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THE TOTAL SYNTHESIS OF (±)-BULNESOL AND RELATED STUDIES[1]

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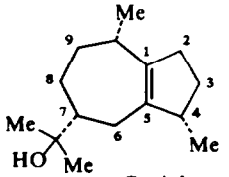
Abstract—A stereoselective route to 1,7-dimethylbicyclo[4.3.1]decan-10-ols **16e**, **19e**, and **79** and the subsequent rearrangement of their methanesulfonate derivatives to the corresponding hydroazulenes **22**, **27**, and **81** is described. The synthesis of the bicyclo[4.3.1]decane intermediates begins with 2-carbethoxycycloheptanones and proceeds via condensation with methyl vinyl ketone and cyclization of the resulting 2-carbethoxy-2-(3-oxobutyl)-cycloheptanones in sulfuric acid. Selective reduction of the derived bicyclo-[4.3.1]decenone carboxylic acids **34** and **69** thereby obtained yields the aforementioned hydroazulene precursors. The 7-methylol-substituted hydroazulene derivative **82** was converted to (±)-bulnesol (**87**) via oxidation to the corresponding acid **83**, esterification with diazomethane and basic isomerization of the resulting ester **84** to the epimer **85**. Treatment of ester **84** with methyllithium afforded 7-epibulnesol (**86**) whereas ester **85** yielded (±)-bulnesol (**87**). In the initial stages of this synthetic scheme a *p*-chlorophenyl ether was employed as a protecting group for the methylol function which was ultimately converted to the C-7 isopropylol grouping of bulnesol. This protecting group was easily removed through reduction to an acid-labile enol ether with lithium in ammonia.

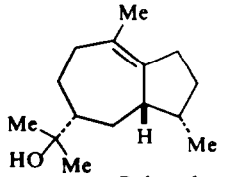
INTRODUCTION

GUAIACUM wood oil contains two isomeric hydroazulenic alcohols, guaiol and bulnesol. The former was first isolated by direct crystallization from the oil in 1892;[2] the latter was not recognized as a separate chemical entity until 1929.[3] Because of its ready availability in pure form and its importance as an odor fixative in perfumery,[4] guaiol became the target of structural studies relatively soon after its discovery.[5,6] However, it was not until 1951 that the currently accepted formula, exclusive of stereochemistry, was securely established. Studies on the stereochemistry first appeared in 1960[7a] and by 1961[7b] the final structural uncertainty was fully clarified. Subsequent X-ray work[7c] confirmed the earlier deductions and placed the structure on secure ground.

Prior to the synthetic work to be described in this report, the assigned structure of bulnesol rested entirely upon its chemical correlation with one of the isomeric dihydroguaiols.[8] Except for some uncertainty regarding the stereochemistry at C-5.[9] the conclusions based on this correlation seemed sound. Futher support for the assigned structure comes from biogentic considerations.[10]



Guaiol



Bulnesol

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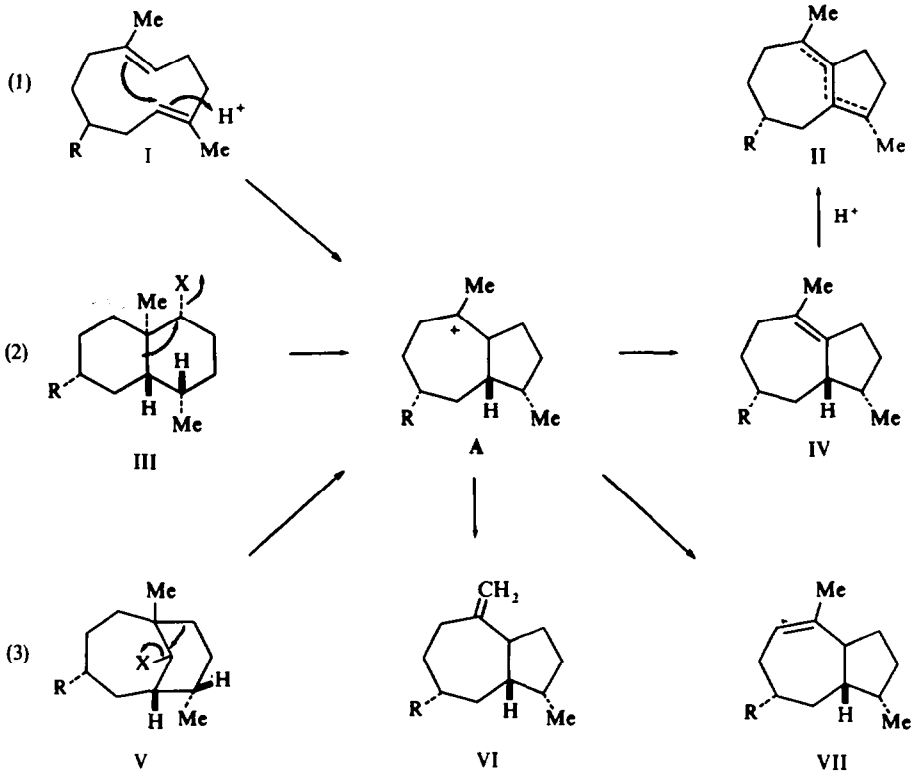
Many of the schemes employed for the synthesis of azulenes involve hydroazulenic precursors and proceed by annelation of a preformed cyclopentane or cycloheptane derivative.[11] Unfortunately, these approaches offer little chance for the stereochemical control required of a rational synthesis of hydroazulenes such as guaiol or bulnesol and alternatives must therefore be sought.*

We considered the three potential approaches exemplified below by equations (1–3). All proceed, at least formally, through the same cationic intermediate **A** which by proton loss could lead directly to the bulnesol-related structure IV and possibly the double bond isomers VI and VII thereof.

The first involves a cation-initiated cyclization of the 1,5-cyclodecadiene derivative I and resembles the proposed biosynthesis of bulnesol.[10] This approach was the least attractive of the three because of stereochemical ambiguities, uncertainties regrading the direction of cyclization,† and possible difficulties in controlling the final location of the tetrasubstituted double bond,‡ not to mention the problems associated with a synthesis of the requisite cyclodecadiene I.[15]

The second of our potential approaches involves a skeletal isomerization of the



* Notable achievements in the synthesis of tricyclic guaiazulenic sesquiterpenes have recently been recorded by Büchi *et al.*[12]

† Analogous 1.5-cyclodecadienes lead predominantly to hydronaphthalene derivatives upon treatment with electrophilic reagents.[13a] However recent findings with oxirane derivatives show that hydroazulenes can also be formed.[13b]

‡ Acidic equilibration of bulnesol leads mainly to isomeric compounds.[14]

decahydronapthalene derivative III. Analogous rearrangements have been carried out on steroidal systems[16] and several applications to a hydronaphthalene derivatives have been reported.[17]

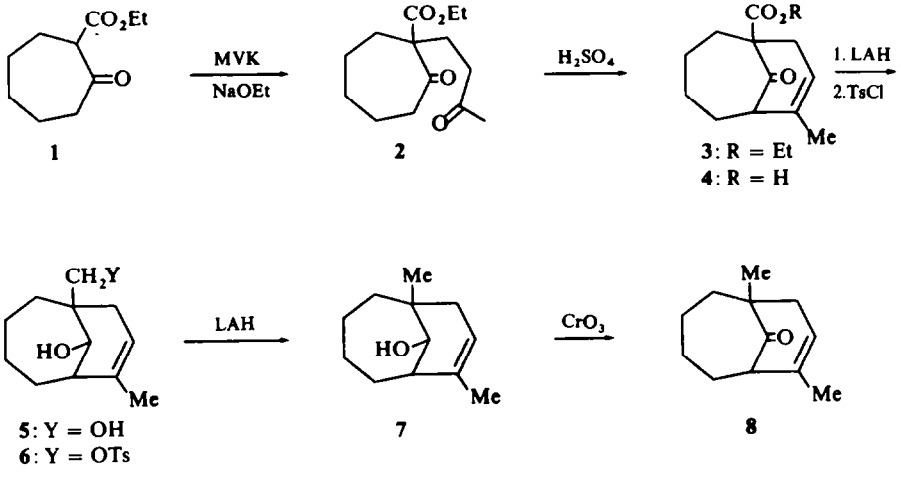
The third route to cation A proceeds via skeletal rearrangement of the bicyclo [4.3.1]dec-10-yl derivative V. A number of related isomerizations of bicyclo[3.2.1]oct-8-yl and bicyclo[3.3.1]non-9-yl derivatives have been examined, mainly in connection with mechanistically oriented solvolysis studies.[18] However, prior to the studies outlines below, hydroazulenes had not yet been prepared by this route.

Both solvolysis routes to cation A (Equations 2 and 3) employ rigid bicyclic precursors whose stereochemistry should be derivable in a predictable manner. Hence, both could be stereochemically unequivocal. Moreover, both employ solvolysis reactions which allow for the generation of cation A or an equivalent species irreversibly, thereby precluding undesired olefin isomerization (e.g. IV → II). Of the two approaches the one based on the bicyclo[4.3.1]dec-11-yl system V seemed to offer several advantages, not the least of which was the opportunity to examine previously uncharted synthetic pathways. We therefore decided to concentrate our efforts in this direction.

Before attempting the synthesis of bulnesol we undertook studies designed to test the feasibility of our overall synthetic plan. These studies were carried out on intermediates which lacked the necessary functionality for introducing the C-7 isopropylol grouping.

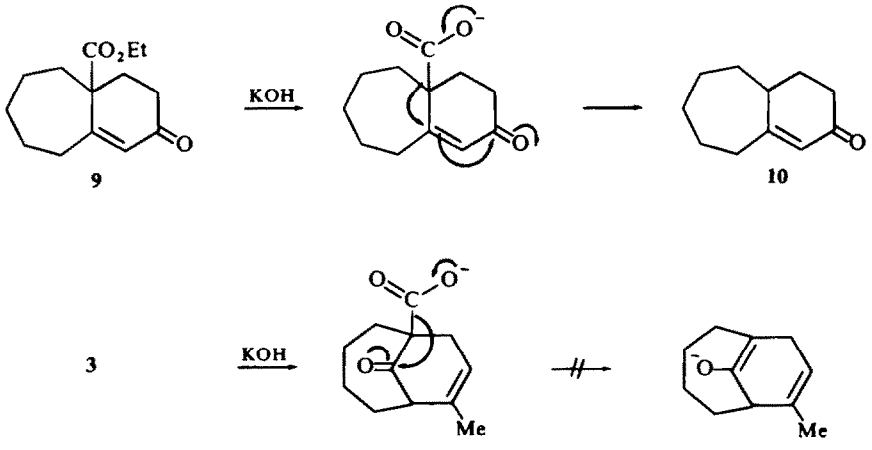
PRELIMINARY STUDIES

CHART I



Prelog *et al.*[19] found that 2-carbethoxycycloheptanone (**1**), upon alkylation with 1,3-dichloro-2-butene, afforded the 2-γ-chlorocrotyl derivative, which subsequently underwent hydrolysis and cyclization in concentrated sulfuric acid to give the bicyclo-[4.3.1]decenone **3**. We modified their sequence by using methyl vinyl ketone as the alkylating agent and conducting the cyclization of the resulting dione **2** at lower temperature and for a considerably shorter reaction time.[20] This modified procedure

yielded 83% of the bicyclic keto ester **3** and 12% of the isomeric keto ester **9**. Purification of the former product was effected through saponification of the mixture whereupon the minor keto ester **9** was converted to the conjugated ketone **10** which could be extracted from the basic solution. Acidification afforded the crystalline keto acid **4** in 83% yield. The success of this separation scheme can be attributed to the markedly lower tendency of the salt of β-keto acid **4** to decarboxylate in comparison to the salt derived from the vinylogous β-keto ester **9**. This behaviour reflects the excessive strain that must be developed in the transition state of decarboxylation reactions involving bridgehead β-keto acids of bicyclo[a.b.1] systems. where a and b are small numbers.*



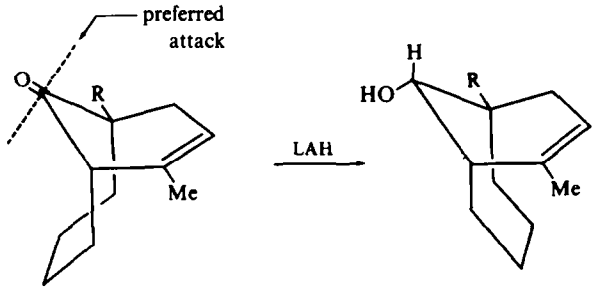
Reduction of the keto acid **4** with LAH in refluxing 1,2-dimethoxyethane (DME) afforded a sharply melting crystalline diol **5** in 86% yield. The reduction therefore appears to be quite stereoselective. Dreiding models show that in approaching the ketonic grouping of keto acid **4** (or the corresponding salt) the hydride reducing agent should experience substantially greater steric interactions with the saturated 4-carbon bridge† than with the unsaturated 3-carbon bridge. The stereochemistry of diol **5** could be tentatively assigned on this basis. Subsequent conversions verified this assignment.

p-Toluenesulfonyl chloride selectively esterified the primary alcohol function of diol **5** in pyridine to give the mono-tosylate derivative **6**. Hydrogenolysis was effected with lithium aluminum hydride in refluxing DME to give the corresponding 1-methylbicyclo[4.3.1]decenol **7** in 67% yield. In contrast, attempted hydrogenolysis of the mesylate derivative (**6**, Y = OMs) of diol **5** under the same conditions led to a

* In the present case. the enolate intermediate would incorporate a *trans*-cycloheptene moiety. For a discussion of the steric aspects of Bredt's rule. see Ref.[21b]

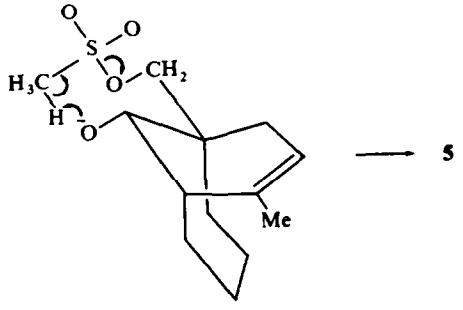
† The conformation of the 4-carbon bridge is not fixed. Two extreme forms can be recognized. one in which the cycloheptane ring adopts a boat conformation and one wherein the cycloheptane ring assumes a chair conformation. Models suggest that the former will be preferred when the one-carbon bridge is trigonal and the 3-carbon bridge is saturated. whereas the latter should predominate when the one-carbon bridge is tetrahedral and the 3-carbon bridge ls unsaturated. We show this preference in our conformational drawings. With ketone **4** and related compounds. the tetramethylene bridge effectively blocks bottom side approach to the C-10 carbonyl in both the chair and boat conformation of the cyclopentanone ring.

14—



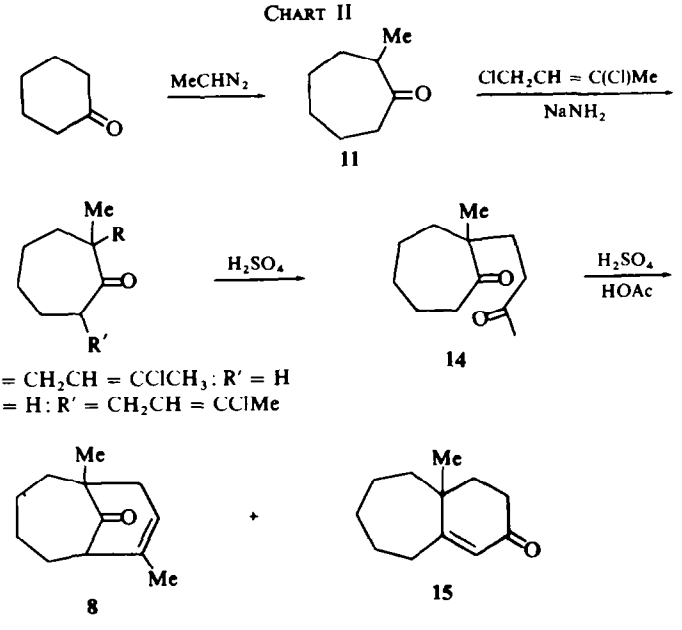
4: R = CO_2H or CO_2 5: R = CH_2OH

substantial recovery of the starting diol **5** indicating that sulfur-oxygen cleavage was the preferred pathway in this case. Conceivably the basic alkoxides generated in this reaction could effect an elimination reaction (intra or intermolecular) on the mesylate, but not the tosylate grouping. One possibility is diagrammed below.



Oxidation of alcohol **7** with Jones reagent[22] afforded the ketone **8**.

CHART II

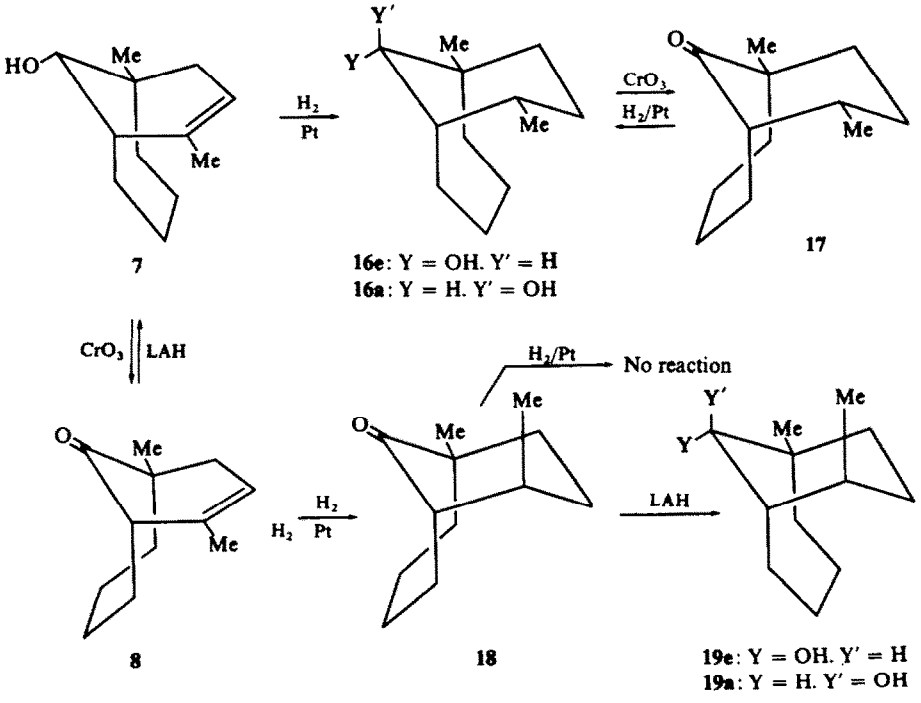


Hoping to develop a more efficient synthesis of ketone **8**, we explored a variation of the above route starting from 2-methylcycloheptanone (**11**) (Chart II). If successful, this scheme would circumvent the two steps required for hydrogenolysis of the methylol grouping. Furthermore, it would be readily applicable to the synthesis of bulnesol since the 5-substituted 2-methylcycloheptanones required for such an application can be efficiently prepared via ring expansion of 4-substituted cycloheptanones with diazoethane.[23]

Alkylation of 2-methylcycloheptanone (**11**) with 1,3-dichloro-2-butene afforded an 86:14 mixture of the monoalkylated products **12** and **13** in 85% yield. This mixture yielded a 3:1 mixture of diones (mainly **14**) and the conjugated ketone **15** upon brief treatment with concentrated sulfuric acid at 0°. Prolonged exposure of either the vinyl chloride or dione mixture to these conditions led to a small amount of the enone **15** and polymeric products; none of the desired bicyclo[4.3.1]decenone **8** could be isolated. These results stand in sharp contrast to those obtained by Prelog[19] and by us with dione **2** and various cyclohexanone counterparts[20] of dione **14**. After a systematic study of reaction conditions, we found that a 1:1 mixture of acetic and sulfuric acid provided the highest ratio of bicyclic ketone **8** to polymer and with this modification, a mixture of ketone **8** (44%), the enone **15** (36%) and recovered dione could be obtained in 64% yield starting from the dione **14**. The apparent sensitivity of the bridged bicyclic unsaturated ketone **8** to strong acid coupled with the non-selectivity of the alkylation step made this more direct approach to ketone **15** somewhat less attractive than the alternative one based on 2-carbethoxycycloheptanone.

Hydrogenation of the unsaturated alcohol **7** over platinum followed by Jones

CHART III



oxidation[22] afforded an 85:15 mixture of the epimeric ketones **17** and **18**. Hydrogenation of the unsaturated ketone **8** under the same conditions led to the same two ketones but in the ratio 20:80, favoring **18**. Clearly, the functionality at C-10 in these unsaturated bicyclo[4.3.1]decene derivatives exerts an important influence on the stereochemistry of their hydrogenation. The stereochemistry of ketones **17** and **18** can be assigned, albeit somewhat tenuously, on the basis of conformational considerations involving the four-carbon bridge of alcohol **7** and ketone **8**. As noted above,* models indicate that this bridge should preferentially form part of a chair-cycloheptane ring when C-10 is tetrahedral whereas trigonal hybridization at C-10 should favor the boat-cycloheptane ring conformation. On this basis, the bottom face of the double bond should be more accessible in the unsaturated ketone **8** than in the corresponding alcohol **7** and hydrogenation of the former olefin should lead to more of the axial methyl epimer **18**.

Support for these assignments came from a comparison of the NMR spectra of ketones **17** and **18**. The methyl doublet of the former isomer showed a coupling constant of 6 Hz whereas the latter displayed a doublet with a coupling constant of 8 Hz. The same trend was observed with the alcohols **16e** and **19e** obtained via reduction of the ketones with LAH. Alcohol **16e** showed a coupling constant of 5 Hz for its Me doublet whereas alcohol **19e** gave rise to a 7-Hz Me doublet, Katritzky *et al.*[24] have noted that equatorially methylated cyclohexane derivatives exhibit a smaller coupling constant (J = 5–7 Hz) than their axially methylated counterparts (J = 7–9 Hz). The same distinction can be made for methylated decahydronaphthalenes.[25]

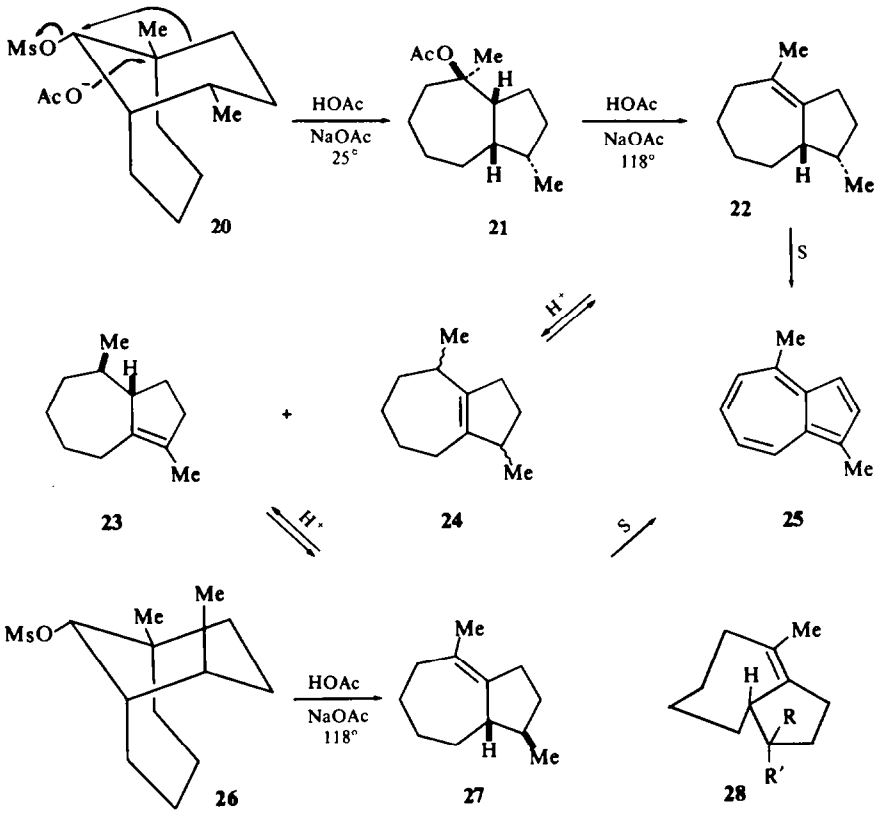
Meerwein–Ponndorf reduction of ketone **17** under equilibrating conditions[26] afforded a 60:40 mixture of alcohols **16e** and **16a** favoring the epimer previously obtained from the unsaturated derivative **7**. A similar reduction of ketone **18** led to an 85:15 mixture of epimeric alcohols **19e** and **19a**, again favoring the equatorial epimer. These findings give further support to the stereochemical assignment of ketones **17** and **18** since the latter, with an axially oriented Me grouping, should give less of the axial alcohol epimer at equilibrium than its equatorially methylated counterpart **17**.

The 80:20 mixture of ketones **17** and **18** upon hydrogenation over platinum in acetic acid afforded a mixture of alcohol **16e** and recovered ketone **18** which could be readily separated by column elution chromatography. The same result was obtained with a 1:1 synthetic mixture of purified samples of ketones **17** and **18**. The former was completely reduced to alcohol **16e** and the latter was recovered unchanged. This finding provided an easy means for separting the epimeric ketones **17** and **18** and further confirmed the assigned stereochemistry since ketone **18**, with an axial Me grouping hindering approach from the top face and the 4-carbon tetramethylene bridge hindering approach from the bottom face,* would expectedly hydrogenate with difficulty. In this regard we were surprised to find that reduction of ketone **18** with LAH yielded the equatorial alcohol **19e** exclusively.† Apparently the tetramethylene bridge exerts considerably greater steric influence that the axial Me grouping with respect to the approach of hydridic species to the C-10 ketonic grouping of **18**.†

* See footnote † on page 2162.

† Cyclohexanones with axial Me groups at the β-positions generally give a predominance of the axial alcohol epimer upon reduction with metal hydrides.[27a] For a pertinent discussion of factors which control the stereochemistry of related reductions, see Ref.[27b]

CHART IV



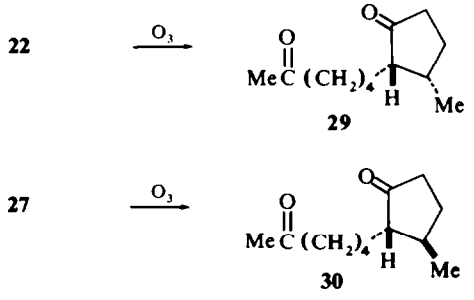
Alcohols **16e** and **19e** required fairly prolonged treatment with methanesulfonyl chloride for complete conversion to their respective mesylate derivatives **20** and **26**. These decomposed completely to a mixture of hydrocarbons upon standing overnight at room temperature. However, freshly prepared samples could be stored for brief periods at low temperatures with no apparent decomposition.

Mesylate **20** rearranged smoothly upon treatment with 0·5-M sodium acetate in acetic acid at reflux. After 3 hr, the hydroazulene **22** was produced in 80% yield along with minor amounts of three other hydrocarbon products (double bond and possibly skeletal isomers) detected by gas chromatography. In the same medium but at room temperature, mesylate **20** gave a 3:2 mixture of acetates (principally **21**) and hydrocarbons (principally olefin **22**). The acetate yielded olefin **22** upon treatment with sodium aceate in refluxing acetic acid, and may therefore be an intermediate in the solvolysis of mesylate **20** at elevated temperature. We base our assigned stereochemistry of this acetate on the assumption of inversion at both reacting centers of mesylate **20**.

Mesylate **26** likewise rearranged smoothly upon treatment with 0·5M sodium acetate in acetic acid at reflux. After 3 hr the hydroazulene **27**, an isomer of the principal hydrocarbon product secured from mesylate **20**, was obtained in 80% yield. Again,

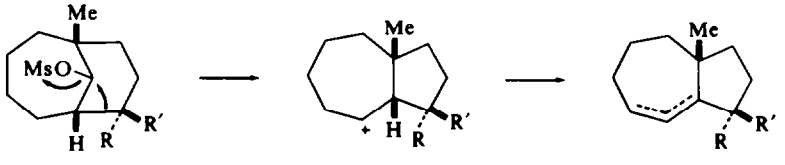
minor amounts of three other hydrocarbon products could be detected by gas chromatography.

Structural confirmation of the solvolysis products **22** and **27** was provided by their IR and NMR spectra, their dehydrogenation to 1,4-dimethylazulene (**25**), and their ozonolysis to the cyclopentanones **29** and **30**. These degradations fully confirm the



carbon skeleton of olefins **22** and **27** and exclude the isomeric hydronaphthalene structures **31** and **32** from further consideration. These latter hydrocarbons would presumably have arisen had the stereochemistry been incorrectly assigned at C-10 in alcohols **16e** and **19e**. In that event, anchimerically assisted solvolysis would have proceeded with migration of the 4-carbon bridge [i.e. **16a** (Y′ = OMs, Y = H) → **31** and **19a** (Y′ = OMs, Y = H) → **32**).

The hydronaphthalenes **31** and **32** may in fact be formed as minor solvolysis products via non-assisted pathways. The hydroazulene isomers **33** and **34**, derived from migration of the methine carbon of mesylates **20** and **26**, may also be presented in minor amounts. That a larger percentage of the solvolysis reaction does not proceed by this pathway may be attributed to the lesser stability of the resulting incipient secondary cation intermediates compared to the tertiary cations derived from the alternative pathway.

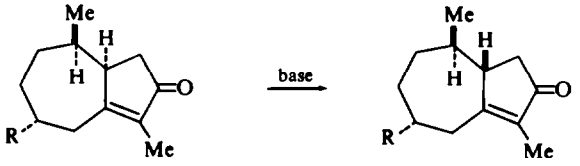


20: R = Me: R′ = H
26: R = H: R′ = Me

33: R = Me: R′ = H
34: R = H: R′ = Me

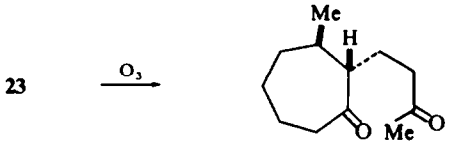
The hydroazulenic olefins **22** and **27** gave essentially identical mixtures of isomers upon treatment with *p*-toluenesulfonic acid in acetic acid at reflux. These olefins were isolated by preparative gas chromatogaphy and identified as **22** (2%), **23** (55%), **24** (22%), and **27** (20%) by their spectral properties.

Olefin **23** appeared to be a single isomer and is assigned the indicated *anti* stereochemistry on the basis of conformational analysis and by analogy with the related unsaturated ketone **35s** shown by Büchi *et al.*[12] to epimerize to the *anti* isomer **35a** upon treatment with base.



35s: R = Me_2CBr **35a**: R = Me_2CBr

Ozonolysis of olefin **23** afforded the cyloheptanone **36** thereby confirming the location of the double bond in the hydroazulene ring system.



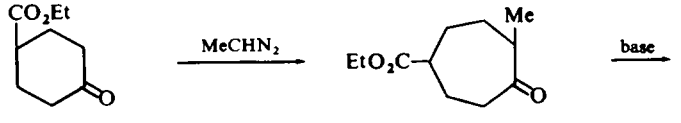
36

Olefin **24** also appeared to be a single isomer according to its NMR spectrum which contained only two methyl doublets. However, conformational analysis indicates an approximately 1:1 mixture of the *cis* and *trans* isomers should be expected at equilibrium. According to Dreiding models, each of the Me groupings experiences nearly the same environment in both isomers and on this basis, a mixture of the two may in fact show only two differentiable Me signals.

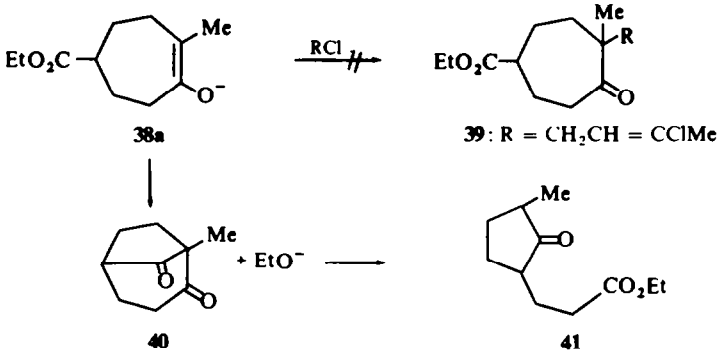
The observed 10:1 equilibrium ratio of olefins **27** and **22** falls nicely into line with that expected on the basis of the indicated stereochemistry. As shown by structure **28**, olefin **22** (**28**; R = H; R′ = Me) suffers from an eclipsed methyl–methylene interaction not present in olefin **27** (**28**; R = CH_3; R′ = H). Thus, the latter should predominate at equilibrium.

THE SYNTHESIS OF BULNESOL

CHART V

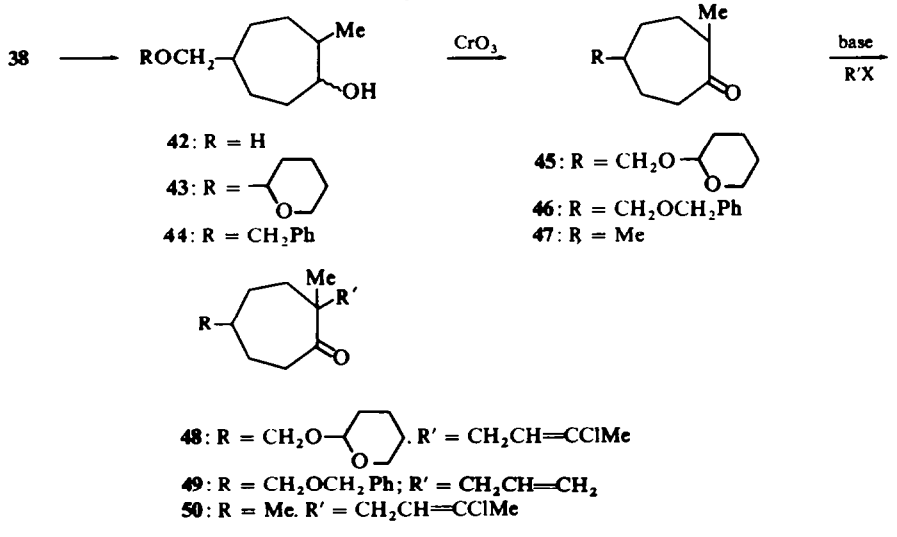


37 **38**



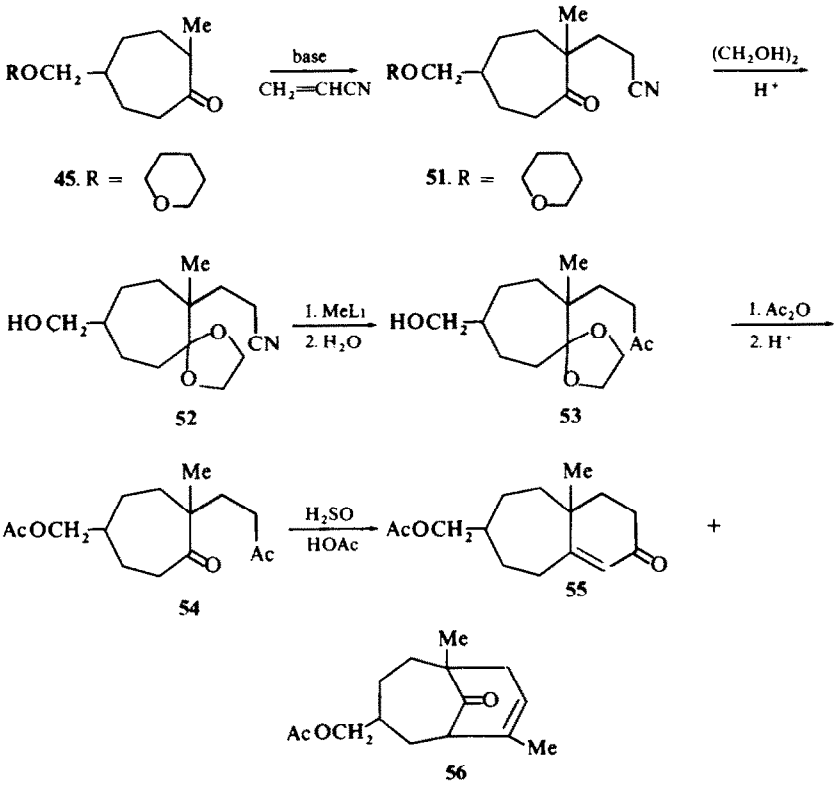
Having satisfactorily attained our preliminary objectives we turned our attention to the next phase of the synthetic program. Our initial efforts in this direction employed as the starting material 5-carbethoxy-2-methylcycloheptanone (**38**) available in high yield through ring expansion of 4-carbethoxycyclohexanone with diazoethane.[23] Although our work with the model series had revealed a number of drawbacks to schemes based on 2-methyl *vs.* 2-carboxycycloheptanones we felt that the most serious of these, the polymerization encountered in connection with the sulfuric acid cyclization step, might not be nearly so facile with highly oxygenated intermediates such as keto ester **39** and the derived dione. Such intermediates would be extensively protonated at the basic oxygen sites in the strongly acidic cyclization medium and further protonation leading to carbonium ions and thence polymers should therefore be inhibited. Unfortunately, we were unable to test this hypothesis with the keto ester **39** as the attempted alkylation of keto ester **38** with 1,3-dichloro-2-butene yielded the cyclopentanone derivative **41** as the only isolable product. Evidently cyclization of the enolate **38a** competes successfully with alkylation. Ethoxide cleavage of the presumed intermediate β-diketone **40** then leads to the rearranged keto ester **41**. This isomerization could also be effect by treating keto ester **38** with ethanolic sodium ethoxide.

CHART VI



The unexpectedly facile base-initiated rearrangement of keto ester **38** necessitated a minor tactical modification. Accordingly, the carbethoxy grouping of keto ester **38** was transformed to a tetrahydropyranyl-blocked methylol grouping by reduction with LAH, selective conversion of the resulting diol **42** to the primary tetrahydropyranyl ether **43**, and Jones oxidation.[22] We were surprised to find that alkylation of the resulting keto ether **45** with 1,3-dichloro-2-butene could not be effected under a variety of conditions. All attempts led to a high recovery of starting ketone. The benzyl ether **46**, prepared via selective benzylation of diol **42** followed by oxidation, likewise failed to alkylate with 1,3-dichloro-2-butene. However, alkylation of this keto ether occurred readily with allyl bromide to give the expected allyl derivative **49**. Furthermore, 2,5-dimethylcycloheptanone (**47**) smoothly afforded the chlorocrotylcycloheptanone **50** upon treatment with 1,3-dichloro-2-butene in base, thus showing that steric factors were probably not responsible for the unreactivity of the enolates derived from ketones **45** and **46**. We can offer no reasonable explanation for these seemingly inconsistent findings at present.

CHART VII



Eventually we succeeded in preparing a useful bicyclo[4.3.1]decane intermediate from the 5-substituted 2-methylcycloheptanone **45**. Cyanoethylation of this ketone could be effected under forcing conditions to give the cyano ketone **51** in 74% yield. Conversion to the ketal **52** followed by treatment with ethereal methyllithium and

hydrolysis with aqueous ammonium chloride afforded the keto ketal **53** in satisfactory overall yield. Acetylation followed by treatment with 5% sulfuric acid in acetic acid to effect ketal hydrolysis gave the diketo acetate **54** in 88% yield. Unfortunately, this dione preferentially cyclized to the bicyclo[5.4.0]undecenone **55** (49% yield) in 1:1 sulfuric acid-acetic acid. The bicyclo[4.3.1]decenone **56** could be isolated in only 19% yield.

In view of the continued difficulties encountered with 2-methylcycloheptanone precursors of the desired bicyclo[4.3.1]decanones, we turned our attention to a route based on 2-carbethoxycycloheptanones analogous to that successfully executed in our preliminary work. Presumably, the required starting material could be prepared via ring expansion of an appropriate 4-substituted cyclohexanone with ethyl diazoacetate.[28] However, before proceeding we had to choose a cyclohexanone with a C-4 substituent which would be convertible to the C-7 isopropylol grouping of bulnesol, and which would also survive the relatively stringent reaction conditions employed for the sequence leading to the bicycle intermediate. Ideally the chosen substituent should also be epimerizable at some stage of the synthetic scheme to ensure the eventual obtainment of the desired C-7 stereoisomer.

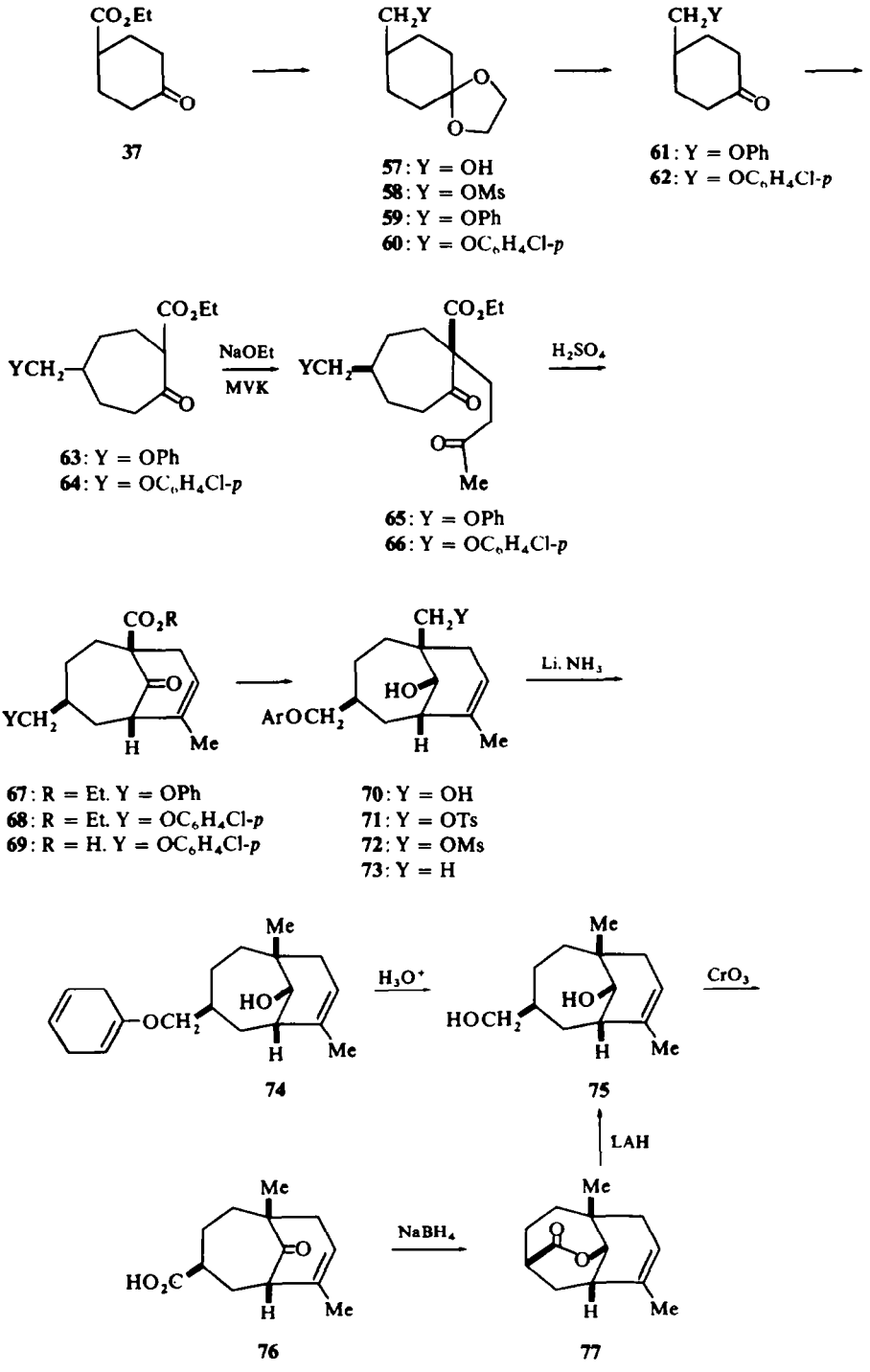
In light of these considerations a blocked methylol grouping seemed like the best choice for a C-4 substituent. However, the standard ester and ether protecting groups appeared entirely inadequate for the vigorous and varied reagents required in the early synthetic stages. Some preliminary studies showed that benzylic ethers readily cleaved under the strongly acidic conditions required for dione cyclization. It should be noted that the loss of a protecting group at any stage prior to the C-1 methylol hydrogenolysis step (cf. **6** → **7**) would pose serious problems in terms of undesired functional group interactions as well as selective functional group manipulations. We therefore decided to prepare the phenoxymethyl derivative **63**. This ether could be expected to survive the gamut of reaction conditions required for the initial transformations and, at an appropriate stage, should be reducible with lithium in ammonia to an acid labile enol ether.

Ketalization of 4-carbethoxycyclohexanone (**37**) followed by reduction with LAH afforded the hydroxy ketal **57**. The corresponding mesylate derivative **58** gave the phenyl ether **59** in 75% yield upon treatment with sodium phenoxide in refluxing terahydrofuran. The cyclohexanone **61**, secured via acidic hydrolysis of ketal **59**, reacted smoothly with ethyl diazoacetate and boron trifluoride in ether to give the β-keto ester **63** in 79% yield. Condensation with methyl vinyl ketone converted this material to the diketo ester **65** in essentially quantitative yield.

Attempted cyclizations of diketo ester **65** in sulfuric acid or mixtures of acetic and sulfuric acids led to virtually complete loss of material. None of the expected keto ester **67** could be isolated nor could the starting material be recovered. We presume that the phenyl grouping of dione **65** and any bicyclic product (e.g. **67**) must undergo sulfonation under these conditions leading to water-soluble sulfonic acid derivatives which are lost during the workup. Attempts to cyclize diketo ester **65** with boron trifluoride[29] afforded only nondistillable polymeric products.

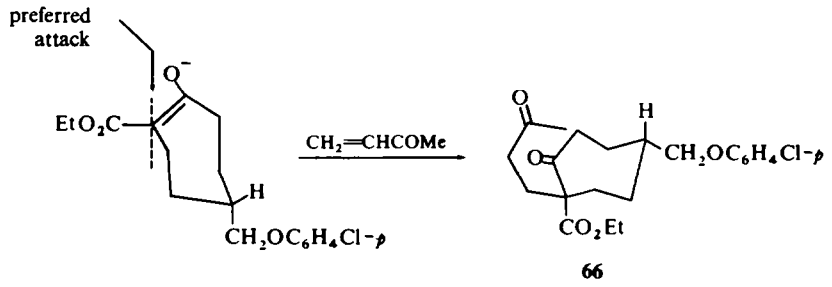
If sulfonation were in fact responsible for the extremely poor material recovery from attempted cyclizations of dione **65** in sulfuric acid, then deactivation of the phenyl ring through substitution of an electron withdrawing group should diminish this tendency. Such indeed was the case. The *p*-chlorophenyl-blocked diketo ester **66**,

CHART VIII


CO2Et
O
37
CH2Y
O
O
57: Y = OH
58: Y = OMs
59: Y = OPh
60: Y = OC6H4Cl-p
CH2Y
O
61: Y = OPh
62: Y = OC6H4Cl-p
CO2Et
YCH2
O
NaOEt
MVK
63: Y = OPh
64: Y = OC6H4Cl-p
CO2Et
YCH2
O
O
Me
65: Y = OPh
66: Y = OC6H4Cl-p
H2SO4
CO2R
O
YCH2
H
Me
67: R = Et. Y = OPh
68: R = Et. Y = OC6H4Cl-p
69: R = H. Y = OC6H4Cl-p
CH2Y
HO
ArOCH2
H
Me
70: Y = OH
71: Y = OTs
72: Y = OMs
73: Y = H
Li. NH3
Me
HO
OCH2
H
Me
74
H3O+
Me
HO
HOCH2
H
Me
75
CrO3
LAH
Me
O
HO2C
H
Me
76
NaBH4
Me
O
O
H
Me
77

prepared from the ketal mesylate **58** along the same lines noted above for the corresponding phenyl derivative, afforded principally the desired bicyclo[4.3.1]decenone **68** along with a small amount of the corresponding bicyclo[5.4.0]undecenone upon treatment with 4:1 sulfuric acid–acetic acid. Saponification of the mixture gave the crystalline keto acid **69** in 65% yield based on dione **66**.

The high yield of sharply melting keto acid **69** obtained via the above sequence suggested that the Michael reaction leading from keto ester **64** to dione **66** proceeded stereoselectively to give mainly one stereoisomer. Assuming a reactant-like transition state for this condensation, as shown below, the indicated isomer would be expected to predominate. Subsequent transformations of keto acid **69** confirmed this assignment.



66

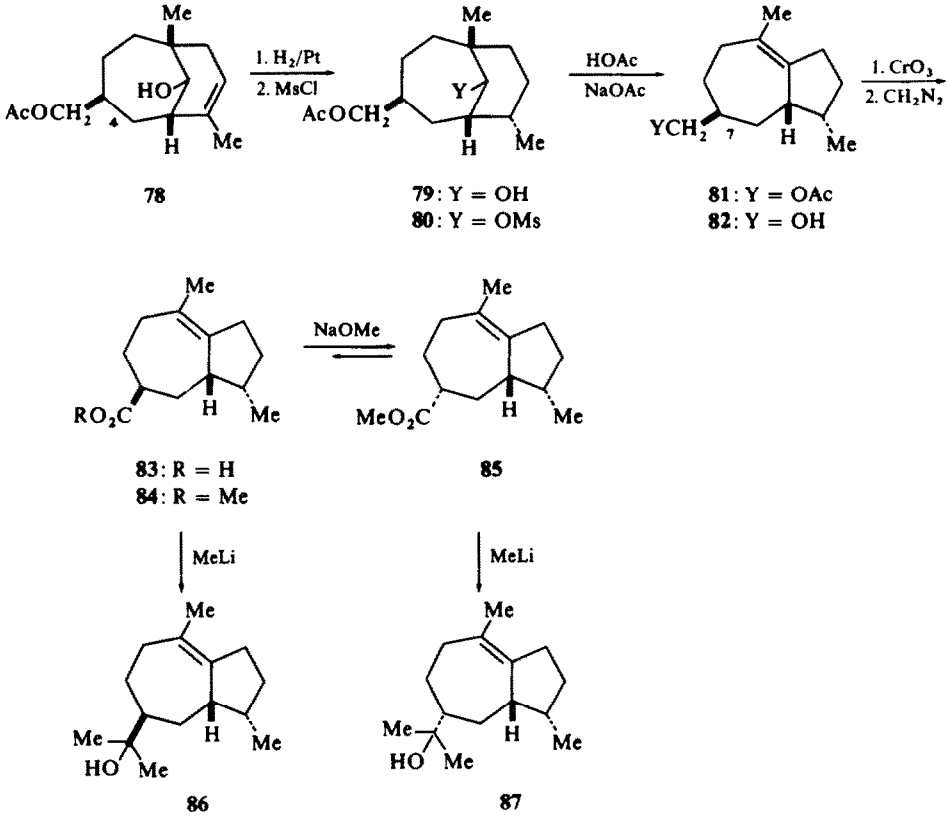
Reduction of the bicyclo keto acid **69** with LAH in refluxing 1,2-dimethoxyethane afforded a mixture of the phenyl and *p*-chlorophenyl diol derivatives **70** (Ar = C_6H_5 and *p*-ClC_6H_4) indicating that hydrogenolysis of the aryl chloride occurred to some extent under these conditions. The *p*-chlorophenyl derivative **60** behaved similarly and, in a control experiment, complete reduction to the phenyl compound **59** took place within 36 hr. Subsequent to these experiments Karabatsos and Shone[30] described similar findings with a variety of aromatic halides. The tosylate derivative **71** of the diol mixture **70** (Ar = C_6H_5 and *p*-ClC_6H_4) was reduced by LAH in refluxing 1,2-dimethoxyethane to a mixture of alcohols **73** (Ar = C_6H_5 and *p*-ClC_6H_4) whose NMR spectrum revealed that further hydrogenolysis of the aryl chloride had occurred. This finding is of little concern at this stage since the chlorine atom has already served its purpose in protecting the aromatic ring from sulfonation during the cyclization reaction (**66** → **68**).

Treatment of the alcohol mixture **73** (Ar = C_6H_5 and *p*-ClC_6H_4) with lithium in ammonia–ethanol followed by hydrolysis of the resulting enol ether derivative **74** with aqueous acid gave the crystalline diol **75** in 80% overall yield. This same crystalline diol was secured upon treatment of the previously obtained bicyclic keto acetate **56** with LAH. An alternative, more direct synthesis of diol **75** was attempted through reduction of the mesylate derivative **72** with lithium in ammonia–ethanol. However, hydrolysis of the resulting enol ether gave none of the desired product presumably owing to preferential sulfur-oxygen cleavage in the reduction step. The tosylate **71** likewise failed to give diol **75** upon treatment with lithium in ammonia followed by hydrolysis.

The stereochemistry of diol **75** was confirmed via oxidation to the keto acid **76** followed by reduction with sodium borohydride. Acidification of the crude reduction product afforded the crystalline tricyclic lactone **77** in 86% yield. The required *cis*

arrangements of the lactone bridge and the unsaturated 3-carbon bridge, which for steric reasons must each span opposite sides of the cycloheptane ring, completely define the relative stereochemistry of lactone **77**. Since reduction of this lactone with lithium aluminum hydride yielded the diol **75**, the stereochemistry of this substance can likewise be unambiguously assigned.

CHART IX



78

79: Y = OH
80: Y = OMs

81: Y = OAc
82: Y = OH

83: R = H
84: R = Me

85

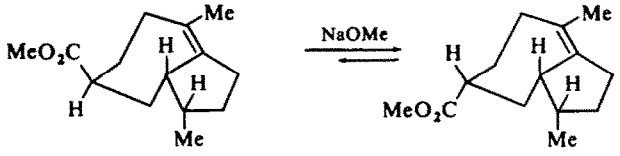
86

87

Diol **75** was selectively acetylated by treatment with acetic anhydride in pyridine. Hydrogenation of the resulting monoacetate **78** over platinum in acetic acid afforded the dihydro derivative **79**, whose stereochemistry can be assigned on the basis of our previous findings with alcohol **7** and the NMR spectrum which reveals a Me doublet with a coupling constant of 5·5 Hz indicative of an equatorial Me group.[24] The mesylate derivative **80** of this alcohol, upon treatment with sodium acetate in acetic acid at reflux, quantitatively yielded a mixture of rearranged unsaturated acetates judged to contain 92% of the desired hydroazulene **81** according to gas chromatography and NMR analysis.

At this point it should be noted that the relative stereochemistry at C-4 in acetate **78** (and therefore at C-7 in acetate **81**) is opposite to that established for bulnesol. We recognized this possibility in the planning stages of the synthesis and felt that if

necessary this center could be inverted through basic equilibrium of the ester **84** or some similar intermediate. This stereochemical conclusion is based on conformational considerations which indicate that the desired epimer **85** should be the more stable one because of the pseudoequatorial orientation of its carbomethoxy group, as opposed to the pseudoxial orientation required in ester **84**.*



84 **85**

Cleavage of the acetate **81** with LAH and oxidation of the resulting alcohol **82** with Jones reagent yielded the acid **83**. Esterification with diazomethane afforded the ester **84** whose gas chromatogram and NMR spectrum attested to its structural and stereochemical homogeneity. In refluxing methanolic sodium methoxide. ester **84** gave way to a 71:29 mixture of epimers **85** and **84** which could be separated by preparative gas chromatography. The major ester **85** afforded racemic bulnesol (**87**) upon treatment with ethereal methyllithium. The minor ester **84** was similarly converted to the tertiary alcohol **86** which showed spectral and chromatographic properties distinctly different from those of bulnesol.

EXPERIMENTAL

The apparatus described in Ref. 32 was used to maintain a N_2 atm over reaction mixtures.

The isolation procedure consisted of thoroughly extracting the reaction mixture with the specified solvent. washing the combined extracts with saturated brine. and drying the extracts over $MgSO_4$. The solvent was removed under reduced press. LAH reductions were processed by carefully adding 1·0 ml water and 0·8 ml 10% NaOH aq for each 0·5 g hydride initially present. The mixture was efficiently stirred to effect granulation of the salts and filtered.

Gas chromatography was performed on F and M Model 700 or 720 instruments equipped with thermal conductivity detectors. Microanalyses were performed by Micro-Tech Laboratories. Inc.. Skokie. Ill.

Ethyl 1-(3-*oxobutyl*)-2-*oxocycloheptanecarboxylate* (**2**)

To a soln of 3·90 g (21·2 mmoles) of **1** in 100 ml 0·02M ethanolic NaOEt was added 1·60 g (23·0 mmoles) methyl vinyl ketone at −20°. The soln was stirred for 1 hr at −10°. the base was neutralized with 1 ml AcOH. and the solvent was removed under reduced press. The product was isolated with ether and distilled affording 4·80 g (89%) of a viscous oil. b.p. 82–85° (0·1 mm). which gave a negative ferric chloride test: λ_{max}^{film} 5·76–5·87 (CO). 7·33. 8·14. 8·60. and 9·78 μ: $\delta_{TMS}^{CCl_4}$ 4·15 ($O\underline{CH_2}CH_3$ quartet, J = 7 Hz), 2·05 (MeCO). and 1·28 ppm ($OCH_2\underline{CH_3}$ triplet. J = 7 Hz).

Ethyl 7-*methyl*-10-*oxobicyclo*[4.3.1]*dec*-7-*enecarboxylate* (**3**).

To 5 ml conc H_2SO_4 was added 4·80 g (18·9 mmoles) of diketo ester **2** at 0°. The purple mixture was stirred for 1 hr at 0° and the viscous mass was then added in a fine stream to 100 ml of rapidly stirred ice-water. Isolation with ether and distillation at 90–99° (0·1 mm), afforded 3·96 g (87%) colorless oil: λ_{max}^{film} 5·75 (CO). 5·85 (CO). 7·88. 8·08. 8·22. 8·48 and 8·70 μ. Peaks at 14·2 (**3**, 83%). 23·5 (**9**, 12%), and 27·0 min (**2**, 5%) were present in the gas chromatogram.†

* The free energy difference between equatorial and axial carboxylic ester groupings in cyclohexane derivatives amounts to 1·2–1·3 kcal/mole.[31]

† A 13 ft. × ¼ in. column of 16% Carbowax 20-M on 60–80 mesh Diatoport S was used for this analysis.

7-Methyl-10-oxobicyclo[4.3.1]*dec-7-enecarboxylic acid* (**4**) *and bicyclo*[5.4.0]*undec-7-en-9-one* (**10**)

A 63·3-g (0·27 mole) sample of keto ester mixture (87% **3** and 13% **9**) was stirred at reflux with a 2 molar excess of 15% methanolic KOH soln for 24 hr. On cooling, the mixture was diluted with water and extracted with ether. The ether extracts were washed with 10% NaOH aq. water, and brine and dried over $MgSO_4$. The solvent was removed under reduced press and the residue was distilled giving 4·0 g (9%) of enone **10**: b.p. 78–80° (0·2 mm); λ_{max}^{film} 5·99 (CO), 6·19 (C=C), 7·51, 7·96, 8·29, and 11·30 μ; $\delta_{TMS}^{CCl_4}$ 5·80 ppm (C=C<u>H</u>CO); semicarbazone derivative, m.p. 211–212° (lit.[19] m.p. 212–214°).

The aqueous alkaline layers were combined, cooled, and acidified with cold HCl aq. The precipitated carboxylic acid **4** was taken up in ether, washed with water and saturated brine, and dried over $MgSO_4$. Removal of solvent afforded 46·0 g (83%) of yellow solid. One recrystallization from chloroform gave 40·2 g (72%) white platelets m.p. 172–173° (lit.[19] m.p. 174°); λ_{max}^{KBr} 2·91–3·08 (acid OH), 5·83 (CO), 7·68, 7·79, 8·00, 8·68, 10·04, 10·65, 11·81, 12·41, and 13·49 μ.

1-*Hydroxymethyl-7-methylbicyclo*[4.3.1]*dec-7-en-10α-ol* (**5**)*

A soln containing 40·2 g (0·19 mole) of keto acid **4** in 350 ml DME was carefully added to 15·3 g (0·40 mole) LAH in 100 ml DME. After 24 hr at reflux, the mixture was processed giving 34·8 g (92%) solid material. Recrystallization from ether–hexane yielded 32·5 g (86%) white platelets, m.p. 93–94°. An analytical sample, m.p. 95·5–96·0°, was obtained after two additional recrystallizations: λ_{max}^{KBr} 3·00 (OH), 9·20, 9·48, 9·49, 10·43, 12·30 and 13·93 μ; $\delta_{TMS}^{CDCl_3}$ 5·33 (olefinic C-H, broad), 4·08 (HOC<u>H</u>CH doublet, J = 6 Hz), 3;49 (HOMe), 3·41 (OH), and 1·69 ppm (vinylic Me). (Found: C, 73·2; H, 10·2. $C_{12}H_{20}O_2$ requires: C, 73·43; H, 10·27%).

1-(p-*Toluenesulfonoxymethyl*)-7-*methylbicyclo*[4.3.1]*dec-7-en-10α-ol* (**6**)*

To a soln containing 37·2 g (0·19 mole) diol **5** and 70 ml pyridine was added dropwise 43·8 g (0·23 mole) *p*-toluenesulfonyl chloride in 30 ml pyridine. After stirring for 72 hr at room temp, the mixture was poured onto ice, and the product was extracted with ether. Removal of solvent gave 65·6 g (98%) pink viscous oil that crystallized on standing. Material of analytical purity was obtained after three recrystallizations from ether–hexane: m.p. 96·5–97·0°; λ_{max}^{KBr} 2·83 (OH), 7·41, 8·37, 8·50, 10·37, 10·49, 11·50, and 14·92 μ; $\delta_{TMS}^{CCl_4}$ 7·68 (aromatic C-H, A_2B_2, J_{AB} = 8 Hz, $\Delta\nu_{AB}$ = 27 Hz), 5·33 (olefinic C-H, broad), 4·04 (HOC<u>H</u>CH doublet, J = 7 Hz), 3·83 (CH_2OTs, AB, J_{AB} = 10 Hz, $\Delta\nu_{AB}$ = 32 Hz), 2·68 (OH), 2·45 (<u>C</u>H$_3$C$_6$H$_4$), and 1·68 ppm (vinylic Me). (Found: C, 65·2; H, 7·5; S, 9·0. $C_{19}H_{26}O_4S$ requires: C, 65·11; H, 7·48; S, 9·15%).

Attempted hydrogenolysis of 1-*methanesulfonoxymethyl-7-methylbicyclo*[4.3.1]*dec-7-en-10α-ol* (**6**, Y = OMs)*

To a well-stirred soln of 3·25 g (16·6 mmoles) diol **5** in 10 ml pyridine at 0° was added 1·95 g (17·0 mmoles) methanesulfonyl chloride. After 1 hr at 0° and 1 hr at room temp, the mixture was diluted with water, and the product was isolated with ether. The solvent was distilled under reduced press to give 3·72 g (81%) light yellow oil: λ_{max}^{film} 2·83 (OH), 7·40, 8·50, 10·20, and 10·50 μ; $\delta_{TMS}^{CCl_4}$ 5·40 (vinylic C-H broad), 4·14 (vinylic C-H broad), 4·14 (OC<u>H</u>CH doublet, J = 6·5 Hz), 4·08 (CH_2OMs, AB pattern, J_{AB} = 10 Hz, $\Delta\nu$ = 28 Hz), 3·22 (OH), 3·05 ($MeSO_2$) and 1·71 ppm (vinylic Me).

The above hydroxy mesylate was added to a stirred suspension of 765 mg (20·0 mmoles) of LAH in 50 ml DME. The suspension was heated at reflux for 14 hr, cooled, and diluted with 100 ml ether. The mixture was processed to give 2·90 g (ca. 75%) oil that solidified on standing. Recrystallization from ether–hexane afforded 2·05 g (52%) crystaline diol **5** m.p. 92–93°: λ_{max}^{KBr} 3·00 (OH), 9·20, 9·48, 9·94, 10·43, 12·30, and 13·93 μ.

1,7-*Dimethylbicyclo*[4.3.1]*dec-7-en-10α-ol* (**7**)*

A. *Hydrogenolysis of hydroxy tosylate* **6**. To a stirred soln containing 13·9 g (0·34 mole) LAH in 250 ml DME was added 64·0 g (0·18 mole) hydroxy tosylate **6** in 150 ml DME at 0°. The cooling bath was removed and the mixture was stirred at reflux for 10 hr. A total of 150 ml DME was removed by distillation, the mixture was cooled, and 300 ml dry ether was added. The alcohol was isolated and distilled through a 6 in. Vigreaux column yielding 22·0 g (67%) oil: b.p. 72–78° (0·3 mm): n_D^{25} 1·5166: λ_{max}^{film} 2·90 (OH), 7·22, 9·22.

* The prefixes "α" and "β" are used to designate relative stereochemistry. As used here, β-substituents are *cis* to the C-1 (bridgehead) substituent. The cyclohexane ring serves as the reference for C-10 substituents.

9·59, and 12·32 μ; $\delta_{TMS}^{CCl_4}$ 5·38 (olefinic C—H, broad), 3·79 (HOCHCH doublet, J = 6 Hz), 2·08 (OH), 1·71 (vinylic Me) and 1·03 ppm (Me). The gas chromatogram* showed a single peak (retention time 4·5 min). (Found: C, 79·9; H, 11·2. $C_{12}H_{20}O$ requires: C, 79·95; H, 11·18%).

B. *Reduction of ketone* **8**. To a stirred suspension of 77 mg (2·02 mmoles) LAH in 5 ml ether was added 270 mg (1·52 mmoles) ketone **8** in 5 ml ether. The mixture was stirred for 2 hr at which time an aliquot was removed and processed. Since the reduction was not complete, the mixture was stirred for an additional 3 hr. Workup and distillation gave 240 mg (86%) of an alcohol, b.p. 52–54° (bath temp) at 0·1 mm. The IR spectrum and VPC retention time 17·3 min (peak enhancement) showed it to be identical with the material prepared in part A.

1,7-*Dimethylbicyclo*[4.3.1]*dec-7-en-10-one* (**8**)

A. *Cyclization of diketone* **14**. A 130-mg (0·45 mmole) sample of material containing 67% dione **14** was dissolved in 1 ml AcOH and added to 1 ml conc H_2SO_4 at 0°. After 15 min, the cooling bath was removed and the mixture was stirred for 1 hr at room temp. The deep red soln was poured in a fine stream into 50 ml of rapidly stirred ice-water and the product was isolated with ether. Distillation [b.p. 50–110° (bath) at 0·1 mm] gave 51 mg (64%) of an oil: λ_{max}^{film} 5·87 (CO), 6·00 (CO), and 6·21 (C=C). The gas chromatogram† gave peaks at 11·0 (**8**, 44%), 22·0 (7%), 30·1 (**15**, 36%), and 34·3 min (**14**, 13%).

B. *Oxidation of alcohol* **7**. A soln containing 11·51 g (63·8 mmoles) alcohol **7** in 65 ml acetone at 0° was treated with 18 mol Jones reagent[22] and the product was isolated with ether. Distillation gave 10·12 g (88%) mobile liquid: b.p. 50–52° (0·1 mm); n_D^{25} 1·5018; λ_{max}^{film} 5·83 (CO), 5·98 (C=C), 7·22, 8·23, 8·62, 8·80, 9·84, 10·60, 10·88, 11·43, 11·97, 12·18, 12·44, 12·90, and 13·20 μ; $\delta_{TMS}^{CCl_4}$ 5·60 (olefinic C—H, broad), 2·76 (CH_2CHCO complex triplet), 2·31–2·08 (H-9, eight lines, split AB pattern), 1·74 (vinylic Me), and 1·02 ppm (Me). The gas chromatogram gave one peak (retention time 11·0 min).

The analytical specimen, b.p. 47–49° (bath) at 0·1 mm, was prepared by short path distillation. (Found: C, 81·1; H, 10·2. $C_{12}H_{18}O$ requires: C, 80·85; H, 10·18%).

2-*Methyl*-2-(3-*chlorocrotyl*)*cycloheptanone* (**12**)

A 7·77-g sample (55·6 mmoles) of **11**[23] (90% pure) was heated at reflux for 3 hr with 1·40 g (61·6 mmoles) $NaNH_2$ in 40 ml of benzene. The soln was cooled, 11·68 g (95·5mmoles) 1,3-dichloro-2-butene in 20 ml benzene was added, and the mixture was maintained at reflux for 2 hr. The cooled soln was poured into dil HCl, and the product was isolated with ether. Distillation at 74–77° (0·1 mm) yielded 10·13 g (85%) oil. The gas chromatogram exhibited peaks at 15·4 (**13**, 14%) and 17·0 min (**12**, 86%).

An analytical sample **12** was prepared by formation of the hydroxymethylene derivative which was isolated *via* extraction with alkali and deformylated with Na_2CO_3 aq. The product, b.p. 69–72° (bath temp) at 0·1 mm, was distilled twice: n_D^{25} 1·4968; λ_{max}^{film} 5·88 (CO), 5·99 (C=C), 7·24, 8·52, 9·51, and 10·60 μ; $\delta_{TMS}^{CCl_4}$ 5·46 (CH_2CH=C triplet, J = 7·5 Hz), 2·33 (CH_2CH=C doublet, J = 7·5 Hz), 2·14 (vinylic Me), 1·64 (ring envelope) and 1·02 ppm (Me). (Found: C, 67·35; H, 9·0; Cl, 16·8. $C_{12}H_{19}ClO$ requires: C, 67·12; H, 8·92; Cl, 16·51%).

2-*Methyl*-2-(3-*oxobutyl*)*cycloheptanone* (**14**)

A 1·01-g sample (4·72 mmoles) chlorocrotyl ketones **12** and **13** (an 86:14 mixture) was added to 10 ml of ice cold conc H_2SO_4 in a large test tube and N_2 was bubbled through the soln by means of a sintered glass dispersion tube for 15 min. The red-orange soln was poured in a fine stream into 125 ml rapidly stirred ice-water. The mobile oil was isolated with ether and distilled, b.p. 65–70° (bath temp) at 0·05 mm, yielding 838 mg (91%) of a mixture of products: λ_{max}^{film} 5·82 (CO), 5·88 (CO), 5·98 (CO), 7·28, 7·37, 8·53, 9·42, 10·40, and 10·60 μ. Peaks at 21·6 (**15**, 22%), 22·4 (**12**, 11%) and 26·0 min (**14**, 67%) were observed in the gas chromatogram.†

1-*Methylbicyclo*[5.4.0]*undec-7-en-9-one* (**15**)

A soln of 404 mg (ca. 2·0 mmoles) dione **14** in 2·0 ml 3M ethanolic KOH was allowed to stand for 3 hr. The mixture was poured into brine and the product was isolated with ether. Distillation [100–120° (bath temp) at 0·1 mm] afforded 300 mg (85%) enone **15**: $\lambda_{max}^{95\%\ EtOH}$ 241 mμ (ε 10,000); λ_{max}^{film} 5·98 (CO), 6·18 (C=C).

* See footnote † on page 2175.

† A 20 ft × ¼ in. column of 20% Carbowax 20-M on 60–80 mesh Chromosorb W was used for this analysis.

7·33. 7·52. 7·86. 7·92. 8·03. 8·10. 8·36. and 10·22 μ; $\delta_{TMS}^{CCl_4}$ 5·79 (C=CHCO). and 1·19 ppm (Me). The semicarbazone derivative. m.p. 204–205°. was recrystallized from EtOH. (Found: C. 66·1; H. 9·1; N. 17·8. $C_{13}H_{21}N_3O$ requires: C. 66·35; H. 8·99; N. 17·86%).

1.7α-*Dimethylbicyclo*[4.3.1]*decan*-10α-*ol* (**16e**)*

A. *Hydrogenation of unsaturated alcohol* **7**. To a soln of 11·30 g (62·80 mmoles) alcohol **7** in 30 ml AcOH was added 150 mg PtO_2. The mixture was hydrogenated at atm press for 30 min. The catalyst was removed by filtration. the filtrate was neutralized with cold 10% NaOH aq. and the product was isolated with ether. Removal of solvent and distillation at 60–63° (0·15 mm) gave 10·10 g (88%) oil: λ_{max}^{film} 2·91 (OH). 9·17. 9·71. 10·30. 10·68. and 11·00 μ; $\delta_{TMS}^{CCl_4}$ 3·46 (HOCHCH doublet. J = 4·5 Hz). 1·81 (OH). 1·00 (Me). and 0·93 ppm (Me doublet. J = 5 Hz). The gas chromatogram† indicated an 85:15 mixture of alcohols **16e** and **19e** (t_R = 20·8 and 22·7 min).

Alcohol **16e** was obtained in pure form by the following procedure. The above described 85:15 mixture of alcohols **16e** and **19e** was oxidized with Jones reagent[22] affording 10·10 g of an 85:15 mixture of ketones **17** and **18**. This mixture was hydrogenated at atm press over 0·3 g PtO_2 in 30 ml AcOH for 24 hr. The mixture was filtered. the filtrate was neutralized with 10% NaOH aq and the product was isolated with ether affording 10·0 g (99%) oil which was chromatographed on 750 g alumina. Ketone **18** (0·98 g. 9%) was eluted with 1:1 hexane–benzene and alcohol **16e** (7·81 g. 79%) was eluted with 10 to 25% ether in benzene. The alcohol fractions distilled at 58–60° (0·1 mm) and solidified on cooling. m.p. 29–31°: λ_{max}^{film} 2·91 (OH). 7·28. 9·17. 9·72. 9·98. 10·30. 10·68. and 11·02 μ. (Found: C. 79·05; H. 12·0. $C_{12}H_{22}O$ requires: C. 79·06; H. 12·16%).

B. *Reduction of ketone* **17** *with lithium aluminum hydride*. To a stirred suspension of 190 mg (5·00 mmoles) LAH in 20 ml ether was added 98 mg (0·55 mmole) ketone mixture (85% **17** and 15% **18**) in 5 ml ether. The mixture was stirred for 1 hr and the product was isolated with ether. Distillation afforded 75 mg (76%) oil. b.p. 55–60° (bath temp) at 0·1 mm. which was shown to be an 85:15 mixture of alcohols **16e** and **19e** by VPC analysis (peak enhancement).†

C. *Meerwein–Ponndorf reduction of ketone* **17**. A mixture of 190 mg (1·05 mmoles) ketone **17**. 408 mg (2·00 mmoles) aluminum isopropoxide. 25 ml isopropyl alcohol. and 1 ml acetone was heated at reflux for 48 hr. About 15 ml solvent was removed by distillation. The aluminum-alkoxide containing residue was neutralized with cold aqueous 5% H_2SO_4. and the product mixture (183 mg. 96%) was isolated with ether. The gas chromatogram‡ showed peaks at 10·0 (**17**. 26%). 16·8 (**16e**. 45%) and 17·1 min (**16a**. 29%). Thus under these conditions. a 61:39 mixture of alcohols **16e** and **16a** was formed.

A 105-mg (0·58 mmole) sample of the above mixture was oxidized with Jones reagent.[22] giving 94 mg (90%) ketone **17**: λ_{max}^{film} 5·88 (CO). 7·24. 8·32. 8·93. 9·37. 10·60. 10·90. and 11·09 μ. The gas chromatogram* exhibited one peak at 10·0 min.

1.7α-*Dimethylbicyclo*[4.3.1]*decan*-10-*one* (**17**)*

A soln contained 630 mg (3·46 mmoles) alcohol **16e** in 15 ml acetone at 0° was treated with 1·2 ml Jones reagent.[22] and the product was isolated with ether. Distillation [45–55° (bath temp) at 0·1 mm] afforded 560 mg (90%) oil: n_D^{25} 1·4892; λ_{max}^{film} 5·88 (CO). 7·24. 8·32. 8·93. 9·37. 10·60. 10·90. and 11·09 μ; $\delta_{TMS}^{CCl_4}$ 0·98 (Me) and 0·97 ppm (CH_3CH doublet. J = 6 Hz): 2,4-dinitrophenylhydrazone derivative. m.p. 117–118°. (Found: C. 79·8; H. 11·2. $C_{12}H_{20}O$ requires: C. 97·95; H. 11·18%). 2,4 Dinitrophenylhydrazone: (Found: C. 59·9; H. 6·6. $C_{18}H_{23}N_4O_4$ requires: C. 59·96; H. 6·71%).

1.7β-*Dimethylbicyclo*[4.3.1]*decan*-10-*one* (**18**)*

A. *Hydrogenation of unsaturated ketone* **8**. A 10·10-g (56·20 mmoles) sample of ketone **8** in 35 ml abs EtOH was stirred over 150 mg reduced PtO_2 in an atmosphere of H_2 until 1·1 equivs of H_2 were taken up. After 5 hr. the mixture was filtered through a pad of diatomaceous earth and the filtrate was concentrated under reduced press. Distillation afforded 8·61 g (86%) oil. b.p. 52–53° (bath temp) at 0·1 mm: λ_{max}^{film} 5·87 (CO). 7·25. 8·32. 8·90. 9·70. and 10·90 μ; $\delta_{TMS}^{CCl_4}$ 0·98 (Me) and 0·94 ppm (CH_3CH doublet. J = 8 Hz). The gas chromatogram† showed peaks at 11·3 (**18**, 80%) and 13·0 min (**17**, 20%).

* See footnote* on page 2176.

† A 10 ft. × ¼ in. column of 10% Ucon 75H. 90.000 polar on 60–80 mesh Gas Pack W was used for this analysis.

‡ A 22 ft. × ⅛ in. column of 1% Carbowax 20-M on 80–100 mesh AW-DMCS Chromosorb G was used for this analysis.

Pure ketone **18** was obtained as follows. A solution containing 7·92 g (44·0 mmoles) ketone mixture (80% **18** and 20% **17**) in 30 ml AcOH was hydrogenated in a Parr apparatus with 250 mg PtO_2 at an initial press of 50 p.s.i. After 5 hr. the rate of hydrogenation decreased markedly. The mixture was filtered through diatomaceous earth and the filtrate was cooled and neutralized with 10% NaOH aq. The product was isolated with ether affording 7·38 g (ca. 93%) material which was chromatographed on 300 g alumina. A total of 4·99 g (63%) ketone **18** was eluted with 1:1 hexane–benzene and 1·02 g (13%) alcohol **16e** was obtained by elution with 10% ether in benzene.

The analytical sample was secured by three successive distillations: b.p. 52–55° (bath temp) at 0·1 mm: n_D^{25} 1·4876: λ_{max}^{film} 5·87 (CO). 7·25. 8·32. 8·88. 9·70. 10·02. 10·60. and 10·90 μ; 2,4-dinitrophenylhydrazone. m.p. 99–100°. (Found: C. 79·9; H. 11·1. $C_{12}H_{20}O$ requires: C. 79·95; H. 11·18%).

B. *Oxidation of alcohol* **19e**. To a soln of 7·99 g (45·0 mmoles) alcohol mixture (80% **19e** and 20% **16e**) in 50 ml acetone was added 12 ml Jones reagent.[22] Workup afforded 7·92 g (98%) of an 80:20 mixture of ketones **18** and **17** according to chromatography.*

1.7β-*Dimethylbicyclo*[4.3.1]*decan*-10α-*ol* (**19e**)†

A. *Reduction of ketone* **18** *with lithium aluminum hydride*. A mixture of 252 mg (6·6 mmoles) LAH. 1·40 g (7·78 mmoles) pure ketone **18** and 20 ml ether was stirred at room temp for 6 hr. Workup gave 1·37 g (96%) of a single alcohol epimer. An analytical sample was obtained by short-path distillation: b.p. 55–57° (bath temp) at 0·1 mm: m.p. 48–53°: λ_{max}^{film} 2·98 (OH). 9·32. 9·62. 9·74. 10·30. 10·63. and 10·98 μ: $\delta_{TMS}^{CCl_4}$ 3·68 (HOC<u>H</u>CH doublet. J = 5 Hz). 1·78 (OH). 1·02 (<u>CH</u>$_3$CH doublet. J = 7 Hz) and 1·01 ppm (Me). The gas chromatogram* exhibited one peak at 19·8 min. (Found: C. 79·1: H. 12·2. $C_{12}H_{22}O$ requires: C. 79·06: H. 12·16%).

B. *Meerwein–Ponndorf reduction of ketone* **18**. A mixture of 180 mg (1·00 mmole) ketone **18**. 408 mg (2·00 mmoles) aluminum Isopropoxide. 25 ml isopropyl alcohol. and 1 ml acetone was heated at reflux for 48 hr. About 15 ml solvent was removed by distillation. The aluminum-alkoxide containing residue was neutralized with cold aqueous 5% H_2SO_4 aq. and the product mixture (170 mg. 94%) was isolated with ether. The gas chromatogram‡ exhibited peaks at 9·2 (**18**. 57%). 13·5 (**19a**. 7%) and 15·4 min (**19e**. 36%). Thus. under these conditions an 84:16 mixture of alcohols **19e** and **19a** was formed.

A 95-mg (0·52 mmole) sample of the above mixture was oxidized with Jones reagent.[22] giving 87 mg (93%) ketone **18**: λ_{max}^{film} 5·87 (CO). 7·25. 8·32. 8·88. 9·70. 10·02. 10·60. and 10·90 μ. The gas chromatogram‡ showed one peak (9·2 min).

Competitive hydrogenation of 1.7α- *and* 1.7β-*dimethylbicyclo*[4.3.1]*decan*-10-*one* (**17**) *and* (**18**)†

A 1:1 mixture of ketones **17** and **18** [120 mg (0·67 mmole)] in 6 ml AcOH was stirred with 20 mg PtO_2 in an atmosphere of H_2. The uptake of H_2 (0·5 molar equiv) ceased after 1 hr. The soln was filtered free of catalyst. and the product. 107 mg (89%). was isolated with ether. The gas chromatogram* showed components at 11·8 (**18**. 49%). 13·4 (**17**. 2%). 21·5 (**19e**. 1%). and 23·1 min (**16e**. 48%).

1.7α-*Dimethylbicyclo*[4.3.1]*decan*-10α-*ol methanesulfonate* (**20**)†

A soln of 1·37 g (7·52 mmoles) alcohol **16e** in 7 ml pyridine at 0° was treated with 950 mg (8·27 mmoles) methanesulfonyl chloride. The cooling bath was removed. and the soln was stirred for 14 hr at room temp. The mixture was poured onto ice. and the oily mesylate **20** (1·90 g. 97%). was isolated with ether: λ_{max}^{film} 7·42. 8·48. 10·76. 10·98. and 11·42 μ; $\delta_{TMS}^{CCl_4}$ 4·73 (OC<u>H</u>CH doublet. J = 5·5 Hz). 2·90 ($MeSO_2$). 1·12 (MeCH doublet. J = 6·5 Hz). and 1·07 ppm (Me).

This mesylate decomposed into a mixture of unsaturated hydrocarbons on standing at room temp for 20 hr.

2α.8α-*Dimethyl*-cis(7βH)-*bicyclo*[5.3.0]*decan*-2β-*ol acetate* (**21**)†

This procedure is based on the method of Foote and Woodward.[18] A 184-mg (0·71 mmole) sample of mesylate **20** was stirred with 2·8 ml 0·5M KOAc in AcOH for 48 hr at room temp. The soln was cooled. neutralized with dil NaOH aq. and the product was isolated with 1:1 ether–hexane. Removal of solvent

* See footnote† on page 2178.

† See footnote* on page 2176.

‡ See footnote‡ on page 2176.

afforded 125 mg of a 3:2 mixture of olefins and acetates: λ_{max}^{film} 5·76 (CO). 7·27. 8·02. and 8·32 μ. The gas chromatogram* of the olefin portion of the mixture gave peaks at 10·4 (**24**. 4%). 12·2 (**23**. 2%). 14·3 (3%). 16·6 (**22**. 82%). and 18·5 min (9%). The gas chromatogram† of the acetate portion of the mixture exhibited peaks at 13·7 (5%). 14·8 (5%). 18·6 (**21**. 80%). and 22·6 min (10%).

The acetate **21** was purified by column chromatography on Florisil: b.p. 65–70° (bath temp) at 0·2 mm: λ_{max}^{film} 5·76 (CO). 7·27. 8·02. and 8·32 μ; $\delta_{TMS}^{CCl_4}$ 1·98 ($MeCO_2$). 1·48 (Me). and 0·91 ppm ($\underline{CH_3}CH$ doublet. J = 6 Hz).

When the acetate mixture was subjected to the solvolysis conditions (0·5M KOAc in AcOH. 3 hr. 118°) an olefin mixture was obtained with peaks at 10·4 (**24**. 9%). 12·2 (**23** trace). 14·3 (3%). 16·6 (**22**. 83%). and 18·5 min (4%) in the gas chromatogram.*

syn-2.8-*Dimethylbicyclo*[5.3.0]*dec*-1-*ene* (**22**)

The procedure of Foote and Woodward[18] was employed. The mesylate **20**. (1·44 g. 5·54 mmoles) was dissolved in 22 ml 0·5M KOAc in AcOH. The soln was heated at reflux for 3 hr. cooled. neutralized with 10% NaOH aq. and the products were isolated with ether. Careful removal of solvent gave 850 mg (94%) mobile oil: b.p. 110–120° at 16 mm (Hickman still): λ_{max}^{film} 7·24. 7·40. 8·65. 9·38. 9·63. 11·25. and 12·33 μ: $\delta_{TMS}^{CCl_4}$ 1·60 (vinylic Me) and 0·85 pp. ($\underline{CH_3}CH$ doublet. J = 7 Hz). The gas chromatogram* showed peaks at 9·1 (**24**. 10%). 10·4 (trace). 12·2 (**23**. 4%). 14·1 (**22**. 82%). and 15·6 min (3%).

The analytical sample. n_D^{25} 1·4952. was obtained by preparative gas chromatography.‡ (Found: C. 87·7: H. 12·2. $C_{12}H_{20}$ requires: C. 87·73: H. 12·27%).

Equilibration of syn *and* anti-2.8-*dimethylbicyclo*[5.3.0]*dec*-1-*ene* (**22**) *and* (**27**).

Preparation of 2.8-*dimethylbicyclo*[5.3.0]*dec*-1(7)-*ene* (**24**) *and* 2.8-*dimethylbicyclo*[5.3.0]*dec*-7-*ene* (**23**). A 60-mg (0·37 mmole) sample olefin **22** was heated at reflux with 25 mg *p*-toluensulfonic acid monohydrate and 5 ml AcOH for 4 hr. Workup gave 49 mg (82%) olefin mixture. In the same manner 60 mg olefin **27** was converted into the identical product mixture [51 mg (85%)]. The gas chromatogram* of each mixture gave peaks at 8·1 (1%). 8·9 (**24**. 21%). 10·4 (**27**. 22%). 12·4 (**23**. 54%). and 13·7 min (**22**. 2%).

A large sample of the equilibrium mixture was prepared as follows. A soln of 1·20 g (4·61 mmoles) mesylate **20** and 440 mg (4·50 mmoles) anhydrous KOAc in 9 ml AcOH was heated at reflux for 4 hr. The deep purple soln was poured onto ice and neutralized with 10% NaOH aq. The olefin mixture. 750 mg (99%). was isolated with ether. The gas chromatogram* exhibited peaks at 8·0 (trace). 8·8 (**24**. 22%). 10·3 (**27**. 20%). 12·3 (**23**. 55%). and 13·6 min (**22**. 2%). Each olefin was isolated by preparative gas chromatography.‡ anti-2.8-*Dimethylbicyclo*[5.3.0]*dec*-7-*ene* (**23**); n_D^{25} 1·4924; λ_{max}^{film} 7·24, 7·52, 8·18, 8·48, 8·67, 8·80, 9·30, and 11·08 μ; $\delta_{TMS}^{CCl_4}$ 1·58 (vinylic Me). and 0·81 ppm ($\underline{CH_3}CH$ doublet. J = 7 Hz). (Found: C. 87·7: H. 12·2. $C_{12}H_{20}$ requires: C. 87·73: H. 12·27%).

2.8-*Dimethylbicyclo*[5.3.0]*dec*-1(7)-*ene* (**24**): n_D^{25} 1·4854; λ_{max}^{film} 7·25. 7·52. 9·02. 10·08. 10·40. 11·70. and 12·48 μ; $\delta_{TMS}^{CCl_4}$ 1·04 ($\underline{CH_3}CH$ doublet. J = 7·5 Hz). and 0·96 ppm ($\underline{CH_3}CH$ doublet. J = 6·5 Hz). (Found: C. 87·4: H. 12·1. $C_{12}H_{20}$ requires: C. 87·73: H. 12·27%).

anti-2.8-*Dimethylbicyclo*[5.3.0]*dec*-1-*ene* (**27**): n_D^{25} 1·4902: λ_{max}^{film} 7·24. 8·00. 8·67. 9·30. 9·47. 10·12. and 12·12 μ: $\delta_{TMS}^{CCl_4}$ 1·63 (vinylic Me) and 1·02 ppm ($\underline{CH_3}CH$ doublet. J = 5 Hz).

1.4-*Dimethylazulene* (**25**)

A. *From* syn-2.6-*dimethylbicyclo*[5.3.1]*dec*-1-*ene* (**22**). In a 10 ml flask fitted with a condenser and a gas inlet tube was placed 570 mg (3·48 mmoles) olefin **22** and 446 mg (13·9 mmoles) sublimed sulfur. The mixture was heated under N_2 at 210–220° for 2 hr. On cooling the dark solid mass was triturated repeatedly with hexane. The hexane soln was washed with 10% NaOH aq and water and dried over $MgSO_4$. The green soln was concentrated to a volume of 20 ml and extracted three times with 10 ml portions conc phosphoric acid. The orange acid extracts were poured in a fine stream into 300 ml ice-water to liberate the azulene which was then isolated with hexane. Distillation, 80–85° (bath temp) at 11 mm, gave 23 mg (4%) blue-black oil; λ_{max}^{film} 6·24, 7·24, 9·72, 12·86, and 13·45 μ. The 1,3,5-trinitrobenzene derivative was

* See footnote † on page 2175.

† See footnote † on page 2178.

‡ A 12 ft × ½ in. column of 20% Carbowax 20-M on 60–80 mesh Chromosorb W was employed.

prepared. A mixture of 22 mg (0·14 mmole) azulene **25**, 26 mg (0·14 mmole) recrystallized 1,3,5-trinitrobenzene (m.p. 122–123°), and 2 ml abs EtOH was heated at gentle reflux for 5 min on cooling, 25 mg (50%) deep purple needles was obtained, m.p. 174–175° (lit.[33] m.p. 177–178°).

B. *From* anti-2.8-*dimethylbicyclo*[5.3.0]*dec*-1-*ene* (**27**). In the above manner. 820 mg (5·00 mmoles) olefinic **27** and 640 mg (20·0 mmoles) sulfur were heated until no more gas was given off (15 min). Workup and distilation gave 56 mg (7%) blue oil: b.p. 80–85° (bath temp) at 11 mm; λ_{max}^{film} 6·24. 7·24. 9·72. 12·85. and 13·45 μ; 1.3.5-trinitrobenzene derivative; purple needles. m.p. 176–177°. A 1:1 mixture with the azulene derivative prepared in part A. gave no m.p. depression.

1.7β-*Dimethylbicyclo*[4.3.1]*decan*-10α-*ol methanesulfonate* (**26**)*

To a soln containing 1·44 g (7·92 mmoles) alcohol **19e** and 7 ml dry pyridine at 0° was added 1·00 g (8·72 mmoles) methanesulfonyl chloride. The resulting soln was stirred for 12 hr at room temp. the mixture was poured onto ice. and the product was isolated with ether. affording 1·95 g (95%) crude mesylate **26**: λ_{max}^{film} 7·42. 8·48. 10·56. 10·72. 10·96. and 11·40 μ; $\delta_{TMS}^{CCl_4}$ 4·53 (O<u>C</u>HCH doublet. J = 5·5 Hz). 2·92 ($MeSO_2$). 1·07 (Me) and 0·99 ppm (<u>C</u>H_3CH doublet. J = 6·5 Hz). This material was used in subsequent experiments without further purification.

anti-2.8-*Dimethylbicyclo*[5.3.0]*dec*-1-*ene* (**27**). The method of Foote and Woodward[18] was used. To 30 ml 0·5M KOAc in AcOH was added 1·90 g (7·30 mmoles) mesylate **26**, and the soln was stirred at reflux for 3 hr. The cooled mixture was neutralized with dil NaOH aq. and saturated with NaCl. The products. 1·18 g (97%). were isolated with ether and distilled: b.p. 100–120° at 16 mm (Hickman still): λ_{max}^{film} 7·24. 8·00. 8·66. 9·30. 9·47. 10·12. and 12·12 μ: $\delta_{TMS}^{CCl_4}$ 1·63 (vinylic Me) and 1·02 ppm (<u>C</u>H_3CH doublet. J = 5 Hz). Peaks at 8·9 (3%). 10·0 (**24**. 10%). 11·6 (**27**. 82%). and 13·5 min (5%) were observed in the gas chromatogram.† The analytical sample. n_D^{25} 1·4886. was secured by preparative gas chromatography.‡ (Found: C. 87·5: H. 12·4. $C_{12}H_{20}$ requires: C. 87·73: H. 12·27%).

cis-3-*Methyl*-2-(5-*oxohexyl*)*cyclopentanone* (**29**). A soln of 340 mg (2·07 mmoles) olefin **22** in 25 ml 1:1 methylene chloride–pyridine was treated at −70° with 5% ozonized O_2. When the reaction was complete. the cold mixture was treated with 2·ml 36% aqueous formaldehyde soln. and allowed to warm to room temp and stand for 1 hr. The soln was diluted with water. and the product was extracted with ether. The extracts were washed with 5% H_2SO_4 aq. $FeSO_4$–2% H_2SO_4 aq. water. $NaHCO_3$ aq. and saturated brine. After drying over $MgSO_4$. the ether was removed under reduced press and the residue was chromatographed on 50 g Florisil. The 50% ether–benzene fractions gave 191 mg (48%) mobile oil. b.p. 78–81° at 0·1 mm (bath temp): λ_{max}^{film} 5·76 (CO). 5·84 (CO). 7·08. 7·35. and 8·58 μ: $\delta_{TMS}^{CCl_4}$ 2·04 (MeCO). and 0·88 ppm (<u>C</u>H_3CH doublet. J = 7 Hz). (Found: C. 73·4: H. 10·3. $C_{12}H_{20}O$ requires: C. 73·43: H. 10·27%).

trans-3-*Methyl*-2-(5-*oxohexyl*)*cyclopentanone* (**30**). According to the above procedure. 370 mg (2·26 mmoles) olefin **27** in 25 ml 1:1 methylene chloride–pyridine was treated with 5% ozonized O_2. The product mixture (402 mg) was chromatographed on 35 g Florisil. The 20% ether–benzene fractions gave 200 mg (45%) pure dione **30**: b.p. 82–85° (bath temp) at 0·15 mm: λ_{max}^{film} 5·77 (CO). 5·84 (CO). 7·32. 8·03. 8·60. and 9·43 μ: $\delta_{TMS}^{CCl_4}$ 2·01 (MeCO). and 1·13 ppm (<u>C</u>H_3CH doublet. J = 6 Hz). (Found: C. 73·45: H. 10·1. $C_{12}H_{20}O_2$ requires: C. 73·43: H. 10·27%).

3-*Methyl*-2-(3-*oxobutyl*)*cycloheptanone* (**36**)

In the above manner. 97 mg (0·59 mmole) purified olefin **23** in 25 ml 1:1 methylene chloride–pyridine was treated at −70° with 5% ozonized O_2. The product was chromatographed on 10 g Florisil. The dione. 178 mg (51%). was eluted with 20% ether–benzene and distilled: b.p. 80–84° at 0·1 mm (bath temp): λ_{max}^{film} 5·83 (CO). 5·87 (CO). 7·30. 8·52. and 10·40 μ: $\delta_{TMS}^{CCl_4}$ 2·03 (MeCO). and 1·05 ppm (<u>C</u>H_3CH doublet. J = 5 Hz).

Ethyl 5-*methyl*-4-*oxocycloheptanecarboxylate* (**38**)

In a 2-l. Erlenmeyer flask containing 1·0 l. 0·40M ethereal diazoethane[34] at −10° was placed 55·60 g (326·0 mmoles) keto ester **37**[35] in 250 ml EtOH. After 5 hr gas evolution ceased and AcOH was added to decompose the excess diazoethane. The ether soln was washed with sat $NaHCO_3$ aq. and dried over $MgSO_4$. Distillation gave 58·95 g (91%). b.p. 65–68° (0·1 mm) fragrant oil shown by NMR analysis to be a 1:1 mixture of epimers: λ_{max}^{film} 5·78 (CO). 5·87 (CO). 7·25. 7·62. 8·01. 8·45. and 9·62 μ: $\delta_{TMS}^{CCl_4}$ 4·10 (O<u>C</u>$H_2$$CH_3$

* See footnote* on page 2176.

† See footnote† on page 2175.

‡ See footnote‡ on page 2180.

quartet. J = 7 Hz). 1·23 (O$\underline{CH_2}CH_3$ triplet. J = 7 Hz). 1·02 ($\underline{CH_3}CH$ doublet. J = 7 Hz). and 1·00 ppm ($\underline{CH_3}CH$ doublet. J = 7 Hz). Only one component was detected in the gas chromatogram.* t_r 11·6 min. (Found: C. 67·0: H. 9·2. $C_{11}H_{16}O_3$ requires: C. 66·64: H. 9·15%).

Attempted preparation of ethyl 2-methyl-2-(3-chlorocrotyl)cycloheptanone-5-carboxylate (**39**)

Ethyl 3-(3-methyl-2-ococyclopentyl)propanoate (**41**). A soln of 460 mg (2·32 mmoles) keto ester **38**. 95 mg (2·43 mmoles) sodium amide. and 10 ml benzene was heated at reflux for 4 hr. On cooling. 305 mg (2·43 mmoles) distilled 1.3-dichloro-2-butene in 5 ml benzene was added and the mixture was stirred at reflux for 2 hr. The cooled soln was poured into dil HCl aq and the product was isolated with ether. Distillation [80–85° (bath temp) at 0·1 mm] yielded 402 mg (87%) sweet smelling oil: λ_{max}^{film} 5·77 (CO). 7·27. 7·58. 8·05. 8·46. and 9·62 μ: $\delta_{TMS}^{CCl_4}$ 4·08 (O$\underline{CH_2}$Me quartet. J = 7 Hz). 1·23 (OCH$_2\underline{Me}$ triplet. J = 7 Hz). and 1·06 ppm ($\underline{CH_3}CH$ doublet. J = 6·5 Hz). The gas chromatogram* exhibited one peak. (t_r 9·9 min).

This compound was obtained under a variety of conditions. For example. 1·02 g (5·15 mmoles) keto ester **38** was heated at reflux with 10 ml EtOH containing ca. 15 mg NaOEt for 5 hr. The soln was cooled and diluted with water and the product was isolated with ether. Distillation gave 805 mg (79%) cyclopentanone **41**.

The 2.4-dinitrophenylhydrazone derivative exhibited m.p. 120·5–121·0° after three recrystallizations from EtOH. (Found: C. 54·1: H. 5·8: N. 14·9. $C_{17}H_{22}N_4O_6$ requires: C. 53·96: H. 5·86: N. 14·81%).

5-Hydroxymethyl-2-methylcycloheptanol (**42**). A mixture containing 58·8 g (0·30 mole) keto ester **38** and 15·2 g (0·40 mole) LAH in 500 ml DME was stirred at reflux for 12 hr. About one-half of the DME was removed by distillation. 350 ml ether was added, and the product was isolated in the usual manner. Removal of solvent afforded 46·52 g (99%) viscous gum: b.p. 100–105° (bath temp) at 0·1 mm: λ_{max}^{film} 3·00 (OH). 7·25. and 9·20–10·20 μ: $\delta_{TMS}^{CDCl_3}$ 3·80 [CH$\underline{CH}$(OH)CH$_2$. complex pattern]. 3·32 (O$\underline{CH_2}$CH doublet. J = 5 Hz). 3·28 (OH). and 0·95 ppm ($\underline{CH_3}CH$ doublet. J = 6·5 Hz).

5-(2-Tetrahydropyranyloxymethyl)-2-methylcycloheptanol (**43**)

The procedure of Barton *et al.*[36] was followed. A soln of 24·0 g (0·29 mole) distilled 2.3-dihydropyran in 50 ml THF was added slowly to a mixture of 46·52 g (0·29 mole) diol **42** and 1·0 ml distilled $POCl_3$ in 200 ml THF at 0°. After 1 hr. the cooling bath was removed and the mixture was stirred for 24 hr at room temp. The soln was poured into sat $NaHCO_3$ aq. and the product was isolated with ether yielding 62·88 g (ca. 89%) yellow oil: λ_{max}^{film} 2·90 (OH). 8·78. 8·90. 9·25. 9·70. 11·00. 11·48. and 12·30 μ.

5-(2-Tetrahydropyranyloxymethyl)-2-methylcycloheptanone (**45**)

Alcohol **43** (62·88 g. ca. 0·26 mole). was dissolved in 600 ml acetone and stirred at −20° while 90·0 ml Jones reagent[22] was added. After being manually swirled at −20° for 15 min. the mixture was treated with 2-propanol to destroy the excess oxidant. The mixture was diluted with water. and the product was isolated with ether giving 48·40 g (ca. 77%) of a mixture of products. A 12·00-g (ca. 50 mmoles) sample was chromatographed on 1200 g alumina which had been previously treated with 12 g pyridine. The fractions eluted with 5% and 10% ether–benzene afforded 5·50 g (46%) colorless oil. b.p. 118–130° (bath temp) at 0·1 mm. which was shown by NMR analysis to be a 1:1 mixture of epimers. The product exhibited: λ_{max}^{film} 5·87 (CO). 8·78. 8·88. 9·24. 9·64. 11·00. 11·48. and 12·25 μ: $\delta_{TMS}^{CCl_4}$ 4·50 [O$\underline{CH}$(CH$_2$)O. broad]. 1·04 ($\underline{CH_3}CH$ doublet, J = 7 Hz), and 1·02 ppm ($\underline{CH_3}CH$ doublet, J = 7 Hz).

5-Benzyloxymethyl-2-methylcycloheptanone (**46**)

A mixture consisting of 800 mg (16·77 mmoles) 50% oil dispersion of sodium hydride. 40 ml THF and. 2·19 g (13·9 mmoles) diol **42** was stirred at 25° for 1 hr. An insoluble alkoxide salt was formed. A soln of 3·52 g (27·8 mmoles) benzyl chloride in 10 ml distilled N.N-dimethylformamide was added. and the mixture was heated at reflux for 12 hr. The cooled mixture was poured into dil HCl aq. and the product was isolated with ether. The thick oil. 4·14 g (>100%). was chromatographed on 200 ml alumina. Elution with 20–75% ether in benzene and distillation [125–131° (bath temp) at 0·1 mm] gave 2·04 g (60%) of a mixture (mainly **44**) of mono alcohols: λ_{max}^{film} 2·91 (OH). 7·31. 9·02. 9·70. 13·56. and 14·32 μ.

This alcohol mixture was dissolved in acetone. and oxidized with 3 ml Jones reagent.[22] Distillation [88–96° (bath temp) at 0·05 mm] yielded 1·64 g (81%) keto ether **46**: λ_{max}^{film} 5·86 (CO). 7·31. 9·02. 13·55. and

* A 15 ft. × ¼ in. column of 10% DC-550 oil on 60–80 mesh Chromosorb W was used for this analysis.

14·32 μ: $\delta_{TMS}^{CCl_4}$ 7·33 (aromatic C—H). 4·45 ($C_6H_5\underline{CH_2}O$). 3·22 ($O\underline{CH_2}CH$ doublet. J = 6 Hz). 1·00 ($\underline{CH_3}CH$ doublet. J = 7 Hz). and 0·98 ppm ($\underline{CH_3}CH$ doublet. J = 7 Hz). The gas chromatogram* exhibited only one peak (10·4 min).

Attempted alkylation of 5-(2-tetrahydropyranyloxymethyl)-2-methylcycloheptanone (**45**) *with 1.3-dichloro-2-butene*

A 360-mg (1·50 mmoles) sample of ketone **45** was stirred at reflux with 78 mg (2·0 mmoles) sodium amide in 18 ml benzene for 4 hr. The soln was cooled. 250 mg (2·00 mmoles) 1.3-dichloro-2-butene in 2 ml benzene was added. and the mixture was heated at reflux for 2 hr. The soln was diluted with water and the product was isolated with ether. Removal of solvent and 1.3-dichloro-2-butene *in vacuo* gave 352 mg (97%) recovered ketone **45**: λ_{max}^{film} 5·87 (CO). 8·78. 8·88. 9·24. 9·64. 11·00. 11·48. and 12·25 μ: $\delta_{TMS}^{CCl_4}$ 4·50 [$O\underline{CH}(CH_2)O$. broad]. 1·04 ($\underline{CH_3}CH$ doublet. J = 7 Hz) and 1·02 ppm ($\underline{CH_3}CH$ doublet. J = 7 Hz).

Ketone **48** could not be prepared under a variety of alkylation conditions. Ketone **45** was always recovered unchanged.

Attempted alkylation of 5-benzyloxymethyl-2-methylcycloheptanone (**46**) *with 1.3-dichloro-2-butene*

A 280-mg (1·14 mmoles) sample of keto ether **46** was heated at reflux with 39 mg (1·00 mmole) sodium amide in 20 ml benzene for 3 hr. A soln of 250 mg (2·0 mmoles) 1.3-dichloro-2-butene in 2 ml benzene was added, and the mixture was heated at reflux for 36 hr. A solid ppt formed during this time, and the reaction mixture tested neutral with universal pH paper. The mixture was poured into dil HCl aq. and the product was isolated with ether. Distillation [100–110° (bath temp) at 0·1 mm] gave 250 mg (90%) of starting keto ether: λ_{max}^{film} 5·86 (CO). 7·31. 9·02. 13·55. and 14·31 μ. The gas chromatogram* showed one peak (10·4 min).

5-Benzyloxymethyl-2-methyl-2-allycycloheptanone (**49**)

A mixture of 246 mg (1·00 mmole) keto ether **46**. 37 mg (0·95 mmole) sodium amide. and 4 ml benzene was heated at reflux for 4 hr. A soln of 242 mg (2·00 mmoles) 3-bromopropene in 1 ml benzene was added and the soln was heated at reflux for 1 hr. The cooled mixture was poured into water and the product was isolated with ether. Distillation [138–152° (bath temp) at 0·1 mm] gave 236 mg (88%) oil: λ_{max}^{film} 5·88 (CO). 6·08 C=C). 7·32. 9·03. 9·71. 10·90. 13·55. and 14·30 μ: $\delta_{CHS}^{CCl_4}$ 7·32 (aromatic C—H). 4·80–5.68 (vinyl C—H. complex pattern). 4·46 ($PhCH_2O$). 3·23 ($O\underline{CH_2}CH$ doublet. J = 6 Hz). and 1·00 ppm(Me).

2.5-Dimethyl-2-(3-chlorocrotyl)cycloheptanone (**50**)

A mixture of 2·40 g (17·1 mmoles) 2.5-dimethylcycloheptanone[23] (**47**). 735 mg (18·8 mmoles) sodium amide. and 20 ml benzene was heated at reflux for 1 hr. To the cooled soln was added 2·50 g (20·0 mmoles) 1.3-dichloro-2-butene in 5 ml benzene. The mixture was heated at reflux for 30 min. cooled. and poured into HCl aq. The products were isolated with ether. Distillation at 65–100° (15 mm) gave 743 mg (31%) recovered ketone **47**. Distillation at 75–84° (0·1 mm) afforded 2·04 g (75%. based on recovered starting material) chlorocrotyl ketone **50**: λ_{max}^{film} 5·88 (CO). 6·01 (C=C). 8·55. 9·30. 9·52. and 9·68 μ: $\delta_{TMS}^{CCl_4}$ 5·41 ($CH_2\underline{CH}$=C. complex pattern). 2·09 (vinyl Me). 1·00 (Me) and 0·92 ppm (CH_3 doublet. J = 6 Hz).

3-[1-Methyl-5-(2-tetrahydropyranyloxymethyl)-2-oxocycloheptyl]propanonitrile (**51**)

To a mixture of 5·09 g (21·3 mmoles) ketone **45**. 5 ml DME, and 0·2 ml 30% methanolic KOH at 0° was added 1·68 g (31·8 mmoles) acrylonitrile. After 2 hr. the cooling bath was removed and the soln was stirred for 10 hr at room temp. The reaction mixture was poured into 100 ml water. and the product was isolated with ether. The thick oil. 6·15 g (ca. 99%). was chromatographed on 550 g alumina that. had been treated with 1% pyridine and 2% water. The early fractions eluted with benzene gave 383 mg (8%) starting material. Elution with 2% and 5% ether–benzene afforded 4·62 g (74%) cyano ketone **51**: λ_{max}^{film} 4·45 (CN). 5·88 (CO). 8·78. 8·88. 9·24. 9·63. 10·23. 10·98. 11·44. and 12·23μ.

3-(1-Methyl-5-hydroxymethyl-2-oxocycloheptyl)propanonitrile ethylene ketal (**52**)

A mixture containing 3·93 g (13·4 mmoles) cyano ketone **51**. 8·40 g (0·13 mole) ethylene glycol. and 0·1 g *p*-toluenesulfonic acid monohydrate in 100 ml benzene was heated at reflux for 72 hr with continuous azeotropic removal of water and ethylene glycol by means of a Dean–Stark trap. The cooled mixture was washed with water. and $NaHCO_3$ aq. saturated brine. and dried over $MgSO_4$. The solvent was distilled

* See footnote* on page 2182.

under reduced press yielding 3·36 g (99%) colorless cyano ketal **52**: λ_{max}^{film} 2·90 (OH), 4·46 (CN), 8·88, 9·28, 9·62, 10·47, and 11·00 μ; $\delta_{TMS}^{CDCl_3}$ 3·90 (OCH_2CH_2O), 3·37 ($HO\underline{CH}_2CH$ doublet, J = 5 Hz), 2·52 (OH), and 0·92 ppm (Me).

5-Hydroxymethyl-2-methyl-2-(3-oxobutyl)cycloheptanone ethylene ketal (**53**)

A 3·25-g (12·8 mmoles) sample of cyano ketal **52** in 100 ml ether was treated with 50 ml 1·0M (50 mmoles) ethereal MeLi. After 12 hr at room temp. the excess MeLi was destroyed by the cautious addition of NH_4Cl aq. The ketone **53** was isolated with ether, giving 3·42 g (98%) rancid smelling oil: λ_{max}^{film} 2·90 (OH), 5·83 (CO), 8·88, 9·28, and 9·62 μ; $\delta_{TMS}^{CDCl_3}$ 3·89 (OCH_2CH_2O), 3·37 ($HO\underline{CH}_2CH$ doublet, J = 5 Hz), 2·59 (OH), 2·13 (MeCO), and 0·87 ppm (Me).

5-Acetoxymethyl-2-methyl-2-(3-oxobutyl)cycloheptanone (**54**)

Keto alcohol **53** [3·25 g (12·0 mmoles)] was dissolved in 25 ml pyridine, 5·10 g (48·5 mmoles) 97% Ac_2O was added, and the soln was allowed to stand at room temp for 12 hr. The product was isolated with ether giving 3·64 g (97%) crude keto acetate. Distillation [182–187° (bath temp) at 0·1 mm] yielded 3·02 g (81%) colorless oil; λ_{max}^{film} 5·75 (CO), 5·83 (CO), 7·32, 8·02, 9·26, and 9·62 μ; $\delta_{TMS}^{CCl_4}$ 3·84 (OCH_2CH_2O), 3·78 ($O\underline{CH}_2CH$ doublet, J = 6·5 Hz), 2·03 (MeCO), 1·94 ($MeCO_2$), and 0·92 ppm (Me).

A soln of 2·39 g (7·65 mmoles) of the above ketal keto acetate in 10 ml AcOH was treated at 0° with 0·5 ml conc H_2SO_4. After 15 min, the red liquid was added in a fine stream to 100 ml of rapidly stirred ice-water. The produce was isolated with ether, and distilled [90–100° (bath temp) at 0·1 mm] giving 1·81 g (88%), fragrant oil λ_{max}^{film} 5·74 (CO), 5·82 (CO), 5·87 (CO), 7·30, 8·02, and 9·60 μ; $\delta_{TM}^{CCl_4}$ 3·83 ($O\underline{CH}_2CH$ doublet, J = 6 Hz), 2·04 (MeCO), 1·98 ($MeCO_2$) and 0·96 ppm (Me).

A mixture of products was obtained when this ketal was hydrolyzed with HCl-acetone soln: λ_{max}^{film} 2·92 (OH), 5·75 (CO, weak), 5·82 (CO, weak), 7·30, 8·02, and 9·50–9·75 μ.

4-Acetoxymethyl-1-methylbicyclo[5.4.0]*undec-7-en-9-one* (**55**) *and 4-acetoxymethyl-1,7-dimethylbicyclo* [4.3.1]*dec-7-en-10-one* (**56**)

A mixture of 1·00 g (3·73 mmoles) diketo acetate **54**, 9·5 g (5 ml) conc H_2SO_4 and 9·5 g (9 ml) AcOH was stirred at 0° for 1 hr and at room temp for 3 hr. The deep purple mass was poured in a fine stream into 200 ml rapidly stirred ice-water, and the product was isolated with ether giving 920 mg (98%) thick yellow oil which was chromatographed on 100 g alumina. The benzene and early 2% ether–benzene fractions afforded 180 mg (19%) of the desired keto acetate **56**; b.p. 78–81° (bath temp) at 0·1 mm; λ_{max}^{film} 5·74 (CO), 5·86 (CO), 7·23, 7·31, 8·03, 8·90, and 9·52 μ; $\delta_{TMS}^{CCl_4}$ 5·48 (olefinic C—H, broad), 3·79 ($O\underline{CH}_2CH$ doublet, J = 6 Hz), 2·72 ($CH_2C\underline{H}CO$, broad), 1·96 ($MeCO_2$), 1·73 (vinylic Me), and 1·02 ppm (Me).

The later 2% ether–benzene and 5% ether–benzene fractions gave 80 mg (8%) starting dione **54**, and the 10% and 20% ether–benzene fractions contained 455 mg (49%) keto acetate **55**; b.p. 105–111° (bath temp) at 0·1 mm; λ_{max}^{film} 5·74 (CO), 5·98 (CO), 7·22, 7·30, 8·02, 8·90, and 9·52 μ; $\delta_{TMS}^{CCl_4}$ 5·70 (C═CHCO), 3·94 ($O\underline{CH}_2CH$ doublet, J = 7 Hz), 1·98 ($MeCO_2$), and 1·02 ppm (Me).

4-(Hydroxymethyl)cyclohexanone ethylene ketal (**57**)

A mixture containing 115·0 g (0·68 mole) ethyl 4-oxocyclohexanecarboxylate (**37**).[35] 210·0 g (3·39 moles) ethylene glycol, and 0·25 g *p*-toluenesulfonic acid monohydrate in 1·21 benzene was heated at reflux for 12 hr with continuous azeotropic removal of water and excess ethylene glycol by means of a Dean–Stark trap. The cooled mixture was washed with water and sat $NaHCO_3$ aq, and dried over $MgSO_4$. The solvent was removed under reduced press yielding 144·5 g ketal ester; λ_{max}^{film} 5·78 (CO), 7·30, 7·60, 7·96, 8·40, 9·04, 9·62, 10·60, and 10·83 μ; $\delta_{TMS}^{CCl_4}$ 4·10 ($O\underline{CH}_2CH_3$ quartet, J = 7 Hz), 3·87 (OCH_2CH_2O), and 1·27 ppm ($OCH_2\underline{CH}_3$ (triplet, J = 7 Hz).

To a stirred suspension containing 26·6 g (0·70 mole) LAH in 1·25 l, anhydrous ether was added 144·5 g (0·68 mole) of the above ketal ester in 250 ml ether over a 45-min period. The soln was heated at reflux for 12 hr and cooled. The mixture was processed in the usual manner. Distillation through a 6 in Vigreaux column afforded 101·8 g (88%) hydroxy ketal **57**; b.p. 88–93° (0·05 mm); λ_{max}^{film} 2·94 (OH), 8·70, 8·97, 9·18, 9·60, 10·50, 10·68, and 11·17 μ; $\delta_{TMS}^{CCl_4}$ 3·87 (OCH_2CH_2O) 3·36 (O—$\underline{CH}$CH unresolved doublet) and 3·21 ppm (OH).

An analytical sample, b.p. 80–83° (bath temp) at 0·1 mm, was obtained on redistillation. (Found: C, 62·5; H, 9·2. $C_9H_{16}O_3$ requires: C, 62·77; H, 9·36%).

4-(Methanesulfonoxymethyl)cyclohexanone ethylene ketal (**58**)

A soln of 44·7 g (0·26 mole) hydroxy ketal **57** in 125 ml pyridine was cooled to 0° and 32·8 g (0·29 mole) methanesulfonyl chloride was added dropwise under N_2 over a 1-hr period. After standing for 2 hr at room temp. the mixture was poured onto crushed ice and the product was isolated with ether affording 61·10 g (94%) yellow solid: λ_{max}^{KBr} 7·38. 8·48. 8·95. 9·12. 10·20. 10·50. and 11·80 μ; $\delta_{TMS}^{CCl_4}$ 4·19 ($O\underline{CH_2}CH$ doublet. J = 6 Hz). 4·04 (OCH_2CH_2O). and 3·08 ppm ($MeSO_2$). An analytical sample. white needles m.p. 39·5–40·0°. was obtained after two recrystallizations from ether–hexane. (Found: C, 47·8; H, 7·1; S, 12·8. $C_{10}H_{18}O_3S$ requires: C, 47·98; H, 7·25; S, 12·81%).

4-(Phenyoxymethyl)cyclohexanone ethylene ketal (**59**)

To a stirred suspension of benzene-washed NaH [from 19·20 g (0·40 mole) of a 50% mineral oil dispersion] in 150 ml THF was added 13·67 g (54·60 mmoles) mesylate **58**, followed by 30·80 g (0·328 mole) distilled phenol. Hydrogen was evolved immediately and. when gas evolution ceased. the mixture was stirred at reflux for 24 hr. Water was added to the cooled soln and the product was extracted with ether. The ether extracts were washed with 10% NaOH aq. water. and saturated brine. and dried over $MgSO_4$. The solvent was distilled under reduced press and the solid residue was recrystallized from ether–hexane giving 10·21 g (75%) phenyl ether **59**: m.p. 68–70°; λ_{max}^{KBr} 6·23 (C=C). 6·68. 6·80. 8·03. 9·10. 9·58. 11·07. 13·06. and 14·32 μ: $\delta_{TMS}^{CCl_4}$ 7·73 (arom C—H. complex pattern). 3·98 (OCH_2CH_2O). and 3·89 ppm ($O\underline{CH_2}CH$ doublet. J = 5 Hz).

An additional 1·85 g (14%). m.p. 62–66°. was obtained from the mother liquor by a second recrystallization. The analytical sample. m.p. 70–71°. was prepared in the manner described below for ketal **60**. (Found: C. 72·5; H. 8·2. $C_{15}H_{20}O_3$ requires: C. 72·55; H. 8·12%).

4-(p-Chlorophenoxymethyl)cyclohexanone ethylene ketal (**60**)

To a stirred suspension of benzene-washed NaH [from 19·0 g (0·40 mole) of a 50% mineral oil dispersion] in 100 ml THF was added 50·8 g (0·40 mole) distilled *p*-chlorophenol. H_2 was immediately evolved. When gas evolution stopped. 33·00 g (0·132 mole) mesylate **58** in 50 ml THF was added and the mixture was stirred at reflux for 24 hr. Water was added to the cooled mixture and the ketal **60** was isolated with benzene. Since the product was contaminated with *p*-chlorophenol. the solid material was taken up in benzene. washed repeatedly with 10% NaOH aq. and water. and dried over $MgSO_4$. The solvent was removed under reduced press yielding 34·10 g (91%) white solid: λ_{max}^{KBr} 6·27. 6·31. (arom C=C). 6·69. 7·79. 8·03. 8·62. 8·98. 9·15. 9·60. 12·08. and 15·10 μ: $\delta_{TMS}^{CCl_4}$ 6·96 (arom C—H. A_2B_2. J_{AB} = 9 Hz. $\Delta\nu_{AB}$ = 24·5 Hz). 3·83 (OCH_2CH_2O). and 3·69 ppm ($O\underline{CH_2}CH$ doublet. J = 5 Hz).

Several recrystallizations from ether–hexane and sublimation. 40° (bath temp) at 0·1 mm. yielded material m.p. 56–57°. However. correct C. H. and Cl analyses could not be obtained owing to contamination by traces of *p*-chlorophenol. This contaminant was removed as follows. A mixture of 300 mg (1·06 mmoles) ketal **60**. 9 ml MeOH. and 1·0 g Na_2CO_3 aq was heated at reflux for 5 hr. The product was isolated with benzene and recrystallized twice from ether–hexane affording white platelets. m.p. 65·0–65·5°. (Found: C. 63·8: H. 6·6; Cl. 12·5. $C_{15}H_{19}ClO_3$ requires: C. 63·72; H. 6·77; Cl. 12·54%).

Hydrogenolysis of 4-(p-chlorophenoxymethyl)cyclohexanone ethylene ketal (**60**)

4-(Phenoxymethyl)cyclohexanone ethylene ketal (**59**). A mixture of 150 mg (0·53 mmole) chlorophenoxy ketal **60**, 100 mg (2·64 mmoles) LAH and 5 ml DME was heated at reflux for 36 hr, and cooled. Ether (10 ml) was added and the product was isolated giving 130 mg (99%) white solid. Recrystallization from ether–hexane gave 114 mg (87%) phenoxy ketal **59** as white needles. m.p. 66–68°: λ_{max}^{KBr} 6·23 (C=C). 6·68. 6·80. 8·03. 9·10. 9·58. 11·07. 13·06. and 14·32 μ.

4-(Phenoxymethyl)cyclohexanone (**61**)

An 8·35-g (34·4 mmoles) sample of ketal **59** in 75 ml acetone containing 3 ml water and 2 ml conc HCl aq was heated at reflux for 1 hr. diluted with water. and extracted with benzene. The combined extracts were washed with 10% NaOH aq. water. and brine. After drying. the solvent was removed under reduced press giving 6·64 g (95%) yellow solid: λ_{max}^{KBr} 5·81 (CO), 6·22 (C=C), 6·67, 6·78, 7·97, 8·46, 9·52, 13·12, and 14·38 μ; $\delta_{TMS}^{CCl_4}$ 7·36 (arom C—H, complex pattern), and 3·99 ppm ($O\underline{CH_2}CH$ doublet, J = 6 Hz).

Recrystallization from hexane yielded 5·88 g (84%) white needles, m.p. 79–80°. A second crop of 420 mg (6%) was also obtained. The analytical sample, m.p. 85–86°, was prepared in the manner described for ketal **60**. (Found: C, 76·6; H, 8·0. $C_{13}H_{16}O_2$ requires: C, 76·44; H, 7·90%).

4-(p-Chlorophenoxymethyl)cyclohexanone (**62**)

A mixture containing 33·20 g (0·118 mole) ketal **60**, 20 ml water and 5 ml conc HCl aq in 400 ml acetone was heated on a steam bath for 1·5 hr, cooled, and extracted with benzene. The combined extracts were washed with 10% NaOH aq and water. After drying, the solvent was removed under reduced press and the residue was recrystallized from ether–hexane affording 24·97 g (90%) white solid; m.p. 53–55°; λ_{max}^{KBr} 5·82 (CO), 6·23, 6·30, (arom C=C), 6·69, 7·98, 8·52, 9·62, 12·02, and 14·95 μ; $\delta_{TMS}^{CCl_4}$ 6·97 (arom C—H. A_2B_2, J_{AB} = 9 Hz. $\Delta\nu_{AB}$ = 24·5 Hz), and 3·81 ppm ($O\underline{CH_2}CH$ doublet, J = 6 Hz).

Several recrystallizations from ether–hexane and sublimation [45° (bath temp) at 0·1 mm] did not alter the melting range. However, correct C, H, and Cl analyses could not be obtained. An analytical sample, prepared in the manner described for ketal **60**, was obtained as white platelets, m.p. 64–65°. (Found: C, 65·3; H, 6·2; Cl, 15·1. $C_{13}H_{15}ClO_2$ requires: C, 65·41; H, 6·33; Cl, 14·85%).

Ethyl 5-phenoxymethyl-2-oxocycloheptanecarboxylate (**63**)

The procedure of Tai and Warnhoff[28] was modified. A soln of 803 mg (3·93 mmoles) ketone **61** in 5 ml anhydrous ether was cooled to −55° and 568 mg (4·00 mmoles) distilled BF_3-etherate was added. After 5 min, 480 mg (4·22 mmoles) ethyl diazoacetate in 5 ml ether was added dropwise to the stirred mixture. N_2 was evolved immediately. The cooling bath was removed and the mixture was stirred at room temp for 15 min, diluted with water, and the product was isolated with ether. Distillation [170–185° (bath temp) at 0·05 mm] afforded 894 mg (79%) colorless viscous oil: λ_{max}^{film} 5·73 (CO), 6·23 (arom C=C). 6·67, 7·60, 8·00, 8·32, 9·32, 9·63, 13·18, and 14·38 μ.

A small sample of material gave an instantaneous purple-black color with alcoholic $FeCl_3$ soln.

Ethyl 5-(p-chlorophenoxymethyl)-2-oxocycloheptanecarboxylate (**64**)

A soln of 11·0 g (46·00 mmoles) ketone **62** in 50 ml ether was cooled to −30° and 7·20 g (50·7 mmoles) BF_3-etherate was added. After 5 min, 5·80 g (50·7 mmoles) ethyl diazoacetate in 5 ml ether was added slowly with stirring. N_2 was evolved immediately and, when gas evolution ceased, the mixture was stirred for 15 min at room temp. The soln was diluted with water, and the product was isolated with ether. Short path distillation at 170–205° (0·05 mm) afforded 11·07 g (74%) thick colorless oil; λ_{max}^{film} 5·74 (CO), 5·85 (CO), 6·08 (chelated CO), 6·24 (arom C=C), 6·69, 8·01, 8·32, 12·05, and 14·90 μ.

A sample gave a blue-purple coloration with alcoholic $FeCl_3$ soln.

An analytical sample, b.p. 190–200° (bath temp) at 0·1 mm, was prepared by redistillation. (Found: C, 62·9; H, 6·6; C, 11·05. $C_{17}H_{21}ClO_4$ requires: C, 62·86; H, 6·52; Cl, 10·92%).

Ethyl 5-phenoxymethyl-2-oxo-1-(3-oxobutyl)cycloheptanecarboxylate (**65**)

A soln of 10 ml 0·05M ethanolic NaOEt and 828 mg (2·86 mmoles) β-keto ester **63** was stirred at −20°, and a soln of 210 mg (3·00 mmoles) distilled methyl vinyl ketone in 5 ml EtOH was added over a 20-min period. The reaction mixture was stirred for 1 hr at −10°, then ethereal glacial AcOH was added to neutralize the base. the soln was diluted with water. and the product was isolated with ether. Distillation [210–215° (bath temp) at 0·05 mm] gave 843 mg (82%) viscous oil: λ_{max}^{film} 5·76–5·87 (CO).6·22 (aromatic C=C). 6·65. 8·00. 8·48. 13·18. and 14·38 μ: $\delta_{TMS}^{CCl_4}$ 7·35 (arom C—H. complex pattern). 4·43 ($O\underline{CH_2}Me$ quartet. J = 7·5 Hz). 3·88 ($O\underline{CH_2}CH$ doublet. J = 4 Hz). 2·12 (MeCO). and 1·33ppm ($OCH_2\underline{CH_3}$ triplet. J = 7·5Hz).

Ethyl 5-(p-chlorophenoxymethyl)-2-oxo-1-(3-oxobutyl)cycloheptanecarboxylate (**66**)

A soln of 10·07 g (31·00 mmoles) β-keto ester **64** and 40 ml 0·05M ethanolic NaOEt was cooled to −15° and 2·45 g (34·1 mmoles) methyl vinyl ketone was added dropwise over a ½ hr period. The mixture was stirred for an additional hr at −15° and ethereal AcOH was added to neutralize the base. The mixture was poured into water and the product was isolated with ether affording 11·48 g (94%) yellow oil: λ_{max}^{film} 5·78–5·86 (CO). 6·24. 6·30 (arom C=C). 6·69. 7·78. 8·03. 8·52. 12·08. and 14·92 μ: $\delta_{TMS}^{CCl_4}$ 6·96 (arom CH. A_2B_2. J_{AB} = 9 Hz. $\Delta\nu_{AB}$ = 24·5 Hz). 4·15 ($O\underline{CH_2}Me$ quartet. J = 7 Hz). 3·71 ($O\underline{CH_2}CH$ unresolved doublet). 2·02 (MeCO). and 1·27 ppm ($OCH_2\underline{CH_3}$ triplet J = 7 Hz).

Attempted preparation of ethyl 4-phenoxymethyl-7-methyl-10-oxobicyclo[4.3.1]*dec-7-enecarboxylate* (**67**)

A. *Sulfuric acid.* A soln containing 3·0 ml conc H_2SO_4 and 520 mg (1·44 mmoles) diketo ester **65** was stirred at 0° for 15 min and at room temp for 1 hr. The purple viscous mixture was poured in a fine stream into 100 ml rapidly stirred ice water. This soln was saturated with NaCl and the product was isolated with ether, giving 12 mg tar.

B. 4:1 *Sulfuric acid-acetic acid.* A mixture of 2·0 ml conc H_2SO_4. 0·5 ml glacial AcOH. and 804 mg (2.23 mmoles) diketo ester **65** was stirred at 0° for 30 min. A total 91 mg gummy residue was obtained by the above isolation procedure: λ_{max}^{film} 5·76 (CO). 5·83 (CO). 5·92 (CO). 6·22. 6·63. 7·95. 8·48. 8·90. and 9·62 μ.

The composition of the mixture was not clear from consideration of this spectrum. It was evident. however. that the phenolic ether group was largely missing from the isolated material.

C. 9:1 *Sulfuric acid-water.* A soln of 180 mg (0·50 mmole) diketo ester **65** in 1·0 ml 90% (by volume) H_2SO_4aq was stirred at 0° for 1·5 hr. Workup as above afforded 82 mg red sticky gum: λ_{max}^{film} 5·78–5·84 (CO). 8·00. 8·88. 9·60 μ.

From spectral evidence. the phenolic ether function was not present in the isolated material.

D. *Boron trifluoride etherate in ether.* A mixture of 2·0 ml (15·8 mmoles) BF_3-etherate. 1·0 ml anhyd ether and 311 mg (0·88 mmole) diketo ester **65** was stirred at room temp. Aliquots were removed. poured into brine. and isolated with ether. Mainly starting material was detected in aliquots taken after 1 hr and 4 hr. However. only a small amount of the aliquot taken after 20 hr could be distilled at 205–215° (bath temp) and 0·05 mm: λ_{max}^{film} 5·78 (CO). 5·98 (CO). 6·24 (arom C=C). 6·67. 8·01. 8·48. 8·90. 13·20. and 14·40 μ.

Further experiments using BF_3-etherate were likewise unsuccessful.

Ethyl 4-(p-*chlorophenoxymethyl*)-7-*methyl*-10-*oxobicyclo*[4.3.1]*dec*-7-*enecarboxylate* (**68**)

A soln of 10·25 g (26·00 mmoles) diketo ester **66** in 4·0 ml glacial AcOH was added over a 15-min period to 16·0 ml conc H_2SO_4 at 0°. The cooling bath was removed and the mixture was stirred at room temp for 2 hr. The deep purple mass was added in a fine stream to a rapidly stirred mixture of 400 ml ice water and 100 ml ether and the soln was stirred for 0·5 hr to dissolve all of the viscous material. The product was isolated with ether. affording 7·75 g (80%) thick yellow oil which was estimated by IR analysis to contain ca. 10% conjugated ketone. The product mixture exhibited the following spectral properties: λ_{max}^{film} 5·74 (CO). 5·83 (CO). 5·98 (CO. weak). 6·24. 6·30 (arom C=C). 6·69. 8·00. 12·05. and 14·90 μ: $\delta_{TMS}^{CCl_4}$ 6·97 (arom C—H. A_2B_2. J_{AB} = 9 Hz. $\Delta\nu_{AB}$ = 24·5 Hz). 5·54 (olefinic C—H. broad). 4·18 ($O\underline{CH_2}Me$ quartet. J = 7 Hz). 3·59 ($O\underline{CH_2}CH$ doublet. J = 5·5 Hz). 1·74 (vinylic Me). and 1·27 ppm ($OCH_2\underline{CH_3}$ triplet. J = 7 Hz).

4-(p-*Chlorophenoxymethyl*)-7-*methyl*-10-*oxobicyclo*[4.3.1]*dec*-7-*enecarboxylic acid* (**69**)

A 7·75-g (20·6 mmoles) sample of keto ester **68** was stirred with 4·08 g (61·8 mmoles) 85% KOH pellets in 30 ml MeOH at reflux for 15 hr. The cooled soln was diluted with water and washed with ether. The aqueous phase was acidified to pH 2 with ice cold conc HCl and the liberated organic material was isolated with ether to give 6·30 g (88%) solid acid **69**. Trituration with hot 1:1 ether–hexane afforded 5·17 g (72%) white solid: m.p. 183–185°: λ_{max}^{KBr} 2·92–3·80 (acid OH). 5·83 (CO). 6·24. 6·31 (arom C=C). 6·69. 7·78. 8·02. 12·08. and 14·95 μ: $\delta_{TMS}^{CDCl_3}$ 9·13 (CO_2H). 7·01 (arom C—H. A_2B_2. J_{AB} = 9 Hz. $\Delta\nu_{AB}$ = 25 Hz). 5·60 (olefinic C—H, broad), 3·72 ($O\underline{CH_2}CH$ doublet, J = 5·5 Hz), and 1·77 ppm (vinylic Me).

The residue was chromatographed on 100 g silica. Elution with 10% ether in benzene afforded an additional 835 mg (8%) crystalline acid **69**. The analytical sample. m.p. 184–185°. was obtained from the first crop after two additional triturations. (Found: C. 65·3; H. 6·15; Cl. 10·2. $C_{19}H_{21}ClO$ requires: C. 65·42: H. 6·07: Cl. 10·16%).

4-(p-*Chlorophenoxymethyl*)-1-*hydroxymethyl*-7-*methylbicyclo*[4.3.1]*dec*-7-*en*-10α-*ol* (**70**)

A soln of 5·50 g (15·8 mmoles) keto acid **69** in 50 ml DME was added to a stirred suspension of 1·30 g (34·3 mmoles) LAH in 100 ml DME. The mixture was heated at reflux for 12 hr and 75 ml DME was removed by distillation. The cooled mixture was treated with 125 ml ether and processed in the usual manner. Removal of solvent afforded 4·98 g (94%) diol **70** contaminated by ca. 33% of the corresponding dechlorinated diol: λ_{max}^{film} 2·94 (OH). 6·24. 6·30 (arom C=C). 6·69. 7·76. 8·02. 8·52. 9·12. 9·45–9·85. 12·10. 13·20. 14·40. and 15·20 μ: $\delta_{TMS}^{CDCl_3}$ 6·92 (arom C—H. A_2B_2. J_{AB} = 9 Hz. $\Delta\nu_{AB}$ = 24·5 Hz). 5·30 (olefinic C—H. broad). 4·04 (HO$\underline{CH}$CH. complex doublet). 3·42 ($HOCH_2$). and 1·71 ppm (vinylic Me).

When the reaction was carried out over a 36-hr period. ca. 75% dechlorination of the phenolic ether occurred.

4-(p-*Chlorophenoxymethyl*)-1-(p-*toluenesulfonoxymethyl*)-7-*methylbicyclo*[4.3.1]*dec*-7-*en*-10α-*ol* (**71**)*

To a well stirred soln of 4·92 g (ca. 14·1 mmoles) diol **70** in 30 ml pyridine at 0° was added 3·22 g (16·9 mmoles) *p*-toluenesulfonyl chloride in 10 ml pyridine. After 0·5 hr at 0° and 24 hr at room temp. the mixture

* See footnote* on page 2176.

was poured onto ice and the mono tosylate **71** was isolated with ether giving 6·89 g (93%) yellow oil: λ_{max}^{film} 2·82 (OH), 2·92 (OH shoulder), 6·24, 6·30 (arom C=C), 6·69, 7·36, 8·01, 8·48, 9·08, 10·40, 11·80–12·30, and 14·97 μ.

4-(p-Chlorophenoxymethyl)-1,7-dimethylbicyclo[4.3.1]*dec-7-en-10α-ol* (**73**)*

The hydroxy tosylate **71** (5·92 g, 12·2 mmoles), was dissolved in 25 ml DME and added to a suspension of 930 mg (24·5 mmoles) LAH in 75 ml DME. The soln was stirred at reflux for 12 hr, and 50 ml DME was removed by distillation. On cooling, 100 ml ether was added and the soln was treated in the described manner affording 3·62 g (90%) 1:1 mixture of alcohol **73** (Ar=*p*-C_6H_4Cl) and the corresponding dechlorinated alcohol: λ_{max}^{film} 2·88 (OH), 6·24 (arom C=C), 6·68, 7·75, 8·00, 9·10, 9·60, 12·08, 14·80, and 15·20 μ.

4-(1,4-Cyclohexadienyloxymethyl)-1,7-dimethylbicyclo[4.3.1]*dec-7-en-10α-ol* (**74**)*

To a soln of 1·69 (0·24 g-atom) Li wire in 125 ml anhyd liquid ammonia was added a mixture of 3·62 g (12·0 mmoles) alcohol **73**, 2·24 g (48·8 mmoles) EtOH and 25 ml ether. After 1 hr, 25 ml EtOH was added cautiously and the ammonia was allowed to evaporate. The residue was neutralized with solid NH_4Cl and the product was isolated with ether after the addition of 75 ml water. Removal of solvent gave 3·43 g (99%) thick oil: λ_{max}^{film} 2·90 (OH), 5·90, 6·02 (C=C), 7·26, 8·30, 10·40, and 14·93 μ; $\delta_{TMS}^{CCl_4}$ 5·62 (CH=CH, broad), 5·28 $CH_2\underline{CH}$=C—Me, broad), 4·41 ($CH_2\underline{CH}$=C—O, broad), 3·68 (HO<u>C</u>HCH doublet, J = 6 Hz), 3·40 (O<u>C</u>H_2CH, broad), 2·69 (allylic CH_2's singlet), 1·91 (OH), 1·71 (vinylic Me), and 1·02 ppm (Me).

4β-Hydroxymethyl-1,7-dimethylbicyclo[4.3.1]*dec-7-en-10α-ol* (**75**)*

A. *Reduction of keto acetate* **56**

A soln containing 171 mg (0·68 mmole) keto acetate **56** and 126 mg (4·50 mmoles) LAH in 20 ml ether was stirred at room temp for 12 hr. The soln was processed in the standard manner giving 140 mg (98%) oil that crystallized on cooling and scratching. Recrystallization from benzene afforded 101 mg (70%) white platelets: m.p. 106–108°; λ^{KBr} 2·97 (OH), 7·48, 9·11, 9·39, 9·57, 9·79, 10·03, 10·28, and 12·62 μ; $\delta_{TMS}^{CDCl_3}$ 5·36 (olefinic C—H, broad), 3·78 (HO<u>C</u>HCH doublet, J = 6 Hz), 3·44 (HO<u>C</u>H_2CH unresolved doublet), 1·77 (OH), 1·73 (vinylic Me), and 1·03 ppm (Me).

B. *Hydrolysis of* 4-(1,4-*cyclohexadienyloxymethyl*)-1,7-*dimethylbicyclo*[4.3.1]*dec-7-en-10α-ol* (**74**)*

A mixture of 3·43 g (11·9 mmoles) enol ether **74**, 125 ml acetone, 5 ml conc HCl and 5 ml water was heated at reflux for 1 hr. The cooled soln was diluted with 100 ml water and the products were isolated with ether. Trituration of the resulting viscous oil (3·28 g) with pentane removed the 2-cyclohexenone leaving a solid diol [2·42 g (97%)]. Recrystallization from hexane–benzene afforded 1·54 g (62%) white powder, m.p. 112–113°. The IR and NMR spectra of this material were identical to those of the diol prepared in part A of this experiment.

The mother liquor was chromatographed on 90 g of silica. Elution with 1:1 ether–benzene afforded 540 mg (21%) crystalline diol, m.p. 105–108°. An analytical specimen, m.p. 113–114°, was obtained by two further recrystallizations from hexane–benzene. (Found: C, 74·4; H, 10·5. $C_{13}H_{22}O_2$ requires: C, 74·24; H, 10·54%).

A 1:1 mixture of diol **75** obtained by method A (m.p. 106–108°) and by method B (m.p. 112–113°) exhibited m.p. 106–109°.

C. *Reduction of* 4β-*carboxy*-1,7-*dimethylbicyclo*[4.3.1]*dec-7-en-10α-ol lactone* (**77**).* A soln of 30 mg (0·15 mmole) lactone **77** in 2 ml ether was added to a stirred soln of 50 mg (1·3 mmoles) LAH in 3 ml ether. After stirring for 12 hr, the mixture was processed yielding 30 mg (98%) white solid. Recrystallization from hexane–benzene gave 20 mg (65%) white powder: m.p. 112–113°; mixed m.p. with the analytical sample from method B, 112–113°

Attempted reduction of 4-(p-*chlorophenoxymethyl*)-1-(*methanesulfoxymethyl*)-7-*methylbicyclo*[4.3.1]*dec-7-en-10α-ol* (**72**)*†

The methanesulfonate derivative **72** of diol **70** was prepared as described above for the corresponding tosylate **71**. A 230-mg sample of this mesylate was treated with 150 mg Li in 6 ml ammonia and 1·2 ml EtOH for 2 hr. The ammonia was allowed to evaporate and the product was isolated with ether. The IR spectrum indicated incomplete reduction of the aromatic ring and the reduction was therefore repeated. Hydrolysis of the enol ether was conducted as outlined above. Chromatography on silica gel gave none of the desired diol **75**.

* See footnote* on page 2176.

† We are indebted to A. R. Hochstetler for performing this experiment.

An attempted hydrogenolysis of the tosylate **71** according to the above procedure likewise failed to give any of the diol **75**.

4β-*Carboxy*-1,7-*dimethylbicyclo*[4.3.1]*dec*-7-*en*-10-*one* (**76**)*

To a manually swirled soln of 2·0 ml Jones reagent[22] in 10 ml acetone at 0° was added 147 mg (0·70 mmole) diol **75** in 5 ml acetone. After swirling at 0° for an additional 15 min, the mixture was treated with 2-propanol to destroy the excess oxidant. Workup in the prescribed manner afforded 151 mg (98%) yellow solid. Recrystallization from EtOAc–heptane gave 124 mg (80%) white powder: m.p. 130–133°; λ_{max}^{KBr} 2·92–3·90 (acid OH), 5·86 (CO), 7·63, 7·72, 7·90, 8·20, and 8·33 μ; $\delta_{TMS}^{CDSl_3}$ 11·10 (CO_2H), 5·56 (olefinic C—H, broad), 1·77 (vinylic Me), and 1·10 ppm (Me).

The analytical sample, m.p. 133–135°, was secured after an additional recrystallization. (Found: C, 70·0; H, 8·3. $C_{13}H_{18}O_3$ requires: C, 70·25; H, 8·16%).

4β-*Carboxy*-1,7-*dimethylbicyclo*[4.3.1]*dec*-7-*en*-10α-*ol lactone* (**77**)*

A stirred soln of 70 mg (0·32 mmole) keto acid **76**, 200 mg (4·25 mmoles) 85% NaOH pellets and 3 ml water was treated with 120 mg (3·16 mmoles) $NaBH_4$. After standing for 12 hr, the mixture was added dropwise to a rapidly stirred solution of 1:1 conc HCl ice. The lactone **77** was isolated with ether yielding 56 mg (86%) pale yellow solid. Recrystallization from pentane gave 48 mg (76%) white needles: m.p. 76–77°; λ_{max}^{KBr} 5·78 (CO), 7·96, 8·41, 9·32, 9·72, and 10·08 μ; $\delta_{TMS}^{CCl_4}$ 5·22 (olefinic C—H, broad), 4·09 (O<u>CH</u> doublet, J = 5 Hz), 1·71 (vinylic Me), and 1·07 ppm (Me).

Sublimation at 50° (0·1 mm) afforded an analytical sample, m.p. 76–77°. (Found: C, 75·7; H, 9·0. $C_{13}H_{18}O_2$ requires: C, 75·69; H, 8·80%).

4β-*Acetoxymethyl*-1,7-*dimethylbicyclo*[4.3.1]*dec*-7-*en*-10α-*ol* (**78**)*

A 1·33-g (6·32 mmoles) sample of diol **75** was dissolved in 25 ml dry pyridine, 681 mg (6·50 mmoles) of 97% Ac_2O was added, and the soln was allowed to stand under N_2 at room temp for 12 hr. The reaction mixture was poured into water and the product was isolated with ether. Removal of solvent yielded 1·54 g (99%) colorless oil: λ_{max}^{film} 2·87 (OH), 5·74, 5·79 (split CO), 7·19, 7·29, 8·00, and 9·60 μ; $\lambda_{max}^{CCl_4}$ 2·82 (OH), 5·74 (CO), 7·20, 7·30, 8·03, and 9·62 μ; $\delta_{TMS}^{CCl_4}$ 5·30 (olefinic C—H, broad), 3·80 (O<u>CH_2</u>CH, unresolved doublet), 3·68 (HO<u>CH</u>CH doublet, J = 6 Hz), 2·40 (OH), 1·97 ($MeCO_2$), 1·70 (vinylic Me) and 1·01 ppm (Me).

Two distillations afforded an analytical sample, b.p. 94–97° (bath temp) at 0·1 mm. (Found: C, 71·6; H, 9·5. $C_{15}H_{24}O_3$ requires: C, 71·39; H, 9·59%).

4β-*Acetoxymethyl*-1,7α-*dimethylbicyclo*[4.3.1]*decan*-10α-*ol* (**79**)*

A 1·45-g (5·77 mmoles) sample of hydroxy acetate **78** was hydrogenated over 75 mg reduced PtO_2 in 10 ml AcOH. H_2 uptake (1·0 molar equiv) was complete within 2 hr and the mixture was filtered, poured into cold 10% NaOH aq. and extracted with ether. The ether extracts were dried over $MgSO_4$ and distilled affording 1·41 g (97%) oil: λ_{max}^{film} 2·86 (OH), 5·74, 5·79 (split CO), 7·20, 8·00, 9·10, 9·62, and 10·15 μ; $\lambda_{max}^{CCl_4}$ 2·82 (OH), 5·74 (CO), 7·30, 8·05, 9·12, 9·62, and 10·15 μ; $\delta_{TMS}^{CCl_4}$ 3·76 (O<u>CH_2</u>CH doublet, J = 5 Hz), 3·43 (HO<u>CH</u>CH doublet, J = 6 Hz), 2·58 (OH), 1·99 ($MeCO_2$), 1·07 (Me), and 1·01 ppm (<u>CH</u> doublet, J = 5·5 Hz).

The analytical sample, b.p. 90–93° (bath temp) at 0·1 mm, was secured after two successive distillations. (Found: C, 70·9; H, 10·2. $C_{15}H_{26}O_3$ requires: C, 70·83; H, 10·30%).

4β-*Acetoxymethyl*-1,7α-*dimethylbicyclo*[4.3.1]*decan*-10α-*ol methanesulfonate* (**80**)*

A soln of 1·35 g (5·31 mmoles) hydroxy acetate **79** in 25 ml pyridine was cooled to 0° and 620 mg (5·84 mmoles) methanesulfonyl chloride was added slowly. The cooling bath was removed and the mixture was stirred for 18 hr. The soln was poured onto ice and throughly extracted with ether. Removal of solvent afforded 1·73 g (98%) mobile oil: λ_{max}^{film} 5·74 (CO), 7·40, 8·02, 8·50, 9·63, and 10·94 μ; $\delta_{TMS}^{CCl_4}$ 4·48 (O<u>CH</u>CH doublet, J = 6 Hz), 3·77 (O<u>CH_2</u>CH doublet, J = 5 Hz), 2·96 ($MeSO_2$), 1·98 ($MeCO_2$), 1·11 (Me), and 1·05 ppm (<u>CH_3</u>CH doublet, J = 6 Hz).

* See footnote* on page 2176.

5β-Acetoxymethyl-2.8α-dimethyl-7βH-bicyclo[5.3.0]dec-1-ene (**81**)*

A mixture of 1·73 g (5·21 mmoles) acetoxy mesylate **80** and 20·8 ml 0·5M KOAc in AcOH was heated at reflux for 3 hr. The soln was poured onto ice and neutralized with 10% NaOH aq. The product was isolated with ether affording 1·20 g (99%) oil: λ_{max}^{film} 5·74 (CO), 7·30, 8·08, 9·50, and 9·65 μ; $\delta_{TMS}^{CCl_4}$ 3·88 (O$\underline{CH_2}$CH doublet, J = 7 Hz).

Two distillations yielded a sample of analytical purity, b.p. 76–78° (bath temp) at 0·1 mm. (Found: C, 76·2; H, 10·2. $C_{15}H_{24}O_2$ requires: C, 76·2; H, 10·2%).

The gas chromatogram† gave peaks at 20·4 (**81**, 92%) and 21·3 min (8%).

5β-Hydroxymethyl-2.8α-dimethyl-7βH-bicyclo[5.3.0]dec-1-ene (**82**)*

To a stirred suspension containing 420 mg (11·0 mmoles) LAH in 25 ml ether was added 1·08 g (4·56 mmoles) acetate **81** in 10 ml ether. The mixture was stirred at room temp for 12 hr, and the product was isolated with ether. Distillation [82–84° (bath temp) at 0·1 mm] afforded 796 mg (90%) colorless oil: λ_{max}^{film} 2·98 (OH), 7·23, 9·44, 9·68, 9·87 μ; $\delta_{TMS}^{CCl_4}$ 3·40 (O$\underline{CH_2}$CH doublet, J = 6·5 Hz), 2·92 (OH), 1·57 (vinylic Me), and 0·77 ppm ($\underline{CH_3}$CH doublet, J = 7 Hz).

Redistillation gave an analytical sample. (Found: C, 80·3; H, 11·4. $C_{13}H_{22}O$ requires: C, 80·35; H, 11·41%).

Methyl 2.8α-dimethyl-7βH-bicyclo[5.3.0]dec-1-ene-5β-carboxylate (**84**)*

A 502-mg (2·58 mmoles) sample of alcohol **82** in 40 ml acetone at 0° was treated with 1·56 ml Jones reagent[22] over a 15-min period. After manual swirling at 0° for 10 min, the mixture was treated with 2-propanol to destroy the excess oxidant. Workup afforded 420 mg (75%) acid **83**: λ_{max}^{film} 2·88–3·80 (acid OH), 5·88 (CO), 7·22, 8·10, and 9·50 μ.

The acidic material, 420 mg (2·0 mmoles), in 5 ml ether was added dropwise to 10 ml 0·5M ethereal diazomethane at 0°. After 1 hr at 0°, AcOH was added dropwise to destroy the excess diazomethane and the product was isolated with ether. Distillation [62–64° (bath temp) at 0·1 mm] afforded 210 mg (47%) mobile liquid: λ_{max}^{film} 5·75 (CO), 8·30, and 8·52; $\delta_{TMS}^{CCl_4}$ 3·61 (CO_2Me), 1·60 (vinylic Me), and 0·79 ppm ($\underline{CH_3}$CH doublet, J = 7 Hz). One peak, t_r 15·9 min, was observed in the gas chromatogram.†

A further distillation gave an analytical sample. (Found: C, 75·4; H, 9·9. $C_{14}H_{22}O_2$ requires: C, 75·63; H, 9·97%).

Methyl 2.8α-dimethyl-7βH-bicyclo[5.3.0]dec-1-ene-5α-carboxylate (**85**)*

A soln of 0·25M methanolic NaOMe was heated at reflux with 210 mg (0·95 mmole) ester **84** for 18 hr. The mixture was cooled, and 1 ml AcOH was added followed by 25 ml water. The product was isolated with ether and distilled to give 188 mg (90%) oil: b.p. 62–65° (bath temp) at 0·1 mm; λ_{max}^{film} 5·75 (CO), 8·30, and 8·54 μ; $\delta_{TMS}^{CCl_4}$ 3·58 (CO_2Me), 1·60 (vinylic Me) and 0·91 ppm ($\underline{CH_3}$CH doublet, J = 6 Hz). The gas chromatogram‡ exhibited peaks at 15·9 (**84**, 29%), and 17·3 min (**85**, 71%). Pure ester **85** was obtained by preparative gas chromatography.‡ (Found: C, 75·4; H, 9·7. $C_{14}H_{22}O_2$ requires: C, 75·63; H, 9·97%).

7-epi-*Bulnesol* (**86**)

To 10 ml of 1·0M ethereal MeLi (10·0 mmoles) at 0° was added slowly 103 mg (0·40 mmole) ester **84** in 5 ml ether. The cooling bath was removed and the mixture was stirred for 10 hr. Excess MeLi was decomposed by adding sat NH_4Cl aq and the alcohol **86** was isolated with ether. Distillation afforded 92 mg (89%) viscous oil: b.p. 78–81° (bath temp) at 0·1 mm: λ_{max}^{film} 2·92 (OH), 7·22, 8·57, 8·75, 8·90, 10·62, 10·90, and 11·20 μ; $\delta_{TMS}^{CDCl_3}$ 1·59 (vinylic Me), 1·36 (OH), 1·17 [Me_2COH] and 0·83 ppm ($\underline{CH_3}$CH doublet, J = 7 Hz).

A 1:1 mixture of synthetic bulnesol (**87**) and 7-*epi*-bulnesol (**86**) exhibited retention times of 16·8 and 17·8 min on the gas chromatogram.† A sample of 7-*epi*-bulnesol was redistilled for analysis. (Found: C, 80·75; H, 11·7. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%).

* See footnote* on page 2176.

† A 17 ft. × ¼ in. column of 12% Carbowax 20-M on 60–80 mesh Chromosorb W was used for this analysis.

‡ A 15 ft. × ½ in. column of 8% FFAP on 60–70 mesh Chromosorb G was used.

DL-*Bulnesol* (87)

A 90-mg (0·40 mmole) sample ester 85 in 5 ml ether was added slowly to a rapidly stirred soln of 5·0 ml (8·0 mmoles) 1·6M ethereal MeLi. After 10 hr at room temp. the excess MeLi was destroyed by the cautious addition of sat NH_4Claq and the product was isolated with ether. Distillation [78–80° (bath temp) at 0·1 mm] gave 76 mg (85%) oil that crystallized on standing: λ_{max}^{KBr} 3·01 (OH). 7·25. 8·19. 8·49. 8·77. and 11·10 μ: $\delta_{TMS}^{CDCl_3}$ 1·67 (vinylic Me). 1·32 (OH). 1·17 [Me_2COH]. and 0·91 ppm ($\underline{CH_3}CH$ doublet. J = 6·5 Hz).

The IR and NMR spectra were identical with those of natural bulnesol.* The two substances also exhibited identical gas chromatographic retention times.† After two successive sublimations at 50° (0·1 mm). the analytical sample. m.p. 77–79°. was secured.‡ (Found: C. 81·0; H. 11·7. $C_{15}H_{26}O$ requires: C. 81·02; H. 11·79%).

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* Provided by Prof. R. B. Bates.

† See footnote† on page 2190.

‡ This substance and its hydrocarbon analogs **22**. **23**. **24**. and **27** were exceedingly sensitive to air oxidation and were therefore stored under nitrogen in the cold immediately after distillation.

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