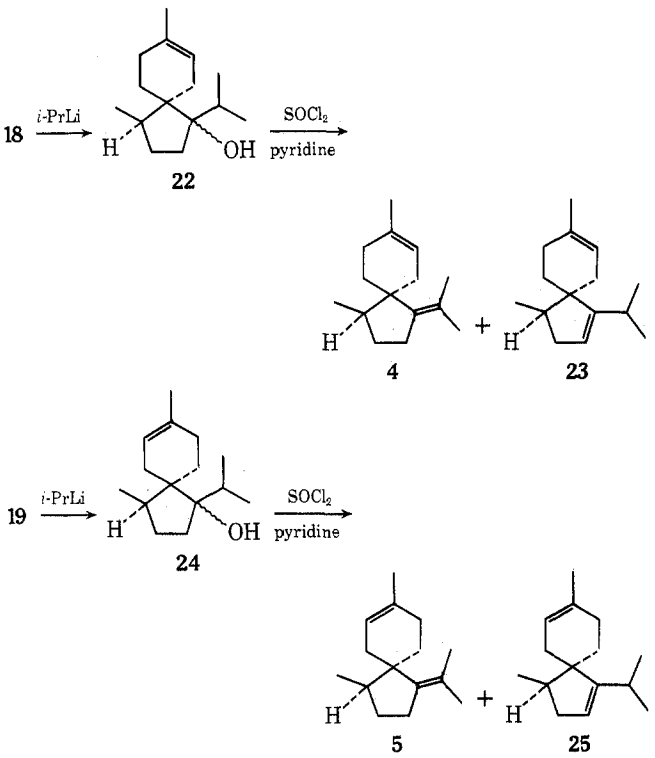


found in the two major isomers reveals that the enone chromatophore and cyclopentane ring of **17** are essentially planar, with only the methyl group partially blocking one face. Since the orientation in the Diels-Alder reaction is well known to be strongly influenced by steric effects,[19] one can predict with confidence that transition state A, in which the isoprene attacks on the opposite fact from the methyl group, would be favored. This would lead to the *S* absolute configuration at the spiro center (C-5), giving rise to **18**, which has the stereochemistry postulated for γ-acoradiene. The lesser major product must be **19**, derived from transition state B, and thus have the *R* configuration at that center, the same as in δ-acoradiene.

The ketones **18**–**21** were only partially separated by VPC under any conditions tried, but were well separated by preparative high-pressure liquid chromatography (0.375 in. × 4 ft Corasil C-18 column, 77% H_2O and 23% acetone). The major product, **18**, was then treated with isopropyllithium in ether (Chart IV). This process gave a 1:1 mixture of recovered ketone **18** and the tertiary alcohol **22**, presumably as a mixture of stereoisomers. The unreacted ketone was shown to result from competing enolization (gas evolution, deuterium incorporation on quenching with D_2O).

Dehydration of the alcohol **22** with thionyl chloride in pyridine gave a mixture of two dienes in a 72:28 ratio. These were readily separated by preparative VPC (40 ft × 0.125 in. SE-30 at 172°). The major product had spectral properties consistent with the endocyclic isomer **23**, whereas the lesser one, $[\alpha]D$ −82°, was identical by VPC and all

Chart IV



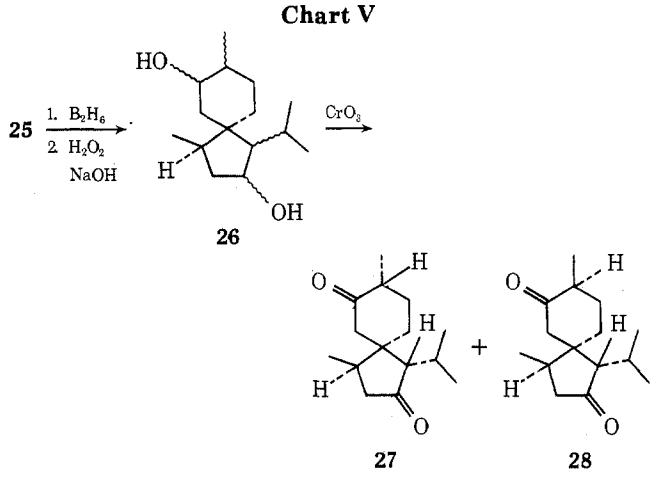
spectral comparisons (MS, NMR, ir) with an authentic sample of α-alaskene[23] [identical with γ-acoradiene (4)] (lit.[6] [α]D $-66°$,[6] $-88°$ [7]), and was cyclized to α-cedrene with formic acid as reported.[6,7]

In like manner, ketone **19** was treated with isopropyllithium and the resulting alcohol **24** dehydrated to a 70:30 mixture of the endocyclic diene **25** and the exocyclic isomer, [α]D $+14°$, which was found to be identical by all criteria (except sign of its optical rotation) with an authentic sample of β-alaskene[23] and its rotation matches that reported[6] ([α]D $+16°$) for its enantiomer, δ-acoradiene. This completes the synthesis of these two natural products[1] and confirms their relative and absolute stereochemistry.

When the above dehydration of the tertiary alcohols **22** or **24** was carried out with $POCl_3$ in pyridine, more vigorous conditions were necessary, and only the endocyclic dienes **23** or **25** were formed. Attempts to convert either **18** or **19** directly into the natural exocyclic dienes **4** or **5** via a Wittig reaction gave back only the starting ketones, even under very forcing conditions.

Hydroboration–oxidation of the endocyclic diene **25** gave a mixture of alcohols **26** (Chart V), which was oxidized with

Chart V



chromic acid (Jones reagent) to a ca. 1:1 mixture of two diketones. This ratio was changed to 70:30 when the mixture was subjected to epimerization conditions with sodium methoxide.

Since the stereochemistry at C-4 and C-5 has been assigned in **25** on the basis of the Diels–Alder reaction and since the stereochemistry adjacent to the ketones is controlled by thermodynamic considerations, these two products can be assigned structures **27** and **28**, respectively. These formulas represent the enantiomers of natural acorone (**1**) and isoacorone (**2**), respectively.[3] The equilibrium mixture of acorone–isoacorone is reported[3] to be 70:30.

The two diketones were separated very cleanly by preparative liquid chromatography (Porasil T, 0.125 in. × 2 ft, 10% $CHCl_3$–90% hexane). The major one, [α]D $-133°$, mp 96.0–97.5°, was identical in all respects except sign of optical rotation with an authentic sample[23] of natural (+)-acorone [mp 96.0–97.5° (lit.[3] [α]D + 139°, mp 98.5–99°)]. The minor one, [α]D $+90°$, mp 94.0–95.5°, was identical in all respects except sign of optical rotation with an authentic sample[23] of natural (−)-isoacorone [mp 94.0–95.5° (lit.[3] [α]D $-92°$, mp 97.0–98.0°)]. Since the optical rotations have the expected opposite signs from the natural products, the stereochemical reasoning given above shows that the relative and absolute stereochemistry assigned to acorone and isoacorone is confirmed.

Experimental Section

General. All routine NMR spectra were run on a Varian A-60 spectrometer in 25–50% CCl_4 solutions unless otherwise stated. NMR spectra of small samples or for higher resolution were run on a Varian XL-100 as 10% deuteriochloroform solutions. All NMR chemical shifts are reported in δ units downfield from internal reference Me_4Si. Infrared spectra were obtained with a Perkin-Elmer Model 457 in CCl_4 solution or as a thin film. All melting points are uncorrected and were determined after at least one recrystallization and drying at 0.1 Torr. Melting points were obtained in open capillaries for abundant samples on a Laboratory Device's Mel-Temp or with an Arthur H. Thomas Hot-Stage apparatus for smaller quantities.

Thin layer chromatography was done on silica gel using Eastman Chromagram sheets 6060 with fluorescent indicator and were visualized with I_2 vapors or a short-wave ultraviolet lamp. Silica gel, 60–200 mesh, high purity, from W. H. Curtin and Co. was used for all column chromatography. Columns were packed as a slurry using the first eluting solvent as the packing solvent. High-pressure liquid chromatography was done with a Waters Associates ALC-100 liquid chromatograph. Either a Beckman GC-45 or Aerograph Hy-Fi 600-C was used for analytical gas chromatography with helium flow rates of 20 ml min^{-1}. A Varian Aerograph 1520 was used for preparative gas chromatography with helium flow rates of 120 ml min^{-1}. All preparative GLC samples were collected manually.

Optical rotations were determined with a Perkin-Elmer 141 polarimeter using the sodium D line and several other wavelengths from a built-in Hg lamp. The cell path length was 1.00 dm and the concentrations used gave experimental values of 0.1–5.0°.

Elemental analyses were done commercially by Chemalytics, Inc., Tempe, Ariz.

Ethyl 5-Isopropyl-2-methylcyclopentanecarboxylate (Ethyl Pulegenate, 13). The following is an improvement of the method described by Yates.[15] To a 2-l. round-bottom flask was added 152.23 g (1.00 mol) of pulegone, 25 g of anhydrous powdered $NaHCO_3$, and 1 l. of anhydrous reagent-grade ether. The mixture was cooled and stirred under N_2 in an ice–salt bath; then 159 g (1.00 mol) of Br_2 was added dropwise over a 30-min period. The mixture was then filtered and added to a cooled EtOH–NaOEt mixture which had been prepared from refluxing 50.6 g (2.2 mol) of Na in 1 l. of dry [$Mg(OEt)_2$] ethanol. This mixture was cooled in ice and the solid NaOEt cake was slowly broken up with a spatula, causing an exothermic reaction. All refluxing subsided after 1 hr. The mixture was stirred overnight, then 2 l. of 5% aqueous HCl and 0.5 l. of ether was added. The aqueous layer was reextracted with ether and the combined extracts were washed and dried, giving 189.4 g of brown oil, which was shown to consist of 85% ethyl

pulegenate and 15% pulegone by GLC (0.125 in. × 3 ft, 3.8% SE-30 at 110°). This oil was added to a warm solution containing 75 g of semicarbazide hydrochloride, 75 g of NaOAc, and 600 ml of H_2O; then enough boiling ethanol (600 ml) was added to give a clear solution. After refluxing for 2.5 hr and then stirring at 25° overnight, the mixture was treated with 2 l. of H_2O and 0.5 l. of petroleum ether. The water layer was extracted twice with 250-ml portions of petroleum ether, the combined extracts were washed and dried, and the solvent was removed, yielding a brown oil. Distillation gave pure (99+% by GLC) ethyl pulegenate, 131.6 g (67%), bp 83–85° (1.0 mm). All physical and spectral properties were in complete accord with those reported by Yates.[15]

2-Carbethoxy-3-methylcyclopentanone (8) by Ozonolysis of 13. Ethyl pulegenate (24.0 g, 0.123 mol) was dissolved in 100 ml of reagent ethyl acetate and cooled to −90° with isopropyl alcohol–liquid nitrogen. Ozonized oxygen (about 0.4 mmol of O_3/min as determined by bubbling into KI solution and titrating liberated KI with thiosulfate solution) was bubbled through this solution, with periodic addition of liquid nitrogen to maintain the cooling bath. The ethyl acetate was then removed at reduced pressure, and the resultant greenish, glassy ozonide mixture was dissolved in 150 ml of glacial acetic acid. The solution was cooled in ice, 45 g of powdered zinc was added, and the solution was stirred for 30 min and then filtered. Neutralizing the acetic acid of this solution with aqueous sodium bicarbonate, ether extraction, drying, solvent removal, and distilling gave 18.55 g (85%) of clear oil, bp 72–74° (0.1 mm), which was 100% pure by GC analysis. The ir and NMR spectra are in complete accord with those of the corresponding product prepared from $Li(CH_3)_2Cu$ and **7**.[16] The optical rotation was $[\alpha]^{25}D$ +66.9° (lit. +78° for the methyl ester[24]) and semicarbazone mp 124–128° (EtOH–H_2O). Anal. Calcd for $C_{10}H_{17}N_3O_3$: C, 52.85; H, 7.54. Found: C, 52.91; H, 7.67.

Ethylene Ketal of 2-Carbethoxy-3-methylcyclopentanone (14). A mixture of 18.80 g (0.11 mol) of 2-carbethoxy-3-methylcyclopentanone (**8**) 150 ml of reagent benzene, and about 25 mg of *p*-toluenesulfonic acid was treated with 20 ml of ethylene glycol and refluxed for 6 hr into a Dean-Stark trap, then for 3 hr into a large Soxhlet extractor filled with anhydrous $MgSO_4$. The solution was then cooled, 100 ml of ether was added, and the solution was washed with saturated brine. Drying, solvent removal, and distilling gave 20.68 g (87%) of clear, colorless oil: bp 84–87° (1.0 mm); NMR 1.03 (d, J = 6 Hz, 3 H), 1.15 (t, J = 7 Hz, 3 H), 1.6–2.1 (m, 4 H), 2.3–2.6 (m, 2 H), 3.84 (m, 4 H, $-OCH_2CH_2O-$), 4.11 ppm (q, J = 7 Hz, 2 H); ir (film) 1752 (C=O, ketone), 1721 cm^{-1} (C=O, ester). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.96; H, 8.53.

Ethylene Ketal of 2-Hydroxymethyl-3-methylcyclopentanone (15). A mixture containing 200 ml of dry ether and 4.55 g of $LiAlH_4$ was treated, dropwise, with 50 ml of an ether solution containing 34.5 g (0.16 mol) of **14**. After stirring at 25° for 30 min, the mixture was treated, carefully, with 0.42 ml of H_2O, then 0.42 ml of 15% NaOH, and then 1.5 ml of H_2O, then filtered, and the solvent was removed. Distillation gave 23.76 g (86%) of **15** as a colorless oil: bp 60–63° (0.1 mm); $[\alpha]^{25}D$ −14.8°; NMR 1.04 (d, 3 H, $-CH_3$), 1.66 (m, 6 H, ring H), 2.74 (t, J = 6 Hz, 1 H, OH), 3.57 (d of d, J = 6 and 3 Hz, 2 H, $-CH_2OH$), 3.87 ppm (s, 4 H, $-OCH_2CH_2O-$); ir 3440 (m, OH), 2960 and 2880 cm^{-1} (s, CH). Numerous attempts to make a crystalline derivative failed. High-resolution mass spectrum: calcd for $C_9H_{16}O_3$, 172.1099; found, 172.1101. Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.55; H, 9.79.

2-Hydroxymethyl-3-methylcyclopentanone (16). To 11.16 g (64 mmol) of ketal alcohol **15** was added 111 ml of 3 *N* HCl and the homogeneous solution was stirred for 2.0 min (±5 sec), then quenched by pouring into 200 ml of saturated brine. Quickly extracting twice with chloroform, drying the combined extracts, and removal of the solvent gave 8.13 g (98%) of **16**: NMR 1.17 (d, J = 6 Hz, 3 H, $-CH_3$), 1.4–2.4 (complex absorption, 6 H), 3.40 (s, 1 H, OH), 3.72 ppm (d of d, J = 5 and 3 Hz, 2 H, $-CH_2OH$); ir 3460 (br, OH), 2965, 2940, 2880 (m, CH), 1735 cm^{-1} (s, C=O). No solid derivatives could be obtained from this compound.

3-Methyl-2-methylencyclopentanone (17). The following method was adapted from a similar one given by Alexandre and Rouessac.[18] A dry ($LiAlH_4$) 70-ml ether solution of **16** (8.13 g, 63 mmol) was treated with 19.7 g of dicyclohexylcarbodiimide (DCC) and 50 mg of Cu_2Cl_2. After refluxing for 2.2 hr, the solid precipitate of dicyclohexylurea was removed by filtration and the filtrate was evaporated at the aspirator. The resulting oily, green residue was rapidly distilled by heating the distillation pot with a hot air gun, and the distillate receiver was cooled in a Dry Ice–acetone bath, giving 4.68 g (67%) of **17** as a clear, colorless, pungent-smelling oil: bp 33–34° (0.1 mm); NMR 1.15 (d, 3 H), 1.8–2.8 (complex absorption, 5 H), 4.89 (d of d, J = 1 and 3 Hz, 1 H), 5.58 ppm (d of d, J = 1 and 3 Hz, 1 H); ir (film) 2980 (m, CH), 1732 (s, C=O), 1641 cm^{-1} (m, C=C); $[\alpha]^{25}D$ 53.5° (213 mg ml^{-1} in EtOH). This material could be stored without polymerization in dilute ether solution at −10°. The semicarbazide adduct (probably not a simple semicarbazone, but this was not investigated because of its insolubility in NMR solvents) had mp 177.5–179° (MeOH). Anal. Calcd for $C_8H_{13}N_3O$: C, 57.46; H, 7.80. Found: C, 57.79; H, 8.06.

4,8-Dimethylspiro[4.5]dec-8-en-1-one, Isomers 18, 19, 20, and 21. Diels–Alder Reactions of 17 and Isoprene. Distilled, dried ($MgSO_4$) isoprene (2 ml) was added to 245 mg (2.22 mmol) of 3-methyl-2-methylenecyclopentanone (**17**) in a 20-mm Pyrex tube, which was cooled to −78° and sealed. After heating to 105° for 1.0 hr, the tube was cooled (−78°) and opened, and the contents were chromatographed on silica gel, eluted with 90% petroleum ether–10% ether. All materials eluting with this solvent system were combined (the solvent was removed) and distilled through a short path at 0.1 mm, yield 161 mg (40%). The expected four adducts **18–21** were only partially separated by VPC, but were well resolved by high-pressure liquid chromatography (77% H_2O, 23% acetone on Corasil C-18 reverse phase, 2 ft × 0.125 in. column) into four peaks with retention times of 32, 38, 44, and 47 min in a ratio of 25:45:10:20, respectively. The two major isomers were characterized from the $SnCl_4$-catalyzed reaction described below.

A mixture of 6.45 g (58 mmol) of 3-methyl-2-methylenecyclopentanone (**17**), 30 ml of isoprene, and 4.10 g (0.2 equiv) of $SnCl_4 \cdot 5H_2O$ was mixed and stirred for 2.5 days. Working up and distilling as above gave 4.95 g (48%) of clear oil, bp 60–66° (0.1 mm). Analysis by liquid chromatography as above gave the same four compounds in a ratio of 27:69:1:3 in their order of elution. By use of a preparative column (4 ft × 0.375 in. Corasil C-18 column), there was obtained, using multiple injections, 1.18 g of the first component, which was identified by reasoning given in the text as **19** and 1.92 g of the second component, identified as **18**. The two minor isomers were not characterized further, but are assigned structures **21** and **20**, respectively, on the basis of their relative amounts.

Compound **18** had NMR 0.96 (d, 3 H), 1.38 (br s, 3 H), 1.3–2.2 (complex, 11 H), 5.30 ppm (br s, 1 H); ir 1735 cm^{-1}. A small sample was further purified by distillation at 0.1 mm in a capillary tube. Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.44; H, 10.09.

Compound **19** had NMR 0.94 (d, 3 H), 1.39 (br s, 3 H), 1.3–2.2 (complex, 11 H), 5.24 ppm (br s, 1 H); ir 1735 cm^{-1}. A small sample was distilled as above. Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.99; H, 10.02.

1-Isopropyl-4,8-dimethylspiro[4.5]dec-8-en-1-ol (Isomers 22 and 24). A dry ($LiAlH_4$) 15-ml pentane solution at 25° containing 23 mmol of isopropyllithium (15 ml of 1.6 *M* commercial solution) was treated, dropwise, with a dry pentane (10 ml) solution containing 1.25 g of **18** (gas evolution) and stirred for 15 min. Careful addition of water followed by drying and evaporation of the pentane layer gave 1.26 g of clear, colorless oil. NMR analysis of this oil indicated it to be about 50% isomeric alcohols **22** and 50% starting material as judged by the relative integration of the vinyl H (5.2–5.4, broad s) and saturated methyl group signals (0.9, m). Column chromatography on silica gel gave 0.52 g of alcohol **22** in the 10% ether–90% benzene fractions and 0.66 g of recovered **18** (slightly contaminated with **22**) in the 15% ether–85% benzene fractions. Alcohol **22** had NMR 0.9 (9 H, Me signals), 1.3–2.3 (complex), 1.62 (br s, 3 H), 5.31 ppm (br s, 1 H); ir 3630 and 3500 cm^{-1}.

In like manner, 1.02 g of compound **19** was treated with excess isopropyllithium. After work-up, it was resubmitted to the reaction conditions two more times. This multiple process gave an estimated 8:1 mixture of alcohol **24** to ketone **19**. Chromatography as above gave 0.76 g of alcohol **24**, with spectra virtually identical with those given by alcohol **22**.

γ-Acoradiene (4) and Endocyclic Isomer 23. To a solution of 0.50 g of alcohol **22** in 5 ml of dry pyridine was added 0.26 g of $SOCl_2$ and the mixture was stirred for 10 min at 25°, then poured into 5% HCl and extracted with ether. The product was filtered through a short column of silica gel with petroleum ether, yield 0.37 g of hydrocarbon material. GLC analysis (40 ft × 0.125 in., 3% SE-30 at 172°) gave two peaks eluting in 68 and 93 min in a ratio of 72:28. Collection from a preparative column (20 ft × 0.375 in., 30% SE-30 at 250°) gave 130 mg of the first component, which was identified as endocyclic diene **23**: 100-MHz NMR 0.80 (d, J = 7 Hz, 3 H), 1.01 (d, J = 7 Hz, 6 H), 1.2–2.5 (complex, 10 H), 1.61 (br s, 3 H), 5.30 (br s, 2 H). Collection of the second peak gave 50 mg of

a compound which was identical with γ-acoradiene (α-alaskene, **4**). It had $[\alpha]^{25}D$ −82° (lit. −66[6] and −88° [7]); 100-MHz NMR 0.88 (d, J = 7 Hz, $-CH_3$), 1.2–2.3 (complex absorption), 1.60–1.75 (multiplet with intense peak maxima at 1.63, 1.69, 1.70, and 1.71), 5.25–5.30 ppm (broad s, C=CH); ir (film) 2840–3020 (complex, CH), 1432–1455 (broad), and medium, sharp peaks at 1375, 1312, 1192, 1138, 1050, 950, 800, and 788 cm^{-1}; high-resolution mass spectrum of P^+, 204.1822 (calcd for $C_{15}H_{24}$, 204.1878). The NMR and ir spectra of **4** were compared to those of α-alaskene[23] and found identical. Also, **4** was stirred as a hexane solution heterogeneously with 98% formic acid at 25° for 24 hr as suggested for converting α-alaskene to α-cedrene,[7] and the resulting major product was identical with natural α-cedrene[23] by GLC comparisons.

δ-Acoradiene (5) and Endocyclic Isomer 25. A solution of 0.21 g of alcohol **24** in 2 ml of dry pyridine was dehydrated with 0.11 g of $SOCl_2$ as for **23**. GLC analysis as before showed two olefins eluting at 68 and 88 min in the ratio 70:30. These were collected by the same preparative method. The first one, 50 mg, was identified as the endocyclic diene **25**, which could be better prepared by $POCl_3$ dehydration of **24**, as described below. The second one, 18 mg, was identified as δ-acoradiene (**5**). It had $[\alpha]^{25}D$ +14° (lit. +16° [6]); 100-MHz NMR 0.82 (d, J = 7 Hz, CH_3), 1.1–2.3 (complex absorption), 1.50–1.70 (m with intense peak maxima at 1.59 and 1.68), 5.30–5.40 ppm (broad s, vinyl H); ir (film) 2840–3000 (complex, CH), 1435–1460 (broad), and medium, sharp peaks at 1380, 1260, 1006, 906, 800, and 733 cm^{-1}; high resolution mass spectrum, P^+ 204.1918 (calcd for $C_{15}H_{24}$, 204.1878). The ir and NMR spectra are identical with ones furnished for β-alaskene.[23] Also, the sample was compared to an authentic sample of β-alaskene[23] and found identical (retention time and peak enhancement) using 3% SE-30 (40 ft × 0.125 in., 160°).

A solution of 0.53 g of alcohol **24** and 0.53 g of $POCl_3$ in 5 ml of pyridine was heated at 92° for 27 hr. Work-up as before gave 0.40 g of diene material which was shown by VPC to be only the endocyclic isomer **25**: 100-MHz NMR 0.80 (d, J = 7 Hz, 3 H), 1.00 (d, J = 7 Hz, 6 H), 1.1–2.5 (m, 10 H), 1.6 (br s, 3 H), 5.32 (br s, 2 H). A sample was purified by distillation in a capillary at 0.1 mm. Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 87.92; H, 11.77.

4,8-Dimethyl-1-isopropylspiro[4.5]deca-2,7-diols (26). A solution of 0.40 g of diene **25** in 20 ml of dry THF (from $LiAlH_4$) was treated with 8 ml of 1.0 M BH_3 in THF (Aldrich) and stirred at 25° for 2 hr. Then H_2O was added, followed by 5 ml of 15% NaOH and 5 ml of 30% H_2O_2. The mixture was stirred for 1 hr, 20 ml of ether and 20 ml of H_2O were added, and the organic layer was washed with brine. Drying and removal of the solvents gave 0.35 g of colorless oil, presumed to be the isomeric mixture of alcohols **26**. This was supported by ir (film), 3200–3600 cm^{-1} (broad, OH), and NMR, no absorption of vinyl H at 5.2–5.4 ppm. The mixture was used in the next reaction without further purification.

(−)-Acorone (27) and (+)-Isoacorone (28). The total crude diol mixture **26** was dissolved in 20 ml of reagent acetone and treated dropwise with ca. 4 ml of Jones reagent until a permanent orange color remained. To the mixture was then added 5 ml of H_2O and 10 ml of ether, and the organic layer was washed with brine, dried, and evaporated, yielding 0.37 g of viscous oil, showing ir 1715 (cyclohexanone) and 1739 cm^{-1} (cyclopentanone) chromatophores. Analytical GLC analysis of this oil showed minor unidentified components and a major peak at 94 min (13% Carbowax 20M, 18 ft × 0.125 in. at 240°) which correspond to authentic samples of acorone (**1**) and isoacorone (**2**) (supplied[23] as a mixture, originally thought to be a pure compound, "neoacorone" [3]). Analysis by high-pressure liquid chromatography (Porasil T, 2 ft × 0.125 in., 10% $CHCl_3$–90% hexane) gave separation into two approximately equal-sized peaks eluting in 52.5 and 65 min, using an elution rate of 5.5 ml/min. Combination of all eluents collected for each peak gave 57 and 63 mg, respectively. Crystallization of the former component from n-hexane gave 27 mg, $[\alpha]^{25}D$ +90°, mp 94.0–95.5°, of material identical, except for sign of rotation, with authentic (−)-isoacorone (mp 94.0–95.5° for a sample isolated in the same way from "neoacorone",[23] lit.[3] $[\alpha]^{25}D$ −92°, mp 97–98°), mass spectrum, 236.1759 (calcd, 236.1776). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.21; H, 10.29. The second component, $[\alpha]^{25}D$ −133°, mp 96.0–97.5°, was identical, except for sign of rotation, with an authentic sample[23] of (+)-acorone [mp 96.0–97.5° (lit.[3] $[\alpha]^{25}D$ +139°, mp 98.5–99°], mass spectrum, 236.1762 (calcd, 236.1776). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.33; H, 10.33.

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Registry No.—**4**, 28400-12-6; **5**, 28400-13-7; **8**, 52475-64-6; **8** semicarbazone, 54688-99-2; **13**, 54712-95-7; **14**, 52475-65-7; **15**, 52475-66-8; **16**, 52475-67-9; **17**, 52599-97-0; **17** semicarbazone, 52475-68-0; **18**, 52475-69-1; **19**, 52521-52-5; **22** α-OH, 54712-96-8; **22** β-OH, 54712-97-9; **23**, 54712-98-0; **24**, 54688-97-0; **25**, 54712-99-1; **26**, 54688-98-1; **27**, 54713-00-7; **28**, 54713-01-8; pulegone, 89-82-7; isoprene, 78-79-5.

References and Notes

(1) Portions of this work were reported at the 166th National Meeting of the American Chemical Society, Chicago, Ill., Aug 29, 1973, and the 29th Southwest Regional Meeting of the American Chemical Society, El Paso, Tex., Dec 5, 1973. A preliminary account of a portion of this work has been published: J. N. Marx and L. R. Norman, *Tetrahedron Lett.*, 4375 (1973).
(2) National Science Foundation Trainee, 1970–1973.
(3) (a) F. Sorm and V. Herout, *Collect. Czech. Chem. Commun.*, **13**, 202 (1948); (b) *ibid.*, **14**, 753 (1949); (c) V. Sykora, V. Herout, J. Pliva, and F. Sorm, *Chem. Listy*, **51**, 1704 (1957); (d) *Chem. Ind. (London)*, 1231 (1956); (e) J. Vrkoc, V. Herout, and F. Sorm, *Collect. Czech. Chem. Commun.*, **27**, 2709 (1962); (f) J. Vrkoc, J. Jonas, V. Herout, and F. Sorm, *ibid.*, **29**, 539 (1964).
(4) R. J. McClure, K. S. Schorno, J. A. Bertrand, and L. H. Zalkow, *Chem. Commun.*, 1135 (1968).
(5) R. Kaiser and P. Naegeli, *Tetrahedron Lett.*, 2009, 2013 (1972).
(6) (a) B. Tomita and Y. Hirose, *Tetrahedron Lett.*, 143 (1970); (b) B. Tomita, T. Isono, and Y. Hirose, *ibid.*, 1371 (1970).
(7) (a) N. H. Anderson and D. D. Syrdal, *Tetrahedron Lett.*, 2277 (1970); (b) *ibid.*, 899 (1972).
(8) C. W. McEachan, A. T. McPhail, and G. A. Sim, *J. Chem. Soc. C*, 579 (1966).
(9) (a) T. G. Crandall and R. G. Lawton, *J. Am. Chem. Soc.*, **91**, 2127 (1969); see also (b) E. J. Corey, N. N. Girotra, and C. T. Mathew, *ibid.*, **91**, 1557 (1969).
(10) J. C. Guest, C. L. Hughes, R. Ramage, and R. Sattar, *J. Chem. Soc., Chem. Commun.*, 527 (1973).
(11) (a) W. Oppolzer, *Helv. Chim. Acta*, **56**, 1812 (1973); (b) T. R. Kasturi and M. Thomas, *Indian J. Chem.*, 777 (1972).
(12) A. R. Pinder, S. J. Price, and R. M. Rice, *J. Org. Chem.*, **37**, 2202 (1972).
(13) (a) J. M. Conia, M. P. Drouet, and J. Gore, *Tetrahedron*, **27**, 2481 (1971); (b) G. L. Lange, H. M. Campbell, and E. Neidert, *J. Org. Chem.*, **38**, 2117 (1973); (c) D. K. Banerjee and G. Subrahmanyam, *Synthesis*, 213 (1973).
(14) Cf. E. J. Eisenbraum and S. M. McElvain, *J. Am. Chem. Soc.*, **77**, 3383 (1955).
(15) P. Yates, M. J. Jorgenson, and P. Singh, *J. Am. Chem. Soc.*, **91**, 4739 (1969), and references cited therein.
(16) J. N. Marx, L. R. Norman, and J. H. Cox, *J. Org. Chem.*, **37**, 4489 (1972).
(17) J. Wolinsky and D. Chan, *J. Org. Chem.*, **30**, 41 (1965).
(18) C. Alexandre and F. Rouessac, *Bull. Soc. Chim. Fr.*, 1837 (1971).
(19) Cf. J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **6**, 16 (1967).
(20) K. L. Williamson and Y. F. L. Hsu, *J. Am. Chem. Soc.*, **92**, 7385 (1970).
(21) A. Tanaka, H. Uda, and A. Yoshikoshi, *Chem. Commun.*, 188 (1967).
(22) K. N. Houk and R. W. Strozier, *J. Am. Chem. Soc.*, **95**, 4094 (1973).
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(24) C. Lucas, J. C. N. Ma, J. A. McClosky, and R. E. Wolf, *Tetrahedron*, **20**, 1789 (1964).