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(30) We determined the RuO_4 concentration of our stock solution by adding a sample of it to an excess of some secondary alcohol (e.g., borneol) in methylene chloride under conditions similar to those described in the oxidation procedure. After the oxidation the mixture was left to stand till it had reached room temperature, and then it was filtered. The RuO_4 concentration was easily calculated from the ketone:alcohol ratio in the filtrate (glc, Carbowax column). For alternative procedures for the quantitative determination of RuO_4, cf. C. Djerassi and R. R. Engle, J. Amer. Chem. Soc., 75, 3838 (1953); W. R. Crowell and D. M. Yost, ibid., 50, 374 (1928).
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(33) There seemed to be a large isotope effect in the reduction of 3: under conditions where $LiAlH_4$ reduction of 3 was complete. $LiAlD_4$ gave a mixture of the desired alcohol 4b (minor product) and 1-bromo-α-fenchocamphorol. However, we have not investigated whether this result of $LiAlD_4$ reduction is reproducible.
(34) We have not investigated why the deuterium content of 5b and 6b was much lower than was expected.

Total Stereoselective Synthesis of α-Atlantone

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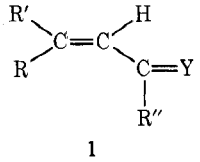
A stereoselective synthesis of α-atlantone (13) has been achieved, the key step involving the allylic rearrangement of tertiary vinyl carbinol 6 to primary allylic acetate 7. Saponification of the latter followed by oxidation using the chromium trioxide–pyridine complex afforded α,β-unsaturated aldehyde 9 of very high stereochemical purity. The synthesis was completed by addition of methallylmagnesium chloride (11) to aldehyde 9 to yield alcohol 12, which upon mild oxidation followed by base-catalyzed isomerization yielded α-atlantone (13), identical in physical and spectral properties with those of the authentic natural product. An alternate route to α,β-unsaturated aldehyde 9 involved preparation of nitrile 10 from ketone 5 *via* a modified Wittig reaction using diethyl cyanomethylphosphonate. Subsequent reduction of nitrile 10 with diisobutylaluminum hydride followed by hydrolysis afforded the desired aldehyde (9).

Until recently atlantones, the major ketones of the essential oil from *Cedrus libanotica* Link., *C. atlantica* Manet, and *C. deodara* Loud. (the "true" cedars), had not been obtained in pure form and were considered to be an inseparable mixture of isomers. In 1971, however, the essential oil from *Cedrus deodara* was found[1] to contain essentially one member of this group, α-atlantone (13). The assigned structure and stereochemistry of this ketone was subsequently confirmed by a total synthesis[2] of α-atlantone by a route that also led to the synthesis of other bisabolane sesquiterpenes.[3]

Since α-atlantone can be viewed as a functionalized trisubstituted olefin of structural type 1, we decided to investigate its possible synthesis *via* a route which we have recently developed[4] for the bishomologation of ketones to such derivatives.



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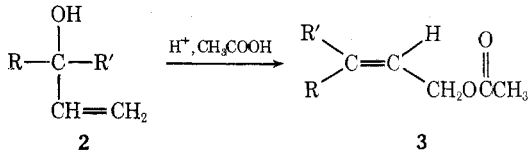
R′ > R in size

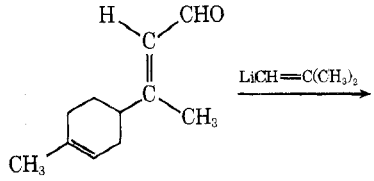
The key step in the synthesis of these functionalized olefins (1) involves the acid-catalyzed rearrangement of a tertiary vinyl carbinol (2) in acetic acid to afford in high yield the primary allylic acetate (3). The starting alcohols (2) for the process are readily obtained *via* addition of vinylmagnesium chloride to an appropriate ketone.



2 3

The tertiary vinyl carbinol required for a synthesis of α-atlantone utilizing the above rearrangement is alcohol 6, obtained in high yield by addition of vinyllithium to the previously reported[5] ketone 5. Diels–Alder reaction of isoprene with methyl vinyl ketone afforded the latter compound (5) as the major product. As expected, the allylic rearrangement of alcohol 6 proceeded smoothly to give the desired primary allylic acetate (7) in approximately 70% yield. Furthermore, as indicated by vpc and nmr analysis of acetate 7 as well as the corresponding alcohol 8 and aldehyde 9, the product appeared to consist predominantly (>90%) of the *E* stereoisomer, the one vital in a stereoselective synthesis of α-atlantone.

Encouraged by the success of the allylic rearrangement, we continued the total synthesis as outlined in Chart I. Saponification of allylic acetate 7 followed by mild oxidation of the corresponding alcohol 8 with the chromium trioxide–pyridine complex[6] proceeded without complications to afford aldehyde 9 in high yield. Initially we had planned to add isobutenyllithium to aldehyde 9 to obtain alcohol 4, which could subsequently be oxidized directly to α-atlantone (13). However, we were unable to obtain



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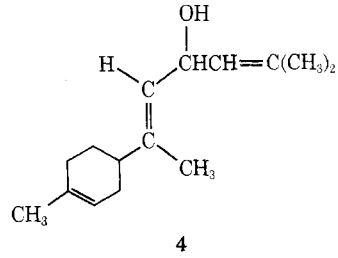

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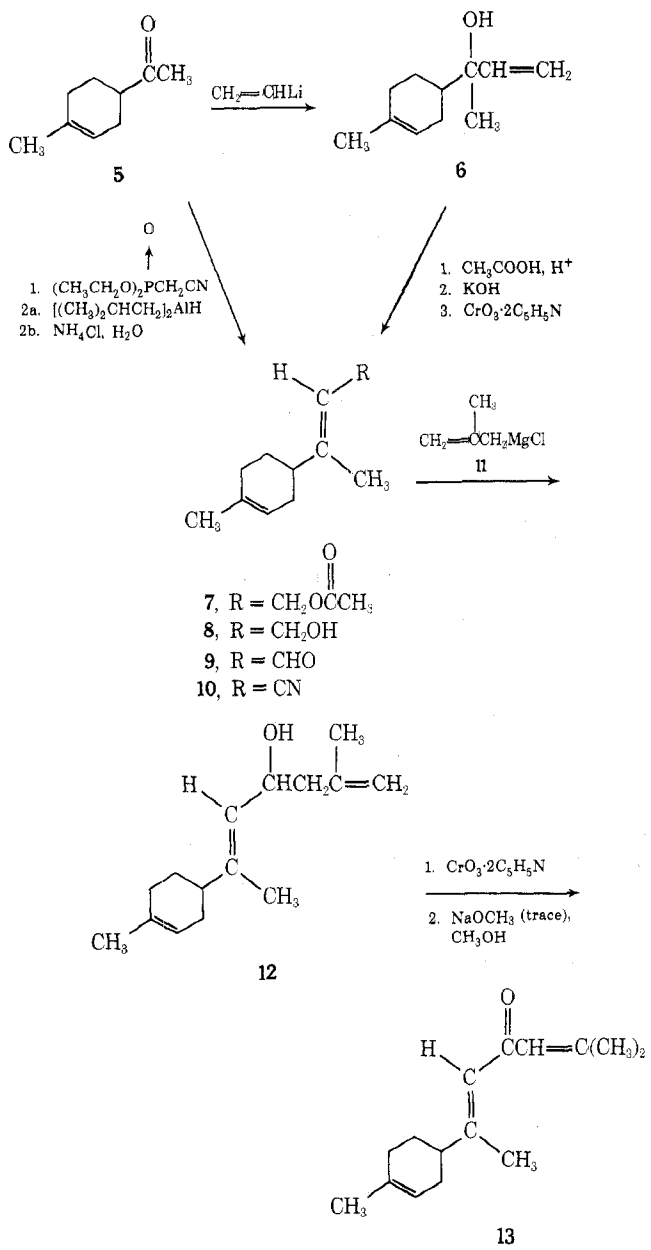
this organolithium derivative in satisfactory yield following the literature procedure[7] for its preparation. We found it more convenient to prepare methallylmagnesium chloride (11), which reacted with aldehyde 9 to yield the unsaturated alcohol 12. Oxidation of the alcohol moiety followed by a facile base-catalyzed isomerization (*via* eno-

late formation) under mild conditions led to formation of α-atlantone (13), identical in physical and spectral properties with those of the authentic natural product.[2]

Chart I



5 6 12 13

An alternate but less stereoselective route to the key intermediate in the synthesis, α,β-unsaturated aldehyde **9**, involved preparation of nitrile **10** from ketone **5** *via* a modified Wittig reaction[8] using diethyl cyanomethylphosphonate. Vpc analysis indicated the product to be an 80:20 mixture of geometric isomers with *E* nitrile **10** as the major component based on analogy with similar Wittig reactions.[8] Subsequent reduction of this nitrile mixture with diisobutylaluminum hydride followed by hydrolysis of the intermediate imine afforded a product whose main component had ir and nmr spectral properties identical with those of aldehyde **9** prepared *via* the other pathway. At present we are completing a project involving a comparison of the stereochemical results found in modified Wittig reactions on several representative ketones *vs.* those obtained in the process involving the allylic rearrangement of an intermediate tertiary vinyl carbinol. Results of this study will be published in the near future.

Experimental Section[9]

Methyl 4-Methyl-3-cyclohexenyl Ketone (5). A mixture of 148 mmol of methyl vinyl ketone (stabilized with 1% hydroquinone) and 150 mmol of isoprene was heated at 140° in a Parr bomb for 3 hr. Distillation afforded 14.71 g (72%) of ketone **5**: bp 90–94° (8.0 mm) [lit.[5a] bp 72–73° (2–3 mm)]; 96% pure[5b] by vpc analysis,[10] oven temperature 150°, retention time 3.8 min; λ_{max} (film) 5.85, 8.54 mμ; δ_{TMS} (CCl_4) 5.32 (C=CH), 2.08 (CH_3C=O), 1.64 ppm (CH_3C=C).

2-(4-Methyl-3-cyclohexenyl)-3-buten-2-ol (6). A solution of 1.164 g (8.43 mmol) of ketone **5** in 5.0 ml of anhydrous ether was added dropwise over a period of 5 min to a mixture of 5.0 ml of 2.5 *M* vinyllithium–tetrahydrofuran solution[11] and 2.0 ml of anhydrous ether at 0°. After this solution was stirred at 0° for an additional 10 min, the reaction was quenched by slow dropwise addition of water and the product was isolated by extraction with ether. The crude product was purified by filtration through a column of Florisil (80 ml, 60–100 mesh). Hydrocarbon polymers evidently present in the vinyllithium reagent were removed by washing the column with 250 ml of hexane, and the vinyl alcohol was subsequently recovered by elution with ether. Evaporative distillation afforded 1.255 g (90%) of alcohol **6**: bp 45–60° (bath temperature, 0.08 mm); λ_{max} (film) 2.91, 3.25, 6.07, 9.06, 9.99, 10.84 mμ; δ_{TMS} (CCl_4) 6.17–4.93 (complex pattern, 4 vinyl H, peaks at 6.17, 5.99, 5.88, 5.70, and 5.32), 1.63 (CH_3C=C), 1.22 ppm (CH_3COH). *Anal.* Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.20; H, 11.01.

3-(4-Methyl-3-cyclohexenyl)-2(*E*)-buten-1-ol Acetate (7). To a solution of 445 mg of *p*-toluenesulfonic acid monohydrate in 10 ml of acetic anhydride and 20 ml of glacial acetic acid cooled in an ice–water bath was added rapidly 1.206 g of tertiary alcohol **6** dissolved in 15 ml of glacial acetic acid. After this mixture was stirred for 30 min at 0° and 15 min at room temperature, the reaction was quenched by pouring the solution into 400 ml of H_2O. The aqueous layer was then extracted thoroughly with pentane; and after washing the combined pentane extracts with aqueous sodium bicarbonate solution, the product was recovered from the organic phase in the usual manner. Evaporative distillation afforded 1.02 g (68%) of colorless oil: bp 70–80° (bath temperature, 0.08 mm); 90% pure[12] by vpc analysis,[10] oven temperature 200°, retention time 4.5 min; λ_{max} (film) 5.74, 6.01, 8.10, 9.73, 10.43 mμ; δ_{TMS} (CCl_4) 5.34 (overlapping triplet and broad singlet, 2 vinyl H), 4.53 (doublet, J = 7 Hz, CH_2OAc), 1.98 ppm [OC(=O)CH_3]. *Anal.* Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.73; H, 9.71.

3-(4-Methyl-3-cyclohexenyl)-2(*E*)-buten-1-ol (8). A solution of 757 mg of allylic acetate **7** and 815 mg of potassium hydroxide in 6 ml of methanol and 1.5 ml of H_2O was refluxed for 15 min. Extraction with ether followed by evaporative distillation afforded 542 mg (90%) of alcohol **8**: bp 65–75° (bath temperature, 0.08 mm); λ_{max} (film) 3.05, 6.02, 9.96 mμ; δ_{TMS} (CCl_4) 4.07 (doublet, J = 7 Hz, CH_2OH), 2.83 (OH), 1.66 ppm (6 H, 2 C=CCH_3). *Anal.* Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.38; H, 11.07.

3-(4-Methyl-3-cyclohexenyl)-2(*E*)-butenal (9). Allylic alcohol **8** was oxidized using the method developed by Ratcliffe and Rodehorst[6] to afford aldehyde **9** in 80% yield: bp 60–70° (bath temperature, 0.03 mm); λ_{max} (film) 5.99, 6.14, 8.32, 8.40, 8.63, 8.90, 10.90, 11.68, 12.60 mμ; δ_{TMS} (CCl_4) 9.97 (doublet, J = 7.4 Hz, CHO), 5.81 (broad doublet, J = 7.4 Hz, C=CHCHO), 5.42 (C=C**H**CH_3), 2.19 (CH_3C=CHCHO), 1.68 ppm (vinyl CH_3). *Anal.* Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.30; H, 10.01.

6-(4-Methyl-3-cyclohexenyl)-2-methyl-1,5(*E*)-heptadien-4-ol (12). Methallylmagnesium chloride (**11**) was prepared by slow dropwise addition (over a period of 75 min) of a solution of 45.9 g of 3-chloro-2-methylpropene in 125 ml of anhydrous ether to a vigorously stirred mixture of 30.6 g of magnesium turnings in 375 ml of anhydrous ether, cooled to −10° in an ice–acetone bath. After the addition had been completed, the mixture was stirred at −10° for an additional 30 min and was then allowed to warm up to room temperature. To a 75-ml portion of this mixture (transferred *via* pipette to another flask) was added dropwise rapidly at 0° a solution of 3.156 g (19.2 mmol) of aldehyde **9** in 30 ml of anhydrous ether. After the reaction mixture was stirred at 0° for 20 min and at room temperature for 10 min, the excess reagent was destroyed, after cooling the flask in an ice bath, by slow addition of 30 ml of saturated aqueous ammonium chloride solution. The product was isolated by extraction with ether and purified *via* filtration through a column of Florisil in a manner analogous to that previously described for the purification of alco-

hol 6. Distillation afforded a quantitative yield of colorless oil: bp 90–102° (bath temperature, 0.07 mm); λ_{max} (film) 2.99, 3.27, 6.06, 9.56, 9.88, 10.16, 11.23 mμ; δ_{TMS} (CCl_4) 5.37 (vinyl H in ring), 5.20 (doublet, J = 8.5 Hz, C=CHCHOH), 4.75 (C=CH_2), 1.76 (1 vinyl CH_3), 1.67 ppm (2 vinyl CH_3). *Anal.* Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.70; H, 11.13.

Preparation of α-Atlantone (13). Oxidation of allylic alcohol 12 was effected using the method developed by Ratcliffe and Rodehorst,[6] followed by conjugation of the crude α,β,β′,γ′-unsaturated ketone using a 0.50 M solution of sodium methoxide in methanol (5 ml/mmol of ketone); reaction time 15 min at room temperature. Extraction of the crude product with ether followed by fractional distillation afforded α-atlantone (13) as a yellow oil in 62% overall yield from alcohol **12**: bp 100–115° (bath temperature, 0.06 mm), 90% pure by vpc analysis,[10] oven temperature 220°, retention time 5.7 min). The nmr and ir spectral properties of the distilled product as well as its physical properties were identical with those previously reported[2] for α-atlantone.

Preparation of α,β-Unsaturated Nitrile 10. To a solution of 6.05 g (112 mmol) of sodium methoxide in 20 ml of absolute ethanol was added dropwise slowly over a period of 15 min a solution of 15.8 g (89.5 mmol) of diethyl cyanomethylphosphonate[13] in 50 ml of absolute ethanol. After this mixture was stirred for 10 min at room temperature, a solution of 7.372 g (53.3 mmol) of ketone 5 in 50 ml of absolute ethanol was added rapidly (with external cooling of the flask using a cold water bath). After 40 min at room temperature, the reaction mixture was poured into 800 ml of water and the product was isolated by extraction with pentane. Short-path distillation afforded nitrile 10 in 95% yield: bp 50–65° (bath temperature, 0.04 mm); 80% pure[14] by vpc analysis,[10] oven temperature 165°, retention time 7.7 min; λ_{max} (film) 4.52, 6.15, 8.66, 12.4 mμ (broad); δ_{TMS} (CCl_4) 5.38 (vinyl H in ring), 5.12 (C=CHCN), 2.06 (CH_3C=CHCN), 1.67 ppm (vinyl CH_3). *Anal.* Calcd for $C_{11}H_{15}N$: C, 81.94; H, 9.38. Found: C, 81.69; H, 9.44.

Reduction of Nitrile 10. To a solution of 6.24 g (38.6 mmol) of nitrile 10 (contaminated with the corresponding Z stereoisomer) in 120 ml of dry benzene cooled to ~15° using a cold water bath was added dropwise rapidly a mixture of 35 ml of 1.62 M diisobutylaluminum hydride–benzene solution and 120 ml of dry benzene. After this mixture was stirred at room temperature for 4 hr, the flask was cooled in a water bath and 500 ml of saturated ammonium chloride solution was added (cautiously until the excess reagent had been hydrolyzed). This mixture was subsequently stirred vigorously at room temperature for 20 min before addition of 300 ml of 1 M H_2SO_4. The product was immediately isolated by extraction with ether and subsequently distilled to afford aldehyde 9 in 75% yield, bp 60–70° (0.03 mm). The ir and nmr spectral properties of this aldehyde were identical with those of the product obtained previously *via* oxidation of allylic alcohol 8.

Registry No.—5, 6090-09-1; 6, 826-57-3; 7, 51230-63-8; 8, 51230-64-9; 9, 51230-65-0; 10, 51230-66-1; 12, 51230-67-2; 13, 26294-59-7; methyl vinyl ketone, 78-94-4; isoprene, 79-79-5; methallyl chloride, 563-47-3.

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(5) (a) A. A. Petrov, *J. Gen. Chem. USSR*, **11**, 309 (1941). (b) A 4% impurity (retention time 2.7 min) *might* be methyl 3-methyl-3-cyclohexenyl ketone on the basis of experimental results previously reported in the literature. A. Manjarrez, T. Rios, and A. Guzman reported that a 95:5 mixture of these two isomeric ketones was obtained and separeted *via* conversion to the corresponding semicarbazones, using reaction conditions nearly identical with those employed in our synthesis. *Cf. Tetrahedron*, **20**, 333 (1964).
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(8) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, New York, N. Y., 1972, pp 682–709.
(9) Reactions were carried out under a nitrogen atmosphere. Unless indicated otherwise, the isolation of reaction products was accomplished by pouring the mixture into water or saturated brine and extracting thoroughly with the specified solvent. Anhydrous magnesium sulfate was used to dry the combined extracts, and the solvent was removed on a rotary evaporator under reduced pressure. Evaporative distillation refers to bulb-to-bulb (Kugelrohr) short-path distillation. Infrared spectra were obtained using a Beckman IR-5A infrared spectrophotometer and nmr spectra were recorded with a Varian A-60 nmr spectrometer. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. 60076.
(10) A 6 ft × 0.125 in. SE-30 column was used for this analysis.
(11) Available from Ventron Corporation, Alfa Products, Beverly, Mass. 01915.
(12) A minor component (retention time 4.0 min, <10% of the mixture was not identified but might be the Z allylic acetate.
(13) Available from Aldrich Chemical Co., Inc., Milwaukee, Wis. 53233.
(14) On the basis of the combustion analysis of this nitrile and its spectral properties, a 20% impurity (retention time 6.3 min) was assumed to be the Z stereoisomeric nitrile. Since the route to α-atlantone *via* the allylic rearrangement of alcohol 6 was highly stereoselective, no effort was made to separate this mixture and further characterize the components.

New Preparation of Desmosterol[1]

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Two new syntheses of desmosterol (24-dehydrocholesterol) are described. The starting material is 3β-hydroxybisnorcholenic acid and 3β-hydroxynorcholenic acid, respectively.

Earlier investigations[3] of the catabolism of cholesterol, in this laboratory, led to the synthesis[4] of Δ^{16}-cholesterol and Δ^{17}-cholesterol, compounds which were to be tested as potential intermediates in the formation of side chain hydroxylated cholesterols. Desmosterol (1), a precursor[5] in the biosynthesis of cholesterol, may be considered as an intermediate in the synthesis of 24,25-dihydroxycholesterol, a side-chain analog of 24,25-dihydroxycholecalciferol,[6] which is a metabolite of vitamin D_3. It has already been reported[7] that desmosterol, on incubation with an enzyme preparation obtained from calf adrenal, produced 4-methyl-3-pentenoic acid and pregnenolone, suggesting that it could be a direct precursor of the steroid hormones. For these reasons we devised general methods of construction of the desmosterol side chain, which may easily be modified for the syntheses of hydroxy and alkyl derivatives.

In the earlier synthesis of 1 the 24,25 double bond was introduced by a Wittig reaction[8] involving a C_{24} steroid aldehyde as well as by the dehydration[9,10] of 25-hydroxycholesterol. We found[11] the latter method to be of little use for the synthesis of related compounds with a hydroxylated side chain. In recent years Bory,[12] Svoboda,[13] and Sheikh[14] have reported specific methods for the synthesis of 24-dehydrocholesterol derivatives bearing an additional double bond in the side chain.