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ACID-CATALYZED CYCLIZATION OF FARNESOL AND NEROLIDOL[1]

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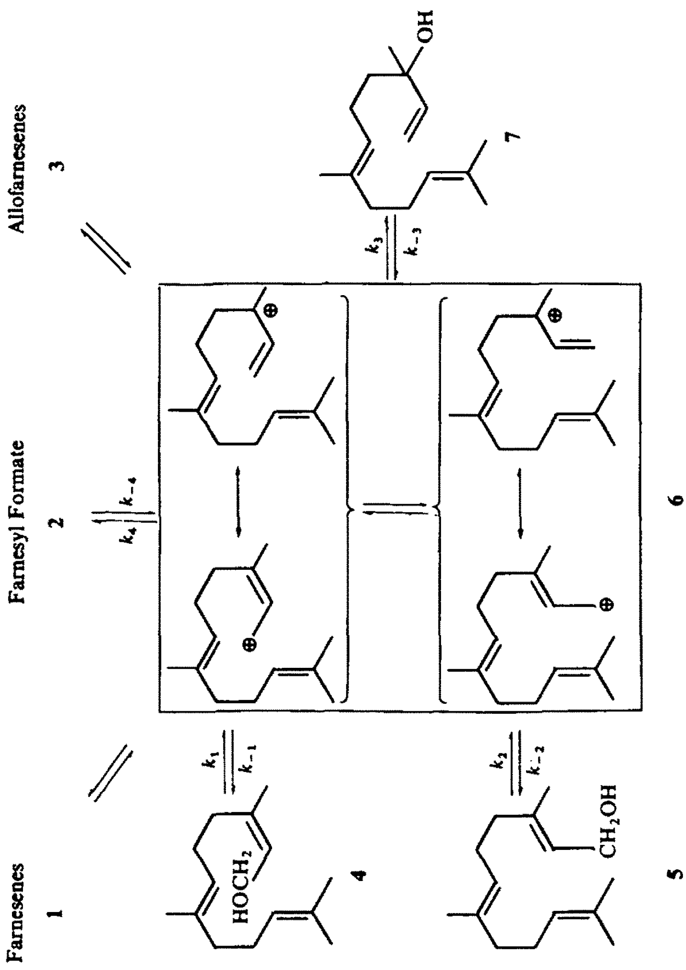
Abstract—As the preliminary phase of a program directed to the construction of polyfunctional catalysts for specifically directed cyclizations, a re-investigation of the acid-catalyzed cyclization of farnesol and related compounds has been undertaken. To simplify the analysis of the complex mixture obtained from these reactions an assay method has been devised which, using 1,2-dimethylnaphthalene as an internal standard, allows (a) the quantitative determination of the total volatile product in terms of polyenes, farnesol, nerolidol, bisabolol, and diols and (b) the quantitative determination of the total cyclic product in terms of monocyclic compounds (*via* 2-(*p*-tolyl)6-methylheptane in the dehydrogenation product) and bicyclic compounds (*via* cadalene in the dehydrogenation product). The preparations of bisabolol, a bisabolyl diol, and 2-(*p*-tolyl)6-methylheptane are described, these and other compounds being necessary for quantitation of the assay procedure. In the cyclization experiments the effects of changes in time, temperature, water content of the formic acid, and identity of the starting alcohol have been tested. For each run, the changes in concentration of starting material and the various products were measured as a function of time. The results from these experiments show that (a) nerolidol reacts somewhat more rapidly than farnesol (b) *cis-trans* and *trans-trans* farnesol react at the same rate and give the same ratio of products (c) the reaction rate falls off rather rapidly with increasing water content of the formic acid (d) even under very mild conditions the reactions proceed rapidly to yield, by the time that the starting alcohol is ca. 90% consumed, a product comprised mainly of monocyclic and bicyclic polyenes and mono alcohols (e) with more prolonged reaction time the concentration of diol derivatives and, probably, triol derivatives, increases (f) with more prolonged reaction time at higher temperatures the concentration of total cyclic material diminishes, probably as the result of polymerization reactions (g) the monocyclic and bicyclic products are formed concurrently rather than sequentially. These data, combined with information obtained from cyclization experiments with pure bisabolol, have led to the conclusion that the pathway to bicyclic compound involves the sequence: farnesol (or nerolidol) → bisabolyl cation → rearranged bisabolyl cation → cadinyl cation → cadinyl derivatives.

INTRODUCTION

ACID-CATALYZED polyene cyclizations have captured the attention of several generations of chemists,[3] much of the interest stemming from the presence of carbocyclic rings in numerous products of natural origin. The terpenes in particular have provided a focal point for such studies,[4] and with the enunciation of the "isoprene rule",[5] the demonstration of mevalonic acid as the biological isoprene equivalent,[6] and the proof that farnesyl pyrophosphate is the *in vivo* precursor of a variety of terpenes,[7] increasingly vigorous programs have been undertaken in various laboratories throughout the world. Although farnesol (as the pyrophosphate) is the known biological precursor of many sesquiterpenes, relatively little work has been done on the *in vitro* acid-catalyzed reaction of this polyolefin. As the preliminary phase of a program directed to the construction of polyfunctional catalysts for specifically-directed cyclizations, a re-investigation of the acid-catalyzed cyclization of farnesol and related compounds has, therefore, been undertaken.

The acid-catalyzed cyclization of farnesol was reported as early as 1913 when


Farnesenes
1
Farnesyl Formate
2
Allofarnesenes
3
k_4
k_{-4}
k_1
k_{-1}
k_2
k_{-2}
k_3
k_{-3}
HOCH$_2$
CH$_2$OH
OH
⊕
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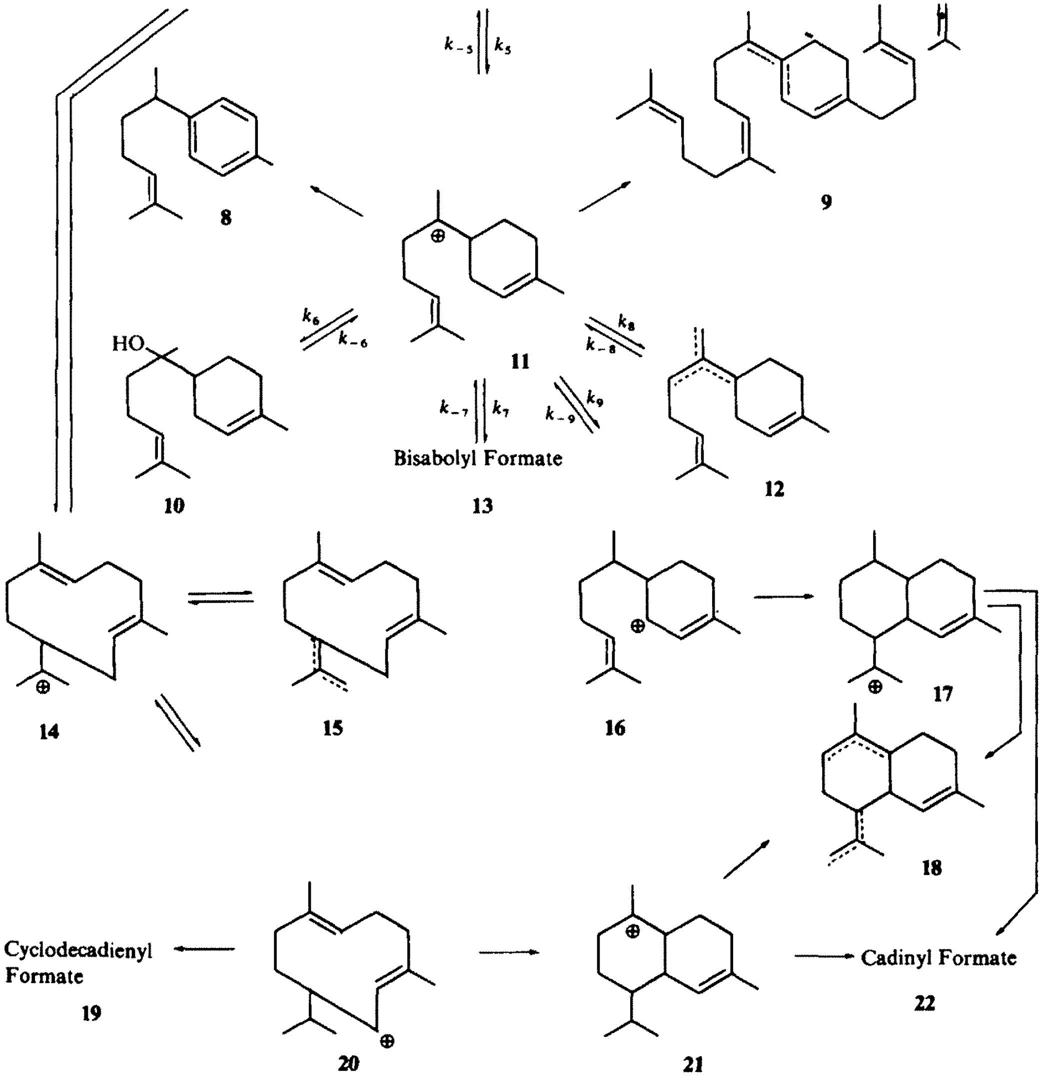
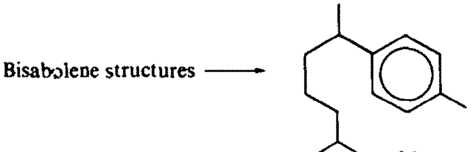


FIG. 1 Products from the acid-catalyzed reaction of farnesol and nerolidol.

it was observed[8] that the action of potassium hydrogen sulfate gave, in addition to the expected dehydration product farnesene, some monocyclic and bicyclic compounds. Later work[9] has corroborated these early findings and identified the monocyclic and bicyclic materials as belonging to the bisabolene and cadalene class, respectively. In 1925 a careful investigation was directed to the products obtained from the acid-catalyzed treatment of nerolidol, the allylomer of farnesol.[10] It was shown that dehydration of nerolidol with acetic anhydride followed by treatment with acetic-sulfuric acid or formic acid at, or below, room temperature, yielded mixtures containing farnesenes (**1**), bisabolenes (**12**), and bisabolol (**10**), while treatment with hot formic acid produced a complex mixture from which a 30% yield of cadalene (**24**) was obtained upon dehydrogenation. Although a number of compounds more or less closely related to farnesol and nerolidol have been studied in the ensuing years, not until 1966, well after the present work commenced, was further work published which was devoted to farnesol itself. This recent investigation has shown that the potassium acid sulfate-catalyzed reaction of farnesol and the DMSO-catalyzed reaction of nerolidol lead to mixtures containing, in addition to unidentified materials, *trans*-β-farnesene, isomeric bisabolenes (**12**), allofarnesenes (**3**), α-curcumene (**8**), and triterpenes (**9**).[11]

The present work has focused on the monocyclic and bicyclic sesquiterpenes that can be produced by the simple proton-catalyzed reaction of farnesol and nerolidol. Biogenetic postulates, originally formulated by Ruzicka and later elaborated by others[5, 12] have interpreted farnesol cyclization in terms of an initial ionization to a farnesyl cation (**6**) followed by intramolecular reaction either with the internal double bond at C_6–C_7 to give a bisabolyl cation (**11**) or with the terminal double bond at C_{10}–C_{11} to give the cyclodecadienyl cation **14**. Various fates are then prescribed for **11** and **14**. For instance, **11** can lose a proton to yield the bisabolenes (**12**), add water to form bisabolol (**10**), or add formate to form bisabolyl formate (**13**). Cation **14** can lose a proton to yield monocyclic trienes (**15**) or add a nucleophile (e.g. water or formate) to give the corresponding monocyclic dienyl compounds (e.g. cyclodecadienyl formate **19**). Alternatively, **11** and **14** can undergo sequential 1,2 hydrogen shifts to yield the allylic cations **16** and **20**, respectively. Each of these is properly constituted to allow a second transannular reaction to take place to form the bicyclic framework of the cadinenes (i.e. **17** from **16** and **21** from **20**). On the basis of Rucizka's observation that the yield of cadinenes (assayed *via* the dehydrogenation product, cadalene (**24**) is improved by increased times and temperatures,[10] it has seemed reasonable to assume that the pathway to the formation of the bicyclic compounds involves the farnesol → bisabolene → cadinene sequence. If one is to attempt to build a catalyst to promote bicyclic compound formation, however, it is important to establish the validity of this surmise, and it is the purpose of the present work to provide some insight into this aspect of the farnesol and nerolidol cyclization reactions.

Assay procedures. Previous work on the cyclization of farnesol and nerolidol has indicated that the product is a rather complex mixture. To simplify the problem of analysis and to gain as accurate an estimate as possible of the monocyclic and bicyclic products, a procedure has been developed using 1,2-dimethylnapthalene as an internal standard which is carried through from the beginning of each experiment. A known amount of the compound to be cyclized is mixed with a known amount of 1,2-dimethylnaphthalene, the mixture is subjected to formic acid-catalyzed cyclization, and the resulting product is hydrolyzed under basic conditions. Control experiments indicated that hydrolysis conditions sufficiently strenuous to convert all of the formate esters to alcohols has no effect on the alcohols and olefins present in the cyclization mixture. At this point the product is assayed by VPC, and the several regions in the chromatogram are identified, in sequence, as polyenes, nerolidol, 1,2 dimethylnaphthalene, bisabolol, farnesol, and diols. Knowing the weight of the starting material, the weight of 1,2-dimethylnaphthalene, and the VPC detector response factors for the various products, the areas under the VPC curves can be translated into absolute yields and their sum cited as a yield of volatile product. In many cases this amounted to 85–100%, although in a number of instances it fell well below this range, occasionally to 30–40%. It is thought that the fraction which is not accounted for as volatile product is present either as triols or triterpene products, both of these classes of compounds being insufficiently volatile to pass through the VPC column under the conditions employed. Subsequent to this VPC analysis the cyclization product is mixed with 10% Pd–C and subjected to dehydrogenation for 5 hr at 280–300° in a slow stream of nitrogen, and the product from this treatment is analyzed by VPC. The several regions of this chromatogram are identified, in sequence, as low molecular weight hydrocarbons (fragmentation products), 2-(*p*-tolyl)6-methylheptane (**23**), 1,2-dimethylnaphthalene, and cadalene (**24**). From the known weights of starting material and 1,2-dimethylnaphthalene and from the known detector response factors, the areas under the VPC curves can be translated into absolute yields and the sum of these cited as the total yield of cyclic product. This value will, of course, depend, among other things, on the extent to which the reaction has progressed.



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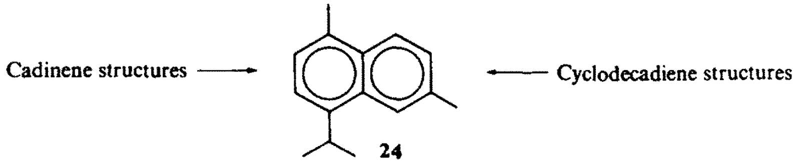

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Cyclization and dehydrogenation products. It was necessary to obtain the various materials of the cyclization mixture in pure form to test their sensitivity to the conditions of the hydrolysis and dehydrogenation steps of the assay and to measure their VPC response factors. To this end several syntheses were undertaken.

Syntheses of bisabolol have been described by Ruzicka and Liguori in 1932[13] and by Manjarrez and Guzman in 1966.[14] For reasons that will be indicated in the ensuing discussion, however, it is doubtful that either of these groups of investigators obtained the pure compound. The method chosen in the present work follows the general pattern laid down by Ruzicka and Ligouri[13] and involves as the terminal

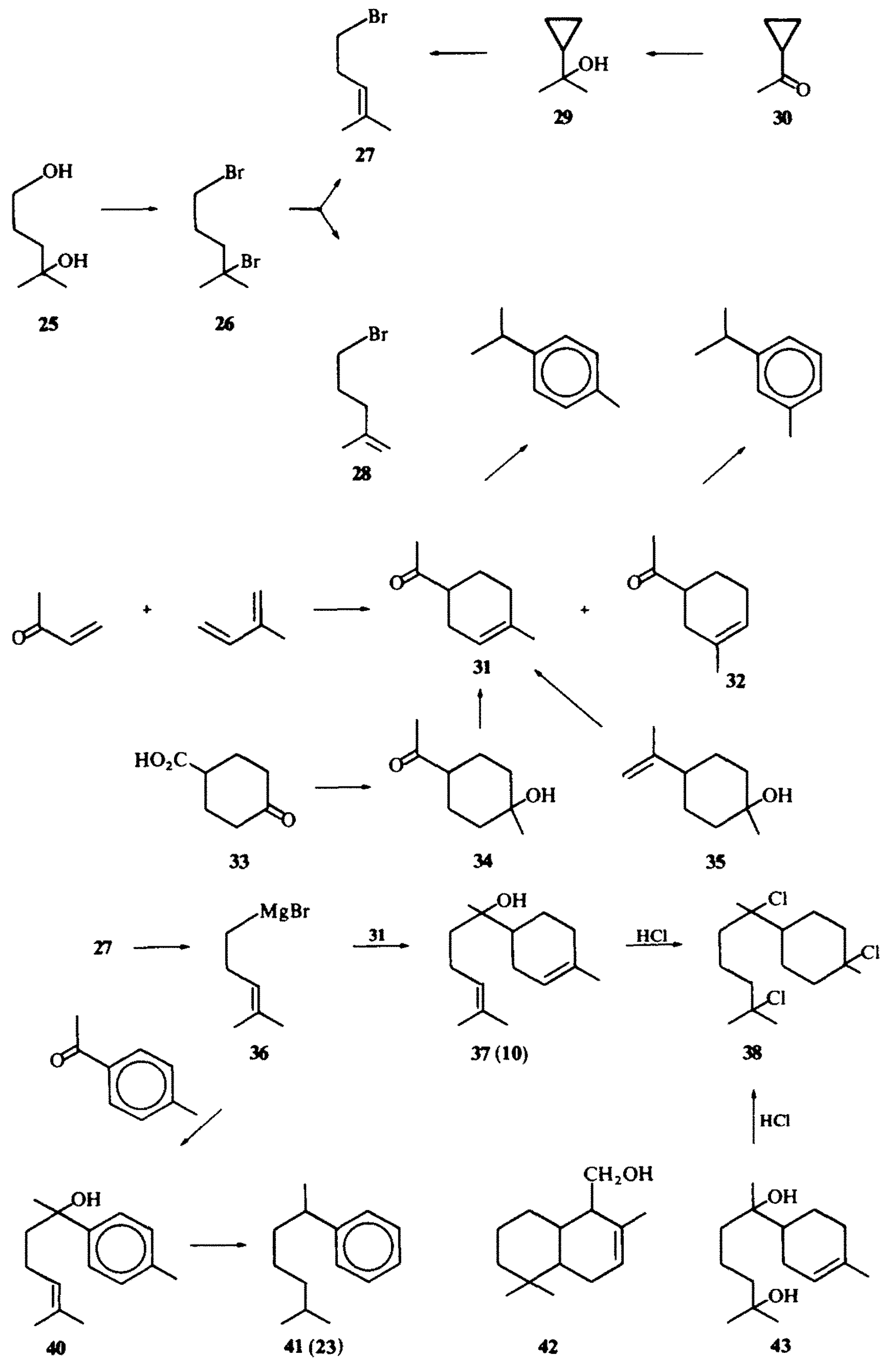

FIG. 2 Synthesis of bisabolol and 2-(*p*-tolyl)6-methylheptane.

step the reaction between 4-acetyl-1-methylcyclohexene (**31**) and 4-methyl-3-pentenylmagnesium bromide (**36**). Preparation of **31** by ozonolysis and dehydration of β-terpineol (**34**)[13] proved to be tedious because of the difficulty in separating pure **34** from the commercially available mixture. Therefore, an alternative method was sought in the Diels-Alder condensation between methyl vinyl ketone and isoprene.[15,16] A quantitative assay of the product from this reaction, previously recognized as containing both **31** and **32**, was obtained by condensing the ketones with methylmagnesium bromide, dehydrating the resulting product, and dehydrogenating this to a mixture of *m*- and *p*-cymene. A VPC analysis of the dehydrogenation product showed that the original mixture contained 3 parts of **31** and 1 part of **32**. Thus, although the desired compound predominates, so much of its extremely difficultly separated isomer is present that this method had to be discarded.* The procedure eventually adopted involves the action of excess methyllithium on 4-ketocyclohexanecarboxylic acid (**33**), obtained by a method modified from that reported in the literature.[18] Unfortunately, even after prolonged reaction times the yields of keto alcohol are rather low, and a recently reported method[19] probably provides a better route to **31**.

The 4-methyl-3-pentenyl bromide (**27**) employed in both of the previously-reported bisabolol syntheses[13,14] was prepared from 2-methyl-2,5-pentanediol (**25**) by conversion to the dibromide **26** followed by selective dehydrohalogenation. A repetition of this synthesis and an analysis of the product *via* VPC and NMR showed, however, that in addition to **27**, the isomeric 4-methyl-4-pentenyl bromide (**28**) is also formed in significant amounts. Since the extent to which **27** is contaminated with **28** appears not to have been recognized by the previous workers, it seems probable that the bisabolols that are reported in the literature must be mixtures of double bond isomers. The product reported by Manjarrez and Guzman is probably also contaminated with structural isomers, since the six-membered ring was constructed by a Diels–Alder reaction between ethyl acrylate and isoprene (see previous discussion), and no separation of isomers was indicated. For the present synthesis a sample of **27** uncontaminated with **28** was prepared by the method of Julia *et al.*[20] by the action of hydrobromic acid on dimethyl cyclopropylcarbinol (**29**), obtained from the ketone **30**. Conversion of **27** to the Grignard reagent (**36**) followed by treatment with **31** yielded bisabolol, probably as a mixture of epimers but uncontaminated with structural or bond isomers. In comparable fashion 2-(*p*-tolyl)6-methylheptane (**41**) was prepared by the interaction of **36** with *p*-methylacetophenone to yield **40** which was then hydrogenated and hydrogenolyzed.

The highest-boiling components observed in the VPC of the crude cyclization product are attributed to diols. One of these was isolated as a crystalline solid from a nerolidol cyclization mixture and was shown to belong to the bisabolene class by conversion to the same trichloro compound (**38**) that is obtained from bisabolol (**37**). The diol is assigned the structure 2-(4-methyl-3-cyclohexenyl)6-methylheptane-2,6-diol (**43**) on the basis of its NMR spectrum which shows resonances at 1·10 and 1·22 ppm corresponding to 9 protons and characteristic of MeC–OH methyl

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* After this portion of the work had been completed a publication appeared which reported that (a) this mixture could be directly assayed by means of a 220 ft capillary VPC column and (b) the ratio of **31**:**32** could be increased to 93:7 by use of a stannic chloride catalyst in the Diels–Alder reaction.

groups,*† a 3-proton resonance at 1·65 ppm characteristic of a $CH_3C=$ methyl group,* and a 1-proton broad singlet characteristic of a vinyl proton in a cyclohexene ring.*

Dehydrogenation experiments. 2-(*p*-Tolyl)6-methylheptane (**23**, **41**), cadalene (**24**), and 1,2-dimethylnaphthalene (the internal standard in the cyclization reactions) were shown to undergo no change under the dehydrogenation conditions used in the assay. A pure sample of commercial farnesol yielded 3% of monocyclic material and 0·3% of bicyclic material under these conditions, while nerolidol yielded 3% of monocyclic material and no bicyclic material; in both cases the major product was comprised of lower-boiling fragmentation substances. Bisabolol was shown to undergo dehydrogenation to 2-(*p*-tolyl)6-methylheptane (**23**, **41**) in 90% yield accompanied by 0·6% of cadalene and 9% of lower-boiling materials presumed to be fragmentation products. Thus, it is apparent that little, if any, of the cadalene that is observed in the dehydrogenation products from the cyclization mixtures has its genesis in any of these materials. In addition to the modes of cyclization depicted in Fig. 1, the possibility of initial carbonium ion formation at the C_{10}–C_{11} double bond also exists and would lead to bicyclic materials of the drimenol series (**42**). While products of this type have not been reported from farnesol, they have been observed from certain relatives of farnesol.[22] To test the possibility that bicyclic

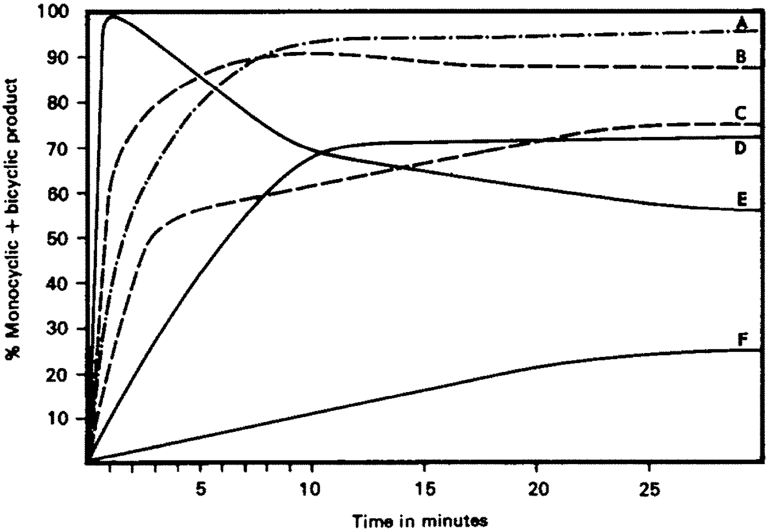

FIG. 3 Acid-catalyzed cyclization of farnesol and nerolidol in 90%, 98% and 100% formic acid at 0° and 30° (A—farnesol, 100% formic acid, 0°; B—nerolidol, 100% formic acid, 0°; C—farnesol, 90% formic acid, 30°; D—farnesol, 98% formic acid, 0°; E—farnesol, 100% formic acid, 30°; F—farnesol, 90% formic acid, 0°).

* EtOH (No. 14) has a Me resonance at 1·22 ppm; Me_2CHOH (No. 44) has a Me resonance at 1·20 ppm; geraniol (No. 279) has Me resonances at 1·62 and 1·68 ppm; Δ^3-carene (No. 273) has a Me resonance at 1·62 ppm; Δ^3-carene (No. 273) has a broad vinyl resonance at 5·23 ppm; β-terpinene shows a singlet at 5·30 ppm and limonene shows a broad singlet at 5·32 ppm. The absence of a peak at 1·60 ppm is also indicative of the absence of the isopropylidene group.

† The resonance at 1·10 ppm appears as a doublet (J = 2 c/s); bisabolol, prepared as outlined in Fig. 2, also possesses a doublet (J = 2 c/s) at 1·07 ppm. Whether these are the result of the presence of epimers or the result of long range spin–spin coupling is not known.

dehydrogenation products might arise from drimenol type structures, a compound was prepared (as a mixture of epimers and, probably, bond isomers) by the sequence: farnesol → farnesal → farnesic acid → bicyclofarnesic acid → **42** (and isomers). When subjected to the standard dehydrogenation conditions no aromatic compounds were obtained from this material. It has been reported, however, that drimenol can be dehydrogenated to 1,2,5-trimethylnaphthalene,[23] although the conditions that were required for aromatization were not specified.

Cyclization experiments. The effects of changes in time, temperature, water content of the formic acid, and identity of starting alcohol are seen in graphical form in Fig. 3. A comparison, over the first third of the reaction, of the rates of cyclization of farnesol at 0° in 90% formic acid, 98% formic acid, and 100% formic acid shows that they fall in the order 1:8:35. The water content of the formic acid, thus, is seen to have considerable effect on the reaction rate, and for this reason particular pains were taken to use strictly anhydrous formic acid (100% reagent) and to dilute this with the calculated quantities of water to obtain the 98% and 90% reagents. A comparison of the reactions carried out with 90% formic acid at 0° and 30° indicates an 18 fold rate increase at the higher temperature. A quantitative comparison of the reactions in 100% formic acid at 0° and 30° was not possible, however, for the reaction is so rapid at 30° that it is essentially complete after 1 minute (the time of the first measurement). In fact, the maximum yield of cyclic material is obtained after only 1 minute and declines with increasing time. Concomitantly, the yields of bisabolol, diols, and total volatile product fall (Table 1), from which it must be assumed that polymerization reactions (dimerization to triterpenes?) are taking place. In studying the polyene cyclizations in this series, Ruzicka[10] chose nerolidol as the starting material in the thought that, since it bears the same relationship to farnesol that the more reactive linalool bears to geraniol, it should cyclize more rapidly. The validity of this rationale

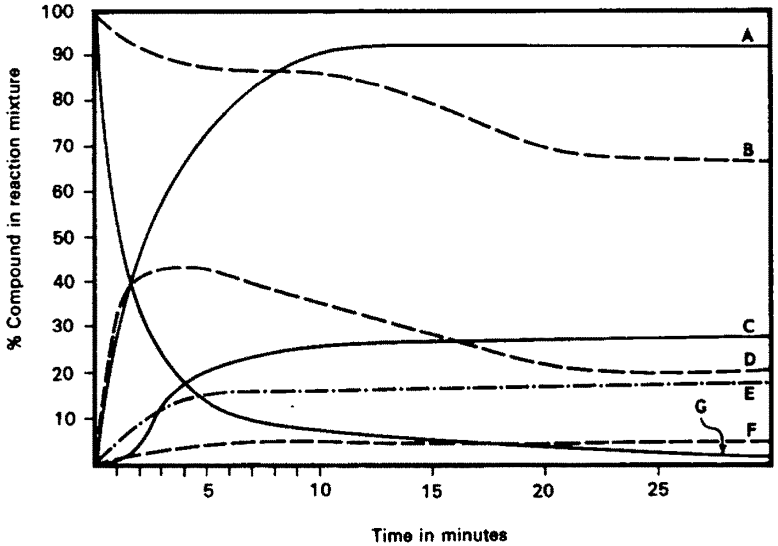

FIG. 4 Product development in reaction of *trans,trans*-farnesol with 100% formic acid at 0° (A—2-(*p*-tolyl)-methylheptane; B—total volatile product; C—diols; D—bisabolol; E—polyenes; F—cadalene; G—farnesol).

TABLE 1. COMPOSITION OF MIXTURES FROM ACID-CATALYZED TREATMENT OF FARNESOL, NEROLIDOL AND BISABOLOL

Olefin	Catalyst	Temp	Time	Polyenes	Nerolidol	Bisabolol	Farnesol	Diols	Total volatile product	2-(*p*-tolyl)-6-methyl-heptane	Cadalene	Total cyclic product
Farnesol (commercial)	100% HCO_2H	0	1	9	3	41	49	trace	102	36	3	39
			3	12		47	18	13	90	61	3	64
			5	18	—	43	9	17	87	75	6	81
			10	18	—	31	3	23	75	86	5	91
			20	19	—	18	trace	24	61	87	7	94
			60	21	—	21	trace	23	65	90	7	97
Farnesol (commercial)	100% HCO_2H	30	1	30	—	23	2	15	70	93	10	~100
			3	22	—	13	—	24	59	70	12	82
			5	20	—	11	—	12	43	75	11	86
			10	24	—	7	—	8	39	57	12	69
			20	28	—	8	—	6	42	50	11	61
			60	37	—	6	—	6	49	30	11	41
Farnesol (commerical)	98% HCO_2H	0	3	4	3	31	62	—	100	27	trace	27
			5	5	2	40	52	—	99	39	3	42
			10	9	—	48	37	3	97	65	4	69
			20	9	—	50	27	11	97	69	3	72
			60	16	—	41	10	24	91	75	8	83
			120	17	—	33	8	32	90	80	10	90
Farnesol (commercial)	90% HCO_2H	0	10	3	4	9	86	—	102	12	—	12
			20	3	5	16	78	—	102	20	1	21
			30	4	5	20	73	trace	102	22	2	24
			60	7	4	27	58	trace	96	31	3	34
			120	7	1	29	48	4	89	30	3	33
			300	7	—	30	29	10	76	43	3	46

Farnesol (commercial)	90% HCO_2H	30	3	14	2	48	42	—	106	47	5	52
			5	15	—	38	32	11	96	53	3	56
			10	19	—	32	20	18	89	58	4	62
			20	21	—	24	8	27	80	65	7	72
			30	22	—	21	5	29	78	70	6	76
			60	22	—	13	1	24	60	88	8	96
trans-trans Farnesol	100% HCO_2H	0	1·5	6	—	41	46	1	94	42	1	43
			3	14	—	38	20	13	85	62	2	64
			5	17	—	43	12	17	89	72	4	76
			10	16	—	35	8	27	86	92	3	95
			20	17	—	20	4	28	69	89	4	93
			60	18	—	18	2	25	63	91	4	95
trans Nerolidol	100% HCO_2H	0	1	7	15	52	25	—	99	58	3	61
			3	13	15	53	15	7	103	75	4	79
			5	17	6	48	4	10	85	83	3	86
			10	19	1	32	1	24	77	84	8	92
			20	19	4	27	3	20	73	80	7	87
			30	15	4	18	4	21	62	82	5	87
Bisabolol	98% HCO_2H	0	60	17	—	41	—	42	100	96	4	100
		45	30	47	—	—	—	—	47	31	8	39
	100% HCO_2H	0	30	11	—	24	—	40	75	98	1	99
			60	15	—	15	—	48	78	99	2	100
		30	30	32	—	6	—	2	40	42	7	49
			60	31	—	8	—	1	40	32	7	39

is supported by the present observation that nerolidol does, indeed, cyclize ca. 1·5 times faster than farnesol. It is interesting to note, however, that the reaction mixture from nerolidol after 1 minute (see Table 1) contains 25% of farnesol* (configuration unknown) and only 15% of nerolidol,* when farnesol is the starting material the amount of nerolidol present at intermediate times never exceeds 1/15 the amount of farnesol. It may be concluded that while nerolidol ionizes more rapidly than farnesol ($k_3 > k_1$ or k_2), the allylic cation reacts with water or, more likely, with formic acid to give farnesol or farnesyl formate more rapidly than nerolidol or nerolidyl formate. Furthermore, it emphasizes the fact that the allylic cation, once formed, does not cyclize immediately but returns in significant amount to the acyclic structures. Although the position of the OH group controls the rate at which cyclization takes place, the geometry of the C_2–C_3 double bond is without effect; commercial farnesol (containing 27% of the *cis-trans* isomer) undergoes cyclization at a rate virtually identical with that of pure *trans-trans* farnesol.

The time dependency of the concentrations of the starting material and the various products are shown in graphical form in Fig. 4 for the reaction of *trans-trans* farnesol with 100% formic acid at 0°. The rate of change in the farnesol concentration is seen to be high in the beginning but then to diminish. When these data are plotted as log of the farnesol concentration vs. time, a straight line is obtained for the first 5 minutes of reaction, indicative of the expected first order kinetics. Beyond the 5 minute point, however, the plot departs sharply from linearity as the reaction slows down. This rate diminution may be due to the accumulation of farnesyl formate which, possessing a less basic oxygen than farnesol itself, might be expected to protonate less readily and, as a consequence, to ionize less readily.†

The concentration of monocyclic compounds in the product (determined in the dehydrogenation mixture as 2-(*p*-tolyl)6-methylheptane) increases rapidly and reaches a maximum after ca. 10 minutes. The bisabolol, however, reaches its maximum value after ca. 5 minutes and declines thereafter. The decline in bisabolol concentration is paralleled by the decline in total volatile product. Since the total cyclization product (i.e. 2-(*p*-tolyl)6-methylheptane + cadalene) is close to 100% the decline in total volatile product must involve the formation of monocyclic triols (i.e. products not sufficiently volatile to appear in the VPC but, nevertheless, convertible to aromatic hydrocarbons upon dehydrogenation). Part of the decline in bisabolol concentration must also be attributed to diol formation; however, since diol formation reaches its maximum after ca. 10 minutes, at which point the bisabolol concentration is still waning, it must be assumed that a steady state with respect to diol generation and depletion (to triol) has been reached.

The polyene fraction, along with bisabolol, reaches its maximum concentration at ca. 5 minutes and remains essentially unchanged thereafter. Whether this is to be ascribed to a steady state of formation and depletion or whether this fraction, once formed, is not susceptible to further alteration is not known. A sample, separated from the alcohols, diols and triols, was subjected to dehydrogenation under the standard assay conditions. The product contained 67% of 2-(*p*-tolyl)6-methyl-

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[*] Whether the farnesol and nerolidol are present as the alcohols or as the formates is not known, since the method for assay does not distinguish between these possibilities.

[†] For example Johnson *et al.*[24] have found that the allylic diene (2-(Δ^3-butenyl)Δ^2-cyclohexenol solvolyzes in formic acid–acetic acid much more rapidly than the corresponding 3,5-dinitrobenzoate.

heptane, 5% of cadalene, and 28% of lower-boiling materials presumed to be fragmentation products from farnesenes. At least a part of the cadalene, thus, has its genesis in material(s) contained in the polyene fraction.

The concentration of bicyclic compounds in the product (determined in the dehydrogenation mixture as cadalene) reaches its maximum after ca. 5 min and remains essentially constant thereafter. Which of the fractions of the reaction mixture contains the progenitor of the cadalene is not known, although it has been shown (see above) that the polyene fraction is at least partly responsible. More cadalene than can be ascribed to this fraction alone is obtained, however, so it must be assumed that mono-, di-, and triol precursors may also be present in the reaction mixture. The simultaneous build up of bisabolol and bicyclic hydrocarbons, the failure of the bicyclic hydrocarbon concentration to increase during the period that the concentration of bisabolol is decreasing, and the failure to achieve significant conversion of pure bisabolol to bicyclic material under conditions which do convert farnesol to bicyclic material (Table 1) all seem to argue that the sequence of farnesol → bisabolol → bicyclic compounds is not tenable. These data suggest, rather, that the cadalene is formed either by (a) dehydrogenation of cadinyl structures arising *via* cyclodecadienyl intermediates (i.e. **6** → **14** → **20** → **21** → **18** and/or **22** or (b) dehydrogenation of a cyclodecadienyl compound. The latter alternative is supported by the observation that the naturally occurring sesquiterpene germacrone (containing a cyclodecadiene structure) yields cadalene when dehydrogenated with palladium on charcoal.[25]

An alternative explanation for the data cited above is also possible, and on the basis of the existing evidence it appears to us to be the more probable one. Although a sample of pure bisabolol in 100% formic acid at 0° yields only 1–2% of cadalene after 30–60 min (conditions under which farnesol yields 4–7% of cadalene), more strenuous treatment (e.g. 100% formic acid at 30° or 98% formic acid at 45°) yields significant amounts of cadalene (i.e. 7–8%). The failure of bisabolol to yield bicyclic products under the milder conditions may simply represent a slower rate of ionization of bisabolol (an ordinary secondary alcohol) as compared with farnesol (an allylic primary alcohol). The significant rate enhancement of ionization in allylic systems is a well-documented phenomenon.* It is postulated, therefore, that the bicyclic compounds arise through the intermediacy of a 6-membered monocyclic entity which is not bisabolol (or bisabolyl formate) *per se* but which is the bisabolyl cation (**11**). This cation has several reaction pathways available to it including (a) the loss of a proton to yield bisabolenes (**12**), (b) the acquisition of a formate moiety to yield bisabolyl formate (**13**), (c) the acquisition of a hydroxyl moiety to yield bisabolol (**10**), and (d) the two-step migration of a proton to yield the allylic cation **16**. If the conversion of **11** proceeds along these pathways at roughly comparable rates (e.g. $k_8 \simeq k_7 \simeq k_6 \simeq k_9$) but if the reverse reactions are very much slower (e.g. $k_{-8} > k_8$, $k_{-7} > k_7$, $k_{-6} > k_6$, $k_{-9} > k_9$), the partitioning between monocyclic and bicyclic compound will be largely determined at the point of initial bisabolyl cation formation. The subsequent reactions in which the bisabolol concentration diminishes and the diol (and, probably, triol) concentration increases are simply a consequence of the greater rate of formic acid addition to the double bonds as compared with the rate of ionization of bisabolyl formate. Thus, the alternative pathway to bicyclic compound

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* For instance, allyl chloride undergoes solvolysis in formic acid 26 times more rapidly than propyl chloride.

formation which involves the cyclodecadienyl cations **14** and **20**, although not completely precluded by this interpretation of the data, appears to be a less probable one. Both pathways to bicyclic compound involve a sequence of two 1,2-hydride shifts to generate a cation suitable for the formation of the second ring (e.g. **11** → **16** and **14** → **20**), and in both instances the resulting cation is stabilized by allylic resonance. Certainly, however, the cations **11** and **16** would not be expected to form with comparable ease. Not only does the proximity factor militate against the formation of **16**, but steric factors also appear to be operative. On the basis of these considerations, therefore, it is concluded that the bicyclic compounds formed in the acid-catalyzed reactions of farnesol and nerolidol probably have six-membered monocyclic precursors.

EXPERIMENTAL

M.ps are corrected, b.ps are uncorrected. The IR spectra were measured on a Perkin–Elmer Infracord spectrometer; the NMR spectra were measured on a Varian Model A-60-A spectrometer and are recorded in ppm downfield shift from TMS, used as an internal standard. VPC analyses were performed with an F and M Model 720 instrument using a 0·25 in × 4·5 ft column packed with 20% (by weight) of Carbowax 20M on 30–60 mesh base-washed firebrick; a flow rate of 50 ml/min of He and column temps of 180–210° were used. Microanalyses were performed by Mikroanalytisches Laboratorium, Vienna, Austria and by Micro-Tech Laboratories, Skokie, Ill.

Synthesis of cyclization and dehydrogenation products

4-Acetyl-1-methylcyclohexene (**31**)—(*A*) via *Diels–Alder reaction.* Following literature directions[15] a mixture of 40 g methyl vinyl ketone and 40 g isoprene was heated in a pressure bomb for 10 hr at 140°. Distillation of the product yielded 40 g keto olefin, b.p. 90–94°, which appeared to be homogeneous by VPC. A semicarbazone of this material was obtained as a colorless solid, m.p. 148·5–149·5° (reported[15] m.p. 149°). The material was assayed for contamination with **32** in the following manner. A 4·14 g (0·03 mole) sample of the keto olefin was treated with 0·04 mole MeMgI, a 3·0 g sample of the resulting alcohol was dehydrated by refluxing for 10 hr with 6 g oxalic acid in 40 ml water, and a 1·4 g sample of the dehydrated compound was dehydrogenated at 210–230° for 8 hr with 0·4 g 10% Pd–C. Although this product also appeared to be homogeneous upon VPC analysis, its IR spectrum indicated that it was a mixture of 1-methyl-4-isopropylbenzene and 1-methyl-3-isopropylbenzene. Quantitative comparisons in the IR between the dehydrogenation product and mixtures containing known amounts of authentic samples of the two cymenes (bands at 722 and 818 cm^{-1} used in the analysis) indicated that the original Diels–Alder product was actually a mixture containing 3 parts of **31** and 1 part of **32**.*

4-Acetyl-1-methylcyclohexene (**31**)—(B) via *4-oxocyclohexanecarboxylic acid* (**33**). Ethyl 1,3,5,-tricyanopentane-3-carboxylate, obtained in 93% yield by the method of Bruson and Reiner,[27] was hydrolyzed[28] and esterified to yield 70% of triethyl 1,3,5-pentanetricarboxylate as a colorless oil; $\bar{\nu}^{\text{liq}}$ 1735 cm^{-1} (ester CO). This material was subjected to a Dieckmann cyclization according to the direction of Linstead and Meade,[29] and diethyl 4-oxocycloheptane-1,3-dicarboxylate was obtained in 60% yield, after distillation, as a colorless oil; b.p. 109–111° (0·3 mm) (reported[18] b.p. 180° (20 mm)); $\bar{\nu}^{\text{liq}}$ 1735 (ester CO), 1660 (chelated CO), 1615 cm^{-1} (olefin). Acid-catalyzed hydrolysis and decarboxylation produced a 68% yield of **33** as colorless needles after recrystallization from benzene and petroleum needles after recrystallization from benzene and petroleum ether (b.p. 63–69°): m.p. 66–67° (reported[30] 67–68°); $\bar{\nu}^{\text{liq}}$ 3100–3300 (OH), 1730 (carboxyl CO), 1710 cm^{-1} (cyclohexanone CO). A toluidide of **33** was obtained as colorless needles after several recrystallizations from aqueous EtOH, m.p. 169–170·5. (Found: C, 72·98; H, 7·48. Calc. for $C_{14}H_{17}NO_2$: C, 72·70; H, 7·41%.)

To a stirred mixture, under N, containing 10 g (1·4 moles) Li wire in 500 ml ether, a soln of 140 g (1 mole) MeI in 150 ml ether was added. The mixture was refluxed for 2 hr, cooled, and treated over a 5 hr period with a soln of 8·0 g (0·056 mole) **33** in 2 l. ether. This mixture was then refluxed for 7 days, cooled, poured onto ice, and the aqueous layer extracted continuously for 3 days. The crude product was treated with 100 ml of 10% aqueous oxalic acid, and the reaction mixture was refluxed overnight and then

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* See footnote page 865.

subjected to steam distillation. Extraction of the distillate yielded 2·6 g crude product which, upon distillation, provided 1·7 g (21%) of **31** as a colorless oil: b.p. 85° (12 mm) (reported[13] 88–89° (12 mm)); $\tilde{\nu}^{\text{liq}}$ 1720 cm^{-1} (CO); NMR (CCl_4) in ppm, 3-proton singlet at 1·63 ($CH_3C\!\!\lessdot$), 6-proton multiplet 1·6–2·6 (ring $C\underline{H}_2$), 3-proton singlet at 2·08 ($C\underline{H}_3CO$), 1-proton singlet (broad) at 5·35 ($=C\underline{H}$).

The semicarbazone of **31** was obtained as colorless plates, m.p. 156·5–157·5° (reported[15] m.p. 149°).

5-Bromo-2-methyl-2-pentene (**27**)—(A) *γ-butyrolactone method.* Following literature procedures[31] γ-butyrolactone was treated with MeMgI to yield 69% of **25**, and this was treated with pyridine and PBr_3 followed by distillation from pyridine to produce, after redistillation, a 42% yield of a colorless liquid: b.p. 68–72° (40 mm) (reported[32] 84–85° (84 mm)); $\tilde{\nu}^{\text{liq}}$ 890 cm^{-1} ($C{=}CH_2$); NMR (CCl_4) in ppm, multiplet at 1·7 ($C\underline{H}_3$ in **27** and **28**), multiplet at 1·9–2·8 ($C\underline{H}_2$ in **27** and **28**), multiplet at 3·3 ($C\underline{H}_2Br$ in **27** and **28**), broad singlet at 4·73 ($=C\underline{H}_2$ of **28**), triplet at 5·10 ($=C\underline{H}$ of **27**). Area measurements of the resonances at 4·73 and 5·10 indicated the mixture to consist of 4·6 parts of **27** and 1·0 part of **28**; VPC analysis indicated the ratio of **27**:**28** to be 5:1.

5-Bromo-2-methyl-2-pentene (**27**)—(B) *Cyclopropylmethylketone method.* Follwong literature procedures,[20] **30** was treated with MeMgI and converted to a 63% yield of **29**, and this was treated with 48% HBr to provide a 55% yield of **27** which was shown by the absence of a band at 890 cm^{-1} in the IR spectrum, by the absence of a resonance at 4·73 ppm in the NMR spectrum, and by the appearance of a single peak in the VPC analysis to consist of a single component, uncontaminated with **28**.

Bisabolol (**10**, **37**). To a cooled soln containing the Grignard reagent from 6·4 g (0·04 mole) of pure **27** (prepared by method B above) in 35 ml ether was added 2·76 g (0·02 mole) of **31** in 25 ml ether. The mixture was refluxed for 2 days and then worked up to give, after distillation through a short column, 1·8 g (40%) of a colorless oil: b.p. 128–130° (1·5 mm) (reported[13] 155–157° (12 mm)); $\tilde{\nu}^{\text{liq}}$ 3500 (OH), no absorption at 890 cm^{-1} ($C{=}CH_2$); NMR (CCl_4) in ppm, 3-proton doublet at 1·07 ($C\underline{H}_3C{-}OH$ from epimeric forms of **37**), 9-proton multiplet at 1·6–1·7 ($C\underline{H}_3C{=}$), 2-proton multiplet at 4·8–5·7 ($\underline{H}C{=}$). A VPC analysis indicated that the product was at least 95% pure.

*2-(*p*-Tolyl)6-methylheptane* (**23**). To a cooled soln containing the Grignard reagent prepared from 6·4 g (0·04 mole) of pure **27** (prepared by method B above) in 65 ml ether was added 2·68 g (0·02 mole) 4-methylacetophenone in 25 ml ether. The mixture was refluxed for 2 days and then worked up to give, after distillation, 2·5 g (57%)2-(*p*-tolyl)6-methyl-5-hepten-2-ol as a colorless liquid; b.p. 110–112° (0·5 mm) (reported[33] 110° (0·35 mm)). A 1·0 g sample of this material was mixed with 0·5 g 10% Pd–C and 4 drops of 70% perchloric acid in 40 ml EtOH and hydrogenated at 15 psi for 5 hr at room temp. Distillation of the crude product of hydrogenation yielded 0·54 g (58%) 2-(*p*-tolyl)6-methylheptane as a colorless oil: b.p. 100–102° (2 mm) (reported 135–136° (15 mm),[34] 100–105° (1 mm)[35]); NMR (CCl_4) identical with that reported.[35]

Cadalene (**24**). A sample of cadalene picrate* was decomposed by passage through an alumina column to yield cadalene as a colorless oil possessing an IR spectrum identical with the published spectrum for this material.[37]

Dehydrogenation experiments

*2-(*p*-Tolyl)6-methylheptane and 1,2-dimethylnaphthalene* were shown to undergo no change upon heating with 10% Pd–C catalyst for 5 hr under a slow stream of N at 280–300° ("standard dehydrogenation conditions" employed in the analytical proceudre). Cadalene under similar conditions yielded a product consisting of 85% unchanged cadalene and 15% of a slightly more volatile material thought to be 1,6-dimethylnaphthalene, although not conclusively identified as such. While this more volatile constituent was never detected in the assay dehydrogenations, it suggests that a factor of ca. 1·2 might be applied to the cadalene yields in the assay dehydrogenations.

Farnesol (**4** *and* **5**). A 0·0855 g sample of farnesol (obtained from the Fluka Co. and comprised of 70% of the *trans-trans* isomer and 27% of the *cis-trans* isomer) was mixed with 0·0313 g 1,2-dimethylnaphthalene (as an internal standard) and heated with 0·1 g 10% Pd–C catalyst at 280–300° for 5 hr under a slow stream of N. The product was separated from the catalyst by centrifugation and filtration through a glass fiber filter disc, the catalyst was thoroughly washed with ether, and the combined ethereal soln was concentrated to give 0·0663 g crude product. Analysis by VPC indicated that the product contained ca. 3% of materials with retention times similar to those of monocyclic compounds, ca. 0·3% of material with a retention time similar to that of cadalene, and the remainder of components of the mixture with

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* We are indebted to Professor W. S. Johnson, Stanford University, for a generous gift of this material.[36]

retention times lower than that of **23** and consisting, presumably, of fragmentation products. Virtually identical results were obtained when a sample of pure *trans-trans* farnesol (**5**) was subjected to dehydrogenation under the same conditions.

Nerolidol (**7**). A sample of nerolidol (comprised of 97% of the *trans* isomer and 3% of the *cis* isomer) was subjected to dehydrogenation under the conditions described above. Analysis of the product by VPC indicated that the product contained ca. 3% of monocyclic material, no cadalene, and 97% of fragmentation substances.

Bisabolol (**10**, **37**). A sample of bisabolol, prepared as described above, was subjected to dehydrogenation under the conditions described above to yield a mixture which was shown by VPC analysis to contain 90% of **23**, ca. 0·6% of cadelene, and ca. 9% of materials with retention times lower than that of **23** presumed to be fragmentation products.

Cyclization experiments

Assay procedure for cyclization reactions. The following procedure records a specific run and is representative of all of the experiments that are summarized in Table 1. A mixture of 0·2237 g commercial farnesol and 0·0400 g 1,2-dimethylnaphthalene was treated at 0° with 10 ml anhyd formic acid. The reaction mixture was stirred in an ice bath for 5 min and then poured into 40 ml 30% NaOH aq containing 50 g ice. The reaction flask was rinsed with 50 ml 95% EtOH, and the basic soln was allowed to stand for 2 hr at room temp. Control experiments showed that this is sufficient time to effect hydrolysis of the formate esters and that the alcohols and olefins produced in the cyclization are stable to these conditions. The soln was then transferred to a 1 l. separatory funnel, and 300 ml brine was added. The soln was extracted with four 100-ml portion ether, and the ethereal soln was dried over $MgSO_4$, filtered, and evaporated to give 0·2824 g crude cyclization product. Analysis by VPC* showed it to contain 0·0367 g (18%) of a lower boiling fraction (polyenes), 0·0962 g (43%) bisabolol, 0·0189g (9%) farnesols, and 0·0410 g (17%) diols. The remaining 13% of starting material is assumed to have been converted to materials sufficiently non-volatile to not come through the VPC column at the temp employed (210°). The crude cyclization product was mixed with 0·2 g 10% Pd–C catalyst and heated for 5 hr at 280–300° in a slow stream of N. The reaction mixture was then cooled, transferred with the aid of dry ether to two 12 ml centrifuge tubes, centrifuged for 10 min, and the ethereal supernatant decanted and filtered through a glass fiber filter disc. The catalyst was washed 3 times with 20 ml portions ether, each time repeating the centrifugation and filtration steps. The combined ethereal soln was evaporated to give 0·1919 g crude dehydrogenation product. Analysis by VPC† showed it to contain 0·1531 g (75%) of **23**‡ and 0·0113 g (6%) cadalene.

Bicyclofarnesol (**42**). A 12 g sample of farnesol was treated with 22 g activated MnO_2[38] in 200 ml anhyd ether, and the mixture was stirred at room temp for 9 days. During this time an additional 40 g MnO_2 was added in 5 portions. The product from this reaction consisted of 11·9 g colorless liquid, $\bar{\nu}^{liq}$ 1690 cm^{-1} (α,β-unsaturated aldehyde). This material was oxidized with Ag ion to 6·5 g farnesic acid, and a 1·0 g sample of farnesic acid was cyclized to bicyclofarnesic acid with a mixture of 0·35 g conc H_2SO_4 in 1·8 g 88% formic acid.[39] Esterification of the bicyclofarnesic acid with diazomethane followed by LAH reduction yielded 0·7 g of **42** as a colorless oil; NMR (CCl_4) in ppm, complex pattern in 0·8–4·0 region ($C\underline{H}_3$, $C\underline{H}_2$, $C\underline{H}$, $C\underline{H}_2O\underline{H}$), 1-proton triplet at 5·32 ($\underline{H}C\!=$ of cyclohexene ring[21]).

Cyclization reactions. Anhyd formic acid was prepared by treatment with and distillation from boric acid according to directions in the literature.[40] This material was used neat for runs specified as taking place in 100% formic acid or was diluted with water for runs specified as taking place in 98% and 90% formic acid. Following the general procedure outlined above, cyclizations using commercial farnesol (70% *trans-trans*, 27% *cis-trans*), *trans-trans* farnesol (prepared by distillation of commercial farnesol through a 36" spinning band column and shown by VPC analysis to contain 97% of the *trans-trans* isomer and 3% of the *cis-trans* isomer), *trans* nerolidol (prepared by distillation of commerical nerolidol

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* The yields are calculated on the basis of the weight of starting farnesol. The peak areas in the VPC plot are corrected for the detector response factor for the various materials being assayed. Relative to the internal standard (1,2-dimethylnaphthalene), the response factors are as follows: 2-(*p*-tolyl)6-methylheptane (0·907), cadalene (1·05) hydrocarbon olefins (1·07), nerolidol (1·07), bisabolol (1·35), farnesol (1·45), diols (2·0).

† See footnote on p. 873.

‡ In some cases compound **23** was accompanied by small amounts of other materials which have been shown (see below) to consist of unsaturated derivatives of **23**.

through a 36-in spinning band column and shown by VPC to contain 98% of the *trans* isomer and 2% of other materials), and bisabolol were carried out and the products assayed.* The results of these experiments are shown in Table 1.

Isolation of 2-(4-methyl-3-cyclohexenyl)6-methylheptane-2,6-diol (**43**) *from nerolidol cyclization.* A 10 g sample of nerolidol was stirred with 100 ml 88% formic acid for 1 hr at room temp. The mixture was poured into 30% NaOH and ice, allowed to stand overnight, and extracted into ether. The ether was dried and evaporated to leave 12 g crude product as a viscous oil. Chromatography of this material on a 3·5 × 25 cm column of alumina (Fisher, neutral grade) yielded the hydrocarbons and mono alcohols in the benzene eluate and a very viscous oil in the AcOEt eluate. Upon standing, the viscous oil solidified, and recrystallization from anhyd ether gave colorless, hygroscopic, easily sublimed needles tentatively characterized as **43**: m.p. 94–96°; $\bar{\nu}^{\text{liq}}$ 3450 cm^{-1} (OH); NMR ($CDCl_3$) in ppm 3-proton doublet at 1·1 ($J = 2$ c/s) (MeC–OH),[22] 6-proton singlet at 1·22 (Me_2C–OH), 3-proton singlet at 1·65 (MeC=), 1-proton broad singlet at 5·40 (H–C=). (Found: C, 74·27; H, 11·59. Calc. for $C_{15}H_{18}O_2$: C, 74·95; H, 11·74%.)

The relation of **43** to bisabolol was demonstrated by converting both materials to the same trichloro compound (**38**). A soln of 0·25 g of the crude diol in 20 ml ether was treated with HCl gas and 5 g anhyd $CaCl_2$, allowed to stand for 3 days at room temp, and then worked up to give 0·30 g crude material, m.p. 74–76°. Recrystallization from MeOH–EtOH afforded **38** as colorless needles, m.p. 75–76° (reported[13] 79–80°). Similar treatment of bisbolol yielded colorless needles, m.p. 75–76°, which showed no depression in m.p. upon admixture with the trichloride prepared from **38**

Identification of product accompanying 2-(p-tolyl)6-methylheptane in the dehydrogenation mixture. A 0·0946 g sample of crude dehydrogenation product which contained ca. 22% of **23** and ca. 20% of materials (2 peaks) with retention times between that of 2-(*p*-tolyl)6-methylheptane and 1,2-dimethylnaphthalene was treated with 0·1 g 10% Pd–C, hydrogenated at room temp, and worked up to give 0·0843 g of product. This was shown by VPC analysis to contain 40% 2-(*p*-tolyl)6-methylheptane and only ca. 4% of the other materials present in the original substance. The materials accompanying **23**, therefore, must be 2-(*p*-tolyl)6-methylheptenes.

Dehydrogenation of hydrocarbon olefin fraction. A 0·0361 g sample of the lower-boiling fraction (polyenes) from a 98% formic acid catalyzed cyclization of farnesol (0°, 20 min) was mixed with 0·0418 g 1,2-dimethylnaphthalene and dehydrogenated under the usual conditions. Analysis of the product by VPC indicated the presence of 67% of monocyclic materials (e.g. 2-(*p*-tolyl)6-methylheptanes and -heptenes) and 5% of cadalene, the remainder being lower-boiling fragmentation products probably arising from farnesenes.

REFERENCES

[1] This work was supported, in part, by grant No. 5 RO1 AMO2398 from the National Institutes of Health to whom the authors express their gratitude.

[2] Shell Oil Co. Fellowship 1960–61, University Fellowship 1961–63, Wheeler Fellowship 1963–64.

[3] [a] F. Tiemann and F. W. Semmler, *Chem. Ber.* **26**, 2708 (1893); O. Wallach and M. Franke, *Liebigs Ann.* **324**, 97 (1902).

[b] L. Ruzicka, *Helv. Chim. Acta* **6**, 483 (1923); I. M. Heilbron, E. D. Kamm and W. M. Owens, *J. Chem. Soc.* **129**, 1630 (1926).

[c] D. C. Hibbit and R. P. Linstead, *Ibid.* 470 (1936); V. C. E. Burnop and R. P. Linstead, *Ibid.* 720 (1940).

[d] H. Schinz *et al.*, *Helv. Chim. Acta* **39**, 1269 (1956).

[e] W. S. Johnson, A. van der Gen and J. J. Swoboda, *J. Am. Chem. Soc.* **89**, 170 (1967); E. E. van Tamelen and R. G. Nadeau, *Ibid.* **89**, 176 (1967).

[4] Good reviews are to be found in [a] L. Ruzicka, *Perspectives in Organic Chemistry* (Edited by A. R. Todd) p. 265. Wiley, Interscience Division, New York (1956). [b] *Biogenesis of Natural Products* (Edited by P. Bernfeld) pp. 155–159, 641–691. MacMillan, New York (1963); [c] A. Eschenmoser, D. Felix, M. Gut, J. Meier and P. Stadler, *The Biosynthesis of Terpenes and Sterols* p. 217' Ciba Foundation Symposium, Churchill, London (1959); [d] J. H. Richards and J. B. Hendrickson, *The Biosynthesis of Steroids, Terpenes, and Acetogenins.* Benjamin, New York (1964).

[5] L. Ruzicka, A. Eschenmoser and H. Heusser, *Experentia* **9**, 357 (1953); L. Ruzicka, *Proc. Chem. Soc.* 341 (1959).

[6] L. D. Wright, E. L. Cresson, H. R. Skeggs, G. D. E. MacRae, C. H. Hoffman, D. E. Wolf and K. Folkers, *J. Am. Chem. Soc.* **78**, 5273 (1956); D. E. Wolf, C. H. Hoffman, P. E. Aldrich, H. R. Skeggs, L. D. Wright

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* Each value shown in Table 1 is the average of at least two VPC determinations.

and K. Folkers, *Ibid.* **78**, 4499 (1956); **79**, 1486 (1957); A. F. Wagner and K. Folkers, *Advances in Enzymology* Vol. 23; p. 471. Wiley, Interscience Division, New York (1961).

[7] F. Lynen, H. Eggerer, U. Henning and I. Kessel, *Angew. Chem.* **70**, 738 (1958); F. Lynen, B. W. Agranoff, H. Eggerer, U. Henning and E. M. Möslein, *Ibid.* **71**, 657 (1959).

[8] F. W. Semmler and K. E. Spornitz, *Chem. Ber.* **46**, 4025 (1913).

[9] L. Ruzicka, *Helv. Chim. Acta* **6**, 492 (1923); E. H. Farmer and D. A. Sutton, *J. Chem. Soc.* 116 (1942).

[10] L. Ruzicka and E. Capato, *Helv. Chim. Acta* **8**, 259 (1925).

[11] Y-R. Naves, *Helv. Chim. Acta* **49**, 1029 (1966).

[12] A. Eschenmoser, L. Ruzicka, O. Jeger and D. Arigoni, *Helv. Chim. Acta* **38**, 1890 (1955); D. H. R. Barton and P. de Mayo, *Quart. Rev.* **11**, 189 (1957); J. B. Hendrickson, *Tetrahedron* **7**, 82 (1959).

[13] L. Ruzicka and M. Liguori, *Helv. Chim. Acta* **15**, 3 (1932).

[14] A. Manjarrez and A. Guzmán, *J. Org. Chem.* **31**, 348 (1966).

[15] K. Alder and W. Vogt, *Liebigs Ann.* **564**, 109 (1949).

[16] A. A. Petrov, *J. Gen. Chem., U.S.S.R.* **11**, 309 (1941); *Chem. Abstr.* **35**, 5873 (1941).

[17] E. F. Lutz and G. M. Bailey, *J. Am. Chem. Soc.* **86**, 3899 (1964).

[18] F. W. Kay and W. H. Perkin, Jr., *J. Chem. Soc.* **89**, 1640 (1906).

[19] O. P. Vig, K. L. Matta, G. Singh and I. Raj, *J. Ind. Chem. Soc.* **42**, 581 (1965).

[20] M. Julia, S. Julia and R. Guégan, *Bull. Soc. Chim. Fr.* 1072 (1960).

[21] N. S. Bhacca, L. F. Johnson and J. N. Shoolery, *NMR Spectra Catalog.* Varian Associates (1962);
[a] B. M. Mitzner and E. T. Theimer, *J. Org. Chem.* **27**, 3359 (1962);
[b] J. R. Dyer, *Applications of Absorption Spectra of Organic Compounds* p. 87. Prentice-Hall, Englewood Cliffs, N.J. (1965);
[c] R. B. Bates, D. M. Gale and B. J. Gruner, *J. Org. Chem.* **28**, 1086 (1963).

[22] [a] For experiments involving farnesic acid see: A. Caliezi and H. Schinz, *Helv. Chim. Acta* **32**, 2556 (1949); **33**, 1129 (1950); **35**, 1637 (1952); C. Collin-Asselineau, E. Lederer and J. Polonsky, *Bull. Soc. Chim. Fr.* 715 (1950); G. Stork and A. W. Burghstahler, *J. Am. Chem. Soc.* **77**, 5068 (1955); P. A. Stadler, A. Nechvatel, A. J. Frey and A. Eschenmoser, *Helv. Chim. Acta* **40**, 1373 (1957); P. A. Stadler, A. Eschenmoser, H. Schinz and G. Stork, *Ibid.* **40**, 2191 (1957);
[b] For experiments involving homofarnesic acid and related compounds see G. Lucius, *Chem. Ber.* **93**, 2663 (1961); *Angew. Chem.* **68**, 247 (1956); *Arch. Pharm.* **291**, 57 (1958); E. J. Corey and R. R. Sauers, *J. Am. Chem. Soc.* **79**, 3925 (1957); **81**, 1739 (1959);
[c] For experiments involving farnesylacetic acid and related compounds see C. Collin-Asselineau and E. Lederer, *Bull. Soc. Chim. Fr.* 320 (1959);
[d] For experiments involving farnesylacetone see V. A. Smit, A. V. Semenovsky and V. F. Kucherov, *Tetrahedron Letters* 2299 (1964); V. A. Smit, A. V. Semenovsky, I. I. Brunovlenskaya, S. L. Portnova and V. F. Kucherov, *Proc. Acad. Sci. U.S.S.R.* **160**, 142 (1965);
[e] For experiments involving farnesyl acetate and methyl farnesate see E. E. van Tamelen, A. Storni, E. J. Hessler and M. Schwartz, *J. Am. Chem. Soc.* **85**, 3295 (1963); E. E. van Tamelen and R. M. Coates, *Chem. Comm.* **409**, 413 (1966).

[23] C. J. W. Brooks and K. H. Overton, *Proc. Chem. Soc., London*, 322 (1957).

[24] W. S. Johnson, W. H. Lunn and K. Fitzi, *J. Am. Chem. Soc.* **86**, 1972 (1964).

[25] Y.-R. Naves, *Perf. and Essent. Record* **40**, 161 (1949).

[26] C. A. Vernon, *J. Chem. Soc.* 423 (1954).

[27] H. A. Bruson and T. W. Reiner, *J. Am. Chem. Soc.* **65**, 23 (1943).

[28] M. Rubin and H. Wishinsky, *J. Org. Chem.* **16**, 443 (1951).

[29] R. P. Linstead and E. M. Meade, *J. Chem. Soc.* 935 (1934).

[30] W. H. Perkin, Jr., *J. Chem. Soc.* **85**, 416 (1904).

[31] G. Gamboni, H. Schinz and A. Eschenmoser, *Helv. Chim. Acta* **37**, 964 (1954).

[32] L. Williman and H. Schinz, *Helv. Chim. Acta* **35**, 2401 (1952).

[33] A. J. Birch and S. M. Mukherji, *J. Chem. Soc.* 2531 (1949).

[34] L. Ruzicka and A. G. Van Veen, *Liebigs Ann.* **468**, 143 (1929).

[35] V. K. Honwald and A. S. Rao, *Tetrahedron* **21**, 2593 (1965).

[36] Prepared by the method of W. S. Johnson and A. R. Jones, *J. Am. Chem. Soc.* **69**, 792 (1947).

[37] B. A. Nagasampagi, S. Dev, C. Rai and K. L. Murthy, *Tetrahedron* **22**, 1949 (1966).

[38] R. J. Gritter and T. J. Wallace, *J. Org. Chem.* **24**, 1051 (1959).

[39] A. Caliezi and H. Schinz, *Helv. Chim. Acta* **32**, 2556 (1949).

[40] H. I. Schlesinger and A. W. Martin, *J. Am. Chem. Soc.* **36**, 1589 (1914).