STUDIES RELATED TO THE SYNTHESIS OF EREMOPHILANE SESQUITERPENES.
CONCERNING THE STRUCTURE OF EREMOPHILENE.

BY

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ABSTRACT

The naturally occurring sesquiterpene, eremophilene, has recently been formulated as (+)-7β-eremophil-3,11-diene. The total synthesis of (±) 2, reported herein, was achieved by the following sequence. Reaction of the hydroxymethylene derivative of 3-isopropenylcyclohexanone 130 with 1-diethylamino-3-pentanone methiodide 122 in the presence of base (Robinson annelation reaction) readily afforded, after aldol ring closure, 1-methyl-7-isopropenyl-Δ1,9-octal-2-one 127. Reaction of compound 127 with ethereal lithium dimethylcuprate 135 resulted in the selective conjugate addition of a methyl group to octalone 127, thus affording in good yield the all-cis product (±)-7β-eremophil-11-en-3-one 128. The relative stereochemistry of the eremophilane derivative 128 was confirmed by chemical correlation with hydroxydihydroeremophilone 30 of known absolute configuration. Reaction of the tosylhydrazone derivative of compound 128 with sodium ethylene glycolate in refluxing ethylene glycol (Bamford-Stevens reaction) afforded (+) 2. Comparison of compound (±) 2 with a sample of authentic eremophilene clearly established that the structural assignment (2) originally proposed for eremophilene was incorrect. Dehydration of the naturally occurring eremoligenol 28 with thionyl chloride and pyridine afforded (+)-eremophil-1(10),11-diene 3 which was shown to be identical with authentic eremophilene. Thus the structure and stereochemistry of eremophilene is correctly represented by formulation 3. The synthesis of eremophil-3,11-diene 2 reported herein establishes a stereoselective synthetic entry into the eremophilane class of sesquiterpenoids.
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INTRODUCTION

Sesquiterpenes are a class of isoprenoid compounds which normally contain fifteen carbon atoms. They are part of a larger group of biogenetically related substances, collectively referred to as the terpenes. The sesquiterpenes as a family of natural products are noted for their wide distribution throughout nature, occurring in a variety of plants and trees, and for their considerable structural diversity. These compounds exhibit a large variety of monocyclic, bicyclic, tricyclic and tetracyclic carbon skeletons and indeed it is on this basis, that is the nature of the carbon skeleton, that sesquiterpenes are often classified.

One such class of sesquiterpenes is the eremophilane group which possess the basic carbon skeleton 1. Of particular note is the vicinal dimethyl system found at C-4 and C-5 of ring A, and the three carbon "isopropyl-type" side chain attached to ring B at C-7. The numbering system shown in 1 is that normally employed for this class of compounds. Until the early 1960's few members of this class of sesquiterpene were known. However, since then, the number of known eremophilanes has grown rapidly to the forty five or so that have been reported to date (1). Interest in the eremophilane sesquiterpenes is, apart from the structural and functional diversity found within this class, primarily due to the fact that the carbon skeleton
is "non-isoprenoid". In fact, for sometime the first isolated members of this group represented the only known exceptions to the "isoprene rule" in the sesquiterpene field (2).

In the past few years this laboratory has been concerned with the synthesis of several classes of sesquiterpenes, and recently, attention was directed to the eremophilane sesquiterpenes. The attraction was in part due to the group's biogenetically anomalous carbon skeleton, and in part due to the fact that, at that time, none of the eremophilanes had been totally synthesized (4). Thus, the specific object of the work reported in this thesis was to establish a general synthetic entry into the eremophilane class of sesquiterpenes and, in particular, to effect an unambiguous synthesis of one member of the group, eremophilene.

Eremophilene, a $C_{15}H_{24}$ hydrocarbon, was first isolated from the roots of *Petasites officinalis* MOENCH (5) and *P. albus* (L.) GAERTN (6) by Herout 1

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1 Early workers, most notably Ruzicka, observed that the basic skeletal structures possessed by the terpenes could formally be considered to be constructed in multiples of isoprene units $i$ joined either in a regular head-to-tail manner, or in an irregular manner.

These structural requirements came to be known as the "isoprene rule" (2) and thus defined the "terpenes". In subsequent years however numerous terpenoid compounds were isolated whose structure disobeyed the isoprene rule in as much as their basic carbon skeletons could not formally be regarded as a sequence of isoprene units. To account for these "non-isoprenoid" substances in terms of a unified definition of terpenes, the isoprene rule was revised (3). This version, "the biogenetic isoprene rule", simply amends the isoprene rule definition of terpenes so as to include those terpenes which have undergone carbon skeletal rearrangement in the course of their biosynthesis.
and coworkers in 1962. Subsequently the skeletal and stereochemical features of eremophilene were elucidated by Hochmannova and Herout (7), who in 1964, on the bases of chemical reaction, infrared (i.r.) and nuclear magnetic resonance (n.m.r.) spectra and a chemical correlation with hydroxy-dihydroeremophilane of known absolute configuration formulated eremophilene as 2. However it should be noted here that recently as a result of our work (8) and a subsequent reinvestigation by Herout et al. (9), this structural assignment was shown to be incorrect and the revised structure 3 was established for eremophilene. That formulation 3 is indeed correct was very recently confirmed by the excellent total synthesis of (†) 3 by Coates and Shaw (10).

TERPENOID BIOSYNTHESIS

A number of references to the biogenetically anomalous eremophilane carbon skeleton have been made in the foregoing, and in subsequent discussion, consideration will be given to a proposed "biogenetically styled eremophilane synthesis". Thus to clarify these and other ensuing points related to the biosynthesis of this group, it is expedient to introduce here a discussion of the biosynthesis of terpenes in general and the eremophilane sesquiterpenes in particular.

Throughout the past twenty years substantial progress has been made in elucidating the biosynthesis of terpenoid compounds. Much of this progress
has resulted from studies in which plausible biogenetic intermediates containing radioisotopic atoms are introduced into plant and animal systems leading, if the precursors are authentic, to an incorporation of the radio-lable in the subsequently isolated terpenes. Thus by such labelling studies it has become quite apparent that the biosynthesis of terpenes proceeds from acetic acid, or its biosynthetic equivalent acetyl coenzyme A, as summarized represented in Figure 1 (11). The successive self condensation of three molecules of acetate affords, after partial hydrolysis β-hydroxy-β-methyl glutaryl coenzyme A. Reduction with nicotinamide-adenine dinucleotide phosphate (NADPH) leads to the mevalonic acid - mevalonolactone system which in turn gives Δ^3-isopentenyl pyrophosphate, after adenine triphosphate (ATP) phosphorylation and subsequent decarboxylation. Rearrangement of the terminal double bond of results in the formation of dimethallyl pyrophosphate which on condensation with a molecule of Δ^3-isopentenyl pyrophosphate (proton loss) yields geranyl pyrophosphate. It is this important intermediate and its cis-double bond isomer neryl pyrophosphate that are the biosynthetic precursors of the monoterpenes, that is the class of terpenoids which (normally) contain ten carbon atoms. In a parallel manner the addition of one molecule of the isoprenoid to geranyl pyrophosphate leads to farnesyl pyrophosphate, whereas the consecutive addition of two molecules of to geranyl pyrophosphate yields geranyl geranyl pyrophosphate. Farnesyl and geranyl geranyl pyrophosphates have been experimentally established (11) as biosynthetic precursors of the sesquiterpenes (C-15) and diterpenes (C-20) respectively. Reductive dimerization of farnesyl pyrophosphate (12,13) gives

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A detailed discussion of specific results of labelling studies will not be presented herein. The reader is referred to the references cited for details.
Figure 1
squalene 13, which is the biosynthetic precursor of the triterpenes (C-30) and the steroids (biosynthetically degraded triterpenes).

The basic carbon skeleton, and to an increasing extent the configurational features, of virtually all of the sesquiterpenes can be accounted for by considering that these substances are biosynthetically derived from cis, and trans-farnesyl pyrophosphate, 14 and 11, via the appropriate cyclizations of cations 15 to 20 (Figure 2) (11, 12). Cations 15 to 20 arise from cis- and trans-farnesyl pyrophosphate upon loss of a pyrophosphate anion, and the appropriate ring closures. These ions should of course be regarded in a formal sense, as the biosynthetic cyclizations of farnesyl pyrophosphate are enzymatically controlled and, as such, may be effected in a partial or concerted manner (11).
Robinson (15), some years ago, suggested that the eremophilane sesquiterpenes may be derived from a precursor which possesses the eudesmane carbon skeleton 21. As depicted below, a 1,2-shift of the angular methyl group of 21 yields cation 22 which exhibits the characteristic eremophilane carbon skeleton. The basic eudesmane skeleton 21 is readily attained via the trans-annular cyclization of cation 19, in turn derived from trans-farnesyl pyrophosphate 11.

![Diagram](image)

A number of specific eudesmanoid derivatives have been suggested in the literature as possible biogenetic precursors of the eremophilane group. One of these, the diol 23, has been suggested (15,16) as a plausible precursor of a naturally occurring compound, eremophilone 26, isolated from *Eremophila Mitchelli*. The postulated series of Wagner-Meerwein rearrangements indicated would lead to the trans-eremophilone derivative 24 which, after ready epimerization, would give the all cis-structure 25, characteristic in the eremophilane group. Subsequent oxidation and dehydration would yield eremophilone. In 1960 Zalkow, Markley and Djerassi (16) suggested that the naturally occurring β-eudesmol 27 (17) was also a plausible eremophilone precursor. An analogous series of 1,2-shifts would lead to the postulated intermediate 28, which after a suitable biosynthetic adjustment of oxidation level, would yield eremophilone 29, (R=0).
While little if any experimental work specifically concerned with the biogenesis of the eremophilane sesquiterpenes has been reported to date, Minato's 1966 isolation of eremoligenol 28, from Ligularia Fischeri Turcz (18) and the very recent conformation of structure 29 (R=H₂) for eremophilene (8,10) lends support to the above proposed biogenesis of these eremophilanes.

STRUCTURE IN THE EREMOPHILANE SESQUITERPENES

As the subject of this thesis is concerned with establishing a synthetic approach to eremophilene and to the eremophilane group per se, it is of importance to consider a number of topics, all of which embrace structural aspects of the eremophilanes. Specifically, it is intended to present in the following sections a discussion of (a) the skeletal and configurational
elucidation of the first isolated eremophilane-type sesquiterpenes, eremophilone and its cogeners, (b) the important structural variations found in the eremophilane group, (c) the original structural elucidation of eremophilene and finally, (d) the salient features of other synthetic approaches to this class of sesquiterpene.

(a) The Structure of Eremophilone and Cogeners

The first naturally occurring compounds found which possess the eremophilane carbon skeleton were isolated in 1932 by Bradfield, Penfold and Simonsen (19,20). Thus, Simonsen and coworkers isolated, from the wood of *Eremophila Mitchelli*, three closely related sesquiterpenic ketones, viz., eremophilone, hydroxydihydroeremophilone and hydroxyeremophilone. In the period between 1932 and 1941, Simonsen's group carried out, by classical methods of structural elucidation, an investigation into the structure of the three eremophilone sesquiterpenes (20). The enormous amount of work carried out and the painstakingly slow progress involved in the problem render a present detailed discussion of the skeletal elucidation of these compounds quite impractical. Thus, suffice to say that after considerable effort by these workers, the skeletal features of eremophilone, hydroxydihydroeremophilone and hydroxyeremophilone were correctly formulated as 26a, 30a and 31a respectively.
By the mid-1950's it had become increasingly important, specifically from the point of view of establishing the biosynthesis of the eremophilanes, to determine the relative and absolute stereochemistry of eremophilone and its co-occurring relatives. To this end, hydroxydihydroeremophilone was subjected to an X-ray crystallographic analysis and assigned the relative configuration indicated by structure \( \text{30} \) (21). Subsequently, Zalkow, Djerassi and coworkers proved the relative configuration of eremophilone \( \text{26} \) and hydroxyeremophilone \( \text{31} \) by a chemical correlation with hydroxydihydroeremophilone (22). Specifically, ketone \( \text{32} \) was obtained from both eremophilone \( \text{26} \) by sodium alcohol reduction followed by chromium trioxide oxidation and from hydroxydihydroeremophilone \( \text{30} \) by treatment of the acetate of \( \text{30} \) with calcium in liquid ammonia. The analogous relative configurational features of hydroxyeremophilone \( \text{31} \) were confirmed on finding that the hydroxy ketone \( \text{30} \) would readily afford hydroxyeremophilone on oxidation with bismuth oxide and acetic acid.

The absolute configuration of the three sesquiterpenic ketones was finally established in 1959 by Zalkow, Markley and Djerassi upon comparison of the
decalone 33 obtained in three steps from hydroxyeremophilone 31 with that obtained in fourteen steps from the hexalone 34 of known absolute stereochemistry (16,23).

(b) Structural Variations in the Eremophilane Sesquiterpenes

In the following section, attention is directed to the various structural and configurational features which are encountered in the naturally occurring eremophilane-type sesquiterpenes.

A survey of the known members of this class of compound readily reveals a number of characteristic stereochemical features. Of immediate note is the consistent cis relationship between the C-14 and C-15 annular methyl groups of ring A. The prevalence of such a cis geometry is, of course, in agreement with the configurational requirements of the 1,2-migrations postulated in the above mentioned eremophilane biogenesis. It is also of interest that the C-7 "isopropyl-type" three carbon side chain of ring B is commonly found either cis or trans to the vicinal methyl substituents. A comparison of nootkatone 35, isolated from Citrus paradisi (24), and eremophilone 26 clearly demonstrates these structural features. In the frequently encountered all-cis geometry, exemplified by eremophilone 26, a notable steric interaction occurs between the axial C-5 and C-7 substituents, which is absent in the related epimeric system 35. A further apparent configurational generality, is
that of the cis-fused ring juncture exhibited by the eremophilanes possessing a saturated C-10 carbon atom. Of the presently known naturally occurring eremophilanes, none exhibit trans-fused A and B rings.

Functionally, these sesquiterpenes are relatively uncomplex. They generally contain ethylenic double bonds and exhibit hydroxyl and ketonic functional groups at one or more of the secondary annular carbon atoms. It is interesting that very few eremophilanes have been isolated which exhibit oxygenated C-1 carbon atoms. A number are known which possess a tertiary hydroxyl group at C-11, for example valerianol, isolated from _Valeriana officinalis_ L. (25). Eremophilanes containing the dehydration related isopropenyl (commonly occurring) and isopropylidiene moieties at C-7 are also known, as is the totally saturated isopropyl side chain moiety. The latter functionalities are illustrated by warbugiadione, isolated from _Warburgia ugandensis_ Sprague (Canellaceae) (26), and nardostachone, isolated from _Nardostachys jatamansi_ D.C. (27). A large number of these compounds contain a three-carbon "isopropyl-type" side chain which has suffered extensive oxidation leading to the formation of unsaturated γ-lactones, as exemplified by eremophil-enolide, isolated from _Petasites hybridus_ (30) and furan derivatives such as the recently isolated (from _Euryops floribundus_ (29)) euryopsonol 40.
Several eremophilanes are known which contain hydroxyl groups esterified with vinyl thiolether carboxylic acid moieties, such as the keto ester S-petasin 41, found in *Petasites officinalis* MOENCH (30).

Bakkenolide-A 42, recently isolated from the Japanese plant *Petasites japonicus* (31), is a structurally interesting sesquiterpene. It appears to be an eremophilane that has undergone skeletal rearrangement resulting in the contraction of the eremophilane ring B from a six to five membered ring. The numbering system shown is that of the eremophilane group. There are four such bakkenolides known at present, varying in the nature of the substituents at C-1 and C-9 (32).

While generally regarded as a separate skeletal class of sesquiterpenes, the aristolanes are closely related to the eremophilanes and as such it is instructive to briefly mention this group here. α-Ferulene 43, from *Ferula*
communis L. (Umbelliferae) (33) and the enantiomeric aristolone 44 from Aristolochia debilis Sieb. et Zucc. (28) serve to exemplify the basic aristolane carbon skeleton. The all-cis-geometry, found in the eremophilanes, is apparently unknown in the aristolane group. The skeletal relationship between the aristolanes and eremophilanes is apparent if one envisions a formal ring closure of the eremophilane C-7 isopropyl-type side chain, by carbon-carbon bond formation between C-6 and C-11, yielding the gem-dimethylcyclopropane ring and concomitantly the characteristic tricyclic aristolane skeleton. It should be noted however, even if somewhat digressively, that the aristolanes are not considered to arise biogenetically from the eremophilanes. Rather it has been proposed that they arise via 1,3-deprotonation of cation 19 (see biosynthetic section), affording the cyclopropane moiety, followed by the appropriate series of 1,2-shifts leading to the aristolane systems, as illustrated below (11).
Thus, in summary, it is apparent that a considerable structural and functional group diversity exists in the eremophilane sesquiterpenes, particularly if such "rearranged eremophilanes" as the bakkenolides and aristolanes are included as members of the group.

(c) Structural Elucidation of Eremophilane

As noted above, the compound of principal synthetic interest herein is eremophilene. Thus, it is important to consider the essential features of the structural elucidation, reported by Hochmannova and Herout in 1964 (7), which led to the formulation of eremophilene as 2.

Quantitative hydrogenation of a sample of natural eremophilene, a C\textsubscript{15}H\textsubscript{24} hydrocarbon, established the presence of two double bonds and gave a product identical with (+)-7\beta-eremophilane 45 (Figure 2), of known absolute configuration (18). The i.r. spectrum of eremophilene indicated the presence of a gem-disubstituted ethylenic double bond (6.06, 11.23 μ) and a tri-substituted ethylenic double bond (5.99, 12.36 μ). Its n.m.r. spectrum gave two three-proton signals at τ 8.22 and τ 8.51 which were attributed to vinyl methyl groups and two vinylic proton signals at τ 5.33 and 4.74, attributed to the two protons of the gem-disubstituted olefin and the single proton of the tri-substituted olefin respectively. The position of the disubstituted double bond was established by selectively hydrogenating eremophilene, using partially deactivated Raney-nickel in ethanol. The resulting product, dihydroeremophilene
Figure 2.
47, exhibited an i.r. doublet (7.21, 7.29 μ) characteristic of a gem-dimethyl group; moreover the olefinic carbon-hydrogen deformation absorbance (11.23μ) exhibited by eremophilene was absent in the dihydro-product, clearly indicating the presence of an isopropenyl double bond in the natural product.

The crucial question regarding the position of the tri-substituted double bond (unconjugated) was then considered. With the presence of an isopropenyl moiety in eremophilene established, three structures representing this compound became possible: 2, 3, and 54.

![Structures](image)

Given the n.m.r. data reported, specifically the τ 8.22 and τ 8.51 methyl group signals, structures 3 and 54 were rendered unsatisfactory. However, in addition to this evidence, a chemical proof of structure was sought.

Ozonolysis of dihydroeremophilene 47 (Figure 2) in ethyl acetate at -75°, followed by decomposition of the intermediate ozonide with hydrogen, afforded a mixture of products which by i.r. contained a keto aldehyde and a hydroxy ketone, formulated as 48 and 49 respectively. Permanganate oxidation of the mixture followed by esterification of the acidic oxidation product 50, (R=H) with diazomethane gave a C₁₆H₂₈O₃ keto ester 50, (R=Me). This material reacted positively in the iodoform test, and exhibited i.r. bands characteristic of methyl ketone (5.85, 7.31 μ) and methyl ester (5.75, 6.94 μ) groups. These facts were taken as evidence substantiating structure
Baeyer-Villiger oxidation of 50 with perbenzoic acid gave the diester 51 which was then hydrolysed to give a mixture of product containing, in addition to acetic acid, the δ-lactone 53, formed by ring closure of the intermediate δ-hydroxy acid 52. The critical successful isolation of acetic acid, identified as the p-bromophenacyl ester, from the reaction mixture clearly discounted structures 3 and 54, and moreover corroborated the above mentioned n.m.r. evidence for the formulation of eremophilene as structure 2.

Finally, the absolute configuration of eremophilene was established by correlation with hydroxydihydroeremophilone 30, of known absolute configuration (21,23). The hydrogenation product obtained from natural eremophilene, (+)-78-eremophilane 45, and the product obtained from the Clemmenson reduction of compound 55 (the catalytic hydrogenation product of hydroxydihydroeremophilone 30) were identical in density, refractive index, optical rotation and infrared spectra.

Thus, the chemical and physical experiments demonstrated by these workers"...constituted an unambiguous proof that the trisubstituted double bond in eremophilene is in the Δ3-position and that formula (2) belongs to this compound" (7).

It should be noted that the only n.m.r. data reported in this structural elucidation was that given for eremophilene.

(d) Other Synthetic Approaches to the Eremophilane Sesquiterpenes

At this point it is necessary to mention a number of recently published reports concerning the synthesis of eremophilane sesquiterpenes. Increased interest in the eremophilanes in the past few years is evident from the number of recent reports of syntheses directed toward these compounds. At the conception of our work in 1966, none of the group had been totally synthesized (4). However, there are currently at hand several reports of synthetic approaches to the eremophilanes and these will be the subject of
the following paragraphs.

The synthesis of racemic isonootkatone (α-vetivone) 64 by Marshall, Faubl and Warne (34) constitutes the first total synthesis of a member of the eremophilane sesquiterpenes. The key step in the sequence was the stereoselective condensation of 2-carbomethoxy-4-isopropylidene-cyclohexanone 57 with trans-pent-3-en-2-one 56. In the presence of sodium methoxide, the keto ester 57 underwent Michael addition to the pentenone 56 affording, after aldol ring closure, a mixture of cis and trans-octalones, 58 and 59, with the cis-derivative 58 predominating.

\[
\begin{align*}
56 & \quad + \quad 57 \\
& \quad \xrightarrow{\text{Sodium methoxide}} \\
& \quad 58 \quad + \quad 59
\end{align*}
\]

61, X=OH
62, X=OMs
63, X=H
In an explanation offered regarding the observed stereochemistry at C-4, Marshall and coworkers suggested that electronic and steric considerations would favor a transition state orientation represented by 65. From models it is apparent that the orientation of the methyl group and hydrogen atom (attached to the pendent C-4 atom) indicated in 65b leads to the establishment of a cis relationship between the C-4 and C-5 (eremophilane numbering) substituents of octalone 58. The sterically less favorable transition state orientation depicted in 66 would conversely lead to the trans-octalone 59.

Subsequent ketalization of octalone 58 followed by reduction of the carbomethoxy group to a methyl group (60 → 61 → 62 → 63) and ketal hydrolysis gave a product which exhibited i.r. and n.m.r. spectra and g.l.c. retention time identical with that of natural isonootkatone, isolated from vetivert acetate (35), a commercial essential oil.

A somewhat similar stereochemical result was obtained recently by Coates and Shaw (36) upon condensation of the pyrrolidine enamine of 2-methylcyclohexan-1,3-dione 67 with trans-pent-3-en-2-one 56. The resulting product afforded in good yield a mixture of the cis and trans-octalones 68. The cis:trans ratio of this product was found to vary between 1:1 and 1:10, depending on the exact reaction conditions used and upon the structure of the cyclohexenone reagent employed. These findings provided an alternate synthetic approach to the
characteristic cis-vicinal methyl groups of the eremophilane carbon skeleton and were subsequently utilized in the synthesis of (±)-Δ\(^{1}(10)\)-aristolene (calarene, β-gurjunene) \(_{75}\) (37), as indicated below.

Selective thiolactamation of a 1:1 mixture of the octalones \(_{68}\), obtained from the reaction of \(_{56}\) and \(_{67}\) in a refluxing mixture of formamide, acetic acid and aqueous sodium acetate, gave the corresponding mixture of the thiolactals \(_{69}\). This epimeric mixture was then treated with Raney nickel in absolute ethanol. The resulting product afforded the analogous mixture of
cis and trans-unsaturated ketones 70 and 71. These isomers were then successfully separated by fraction distillation through a spinning-band column. Reaction of the cis-dimethyloctalone 70 with ethyl carbonate in the presence of sodium hydride in 1,2-dimethoxyethane gave a mixture of keto and enol tautomers, formulated here as 72. This material upon refluxing with ethereal methyl lithium followed by acid catalyzed dehydration of the intermediate tertiary alcohol, gave the α,β-unsaturated ketone 73. A stereoselective introduction of the required gem-dimethylcyclopropane moiety was effected via an interesting application of the thermal decomposition of pyrazolines. Treatment of the α,β-unsaturated ketone 73 with one equivalent of hydrazine in refluxing absolute ethanol gave the Δ2-pyrazoline 74 which in turn afforded, on thermal decomposition with potassium hydroxide, a stereochemically homogeneous product, (±)-Δ1(10)-aristolene 75. This material was found to be chromatographically (g.l.c.) and spectroscopically (i.r., n.m.r.) identical to the naturally occurring Δ1(10)-aristolene.

Recently, Brown and coworkers (38) reported the total synthesis of racemic tetrahydroeremophilone 89, a reduction product of eremophilone. Unlike the Robinson annelation reaction approaches of Marshall and Coates, discussed above, Brown utilized a synthetic scheme which involved as the principal step a "biogenetic-like" trans-antiparallel cyclization of an olefinic compound, appropriately designed to yield, after subsequent structural modification the desired bicyclic system.

The starting material for this synthesis, 3-methyl-4-carbomethoxy-5-isopropylcyclohex-2-enone 77, was alkylated with trans-1-bromopent-3-ene 76, yielding the keto ester 78. Hydrolysis and decarboxylation of this material gave the enone 79. The required trienes 80 were then readily obtained by treatment of 79 with methyl lithium followed by phosphorus oxychloride-pyridine dehydration. The reported overall yield of 80 from 77
was 22%. Ring closure was then achieved by reacting the triene mixture 80

\[ \text{Br} + \text{CO}_2\text{Me} \rightarrow \text{CO}_2\text{R} \]

with anhydrous formic acid at room temperature for 20 minutes. The resulting product contained a mixture of esters 81 and 82, which were epimeric at C-7. Of particular importance was the stereoselective realization of the cis-vicinal methyl group moiety in the "eremophilane" ring A. Reductive cleavage of these formates with lithium aluminum hydride yielded the related alcohols 83 and 84. These isomers were "partially separated" on
alumina, and exhibited a ratio 2:3 respectively. The \( \beta \)-epimer \( 83 \), isolated by chromatography, was oxidized with Jones' reagent to the corresponding ketone, which was then subjected to Wolf-Kishner reduction yielding the all-cis-desoxy derivative \( 85 \). Photooxidation of \( 85 \) followed by immediate lithium aluminum hydride reduction gave a product containing the epimeric alcohols \( 86 \). Cleavage of the exocyclic double bond of compound \( 86 \) was effected by reaction with one equivalent of ozone-saturated methylene chloride at \(-70^\circ\). Zinc-acetic acid reduction of the intermediate ozonide gave, after appropriate work up, a mixture of the epimeric ketols \( 87 \).

Finally, removal of the C-10 hydroxyl group of \( 87 \) was accomplished by calcium-ammonia reduction of the corresponding acetate \( 88 \). The \((\pm)\)-tetrahydroeremophilane \( 89 \) thus obtained was found to be identical "in all respects" to the cis-tetrahydroeremophilone derived by known procedures from naturally occurring hydroxydihydroeremophilone.

The final synthetic approach to the eremophilanes to be considered herein is that recently outlined by Heathcock and coworkers. The finding that the unsaturated acid \( 90 \) on treatment with refluxing anhydrous formic acid gave a 2:1 equilibrium mixture \(^3\) of lactones \( 91 \) and \( 92 \) suggested that synthetic entry into this family of natural products could plausibly be realized via a "methyl-migration route" (39). In a preliminary report by Heathcock and Kelly (39) the merits of this possible approach were considered and a number of literature examples of applicable 1,2-methyl migrations were given, further supporting the feasibility of such a "biogenetically styled" eremophilane synthesis. An example cited (39) was the conversion of the diacetoxyhydroxyl steroid \( 93 \) to the rearranged olefin \( 94 \).

In a subsequent publication, Heathcock and Amano reported the result

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\(^3\) Treatment of pure \( 91 \) or pure \( 92 \) under identical conditions afforded the same 2:1 mixture.
of an attempted experimental verification of their proposed approach (40). The hydroxy acid \textbf{100} was selected as a suitably designed antecedent which, on treatment with acid, might reasonably give rise to the desired 1,2-methyl migration. It was hoped that relief of the 1,3-diaxial steric interaction between the C-1 and C-10 methyl groups of compound \textbf{100} would energetically enhance the feasibility of the desired rearrangement. Moreover, the rearranged product would be appropriately functionalized for extension to the eremophilane skeleton.

The synthesis of \textbf{100} was accomplished as follows. The readily available unsaturated acid \textbf{95} was reduced with lithium aluminum hydride yielding the related unsaturated alcohol \textbf{96}. Subsequent epoxidation of this compound with m-chloroperbenzoic acid gave a product containing the stereoisomeric mixture of epoxy-alcohols \textbf{97} and \textbf{98} in a 3:2 ratio, respectively. Treatment of this mixture with methylmagnesium iodide in refluxing tetrahydrofuran
followed by acidic hydrolysis resulted in an opening of the oxirane ring, and readily afforded the diol 99 in 71% yield, based on oxirane 97. Subsequent conversion to the desired hydroxy acid 100 was accomplished by chromic acid-acetone oxidation of 99.

Unfortunately, formic acid treatment of the hydroxy acid 100 under various conditions did not result in the desired methyl migration. Reaction of 100 with formic acid at room temperature smoothly afforded the dehydration product 101. The analogous reaction at reflux yielded a complex mixture of at least seven products. Thus, it was apparent that the 1,3-diaxial steric interaction cited above is most efficiently alleviated by simple proton loss, rather than by a 1,2-shift of the C-10 angular methyl group. Similarly, reaction of the γ-lactone 102 (obtained by sodium methoxide treatment of the methyl ester of 100) with formic acid at 85° gave a 1:1 mixture of the γ- and δ-lactones 104 and 105. The reaction was considered to proceed via the unsaturated acid 103. In both systems then (100 and 102), the 1,3-diaxial methyl interactions are relieved immediately by proton loss yielding an
unsaturated acid; a subsequent reprotonation of the ethylenic double bond of the olefinic acids 101 and 103 does not give rise to the required 1,2-methyl shift. Hence it was concluded that a "methyl-migration" approach to the synthesis of eremophilanes, at least via the above intermediates, was unfortunately not possible.

In summary then, the present literature affords basically two successful synthetic approaches to the eremophilane sesquiterpenes: (1) The Robinson annelation variations reported by Marshall and Coates, and (2) the acid induced triene cyclization method of Brown. Each of these schemes unfortunately necessitate, at some point in the synthetic sequence, a rather difficult separation of stereoisomeric products.
DISCUSSION

As noted in the Introduction, the object of the work presented herein was the development of a general synthetic entry into the eremophilane family of sesquiterpenes. Thus, the stereoselective total synthesis of eremophilene, one of the simpler members of this group, was undertaken as a vehicle for the development of such a scheme. At the conception of this work, the structure and absolute configuration of eremophilene were formulated as (+)-eremophil-3,11-diene \( \text{2} \) (7).

The basic stereochemical problems to be resolved in the synthesis of this structure were considered to be: (1) the introduction of the vicinal annular methyl groups at C-4 and C-5 of ring A, (2) the establishment of a cis-A/B ring junction, and (3) the establishment of a cis-relationship between the angular methyl group at C-5 and the C-7 isopropenyl group. The realization of a cis-relationship between the C-4 and C-5 vicinal methyl groups would, of course, be an additional requirement in a general
synthetic approach to the eremophilanes.

The following paragraphs outline the approach considered in the solution of these synthetic problems.

In recent years, an active interest has developed in the copper-catalysed reaction of Grignard reagents with \(\alpha,\beta\)-unsaturated carbonyl systems. The reaction of a Grignard reagent with an \(\alpha,\beta\)-unsaturated ketone generally affords a mixture of compounds derived from either 1,2-addition or 1,4-addition of the Grignard reagent to the unsaturated carbonyl system. Normally, this reaction heavily favours formation of 1,2- rather than 1,4-adducts. However, in the presence of a small amount (1-5 mole percent) of a copper (I) salt the otherwise identical system leads predominantly to the 1,4-addition product(s). This fact of course, has been widely recognized since the early observation by Kharash and Tawney (41) that the presence of 1 mole percent of copper (I) chloride significantly altered the course of methylmagnesium bromide addition to isophorone 106. Thus, the uncatalysed reaction afforded solely 1,2-addition products whereas in the presence of copper (I) chloride, the product mixture contained 92% of the 1,4-adduct, 3,3,5,5-tetramethylcyclohexanone 107 and 8% of the 1,2-addition product, 2,4,6,6-tetramethylcyclohex-1,3-diene 108.
In the course of subsequent investigations into the nature of these copper-promoted additions to enone systems, additions to a number of octalones were examined, the results of which suggested a possible applicability of this reaction to the synthesis of the eremophilanes, specifically with respect to the solution of problems (1) and (2) noted above. Of particular interest was the report by Marshall, Fanta and Roebke (28) concerning a study of such addition reactions involving substituted Δ¹,⁹-octal-2-ones. Treatment of the readily prepared Δ¹,⁹-octal-2-one 109 (R=H) with an ether-THF solution of methylmagnesium iodide and copper (II) acetate gave, upon hydrolysis, a product (80% yield) containing 99% of the cis-decalone 110 (R=H). None of the possible 1,2-addition products or the C-9 epimeric trans-decalone were detected. Similar treatment of 10-methyl-Δ¹,⁹-octal-2-one 109 (R=Me) gave, a product containing 40% cis-5,10-dimethylene decal-2-one 110 (R=Me) and 60% of the 1,2-adducts 111 (R=Me).


Interestingly, Birch and Robinson (42) observed earlier that the octalone 109 (R=Me) underwent essentially only 1,2-addition upon reaction with methylmagnesium iodide in the presence of copper (I) bromide.

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5 Interestingly, Birch and Robinson (42) observed earlier that the octalone 109 (R=Me) underwent essentially only 1,2-addition upon reaction with methylmagnesium iodide in the presence of copper (I) bromide.
Marshall and his colleagues explained these results as follows. Attack of the alkylating reagent at the β-carbon atom of the α,β-unsaturated carbonyl system must occur perpendicular to the π electron system (43), as depicted in structure 112. Thus, this stereoelectronic requirement may be equally satisfied by attack from above (β) or below (α) the plane of the molecule. α-Attack of either octalone 109 (R=H) or 109 (R=Me), leading to the trans-decalones, would be precluded due to steric interaction of the approaching alkylating reagent with the axial C-4, C-5 and C-7 substituents. On the other hand, β-attack at C-9 of the octalone 109 (R=H) would be less hindered sterically, thus readily affording the cis-fused 1,4-addition product 110 (R=H). β-Attack on the octalone 109 (R=Me), however would result in the development of a gauche interaction between the incoming "methyl group" and the axial C-10 methyl substituent of the octalone. Marshall suggested that this developing 1,2-methyl-methyl interaction would be alleviated as the system approached a transition state geometrically similar to that represented by enolate conformer 113, in which the C-9 angular methyl group is equatorially oriented with respect to the ring B. However, concommitent with this change would be the development of steric interaction between the substituent on C-1 and the axial substituents of C-5 and C-7 as well as between the axial substituent of C-3 and that of C-5. In support
of this concept is the observation that the copper (II) acetate catalysed reaction of methylmagnesium bromide with either 10-methyl-7α-isopropyl- or 10-methyl-7α-isopropenyl-Δ₁,⁹-octal-2-one affords only the 1,2-addition products and none of the conjugate addition products (28).

\[
\text{R}=\text{isopropyl or isopropenyl}
\]

The above explanation is, of course, a partial one as the role of the copper catalyst in effecting conjugate addition was not considered (28).

At this time, no literature precedent had been found which recorded the conjugate addition of a methyl Grignard reagent to a compound containing the 1-methyl-Δ₁,⁹-octal-2-one moiety. However, Theobald has reported (44) the successful Michael addition of cyanide ion to 1,10-dimethyl-7β-isopropenyl-Δ₁,⁹-octal-2-one (α-cyperone). The reaction
product obtained from a refluxing ethanolic solution of octalone 117, potassium cyanide and ammonium chloride gave a 42:58 mixture of the cis- and trans-keto amides 118 and 119. It is suggested (44) that these compounds arise via a 2-keto assisted hydrolysis of the intermediate β-cyano ketones, as depicted below for the trans case. The cyanide ion is evidently sterically less requiring than the methylating reagent involved in the copper-catalysed Grignard additions, thus additionally giving rise to the trans-isomer 119, via α-attack on octalone 117.

With regard to the proposed eremophilane synthesis, this reaction illustrates two important points: (1) The ultimate stereochemical fate of the C-1 methyl group, in this reaction and in an analogous conjugate Grignard addition reaction, is thermodynamically controlled as, subsequent

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6 The keto amides 118 and 119 are tautomerically related to the hydroxy lactams 120 and 121. Infrared spectra, show that the hydroxy lactam form is heavily favoured, both in chloroform and in nujol (44).
to carbon-carbon bond formation at the 8-carbon atom, an enolate ion is formed in both addition reactions. Hence, a subsequent thermodynamic protonation of the enolate anions assures a cis-relationship between the C-1 and C-9 substituents of the resulting decalones regardless of the stereochemistry of the A/B ring junction of the conjugate addition products. (2) The successful Michael addition of cyanide ion to octalone 117 suggested that conjugate methylation of an eremophilane antecedent such as octalone 116 appropriately functionalized at C-7, would not be precluded due to an intramolecular steric interaction involving the C-1 methyl group. Moreover, if successful, such a methylation could be expected to afford the required all-cis stereochemistry at C-1, C-9 and C-10 of the resulting decalone.

The proposed scheme for the introduction of the 7β-isopropenyl group of eremophilane remains to be discussed.

The 7β-isopropenyl substituent of eremophilene was considered to be most conveniently realized in a manner similar to that employed in the synthesis of α-cyperone 117 (45). As reported by Howe and McQuillin (45), Robinson annelation of (+)-dihydrocarvone 123 with 1-diethylamino-3-pentanone methiodide 122 in the presence of base afforded, upon aldol ring closure, a mixture of C-10 epimeric octalones 124. Analogously, condensation of the methiodide salt 122 with the known 3-isopropenylcyclohexanone 125, R=H₂ (or its hydroxymethylene derivative 125, R=CHOH) would
be expected to lead to the eremophilane antecedent 127. Following condensation (and deformylation), aldol cyclization would likely proceed via the intermediate diketone conformer 126a as the epimerizing conditions of the alkaline reaction medium would clearly establish a cis relationship between the epimerizable "C-10" hydrogen atom and the "C-7" isopropenyl group. Moreover, the C-10 position of the product octalone 127 is also epimerizable thus ensuring the equatorial orientation of the C-7 isopropenyl substituent.

For reasons considered above, conjugate methylation of octalone 127 would then be expected to yield the all-cis-eremophilone derivative 128 which in turn, in two steps, would afford (+)-eremophil-3,11-diene 2, the racemic mixture corresponding to the proposed structure of eremophilene (7).

In summary then, from a consideration of the reports by Marshall (28) and Theobald (44) it was concluded that the cis-vicinal methyl groups and cis-A/B ring junction exhibited in the eremophilane sesquiterpenes might conveniently be realized synthetically via the conjugate addition of a
methyl Grignard reagent to a suitably substituted 1-methyl-Δ¹⁻⁹-octal-2-one
derivative. This derivative in turn appeared accessible via a Robinson
annelation reaction involving the readily available 3-isopropenylcyclohexanone.

The starting material for the present synthesis, 3-isopropenylcyclo-
hexanone, was prepared by a procedure essentially identical with that
reported by House, Latham and Slater (46). Thus, commercial 2-cyclohexenone
upon treatment with isopropenylmagnesium bromide and 5 mole percent copper (I) chloride in dry THF, afforded, after hydrolysis, the desired 3-
isopropenylcyclohexanone in 70% yield. The procedure reported by House
and coworkers differs in the use of copper (I) iodide rather than the
copper (I) chloride catalyst employed above. The product thus obtained
exhibited the appropriate spectroscopic properties. The i.r. spectrum
exhibited a strong saturated carbonyl absorbance and 5.85 μ and absorbances
at 6.12 and 11.20 μ attributed to the stretching and deformation vibration
of the ethylenic double bond in the incorporated isopropenyl group.
Nuclear magnetic resonance signals at τ 5.22, a vinyl proton multiplet, and
τ 8.22, a vinyl methyl group singlet, were in agreement with the data
reported for structure 130 (46). Spectroscopic (i.r., n.m.r.) and g.l.c.
evidence indicated that little, if any, 1,2-addition product had formed.

An interesting and important feature of this reaction is the demonstra-
tion that vinyl Grignard reagents will undergo copper catalysed conjugate
addition to α,β-unsaturated ketones in a manner analogous to that of aryl
and alkyl Grignard reagents.

At this point, it was considered synthetically efficient to prepare
the hydroxymethylene derivative of ketone 130 for use in the subsequent
Robinson annelation reaction. Hydroxymethylene ketones, or 2-formyl ketones

7 Relative to the number of moles of organo-metallic reagent present.
have long been used to activate methylene or methyl group protons located α to a carbonyl group. The synthetic utility of these derivatives in alkylation reactions is simply derived from the fact that the conjugate base of the 2-formyl ketone is significantly more stable than that of the parent ketone, hence rendering possible a facile alkylation at the activated α-carbon atom. Moreover, the activating formyl group may be readily introduced, by base-catalyzed condensation of the parent ketone with an alkyl formate ester, and subsequent to alkylation, may be readily removed by treatment with aqueous base.

Thus, the reaction of 3-isopropenylcyclohexanone 130 with ethyl formate and sodium methoxide in dry benzene gave, after suitable work-up and reduced pressure distillation, the desired hydroxymethylene derivative 131 in 75% yield. This material gave the following spectroscopic data. The unsaturated carbonyl absorbances at 6.02 and 6.22 μ in the infrared indicated the expected predominance of the keto-enol 131b and formyl-enol 131c tautomeric forms. A strong absorbance at 11.15 μ established the presence of the isopropenyl double bond. The n.m.r. spectrum of this compound was particularly informative. A three-proton singlet at τ 8.26 and a two-proton unresolved multiplet at τ 5.25 were readily assigned to the vinyl methyl group and vinyl hydrogen atoms of the C-5 isopropenyl substituent.
A sharp one-proton singlet at $\tau$ 1.4 and a very broad one-proton multiplet at $\tau$ -4.0 were also evident. Assignment of these resonances requires brief comment on the tautomeric equilibria represented above. Nuclear magnetic resonance studies (47) of 2-formylcyclohexanone and a number of related compounds, have established that the enolic tautomers of these compounds, e.g. $^{131b}$ and $^{131c}$, are normally predominant to the extent of 99%. Moreover, the equilibrium between the two possible enolic forms is faster (relative to n.m.r. spectra averaging) than the corresponding equilibria between the formyl ketone, e.g. $^{131a}$ and the two enolic tautomers. Accordingly, the above mentioned $\tau$ 1.4 signal was designated as the signal average of protons $H_a$ and $H_b$ of the enols $^{131b}$ and $^{131c}$; analogously, the broad $\tau$ -4.0 signal was readily attributed to the hydrogen-bonded hydroxyl hydrogens of $^{131b}$ and $^{131c}$. Simple calculations (47) revealed that the enolic mixture was composed of approximately 22% $^{131c}$ and 78% $^{131b}$.
Consideration was then directed to the synthesis of octalone 127. Robinson annelation reaction (48) employing l-diethylamino-3-pentanone methiodide 122 and hydroxymethylene derivative 131 carried out in the presence of methanolic sodium methoxide at room temperature for 48 hours, afforded, upon acidification and ether isolation, a crude formyl diketone 132. This intermediate was then directly treated with aqueous potassium hydroxide. The crude deformylated material subsequently isolated showed a strong saturated carbonyl absorbance at 5.86 μ and a weak unsaturated carbonyl absorbance at 6.02 μ in the infrared, thus indicating that aldol cyclization was incomplete. Hence, to effect ring closure to the desired octalone 127, this material, containing mainly the diketone 126, was refluxed with methanolic sodium methoxide for five to six hours. The product thus obtained was fractionally distilled affording octalone 127 in 64% yield, based on hydroxymethylene 131. The spectroscopic properties of analytical samples of this compound, obtained either by preparative g.l.c. or by purification via the hydrolysis of its oxime 159, substantiated the assigned structure 127. The ultraviolet spectrum (u.v.) showed an absorbance at 249.5 μ (ε =14,600). An unsaturated carbonyl absorbance at 6.00 μ and olefinic absorbances at 6.20 and 11.25 μ appeared in the i.r. spectrum. The n.m.r. spectrum showed an unresolved multiplet at τ 5.26, which was assigned to the vinyl protons. A poorly resolved quartet at τ 8.22 (J = 1.2 and 1.8 Hz) was attributed to the C-1 methyl group which was homoallylically coupled to (47) the axial protons at C-10 and C-8. Similarly a triplet at τ 8.25 (J = 1.2 Hz) was attributed to the isopropenyl methyl group being allylically coupled (47) to the vinyl protons. The above chemical shift assignments were established by a decoupling experiment in which the olefinic protons at τ 5.26 were irradiated thus effecting the collapse of the τ 8.25 triplet to a sharp singlet, leaving the τ 8.22 quartet unchanged. As noted above, assignment
of the β-orientation of the C-7 isopropenyl group is made on the basis that the C-10 position is epimerizable under the reaction conditions.

The elemental analysis of this compound (as well as all other previously unreported compounds which have been synthesized herein) gave results in complete agreement with the calculated values.

With the synthesis of the desired octalone \textbf{127} complete, introduction of the C-5\textsuperscript{8} angular methyl group of the eremophilane system remained to be accomplished. To this end, octalone \textbf{127} was treated with a tetrahydrofuran-ethyl ether solution of methylmagnesium iodide and copper (II) acetate monohydrate. The copper acetate-tetrahydrofuran system has been successfully employed by Marshall (28) in the alkylation of a variety of octalones.

\textsuperscript{8} Unless otherwise noted, eremophilane system numbering will be henceforth employed.
After hydrolysis and work-up, a product was obtained which exhibited a weak saturated carbonyl peak at 5.85 μ. Analysis by g.l.c. indicated that this material contained a complex mixture of at least 10 components. Preparative g.l.c. isolation of one of these components afforded an analytical sample shown to be identical to authentic (±)-eremophil-11-en-3-one 128 prepared as subsequently described below. Unfortunately the composition of the products obtained from a number of such reactions varied somewhat irreproducibly both in complexity and percent of the 1,4-adduct 128 (10-25%). Thus it was concluded that the copper-catalyzed Grignard addition approach to the eremophilane derivative 128 was not synthetically useful.

These results were in agreement with those reported in a subsequently observed paper by Ireland and colleagues (50). These workers reported that, despite repeated attempts, the copper (I) bromide catalysed conjugate addition of methyl Grignard reagent to the ketal octalone 133 was unsuccessful.

At this juncture, attention was directed to a recent report by House, Respess and Whitesides (51) concerning an investigation into the role of copper in conjugate Grignard additions. In the course of this investigation two ether soluble methyl copper-ate complexes (52) were prepared which exhibited a remarkable selectivity toward effecting preferential conjugate addition - as opposed to 1,2-addition - of a methyl group to α,β-unsaturated
ketones. For example, reaction of trans-pent-3-en-2-one 136 with either methyl copper-tri-n-butylphosphine 134 or lithium dimethylcuprate 135 afforded a product containing > 99% of the 1,4-adduct, 4-methyl-pentan-2-one 137. Of the two complexes, lithium dimethylcuprate 135 was particularly attractive in that it could be conveniently prepared simply by the addition of two equivalents of ethereal methyl lithium to a cold (0°) ethereal slurry containing one equivalent of copper (I) iodide. Thus, the selectivity exhibited by these organo-copper complexes upon reaction with ketone 136 and other α,β-unsaturated ketones, in addition to the facile preparation of 135, suggested an obvious applicability to the eremophilene synthesis.

Thus, it was found that reaction of octalone 127 with an excess of ethereal lithium dimethylcuprate, at 0° and under nitrogen for two hours, gave, upon acid hydrolysis, a product shown by g.l.c. to contain 77% of the desired 7β-eremophil-11-en-3-one 128. An analytical sample, obtained by
preparative g.l.c., afforded spectroscopic data in complete agreement with that required by formulation 128. Of particular note in the i.r. was the strong saturated carbonyl absorbance observed at 5.86 μ and the absorbances due to the isopropenyl double bond appearing at 6.10 and 11.27 μ. The n.m.r. spectrum (Figure 3) gave a two-proton multiplet at τ 5.33, assigned to the C-12 vinyl protons, a one-proton quartet at τ 7.17 (J₄,14 = 6.7 Hz) due to the C-4 proton, and a poorly resolved triplet at τ 8.29 readily attributed to the C-13 vinyl methyl group. The C-14 and C-15 methyl groups afforded a doublet at τ 9.11 (J₄,14 = 6.7 Hz) and a singlet at τ 9.21, respectively. Frequency-swept decoupling experiments confirmed the chemical shift assignments. Strong irradiation at τ 5.33 effected the collapse of the τ 8.29 triplet to a sharp singlet, thus confirming allylic coupling between the C-12 and C-13 protons. Similarly, strong irradiation at τ 7.17 resulted in a partial collapse of the τ 9.11 doublet to a poorly resolved triplet. This was taken as evidence in support of the above assignment of the τ 7.17 and τ 9.11 signals.

Some mention of the quenching procedure of the reaction of octalone 127 with lithium dimethylcuprate 135 should be made. Subsequent to conjugate addition of a methyl group to a given α,β-unsaturated ketone, an enolate anion is formed which is ultimately ketonized by protonation during the reaction work-up procedure. The quenching procedure given by House et. al. required pouring the reaction mixture into vigorously stirred saturated aqueous ammonium chloride. In preliminary experiments, these workers found that the inverse procedure, addition of the ammonium chloride solution to the reaction mixture, led to a complex mixture containing both mono- and di-alkylation products. Ketonization of the 1,4-addition derived enolate is evidently faster than the acid destruction of the organo-copper species,
Figure 3. Nuclear Magnetic Resonance Spectrum of (†)-7β-eremophil-11-en-3-one.
hence, the saturated ketone thus formed rapidly undergoes further alkylation by 1,2-addition of the unreacted methyl copper species. However, application of the recommended ammonium chloride quenching procedure in our case gave a complex mixture of products. Subsequently it was found that an increase in the acidity of the quenching medium was required. Thus, slow addition of the reaction mixture to vigorously stirred 1 M aqueous hydrochloric acid afforded a considerably less complex product mixture containing the desired decalone and only a small number of minor components.

It might correctly be argued that the spectroscopic evidence given above would not preclude assignment of an α-orientation to both the C-4 and C-5 methyl substituents, rather than the β-orientation indicated in structure 128. An α-configuration at C-4 and C-5 would, of course, result from an α- rather than β-attack of the alkylating reagent on octalane 127. Sterically, this appears less likely. However, the relative stereochemistry indicated in structure 128 was confirmed by chemical correlation of this compound with hydroxydihydroeremophilone 30, of known absolute configuration. Specifically, as described below, reduction of decalone 128 led to an eremophilane, which was subsequently found to be spectroscopically identical with authentic (+)-7β-eremophilane 45, obtained from hydroxydihydro-eremophilone 30 by literature procedures (22).

The reaction of (±)-eremophil-11-en-3-one 128 with semicarbazide hydrochloride and sodium acetate in refluxing ethanol readily afforded the corresponding semicarbazone 137, in 65% yield. The i.r. spectrum of an analytical sample of this crystalline material showed, in addition to the isopropenyl double bond absorbance at 11.20 μ, strong carbonyl and N-H deformation absorbances at 5.95 and 6.40 μ, respectively. The n.m.r. spectrum of this compound further confirmed structural assignment 137. The one- and two-proton broad multiplets appearing at τ 1.40 and τ 4.24 were
readily assigned to the secondary and primary amide hydrogen atoms, respectively. Signals due to the isopropenyl group protons appeared as an unresolved multiplet at $\tau$ 5.27 (-C$_{12}$=H$_2$) and a poorly resolved triplet at $\tau$ 8.27 (-C$_{13}$H$_3$). A three-proton singlet at $\tau$ 9.24 was attributed to the C-15 angular methyl group. Finally, a $\tau$ 9.06 ($J_{4,14} = 6.8$ Hz) doublet and a poorly resolved one-proton quartet centered at $\tau$ 7.25 ($J_{4,14} = 6.8$ Hz) were assigned to the methyl and tertiary hydrogen substituents of C-4, respectively.

Haung-Minlon reduction (53) of the semicarbazone 137 (50) was accomplished upon treatment of this material with excess hydrazine hydrate and base in refluxing diethylene glycol. The reaction cleanly afforded (†)-eremophil-11-ene 138 in high yield. The i.r. spectrum of an analytical sample of olefin 138, obtained by preparative g.l.c., exhibited the expected olefinic stretching and deformation absorbances at 6.08 and 11.28 $\mu$, respectively. Both the carbonyl and the N-H absorbances previously observed in the 5.5-6.5 $\mu$ region were now absent. The n.m.r. spectrum of 138 showed an unresolved multiplet at $\tau$ 5.38, attributed to the two C-12 olefinic protons and a three-
proton, poorly resolved triplet at τ 8.32 due to the C-13 vinyl methyl group. A singlet appearing at τ 9.17 was assigned to the tertiary C-15 methyl group and a τ 9.28 (J_{4,14} = 6.5 Hz) doublet was readily attributed to the secondary C-14 methyl group.

Reduction of the olefin 138 to (±)-7β-eremophilane 45 was accomplished by hydrogenating an ethanolic solution of compound 138 in the presence of platinum oxide catalyst. An analytical sample of the resulting product, isolated by preparative g.l.c., afforded spectroscopic data in complete agreement with that required by structure 45. Of particular importance in the infrared spectrum was the absence of the 6.08 and 11.28 μ olefinic absorbances and the appearance of a sharp doublet at 7.22 and 7.30 μ, characteristic of an isopropyl substituent. Moreover, comparison of the i.r. spectrum of this material with a copy of the i.r. spectrum of authentic (+)-7β-eremophilane⁹ suggested that the two substances were indeed identical. The n.m.r. spectrum of the synthetic eremophilane showed a six-proton doublet centered at τ 9.15 (J_{11,12(13)} = 6 Hz), attributed to the magnetically equivalent C-12 and C-13 isopropyl methyl groups. A three-proton singlet appeared at τ 9.16 which was assigned to the angular C-15 methyl group. The signal due to the annular C-14 methyl group appeared as a doublet at τ 9.28 (J_{4,14} = 6.5 Hz). It is interesting that, as might reasonably be expected, hydrogenation of the Δ^{11}-double bond in 138 did not significantly influence the chemical shift of the C-14 and C-15 methyl groups. This is apparent upon comparison of the above noted C-14 and C-15 methyl group signal positions in the n.m.r. spectra of 45 and 138.

Consideration was then directed to the conversion of authentic hydroxy-dihydroeremophilone 30 to (+)-7β-eremophilane 45. This reaction sequence

⁹ We are indebted to Dr. H. Ishii for a copy of the i.r. spectrum of (+)-7β-eremophilane.
has been previously reported (22) along with the characterization of the compounds therein. Thus hydroxydihydroderemophilone \textsubscript{30}\textsuperscript{10} underwent acetylation upon treatment with acetic anhydride in dry pyridine. A crystalline product was isolated from the reaction mixture which, after recrystallization, exhibited a melting point (68-71°) and i.r. spectrum (3.42, 5.73, 5.80, 7.70-8.5, 11.10 µ) corresponding to that previously reported for hydroxydihydroeremophilone acetate \textsubscript{139}.

Subsequent treatment of the keto acetate \textsubscript{139} with calcium in liquid ammonia at -33° (22), followed by appropriate work-up afforded a crude oil containing the deacetoxylated product, (+)-7β-eremophil-11-en-9-one \textsubscript{140}.

The very generous sample of authentic hydroxydihydroeremophilone obtained from Dr. L.H. Zalkow is gratefully acknowledged.

It is pertinent to note here that the C-10 position of ketone \textsubscript{140} is epimerizable, thus in principle enabling, under the conditions of this reaction, the formation of decalone derivatives containing either cis- or trans-fused A/B ring junctions. However, it has been previously established that the cis-fused A/B ring system of 7β-eremophil-11-en-9-one \textsubscript{140} is thermodynamically favoured over the corresponding trans-fused system (22). This is predominantly due to the presence of the 7β-isopropenyl substituent. Thus upon consideration of the trans-fused stereoisomer, it is apparent that the chair-chair conformer \textsubscript{141a} necessitates a very substantial 1,3-diaxial steric interaction between the axial C-5 methyl and C-7 isopropenyl substituent. This 1,3-diaxial interaction would be absent in the related chair-boat conformer \textsubscript{141b}. Of the alternative cis-fused conformers \textsubscript{140a} and \textsubscript{140b}, the latter is favoured, predominantly due to the absence of 1,3-diaxial interaction between the β C-5 and C-7 substituents. As both trans-fused conformers \textsubscript{141a} and \textsubscript{141b} are obviously thermodynamically less stable than the cis-conformer \textsubscript{140b}, cis-7β-eremophil-11-en-9-one \textsubscript{140} is the product formed under the alkaline conditions of the above mentioned reaction.
Repeated chromatography of this crude oil on Woehlm neutral alumina enabled the isolation of g.l.c. pure 140. This material exhibited an i.r. spectrum (3.45, 5.86, 6.08, 11.20 μ) in accordance with that previously reported for (+)-7β-eremophil-11-en-9-one. In addition, the n.m.r. spectrum of 140 indicated an unresolved multiplet at 5.26 due to the C-12 vinyl protons and an unresolved triplet at 8.27 due to the C-13 vinyl methyl group. The C-14 and C-15 annular methyl groups appeared as a three-proton doublet at 9.23 (J_{4,14} = 5.9 Hz) and a three-proton singlet at 8.97, respectively.

Reduction of the C-9 carbonyl function of the thus obtained cis-dihydroeremophilone 140 was effected by Haung-Minlon reduction, as described earlier (22). The reaction of ketone 140 with excess hydrazine hydrate and base in refluxing diethylene glycol followed by ether isolation gave a product shown by g.l.c. to contain 65% of the desired cis-olefin (+)-138 and several other relatively minor components. Preparative g.l.c. isolation afforded an analytical sample which exhibited an i.r. spectrum in agreement with that required by structure 138.
Comparisons were then carried out which conclusively established that the authentic (±)-7β-eremophil-11-ene (derived from (+)-30) and racemic (±)-7β-eremophil-11-ene (derived from (±)-128, as described above) were identical by refractive index, i.r., n.m.r. and g.l.c. retention times on four different columns. Figure 4 shows the comparison i.r. spectra of the "natural" and "synthetic" 7β-eremophil-11-enes.

The final step in the conversion of natural hydroxydihydroeremophilone 30 to (±)-7β-eremophilane was accomplished by catalytic reduction of (±)-eremophil-11-ene with hydrogen and platinum oxide. An analytic sample of the authentic (+)-7β-eremophilane, obtained by preparative g.l.c., exhibited an i.r. spectrum in accordance with that previously determined for (+)-45.9

Subsequent comparison of the thus obtained authentic (+)-45 with the corresponding racemic 7β-eremophilane (derived from decalone, as described above) clearly established that the two materials were identical by refractive index, i.r., n.m.r. and g.l.c. retention times on three different columns. Figure 5 shows the comparison i.r. spectra of the "natural" and "synthetic" 7β-eremophilanes 45.

The above correlation of the dextrorotatory and racemic compounds (±)-138, (±)-138 and (+)-45, (±)-45 conclusively established that the relative stereochemistry of (±)-7β-eremophil-11-en-3-one was correctly represented by structure 128. Thus, the successful stereoselective conjugate addition of lithium dimethylcuprate to octalone clearly enabled a new and convenient synthetic entry into the eremophilane class of sesquiterpenes.

With the stereochemistry of the crucial eremophilane derivative established, it is worthwhile to consider at this point the nature of the reaction by which this compound was synthesized. Although the mechanism involved in the reaction of lithium dimethylcuprate with α,β-unsaturated ketones is as yet unestablished, an interesting hypothesis concerning
Figure 4. Infrared Spectra of: (a) (+)-7β-Eremophil-11-ene. (b) (−)-7β-Eremophil-11-ene.
Figure 5. Infrared Spectra of: (a) (+)-7β-Eremophilane. (b) (±)-7β-Eremophilane.
this reaction has been proposed by House and coworkers (51,54) and this will be outlined below.

It has been suggested by these workers that the ether soluble lithium dimethylcuprate complex \( 135 \) exists in rapid equilibrium with methyl lithium and methyl copper \( 142 \). The latter organometallic compound is a yellow, ether insoluble, and apparently polymeric material, which may be readily prepared by reacting equimolar amounts of methyl lithium and copper (I) iodide in dry ether (52). As depicted in equation (1), the equilibrium concentrations of both methyl lithium and the methyl copper species \( 142 \) are

\[
\text{MeLi} + (\text{MeCu})_n \rightleftharpoons \text{Me}_2\text{CuLi}^+ \quad (1)
\]

normally extremely small in that the equilibrium lies far to the right. The position of the equilibrium was evidenced by the observation that ethereal lithium dimethylcuprate exhibits a relatively low reactivity (relative to methyl lithium) toward carbonyl functions (51,54). Moreover, n.m.r. data, obtained from variable temperature studies of the lithium dimethylcuprate system, has been reported (51) which supports both the existence and position of equilibrium (1).

House has suggested that the addition of lithium dimethylcuprate to an \( \alpha,\beta \)-unsaturated ketone proceeds \textit{via} a one-electron transfer mechanism. The complete or partial transfer of an electron from the copper (I) atom of the ate-complex \( 135 \) to the \( \alpha,\beta \)-unsaturated carbonyl system \( 136 \) would lead to the formation of an anion-radical \( 144 \) or a charge transfer complex. Such electron transfer from the copper atom of \( 135 \) would likely be enhanced by the net negative charge of the complex (52). Subsequent transfer of a methyl radical from the transient dimethyl copper (II) species \( 143 \) to the \( \beta \)-position of anion-
radical 144, or the collapse of the charge transfer complex would yield the alkylated enolate 145 and methyl copper 142. Ketonization 145 during work-up would then afford the final product, 137.

Although it remains to be experimentally established for the above α,β-unsaturated ketone system, some support for House's postulate is derived from the ethereal reaction of lithium dimethylcuprate with fluorenone 146 (51). The electron spin resonance (e.s.r.) spectrum of this green solution clearly indicated the presence of the relatively stable anion-radical 147. Moreover, unlike the reaction of ethereal methylmagnesium bromide with 146 which failed to exhibit an e.s.r. spectrum and simply led to 9-methylfluorenol, the lithium dimethylcuprate reaction afforded diol 148 as a significant reaction product. Thus the implication was that diol 148 was formed via a coupling reaction involving the anion-radical 147 which had been generated by the organocopper reagent. As House has suggested, the applicability of these findings to a distinctly different molecular system is of course tenuous. However it does indicate that such ion-radical systems may be generated by lithium dimethylcuprate.
Assuming that the reaction of lithium dimethylcuprate with $\alpha,\beta$-unsaturated ketones proceeds as described above, the stereoselectivity observed in the addition of this organocopper reagent to octalone 127 is most probably due to steric factors. Thus, approach of the alkylating reagent from the a-side of octalone 127 would result in significant steric interaction between the incoming reagent and the axial C-4, C-5 and C-7$_{12}$ hydrogens. $\beta$-Approach on the other hand would be significantly less hindered. Complete or partial transfer of an electron from a molecule of lithium dimethylcuprate situated on the ring A $\beta$-face of the octalone, 127a, would afford the anion-radical or charge transfer complex represented by structure 149. Subsequent transfer of a methyl radical to the C-9 position of 149, or collapse of the charge transfer complex would give the enolate 150. Upon hydrolysis, 150 would yield the all-cis-decalone 128a.

12 The numbering employed here is that of the $\Delta^{1,9}$-octal-2-one system.
Conversion of decalone 128 into (E)-eremophil-3,11-diene 2 was considered to be most efficiently accomplished by subjecting the tosylhydrazone derivative of ketone 128 to the Bamford-Stevens reaction (56) rather than to a sequence involving metal hydride reduction of ketone 128 and subsequent dehydration of the resulting alcohol. Humber, Pinder and Williams (17) recently reported that tosylhydrazone 151, upon heating with sodium ethylene glycolate in ethylene glycol (Bamford-Stevens reaction), cleanly afforded an isomerically homogeneous product shown to be α-eudesmol 152. Thus, it was suggested that application of the Bamford-Stevens reaction in
the eremophilane case might enable the specific introduction of the required $\Delta^3$-double bond.

To this end, decalone 128 was refluxed with methanolic p-toluenesulphonyl-hydrazine thus yielding the crystalline tosylhydrazone 153. The i.r. spectrum of this compound exhibited bands at 6.10, 6.25 and 6.92 $\mu$ attributed to the aromatic double bond stretching vibrations. A strong absorbance at 8.58 $\mu$ was assigned to the $S=O$ stretching frequency. The characteristic 11.2 $\mu$ isopropenyl double bond absorbance was also present. The n.m.r. spectrum showed an $A_2B_2$ quartet centered at $\tau$ 2.44 ($J_{ab} \sim 8$ Hz, $(\delta_b - \delta_a) \sim 58$ Hz) assigned to the four aromatic protons of the tosyl moiety. The isopropenyl group protons appeared as a three-proton poorly resolved triplet at $\tau$ 8.32, due to the C-13 methyl group, and a two-proton unresolved multiplet at $\tau$ 5.36, assigned to the C-12 vinyl protons. A poorly resolved one-proton quartet,
appearing at $\tau 7.37$ ($J_{4,14} = 6.5$ Hz) and a three-proton doublet centered at $\tau 9.12$ ($J_{4,14} = 6.5$ Hz) were attributed to the hydrogen and methyl substituent of C-4, respectively. Finally, a singlet at $\tau 7.61$ was assigned to the aromatic methyl group and a singlet at $\tau 9.43$ was attributed to the angular methyl group at C-5. The chemical shift of the latter methyl group is noteworthy. The signals attributed to the C-15 protons in the related ketone 128 and semicarbazone 137 appear at $\tau 9.21$ and $\tau 9.24$, respectively. The relatively high field $\tau 9.43$ methyl group signal suggests the operation of a diamagnetic shielding effect (47) involving the C-15 methyl protons and the $\pi$ electron system of the tosyl group.

Conversion of tosylhydrazone 153 into (±)-eremophil-3,11-diene 2 was then effected by reacting the hydrazone with sodium ethylene glycolate in refluxing ethylene glycol for two hours. After appropriate work-up a pale yellow liquid was isolated which was shown by g.l.c. analysis to contain one major component (ca. 90%) and several unidentified components of significantly greater retention times. An analytical sample of the major component was isolated by preparative g.l.c. This compound exhibited the expected olefinic absorbances at 6.11 and 11.28 $\mu$ in the i.r. spectrum, shown in Figure 6.

The n.m.r. spectrum of compound 2 proved to be particularly informative. As indicated in Figure 7, the spectrum showed one- and two-proton unresolved multiplets at $\tau 4.70$ and $\tau 5.35$ attributed to the C-3 and C-12 vinyl protons, respectively. The two vinyl methyl group signals appeared as a poorly resolved triplet at $\tau 8.30$ ($J \approx 1$ Hz) and an unresolved multiplet at $\tau 8.40$. The latter signals were assigned to the C-13 and C-14 methyl groups, respectively. The signals due to the C-5 angular methyl group appeared as a sharp $\tau 8.96$ singlet. A number of frequency-swept decoupling experiments were performed which confirmed the above chemical shift
Figure 6. Infrared Spectrum of (1S,7S)-Eremophil-3,11-diene.
Figure 7. Nuclear Magnetic Resonance Spectrum of (±)-7β-Eremophil-3,11-diene.
Figure 8. Infrared Spectrum of: (a) Natural Eremophilene. (b) Eremophilene Derived from Eremoligenol 28.
Figure 9. Nuclear Magnetic Resonance Spectrum of Natural Eremophilene.
assignment and supported the structural assignment for the Bamford-Stevens reaction product. Irradiation of the C-12 vinyl protons at $\tau$ 5.35 resulted in the collapse of the $\tau$ 8.30 triplet to a sharp singlet, thus confirming allylic coupling between the C-12 olefinic and C-13 methyl protons. Strong irradiation of the C-3 vinyl proton at $\tau$ 4.70 effected a substantial sharpening of the $\tau$ 8.40 multiplet thus confirming allylic coupling between the protons at C-3 and C-14. A corresponding irradiation of the $^{14}\text{H}_3$ multiplet at $\tau$ 8.40 resulted in a sharpening of the $\tau$ 4.70 multiplet, further confirming coupling between the C-3 and C-14 protons.

The reaction mechanism of the Bamford-Stevens reaction merits brief comment. It has been recognized for some time that in the presence of alkoxide bases the thermal decomposition of tosylhydrazones of aromatic or aliphatic ketones and aldehydes proceeds via initial anion formation followed by an elimination of the tosylate anion, affording an intermediate diazo compound, as depicted below (56,58). The fate of this intermediate normally depends upon the nature of the reaction solvent. Thus, in an "aprotic" medium (e.g., diglyme, diethyl Carbitol) the thermally unstable diazo compounds decompose via carbenes affording the appropriate carbon-hydrogen insertion products. In proton-donating solvents (e.g., ethylene glycol, diethylene glycol) the diazo intermediates are competitively protonated thus
giving rise to decomposition predominantly via cationic intermediates (diazonium cations and/or carbonium ions) which are subsequently neutralized upon reaction with the solvent, Wagner-Meerwein rearrangement and/or proton loss (57). For simplicity, both pathways in the above scheme are represented as terminating with olefin formation. In recent years considerable effort has been expended toward elucidating the mechanistic details of the Bamford-Stevens reaction. Suffice to say here that this work has clearly demonstrated that the balance between the competitive carbenoid and cationic processes operative in a given Bamford-Stevens reaction is a function of both the proton donating ability of the solvent system (57) and the nature of the aliphatic or aromatic moiety of the tosylhydrazone derivative (58,59). Thus, in light of the existing relevant literature (17,57), the conversion of tosylhydrazone 153 into eremophil-3,11-diene 2 under the reaction conditions cited above most likely proceeded via a cationic pathway, olefin formation resulting due to a facile loss of the C-4 proton of 153.

Comparison of a sample of the synthetic (±)-7β-eremophil-3,11-diene 2 with an authentic sample of natural eremophilene unambiguously established that the two sesquiterpenes were not identical. This was immediately apparent upon comparison i.r. spectra of these compounds; the i.r. spectra of (±)-2 and natural eremophilene are reproduced in Figures 6 and 8 respectively. Similarly the n.m.r. spectra of the two olefins, shown in Figures 7 and 9, indicated marked differences, particularly in the 8 to 9.5 τ region. Finally, the

13 A sample of authentic eremophilene obtained from Dr. J. Krepinsky is gratefully acknowledged; a copy of the n.m.r. and i.r. spectrum of this compound was obtained from Dr. R.B. Bates, to whom gratitude is also expressed.

14 The n.m.r. spectrum of authentic eremophilene shown in Figure 9 is in complete agreement with that recently reported for this compound (9). Note that the C-14 methyl group doublet centered at τ 9.15 (J4,14 = 6 Hz) is partially hidden in this spectrum.
natural and synthetic eremophilenes exhibited non-identical g.l.c. retention times which further corroborated the above evidence.

Subsequently, the availability of a sample of the recently isolated eremoligenol 28 \(^{(18)}\)\(^{15} \) enabled the correct structural assignment of eremophilene. Thus, dehydration of eremoligenol 28 with thionyl chloride in dry pyridine (18) afforded a liquid product which contained a mixture of olefins.

Preparative g.l.c. isolation afforded an analytical sample of the major isomer. This compound exhibited an i.r. spectrum (Figure 8) which was found to be superimposable upon that of authentic eremophilene. Moreover, the identity of these substances was further demonstrated by their identical g.l.c. retention times on three different columns. Hence, it was clearly apparent the original structural assignment for eremophilene required revision to that represented by 3.

The very recent total synthesis of racimic 28 and 3 by Coates and Shaw (10)\(^{16} \) has confirmed the current structural and stereochemical assignments for eremoligenol and eremophilene. The synthesis of these compounds was

\(^{15}\) The gift of an authentic eremoligenol sample from Dr. H. Ishii is gratefully acknowledged.

\(^{16}\) The author gratefully acknowledges a preprint of this work forwarded by Professor Coates.
realized via the general synthetic approach to the eremophilane sesquiterpenes previously developed by these workers in the synthesis of \( \Delta^{1(10)} \)-aristolone 75. The starting material in the eremoligenol and eremophilene synthesis was the carbethoxy ketone 154, obtained as described in the Introduction. Treatment of the sodium salt of 154 with acetyl chloride in dimethoxyethane afforded the corresponding carbethoxy enol acetate 155. Reduction of the unpurified enol acetate 155 with lithium in liquid ammonia followed by

treatment with ammonium chloride gave the ester 157, in 34% overall yield from 154. It was suggested by Coates and Shaw that this rather interesting reaction likely proceed via an \( \alpha,\beta \)-unsaturated ester intermediate which upon further reduction would yield the ester enolate anion 156. It was considered that the thermodynamically unfavourable \( \beta \)-orientation of the carbethoxy substituent resulted by way of a kinetic protonation of anion 156 from the sterically less hindered \( \alpha \)-side of the intermediate. Evidence in support of the \( \beta \)-stereochemical assignment was derived from the fact
that, as indicated below, ester 157a underwent epimerization to the corresponding \( \alpha \)-epimer. A diamagnetic shielding due to the axial carbethoxy group in 157a resulted in the observation of a \( \tau \) 9.18 chemical shift for the angular methyl group. Equilibration to the more stable equatorial

![157a to 158](image)

epimer 158 (presumably by base epimerization) was indicated by the absence of this shielding effect as reflected in the appearance of the corresponding angular methyl group signal at lower field, \( \tau \) 9.05. Subsequent reaction of the ester 157 with excess methyl lithium in ether gave an alcoholic product shown to be identical (i.r., n.m.r.) with a sample of authentic eremoligenol 28. Dehydration of the alcohol 28 with thionyl chloride in dry pyridine gave, after g.l.c. purification, a compound which exhibited n.m.r. and i.r. spectra which were indistinguishable from those of authentic eremophilene 3.

Thus in conclusion, the structure 2 originally proposed (7) for eremophilene has been shown to be incorrect. Moreover, it has been demonstrated herein that eremophilene is related to eremoligenol by dehydration and as such, the structure and stereochemistry of eremophilene is correctly represented by formulation 3. The synthesis of (\( \pm \))-eremophil-3,11-diene 2 described in this thesis has concomitantly established a remarkably stereoselective synthetic entry into the eremophilane class of sesquiterpenoids.
The generality of the above conjugate addition approach to the eremophilane sesquiterpenes is currently being investigated in this laboratory. It is worthwhile to note here that lithium dimethylcuprate is a reagent which offers a considerable synthetic utility. The use of lithium dimethylcuprate in the selective conjugate methylation of $\alpha,\beta$-unsaturated ketones affords a marked advantage over previously available methods. Moreover, this copper-ate complex, as well as a number of other lithium dialkyl- and divinylcuprate complexes (e.g., the diethyl-, di-n-butyl-, diphenyl-, and di-l-propienylcuprate analogues) have recently been successfully prepared and employed in a number of other interesting and synthetically useful reactions (63). There can be little doubt that these organo-copper reagents possess an intriguing potential applicability to the field of natural products synthesis in particular, and certainly to synthetic organic chemistry in general.
EXPERIMENTAL

Except where otherwise detailed, the reaction products were isolated by repeated extraction with the solvent specified, the combined extracts were then consecutively washed and dried with the reagents indicated in the parentheses, concentrated initially at water aspirator pressure and finally at vacuum pump pressure (1-10 mm). All melting points were determined on a Kofler block and are uncorrected. Ultraviolet spectra were recorded in methanol on a Cary 14 recording spectrophotometer. Infrared spectra (i.r.) were recorded on a Perkin-Elmer Infracord model 137 spectrophotometer or a Perkin-Elmer model 421 Grating spectrophotometer, all comparison i.r. spectra were obtained using the latter instrument. Nuclear magnetic resonance (n.m.r.) spectra were determined in deuteriochloroform (tetramethylsilane as internal standard) and recorded on a JEOLCO C-60-H spectrometer, a Varian A-60 or Varian HA-100 spectrometer. Signal positions are given in the Tiers τ scale with multiplicity and proton assignment in parentheses. Gas-liquid chromatography (g.l.c.) was carried out with an Aerograph Autoprep, model 700, using helium as a carrier gas at a flow rate of 80-85 ml min⁻¹. The following 1/4" x 10' columns were employed using 60/80 mesh Chromsorb W. as an inert packing support: A, 20% SE30; B, 20% Apiezon-J; C, 20% FFAP; D, 10% FFAP; E, 15% QF-1; F, 20% Carbowax. The g.l.c. columns are noted, with column temperature, in parentheses. Microanalyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of
British Columbia, Vancouver.

3-Isopropenylcyclohexanone 130

The procedure employed was essentially that of House, Latham and Slater (46).

A solution of isopropenyl magnesium bromide (from 12.7 g (0.53 mole) of magnesium turnings, 87.4 g (0.74 mole) of 2-bromopropene in 70 ml of dry tetrahydrofuran (THF)) under nitrogen, was diluted with 350 ml of dry THF then cooled to 0°. To this stirred solution was added 2.61 g (26.4 mmol) of anhydrous CuCl followed by the dropwise addition of 24.2 g (0.25 mole) of 2-cyclohexenone in 150 ml of THF over 20 min. The reaction mixture was stirred at 0° for 2 hr, then poured into a stirred aqueous solution of ammonium chloride-ammonium hydroxide (pH 8) at 0°. The reaction product was isolated with ether (dil. NH₄OH, water, brine). Distillation of the resulting oil gave 24.54 g (70.5%) of essentially g.l.c. pure (column A, 150°) 3-isopropenylcyclohexanone 130, b.p. 68-72° (7.5 mm) (lit.⁴⁶ 80.5-84° (8mm)), n_D^26.0 1.4749 (lit.⁴⁶ 1.4743-1.4749). Infrared (film), λ_max 5.85, 6.12, 11.20 μ; n.m.r., τ 5.22 (unresolved multiplet, =CH₂), 7.62 (broad multiplet, α-CH₂), 8.24 (singlet, -CH₃).

3-Isopropenylcyclohexanone hydroxymethylene 131

The procedure employed is similar to that given by Sorm et. al. (60).

To a stirred slurry containing 31.6 g (0.58 mole) of sodium methoxide in 160 ml of dry benzene was added a solution of 43.3 g (0.58 mole) of ethyl formate in 160 ml of dry benzene. The system was then cooled externally with ice to ca. 0° then a solution of 26.4 g (0.20 mole) of 3-isopropenylcyclohexanone 130 in 160 ml of dry benzene was added dropwise over 20 min. The reaction mixture was placed under nitrogen, the system allowed to come gradually to room temperature then stirred for 50 hr. To the resulting yellow
colloidal system was added 500 ml of water; after stirring well it was extracted several times with 7% aqueous sodium hydroxide. The combined alkaline extracts were acidified (pH 3) with 12 M hydrochloric acid, cooled and the product isolated with ether (water, brine) affording 27.58 g of red-brown oil. Distillation gave 20.65 g (75%) of the hydroxymethylene as a pale yellow oil, b.p. 60-76° (0.03 mm), 101-102° (4 mm), ν_D^19.3 1.5198. Ultraviolet, λ_max 283 μm; i.r. (film), λ_max 6.02, 6.22 (broad), 11.15 μ; n.m.r., ν_neat 8.26 (singlet, -CH₃), 5.25 (unresolved multiplet, =CH₂), 7.7 (broad multiplet, α-H₂), 1.4 (singlet, -CHO), -4.0 (very broad multiplet, =CHOH).

1-Methyl-7β-isopropenyl-Δ¹,9-octal-2-one

The procedure employed was similar to that given by Banerjee, Chatterjee and Bhattacharya (49).

To a stirred solution of 15.9 g (0.10 mole) of commercial 1-diethylamino-3-pentanone in 70 ml of dry benzene under nitrogen at 0° was added dropwise 14.6 g (0.10 mole) of freshly distilled methyl iodide. The reaction mixture was stirred for 3 hr at 0° then stored in a refrigerator overnight. After evaporating the benzene and excess methyl iodide, the resulting viscous colorless methiodide salt was dissolved in 40 ml of methanol for subsequent use in the Robinson annelation reaction.

The above methanolic methiodide solution was added dropwise over 20 min to a stirred solution of 2.41 g (44.7 mmoles) of sodium methoxide and 11.70 g (70.4 mmoles) of 3-isopropenylcyclohexanone hydroxymethylene in 60 ml of methanol. The reaction mixture was stirred under nitrogen at room temperature for 26 hr then poured into a cold saturated aqueous ammonium sulfate solution which had been further acidified with hydrochloric acid. The resulting colloidal system was thoroughly extracted with ether; the
combined extracts yielded 16.12 g of crude product after concentration. Deformylation was effected by stirring the concentrate in 630 ml of 2% aqueous sodium hydroxide for 1 hr at room temperature under nitrogen. The resulting alkaline solution was acidified (pH 6) and the product isolated with ether (water, brine) giving 14.52 g of yellow oil. The i.r. spectrum of this material exhibited a significantly stronger saturated (5.86 μ) than unsaturated (6.02 μ) carbonyl absorbance. Thus, ring closure was completed by refluxing the crude product in a solution of 0.5 g of sodium methoxide in 125 ml of dry methanol for 5-6 hr at which time the unsaturated carbonyl absorbance of acid quenched aliquots of the reaction mixture had attained a maximum intensity (starting material present). The methanol was evaporated, 50 ml of water added, the system acidified (pH 5) with hydrochloric acid and the crude product isolated with ether (water, brine). Fractional distillation gave 10.56 g of pale yellow liquid in four fractions: (I) 0.59 g, 73.80° (5 mm); (II) 2.25 g, 110-128° (0.3 mm); (III) 6.55 g, 127-131° (0.3 mm); (IV) 1.17 g, 132-178° (0.3 mm). Fraction (I) was shown to be identical to 3-isopropenylcyclohexanone \textsuperscript{130} (i.r., g.l.c). Fractions II, III and IV contained 92, 94 and 95% respectively of octalone \textsuperscript{127} as determined by g.l.c. (column B, 230°). The octalone yield, based on the hydroxymethylene derivative \textsuperscript{131} was thus 64%. Analytical samples of octalone \textsuperscript{127} were obtained via hydrolysis of its oxime \textsuperscript{159} and by preparative g.l.c. (column B, 230°), b.p. 127-131° (0.3 mm), \( n_D^{23.5} 1.5320 \). Ultraviolet, \( \lambda_{\text{max}}^{\text{D}} 249.5 \text{ m} \mu \) (ε = 14,600); i.r. (film); \( \lambda_{\text{max}} 6.00, 6.20, 11.25, 11.82 \mu; \) n.m.r., \( \tau = 5.26 \) (unresolved multiplet, \(-\text{CH}_2\)), 8.22 (poorly resolved quartet, \(-\text{C'H}_3\), J \( \cong \) 1.2 and 1.8 Hz, homoallylic coupling (47)), 8.25 (triplet, isopropenyl \(-\text{CH}_3\), J = 1.2 Hz, allylic coupling (47)). The chemical shifts assigned to the vinylic methyl groups were established by a decoupling experiment in which the olefinic protons of the isopropenyl group (\( \tau = 5.26 \)) were strongly irradiated...
thus effecting collapse of the τ 8.25 triplet to a sharp singlet, while the τ 8.22 quartet remained unaffected.

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

1-Methyl-7-isopropenyl-Δ^{1,9}-octal-2-one oxime 159

To an aqueous solution of 0.170 g (2.45 mmoles) of hydroxylamine hydrochloride and 0.333 g (2.95 mmoles) of sodium acetate trihydrate was added 0.500 g (2.45 mmoles) of the α,β-unsaturated ketone 127. Methanol was added until a clear solution was obtained. The reaction mixture was then stirred overnight at room temperature yielding, after filtration and drying, 0.370 g (69%) of colorless crystals. Recrystallization from methanol afforded an analytical sample, m.p. 163-165°. Ultraviolet, \( \lambda_{\max} \) 243 μm; i.r. (CHC13), \( \lambda_{\max} \) 2.82, 3.10, 3.44, 6.08, 10.50, 11.18 μ; n.m.r., τ 8.15, 8.26 (singlets, vinylic CH\(_3\) groups), 5.30 (singlet, =CH\(_2\)), 1.63 (broadened singlet, =NOH).

Anal. Calcd. for C_{14}H_{21}ON: C, 76.66; H, 9.65; N, 6.39. Found: C, 76.84; H, 9.55; N, 6.21.

1-Methyl-7-isopropenyl-Δ^{1,9}-octal-2-one 127 from its oxime 159

Hydrolysis of the oxime 159 to the α,β-unsaturated ketone 127 was realized by refluxing for 25 hr a solution of 0.183 g of the oxime, 0.46 g of oxalic acid and 2.7 ml of 37% aqueous formaldehyde dissolved in 9 ml of methanol, 4 ml of water and 5 ml of 80-100° petroleum ether. The product was isolated with ether (water, brine). Reduced pressure distillation gave a small analytical sample of pure octalone 127, the data for which is given above.

(‡)-7β-Eremophil-11-en-3-one 128

The procedure employed is similar to that of House, Respess and Whitesides (51).
To a stirred slurry containing 6.02 g (31.3 mmoles) of copper (I) iodide in 120 ml of anhydrous ether at 0° and under N₂, was added 39.4 ml of 1.59 M (62.6 mmoles) of ethereal methyl lithium by injection from a dry syringe. The resulting essentially clear, slightly tan coloured solution containing the lithium dimethyl copper reagent was stirred for 5 min with cooling, then a solution containing 2.00 g (10.4 mmoles) of octalone 127 in 80 ml of anhydrous ether was added dropwise over 15 min. The reaction mixture was stirred at 0° for an additional 1.75 hr then slowly added to 800 ml of vigorously stirred 1.2 M aqueous hydrochloric acid. The reaction product was isolated with ether (water, brine) giving 2.185 g of a pale yellow liquid which was found by g.l.c. (column C, 215°) to contain 77% decalone 128 (yield ca. 80%) in addition to 5% starting material and several unidentified components. An analytical sample was obtained by preparative g.l.c. (column C, 215°), b.p. 123.5-124.5 (0.03 mm), nD 20.0 1.5041. Infrared (film), λmax 5.86, 6.10, 6.93, 10.59, 11.27 μ; n.m.r., τ 5.33 (unresolved multiplet, -CH₂), 7.17 (quartet, -C⁴H, J₄₁₄ = 6.7 Hz), 8.29 (poorly resolved triplet, -C¹³H₃), 9.11 (doublet, -C¹⁴H₅, J₁₄₄ = 6.7 Hz), 9.21 (singlet, -C¹⁵H₃). The coupling assignments were confirmed by two frequency-swept decoupling experiments. The olefinic protons at τ 5.33 were irradiated effecting the collapse of the τ 8.29 triplet to a sharp singlet. Similarly, strong irradiation of the τ 7.17 quartet resulting in a partial collapse of the τ 9.11 doublet to a poorly resolved triplet, which was taken as evidence of coupling between the C-4 and C-14 protons.


(†)-78-Eremophil-11-en-3-one tosylhydrazone 153

The procedure employed is similar to that given by Djerassi et. al. (61).
To a solution containing 2.00 g (7.36 mmoles) \(^{17}\) of decalone \(^{128}\) and several drops of acetyl chloride in 16 ml of methanol was added 1.680 g (9.08 mmoles) of p-toluenesulfonylhydrazide. The system was placed under nitrogen, refluxed for 40 min, allowed to cool to room temperature and finally to 0°. The yellowish crystals (1.977 g) thus afforded were separated by filtration. Recrystallization from methanol gave 1.656 g (58%) of colorless needles, m.p. 159-161°. Infrared (CHCl\(_3\)), \(\lambda_{\text{max}}\) 6.10, 6.25, 6.92, 8.58, 11.2 \(\mu\); n.m.r., \(\tau\) 9.43 (singlet, -C\(^{15}\)H\(_3\)), 9.12 (doublet, -C\(^{14}\)H\(_3\), \(J_{4,14} = 6.5 \text{ Hz}\)), 8.32 (poorly resolved triplet, -C\(^{13}\)H\(_3\)), 7.61 (singlet, aromatic CH\(_3\)), 7.37 (poorly resolved quartet, -C\(^4\)H, \(J_{4,14} = 6.5 \text{ Hz}\)), 5.36 (unresolved multiplet, =C\(^{12}\)H\(_2\)), 2.44 (A\(_2\)B\(_2\) quartet, four aromatic protons, \(J_{ab} \approx 8 \text{ Hz}, (\delta_b - \delta_a) \approx 58 \text{ Hz}\)).

Anal. Calcd. for C\(_{22}\)H\(_{32}\)O\(_2\)N\(_2\)S: C, 68.00; H, 8.30; H, 7.21; S, 8.25.
Found: C, 68.22; H, 8.41; N, 7.41; S, 8.11.

(\(\pm\))-7-B-Eremophil-11-en-3-one semicarbazone \(^{137}\)

Water was added dropwise to a solution of 5.00 g of decalone \(^{128}\) in 50 ml absolute ethanol until a slight permanent cloudiness was established. A few drops of ethanol were added to just clear the solution and 5.00 g of semicarbazide hydrochloride and 7.50 g of sodium acetate were added. The system was refluxed for 30 min then cooled to room temperature and the crystals thus formed were separated by filtration yielding 5.222 g of crude semicarbazone \(^{137}\). Recrystallization from ethanol gave, after vacuum drying, 3.205 g (64.8%) \(^{18}\) of colorless plates, m.p. 191.5-194.5°. Infrared (CHCl\(_3\)), \(\lambda_{\text{max}}\) 5.95, 6.40, 6.92, 11.20 \(\mu\); n.m.r., \(\tau\) 1.40 (broad multiplet, =N-NH), 4.24 (broad multiplet, -CONH\(_2\)), 5.27 (unresolved multiplet, =C\(^{12}\)H\(_2\)), 7.25

\(^{17}\) Starting material 81% decalone

\(^{18}\) Starting material was 82% decalone
(poorly resolved quartet, -C\textsubscript{4}H\textsubscript{4}, J\textsubscript{14,1} \sim 6.8 Hz), 8.27 (poorly resolved triplet, -C\textsubscript{13}H\textsubscript{3}), 9.06 (doublet, -C\textsubscript{14}H\textsubscript{3}, J\textsubscript{14,1} \sim 6.8 Hz), 9.24 (singlet, -C\textsubscript{15}H\textsubscript{3}).

Anal. Calcd. for C\textsubscript{16}H\textsubscript{27}ON\textsubscript{3}: C, 69.27; H, 9.81; N, 15.15. Found: C, 69.20; H, 9.98; N, 15.05.

(\dagger)-7β-Eremophil-3,11-diene 2

The Bamford-Stevens reaction procedure employed was similar to that given by Corey and Sneen (62).

To a stirred solution obtained from the gradual addition of 10.0 g of sodium metal to 100 ml of ethylene glycol was added 1.500 g (3.87 mmoles) of tosylhydrazone 153. The system was placed under nitrogen then refluxed for 2 hr. The flask and contents were cooled until slightly warm then the reaction mixture was poured into 200 ml of water. The product, isolated with ether (water, brine), yielded 0.896 g of yellow liquid which was shown by g.l.c. (column D, 120 and 135°) to contain a single major component (ca. 90%) and several considerably more polar components which were not identified. An analytical sample of (\dagger)-eremophil-3,11-diene 2 was collected by preparative g.l.c. (column D, 170°), b.p. 85-88° (bath temp.) (0.4 mm)\textsuperscript{19} n\textsubscript{D} 1.5052. Infrared (film), \(\lambda\)\textsubscript{max} 6.11, 6.95, 7.32, 11.28, 12.03, 12.48 μ; n.m.r., \(\tau\) 4.70 (unresolved multiplet, -C\textsubscript{3}H), 5.35 (unresolved multiplet, \(=C\textsubscript{12}H\textsubscript{2}\)), 8.30 (triplet, -C\textsubscript{13}H\textsubscript{3}), 8.40 (multiplet, -C\textsubscript{14}H\textsubscript{3}), 8.96 (singlet, -C\textsubscript{15}H\textsubscript{3}). The above proton signal assignments were confirmed by frequency-swept decoupling experiments. Irradiation at \(\tau\) 5.35 resulted in an observed collapse of the poorly resolved triplet at \(\tau\) 8.30 to a sharp singlet, thus establishing allylic coupling between the C-12 and C-13 protons. Similar

\textsuperscript{19} This value obtained from a separated run of this reaction.
irradiation of the C-3 vinyl proton at \( \tau 4.70 \) effected a substantial sharpening of the \( \tau 8.40 \) multiplet. This result, and the observed sharpening of the \( \tau 4.70 \) multiplet upon irradiation of \( \tau 8.40 \) clearly demonstrated allylic coupling between the C-3 and C-14 protons of structure 2.

Anal. Calcd. for \( \text{C}_{15}\text{H}_{24} \): C, 88.16; H, 11.84. Found: C, 88.36; H, 11.98.

\((\pm)-78\text{-Eremophil-11-ene 138 from semicarbazone 137}\)

For an analogous procedure see Church, Ireland and Shridar (50).

A stirred solution containing 2.00 g (7.5 mmoles) of semicarbazone 137, 1.82 ml (32.2 mmoles) of 85% hydrazine hydrate, 1.87 (30.9 mmoles) of potassium hydroxide in 20 ml diethylene glycol was gradually heated to 160-165° and thus maintained for 21 hr. As thin-layer chromatography (t.l.c.) indicated little or no product formation the temperature was increased to 190-195° and thus refluxed for 24 hr. The reaction mixture was then cooled to room temperature then poured into 100 ml of water. The product, isolated with ether (water, brine) was a yellow oil (1.466 g) which was shown by g.l.c. (column D, 140°) to be 97% olefin 138 (91% yield). These conditions were employed in collecting an analytical sample which was found to be identical (\( n_D \), i.r., n.m.r., g.l.c. retention times on columns A, 180°; B, 180°; C, 168°; E, 120°) with a sample of authentic \((\pm)-78\text{-eremophil-11-ene 138 derived from (+)-hydroxydihydroeremophilone 30}\), as detailed below.

Anal. Calcd. for \( \text{C}_{15}\text{H}_{26} \): C, 87.30; H, 12.70. Found: C, 87.02; H, 12.79.

\((\pm)-78\text{-Eremophilane 45}\)

A solution containing 648 mg (3.15 mmoles) of \((\pm)-eremophil-11-ene 138\) and 0.70 g of platinum oxide in 25 ml of ethanol was stirred at room temperature under hydrogen overnight. The reaction mixture was filtered and concentrated yielding 596 mg of a colorless oil shown by g.l.c. (column D,
135°) to be 95% (+)-7β-eremophilane 45. An analytical sample was collected by preparative g.l.c. (column D, 135°), nD23.6 1.4820. Infrared (film), λmax 3.4, 6.90, 6.82, 7.30, 7.22, 10.00, 10.81 μ; n.m.r., τ 9.15 (doublet, -C12H3 and -C13H3, J11,12(13) = 6 Hz), 9.16 (singlet, -C15H3), 9.28 (doublet, -C14H3, J4,14 = 6.5 Hz). This material was found to be identical (nD, i.r., n.m.r., and g.l.c. retention time on columns A, 158°; C, 158°; E, 120°), with authentic (+)-7β-eremophilane 45 derived from hydroxydihydroeremophilone 30, as detailed below.


(+)-Hydroxydihydroeremophilone Acetate 139

The procedure followed is that of Djerassi, Mauli and Zalkow (22).

A solution of 1.000 g (4.68 mmoles) of hydroxydihydroeremophilone 30, 4.25 ml of acetic anhydride dissolved in 8.5 ml of dry pyridine was stored in a refrigerator for 2 days. The reaction mixture was then poured into 15 ml of water and the product isolated with chloroform (1.2 M hydrochloric acid, dilute sodium bicarbonate, water, brine) giving 1.188 g of oil which crystallized on standing at 0°. Recrystallization from methanol gave 416 mg of the keto acetate 139 as colorless plates, m.p. 68-71°. Infrared (CHCl₃), λmax 3.42, 5.73, 5.80, 7.90-8.5, 11.10 μ. An additional 658 mg of the crude keto acetate was recovered from the mother liquor (yield ca. 90%).

(+)-7β-Eremophil-11-en-9-one 140

The procedure followed is that of Djerassi, Mauli and Zalkow (22).

To a vigorously stirred solution of 7.45 g of calcium metal in 185 ml of liquid ammonia at -33° was added dropwise over 25 min a solution of 765 mg (3.02 mmoles) of keto acetate 139 in 15 ml of dry toluene. The reaction mixture was thus stirred for a further 10 min then 7.45 ml of bromobenzene
was added dropwise (exothermic) followed by the careful addition of 36 ml of water. The ammonia was then evaporated and the product isolated with chloroform (0.6 M hydrochloric acid, water, brine) giving 706 mg of yellow oil. The crude eremophil-11-en-9-one thus obtained was found to be significantly contaminated with an unidentified aromatic impurity, as indicated by t.l.c. and i.r. Successive column chromatography (Woelm neutral alumina, activity I) subsequently afforded 84 mg of the desired ketone which was slightly contaminated and 129 mg of precious g.l.c. pure (column E, 205°) (+)-eremophil-11-en-9-one. Infrared (film), $\lambda_{\text{max}}$ 3.45, 5.86, 6.08, 11.20 $\mu$; n.m.r., $\tau$ 9.23 (doublet, $-\text{C}^{14}\text{H}_3$, $J_{4,14} = 5.9$ Hz), 8.97 (singlet, $-\text{C}^{15}\text{H}_3$), 8.27 (unresolved triplet, $-\text{C}^{13}\text{H}_3$), 5.26 (unresolved multiplet, $=\text{C}^{12}\text{H}_2$).

(+)-7β-Eremophil-11-ene from (+)-7β-eremophil-11-en-9-one

A solution containing 190 mg of (+)-eremophil-11-en-9-one in 2.0 ml of 85% hydrazine hydrate, 0.75 g of potassium hydroxide in 10 ml of diethylene glycol was refluxed for 2 hr, then the excess hydrazine was distilled off slowly by draining the water condenser and allowing the temperature to gradually increase to 205-215°. The system was then refluxed at this temperature for 8 hr. After cooling, the reaction mixture was diluted with 20 ml of water and the product isolated with ether (water, brine). The colorless liquid (145 mg) thus obtained was shown by g.l.c. (column D, 140°) to contain 65% of the desired olefin (yield ca. 53%). An analytical sample was obtained by preparative g.l.c. (column D, 140°), $n_D^{23.6} = 1.4933$. Infrared (film), $\lambda_{\text{max}}$ 3.4, 6.08, 6.90, 7.28, 7.23, 11.28 $\mu$; n.m.r., $\tau$ 5.36 (unresolved multiplet, $=\text{C}^{12}\text{H}_2$), 8.30 (poorly resolved triplet, $-\text{C}^{13}\text{H}_3$), 9.16 (singlet, $-\text{C}^{15}\text{H}_3$), 9.26 (doublet, $-\text{C}^{14}\text{H}_3$, $J_{4,14} = 6.6$ Hz).
(+)-7β-Eremophilane 45

A solution containing 94 mg of (+)-7β-eremophil-11-ene 138 and 94 mg of platinum oxide in 4 ml of absolute ethanol was stirred at room temperature overnight under hydrogen. The resulting solution was filtered and concentrated yielding 80 mg of colorless oil which was shown by g.l.c. (column F, 140°) to contain 78% of (+)-7β-eremophilane 45 (yield ca. 64%). An analytical sample was collected by preparative g.l.c. (column F, 140°), nD 1.4820. Infrared (film), \( \lambda_{\text{max}} = 3.4, 6.90, 6.82, 7.30, 7.22, 10.00, 10.81 \mu \); n.m.r., \( \tau = 9.15 \) (doublet, \(-\text{C}^{12}\text{H}_3\) and \(-\text{C}^{13}\text{H}_3\), \(J_{11,12(13)} = 6\) Hz), 9.16 (singlet, \(-\text{C}^{15}\text{H}_3\)), 9.28 (doublet, \(-\text{C}^{14}\text{H}_3\), \(J_{4,14} = 6.5\) Hz).

Eremophilene 3 from eremoligenol 28

The procedure employed is that of Ishii, Tozyo and Minato (18).

To a solution of 44.1 mg (0.198 mmole of eremoligenol 28 in 0.5 ml of dry pyridine at 0° was added 0.05 ml of thionylchloride. After several minutes at 0° the reaction mixture was allowed to come to room temperature and thus react for 1 hr. It was then quenched in several milliters of ice-water and the product isolated with ether (2 N sulfuric acid, dilute sodium bicarbonate, water, brine) yielding 34.4 mg of yellow oil. An analytical sample, collected by g.l.c. (column B, 180°), exhibited an infrared spectrum identical to that of natural eremophilene.

(†)-7β-Eremophil-11-en-3-one 128 by copper (II) acetate catalyzed Grignard addition

To a stirred ethereal solution of methylmagnesium iodide (from 71.4 mg (2.94 mmoles) of magnesium turnings, 0.19 ml (3.04 mmoles) of methyl iodide in 3.2 ml of anhydrous ether) at -10° under \(N_2\) was added a solution containing 48.8 mg (0.245 mmole) of copper (II) acetate monohydrate, 200 mg (0.980 mmole) of octalone 127 in 4.8 ml of dry tetrahydrofuran
dropwise over 30 min. The cold bath was then removed and the yellow colloidal reaction mixture allowed to come to room temperature and thus remain over 4 hr. After refluxing for 1.5 hr the resulting grey heterogeneous system was poured slowly into vigorously stirred 1.2 M hydrochloric acid. The product was isolated with ether (dilute sodium bicarbonate, water, brine) giving 190 mg of orange oil. This material exhibited a strong saturated carbonyl (5.85 μ) and weak unsaturated carbonyl (6.00) absorbance and was subsequently shown by g.l.c. (column D, 180°) to contain 25% of the desired decalone 128 (peak enhancement), 12% starting material in addition to at least 14 other components. An analytical sample of decalone 128 was isolated from this reaction mixture by preparative g.l.c. (column D, 160°) and exhibited an infrared spectrum superimposable upon that of authentic (±)-7β-eremophil-11-en-3-one. It should be noted that the product compositions obtained from a number of such reactions varied somewhat irreproducibly in complexity and percent 1,4-adduct (10 to ~25%).
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