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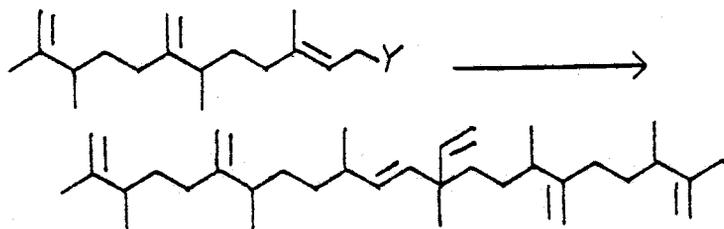
Arden R. Strycker for the degree of Doctor of Philosophy
in Chemistry presented on November 3, 1981

Title: APPROACHES TO THE SYNTHESIS OF BOTRYOCOCCENE:
SYNTHESIS OF THE HALF MOLECULE

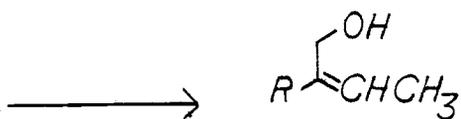
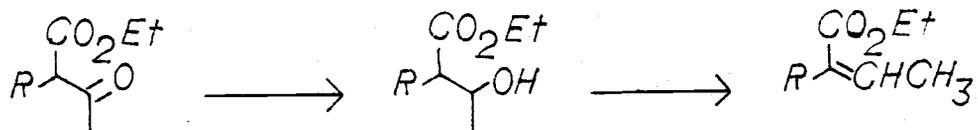
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Elliot N. Marvell

Botryococcene, a $C_{34}H_{58}$ diterpene, is a geochemically important hydrocarbon produced by Botryococcus braunii. Botryococcene is structurally built up of two identical units asymmetrically joined. We have synthesized the half molecule ($Y = OH$) by following a repeating scheme to produce a thirteen carbon section



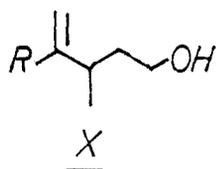
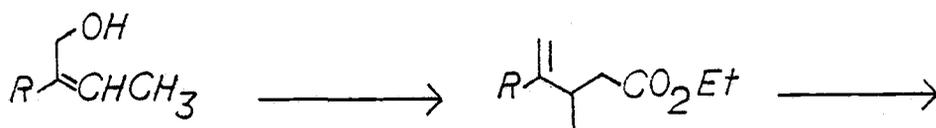
and a two plus two process to produce the final four carbons. The repeating method involves an alkylation of acetoacetic ester followed by a reduction-dehydration procedure leading to an allylic alcohol. A Claisen rearrangement



$R = \text{Me-}$ 1st cycle

$R = \text{CH}_2\text{-CH(CH}_3\text{)-CH}_2\text{-}$ 2nd cycle

of this alcohol with subsequent reduction gave the seven and then thirteen carbon sections. The final four carbons were added to



X with the Stork masked aldehyde anion process to give a methyl ketone. Addition of vinyl lithium gave a tertiary allylic alcohol. This was transformed into the half molecule via an unsaturated aldehyde in two steps. The overall yield of the first two stages was 4.5% and for the last six steps 32%. Thus, synthesis of the half molecule was achieved in 20 steps with a total yield of 1.4%.

Approaches to the Synthesis of
Botryococcene: Synthesis of
the Half Molecule

by

Arden R. Strycker

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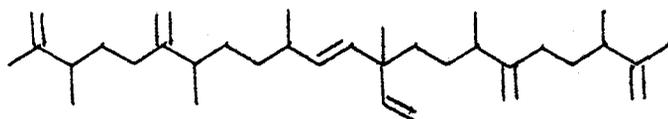
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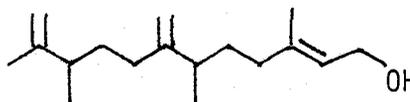
APPROACHES TO THE SYNTHESIS OF BOTRYOCOCCENE:
SYNTHESIS OF THE HALF MOLECULE

INTRODUCTION

Botryococcus braunii, a green algae found growing under a variety of environmental conditions, produces an unusually high percentage of hydrocarbons. Because of the recent concern about the depletion of non-renewable energy sources, some workers have examined this algae as a potential source of oil. R. E. Cox et al. have determined the structure of the major high molecular weight hydrocarbon present, botryococcene 6, by analytical, spectral, and degradative methods



6



10

(25). We intend to confirm their structural assignment by comparing a sample isolated from the algae with a sample synthesized by unequivocal methods.

Our synthetic strategy incorporated a repetitive process patterned after terpene syntheses developed by Johnson et al. to prepare a thirteen carbon unit (27). A four carbon segment was to be added to produce the seventeen carbon half molecule 10. The final stage in the synthetic scheme would couple the two halves asymmetrically to

give the thirty-four carbon botryococcene. This last stage was based on the elegant procedure developed by Baldwin et al. (79). The reality has not proved as simple and considerable modification of this scheme has had to be developed.

HISTORICAL

Botryococcene and its isomer isobotryococcene, isolated from the green algae Botryococcus braunii of the order Chlorophyceae, are the subjects of several recent studies. These hydrocarbons make up the unusual 'cup' of oil surrounding each of the algal cells during a particular growth stage. And it is the unique cellular structure of this algae that has led to the conclusion that certain boghead coal deposits resulted from once living colonies of Botryococcus braunii. Current work is continuing on the possible uses for this oil as one solution to the increasing cost of transportation fuels. But before this alternative can be practical, many of the complicated physiological details must be characterized and understood.

Microscopic studies of torbanite (a high grade oil shale) and coorongite (a thin rubbery deposit found near lake shores in Australia) led Blackburn (1) and Temperley (2) to the conclusion that the yellow globules found in these deposits were the remains of the algae Botryococcus braunii. Since then, there have been a number of studies relating this algae to certain geological formations (see for example E. Gelpi et al. (3) and the references therein). Curiously, it was the hydrocarbon content in coorongite that erroneously excited the first Australian oil seekers in the 1890's (4). More recently, botryococcane was found in certain crude oils in very high concentrations of 1% and 1.4% (5).

The unusually high percentage of hydrocarbons produced by the algae has excited some workers (6-11). Depending on the circumstances, botryococcene and other related compounds have comprised 30% to 90%

of the dried mass. L. W. Hillen et al. (11) cracked a sample of this Botryococcus oil. Upon distillation he obtained 67 wt % petrol, 15 wt % aviation turbine fuel, 15 wt % diesel, and 3 wt % residual oil.

Botryococcus braunii has been able to live under an extremely wide range of physical conditions. It has grown successfully in fresh or brackish waters, in neutral waters with pH 4.5 to pH 8, and has been reported in lakes from Scandinavia, Africa, Australia, North America, and Great Britain (12).

Blackburn (1) and Temperley (2) describe in detail the morphological structure. Unique from other algal forms, each cell embeds itself in a globule or 'cup' of oil. As the cell divides, its daughter cells remain in this cup secreting more oil. Eventually this develops into a colony that usually floats on the water surface. Certain threads connect one colony to another to form larger compound colonies. Under normal circumstances, the alga appears green. However, when deprived of nutrients, the alga turns to an orange color which characterizes the senescent or 'resting' stage. When added to a fresh culture medium, the alga reverts back to its green state within one week (13). Sometimes the brown stage gives rise to massive rust colored algal 'blooms.'

Belcher (12) determined that under specified conditions, a culture of Botryococcus braunii grew exponentially (as measured by number of colonies) for about five weeks before leveling off (mean generation time of one week). However, the alga's dry weight continued to increase at the same rate for another twelve weeks before becoming constant. During the first five weeks, the colonies were green and did not float on the surface. But following this exponential growth, the colonies

turned red and rose to the water surface. The red color was attributed to the accumulation of certain carotenoids and was not an indication of the physiological 'resting' stage which has only been observed in uncultured samples. Belcher (12) also noted the particularly slow growth Botryococcus braunii exhibited. It was thought that the diffusion of carbon dioxide and mineral salts into the cell was limited because the cup of oil often covers 90% or more of the cell wall. It was also thought that the mass production of the oily material for no apparent reason might have been wasteful to colony growth (12).

C. Lageau et al. (14, 15) studied in more detail the biosynthesis of the long chain hydrocarbons. The cell wall was defined by an internal fibrillar layer, largely composed of polysaccharide material, and several external trilaminar sheaths (14). The investigators isolated the hydrocarbons from the various parts of the cell and characterized them with GC-MS studies (Table 1). C. Lageau et al. (14) found that the hydrocarbons made up 15% dry wt of the algae, and that 95% of these hydrocarbons were located in the external pool. The low concentration of hydrocarbons (0.75% dry wt) located in the internal pool compared reasonably with that of other green unicellular algae (16).

It has been considered generally that the hydrocarbons were produced from within the cell of Botryococcus braunii and then secreted to the outer walls (1,2). But C. Lageau et al. (15) found this to be incorrect. Since it has generally been thought that long chain hydrocarbons are synthesized from fatty acids in the range C_{14} - C_{18} (17), C. Lageau et al. looked for such a substrate to be used for labelling studies. They found that palmitic acid [$9,10$ - 3H] was quickly incorporated and tritiated hydrocarbons were subsequently

Table 1. Analysis of the hydrocarbon pools occurring in Botryococcus braunii in the green state (14)

Relative abundance of the pools (%)		Hydrocarbon content of each pool (as % of culture dry wt)	Nature of the main hydrocarbons present in each pool					
			$2\Delta C_{25}$	$2\Delta C_{27}$	$2\Delta C_{29}$	$2\Delta C_{31}$	$3\Delta C_{29}$	
External pool	a	3	0.5	trace	14	45	21	20
	b	92	13.8	trace	14	45	21	20
Internal pool	c	5	0.75	3	33	38	17	19

- a) Hydrocarbons of the free globules present in the culture medium (separated before mechanical treatment and extracted with hexane).
- b) Hydrocarbons saturating the outer walls and giving rise to the associated globules (hexane extracts).
- c) Hydrocarbons of the cytoplasmic inclusion ($CHCl_3$ - CH_3OH extract).

produced. After treating the algae with tritiated palmitic acid, the investigators resuspended the colonies in a fresh medium containing unlabelled palmitic acid. The values of α were compared (Table 2).

Because α did not increase when the algae were added to the unlabelled palmitic acid, it was concluded that fast hydrocarbon migration from the internal pool to the external pool did not occur. If the cells were able to catabolize the hydrocarbons under normal conditions, one would expect α to decrease. This was not observed either. The small increase in α that was observed was explained by the production of labelled hydrocarbons from residual amounts of tritiated palmitic acid in the cell during the chase period. It was suggested that at least the final steps of hydrocarbon production occurred in the outer cell wall.

But showing that the algae produced the hydrocarbons in the outer cell wall has been very difficult. Murray and Thomson (18) prepared axenic cultures from single cell isolates of the alga and could only obtain unsaturated C_{17} hydrocarbons. One explanation given for this difference was that bacteria and motile protozoa, known to be present from light and scanning electron microscopy, were at least partly responsible for the production of the long chain hydrocarbons. But because the hydrocarbon content is extremely dependent on the physiological state of the alga, and because the characteristic 'mulberry' habit or super colony structure of the alga is destroyed by the purification process, the absence of long chain hydrocarbons could also be explained by the atrophy of the external trilaminar sheath (15). As far as the author is aware, this question is still unanswered.

Some efforts have been made to determine the composition of this oil (13, 19). The algae in the normal green state were extracted with

Table 2. Pulse-chase experiments (15)

Culture condition (days labelled: days unlabelled)	Control group			
	Contribution of hydrocarbons to total lipid radioactivity (%)	Labelling of external dienic hydrocarbons	Labelling of internal dienic hydrocarbons	external/ internal (α)
Culture I (1:1)	4.1	4.05	0.19	21.3
Culture II (5:5)	16.6	9.75	0.53	18.4
Culture III (35:12)	27.3	12.85	1.5	8.6
Culture	Transferred to an unlabelled medium			
	Contribution of hydrocarbons to total lipid radioactivity (%)	Labelling of external dienic hydrocarbons	Labelling of internal dienic hydrocarbons	external/ internal (α)
Culture I	11.9	4.85	0.24	20.2
Culture II	20.1	10.5	0.61	17.2
Culture III	30.3	12.7	1.55	8.2

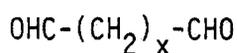
acetone, concentrated, purified on alumina, and finally analyzed. By GLC eleven high molecular weight hydrocarbons were found and conveniently divided into three series. Series A had the general formula C_nH_{2n-2} , while series B had the general formula C_nH_{2n-4} . The compounds of series C were not analyzed because of their relatively low concentration (Table 3). Mass spectral data suggested that little or no branching of these hydrocarbons existed (13).

Table 3. GLC and GC-MS results for hydrocarbons in *Botryococcus braunii* (13)

Peak	Series	Relative composition (%)	Formula	Cultured		
				High light 3 weeks	High light 6 weeks	High light 6 weeks 1/10 N ₂
1	A	0.3		trace	-	trace
2	A	1.0		-	trace	1.5
3	B	0.2		-	-	-
4	A	7.2	$C_{27}H_{52}$	12.3	6.0	5.0
5	B	0.9		-	-	-
6	A	32.6	$C_{29}H_{56}$	59.0	37.0	20.0
7	C	4.8		-	1.0	-
8	B	23.0	$C_{29}H_{54}$	-	7.0	22.5
9	A	25.1	$C_{31}H_{60}$	28.5	49.0	47.0
10	C	1.9		-	-	-
11	B	3.0	$C_{31}H_{58}$	-	-	-
Botryococcene		-	$C_{34}H_{58}$	-	-	4.3

B. A. Knights et al. (19) investigated the structures for the compounds from peaks 4, 6, and 9. Infrared spectroscopy of these compounds showed the presence of a vinyl group (1638, 990, and 908 cm^{-1}) and a cis disubstituted double bond (720 cm^{-1}).

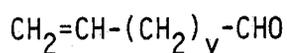
Ozonolysis of the hydrocarbons produced three aldehyde products as determined by GLC. From GC--MS of these aldehydes, the O-methyloxime derivatives, and the methyl esters of the corresponding acids, the authors determined these aldehydes to be the dialdehydes 1a-c in the same relative proportions as the parent hydrocarbons. A partial ozonolysis was also carried out on the hydrocarbons by using a shorter reaction time. They found four products which after a similar



$$\underline{1a} \quad x = 15$$

$$\underline{1b} \quad x = 17$$

$$\underline{1c} \quad x = 19$$

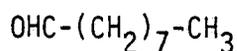


$$\underline{2a} \quad y = 15$$

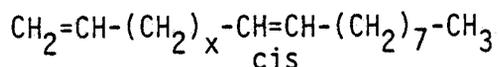
$$\underline{2b} \quad y = 17$$

$$\underline{2c} \quad y = 19$$

treatment were identified as the aldehydes 2a-c and 3. Based on this information, the identity of peaks 4, 6, and 9 was thought to be heptacos-1,18-diene 4a, nonacos-1,20-diene 4b, and hentriaconta-1,22-diene 4c respectively (19). It was not conclusively shown that the structure



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$$\underline{4a} \quad x = 15$$

$$\underline{4b} \quad x = 17$$

$$\underline{4c} \quad x = 19$$

of the hydrocarbons were the unbranched isomers. However, the fact that no discontinuities were found in any of the mass spectral data, as would be expected for branched structures, strongly supported the authors' conclusion.

It has generally been found that for the green stage of algal

growth, about 15% dry wt of oil can be obtained from Botryococcus braunii by extraction and purification. However, the extracts of the uncultured orange bloom, a common form of the senescent or resting stage, have been quite varied in content and in quantity. Maxwell et al. (20) reported that they obtained an oil fraction (76% dry wt) comprised of two compounds, termed botryococcene and isobotryococcene, in a ratio of 9:1, as determined by GLC, from Botryococcus braunii isolated from Oakmere, Cheshire, England. The botryococcenes were found to be 96% pure. Swain and Gilby (21) isolated 90% oily materials from Lakes Nicaragua and Managua in Nicaragua. Fred Wolf et al. (22) observed the presence of botryococcene and isobotryococcene from senescent forms isolated from California and Oklahoma. The quantities of these isomers or any others not mentioned were not given. Wake and Hillen (23) isolated 31% dry wt of oily material from a 'bloom' on the Darwin River Reservoir in Australia, a value consistent with other samples taken from lakes in Australia (11). Furthermore, the composition was found to be quite different (Table 4). In addition, A. G. Douglas et al. (24) found that a bloom of Botryococcus braunii isolated from the surface of Oakmere, Cheshire, England, contains 0.014% dry wt of fatty acids. Palmitic, oleic, and octacosenoic acids were found to be the most abundant ones. This contrasted with early reports that the oil extracts were presumed to be largely fatty acids (1, 2).

J. R. Maxwell et al. (20, 25) have investigated in detail the properties of botryococcene and isobotryococcene in order to determine their structures. It was inferred from the infrared bands 892, 916 and 1002, and 979 cm^{-1} that its structure contained an exomethylene,

Table 4. Composition of oil from *Botryococcus braunii*, Darwin River Reservoir, November 1976 (23)

Compound	Composition (%)
Isobotryococcene	4
Botryococcene	9
C ₃₄ H ₅₈	11
C ₃₆ H ₆₂	34
C ₃₆ H ₆₂	4
C ₃₇ H ₆₄	20
Other	18

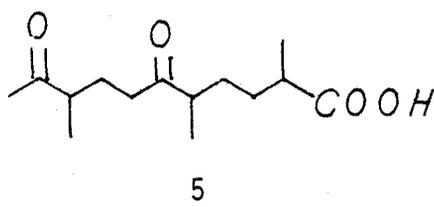
a vinyl, and a trans disubstituted carbon-carbon double bond. The intensity of these bands were consistent with the presence of four exomethylene, one vinyl, and one trans disubstituted double bonds for botryococcene, and three exomethylene, one vinyl, and one trans disubstituted carbon-carbon double bonds for isobotryococcene.

The ¹H NMR showed a sharp singlet at δ 4.6 and was assigned to exomethylene protons--eight for botryococcene and six for isobotryococcene. The ABX pattern for the vinyl protons correlated well with the splitting in the δ 4.7-5.8 region. Other small differences between the proton spectra for the two isomers were observed, but no conclusions were drawn. Integration from the methyl region suggested the presence of five or six methyl groups for both isomers (20).

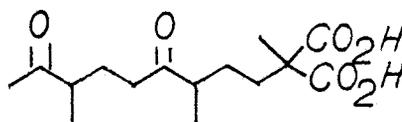
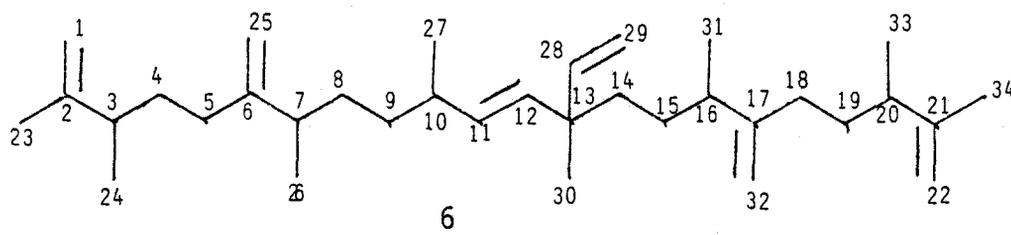
Hydrogenation of both isomers gave one molecule, botryococcane. From the mass spectrum and related information, it was determined that botryococcene and isobotryococcene have the formula C₃₄H₅₈ and botryococcane the formula C₃₄H₇₀. The very intense ions at mass 449 and 448 of botryococcane, due to the loss of an ethyl group, supported the

conclusion that the vinyl group was attached to a tetrasubstituted carbon. This was also supported by the high frequency of 1002 cm^{-1} observed in the infrared spectrum for the vinyl double bond (20). Partial reduction was successful with the reagent P-2 nickel boride, which is known to reduce vinyl groups exclusively. The product, dihydrobotryococcene, was shown by ^1H NMR to have lost the vinyl protons (20).

Permanganate--periodate oxidation of botryococcene gave one major product which was identified as the diketo acid 5 (25).



^{13}C NMR of botryococcene and dihydrobotryococcene identified eight methyls, eight saturated and five unsaturated methylenes, five saturated and three unsaturated methines, and one saturated unsaturated quaternary carbons in botryococcene (Table 5)(25). Structure 6 was proposed for botryococcene. The other



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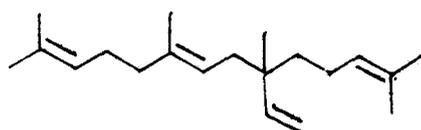
Table 5. ^{13}C NMR chemical shifts (from TMS) and assignments for botryococcene and dihydrobotryococcene (25)

Carbon	Botryococcene	Dihydrobotryococcene
1,22	109.8	109.8
2,21	149.9	150.1
3,20	41.2	41.3
4,19	33.7	33.7
5,18	31.9	31.9
6,17	154.7 154.9	155.1
7	40.8	40.9
8	33.6	33.7
9	35.2	35.4
10	37.4	37.7
11	134.0	134.0
12	136.1	137.4
13	42.0	38.6
14	39.3	39.0
15	30.4	30.2
16	40.3	40.4
23,34	20.0	20.0
24,33	19.1	19.1
25,32	107.5 107.7	107.5
26,31	20.4 20.6	20.5 20.7
27	21.3	21.7
28	147.0	33.9
29	111.2	8.7
30	23.9	23.0

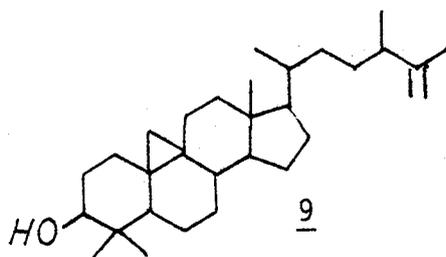
product from the permanganate--periodate oxidation, the diketo dicarboxylic acid 7, would easily undergo decarboxylation to give the carboxylic acid 5.

Botryococcene appears terpenoid in origin, assuming dimethylated C₁₅ units linked tail-to-tail to give the saturated quaternary carbon in 6, a precedent for such a linkage existing in isodigeranyl 8. The pattern of methylation is unusual for an acyclic isoprenoid but a similarity exists with the methylated side chain of cyclolaudenol 9 (25).

It is fitting that the product of a very unusual algae is so unusual.



8

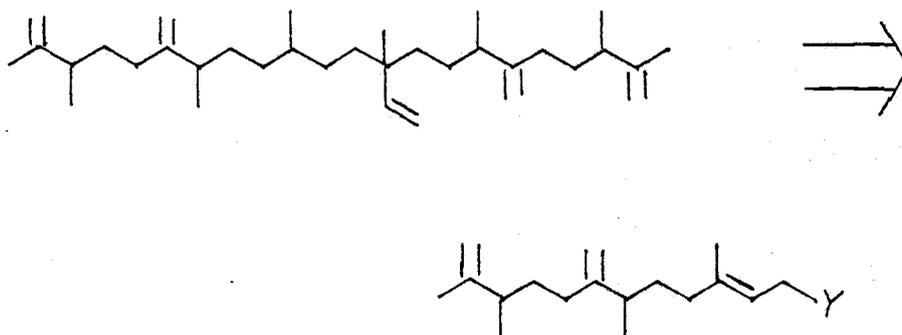


9

DISCUSSION

An unequivocal synthesis of a new compound is the final step in the identification of its structure, determined first by spectral and other analytical methods. As was noted earlier, botryococcene has been assigned a structure principally by the use of these methods. We intend to verify that structure by an unequivocal synthesis, and thus, corroborate the presently accepted structure.

Clearly, the most efficient retrosynthetic approach to botryococcene must treat the thirty-four carbon molecule as the combination of two identical seventeen carbon units which have been joined asymmetrically. Each of these sub-units can be further subdivided into



three isoprene units, two of which contain an extra methyl at C_3 . The use of some repeating process, such as the one developed by Johnson for terpene syntheses, seemed appropriate at least for the two equivalent methylated units. One additional feature of these units which is unique as far as terpenes in general are concerned is the less stable position of the double bond. Indeed, any scheme devised must permit positioning of the double bond in the terminal

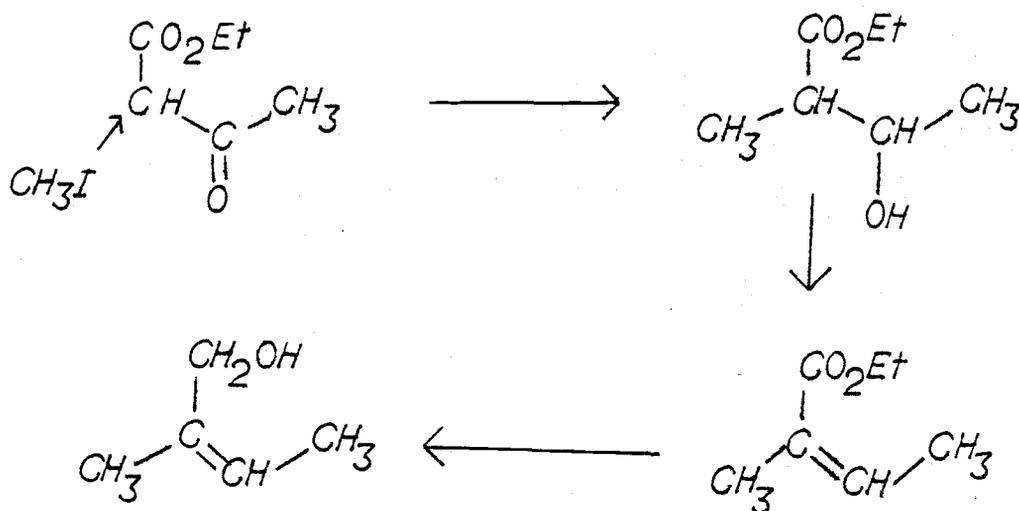
position. Finally, the third unit could be added via an α,β unsaturated ester, a number of preparative methods having been developed recently to accomplish such additions.

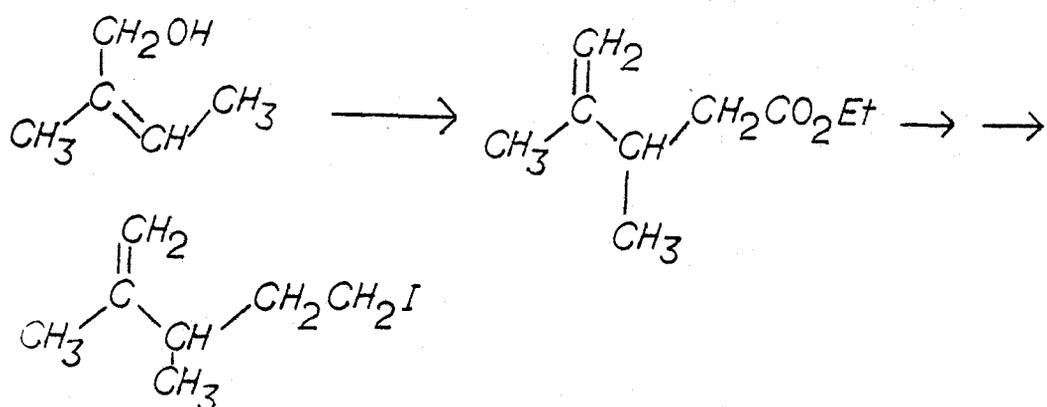
I. Synthesis of 3,4-Dimethyl-4-pentenyl Units

A. Plan of Synthesis

Any synthesis route which incorporates a repetitive process must satisfy a number of rather restrictive constraints. In the present case these would include the following. First there must exist one key reaction which sets up the repetitive process, and thus the functionality which permits this must result from the initial set of reactions. Second the process must install the terminal olefinic group and must not include any reaction which would permit its equilibration to the more stable position. Third the scheme is inherently likely to have a number of steps so reactions of high yield are needed, and fourth starting materials of low cost would be desirable.

The scheme chosen uses as the key reaction an alkylation of acetoacetic ester, and the terminal double bond is installed by a Claisen rearrangement. Thus, the overall process of installing a single unit proceeds as shown. Clearly this scheme meets the

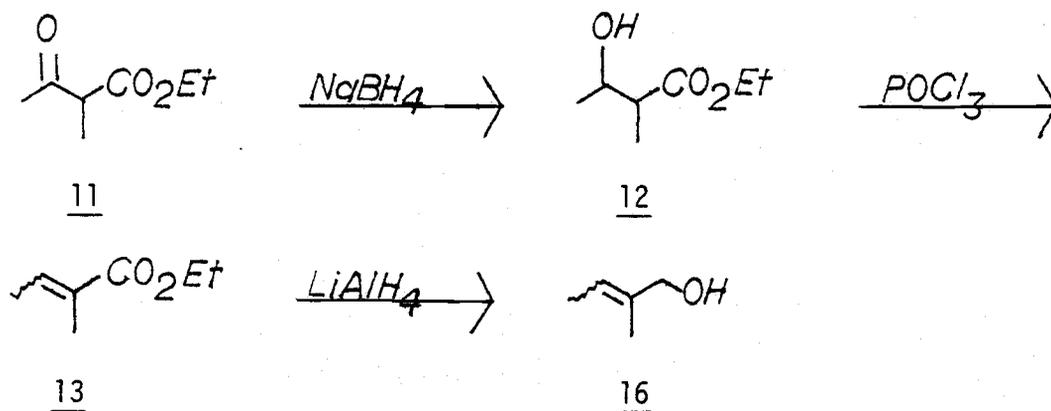




constraints noted and has the added advantage of providing a convenient function to permit addition of the final four carbon unit.

B. Experimental Results

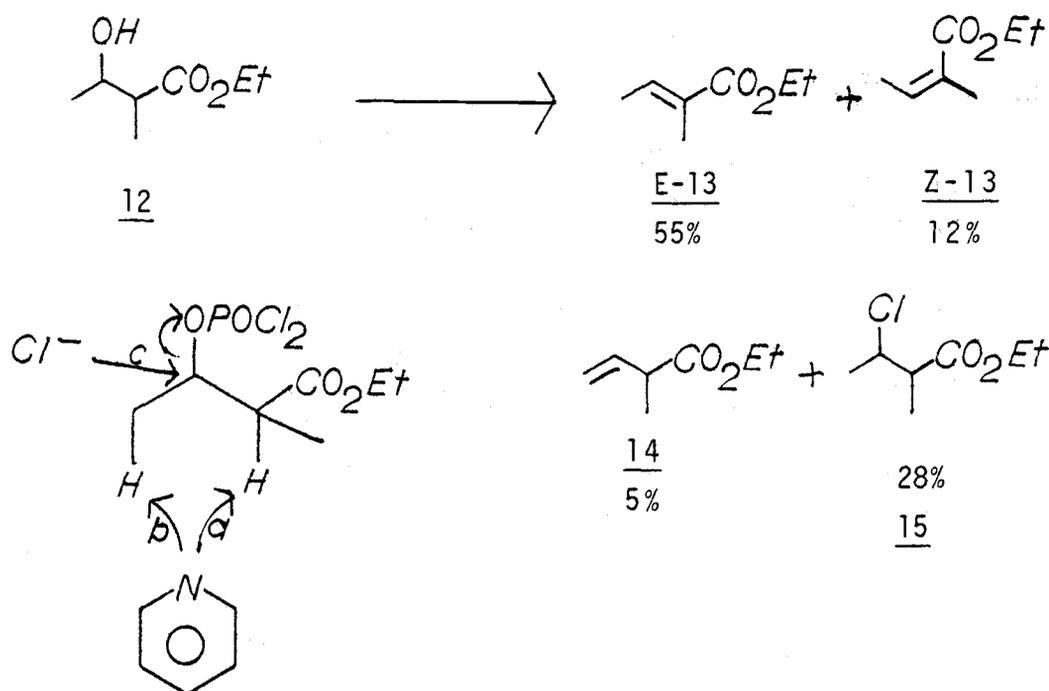
In general this repetitive process functioned very well and largely as anticipated. The precursor for the Johnson modification of the Claisen rearrangement, allylic alcohol 16, was prepared



conveniently and in reasonable yield as shown. The only reaction which posed any problems was the dehydration of the β -hydroxy ester. Four products were isolated, the olefinic esters as expected, but the relatively large amount of β -chloro ester was surprising since β -hydroxy esters are usually readily dehydrated. Obviously the transition state for the substitution does not show much sensitivity to

steric problems. Fortunately the chloro ester does not cause much problem since it is readily converted to the unsaturated ester by sodium ethoxide treatment.

Scheme 1



The minor olefin 14 was not isolated, but the assigned structure is consistent with the observed data. Its retention time on the glc column was very similar to the other olefins. The amount of material relative to the total obtained was very small (5%)--an expected result for a possible but less likely product.

The other two isomers were isolated by preparative glc. The infrared spectrum of both isomers showed only one carbonyl peak at 1710 cm^{-1} . This value is consistent with α, β unsaturated ester carbonyls which are shifted about 30 cm^{-1} due to weakening of the

carbon-oxygen double bond. The absorption at 740 cm^{-1} is typical for trisubstituted carbon-carbon double bonds. The major isomer isolated by glc showed a multiplet at $\delta 6.6-6.9$ in the ^1H nmr spectrum for the vinyl proton and was assigned to the E isomer, while the spectrum of the other isomer showed this multiplet at $\delta 5.8-6.1$. The E isomer would be the least sterically hindered, hence the major isomer. The assignment of the major product as the E isomer was further supported by comparing with known spectra. Its ^1H nmr spectrum was identical with a published spectrum of ethyl E-2-methyl-2-butenoate (26).

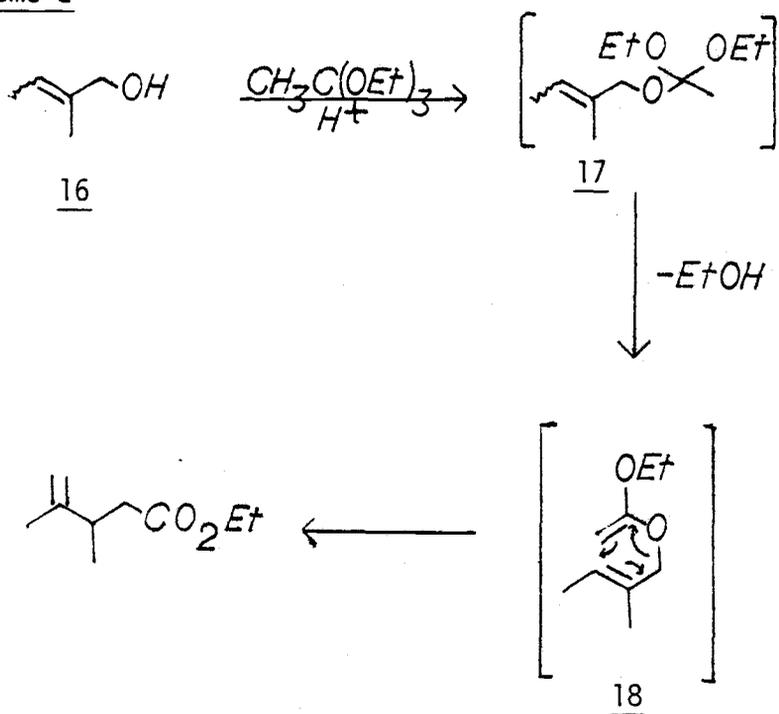
The product identified as the chloro ester 15 showed its ester carbonyl absorption at 1730 cm^{-1} . A distinctive absorption at 640 cm^{-1} suggested the presence of a chlorine atom, and the absence of any O-H stretch absorption showed the loss of the hydroxyl group. The presence of two $\text{CH}_3\text{CH-}$ groups, each in a different environment, was demonstrated by the methyl doublets at $\delta 1.5$ and $\delta 2.6$ in the ^1H nmr. The presence of two doublets for each methyl group was rationalized by the presence of diastereomers. Finally, the hydrogen α to the chlorine atom resonates at $\delta 4.2-4.5$ in the ^1H nmr.

The alcohol 16 was obtained by reduction of ester 13 with lithium aluminum hydride. Though this reaction often leads to some double bond reduction, no 2-methyl-1-butanol was detected in the product. The spectral data noted in the experimental section are generally unexceptional and provide adequate evidence of structure. One feature deserves special note since both E and Z isomers are expected. The $\text{CH}_2\text{-O}$ protons appear as a pair of singlets at 3.88 and 4.03 in an intensity ratio of 4 to 1. The ester 13 was a 4:1 mixture of E to Z isomers, and there being no reason for this ratio to be altered

in the reduction, the 3.88 resonance was assigned to the E isomer and that at 4.03 to the Z.

The one step of all these in the repetitive scheme which failed to come up to expectations was the Claisen rearrangement process. This step is the heart of the entire scheme and considerable effort was expended to try to maximize the yield. Initially the reaction was carried out under the conditions described by Johnson et al. (scheme 2) (27). But the yield was considerably lower than those

Scheme 2



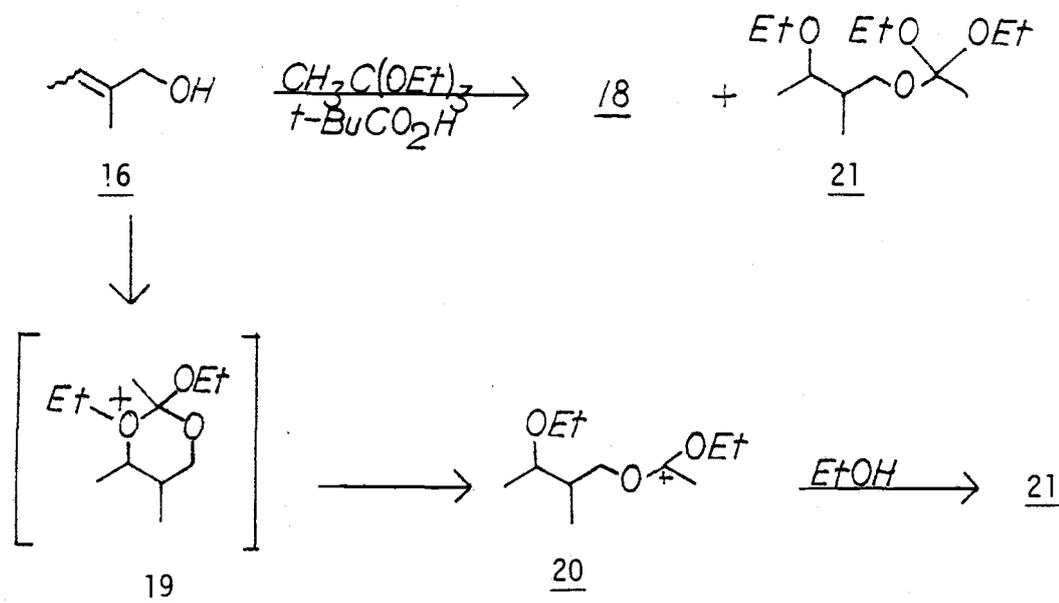
reported (50% vs. ca. 90% in their cases). Several peculiar features were observed for our case. It was noticed that after one hour with

propanoic acid as the catalyst the reaction appeared to be complete. Isolation of the products gave the ester 18, but accompanied by a substantial amount of material that appeared to be the intermediate 17. Recycling of the intermediate did improve the yield, but surprisingly, the yield was not improved to the extent expected from the amount of intermediate involved.

Second, as illustrated in experimental procedure B, the acid catalyst was actually destroyed as the reaction progressed. Addition of more propanoic acid did induce further reaction. Furthermore, an ester odor was detectable in the distillate. Ethyl propanoate was presumably being formed. It did not prove possible to obtain more than a disappointing 40-50% yield by varying the catalyst quantity and the reaction time. Extended heating gave a complex mixture of higher molecular weight materials. Thus an alternative catalyst was sought.

Pivalic acid was chosen because it is a weak acid like propanoic acid, but it should not esterify so rapidly due to the increased steric hindrance. This choice proved reasonable in that while the catalyst did eventually form an ester, it did not do so quickly enough to compete with the Claisen rearrangement. Unfortunately in the more important test, this catalyst failed since we obtained only 50% yield of the ester. Among the many other products, a substantial amount of a compound tentatively assigned the structure 21 was also obtained (scheme 3). It is possible that 21 is formed via an intermediate like 19 leading to the very stable carbonium ion 20. We have not been able to determine just why this process might compete with the concerted rearrangement.

Scheme 3

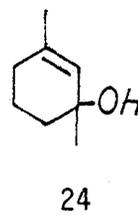
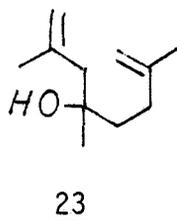
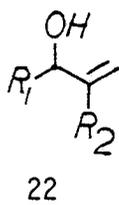


The structure of the intermediate was known to be a saturated ether from the absence of any olefinic carbons in the ^{13}C nmr spectrum, the absence of any olefinic protons in the ^1H nmr spectrum, and the presence of the 1370 cm^{-1} and 1150 cm^{-1} peaks (but none at $3600\text{-}3200\text{ cm}^{-1}$ or $1800\text{-}1700\text{ cm}^{-1}$) in the infrared. The multiplet at $3.2\text{-}3.7\text{ ppm}$ (7H) and at $4.0\text{-}4.4\text{ ppm}$ (2H) implied a compound like that of structure 21. The methyl groups at $\delta 1.0$ (multiplet), 1.14 (triplet), 1.37 (singlet), and 1.45 (doublet) were also consistent with this structure.

After a number of trials we eventually developed a procedure which gave ca. 70% yields. This involved a short reaction time, separation of the desired ester by distillation and recycling the

remainder with additional orthoacetate and catalyst (pivalic acid). Naturally this is more tedious than would be most advantageous, but no alternate process proved successful.

Our results with the Claisen rearrangement of this type are by no means unique. The original paper by Johnson et al. impressively demonstrated the use of triethyl orthoacetate to prepare γ, δ unsaturated esters from allylic alcohols (27). All alcohols represented were of the general formula 22. With the use of propanoic acid in catalytic amounts, they were able to obtain yields (heating at 138°C for 1-2 hr.) near 90% with very high stereoselectivity. Similar results have been reported by other groups, all using alcohols of the general type 22.

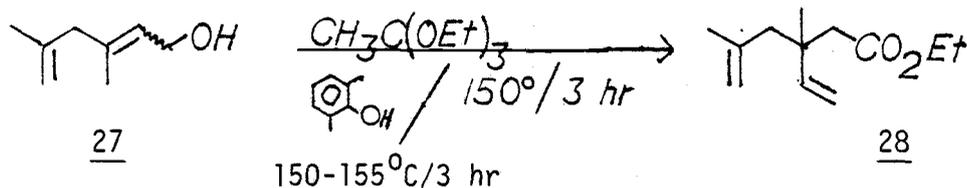
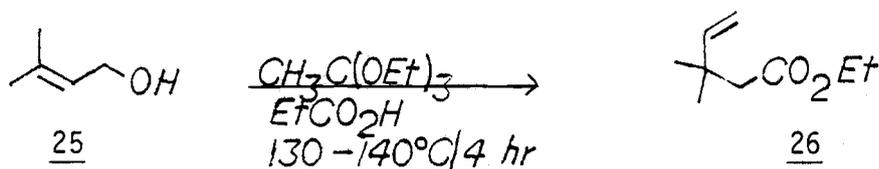


Esterification of the catalyst by any alcohol present appears to be a general phenomenon. Indeed, Johnson et al. reported this observation first and listed the following alternative catalysts: 2,4-dinitrophenol, ammonium nitrate, diphenylacetic acid, pivalic acid, and mesitoic acid (28). They also described a procedure with toluene as the solvent instead of triethyl orthoacetate. Since then, most workers have used one of these variations in their work.

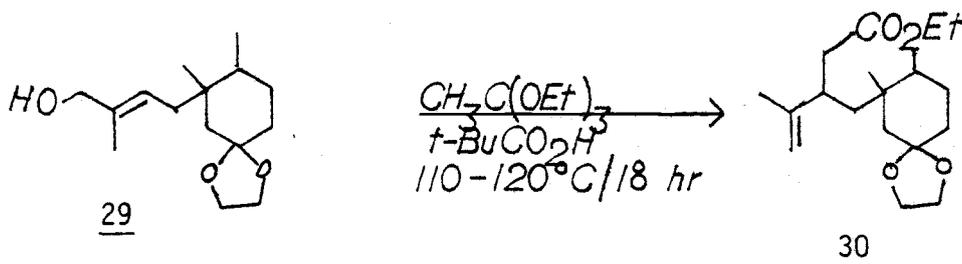
While not unexpected, it is also generally observed that the yields in this rearrangement are a strong function of the alcohol substrate. Those alcohols which have caused the greatest problems

fall into two main categories. The first are tertiary alcohols, as Parker and Kosley have noted (29). As one example they cited alcohol 23 from which no rearranged products were obtained. Büchi and Pickenhagen reported a 20% yield from the tertiary alcohol 24 (30).

The second category includes all alcohols having alkyl substituents on the γ carbon of the alcohol. Y. Nakado et al. report a 54% yield from the alcohol 25 (31). Similarly, Y. Fujita et al.

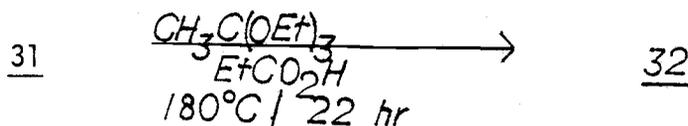
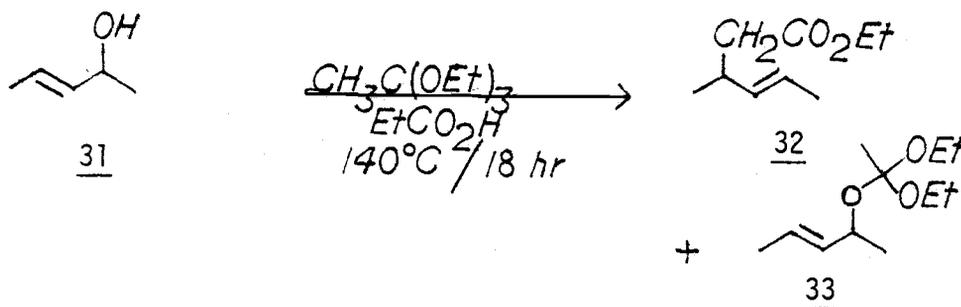


rearranged the alcohol 27 under the conditions specified isolating 83% of the product (32). They also commented that acid catalysts like 2-methylpropanoic acid, and presumably pivalic acid, and propanoic acid were not suitable because of esterification with the substrate alcohol 27. Ziegler et al. used pivalic acid to effect the rearrangement with alcohol 29 (33). They did not purify the ester 30, but did report 80% overall yield to the hydrolyzed ketal after



distillation. The structural similarity between alcohol 29 and 16 made this example particularly interesting.

Hill et al. reported difficulty with the rearrangement of alcohol 31 (34). Under the normal conditions (140°C|18 hr) two main



products were obtained. One of these was identified as the intermediate 33. Prolonged heating produced a better but still modest yield (68%).

It should also be noted that alcohol 16 is actually a mixture of E and Z isomers, with the E isomer being the major one (80%). One possible explanation of the low yields obtained could be that the Z isomer reacts significantly slower than the E isomer.

The ratio of E:Z isomers was 82:18 for the olefinic ester 13 and 80:20 for the alcohol 16 (integration of the singlet methylene protons). When the alcohol 16 was heated for 1.5 hr. in triethyl orthoacetate and a catalytic amount of propanoic acid, 50% of the rearranged product was obtained along with a second fraction which was largely the intermediate 17. The ratio of E:Z isomers for the intermediate 17 was 60:40 as determined by integration of the singlet methylene protons. Since the intermediate 17 represents most of the

unrearranged reactant, it is clear that the Z isomer is much less reactive than the E isomer in the rearrangement process. This result was based on a single observation and was not confirmed by a more rigorous study.

It is clear that the problems associated with rearrangement of 16 are common to alcohols of this type in this Claisen rearrangement. The extent to which the Z isomer of the alcohol contributes to the difficulties is uncertain, but could be significant since the lower rate of rearrangement would permit more intrusion by side reactions. At present the sole solution available is the judicious choice of catalyst and reaction conditions.

The final step which completes the generation of the initial segment in the repetitious process was reduction of the ester 18 to an alcohol 34. This was accomplished in high yield with lithium aluminum hydride. The structure of this key intermediate in the synthesis was established firmly by a combination of spectral methods. A broad band in the infrared spectrum between 3550-3100 cm^{-1} , a ^{13}C nmr resonance at 61 ppm and a triplet at 3.50 in the ^1H nmr spectrum proved the presence of a $-\text{CH}_2\text{CH}_2\text{OH}$ grouping. Two ^{13}C nmr peaks at 109.5 and 149.5 combined with an 890 cm^{-1} band in the infrared to provide clear evidence for a $\text{CH}_2=\text{C}$ fragment. Further support for this was found in the multiplet (2H) at δ 4.6-4.8 in the ^1H nmr spectrum. Furthermore a three hydrogen singlet showing long range coupling at 1.67 indicated an allylic methyl, hence $\text{CH}_3-\text{C}=\text{CH}_2$. The final touches were added by noting a three hydrogen doublet at 1.02 and a sextet (1H) at 2.31 implicating the presence of a $\text{C}(\text{CH}_3)_2\text{CH}_2-$ group.

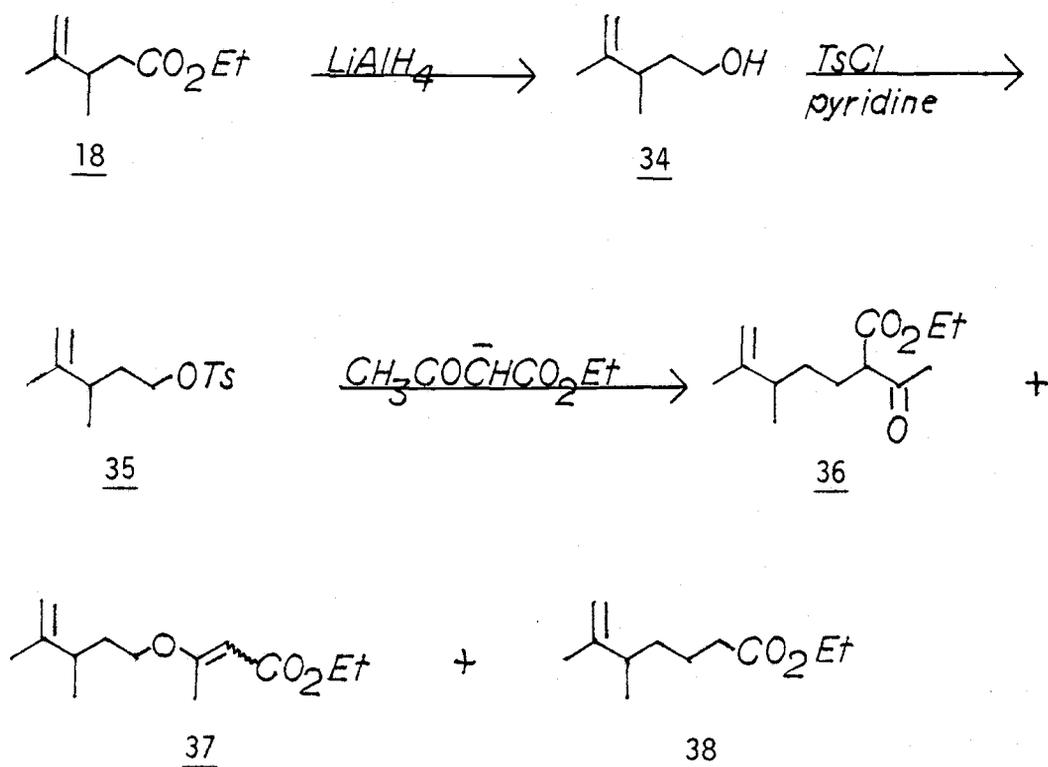
Combined, these pieces unequivocally produce the structure 34 for this alcohol.

This result is satisfying in view of the ^{13}C nmr spectrum of the ester 18, which raised some questions about the structure of that molecule. The absence of a resonance for the disubstituted olefinic carbon was explicable since its intensity is expected to be low. More troublesome was the question of the ester carbonyl resonance. A weak band at $\delta 190$ might be assignable to that carbon, but the assignment must be considered dubious. The position of the resonance is abnormal and has no precedent. Furthermore, it would seem surprising to see the carbonyl resonance where the olefinic carbon resonance was lost in the noise. Thus we believe this 190 peak is spurious and the carbonyl resonance is simply not visible because of its low intensity. Since all other data are in accord with the structural assignment for 18, no loose ends remain.

C. The Second Repetition

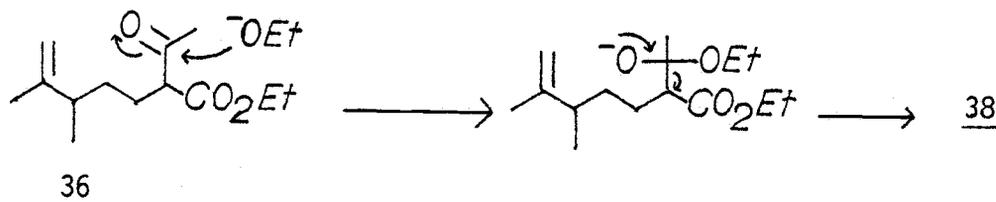
The second repetition proceeds exactly as did the first except that the methyl group is replaced by the 3,4-dimethyl-4-pentenyl unit in the alkylation of acetoacetic ester. Initially the tosylate 35 of the alcohol 34 was used in this alkylation (scheme 4). The alkylation gave a mixture of products, of which the major product was the keto ester 36, isolated in ca. 40% yield. Also present, was the O-alkylated product 37 which was identified by its infrared bands (1720 cm^{-1} and 1630 cm^{-1}). The ^1H nmr confirmed this showing a singlet at $\delta 2.2$ ($\text{CH}_3\text{C}=\text{}$) and a second singlet at $\delta 4.86$ ($\text{C}=\text{CHCO}_2\text{Et}$).

Scheme 4



Presence of the ester 38 was rationalized via a retrograde acetoacetic ester synthesis (scheme 5), although its formation was surprising.

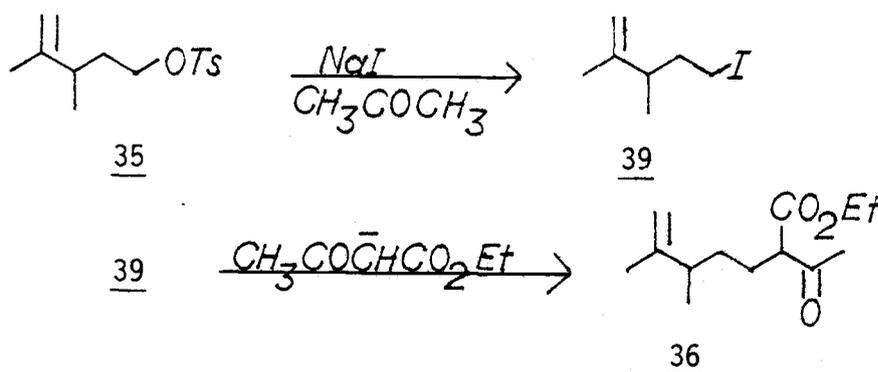
Scheme 5



Ambident nucleophiles often cause problems, partitioning the reaction between the two (or more) different nucleophilic centers. Ethanol generally favors attack by the less electronegative atom,

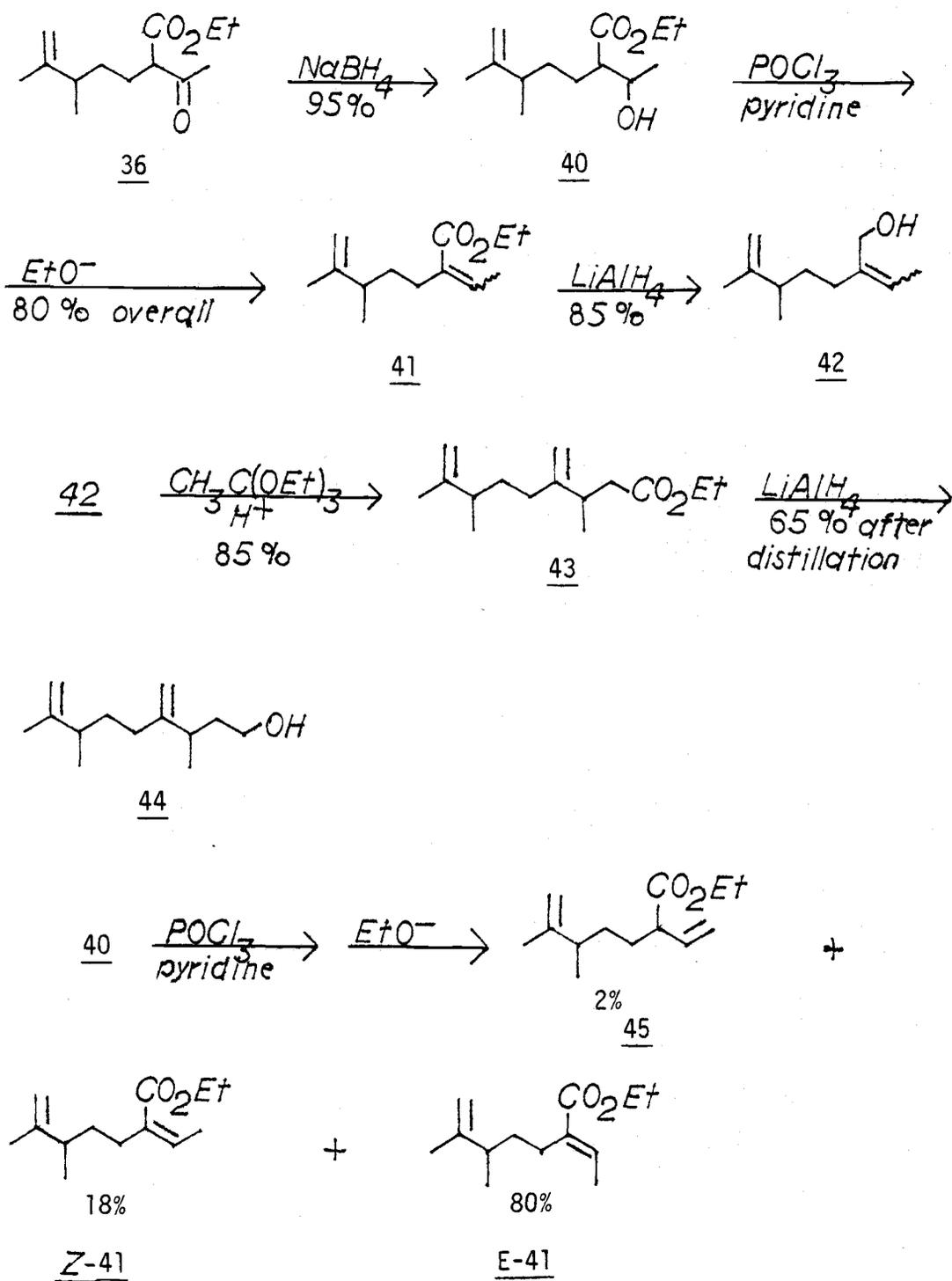
carbon. But in this case, the tosyl group increases the "hardness" of the substrate favoring attack by the more electronegative atom, oxygen. Replacing the tosylate with an iodide should decrease the "hardness" of the substrate aiding reaction of carbon. Indeed, treating ethyl acetoacetate with the iodide 39 gives the desired product without significant diversion to the enol ether.

The only product isolated from the alkylation reaction was the keto ester 36, indicated by the presence of only two bands in the carbonyl region (1740 and 1720 cm^{-1}). Many sections of the ^{13}C nmr spectrum showed pairs of peaks of almost identical chemical shift and intensity which suggested the presence of diastereomers, as expected.



The sequence of reactions was then repeated with the keto ester 36 to give finally the alcohol 44 (scheme 6). As before, the dehydration process gave a stereoisomeric mixture of olefinic esters. The isomeric distribution was determined by glc, and the single olefinic proton resonates for the Z and E isomers at $\delta 5.90$ and $\delta 6.70$ respectively. Interestingly the proportion of isomers in this case is almost exactly the same as for 13. Since the major isomer has its

Scheme 6

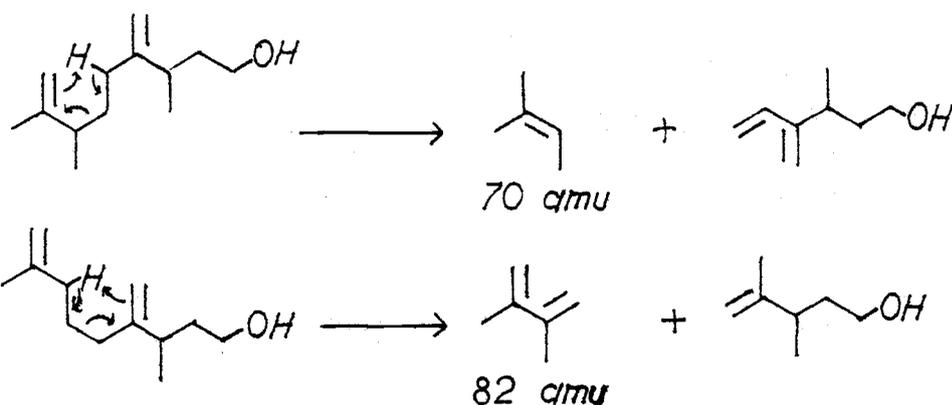


olefinic proton resonance at 6.70 ppm, it was assigned the E stereochemistry. Similarly, the CH₂-O protons for the alcohol 42 appeared as a pair of singlets at 3.91 and 4.05 in an intensity ratio of 4:1. Analogous to the alcohol 16, the 3.91 resonance was assigned to the E isomer and the 4.05 resonance was assigned to the Z isomer. In general, the chemical shifts of these protons for the allylic alcohols appear to be dependent upon the stereochemistry of the double bond--those protons for the E isomer being farther upfield.

Results of the individual steps in the second sequence were strikingly similar to those in the first sequence. It should be mentioned that reduction of the olefinic ester 41 to the alcohol 42 gave a few percent of 2-ethyl-5,6-dimethyl-6-hepten-1-ol 46, a product of overreduction. It was detected only when it appeared as one of several products from an unsuccessful reaction. Since it was a minor constituent and difficult to separate from the desired product, no attempt to separate it was made during the synthesis.

Completion of the double cycle at alcohol 44 makes this a key compound whose structural identity must be clearly established. The molecule produces a clear parent ion peak in the mass spectrum at 196 amu, appropriate for the molecular formula C₁₃H₂₄O. The oxygen is accounted for by a hydroxyl function (broad infrared band 3100-3600 cm⁻¹). Of the thirteen carbons, all different since there are thirteen distinct resonances in the ¹³C nmr, eleven are defined as follows. The ¹H nmr spectrum has a triplet at 3.53 ppm indicative of a -CH₂CH₂OH entity. Presence of two terminal methylene groups was illustrated both by the set of four carbon resonances at 107.81, 109.83, 149.15 and 154.16, as well as the four hydrogen multiplet

at 4.6-4.8 in the ^1H nmr spectrum. A singlet (3H) at 1.66 confirms the allylic methyl group, and a doublet (6H) at 1.03 ppm gives evidence of two CHCH_3 groups. In view of the mode of synthesis it is very difficult to assign a structure other than 44. but the assignment is bolstered by two significant rearrangement peaks in the mass spectrum at 70 and 82 amu. Both can be nicely rationalized via McLafferty rearrangements as shown below. Thus we feel that the structural assignment to this alcohol is on sound ground.



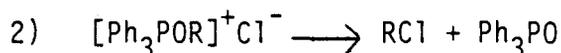
This completes the synthesis of the two methylated isoprene units. With the leaving group in the proper position, the addition of the final four carbon unit to make the half molecule is possible. The overall yield from the β -keto ester 11 is 4.5% for fourteen steps, or an average of 80%/step.

II. Addition of the Terminal Four Carbon Unit

The terminal four carbon unit is composed of a 2-buten-1-ol entity joined to the original thirteen carbon chain at C₃ of the butenol. While it would seem most expedient to add all four carbons in a single step, it would also be possible to introduce these two at a time in a pair of steps. The first would require formation of a bond between carbons of sp³ and sp² type, a process for which a number of organometallic methods have been developed recently, if the double bond is to be inserted directly. Obviously the two plus two route permits a wider range of possibilities. However, in either case the thirteen carbon unit must serve either as an organometallic reagent or as substrate for a nucleophilic substitution. Hence, the initial step in this final sequence must be the conversion of the alcohol 44 to a function appropriate for either purpose. For this use of an alkyl bromide seemed ideal.

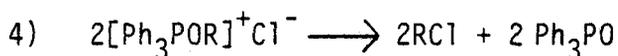
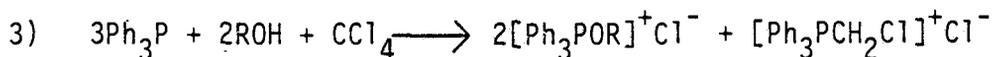
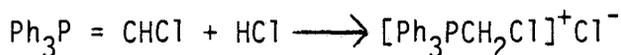
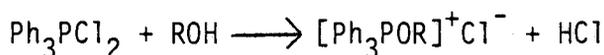
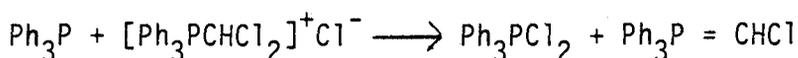
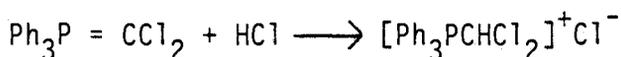
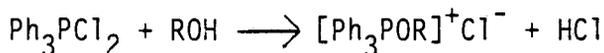
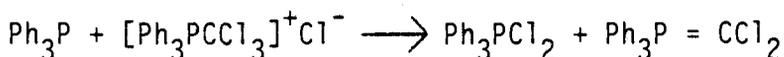
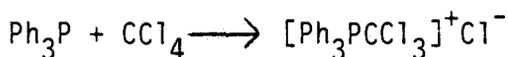
A. Formation of the Bromide

Presence of the two terminal double bonds, subject to ready rearrangement under acid conditions, limits the choice of methods to convert the alcohol 44 to a bromide. The reagent CBr₄/Ph₃P appeared ideal since it involves relatively non-acidic conditions and the reaction can be carried out under mild conditions generally. The mechanism of this reaction is rather complex. One important route is that of equations 1 and 2 (shown for CCl₄) (35, 36).



Note that this indicates a ratio of 1:1:1 for the three reactants.

However, a more complex sequence also plays a role as illustrated in the set of equations with a summary below.

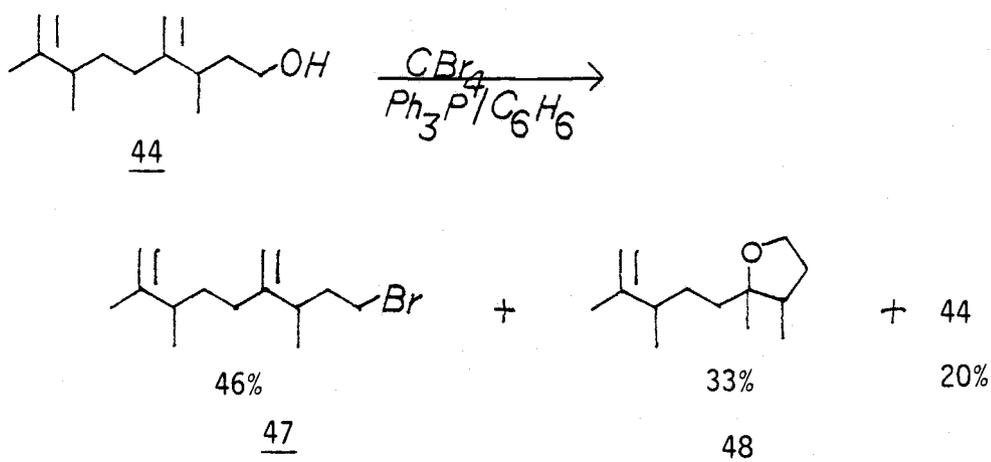


Overall this requires a reagent ratio of 3:2:1, and since the two routes each produce about 50% of the product, the resultant requires a ratio of Ph_3P to ROH of ca. 1.25:1.0.

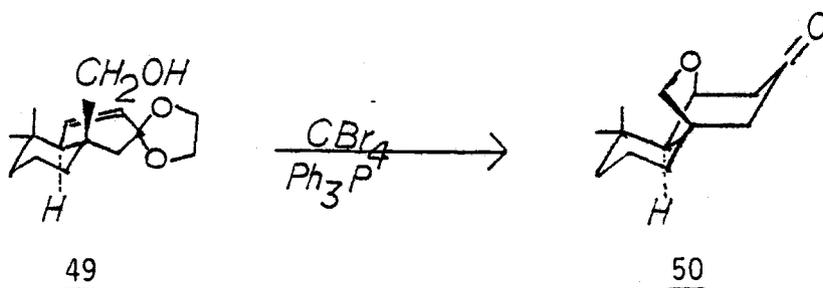
It has generally been presumed that the use of carbon tetrabromide instead of carbon tetrachloride would make little difference in this discussion. However, Hooz and Gilani state that a molar ratio of 2:1 ($\text{Ph}_3\text{P}:\text{ROH}$) is required to effect this conversion (37). This suggests that the competitive pathway described by the longer set of equations is a more rapid one with respect to that described by

equations 1 and 2. However, that cannot be the sole route, and the final answer is not yet clear.

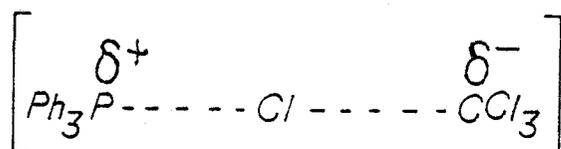
Indeed, it was found that when the alcohol 44 was treated with $\text{CBr}_4/\text{Ph}_3\text{P}$ in benzene, each of the reagents being equimolar with the alcohol, a mixture of products was isolated. The presence of the



recovered alcohol merely demonstrated that under these conditions, only part of the alcohol was able to react. Formation of the ether 48, however, was unexpected. Some precedence for such a product has been provided by Dailey and Fuchs (38). When alcohol 49 was treated with triphenylphosphine and carbon tetrabromide, they isolated only the cyclized product 50. Although their alcohol had a very different



structure from ours, a tetrahydrofuran was again obtained. It would appear that the acid produced in the more complex mechanism could be responsible for the ether formation. A procedure was developed by Hayashi et al. which should remedy this problem (39). It has been suggested that the intermediate complex 51 forms and reacts with



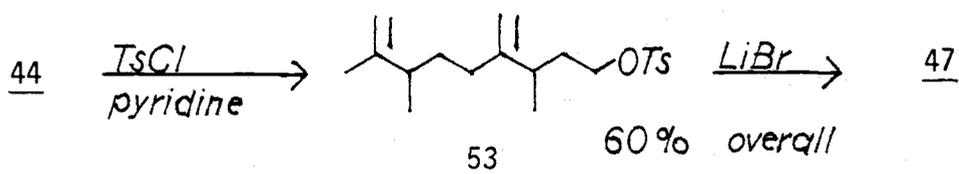
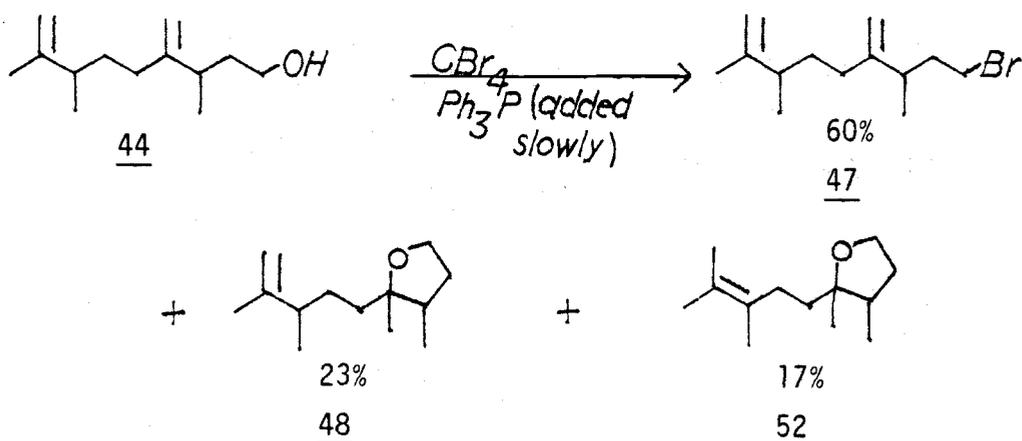
51

alcohol in equation 1. Hayashi et al. reasoned that if triphenylphosphine were added to the reaction mixture of the alcohol and carbon tetrabromide very slowly, only one equivalent of triphenylphosphine would be required because equation 1 would be the sole source of $[\text{Ph}_3\text{POR}]^+\text{Cl}^-$ (39).

Indeed, when this procedure was followed with the alcohol 44, the reaction went to completion (scheme 7). However, the ether formation still persisted.

To separate the bromide 47 from the ethers 48 and 52 required the use of a silica gel column. Obviously, this was most undesirable, and therefore an alternative procedure which required two steps was employed (scheme 7). The overall yield was modest, but the bromide was obtained free of any side products and under very mild conditions. Furthermore, when the alkyl iodide was required later, the same general procedure was used.

Scheme 7

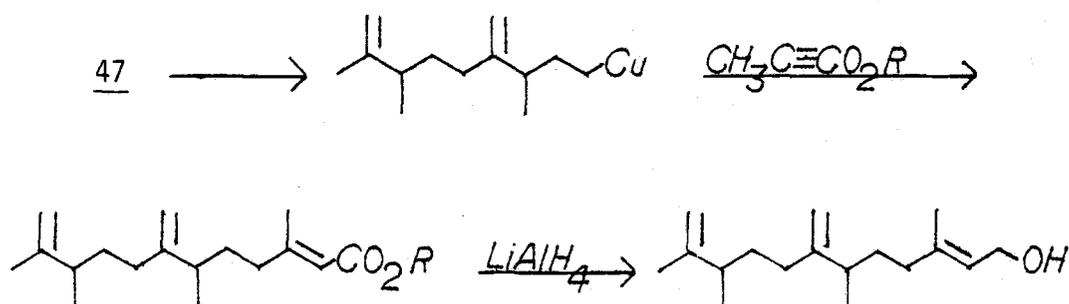


The bromide **47** was adequately characterized by spectral methods. Absorption at 670 cm^{-1} gave evidence for the carbon-bromine group as did the triplet ($-\text{CH}_2\text{CH}_2\text{Br}$) at $\delta 3.30$ in the ^1H nmr spectrum. ^{13}C nmr showed the presence of thirteen carbons, and in particular the four which indicate the terminal carbon-carbon double bonds. And finally, the mass spectrum showed two mass peaks at 258 and 260 with relative intensities of 1.5% and 1.2%, respectively.

B. Organometallic Methods

At this point the main fragment is in proper condition to be used as a generator of organometallic species, or as a nucleophilic

substrate. We chose first to use it in an organometallic form, an expedient choice since organo-copper reagents add 1,4 to α,β -unsaturated carbonyls. Thus a two step process could be envisioned, leading directly to the desired half molecule in the form of an alcohol. Following the general procedure of Anderson *et al.*, pentyl



bromide as a model was converted to a copper reagent and added in good yield to methyl tetrolate (40, 41). Unfortunately when this convenient procedure was attempted with 47, only the dimer 54 was obtained. The assignment of structure to this product was based on the presence of the $>\text{C}=\text{CH}_2$ proton resonances in the ^1H nmr, the absence of any functional group bands in the infrared spectrum, and the parent ion at 358 in the mass spectrum. The ^{13}C spectrum was misleading in that it contained one extraneous peak. All other information accorded well with the assigned structure.

There are three processes which could conceivably account for the formation of the dimer 54. The first is that the copper species can react with another halide molecule as shown in equation 6. Whitesides *et al.* studied a closely related reaction, the treatment of alkyl halides with dialkyl cuprates (42). Equation 7 is a typical example.

products were obtained. This suggested that the structural differences in the alkyl group in some way influenced the formation of the dimer 54.

A third possible route, thermal oxidative coupling process, seems to be the best explanation. It has been observed that $\text{CuCl}_2 \cdot \text{TMEDA}$ works as well in the oxidative coupling process as does oxygen. And presumably, $\text{CuI}_2 \cdot \text{TMEDA}$ would also function very well. No precautions were taken to remove any traces of copper (II) iodide in our reactions. However, Kauffmann has demonstrated that the alkyl group often affects the relative proportion of products to a greater extent than does the presence or absence of any copper (II) ions (Table 6).

Table 6. Reaction of alkylmagnesium bromides with one mole of CuCl_2 (yields in brackets with CuCl) in ether at 0°C to form the coupling product (R-R) and the disproportionation products (RH, alkene) (44).

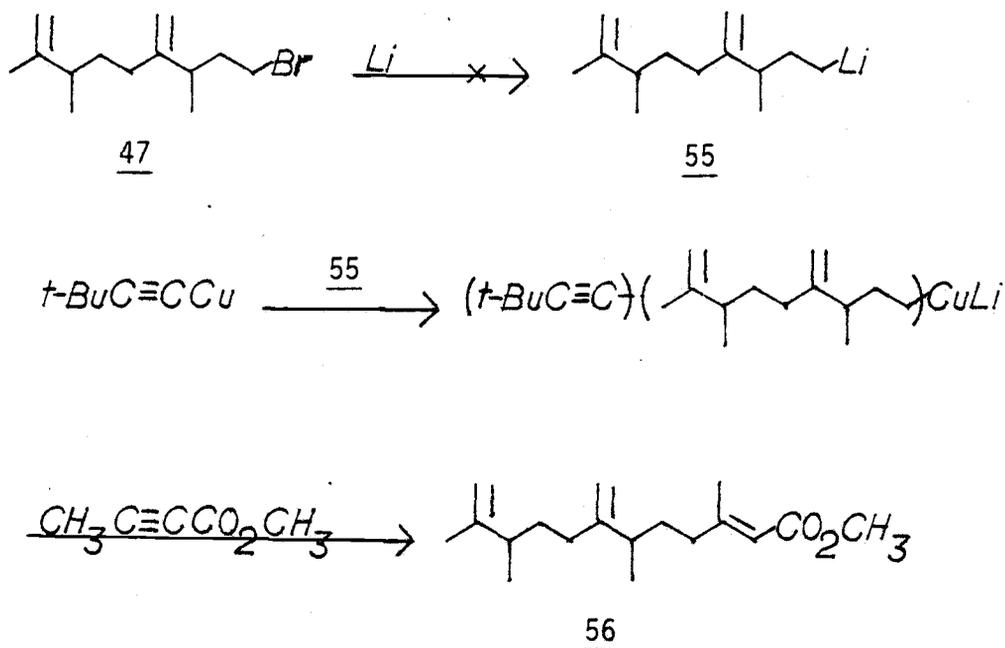
R	R-R	RH	Alkene
C_8H_{15} -	9 (3)	47 (47)	43 (49)
 -	58 (26)	21 (39)	21 (34)
 -	1	46	42

As a result neither the route to the dimer nor any mode of action to eliminate it was devised. Accordingly our further attempts to use this general approach took a slightly different turn.

A number of investigators have developed mixed cuprates which will also add in a conjugate fashion (45-50). In each case, one of

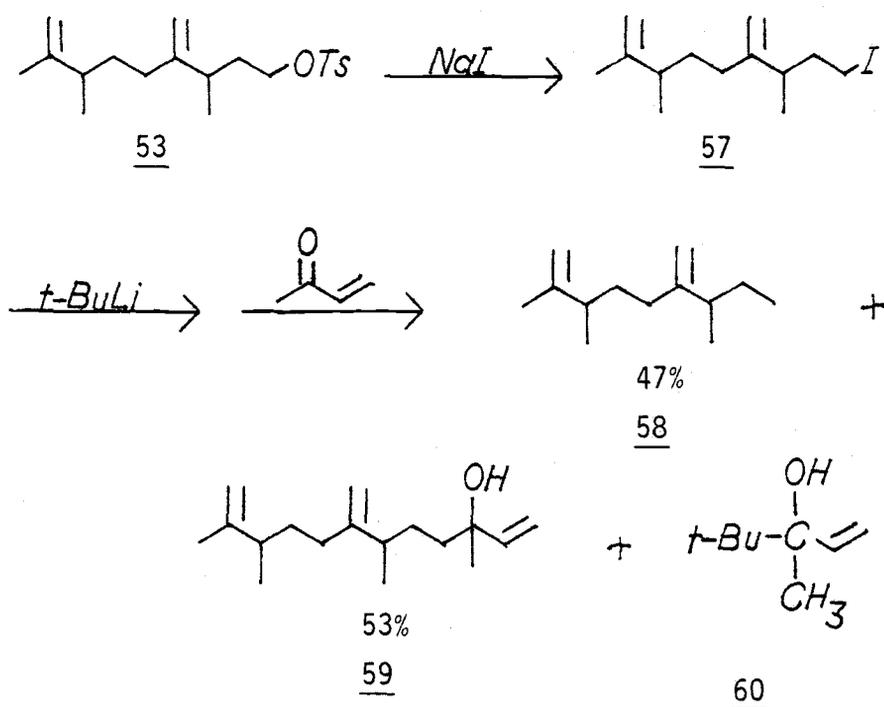
the two alkyl groups associated with the copper was one that binds very strongly, allowing the other alkyl group to be transferred selectively. This is an economic necessity since only one group is transferred from a dialkyl cuprate to the substrate. The non-transferrable group, 3,3-dimethyl-1-butyne, developed by Herbert O. House, was chosen here because the intermediate is more readily soluble in ether solvents (50). This appeared to be important because one of the possible problems with the alkyl copper species leading to the dimer was its lack of solubility in diethyl ether. The procedure as outlined in scheme 8, was used. Unfortunately, all attempts to obtain the alkyl lithium 55 from the bromide 47 were unsuccessful.

Scheme 8



Failure to obtain a lithium reagent from bromide 47 and lithium metal prompted an examination of other routes to alkyllithium compounds. A specially attractive method would appear to utilize lithium-halogen exchange. Unfortunately, the method is very effective for preparing aryllithiums, but suffers with alkyllithiums from unfavorable equilibria. Control of this problem by concentration means alone is not very useful since serious separation problems can result. However, one trick which has proven successful in many cases is to use tert-butyllithium with a primary iodide. Since even with this an excess of tert-butyllithium must be used, the generation of a suitable copper reagent from the resultant mixture appeared fraught with difficulties. Thus we searched for a different four carbon unit to add. For this purpose, methyl vinyl ketone seemed suitable. Tertiary vinyl carbinols can readily be rearranged to their allylic rearrangement partners, in the present case the desired terminal allylic alcohol. Any excess 3,4,4-trimethyl-1-penten-3-ol derived from the tert-butyllithium should be easily removed by distillation.

Treatment of the iodide 57 with tert-butyllithium in three-fold excess followed by addition of a large excess of methyl vinyl ketone did indeed produce the desired alcohol 59. Surprisingly, this was accompanied by a rather large amount of the hydrocarbon 58. Obviously because no 57 was recovered and 58 + 59 account for more than 90% of iodide used, the conversion to the lithium reagent was successful. Unfortunately however, the lithium reagent appears to act as a hindered reagent causing a very large amount of enolization rather than direct addition to the carbonyl.

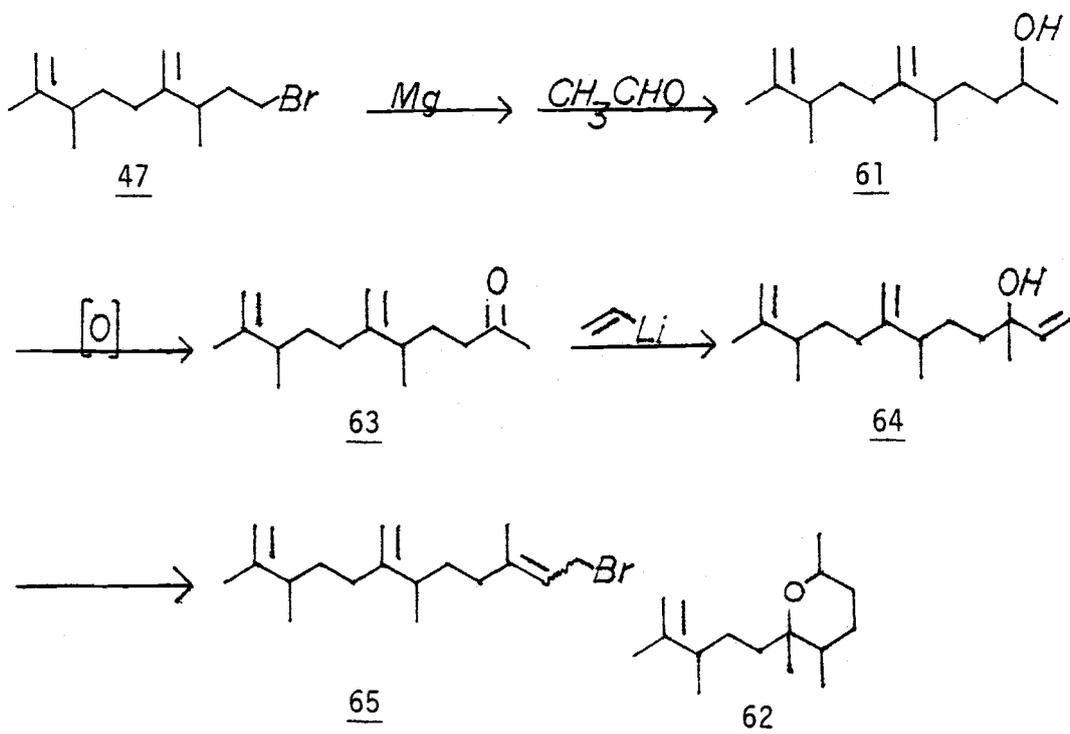


The hydrocarbon was separated and identified by the presence of a broad singlet (4H) at 4.6 and a molecular ion peak at 180 amu in the mass spectrum. The alcohols 59 and 60 were not separated but the two were identified spectrally from resonances at 4.65, 4.9-6.2 (borderline ABX) and 0.92 (s).

C. The Two Plus Two Route

Loss of about half of the iodide 57 in the lithium/methyl vinyl ketone reaction is not acceptable and prompted a search for an alternate route. A two carbon plus two carbon process leading through a methyl ketone with final addition of a vinyl Grignard seemed a reasonable choice. The methyl ketone could be generated from the bromide 47 via a Grignard, addition to acetaldehyde and oxidation. The first step was carried out as proposed but did not give the alcohol 61 as expected, giving instead the cyclized product 62. Ring closure of

Scheme 9



the alcohol was clearly occurring during work-up in the presence of dilute aqueous hydrochloric acid. This indicated a very great sensitivity of the alcohol to very mild acid. To circumvent any such difficulties, we decided to convert the Grignard directly to the methyl ketone 63, by-passing the alcohol.

Reaction of an organomagnesium reagent with acetonitrile (51), dimethylacetamide (52), acetic anhydride (52), acetyl chloride (-78°C) (53), diethyl phenyl orthoacetate (54), acylimidazolidine (55), S-(2-pyridyl) thioacetate (56), 8-acyloxyquinoline (57), 2-acyloxy-3-methylpyrazine (58), and N-(methylaminopyridine) acetamide (59) and of the organomanganese with acetyl chloride (60) have all been used successfully in some cases.

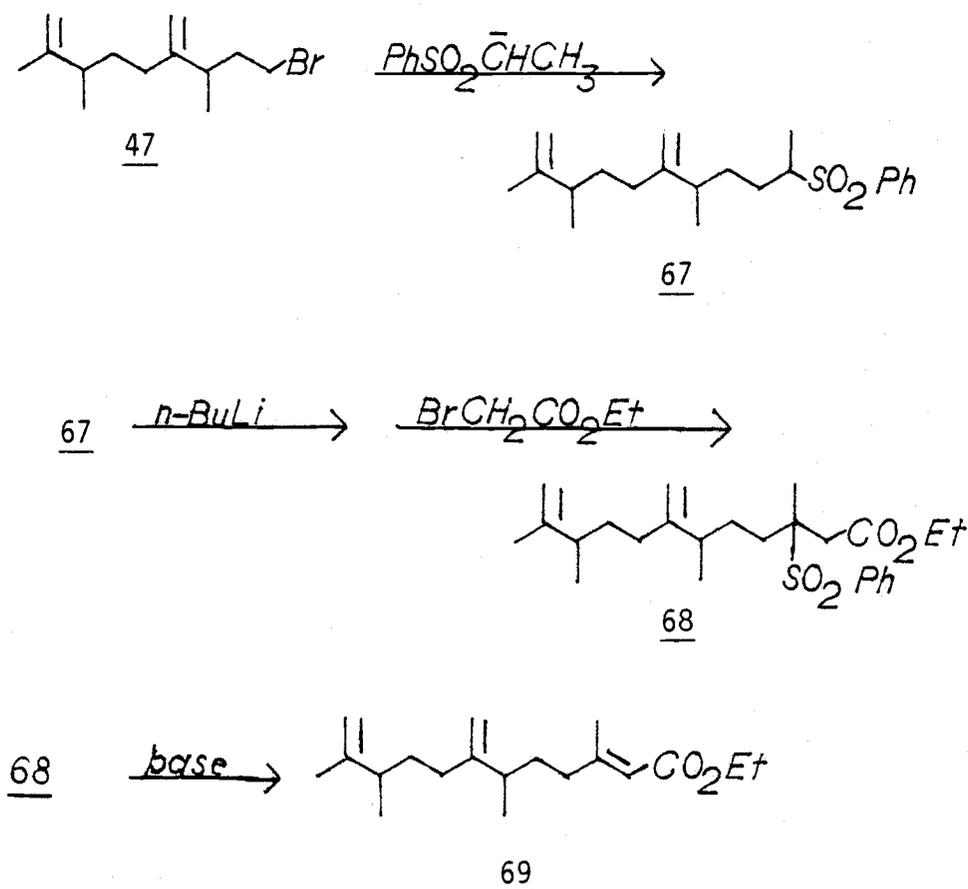
Of these various methods the use of acetyl chloride at low

temperature in tetrahydrofuran has proved most effective. Attempts to apply this procedure to 47 gave a mixture of recovered bromide, hydrocarbon 58 and at least four unidentified products. Obviously the modest amount of Grignard formed was not sufficiently reactive under these conditions and was destroyed during work-up. The use of acetylimidazide which permits reactions at a higher temperature led to no greater success. Though so far unexplicable, it appeared that the use of tetrahydrofuran as a solvent was hindering formation of the Grignard reagent, a process which occurs readily and in good yield in diethyl ether. A last attempt to use an organomanganese reagent prepared in diethyl ether gave rise to a mixture of products in which a ketone was barely detectable.

D. The Bromide 47 as Nucleophilic Substrate

At this point it had become clearly evident that organometallic reagents derived from 47 act as badly hindered compounds not eminently suitable for preparative purposes. Since 47 is a primary halide it seemed reasonable to expect it to participate readily as substrate for a nucleophilic displacement. Of the many reactions of this type available, the general scheme of Julia utilizing sulfone anions seemed very appealing (61). Specifically tested procedures for the introduction of the very four carbon group we desired were already available (scheme 10).

Scheme 10

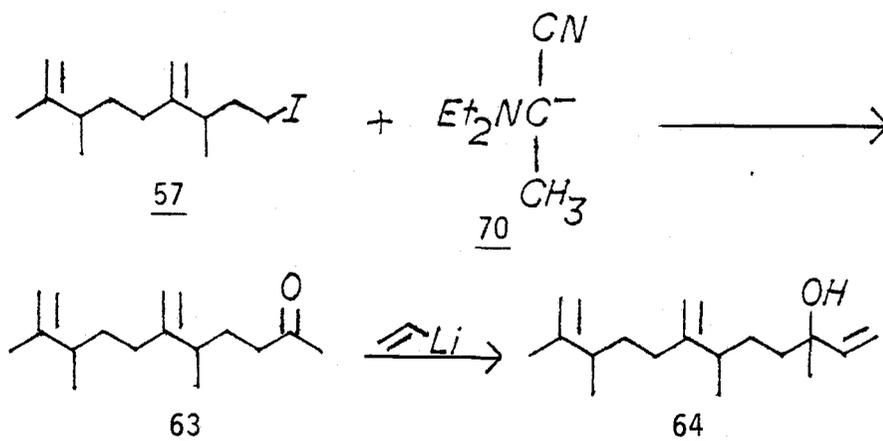


The first step in this scheme proved totally satisfactory, giving 75% of the purified phenyl sulfone 67. However the anion of this sulfone produced the ester 68 in low yield, never exceeding 23%. While it might appear that the anion of such a heavily substituted sulfone would be severely hindered and thus lead inevitably to such poor yields, this had not been observed with model compounds of comparable complexity. Furthermore, the isolation of 68 in pure form was difficult because the by-products were not readily separable.

Evidence that the ester 68 was formed comes from the following spectral results. An infrared band at 1740 cm^{-1} indicates the presence of a saturated ester, while bands at 730 and 690 cm^{-1} along with

a five hydrogen multiplet at 7.4-8.0 shows a monosubstituted phenyl. Bands at 1380 and 1150 cm^{-1} characterize the sulfone moiety, while a doublet (6H) at 1.0, singlet (3H) at 1.6 and a singlet (4H) at 4.7 provide presumptive evidence of the nature of the remainder of the molecule. Oddly enough, the only peak in the ^{13}C nmr spectrum possibly attributable to the ester carbonyl carbon was at 209 ppm. Since this lies some 30 ppm downfield from the normal range for carbons of this type, it must be the result of an impurity or some instrumental aberration.

A modified approach to this two plus two route was developed based on the masked carbonyl anion reaction of Stork *et al.* (62).



The iodide **57** reacted with the aminonitrile anion **70** to give the methyl ketone **63** in high yield. This ketone was identified spectrally by means of the 1720 cm^{-1} band in the infrared, the peak at 298.85 ppm in the ^{13}C spectrum and a three hydrogen singlet at 2.00 in the ^1H nmr spectrum. All characteristic bands for the remaining skeletal groups were in evidence and the molecular ion peak at 222 was present in the mass spectrum.

The alcohol **64** was readily prepared by treating **63** with vinyl-lithium. No problems surfaced in this step which proceeded in good

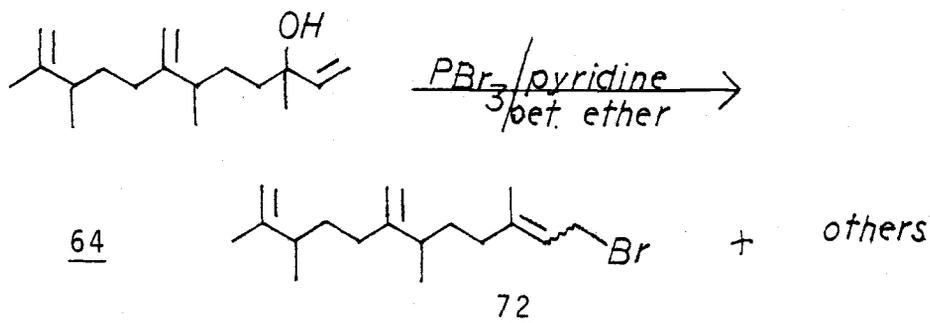
yield. Evidence for the structure of this alcohol included the normal spectral data associated with the main carbon skeleton including the rearrangement peaks at 70 and 82 amu discussed earlier. A broad infrared band at 3200-3600 cm^{-1} shows the presence of a hydroxyl group, and the absence of any resonance between 3.0 and 4.5 shows it must be tertiary. A three hydrogen singlet at 1.27 suggests a $\text{CH}_3\text{-C-OH}$ group, and the ^{13}C nmr spectrum indicates six olefinic carbons, one C-O and a total of seventeen carbons all different. Finally, the ^1H nmr shows a typical near ABX pattern for a terminal vinyl group not coupled to any additional protons. Analysis of this portion of the spectrum by the procedure of Castellano and Waugh gave two sets of acceptable parameters and calculated spectra (Table 7) (63). It is difficult, and perhaps unnecessary, to distinguish between these two. However the $J_{\text{AB}} = 1.49$ for set A corresponds better to expectations since most sp^2 geminal couplings are small and positive.

All that remains to complete the synthesis of the half molecule is the rearrangement of the hydroxyl group from the tertiary carbon to the primary carbon, converting the double bond to the more stable position. This can conceivably be done very neatly by treating the alcohol with a suitable brominating or chlorinating agent, allowing the double bond to rearrange to the more thermodynamically stable position, thus producing directly the halogen derivative required for the coupling process.

The tertiary alcohol 64 was treated with phosphorus tribromide in pyridine and petroleum ether according to the procedure of Isler (77). And while this reaction appeared to give a bromide, separation

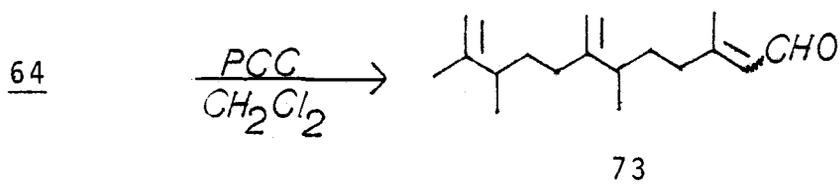
Table 7. Observed and predicted intensities (normalized to 12) for the vinyl portion of the ^1H nmr spectrum of alcohol 64. Set A represents that for $\delta_A = 5.00$, $\delta_B = 5.16$, $\delta_C = 5.85$ ppm, $J_{AB} = 1.49$, $J_{BC} = 17.02$, and $J_{AC} = 10.89$ cps. Set B represents that for $\delta_A = 4.96$, $\delta_B = 5.22$, and $\delta_C = 5.84$ ppm, $J_{AB} = -1.42$, $J_{BC} = 18.04$, and $J_{AC} = 9.38$ cps.

δ (ppm)	obs	A	B
6.03	-	0.00	0.00
6.01	0.35	0.68	0.68
5.90	0.77	0.84	0.86
5.83	1.00	1.08	1.09
5.73	1.40	1.41	1.41
5.71	-	0.00	0.00
5.25	2.70	1.08	1.09
5.23		1.41	1.21
5.08		0.77	0.99
5.061	3.94	0.75	0.53
5.058		1.25	1.04
5.04		0.99	1.20
4.95	1.85	0.91	0.69
4.94		0.84	1.06
4.29		-	0.00



of the products gave a nonpolar fraction which appeared to contain mixtures of several isomers. The mass spectrum did not show a mass peak at 313, but did show a relatively intense peak at 232. This corresponded to the loss of hydrogen bromide. The ^1H nmr, however, indicated that the terminal double bonds had largely rearranged to the more stable trisubstituted positions. This was shown by the overly intense peak at $\delta 1.7$ corresponding to allylic methyl groups, and the weaker peak at $\delta 4.6-4.8$ for the protons of the terminal double bond. One would expect to obtain an integration ratio of 4:1 for the terminal double bond protons to the other olefinic proton. Instead a ratio of 1:2 was obtained. The reaction conditions obviously were not suitable. An alternative two step procedure was examined because of the non-acidic conditions involved.

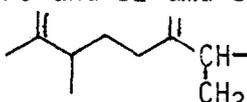
Many workers have successfully rearranged tertiary allylic alcohols by treating them with chromium oxidation reagents. Treatment of the alcohol 64 with pyridinium chlorochromate gave the aldehyde



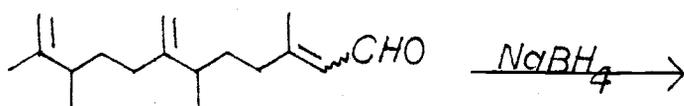
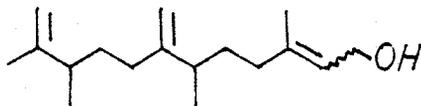
in 88% yield. The reaction proceeded slowly (20 hr), monitored by thin layer chromatography, and characterization of the product indicated a trace of the alcohol 64 present in the final mixture.

The aldehyde was identified by the carbonyl peak at 1670 cm^{-1} in the infrared spectrum. The expected mass peak at 248 amu was also observed. The ^1H nmr showed an aldehyde proton resonance at 9.88 and 9.96 assigned to the two geometric isomers. The terminal double bonds were also observed (δ 4.6-4.8) and integrated with the olefinic and aldehyde protons in a ratio of 4:1:1 respectively.

The alcohol 74 was obtained by reducing the aldehyde 73 with sodium borohydride. The broad peak at $3550\text{-}3100\text{ cm}^{-1}$ indicated compound 74 was an alcohol. The peaks at 890 and 760 cm^{-1} indicated the presence of a terminal and a non-terminal double bond. The ^{13}C nmr shows peaks at 107.51, 109.55, 149.79, and 154.43 for the two terminal double bonds. The peaks at 123 and 140 represent the carbons for the other double bond. The seventeen carbon peaks coupled with the weak mass peak at 250 suggests the empirical formula $\text{C}_{17}\text{H}_{30}\text{O}$. The doublet at 1.01 ppm, the singlet at 1.62 ppm, the multiplet at 4.6-4.8 in the ^1H nmr, and the rearrangement fragments at 70 and 82 amu suggests as discussed earlier that the frag-

ment  is intact in this structure. The multiplet at 3.9-4.1 (2H), the multiplet at 5.2-5.4 (1H), and the other information just mentioned suggests that the fragment

$\text{>C=CHCH}_2\text{OH}$ is also present. Finally, the singlet methyl at 1.62 integrates for two methyl groups. Combining these fragments leads directly to the structure for alcohol 74.

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Summary

A preliminary comparison of the spectral properties of the half molecule with that of botryococcene as observed by Maxwell supports the structure they obtained (20, 25). The peak at 892 cm^{-1} for botryococcene agrees with the peak at 890 cm^{-1} for the half molecule and both are assigned to an exomethylene unit. The singlet at $\delta 4.6$ observed in the proton spectrum of botryococcene is found at exactly the same position as the terminal double bond hydrogens for the half molecule. A comparison of the ^{13}C nmr peaks is given in Table 9. While we did not identify the shift for each carbon in the range 30-50 ppm, we did observe the same number of carbons in this region for botryococcene. The close agreement of the two structures strongly supports the established conclusions of Maxwell.

Table 9. A comparison of chemical shifts for some carbons in botryococcene with those of alcohol 64.

Carbon	Botryococcene	Alcohol <u>64</u>
14	39.3	29.4
15	30.4	31.4
16	40.3	33.2
18	31.9	39.9
19	33.7	40.2
20	41.2	40.8
17	154.9	154.1
21	149.9	149.6
22	109.8	109.5
31	20.6	18.7
33	19.1	19.6
34	20.0	20.2
32	107.5	107.5

EXPERIMENTAL

General. Nuclear magnetic resonance spectra were obtained on Varian EM-360 (60 MHz) and Varian HA-100 (100 MHz) spectrometers for proton spectra and a Varian FT-80A (80 MHz) for carbon spectra. Tetramethylsilane was used as an internal standard for proton spectra and deuteriochloroform for carbon spectra. Brackets are used to indicate peaks of isomeric carbons when diastereomers are present in samples for carbon spectra. Infrared spectra were obtained on a Perkin-Elmer 727B infrared spectrophotometer with a polystyrene film standard. Low resolution mass spectra were obtained from an Atlas CH7 instrument.

Glpc analyses were performed on a Varian A 90-P3 and Varian Aerograph Autoprep A-700, each having a thermal conductivity detector. The columns used are given below:

Column 1. 8'x $\frac{1}{4}$ " 4% SE-30 on Chromosorb W 45/60

Column 2 4'x $\frac{1}{4}$ " 5% OV-17 on Chromosorb G 45/60

Column 3 2'x $\frac{1}{4}$ " 9% SE-30 on Chromosorb W 45/60

Column 4 4'x $\frac{1}{4}$ " 3% SF-96 on Chromosorb W 45/60

Silica Woelm (100-200 Aktiv.), activity 1, was used for all column chromatography separations.

Unless otherwise stated, solvents were removed under reduced pressure with a Büchi model R rotary evaporator. To prepare Grignard reagents on a small scale, a few magnesium turnings were scraped with emery paper and broken into smaller pieces. Standard initiating methods were then employed with reasonable success.

Ethyl 2-methyl-3-hydroxybutanoate 12

To 500 ml of absolute ethanol was added 9.5 g (0.25 moles) of sodium borohydride. After the mixture had been cooled in an ice bath, 63.5 g (0.44 moles) of ethyl 2-methyl-3-oxobutanoate 11, prepared according to the procedure of Marvel and Hager (64), was dripped in over a 30 minute period. The solution was then stirred at room temperature for 90 min. and 100 ml of 2.5N hydrochloric acid was quickly added. The solution was stirred for 30 min, and then was neutralized (K_2CO_3) and the ethanol distilled. The product was taken up in diethyl ether, the solution was dried ($MgSO_4$) and then concentrated giving 60.6 g of crude product, 85% pure by glc (column 1, $R_f = 0.40$ relative to ethyl benzoate), overall yield of the hydroxy ester 12: bp 71-73°C/5 mm (lit. (65) 176-180°C); ir (neat) 3600-3150 (O-H stretch), 3000-2850, 1730 (C=O ester), 1455, 1375, 1260, 1180, 1090, 1040 cm^{-1} ; 1H nmr (CCl_4) δ 1.12 (d, 3H, J = 6.5 Hz), 1.14 (d, 3H, J = 6.5 Hz), 1.26 (t, 3H), J = 7 Hz), 2.2-2.5 (m, 1H, $-CHCO_2Et$), 3.5-3.8 (br s, 1H, $-OH$), 3.5-4.0 (m, 1H, $-CHOH$), 4.13 (q, 2H, J = 7 Hz) [lit. (66) ir (film) 3500 & 1730 cm^{-1}].

Ethyl 2-methyl-2-butenolate 13

The method of Rinehart and Perkins was followed (67). To a solution of 32.2 g (0.22 moles) of the hydroxy ester 12 in 250 ml of pyridine, was added 54.2 g (0.35 moles) of freshly distilled phosphorus oxychloride over a 45 minute period. The solution was

stirred in an oil bath (100-110°C) for 2.5 hours. The cooled solution was added to 150 g of cracked ice. The crude product was extracted with petroleum ether (30-60°C), the solution was dried (MgSO_4), and then was concentrated under reduced pressure. Gas chromatography showed the presence of four compounds (column 1, relative peak area, R_f relative to ethyl benzoate). Peak 1 (5%, 0.26) was presumed to be ethyl 2-methyl-3-butenate 14. Peak 2 (12%, 0.32) was identified as ethyl Z-3-methyl-2-butenate 13. Peak 3 (55%, 0.40) was identified as ethyl E-2-methyl-2-butenate 13. And peak 4 (28%, 0.57) was identified as ethyl 2-methyl-3-chlorobutanoate 15. Distillation with a spinning band column gave 13.7 g (49%) of the olefin 13 and 11.0 g (0.066 moles) of ethyl 2-methyl-3-chlorobutanoate 15: bp 115°C/60 mm; ir (neat) 3000-2850, 1730 ($\text{C}=\text{O}$ ester), 1450, 1380, 1260, 1160, 1080, 640 cm^{-1} ; ^1H nmr (CCl_4) δ 1.28 (t, 3H, $J = 7$ Hz), 1.21 & 1.29 (d, 3H, $J = 7$ Hz), 1.49 & 1.53 (d, 3H, $J = 6.5$ Hz, $\text{CH}_3\text{CHCl-}$), 2.54 & 2.72 (quintet, 1H, $J = 7$ Hz), 4.15 (q, 2H, $J = 7$ Hz), 4.2-4.5 (m, 1H, $-\text{CHCl-}$).

The chloroester 15 was added to a sodium ethoxide solution prepared from 2.3 g (0.10 moles) of sodium in 50 ml of anhydrous ethanol. After having been stirred for 45 min, the solution was acidified with 25 ml of 2N hydrochloric acid, this solution was extracted with petroleum ether (30-60°C), and the extract was dried (MgSO_4). The solvent was removed and the product was distilled, giving 6.0 g (70%) of the olefin 13. The total olefin obtained was 19.7 g (70%): bp 81-83°C/60 mm (lit. (68) 153-156°C); ir (neat) 3000-2850, 1710 ($\text{C}=\text{C}-\text{C}=\text{O}$ ester), 1650 ($-\text{C}=\text{C}-$ trisubstituted), 1450, 1380, 1260, 1140, 1080, 1040, 740 cm^{-1} ; ^1H nmr (E isomer, CCl_4) δ 1.26 (t, 3H,

J = 7 Hz), 1.7-1.9 (m, 6H), 4.13 (q, 2H, J = 7 Hz), 6.6-6.9 (m, 1H, $\underline{\text{HC}}=\text{C}$); ^1H nmr (Z isomer, CCl_4) δ 1.29 (t, 3H, J = 7 Hz), 1.8-2.1 (m, 6H), 4.16 (q, 2H, J = 7 Hz), 5.8-6.1 (m, 1H, $\underline{\text{HC}}=\text{C}$).

2-Methyl-2-buten-1-ol 16

A mixture containing 24.7 g (0.65 moles) of lithium aluminum hydride and 350 ml of anhydrous diethyl ether was prepared under a nitrogen atmosphere. A solution of 42.3 g (0.33 moles) of the olefinic ester 13 in 150 ml of anhydrous diethyl ether was added over a 90 minute period to the hydride mixture. After the mixture had been stirred for an additional 60 min, 30 g of ethyl acetate was added. Finally, 250 ml of ammonium chloride solution (saturated) followed by 500 ml of diethyl ether was added. The solution was filtered, and then extracted with diethyl ether. The extract was dried (MgSO_4) and then concentrated to give 25.6 g (90%) of the olefinic alcohol 16: bp $85^\circ\text{C}/70$ mm (lit (69) 138°C); ir (neat) 3650-3100 (O-H stretch), 3050, 3000-2850, 1460, 1390, 1070, 1050, 1010, 960, 830, 780 cm^{-1} ; ^1H nmr (CCl_4) δ 1.5-1.8 (m, 6H, $\underline{\text{CH}}_3-\text{C}=\text{C}$), 2.68 (s, 1H, -OH), 3.88 & 4.03 (s, 2H, $-\underline{\text{CH}}_2\text{OH}$, by integration E:Z = 80:20), 5.2-5.6 (m, 1H, $\underline{\text{CH}}=\text{C}$); ^{13}C nmr ($\text{CDCl}_3/\text{CCl}_4$) δ 13.00, 13.35, 68.53 ($-\underline{\text{CH}}_2\text{OH}$), 130.05 & 135.54 ($\underline{\text{C}}=\underline{\text{CH}}$).

Ethyl 3,4-dimethyl-4-pentenoate 18

Method A. The method of Johnson et al. was used (27). To 450 ml of triethyl orthoacetate and 1.6 ml of propanoic acid was

added 27.6 g (0.32 moles) of the alcohol 16. The solution was stirred in an oil bath (140°C) for 90 min while ethanol was removed by distillation. Distillation of the residual material with a spinning band column gave 24.1 g (48%) of the ester 18 and 10.7 g of a second fraction. Ester 18: bp 47°C/4 mm; ¹H nmr (CCl₄) δ 1.02 (d, 3H, J = 6.5 Hz), 1.25 (t, 3H, J = 7 Hz), 1.75 (s, 3H), 1.9-2.8 (m, 3H), 4.10 (q, 2H, J = 7 Hz), 4.6-4.8 (m, 2H, C=CH₂).

The intermediate, 2-methyl-2-butenyl diethyl orthoacetate 17, was identified as a major component in the second fraction (bp 62-80°C/5 mm): ¹H nmr (CCl₄) δ 1.14 (t, 6H, J = 7 Hz), 1.36 (s, 3H), 1.5-1.7 (m, 6H, presumably CH₃C=CHCH₃), 3.1-3.7 (m, 4H), 3.81 & 3.98 (s, 2H), 5.2-5.6 (m, 1H).

To the second fraction was added 0.5 ml of propanoic acid. The solution was heated in an oil bath (140-150°C) for 1 hour. Distillation with a spinning band column produced 2.6 g (5%) of the ester 18 and 6.6 g of another fraction (bp 78°C/1 mm). Further heating of this fraction produced a complex mixture of products which were not identified. Total yield of the ester 18 was 26.7 g (53%).

Method B. To 50 g of triethyl orthoacetate was added 3.2 g (0.037 moles) of the alcohol 16. The solution was placed in an oil bath (135°C) and stirred while ethanol was removed. Small amounts of propanoic acid were added as shown (Table 8). Each aliquot was added when distillation of the volatiles ceased from the previous aliquot. The solution was then refluxed for 19 hrs. Distillation with a short column packed with glass helices gave 2.5 g (43%) of the ester 18: bp 50-55°C/6 mm.

Table 8. Timetable for addition of propanoic acid to the orthoester solution.

Reaction Time (min)	Acid added (g)	Total Distillate (g)
0	0.25	0.0
15	0.15	0.4
40	0.10	1.5
110	0.30	3.6
120	-	3.6

Method C. To 550 g of triethyl orthoacetate and 1 g of pivalic acid was added 42.4 g (0.49 moles) of the alcohol 16. The solution was stirred in an oil bath (140-150°C) for 24 hrs. Distillation with a spinning band column gave 41.4 g (55%) of the ester 18 (bp 47°C/5 mm) and 26.3 g of a second product which was tentatively identified as 2-methyl-3-ethoxybutyl diethyl orthoacetate 21: bp 57°C/0.5 mm; ir (neat) 3000-2850, 1450, 1370, 1220, 1150, 1040, 940 cm⁻¹; ¹H nmr (CCl₄) δ 0.9-1.1 (m, 3H), 1.14 (t, 9H, J = 7 Hz), 1.37 (s, 3H), 1.45 (d, 3H, J = 7 Hz), 2.0 (m, 1H), 3.2-3.8 (m, 7H), 3.9-4.4 (m, 2H); ¹³C nmr (CDCl₃/CCl₄) δ 15, 19, 20, 20, 21, 39, 57, 57, 63, 68, 113 (-OC(OEt)₂).

Method D. To 132 g (0.81 moles) of triethyl orthoacetate and 0.8 g (8 mmoles) of pivalic acid was added 9.7 g (0.11 moles) of the alcohol 16. The solution was stirred in an oil bath (140°C) with simultaneous distillation of ethanol for 2 hrs. Distillation with a spinning band column gave 8.0 g (46%) of the pentenoate 18 (48°C/5 mm) and 5.5 g of a second fraction (50-115°C/5 mm). Glc

of the second fraction (column 4, column temperature 80°C, helium flow 60 ml/min) showed (relative peak area, retention time) that the intermediate 17 was the main constituent (50%, 4.9 minutes) and that (2-methyl-2-butenyl)-2,2-dimethylpropanoate 71 (9%, 2.2 mins) was also present: ir (neat) 3000-2850, 1730 (C=O ester), 1480, 1460, 1380, 1280, 1150, 1030, 780 cm^{-1} ; ^1H nmr (CCl_4) δ 1.17 (s, 9H), 1.6-1.8 (m, 6H), 4.40 (s, 2H), 5.3-5.6 & 6.9-7.1 (m, 1H); ^{13}C nmr (CDCl_3) δ 13.13, 27.18, 39, 69.98 ($-\text{OCH}_2-$), 123.19 ($\text{C}=\text{CHCH}_3$), 161 (C=O ester).

The second fraction was added to 150 ml of triethyl orthoacetate and 0.2 g of pivalic acid. The solution was stirred in an oil bath (140°C) for 27.5 hrs. Distillation with a spinning band column gave 4.2 g (25%) of the ester 18 (bp 47°C/5 mm). A total of 12.2 g (70%) of the ester 18 was obtained: bp 46-48°C/5 mm; ir (neat) 3060, 3000-2850, 1740 (C=O ester), 1640, 1460-1440, 1370, 1280, 1170, 1060, 1030, 890 cm^{-1} ; ^1H nmr (CCl_4) δ 1.05 (d, 3H, $J = 6$ Hz), 1.22 (t, 3H, $J = 7$ Hz), 1.72 (d, 3H, $J = 1$ Hz), 2.1-2.8 (m, 6H, $\text{CH}_3\text{CHCH}_2-$), 4.07 (q, 2H, $J = 7$ Hz), 4.6-4.8 (m, 2H, $-\text{C}=\text{CH}_2$); ^{13}C nmr ($\text{CDCl}_3/\text{CCl}_4$) δ 15, 20, 20, 38, 41, 60 ($\text{CH}_3\text{CH}_2\text{O}-$), 110 ($\text{C}=\text{CH}_2$), 190 ($\text{C}=\text{O}$ ester?).

3,4-Dimethyl-4-penten-1-ol 34

Under nitrogen, 6.1 g (0.16 moles) of lithium aluminum hydride was added to 200 ml of anhydrous diethyl ether and the mixture was cooled in an ice bath. To this was added a solution of 26.7 g (0.17 moles) of the ester 18 in 150 ml of anhydrous diethyl ether and

the suspension was stirred at room temperature for 60 min. Sufficient water and 2N sulfuric acid was added to dissolve the salts. The aqueous portion was extracted with diethyl ether, and the extract was washed with potassium carbonate and sodium chloride solutions, dried (MgSO_4), and concentrated under reduced pressure. This gave 18.0 g (90%) of the pentenol 34; (lit. (70) 72-75°C/14.5 mm); ir (neat) 3550-3100, 3080, 3000-2850, 1650, 1450, 1380, 1050, 1000, 890 cm^{-1} ; ^1H nmr (CCl_4) δ 1.02 (d, 3H, $J = 6.5$ Hz), 1.4-1.7 (m, 2H), 1.67 (d, 3H, $J = 1$ Hz), 2.31 (sextet, 1H, $\text{CH}_3\text{CHCH}_2^-$), 2.71 (s, 1H, $-\text{OH}$), 3.50 (t, 2H, $J = 6.5$ Hz, $-\text{CH}_2\text{CH}_2\text{OH}$), 4.6-4.8 (m, 2H, $\text{C}=\text{CH}_2$); ^{13}C nmr (CDCl_3) δ 18, 19, 37.2, 37.6, 61 ($-\text{CH}_2\text{OH}$), 109.5 ($\text{C}=\text{CH}_2$), 149.5 ($\text{C}=\text{CH}_2$) [lit. (71) ir, ^1H nmr, mass spectrum, and CHN analysis].

2,3-Dimethyl-5-iodopentene 39

The method of Schleyer was used to make the tosylate (72). A pyridine solution was prepared by combining 13.0 g (0.114 moles) of the pentenol 34, 44.6 g (0.234 moles) of p-toluenesulfonylchloride, and 150 ml of anhydrous pyridine. After standing for 19 hrs (0°C), the solution was poured into 200 g of ice and the mixture was stirred for 15 min. The tosylate was taken up in diethyl ether, and the solution was washed with 9N phosphoric acid and saturated sodium bicarbonate solution, dried (MgSO_4), and concentrated under reduced pressure. This gave 31 g of crude tosylate 35. To convert the tosylate to an iodide the method of Eglinton and Whiting was used (73). The crude tosylate 35 was added to 51.6 g (0.34 moles)

of sodium iodide in 500 ml of acetone (reagent grade). The solution was stirred and refluxed for 17 hrs, after which the acetone was removed under reduced pressure. The residue was triturated with diethyl ether, and the ether solution was washed with sodium thiosulfate solution, dried (MgSO_4), and concentrated giving 18.0 g (70% overall) of the iodide 39: bp $40^\circ\text{C}/0.5$ mm; ir (neat) 3060, 3000-2850, 1640, 1450, 1375, 1240, 1180, 890 cm^{-1} ; ^1H nmr (CCl_4) δ 1.02 (d, 3H, $J = 6.5$ Hz), 1.65 (d, 3H, $J = 1$ Hz), 1.84 & 1.87 (q, 2H, $-\text{CHCH}_2\text{CH}_2\text{I}$), 2.33 (sextet, 1H, $J = 6.5$ Hz), 3.10 & 3.13 (t, 2H, $-\text{CH}_2\text{CH}_2\text{I}$), 4.77 (s, 2H, $\text{C}=\text{CH}_2$); ^{13}C nmr (CDCl_3) δ 4.58 ($-\text{CH}_2\text{I}$), 18.4, 19.09, 38.62, 41.86, 110.96 ($\text{C}=\text{CH}_2$), 147.1 ($\text{C}=\text{CH}_2$).

Ethyl 2-(1-oxoethyl)-5,6-dimethyl-6-heptenoate 36

Method A. Sodium ethoxide solution from 0.6 g (0.026 moles) of sodium was treated with 3.4 g (0.026 moles) of ethyl acetoacetate and the solution was stirred for 45 min. To this solution was added 5.3 g (0.020 moles) of the tosylate 35 and the mixture was refluxed for 4 hrs. Hydrochloric acid (40 ml, 1 N) was added, and the solution was extracted with diethyl ether. The ether extract was washed with distilled water, dried (MgSO_4), and concentrated. Distillation gave 1.4 ml (bp $50-115^\circ\text{C}/0.7$ mm) of product. Glc (column 3) showed 4 main products (relative peak area, R_f relative to cyclododecane). Peak 1 (10%, 0.054) was identified as ethyl-5,6-dimethyl-6-heptenoate 38: ^1H nmr (CCl_4) δ 1.00 (d, 3H, $J = 6.5$ Hz), 1.23 (t, 3H, $J = 7$ Hz), 1.64 (d, 3H, $J = 1$ Hz), 1.1-2.4 (m, 4H), 2.20 (m, 3H, $\text{CH}_3\text{CH}-$ & $-\text{CH}_2\text{CH}_2\text{CO}_2\text{Et}$), 4.07 (q, 2H, $J = 7$ Hz), 4.66 (s, 2H).

Peak 2 (12%, 0.13) was not identified. Peak 3 (68%, 0.21) was

identified as the keto ester 36: ^1H nmr (CCl_4) δ 1.0 (d, 3H), 1.3 (t, 3H), 1.3-2.1 (m, 5H), 1.6 (s, 3H), 2.1 (s, 3H, $\text{CH}_3\text{C}=\text{O}$ ketone), 3.2 (t, 1H, $-\text{CH}_2\text{CHC}=\text{O}$ ketone), 4.1 (q, 2H), 4.7 (s, 2H).

Peak 4 (11%, 0.29) was identified as (3,4-dimethyl-4-pentenyl) enol ether of ethyl acetoacetate 37: ir (CCl_4) 3080, 3000-2850, 1720, 1630 (s), 1450, 1380, 1350, 1140, 1060, 890 cm^{-1} ; ^1H nmr (CCl_4) δ 1.00 & 1.05 (d, 3H, $J = 6.5$ Hz), 1.22 & 1.27 (t, 3H, $J = 7$ Hz), 1.5-2.5 (m, 3H), 1.67 (d, 3H, $J = 1$ Hz), 2.12 & 2.23 (s, 3H), 3.69 (t, 2H, $J = 6.5$ Hz), 4.05 & 4.16 (q, 2H, $J = 7$ Hz), 4.71 (s, 2H), 4.86 (s, 1H, $\text{C}=\text{CH}$).

Method B. The preparation of the carboxylate was effected by adding 1.7 g (13 mmoles) of ethyl acetoacetate to an ethoxide solution (0.3 g sodium in 10 ml of anhydrous ethanol). To this was added 1.4 g (6.3 mmoles) of the iodide 39. After having been refluxed for 7 hrs, the solution was cooled, acidified with 10 ml of hydrochloric acid, and extracted with diethyl ether. The ethereal solution was washed with potassium carbonate solution, dried (MgSO_4), and concentrated. This gave 1.8 g of recovered material. It was determined by glc (internal standard cyclododecane) that all of the material went through the column. The material recovered was found to contain 25% ethyl acetoacetate, 14% of the iodide 39, and 61% of the keto ester 36, or ca. 95% of theoretical yield based on the recovered iodide. A sample was collected by preparative glc (column 3, $R_f = 2.2$ relative to cyclododecane) for spectral analysis: bp 93-96 $^\circ\text{C}/1$ mm; one spot by tlc (solvent $\text{CH}_2\text{Cl}_2 + 1\%$ CH_3COCH_3 , $R_f = 0.58$); ir (neat) 3060, 3000-2850, 1740 ($\text{C}=\text{O}$ ester), 1720 ($\text{C}=\text{O}$ ketone), 1640, 1620, 1450, 1370, 1240, 1150, 1060, 1030, 890 cm^{-1} ;

^1H nmr (CCl_4) δ 0.95 (d, 3H, $J = 6.5$ Hz), 1.2-2.2 (m, 5H), 1.21 (t, 3H, $J = 7$ Hz), 1.60 (d, 3H, $J = 1$ Hz), 2.06 (s, 3H, $\text{CH}_3\text{C}=\text{O}$ ketone), 3.16 (t, 1H, $J = 7$ Hz), 4.11 (q, 2H, $J = 7$ Hz), 4.63 (s, 2H, $\text{C}=\text{CH}_2$); ^{13}C nmr (CDCl_3) δ 13.12, [17.52, 17.74], [18.61, 18.74], 25.18, 27.64, 31.44, 40.11, 58.78 & 60.13 ($-\text{OCH}_2\text{CH}_3$ & $-\text{CHCO}_2\text{Et}$), [109.11, 109.22] ($\text{C}=\text{CH}_2$), [147.94, 148.02] ($\text{C}=\text{CH}_2$), 168.79 ($\text{C}=\text{O}$ ester), [201.61, 201.70] ($\text{C}=\text{O}$ ketone); mass spectrum m/z (rel intensity): 208 (6), 143 (9), 109 (10), 97 (15), 96 (100), 81 (26), 55 (21), 43 (61), 41 (29); Anal. Calcd for $\text{C}_{13}\text{H}_{22}\text{O}_3$: C, 68.99; H, 9.80. Found: C, 68.88; H, 9.74.

Ethyl 2-(1-hydroxyethyl)-5,6-dimethyl-6-heptenoate 40

To a solution of 1.1 g (0.030 moles) of sodium borohydride in 60 ml of absolute ethanol, was added 9.8 g (0.043 moles) of the keto ester 36. After having been stirred for 90 minutes, the solution was acidified with 12 ml of 2.5N hydrochloric acid and this solution was stirred for another 30 min. The ethanol solution was neutralized (K_2CO_3) and the ethanol was evaporated under vacuum. The organic residue was extracted with diethyl ether, dried (MgSO_4), and concentrated, giving 9.4 g (95%) of the hydroxy ester 40. A sample was collected by preparative glc (column 3, $R_f = 2.5$ relative to cyclo-dodecane) for spectral analysis: ir (neat) 3600-3200 br (O-H stretch), 3060, 3000-2850, 1735 ($\text{C}=\text{O}$ ester), 1640, 1450, 1370, 1160, 1090, 1020, 980, 880 cm^{-1} ; ^1H nmr (CCl_4) δ 1.00 (d, 3H, $J = 6.5$ Hz), 1.11 & 1.14 (d, 3H, $J = 6$ Hz, CH_3CHOH), 1.27 (t, 3H, $J = 7$ Hz), 1.2-2.7 (m, 7H), 1.64 (s, 3H), 3.79 (quintet, 1H, $J = 6$ Hz,

-CHCH(OH)CH₃), 4.14 & 4.16 (q, 2H, J = 7 Hz), 4.68 (s, 2H, C=CH₂);
¹³C nmr (CDCl₃) δ14.33, [19.53, 19.95, 20.47], 21.54, [25.38, 28.45],
 [27.31, 27.35], [32.29, 32.41, 32.76, 32.93], 41.20, [52.53, 52.62,
 52.92], 60.44, 68.37, [109.73, 109.82, 110.03](C=CH₂), 175 (C=O
 ester); mass spectrum m/z (rel intensity): 228 (2), 143 (42), 137
 (25), 132 (25), 121 (17), 114 (29), 101 (28), 99 (24), 97 (23),
 96 (100), 95 (41), 87 (17), 86 (20), 84 (31), 83 (21), 82 (26),
 81 (45), 73 (35), 70 (57), 69 (75), 68 (21), 67 (34), 55 (69), 45
 (54), 43 (49), 41 (91), 39 (27), 29 (51), 27 (30).

Ethyl 2-ethenyl-5,6-dimethyl-6-heptenoate 41

The method of Rinehart and Perkins was used (67). To a solution of 20.9 g (0.14 moles) of freshly distilled phosphorus oxychloride and 150 ml of dry pyridine was slowly added 16.7 g (0.073 moles) of the hydroxy ester 40. The solution was stirred 1 hr at room temperature and 2 hrs in an oil bath (100-110°C). The solution was then added to 200 g of ice. The products were extracted with petroleum ether (30-60°C), and the extract was washed with 2N hydrochloric acid and distilled water, dried (MgSO₄), and concentrated.

This oil was treated with a sodium ethoxide solution (1.4 g sodium in 60 ml anhydrous ethanol). After 45 min, the ethoxide solution was acidified with 15 ml 4N hydrochloric acid. The resultant mixture was filtered, and the filtrate was extracted with diethyl ether. The ether solution was dried (MgSO₄), and concentrated. Gas chromatography (column 3) showed the presence of three isomers (relative peak area, R_f relative to cyclododecanone), ethyl 2-vinyl-5,6-dimethyl-6-heptenoate 45 (2%, 0.49), ethyl

Z-2-ethenyl-5,6-dimethyl-6-heptenoate 41 (18%, 0.52), and ethyl E-2-ethenyl-5,6-dimethyl-6-heptenoate 41 (80%, 0.55). Isolated was 12.6 g (80%) of the ester 41; ir (neat) 3060, 3000-2850, 1705 (C=CH-C=O ester), 1640, 1440, 1370, 1260, 1180, 1130, 1050, 890, 780 cm^{-1} ; ^1H nmr (both isomers, CCl_4) δ 1.06 (d, 3H, $J = 7$ Hz), 1.2-2.4 (m, 5H), 1.26 & 1.29 (t, 3H, $J = 7$ Hz), 1.68 (d, 3H, $J = 1$ Hz), 1.77 (d, 3H, $J = 7$ Hz, $\text{CH}_3\text{CH}=\text{C}$), 4.14 & 4.16 (q, 2H, $J = 7$ Hz), 4.6-4.8 (m, 2H, $\text{C}=\text{CH}_2$), 5.90 & 6.70 (q, 1H, $J = 7$ Hz, $\text{CH}_3\text{CH}=\text{C}$); ^{13}C nmr (CDCl_3) δ 13.92, 14.16, 18.75, 19.59, 24.46, 33.94, 41.28, 60.11 ($\text{CH}_3\text{CH}_2\text{O}-$), [109.51, 109.57] ($\text{C}=\text{CH}_2$), 133.64 ($\text{C}=\text{CHCH}_3$), 136.60 ($\text{C}=\text{CHCH}_3$), 149.4 ($\text{C}=\text{CH}_2$), 157.8 (C=O ester); mass spectrum (E isomer) m/z (rel intensity: 210 (10), 165 (7), 164 (8), 141 (37), 113 (34), 109 (34), 108 (27), 107 (21), 95 (32), 83 (100), 70 (47), 67 (47), 55 (59), 53 (25), 41 (68), 39 (25), 29 (30); high resolution mass spectrum: calcd. for $\text{C}_{23}\text{H}_{22}\text{O}_2$: 210.162. Found: 210.162.

2-Ethenyl-5,6-dimethyl-6-hepten-1-ol 42

A solution of 6.9 g (0.033 moles) of the olefinic ester 41 in 20 ml of anhydrous diethyl ether was slowly added to 1.4 g (0.037 moles) of lithium aluminum hydride in 30 ml of anhydrous diethyl ether that had been cooled in an ice bath. After having been stirred for 30 min at room temperature, the solution was treated with 50 ml of saturated ammonium chloride solution. The mixture was filtered and the filtrate was extracted with diethyl ether. The extract was dried (MgSO_4), concentrated, and distilled to give 4.7 g (85%) of the olefinic alcohol 42. A sample was collected by preparative glc (column 3, $R_f = 0.32$ relative to cyclododecanone) for spectral

analysis: bp 55-57°C/0.04 mm; ir (neat) 3550-3100 br (O-H stretch), 3060, 3000-2800, 1640, 1450, 1370, 1000, 890 cm^{-1} ; ^1H nmr (both isomers, CCl_4) δ 1.02 (d, 3H, $J = 6.5$ Hz), 1.2-2.3 (m, 9H), 1.67 (s, 3H, $\text{CH}_3\text{C}=\text{CH}_2$), 3.91 & 4.05 (s, 2H, $-\text{CH}_2\text{OH}$ by integration E:Z = 80:20), 4.6-4.8 (m, 2H, $\text{C}=\text{CH}_2$), 5.40 (q, 1H, $\text{C}=\text{CHCH}_3$); ^{13}C nmr (CDCl_3) δ 12.82, 18.85, 19.63, 25.68, 33.37, 41.30, 67.15 ($-\text{CH}_2\text{OH}$), 109.56 ($\text{C}=\text{CH}_2$), 120.76 ($\text{C}=\text{CHCH}_3$), 140.06 ($\text{C}=\text{CHCH}_3$), 149.70 ($\text{C}=\text{CH}_2$); mass spectrum m/z (rel intensity): 168 (1), 150 (21), 137 (31), 135 (19), 121 (19), 107 (32), 98 (22), 95 (27), 93 (26), 84 (26), 83 (47), 82 (33), 81 (43), 80 (49), 79 (34), 70 (67), 69 (55), 67 (54), 55 (87), 53 (26), 43 (41), 41 (100), 39 (28), 29 (23).

Ethyl 3,7,8-trimethyl-4-methylene-8-nonenoate 43

The method of Johnson et al. (27) was modified as described earlier. A solution containing 2.0 g (12 mmoles) of the olefinic alcohol 42 and 5 drops of pivalic acid in 30 ml of triethyl orthoacetate was stirred in an oil bath (140-150°C) for 90 min. The product was separated by distillation giving 2.5 g (85%) bp 65°C/0.07 mm of the olefinic ester 43. A sample was collected by preparative glc (column 3, $R_f = 2.7$ relative to cyclododecane) for spectral analysis: ir (neat) 3070, 3000-2850, 1740 ($\text{C}=\text{O}$ ester), 1640, 1450, 1370, 1160, 1050, 890 cm^{-1} ; ^1H nmr (CCl_4) δ 1.03 (d, 3H, $J = 6.5$ Hz), 1.05 (d, 3H, $J = 6.5$ Hz), 1.3-2.8 (m, 8H), 1.22 (t, 3H, $J = 7$ Hz), 1.65 (s, 3H, $\text{CH}_3\text{C}=\text{CH}_2$), 4.07 (q, 2H, $J = 7$ Hz), 4.6-4.8 (m, 4H, $\text{C}=\text{CH}_2$); ^{13}C nmr ($\text{CDCl}_3/\text{CCl}_4$) δ 14.23, 18.68, 19.72, 19.82, 32.09, 33.09, [36.05, 36.10], 40.54, 40.82, 59.53 ($\text{CH}_3\text{CH}_2\text{O}-$),

107.82 & 107.98 ($\underline{\text{C}}=\underline{\text{CH}}_2$), 148.90 & 153.04 ($\underline{\text{C}}=\underline{\text{CH}}_2$), 171.41 (C=O ester); mass spectrum m/z (rel intensity): 238 (4), 223 (8), 192 (13), 169 (13), 168 (15), 151 (13), 150 (47), 135 (28), 123 (95), 122 (35), 121 (28), 109 (25), 107 (23), 95 (100), 83 (30), 82 (60), 81 (57), 79 (22), 70 (47), 69 (29), 67 (53), 55 (52), 43 (22), 41 (68), 29 (33); Anal. Calcd for $\text{C}_{15}\text{H}_{26}\text{O}_2$: C, 75.58; H, 10.99. Found: C, 75.56; 10.90.

3,7,8-Trimethyl-4-methylene-8-nonen-1-ol 44

A solution of 14.1 g (59 mmoles) of the olefinic ester 43 in 30 ml of anhydrous diethyl ether was added to 2.3 g (61 mmoles) of lithium aluminum hydride in 70 ml of anhydrous diethyl ether cooled in an ice bath. The reaction mixture was stirred for 60 min at room temperature. Then 30 ml of distilled water followed by 50 ml of 6N sulfuric acid was carefully added. The mixture was extracted several times with diethyl ether and the combined extract was washed with potassium carbonate and ammonium chloride solutions, dried (MgSO_4), and concentrated giving 11.4 g of crude product. Distillation gave 7.6 g (65%) of the alcohol 44: bp $66^\circ\text{C}/0.10$ mm; one spot by tlc (solvent CH_2Cl_2 , $R_f = 0.21$); ir (neat) 3600-3100 br (O-H stretch), 3070, 3000-2850, 1640, 1450, 1370, 1050, 890 cm^{-1} ; ^1H nmr (CCl_4) δ 1.03 (d, 6H, $J = 6.5$ Hz), 1.3-2.5 (m, 9H), 1.66 (s, 3H, $\text{CH}_3\text{C}=\underline{\text{CH}}_2$), 3.53 (t, 2H, $J = 6.5$ Hz, $-\text{CH}_2\underline{\text{CH}}_2\text{OH}$) 4.6-4.8 (m, 4H, $\text{C}=\underline{\text{CH}}_2$); ^{13}C nmr ($\text{CDCl}_3/\text{CCl}_4$) δ 18.73, 19.72, 20.16, 31.32, 33.23, 36.74, 38.29, 40.91, 60.90 ($-\underline{\text{CH}}_2\text{OH}$), 107.81 & 109.83 ($\text{C}=\underline{\text{CH}}_2$), 149.15 & 154.16 ($\underline{\text{C}}=\underline{\text{CH}}_2$); mass spectrum m/z (rel intensity): 196 (1),

152 (37), 123 (64), 109 (39), 95 (47), 93 (20), 83 (33), 82 (100), 81 (51), 70 (60), 69 (29), 67 (75), 55 (60), 41 (68).

2,3,7-Trimethyl-6-methylene-9-bromo-1-nonene 47

Method A. A method analogous to the preparation of alkyl chlorides by Hooz and Gilani was used (37). A solution of 2.05 g (7.8 mmoles) of triphenylphosphine and 2.9 g (8.7 mmoles) of carbon tetrabromide in 30 ml of benzene was prepared. The solution was treated with 1.5 g (7.6 mmoles) of the alcohol 44 and the mixture was stirred at room temperature for 21 hrs. After the benzene had been distilled under reduced pressure, the product was taken up in petroleum ether (30-60°C). The mixture was filtered and the filtrate was concentrated under reduced pressure. Three products were isolated by column chromatography (CH₂Cl₂ through silica gel). The first fraction contained 0.9 g (46%) of the bromide 47: $R_f = 0.70$ (solvent CH₂Cl₂); ir (neat) 3070, 3000-2850, 1640, 1450, 1370, 1260, 890, 670 (C-Br) cm⁻¹; ¹H nmr (CCl₄) δ 1.02 (d, 3H, J = 6.5 Hz), 1.04 (d, 3H, J = 6.5 Hz), 1.64 (s, 3H), 1.2-2.5 (m, 8H), 3.30 (t, 2H, J = 7 Hz, -CH₂CH₂Br), 4.68 (s, 2H), 4.76 (s, 2H); ¹³C nmr (CDCl₃) 18.79, 19.54, 19.78, 29.67, 31.49, 31.97, 33.31, 38.52, 40.97, 108.49 & 109.69 (C=CH₂), 149.64 & [152.92, 152.95] (C=CH₂); mass spectrum m/z (rel intensity): 260 (1.2), 258 (1.5), 123 (34), 109 (20), 95 (32), 83 (25), 82 (84), 81 (38), 70 (100), 69 (37), 67 (52), 55 (72), 53 (23), 41 (82), 39 (26), 29 (18), 27 (20).

The second fraction contained 0.5 g (2.5 mmoles) of 1-(3,4-dimethyl-4-pentenyl)-1,2-dimethyltetrahydrofuran 48: $R_f = 0.43$ (solvent CH₂Cl₂); ir (neat) 3070, 3000-2850, 1640,

1460, 1380, 1060, 1040, 890, 860 cm^{-1} ; ^1H nmr (CCl_4) δ 0.9 (d, 3H), 1.05 (s, 3H), 1.3 (br d, 3H), 1.6 (s, 3H), 1.1-2.4 (m, 8H), 3.6 (t, 2H), 4.6 (s, 2H); ^{13}C nmr ($\text{CDCl}_3/\text{CCl}_4$) [14.23, 14.87], [18.73, 19.83, 19.95, 20.03, 20.15], 24.02, [28.53, 28.94], [31.59, 31.66], [33.75, 34.08], [38.13, 38.21], [40.87, 41.04, 41.56, 41.73], 43.57, [64.19, 64.53] ($-\text{OCH}_2-$), [82.81, 83.14] ($-\text{OC}-$ tetrasubstituted carbon), [109.64, 109.71] ($\text{C}=\text{CH}_2$), [149.26, 149.32] ($\text{C}=\text{CH}_2$); mass spectrum m/z (rel intensity): 196 (1), 147 (2), 129 (13), 99 (95), 57 (22), 56 (22), 55 (47), 43 (100), 41 (89), 39 (25), 29 (23).

The third fraction contained 0.3 g (1.5 mmoles) of the alcohol 44: $R_f = 0.21$ (solvent CH_2Cl_2).

Method B. The method of Hayashi *et al.* was used (74). A solution of 1.0 g (5.1 mmoles) of the alcohol 44 and 2.6 g (7.8 mmoles) of carbon tetrabromide in 5 ml of benzene was prepared. A solution containing 1.4 g (5.3 mmoles) of triphenylphosphine in benzene was added with stirring over a 45 min period. The solution was allowed to stir overnight. After the benzene had been removed at reduced pressure, the products were taken up in petroleum ether (30-60°C). The mixture was filtered and the filtrate was washed with sodium bicarbonate and brine solutions, dried (MgSO_4), and concentrated under reduced pressure. Two main fractions were separated by column chromatography (CH_2Cl_2 through silica gel). Obtained from the first fraction was 0.8 g (60%) of the bromide mixture. Glc (column 3, column temperature 125°C, helium gas flow 60 ml/min) gave a number of peaks. The major one (retention time 2.6 minutes) was identified as the bromide 47: $R_f = 0.7$ (solvent CH_2Cl_2).

Obtained from the second fraction was 0.4 g of an ether mixture which appeared as one spot by tlc (solvent CH_2Cl_2 , $R_f = 0.5$). Glc (column 3, column temperature 120°C , helium gas flow 60 ml/min) showed two major peaks. Peak 1 (ca. 58%) was determined to be the ether 48: retention time 1.3 min.

Peak 2 (ca. 42%) was determined to be the ether 1-(3,4-dimethyl-3-pentenyl)-1,2-dimethyl tetrahydrofuran 52: retention time 1.9 min; ^1H nmr (CCl_4) δ 0.8-1.3 (m, 6H), 1.3-2.4 (m, 7H), 1.6 (s, 9H), 3.7 (t, 2H).

Method C. The method of Schleyer was used to make the tosylate (72). A solution containing 579 mg (2.95 mmoles) of the alcohol 44 and 2.5 g (13.1 mmoles) of p-toluenesulfonyl chloride in 30 ml of pyridine was stored (0°C) in a stoppered flask for 19 hrs. The pyridine solution was then added to 50 ml of distilled water. The solution was extracted with diethyl ether, and the extracts were washed 8 times with 2N hydrochloric acid, and once each with sodium bicarbonate and brine solutions, dried (MgSO_4), and concentrated under reduced pressure.

The crude tosylate was added to a solution of 1.0 g (12 mmoles) of anhydrous lithium bromide in 15 ml of acetone (freshly distilled from potassium permanganate) and allowed to stir overnight. The acetone was removed under reduced pressure and the residue dissolved in water. The product was extracted from the aqueous layer with diethyl ether. The ether solution was washed with brine, dried (K_2CO_3), and concentrated. Separation by column chromatography yielded 40 mg (0.11 mmoles) of the tosylate 53 (solvent

CH_2Cl_2 , $R_f = 0.5$) and 430 mg (60% based on recovered tosylate) of the bromide 47: $R_f = 0.7$ (solvent CH_2Cl_2).

Methyl 3,6,10,11-tetramethyl-7-methylene-2,11-dodecadienoate 56

The method of Anderson et al. was used (41). All transfers with liquid reagents were performed with syringes through septum caps. Nitrogen was used throughout as an inert atmosphere.

The alkyl Grignard was prepared from 0.40 g (1.5 mmoles) of the bromide 47 and 0.09 g (3.7 mmoles) of magnesium turnings in 1 ml of anhydrous diethyl ether. Several drops of dibromoethane were used to initiate the reaction. The Grignard reagent was added to a cooled (-40°C) solution of 0.33 g (1.7 mmoles) of cuprous iodide¹ and 0.6 g tetramethylethylenediamine in 7 ml of anhydrous tetrahydrofuran and the mixture was stirred for 75 min (negative Gilman test).

The solution was then cooled to -65°C . A solution of 0.2 g (2 mmoles) of methyl tetrolate² in 5 ml of anhydrous tetrahydrofuran was added and the mixture was stirred for 1.5 hours with a Vibro-mixer. Addition of the ester caused the slurry to change from a light yellow to a light green color. The reaction was quenched with 2 ml of

¹Cuprous iodide (98% pure) was obtained from Alfa Products. It was further purified by extracting with tetrahydrofuran in a Soxhlet extractor for 48 hours and drying under vacuum over concentrated sulfuric acid for 3 days.

²Tetrollic acid was first prepared according to the method of Henbest et al. (75) and then esterified with diazomethane.

methanol (-65°C). When the solution had warmed to room temperature, 2 ml of ammonium chloride solution was added. The solids were removed and the product was extracted into diethyl ether. The ether solution was washed with 1N hydrochloric acid, sodium bicarbonate and brine solutions, dried (MgSO₄), and concentrated under reduced pressure. Separation by column chromatography (CH₂Cl₂ through silica) gave a main fraction of 120 mg (0.33 mmoles) of a hydrocarbon identified as 2,3,7,12,16,17-hexamethyl-6,13-dimethylene-1,17-octadecadiene 54: R_f = 0.7 (solvent CH₂Cl₂); ir (neat) 3070, 3000-2850, 1640, 1450, 1370, 1260, 890 cm⁻¹; ¹H nmr (CCl₄) δ 0.98 (d, 6H, J = 6.5 Hz), 1.00 (d, 6H, J = 6.5 Hz), 1.64 (d, 6H, J = 1 Hz), 1.1-2.4 (m, 20H), 4.68 (s, 8H); ¹³C nmr (CDCl₃/CCl₄) δ 18.77, 19.73, 20.16, 27.59, 29.64, 31.53, 33.37, 35.64, 39.95, 40.94, 107.43 & 109.80 (C=CH₂), 149.17 & 154.38 (C=CH₂); mass spectrum m/z (rel intensity); 358 (2), 205 (5), 177 (10), 163 (16), 151 (26), 149 (27), 137 (25), 135 (26), 124 (19), 123 (82), 122 (28), 121 (48), 110 (22), 109 (77), 108 (36), 107 (38), 97 (28), 96 (32), 95 (100), 93 (27), 83 (55), 82 (86), 81 (69), 79 (27), 71 (18), 70 (74), 69 (88), 67 (68), 57 (26), 55 (100), 43 (28), 41 (98).

2,3,7-Trimethyl-6-methylene-9-iodo-1-nonene 57

The method of Schleyer was used to make the tosylate (72). A solution containing 2.6 g (14 mmoles) of p-toluenesulfonyl chloride and 0.525 g (2.67 mmoles) of the alcohol 44 in 25 ml of anhydrous pyridine was stored in a stoppered flask for 29 hrs. The pyridine solution was added to 25 ml of distilled water. The solution was extracted with diethyl ether, and the extracts were washed several

times with 2N hydrochloric acid, and then with sodium bicarbonate and brine solutions. The ethereal solution was dried (K_2CO_3), and the product concentrated under reduced pressure.

The crude tosylate was added to a solution of 2.0 g (13 mmoles) of sodium iodide in 15 ml of acetone (freshly distilled from potassium permanganate). The flask was covered with aluminum foil and the solution was stirred for 21 hrs. at room temperature. The acetone was removed under reduced pressure, and the solids were then triturated with petroleum ether (30-60°C). The extract was washed with sodium hydrogen sulfate and brine solutions, and then was dried (K_2CO_3). The product was concentrated under reduced pressure and purified by column chromatography (CH_2Cl_2 through silica gel) giving 0.573 g (70% overall) of the iodide 57: $R_f = 0.75$; ir (neat) 3080, 3000-2850, 1650, 1460, 1380, 1240, 1180, 890 cm^{-1} ; 1H nmr ($CDCl_3$) δ 1.09 (d, 6H, $J = 6.5$ Hz), 1.72 (s, 3H), 1.2-2.4 (m, 8H), 3.16 (t, 2H, $J = 7$ Hz), 4.75 & 4.82 (s, 4H, $C=CH_2$); ^{13}C nmr ($CDCl_3$) δ 5.04 ($-CH_2I$), 18.83, 19.63, 19.78, 31.46, 33.38, 39.35, 40.55, 40.75, 40.98, 108.59 & 109.71 ($C=CH_2$), 149.69 & 152.82 ($C=CH_2$); mass spectrum m/z (rel intensity): 306 (11), 236 (16), 151 (22), 123 (49), 109 (35), 95 (43), 83 (30), 82 (79), 81 (59), 70 (89), 69 (56), 67 (63), 55 (89), 53 (26), 43 (20), 41 (100), 39 (26), 29 (24), 27 (20).

3,6,10,11-Tetramethyl-7-methylene-1,11-dodecadien-3-ol 59

A solution containing ca. 0.4 ml (2M, ca. 0.8 mmoles) of t-butyllithium/pentane in 10 ml of anhydrous diethyl ether under

argon was cooled (-78°C). The solution was treated with 80 mg (0.26 mmoles) of the iodide 57 in 2 ml of anhydrous diethyl ether and stirred for 30 min. Excess methyl vinyl ketone was added and the solution was stirred for 5 min. (-78°C) and 30 min. (room temperature). The solution was treated with 10 ml of hydrochloric acid and was extracted several times with diethyl ether. The ethereal solution was dried (MgSO_4), washed with sodium bicarbonate and brine solutions, and the product was concentrated. Separation by column chromatography (CH_2Cl_2 through silica gel) gave two main fractions. The first contained 20 mg (0.11 mmoles) of 2,3,7-trimethyl-6-methylene-1-nonene 58: $R_f = 0.68$; ^1H nmr (CCl_4) δ 1.0 (d, 6H), 1.2 (br s, 3H), 1.6 (s, 3H), 1.2-2.4 (m, 8H), 4.6 (s, 4H); mass spectrum m/z (rel intensity): 180 (3), 151 (9), 123 (23), 109 (14), 95 (33), 82 (58), 81 (36), 70 (51), 69 (35), 67 (41), 55 (59), 53 (24), 41 (100), 39 (31), 29 (43).

The second fraction contained 45 mg of a mixture of 3,4,4-trimethyl-1-penten-3-ol 60 and the alcohol 59 in a ratio of 30:70 respectively as determined by integration: $R_f = 0.3$; ^1H nmr (CCl_4) δ 0.92 (s, 9H, t-Bu-), 1.01 (d, 3H, $J = 6.5$ Hz), 1.03 (d, 3H, $J = 6.5$ Hz), 1.20 (s, 3H for each compound), 1.65 (s, 3H), 1.2-2.4 (m, 11H for (59), 1H for (60)), 4.65 (br s, 4H), 4.9-6.2 (m, 3H for each compound, borderline ABX).

5,9,10-Trimethyl-6-methylene-10-undecen-2-ol 61

The alkyl Grignard was prepared by adding 0.12 g (0.46 mmoles) of the bromide 47 to 50 mg (2.1 mmoles) of magnesium turnings in

0.5 ml of anhydrous diethyl ether. The magnesium turnings were cleaned with emery paper and the solution was protected from the air by nitrogen. After the Grignard had been transferred to another flask, 1 ml of freshly distilled acetaldehyde was added and the reaction mixture was stirred for 30 min. The solution was acidified with 2 ml of 1N hydrochloric acid. The mixture was extracted with diethyl ether and the extracts were washed with sodium bicarbonated and brine solutions, dried (MgSO_4), and concentrated under reduced pressure. Separation by column chromatography (CH_2Cl_2 on silica gel $R_f = 0.7$) gave 85 mg (83%) of 1-(3,4-dimethyl-4-pentenyl)-1,2,5-trimethyl tetrahydropyran 62: ir (neat) 3080, 3000-2850, 1640, 1450, 1380, 1260, 1090, 890 cm^{-1} ; ^1H nmr (CCl_4) δ 1.0 (d, 6H, $\text{CH}_3\text{CH-}$), 1.1-2.4 (m, 10H), 1.2 (d, 3H), 1.3 (s, 3H), 1.6 (s, 3H), 3.4 (m, 1H), 4.7 (s, 2H).

Phenyl 2-(5,9,10-trimethyl-6-methylene-10-undecenyl) sulfone 67

The method of Julia et al. was used (61). One milliliter of 1.6M butyllithium in hexane (1.6 mmoles) was added to 0.28 g (1.6 mmoles) of ethyl phenyl sulfone³ in 15 ml of anhydrous tetrahydrofuran (-78°C). The solution was stirred for 45 minutes while warming gradually to -25°C . The solution was cooled again (-50°C), and 53 mg (0.20 mmoles) of the bromide 47 was added and the mixture was stirred for one hour while slowly warming to -10°C . The reaction

³Phenyl ethyl sulfone was prepared according to the method of Bordwell & Boutan (77). Phenyl ethyl sulfide was prepared from thiophenoxide and ethyl bromide.

was quenched with 5 ml of ammonium chloride solution, and the product was extracted with diethyl ether. The ether extract was washed with brine, dried (MgSO_4), and concentrated under reduced pressure. Separation by column chromatography ($\text{CH}_2\text{Cl}_2 + 3\% \text{CH}_3\text{COCH}_3$ through silica, $R_f = 0.55$) gave a number of fractions, but cleanly separated 54 mg (75%) of the sulfone 67: ir (neat) 3080, 3000-2850, 1650, 1450, 1310, 1150, 890, 760, 730, 690 cm^{-1} ; ^1H nmr (CCl_4) δ 1.0 (d, 6H), 1.2 (d, 3H), 1.6 (s, 3H), 1.0-2.4 (m, 10H), 2.6-3.1 (m, 1H), 4.7 (s, 4H), 7.4-8.0 (m, 5H); ^{13}C nmr (CDCl_3) δ [13.01, 13.13], 18.81, 19.61, 20.18, 27.20, [31.18, 31.59], 32.33, 33.37, 39.93, 40.85, 60.12 ($-\text{CHSO}_2\text{Ar}$), [107.89, 108.12] & 109.45 ($\text{C}=\text{CH}_2$), 128.04, 128.50, 128.85, 129.08, 133.31 & 133.41 (aromatic carbons), 149.59 & [153.28, 153.71] ($\text{C}=\text{CH}_2$); mass spectrum m/z (rel intensity): 348 (5), 333 (6), 305 (5), 225 (10), 206 (20), 151 (20), 143 (45), 137 (83), 136 (39), 125 (22), 124 (25), 123 (100), 122 (35), 121 (46), 109 (67), 108 (25), 107 (43), 96 (20), 95 (84), 94 (25), 93 (26), 83 (34), 82 (48), 81 (58), 79 (27), 78 (21), 77 (41), 70 (24), 69 (58), 67 (47), 55 (76), 43 (20), 41 (65).

Ethyl 3-(phenylsulfonyl)-3,6,10,11-tetramethyl-7-methylene-11-dodecenoate 68

The method of Julia et al. was used (76). A solution of 45 mg (0.13 mmoles) of the sulfone 67 and 1 ml of hexamethylphosphoric triamide in 15 ml of anhydrous tetrahydrofuran was prepared and cooled (-78°C). About 0.3 ml (1.6M, 0.5 mmoles) of N-butyllithium/hexane solution was added and the solution was stirred for 1.5hrs, while slowly warming to 0°C . The solution

was cooled (-78°C), then treated with ca. 0.25 ml (2 mmoles) of ethyl bromoacetate. The solution was allowed to warm to room temperature and then was stirred overnight. Ammonium chloride was added. The mixture was extracted with petroleum ether ($30-60^{\circ}\text{C}$), and the extracts were washed 8 times with distilled water and once with brine, dried (MgSO_4), and concentrated under reduced pressure. Separation by column chromatography ($\text{CH}_2\text{Cl}_2 + 1\% \text{CH}_3\text{COCH}_3$ through silica), gave 2 minor fractions ($R_f = 0.55$ & 0.40), 20 mg (0.057 mmoles) of the sulfone 67 ($R_f = 0.45$), and 13 mg (23%) of the sulfonyl ester 68 ($R_f = 0.32$): ir (neat) 3080, 3000-2850, 1740 ($\text{C}=\text{O}$ ester), 1650, 1450, 1380, 1300, 1150, 1030, 890, 790, 760, 730, 690 cm^{-1} ; ^1H nmr (CCl_4) δ 1.0-2.4 (m, 13H), 1.0 (d, 6H), 1.2 (t, 3H), 1.6 (s, 3H), 2.1 & 2.5 (s, 2H), 4.1 (q, 2H), 4.7 (s, 4H), 7.4-8.0 (m, 5H); ^{13}C nmr (CDCl_3) δ 14, 19, 20, 20, 28, 29, 31, 33, 37, 39, 40, 41, 60 & 61 ($-\text{OCH}_2-$ & $-\text{SO}_2\text{C}-$), 108 & 109 ($\text{C}=\text{CH}_2$), 209 ($\text{C}=\text{O}$ ester ?); mass spectrum m/z (rel intensity): 290 (4), 241 (7), 213 (35), 185 (30), 157 (21), 149 (27), 144 (20), 143 (20), 139 (27), 137 (30), 123 (50), 121 (41), 111 (39), 109 (49), 108 (31), 107 (35), 101 (31), 98 (36), 95 (80), 93 (22), 85 (26), 83 (51), 82 (44), 81 (42), 79 (22), 77 (39), 71 (17), 70 (34), 69 (53), 67 (47), 57 (30), 55 (100), 43 (55), 41 (88), 29 (48).

5,9,10-Trimethyl-6-methylene-10-undecen-2-one 63

The method of Cahiez et al. was followed (60). The Grignard reagent, prepared from 14 mg (0.58 mmoles) magnesium turnings and 53 mg (0.17 mmoles) of the iodide 57 in 0.5 ml of anhydrous diethyl ether, was added to 60 mg (0.20 mmoles) of manganese (II) iodide

in 1.0 ml of anhydrous diethyl ether (-30°C). The solution was stirred for 1 hr. To this solution was added 0.2 ml (ca 2.5 mmoles) of acetyl chloride (freshly distilled). The solution was stirred for 15 min. (-30°C) and for 2.5 hr. at room temperature. Five milliliters of ammonium chloride solution was added. The aqueous layer was extracted three times with diethyl ether. The ether layer was washed with sodium bisulfite, sodium bicarbonate, and brine solutions, dried (MgSO_4), and the product was concentrated under reduced pressure to give 41 mg of a mixture. The mixture was not separated, but the ketone 63 was found to be present in only trace amounts. The mixture appeared to be mainly comprised of the iodide 57 and a hydrocarbon tentatively identified as 54: ir (neat) 3080, 3000-2850, 1720 (very weak), 1640, 1450, 1380, 1260, 890, 800 cm^{-1} ; ^1H nmr (CCl_4) δ 1.0 (d), 1.1-2.4 (m), 1.6 (s), 3.0 (t), 4.5-4.7 (m) (integration of the triplet and the last multiplet gave a ratio of 16:84); mass spectrum m/z (rel intensity): 358 (1.5), 151 (16), 123 (53), 121 (20), 109 (57), 97 (25), 95 (96), 83 (57), 82 (48), 81 (52), 70 (44), 69 (100), 67 (48), 57 (29), 55 (94), 43 (34), 41 (83).

5,9,10-Trimethyl-6-methylene-10-undecen-2-one 63

The method of Stork *et al.* was used (62). To a cooled solution (-78°C) of 51 mg (0.50 mmoles) of diisopropyl amine, 0.3 ml (1.6M, 0.5 mmoles) of N-butyllithium/hexane, and 64 mg hexamethylphosphoric triamide in 2 ml tetrahydrofuran was added 62 mg (0.49

mmoles) of 2-(N,N-diethylamino)propionitrile⁴ and the mixture was stirred for 45 min. under nitrogen. To this was added 59 mg (0.19 mmoles) of the iodide 57 and the solution was stirred for 1 hr. (-78°C) followed by 1 hr at room temperature. After 5 ml of ammonium chloride solution had been added, the solution was extracted with petroleum ether (30-60°C), and the ether solution was removed under reduced pressure.

The residue was taken up in 25 ml of 95% ethanol and ca. 2 g of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ and the solution was refluxed for 1 hr. The solution was diluted with distilled water, and the mixture was extracted with petroleum ether (30-60°C). The extracts were washed with 1N hydrochloric acid, sodium bicarbonate, and brine solutions, and dried (MgSO_4). After the solvent had been removed under reduced pressure, 40 mg (95%) of the ketone 63 was isolated by column chromatography (CH_2Cl_2 through silica gel): $R_f = 0.5$; ir (neat) 3070, 3000-2850, 1720, 1640, 1450, 1370, 1160, 890 cm^{-1} ; ^1H nmr (CCl_4) δ 0.99 (d, 3H, $J = 6.5$ Hz), 1.01 (d, 3H, $J = 6.5$ Hz), 1.2-2.5 (m, 10H), 1.63 (s, 3H), 2.00 (s, 3H), 4.6-4.8 (m, 4H); ^{13}C nmr (CDCl_3) δ 18.63, 19.63, 19.99, 28.87, 31.14, 31.18, 33.16, 39.33, 40.86, 41.40, 107.97 & 109.53 ($\text{C}=\underline{\text{C}}\text{H}_2$), 149.54 & 153.51 ($\underline{\text{C}}=\text{CH}_2$), 208.85 ($\text{C}=\text{O}$); mass spectrum m/z (rel intensity): 222 (2), 205 (10), 164 (35), 149 (31), 135 (39), 123 (49), 121 (49), 109 (98), 108 (59), 107 (40), 95 (89), 93 (30), 83 (24), 82 (58), 81 (40), 79 (34), 70 (48), 69 (31), 67 (57), 55 (55), 43 (100), 41 (73), 39 (20);

⁴Prepared by treating 2-(N,N-diethylamino) acetonitrile anion with methyl iodide.

high resolution mass spectrum: Calcd. for $C_{15}H_{26}O$: 222.198.

Found: 222.199.

3,6,10,11-Tetramethyl-7-methylene-1,11-dodecadien-3-ol 64

To a solution of 0.3 ml (1.0M, 0.3 mmoles) of vinyl lithium/tetrahydrofuran in 3 ml of diethyl ether ($0^{\circ}C$) was added 29 mg (0.13 mmoles) of the ketone 63 and the resultant solution was stirred for 1 hr. Five milliliters of ammonium chloride solution was then added. The product was extracted with diethyl ether, and the combined ether extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Separation by column chromatography (CH_2Cl_2 through silica gel) gave 30 mg (90%) of the alcohol 64: $R_f = 0.40$; ir (neat) 3600-3200, 3080, 3000-2850, 1640, 1460, 1380, 920, 890 cm^{-1} ; 1H nmr (CCl_4) δ 1.14 (d, 3H, $J = 6.5$ Hz), 1.16 (d, 3H, $J = 6.5$ Hz), 1.27 (s, 3H), 1.67 (s, 3H), 1.4-2.5 (m, 11H), 4.6-4.8 (m, 4H), 4.9-6.0 (m, 3H, borderline ABX pattern, see discussion); ^{13}C nmr ($CDCl_3$) δ 18.68, [19.60, 19.65]. [20.14, 20.22], [27.35, 27.60]. 29.36, 31.36, 33.15, 39.93, [40.10, 40.16], 40.83, [72.96, 73.00] ($\underline{C-OH}$), 107.49 & 109.50 ($C=\underline{CH_2}$), 111.41 ($CH=\underline{CH_2}$), [143.03, 145.09] ($-\underline{CH=CH_2}$), [149.51, 149.56] & 154.09 ($\underline{C=CH_2}$); mass spectrum m/z (rel intensity): 165 (6), 164 (8), 163 (6), 123 (25), 122 (28), 121 (17), 109 (40), 108 (36), 107 (40), 95 (56), 93 (27), 83 (30), 82 (54), 81 (48), 79 (24), 71 (100), 70 (34), 69 (42), 67 (44), 55 (66), 43 (64), 41 (76).

2,3,7,10-Tetramethyl-6-methylene-12-bromo-1,10-dodecadiene 72

The method of Isler et al. was used (77). To a cooled solution (-5°C) of 2.9 μl (0.036 mmoles) of pyridine in 1 ml of petroleum ether ($30-60^{\circ}\text{C}$) was added 27 mg (0.11 mmoles) of the alcohol 64. Then 4.9 μl (0.052 mmoles) of phosphorus tribromide was added and the solution was stirred for 45 min. The solution was added to 10 g of ice. The aqueous layer was extracted several times with petroleum ether ($30-60^{\circ}\text{C}$). The petroleum ether was washed with sodium bicarbonate and brine solutions, dried (MgSO_4), and the product was concentrated under reduced pressure. Separation by column chromatography using silica gel (methylene chloride eluant) gave 21 mg of a hydrocarbon fraction which was found to contain a mixture of compounds. The solution appeared to darken over several days at room temperature: $R_f = 0.7$; ^1H nmr (CDCl_3) δ 1.0-2.3 (m, with intense peaks at δ 1.0-1.1 and 1.6-1.8), 4.64 (br s), 4-8-5.1 (m) (integration of the last two groups showed a ratio of 1:2 respectively); mass spectrum m/z (rel intensity): 232 (28), 175 (36), 162 (38), 149 (24), 147 (37), 135 (31), 133 (46), 121 (62), 120 (30), 119 (47), 109 (29), 108 (27), 107 (100), 105 (39), 95 (58), 94 (22), 93 (71), 83 (27), 82 (27), 81 (70), 79 (57), 77 (28), 69 (45), 67 (51), 55 (72), 53 (28), 41 (89).

3,6,10,11-Tetramethyl-7-methylene-2,11-dodecadienal 73

The method of Corey and Suggs was used (78). To a cooled solution (0°C) of 61 mg (0.28 mmoles) of pyridinium chlorochromate in 3 ml of dry methylene chloride was added 27 mg (0.11 mmoles) of the

alcohol 64. The solution was stirred for 1.5 hr while warming to room temperature and 18.5 hr at room temperature. The solution was diluted with diethyl ether (several times the original volume) and decanted. The residue was washed with more diethyl ether, and the ether was added to the first fraction. The combined ether fractions were passed through a Florisil column, and the product was concentrated under reduced pressure. Separation with a silica gel column (chloroform solvent) gave 24 mg (88%) of the aldehyde 73: $R_f = 0.47$; ir (neat 3080, 3000-2850, 1670, 1640, 1450, 1380, 890 cm^{-1}); ^1H nmr (CDCl_3) δ 1.01 (d, 6H, $J = 6.5$ Hz), 1.3-2.4 (m, 8H), 1.63 (s, 3H), 1.94 & 2.13 (d, 3H, $J = 1$ Hz), 2.49 (t, 2H, $J = 8$ Hz), 4.6-4.8 (m, 4H), 5.7-5.9 (m, 1H), 9.88 & 9.96 (d, 1H, $J = 6$ Hz); mass spectrum m/z (rel intensity): 248 (1.9), 233 (5), 149 (22), 135 (23), 123 (33), 121 (38), 109 (50), 108 (25), 107 (33), 97 (39), 95 (74), 93 (24), 84 (40), 83 (36), 82 (69), 81 (45), 71 (29), 70 (49), 69 (48), 67 (54), 55 (76), 43 (40), 41 (100).

3,6,10,11-Tetramethyl-7-methylene-2,11-dodecadien-1-ol 74

A solution of 50 mg (0.20 mmoles) of the aldehyde 73 in 0.5 ml of absolute ethanol was added to a solution of 21 mg (0.56 mmoles) of sodium borohydride in 1.0 ml absolute ethanol. The solution was stirred at room temperature for 1.5 hr. Sufficient acid (0.5 ml of 1N hydrochloric acid) was quickly added to quench the reaction. The solution was diluted with water and the aqueous solution was extracted several times with diethyl ether. The ether layer was washed with sodium bicarbonate and brine solutions, dried (MgSO_4),

and the product concentrated under reduced pressure. Separation on a silica gel column (chloroform solvent) gave 32 mg (64%) of the alcohol 74: $R_f = 0.23$; ir (neat) 3550-3100, 3080, 3000-2850, 1640, 1450, 1380, 1000, 890, 760 cm^{-1} ; ^1H nmr (CCl_4) δ 1.01 (d, 6H, $J = 6.5$ Hz), 1.2-2.3 (m, 11H), 1.62 (s, 6H), 3.9-4.1 (m, 2H), 4.6-4.8 (m, 4H), 5.2-5.4 (m, 1H); ^{13}C nmr (CDCl_3) δ 18.80, [19.73, 19.76], [20.14, 20.19], 29.86, 31.53, 33.31, 34.15, 37.34, 39.66, 40.97, 59.28, 107.51 & 109.55 ($\text{C}=\underline{\text{CH}}_2$), [123.17, 123.96], [139.94, 140.29] ($\text{C}=\underline{\text{CH}}-$), 149.79 & 154.43 ($\text{C}=\underline{\text{CH}}_2$); mass spectrum m/z (rel intensity): 250 (0.6), 123 (26), 121 (22), 109 (39), 107 (27), 95 (48), 84 (25), 83 (40), 82 (80), 81 (41), 71 (25), 70 (33), 69 (59), 67 (43), 55 (72), 53 (21), 43 (33), 41 (100).

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