Stereoselective synthesis of (±)-eremophil-3,11-diene and related compounds. Concerning the structure of eremophilene

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An efficient, stereoselective synthesis of (±)-eremophil-3,11-diene (**3**) is described. The key step of the synthetic sequence involves the conjugate addition of lithium dimethylcopper to the octalone **7**, which produces (±)-eremophil-11-en-3-one (**12**) in good yield. The latter is converted, *via* the tosylhydrazone derivative **13**, into compound **3**. Comparison of **3** with eremophilene indicates that the initial structural proposal for the latter sesquiterpene is in error. Evidence is presented which demonstrates that eremophilene is correctly represented by structure **4**.

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The biogenetically interesting (1) eremophilane class of sesquiterpenes possess the basic carbon skeleton **1**. Since the isolation of eremophilone (**2**) by Simonsen and co-workers (3), the number of known, naturally occurring eremophilane-type sesquiterpenes has, particularly in recent years, grown rapidly.[1] Structurally, one of the simplest members of this class is eremophilene, a $C_{15}H_{24}$ hydrocarbon first isolated from *Petasites officinalis* Moench. (5) and from *P. albus* (L.) Gaertn. (6). In 1964, Hochmannová and Herout (7), on the basis of nuclear magnetic resonance (n.m.r.) spectra, a fairly extensive chemical degradation, and correlation with hydroxydihydroeremophilone (**2**) (2), assigned structure **3** to eremophilene.

In connection with an interest in developing general methods for the total synthesis of various eremophilane-type sesquiterpenes, we report in this paper an efficient and stereoselective total synthesis of racemic **3**, and present evidence which invalidates the original structural proposal (7) for eremophilene. It should be immediately noted, however, that very recently, after our synthetic work had appeared in preliminary form (8), Křepinský *et al.* (9) presented spectroscopic and structural evidence which also disagreed with the initial structural proposal for eremophilene (7) and, on the basis of this evidence, assigned structure **4** to this sesquiterpene.[2] This latter assignment has very recently been confirmed by a stereoselective total synthesis of (±)-**4**.[3] We also present, in this paper, evidence which confirms that eremophilene is indeed correctly represented by structure **4**.

The starting material for our synthesis, 3-isopropenylcyclohexanone (**5**), was readily prepared, essentially by the procedure of House and co-workers (10). Thus, cuprous chloride-catalyzed conjugate addition of isopropenyl magnesium bromide to 2-cyclohexen-1-one gave the desired cyclohexanone derivative (**5**) in 71% yield. Sodium methoxide-catalyzed condensation of ketone **5** with ethyl formate in dry benzene afforded, in 75% yield, the corresponding hydroxymethylene derivative **6**, b.p. 101–102° at 4 mm, λ_{max} 283 mμ. The latter, upon treatment with 1-diethylamino-3-pentanone methiodide in the presence of sodium methoxide in methanol gave, after deformylation, ring closure, and appropriate work-up (for a similar procedure, see ref. 11), a 64% yield of the desired substituted octalone **7**, b.p. 127–131° at 0.3 mm. The spectral data obtained for this compound were in complete agreement with the assigned structure. Of particular pertinence were the ultraviolet (u.v.) spectrum (λ_{max} 249 mμ, $\varepsilon = 14\,600$) and the n.m.r. spectrum, which exhibited signals at τ 5.26 (unresolved multiplet, $=C^{12}H_2$),[4] τ 8.22 (doublet of doublets, $—C^{14}H_3$), and τ 8.25 (triplet, $—C^{13}H_3$). The chemical shifts assigned to the vinylic methyl groups ($—C^{13}H_3$ and $—C^{14}H_3$) were confirmed by a frequency-sweep decoupling

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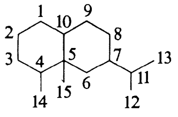
[1] At the present time, there are approximately 45 known eremophilane-type sesquiterpenoids. For a recent tabulation, see ref. 4.

[2] We acknowledge private communications from Professors R. B. Bates and V. Herout regarding this matter. We are also grateful to Dr. J. Křepinský for a preprint of their communication.

[3] R. M. Coates and J. E. Shaw. Private communication from Professor Coates, to whom we are grateful for a preprint concerning their work.

[4] To avoid confusion, the numbering employed is that normally used for eremophilane-type sesquiterpenes.



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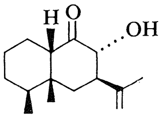

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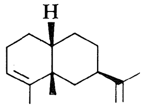

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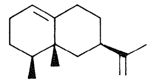


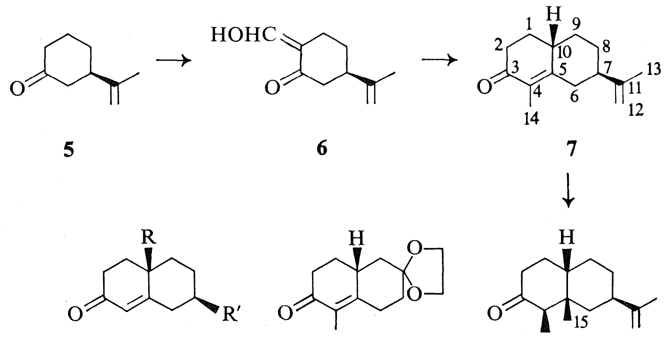
4

experiment in which the olefinic protons at C-12 were strongly irradiated, whereupon the triplet at τ 8.25 collapsed to a strong, sharp singlet, while the signal at τ 8.22 remained unaffected.

The stereochemistry of the octalone **7** was assigned as shown, since, under the basic conditions involved in the preparation of this compound, the bridgehead position at C-10 would be epimerizable. Obviously, therefore, the molecule would adopt a configuration which would allow the sterically bulky isopropenyl group to adopt an equatorial orientation, with ring B in the chair conformation. This requires that the isopropenyl group be *cis* to the hydrogen at C-10.

In order to produce the characteristic eremophilane-like skeleton from the octalone **7**, it was necessary, at this stage, to introduce an angular methyl group at C-5. In particular, we wished to carry out this introduction in a stereoselective manner such that the product would contain *cis*-fused six-membered rings. At the outset, it appeared that this might be conveniently accomplished by use of the copper salt – catalyzed conjugate addition of methyl magnesium bromide (or iodide) to the α,β-unsaturated ketone system of **7**. This type of reaction had been successfully employed (12, 13) in the case of a number of 1 (9)-octal-2-ones (e.g. **8**, **9**, and **10**) and, stereochemically, resulted in each case in the formation of the corresponding *cis*-fused decalone system. It should be noted, however, that a number of years ago, Ireland and coworkers (14) reported an unsuccessful attempt to introduce, by cuprous bromide – catalyzed 1,4-addition of methyl magnesium bromide, an angular methyl group into the octalone **11**. It thus appeared that, although the conjugate addition of methyl Grignard reagent was successful with 1 (9)-octal-2-ones bearing no substituent on C-1 (as in **8**, **9**, and **10**), this reaction failed when there was a methyl group (or, presumably, another alkyl group) present on C-1 (as in **11**). Indeed, we have found, in agreement with Ireland's observation (14), that the copper-salt – catalyzed conjugate addition of methyl magnesium iodide to the octalone **7** was extremely difficult to accomplish. In fact, even the use of the reportedly (12) superior catalyst, cupric acetate in tetrahydrofuran, gave no synthetically useful result. Thus, although the latter procedure (12) afforded a crude product which exhibited a significant saturated carbonyl absorption in the infrared (i.r.) (5.85 μ), analysis of this crude material by gas–liquid chromatography (g.l.c.) showed that it was a complex mixture consisting of at least ten components. One of these components, which was formed in varying amounts (approximately 10–25% of the mixture) depending upon the experimental conditions employed, exhibited a g.l.c. retention time and i.r. spectrum (after isolation by preparative g.l.c.) identical with those of the authentic desired decalone **12**, which was eventually prepared by another method (see below). Thus, although this reaction was partially successful, the low yield of the desired compound **12**, as well as the complex nature of the reaction product, precluded its further use in our synthetic work.

In view of the above situation, we considered other routes for the conversion of octalone **7** into the decalone **12** and were attracted by a recent report by House and co-workers (15) who found that the reagents lithium dimethylcopper and "methylcopper-tri-*n*-butylphosphine complex" very selectively add a methyl group to the β carbon of an α,β-unsaturated ketone system. We therefore explored the use of these reagents for the crucial introduction of an angular methyl group in the octalone **7** and found that lithium dimethylcopper, which is prepared simply by reaction of ethereal methyllithium with cuprous iodide (molar ratio 2:1, respectively) at 0° under nitrogen, was excellent for this purpose. Thus, reaction of octalone **7** with an excess of lithium dimethylcopper in ether at 0° and under nitrogen for 2 h gave, after appropriate work-up, a 77% yield of the desired (±)-eremophil-11-en-3-one (**12**). The spectral properties of the latter were in complete agreement with the assigned structure. The compound exhibited no strong



5 **6** **7**

8, R = R′ = H
9, R = CH_3, R′ = H
10, R = CH_3, R′ = $CH(CH_3)_2$

11 **12**

u.v. absorption above 215 mμ, and showed a saturated carbonyl absorption (5.86 μ) in the i.r. The n.m.r. spectrum, when compared with that of the starting material (**7**), was particularly instructive, showing signals for two olefinic protons (τ 5.33, $=C^{12}H_2$), one vinyl methyl group (τ 8.29, $—C^{13}H_3$), one secondary methyl group (τ 9.11, $—C^{14}H_3$), and one tertiary methyl group (τ 9.21, $—C^{15}H_3$). In addition there appeared a one-proton quartet (1:3:3:1) at τ 7.17, readily attributable to the lone hydrogen on C-4.

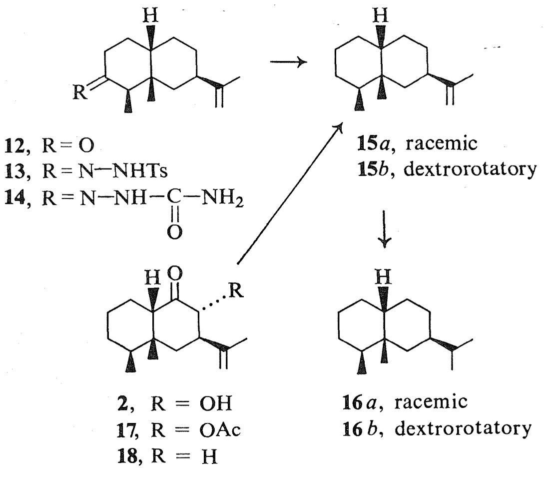
The work-up procedure following the reaction of the octalone **7** with lithium dimethylcopper requires some comment. It had already been noted (15) that, in reactions of this type, hydrolysis of the excess organometallic reagent by addition of water to the ethereal reaction mixture led to the formation of significant amounts of di-addition products. This was attributed (15) to hydrolysis of the intermediate enolate formed from conjugate addition, followed by 1,2-addition of a residual unhydrolyzed "methylcopper" species to the resultant saturated ketone. These workers circumvented this difficulty by altering the isolation procedure so that the reaction mixture was poured into water or aqueous ammonium chloride with vigorous stirring. We found, however, that in the reaction of lithium dimethylcopper with octalone **7**, the latter work-up procedure did not eliminate di-addition and, in fact, produced a product which contained only a relatively small amount of the desired decalone **12**. Therefore, since we felt that the excess organometallic reagent would be destroyed much more rapidly by a stronger acid and would thus no longer be available for subsequent 1,2-addition to the saturated carbonyl of **12**, we carried out the hydrolysis by slowly pouring the reaction mixture into rapidly stirred dilute hydrochloric acid. This procedure proved successful and produced a clean product which contained, in addition to a small amount of starting material (**7**), the desired (±)-eremophil-11-en-3-one (**12**) as the only major component.

Having successfully introduced a methyl group at the bridgehead position of octalone **7**, it became important to determine the stereochemistry of the product (**12**). Although, as noted previously, the copper salt-catalyzed conjugate addition of methyl magnesium halides to various 1(9)-octal-2-ones had invariably resulted in the formation of the corresponding *cis*-fused decalone derivatives, the obscurity of the mechanism of the reaction of lithium dimethylcopper with α,β-unsaturated ketones (15, 16) required that caution be used in assuming that decalone **12** should also possess *cis*-fused six-membered rings. We therefore obtained independent and unambiguous evidence which showed that **12** had the stereochemistry shown.

(±)-Eremophil-11-en-3-one (**12**) was converted, by standard procedure, into the corresponding tosylhydrazone **13**, m.p. 159–161°. Treatment of the latter with sodium borohydride in dioxane (17) gave, in good yield, (±)-eremophil-11-ene (**15***a*). Alternatively, the hydrocarbon (**15***a*) was also obtained by Huang–Minlon reduction (18) of the semicarbazone derivative (**14**) of compound **12**. An analytically pure sample of **15***a* was obtained by preparative g.l.c. and exhibited, in the n.m.r. spectrum, signals at τ 5.38 (unresolved multiplet, $=C^{12}H_2$), τ 8.32 (triplet,

—$C^{13}H_3$), τ 9.18 (singlet, —$C^{15}H_3$), and τ 9.28 (doublet, —$C^{14}H_3$, $J_{4,14}$ = 6.5 Hz). Hydrogenation of compound **15*a*** over platinum in ethanol gave, in 84% yield, (±)-7β-eremophilane (**16*a***).

Authentic (+)-eremophil-11-ene (**15*b***) and (+)-7β-eremophilane (**16*b***) were obtained by literature procedures (see ref. 19) from hydroxydihydroeremophilone (**2**),[5] a naturally occurring sesquiterpenoid of known absolute configuration (2). Thus, reduction of hydroxydihydroeremophilone acetate (**17**) with calcium in liquid ammonia afforded, in good yield, (+)-dihydroeremophilone (**18**), which, upon Huang–Minlon reduction (18), gave (+)-eremophil-11-ene (**15*b***).[6] The i.r. and n.m.r. spectra of the latter were identical with the corresponding spectra of synthetic (±)-eremophil-11-ene (**15*a***) obtained as described above. In addition, the two compounds exhibited identical g.l.c. retention times on a number of different columns. Hydrogenation of compound **15*b*** over platinum in ethanol produced authentic (+)-7β-eremophilane (**16*b***) (6, 20)[7] which exhibited spectra (i.r., n.m.r.) and g.l.c. retention times identical with those of synthetic (±)-7β-eremophilane (**16*a***) (see above). These two comparisons (**15*a*** with **15*b***, and **16*a*** with **16*b***) conclusively demonstrated that the conjugate addition of lithium dimethylcopper to octalone **7** had, in fact, proceeded to give the desired, *cis*-fused (±)-eremophil-11-en-3-one (**12**).



12, R = O
13, R = N—NHTs
14, R = N—NH—C(=O)—NH$_2$

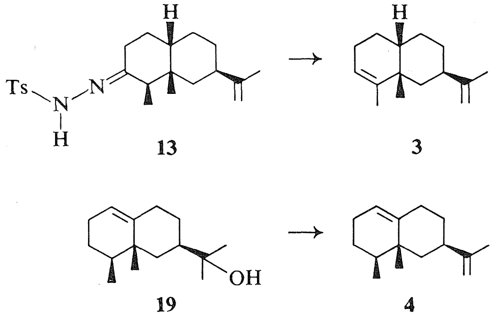
15*a*, racemic
15*b*, dextrorotatory

2, R = OH
17, R = OAc
18, R = H

16*a*, racemic
16*b*, dextrorotatory

When the tosylhydrazone derivative **13** was heated with sodium ethylene glycolate (Bamford–Stevens reaction) (21), (±)-eremophil-3,11-diene (**3**) was formed in high yield. An analytical sample of this compound was obtained by preparative g.l.c. and exhibited n_D^{20} 1.5052. The n.m.r. spectrum showed a one-proton signal at τ 4.70 (unresolved multiplet, —C^3H), a two-proton signal at τ 5.35 (multiplet, =$C^{12}H_2$), and three 3-proton signals at τ 8.30 (triplet, —$C^{13}H_3$), τ 8.40 (multiplet, —$C^{14}H_3$), and τ 8.96 (singlet, —$C^{15}H_3$). The chemical shifts assigned to the vinylic methyl groups were confirmed by frequency-sweep decoupling experiments. Irradiation of the C-3 proton at τ 4.70 caused substantial sharpening of the multiplet at τ 8.40, while irradiation of the C-12 protons at τ 5.35 caused the poorly resolved triplet at τ 8.30 to collapse to a strong, sharp singlet.

Comparison of our synthetic (±)-eremophil-3,11-diene (**3**) with an authentic sample of eremophilene[8] clearly showed that the two compounds were different. Firstly, the two compounds exhibited different g.l.c. retention times. Secondly, the i.r. spectrum of (±)-eremophil-3,11-diene (**3**) differed, particularly in the "finger-print" region, from the i.r. spectrum of eremophilene. Finally, there were significant differences in the corresponding n.m.r. spectra. The n.m.r. spectrum (9) of eremophilene exhibited unresolved multiplets at τ 4.70 (1H) and τ 5.32 (2H), a triplet at τ 8.29 (3H), a singlet at τ 9.11 (3H), and a doublet (J = 6 Hz) at τ 9.15. Thus, although the n.m.r. spectra of (±)-eremophil-3,11-diene (**3**) and eremophilene were quite similar in the low-field region, the spectrum of **3** clearly showed, at high field,



13 **3**

19 **4**

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[5] We are very grateful to Professor L. H. Zalkow for a generous sample of hydroxydihydroeremophilone.

[6] Djerassi and co-workers (ref. 19) named this compound *cis*-desoxydihydroeremophilone.

[7] We thank Dr. H. Ishii for a copy of the i.r. spectrum of (+)-7β-eremophilane.

[8] We are very grateful to Dr. J. Křepinský for an authentic sample of eremophilene and to Professor R. B. Bates for a copy of the i.r. and n.m.r. spectrum of this compound.

two vinylic methyl groups and one tertiary methyl group, while the spectrum of eremophilene showed the presence of only one vinylic methyl group, one tertiary methyl group, and one secondary methyl group.

The stereoselective total synthesis of (±)-eremophil-3,11-diene (**3**), carried out as described above, clearly demonstrated that the original structural proposal (7) for the sesquiterpene eremophilene was incorrect. However, as already noted, Křepinský *et al.* (9), on the basis of new structural and spectroscopic evidence, recently assigned structure **4** to this compound. If this new proposal were correct, then eremophilene (**4**) should be related (by dehydration) to eremoligenol, a naturally occurring sesquiterpene which was isolated from *Ligularia fischeri* Turcz. and was shown to possess structure **19** (20). In fact, the dehydration of eremoligenol (**19**) had already been carried out (20) although the product was not compared with eremophilene (**4**). We were able to secure a sample of eremoligenol (**19**)[9] and found that, upon dehydration with thionyl chloride in pyridine, it gave a hydrocarbon which was identical (i.r., n.m.r., g.l.c.) with authentic eremophilene (**4**).[10] This experiment confirmed that eremophilene is indeed correctly represented by structure **4**.

It should be noted that the conjugate addition of lithium dimethylcopper to the octalone **7**, which stereoselectively produced the decalone **12**, is of particular significance, since this reaction provides a simple and efficient entry into the vicinal dimethyl system found in eremophilane-type sesquiterpenes. We are currently applying this reaction to the synthesis of sesquiterpenes belonging to the eremophilane group.

Experimental

Melting points, which were determined on a Kofler block, and boiling points are uncorrected. Ultraviolet spectra were measured in methanol solution on a Cary spectrophotometer, model 14. Routine i.r. spectra were recorded on a Perkin–Elmer Infracord model 137 spectrophotometer, while all comparison spectra were recorded on a Perkin–Elmer model 421 spectrophotometer. Nuclear magnetic resonance spectra were taken in deuteriochloroform solution on either a Varian Associates model A-60 spectrometer, a Jeolco C-60-H spectrometer, or a Varian Associates model HA-100 spectrometer, with the latter being used for decoupling experiments. Line positions are given in the Tiers τ scale, with tetramethylsilane as an internal standard; the multiplicity, integrated peak areas, and proton assignments are indicated in parentheses. Gas–liquid chromatography was carried out on an Aerograph Autoprep, model 700. The following columns (10 ft × 1/4 in.) were employed, with the inert, supporting material being 60/80 mesh Chromosorb W in each case: column A, 20% Apiezon J; column B, 20% FFAP; column C, 10% FFAP; column D, 15% QF-1; column E, 20% SE30; column F, 20% Carbowax 20M. The specific column used, along with the column temperature, are indicated in parentheses. The carrier gas (helium) flow-rate was 80–85 ml/min in each case. Microanalyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia, Vancouver.

3-Isopropenylcyclohexanone (5)

This compound was prepared by the reaction of 2-cyclohexen-1-one with isopropenyl magnesium bromide in the presence of anhydrous cuprous chloride in dry tetrahydrofuran. The procedure employed was essentially identical with that described by House and co-workers (10). From 24.2 g of 2-cyclohexen-1-one there was obtained 24.5 g (71%) of pure 3-isopropenylcyclohexanone as a clear colorless oil, b.p. 69–72° at 7.5 mm, n_D^{26} 1.4749; lit. b.p. 80.5–84° at 8 mm, n_D^{26} 1.4743–1.4749 (10). Infrared (film), λ_{max} 5.85, 6.12, 11.20 μ; n.m.r., τ 5.22 (unresolved multiplet, 2H, $=CH_2$), 8.24 (broadened singlet, 3H, vinyl methyl).

Preparation of Hydroxymethylene Derivative 6

To a stirred slurry of sodium methoxide (31.6 g) in 160 ml of dry benzene was added a solution of ethyl formate (43.3 g) in dry benzene (160 ml). The resulting mixture was cooled to 0° and then a solution of 3-isopropenylcyclohexanone (26.4 g) in 160 ml of benzene was added dropwise, over a period of 20 min. The mixture was allowed to warm to room temperature and then stirred, under an atmosphere of nitrogen, for 50 h. Water (500 ml) was added, the mixture was thoroughly shaken, and the layers separated. The organic layer was extracted with two portions of dilute aqueous sodium hydroxide. The combined aqueous layer and alkaline extracts were cooled, acidified with concentrated hydrochloric acid, and thoroughly extracted with ether. The combined extracts were washed with water and dried over anhydrous sodium sulfate. Removal of the solvent gave a red-brown oil which, upon distillation under reduced pressure, afforded 21 g (75%) of the hydroxymethylene derivative **6** as a light-yellow oil, b.p. 101–102° at 4 mm, n_D^{20} 1.5198. Ultraviolet, λ_{max} 283 mμ; i.r. (film), λ_{max} 6.02, 6.22, 11.15 μ. The instability of this compound precluded the acquisition of satisfactory analytical data.

Preparation of Octalone 7

To a stirred solution of sodium methoxide (2.4 g) in 60 ml of dry methanol was added 11.7 g of the hydroxymethylene derivative **6**. A solution of 1-diethylamino-3-pentanone methiodide (from 15.9 g of 1-diethylamino-3-pentanone and 14.6 g of methyl iodide) in 40 ml of dry methanol was then added dropwise over a period of 20

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[9] We thank Dr. H. Ishii for a sample of this compound.

[10] This reaction has also been independently carried out by R. M. Coates and J. E. Shaw, who dehydrated (±)-eremoligenol to (±)-eremophilene. See footnote 3.

min and the resulting solution was stirred at room temperature, under an atmosphere of nitrogen, for 26 h. The solution was poured into ice-cold dilute hydrochloric acid which had been saturated with ammonium sulfate. The resulting mixture was extracted thrice with ether, and the combined ether extracts were concentrated under reduced pressure. The residual material was stirred for 1 h, under nitrogen with 630 ml of 2% aqueous sodium hydroxide (deformylation). The basic mixture was extracted with ether and the ether extract was dried over anhydrous sodium sulfate. Removal of the solvent afforded a yellow oil (14.5 g) which exhibited in the i.r., a strong saturated carbonyl absorption (5.86 μ) and only a weak α,β-unsaturated carbonyl absorption (6.02 μ). Therefore, the oil was dissolved in 125 ml of dry methanol containing 0.5 g of sodium methoxide and the resulting solution was refluxed for approximately 6 h, at which time the α,β-unsaturated carbonyl absorption, in the i.r., of an acid-quenched aliquot of the reaction solution, had attained a maximum intensity. After removal of the methanol under reduced pressure, the residual material was diluted with water (50 ml), acidified with dilute hydrochloric acid, and then extracted with ether. The combined ether extracts were washed once with water and dried (anhydrous sodium sulfate). Removal of the ether yielded a pale-yellow oil which, upon distillation under reduced pressure gave, in addition to a small amount (0.6 g) of 3-isopropenylcyclohexanone, 10 g (70%) of a pale-yellow oil, b.p. 127–131° at 0.3 mm. This material contained, as shown by g.l.c. (column A, 230°), approximately 92% of the desired octalone (**7**). An analytical sample of **7** was obtained by preparative g.l.c. (column A, 230°) and exhibited n_D^{24} 1.5320. Ultra violet, λ_{max} 249 mμ (ε = 14 600); i.r. (film), λ_{max} 6.00 6.19, 11.25 μ; n.m.r., τ 5.26 (unresolved multiplet, 2H, $=C^{12}H_2$), 8.22 (poorly resolved quartet, 3H, $—C^{14}H_3$, $J = 1.2$ and 1.8 Hz, homoallylic coupling (ref. 22 p. 110)), 8.25 (triplet, 3H, $—C^{13}H_3$, $J = 1.2$ Hz, allylic coupling (ref. 22 p. 108)). The chemical shifts assigned to $—C^{13}H_3$ and $—C^{14}H_3$ were confirmed by a frequency-sweep decoupling experiment in which the olefinic protons at C-12 were strongly irradiated, whereupon the triplet at τ 8.12 collapsed to a strong, sharp singlet, while the quartet at τ 8.22 remained unaffected.

Anal. Calcd. for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.43; H, 10.03.

The oxime derivative of octalone **7**, after recrystallization from methanol, exhibited m.p. 163–165°.

Anal. Calcd. for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.39. Found: C, 76.84; H, 9.55; N, 6.21.

*(±)-Eremophil-11-en-3-one (**12**) and Derivatives (**13**, **14**)*

The following reaction was carried out under an atmosphere of dry nitrogen. To a stirring, ice-cold (0°) slurry of cuprous iodide (6.0 g) in 120 ml of anhydrous ether was added, by injection from a dry syringe, 39.4 ml of 1.59 *M* ethereal methyllithium. The resulting tan-colored solution, containing the lithium dimethylcopper reagent, was stirred at 0° for 5 min, and then a solution of octalone **7** (2.0 g) in 80 ml of anhydrous ether was added dropwise over a period of 20 min. The reaction mixture was stirred for an additional 2 h at 0°, and then poured into 800 ml of vigorously stirred 1.2 *N* hydrochloric acid. The resulting mixture was extracted thoroughly with ether. The combined ether extracts were washed with water and dried over anhydrous sodium sulfate. Removal of the solvent gave a light-yellow oil which, upon distillation under reduced pressure, afforded 1.9 g of a clear colorless liquid, b.p. 123.5–124.5° at 0.03 mm. This material contained, as shown by g.l.c. (column B, 215°), approximately 5% starting material (octalone **7**), 82% of the desired (±)-eremophil-11-en-3-one (**12**), and a number of minor, unidentified components. Preparative g.l.c. (column B, 215°), allowed the isolation of an analytical sample of compound **12**, n_D^{20} 1.5041. Infrared (film), λ_{max} 5.86, 6.10, 11.27 μ; n.m.r., τ 5.33 (unresolved multiplet, 2H, $=C^{12}H_2$), 7.17 (quartet, 1H, $—C^4H$, $J_{4,14} = 6.7$ Hz), 8.29 (poorly resolved triplet, 3H, $—C^{13}H_3$), 9.11 (doublet, 3H, $—C^{14}H_3$, $J_{4,14} = 6.7$ Hz), 9.21 (singlet, 3H, $—C^{15}H_3$).

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.61; H, 10.71.

Reaction of (±)-eremophil-11-en-3-one (**12**) with *p*-toluenesulfonylhydrazine under standard conditions afforded a good yield of the tosylhydrazone (**13**), which, after recrystallization from methanol, exhibited m.p. 159–161°.

Anal. Calcd. for $C_{22}H_{32}N_2O_2S$: C, 68.00; H, 8.30; N, 7.21; S, 8.25. Found: C, 68.22; H, 8.41; N, 7.41; S, 8.11.

Reaction of compound **12** with semicarbazide afforded the corresponding semicarbazone **14**, which was recrystallized from methanol, m.p. 191.5–193.5°.

Anal. Calcd. for $C_{16}H_{27}N_3O$: C, 69.27; H, 9.81; N 15.15. Found: C, 69.20; H, 9.98; N, 15.05.

*(±)-Eremophil-11-ene (**15a**)*

*(a) From Tosylhydrazone **13***

A stirred solution of the tosylhydrazone **13** (0.5 g) and sodium borohydride (0.3 g) in 20 ml of dioxane was refluxed, under an atmosphere of nitrogen, for 20 h. The dioxane was removed under reduced pressure and the residue was diluted with water. The resulting mixture was extracted thoroughly with pentane. The combined extracts were washed with water, dried (anhydrous sodium sulfate), and concentrated. The residual colorless oil (0.27 g) was shown by g.l.c. (column D, 130°) to contain 95% of (±)-eremophil-11-ene (**15*a***), with only minor impurities. An analytical sample of **15*a*** was collected by preparative g.l.c. (column D, 130°) and exhibited n_D^{24} 1.4933. Infrared (film), λ_{max} 6.10, 11.28 μ; n.m.r., τ 5.38 (unresolved multiplet, 2H, $=C^{12}H_2$), 8.32 (poorly resolved triplet, 3H, $—C^{13}H_3$), 9.18 (singlet, 3H, $—C^{15}H_3$), 9.28 (doublet, 3H, $—C^{14}H_3$, $J_{4,14} = 6.5$ Hz). This material was shown to be spectroscopically (i.r., n.m.r.) identical with (+)-eremophil-11-ene (**15*b***) obtained from hydroxydihydroeremophilone (**2**) (see below).

Anal. Calcd. for $C_{15}H_{26}$: C, 87.30; H, 12.70. Found: C, 87.02, H, 12.79.

*(b) By Huang–Minlon Reduction of Semicarbazone **14***

A stirred solution of the semicarbazone **14** (2.0 g), 85% hydrazine hydrate (1.8 ml), and potassium hydroxide (1.9 g) in 20 ml of diethylene glycol was heated to 190–195° and maintained at this temperature for 24 h. The cooled solution was poured into water (100 ml) and the resulting mixture was extracted thoroughly with ether. The combined extracts were washed with water, dried (anhydrous sodium sulfate), and concentrated, yielding 1.47 g of a pale-yellow oil. The latter material showed virtually one component by g.l.c. (column C, 140°). An analytical sample, obtained by preparative g.l.c. (column C, 140°), was identical in all respects with (±)-eremophil-11-ene (**15***a*) obtained as described above.

(±)-7β-Eremophilane (16a)

This compound was obtained by hydrogenation (platinum oxide, ethanol) of (±)-eremophil-11-ene (**15***a*), at room temperature and atmospheric pressure. From 0.65 g of **15***a* there was obtained 0.6 g of (±)-7β-eremophilane. An analytical sample of the latter, obtained by preparative g.l.c. (column C, 135°), exhibited n_D^{24} 1.4820. Infrared (film), 6.82, 6.92, 7.25, 7.32 μ; n.m.r., τ 9.15 (doublet, 6H, —$C^{12}H_3$ and —$C^{13}H_3$, J = 6.0 Hz), 9.16 (singlet, 3H, —$C^{15}H_3$), 9.28 (doublet, 3H, —$C^{14}H_3$, $J_{4,14}$ = 6.8 Hz). The i.r. and n.m.r. spectra of this compound were found to be identical with the corresponding spectra of authentic (+)-7β-eremophilane (**16***b*) obtained from hydroxydihydroeremophilone (**2**) (see below).

(+)-Dihydroeremophilone (18)

Hydroxydihydroeremophilone acetate (**17**), which was obtained by acetylation (19) of hydroxydihydroeremophilone (**2**), was reduced with calcium in liquid ammonia. The procedure employed was identical with that reported by Djerassi and co-workers (19). The product, (+)-dihydroeremophilone (**18**), was obtained in 60% yield. Infrared (film), λ_{max} 5.86, 6.08, 11.20 μ; n.m.r., τ 5.26 (unresolved multiplet, 2H, =$C^{12}H_2$), 8.27 (poorly resolved triplet, 3H, —$C^{13}H_3$), 8.97 (singlet, 3H, —$C^{15}H_3$), 9.23 (doublet, 3H, —$C^{14}H_3$, $J_{4,14}$ = 5.9 Hz).

(+)-Eremophil-11-ene (15b)

This compound was obtained, according to a literature procedure (19), by Huang–Minlon reduction of (+)-dihydroeremophilone (**18**). An analytical sample of **15***b*, obtained by preparative g.l.c. (column C, 140°), gave spectra (i.r., n.m.r.) and g.l.c. retention times (four different columns: A, 180°; B, 168°; D, 120°; E, 180°) identical with those of synthetic (±)-eremophil-11-ene (**15***a*), obtained as described above.

(+)-7β-Eremophilane (16b)

Hydrogenation of (+)-eremophil-11-ene (**15***b*) (see ref. 20) at room temperature and atmospheric pressure over platinum in ethanol afforded (+)-7β-eremophilane (**16***b*). An analytical sample was obtained by preparative g.l.c. (column F, 140°). This material exhibited i.r. and n.m.r. spectra, as well as g.l.c. retention times on three different columns (D, 120°; E, 158°; B, 158°) identical with those of synthetic (±)-7β-eremophilane (**16***a*) prepared as described above.

(±)-Eremophil-3,11-diene (3)

The Bamford–Stevens reaction (21) on the tosylhydrazone **13** was carried out as follows. Sodium metal (10.0 g) was dissolved in ethylene glycol (100 ml). To this solution was added 1.5 g of the tosylhydrazone **13**, and the solution was then refluxed, under an atmosphere of nitrogen, for 2h. The solution was cooled and poured into ice-cold water. The resulting mixture was extracted thoroughly with ether. The combined extracts were washed twice with water and dried over anhydrous sodium sulfate. Removal of the ether gave a yellow oil, which upon distillation under reduced pressure afforded 0.75 g (95%) of a clear colorless liquid, b.p. 85–88° (bath temperature) at 0.38 mm, which was shown by g.l.c. (column C, 135°) to be approximately 90% pure. An analytical sample of the major component, (±)-eremophil-3,11-diene (**3**), was collected by preparative g.l.c. (column C, 135°) and exhibited n_D^{20} 1.5052. Infrared (film), λ_{max} 6.10, 6.95, 7.32, 11.28 μ; n.m.r., τ 4.70 (unresolved multiplet, 1H, —C^3H, width at half-height = 8 Hz), 5.35 (unresolved multiplet, 2H, =$C^{12}H_2$, width at half-height = 3.5 Hz), 8.30 (triplet, 3H, —$C^{13}H_3$), 8.40 (unresolved multiplet, 3H, —$C^{14}H_3$), 8.96 (singlet, 3H, —$C^{15}H_3$). The chemical shifts assigned to the vinylic methyl groups were confirmed by frequency-sweep decoupling experiments. Thus, strong irradiation of the olefinic signal at τ 4.70 (—C^3H) caused considerable sharpening of the multiplet at τ 8.40, while similar irradiation of the C-12 protons (τ 5.35) caused the triplet at τ 8.30 to collapse to a strong, sharp singlet. The i.r. and n.m.r. spectra of (±)-eremophil-3,11-diene (**3**) were clearly different from the corresponding spectra of an authentic sample of eremophilene (**4**). Also, the g.l.c. retention times (column C, 135°) of the two compounds were different.

Anal. Calcd. for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.36; H, 11.98.

Eremophilene (4) by Dehydration of Eremoligenol (19)

The dehydration of eremoligenol (**19**) was carried out by a procedure identical with that described by Ishii, Tozyo, and Minato (20). From 44 mg of eremoligenol there was obtained 34 mg of crude product as a pale-yellow oil. An analytical sample of eremophilene was obtained from the crude product by means of preparative g.l.c. (column A, 180°). Infrared (film), λ_{max} 6.08, 6.85, 7.28, 11.30 μ; n.m.r., τ 4.70 (multiplet, 1H, —C^1H, width at half-height = 7 Hz), 5.32 (multiplet, 2H, =$C^{12}H_2$, width at half-height = 4 Hz), 8.29 (triplet, 3H, —$C^{13}H_3$), 9.11 (singlet, 3H, —$C^{15}H_3$), 9.15 (doublet, 3H, —$C^{14}H_3$, $J_{4,14}$ = 6 Hz). This material was shown to be identical (i.r., n.m.r., g.l.c. retention times on three different columns: A, 180°; C, 140°; F, 185°) with an authentic sample of natural eremophilene.

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1. W. PARKER and J. S. ROBERTS. Quart. Rev. London, **21**, 331 (1967).
2. L. H. ZALKOW, F. X. MARKLEY, and C. DJERASSI. J. Am. Chem. Soc. **82**, 6354 (1960), and references therein.
3. A. E. BRADFIELD, A. R. PENFOLD, and J. L. SIMONSEN. J. Chem. Soc. 2744 (1932).
4. G. OURISSON, S. MUNAVALLI, and C. EHRET. International tables of selected constants. Vol. 15. Data relative to sesquiterpenoids. The Pergamon Press, Ltd., New York. 1966.
5. J. HOCHMANNOVÁ, L. NOVOTNÝ, and V. HEROUT. Collection Czech. Chem. Commun. **27**, 1870 (1962).

6. J. HOCHMANNOVÁ, L. NOVOTNÝ, and V. HEROUT. Collection Czech. Chem. Commun. **27**, 2711 (1962).
7. J. HOCHMANNOVÁ and V. HEROUT. Collection Czech. Chem. Commun. **29**, 2369 (1964).
8. E. PIERS and R. J. KEZIERE. Tetrahedron Letters, 583 (1968).
9. J. KŘEPINSKÝ, O. MOTL, L. DOLEJŠ, L. NOVOTNÝ, V. HEROUT, and R. B. BATES. Tetrahedron Letters, 3315 (1968).
10. H. O. HOUSE, R. A. LATHAM, and C. D. SLATER. J. Org. Chem. **31**, 2667 (1966).
11. D. K. BANERJEE, S. CHATTERJEE, and S. P. BHATTACHARYA. J. Am. Chem. Soc. **77**, 408 (1955).
12. J. A. MARSHALL, W. I. FANTA, and H. ROEBKE. J. Org. Chem. **31**, 1016 (1966), and references therein.
13. J. A. MARSHALL and H. ROEBKE. J. Org. Chem. **33**, 840 (1968).
14. R. F. CHURCH, R. E. IRELAND, and D. R. SHRIDHAR. J. Org. Chem. **27**, 707 (1962).
15. H. O. HOUSE, W. L. RESPESS, and G. M. WHITESIDES. J. Org. Chem. **31**, 3128 (1966).
16. H. O. HOUSE and W. F. FISCHER, JR. J. Org. Chem. **33**, 949 (1968).
17. L. CAGLIOTI. Tetrahedron, **22**, 487 (1966), and references therein.
18. HUANG-MINLON. J. Am. Chem. Soc. **68**, 2487 (1946).
19. C. DJERASSI, R. MAULI, and L. H. ZALKOW. J. Am. Chem. Soc. **81**, 3424 (1959).
20. H. ISHII, T. TOZYO, and H. MINATO. J. Chem. Soc. C, 1545 (1966).
21. W. R. BAMFORD and T. S. STEVENS. J. Chem. Soc. 4735 (1952).
22. N. S. BHACCA and D. H. WILLIAMS. Applications of nuclear magnetic resonance spectroscopy in organic chemistry. Holden-Day, Inc., San Francisco. 1964.