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# Cyclization Studies with (±)-10,11-Oxidofarnesyl Acetate, Methyl Farnesate, and Methyl (±)-10,11-Oxidofarnesate

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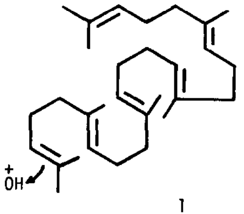
As models for lanosterol biosynthesis and for more elaborate biogenetic-type total synthesis in the di- and triterpenoid series, the nonenzymic cyclization of methyl farnesate, methyl (±)-10,11-oxidofarnesate and (±)-10,11-oxidofarnesyl acetate was studied. In addition to the 10,11-halohydrin, *N*-bromosuccinimide/water was observed to convert methyl farnesate to bromobicycles **40** and **41**. Acid-catalyzed cyclization of (±)-10,11-oxido farnesate and the corresponding 2,3-cis isomer produced *inter alia* 3-hydroxy octalins **20a** and **21a**. Similarly, methyl (±)-10,11-oxidofarnesate was transformed to *inter alia* the hydroxylated bicyclic esters **34** and **35**. Mechanistic and other aspects of these reactions are taken up.

In 1961, when these studies were initiated, two groups had published six years earlier (*1*, *2*) detailed interpretations of the enzymatic conversion of squalene to lanosterol and other polycyclic triterpenes, including stereoelectronic rationale for the overall oxidation, cyclization, and rearrangement reactions which must be involved. Although the two proposals differ in important detail, both feature attack by "hydroxonium ion" ($OH^+$) (or a biological equivalent), synchronized with polycyclization (**1**), which in the lanosterol case affords the protosterol sys-



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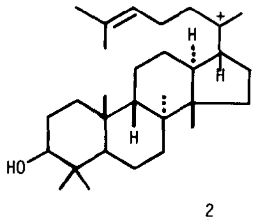

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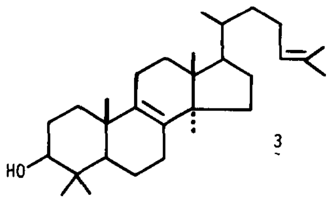

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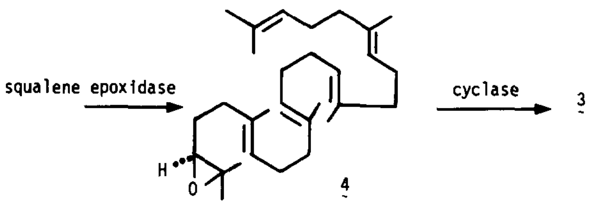
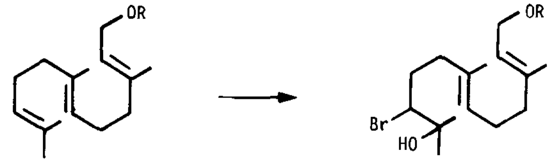
tem **2**, isomerizable by means of a series of 1,2 hydrogen/methyl shifts and final proton loss to the parent (**3**) of all other sterols. During the 1960s, several provocative biochemical alternatives to these pioneering and incisive ideas were suggested, including the radical equivalent of the carbonium ion pathway (*3*); initial formation of a monocarbocyclic peroxide by a (2 + 4) cycloaddition of dioxygen to the 2,6-diene moiety (*4*); and a two-step process involving nonoxidative cyclization to lanostadiene, followed by interpolation of oxygen at C-3 (*5*). As an originally unforeseen outgrowth of studies in our laboratories, it was later established (*6, 7*), however, that lanosterol is in fact produced in nature by a route different from all the above, namely prior formation of 2,3-oxido squalene (**4**) and conversion of this epoxide to lanosterol. Thus the studies reported preliminarily as communications (*8, 9*) and now detailed in this paper possess more biological significance than was anticipated at the time they were conceived and carried out.



Bearing the above developments in mind, one can consider four major aspects of investigating, from the organic chemical point of view, the oxidation–cyclization of squalene to lanosterol: (1) the oxidation of squalene, or model thereof, at a terminal olefinic position; (2) conversion to the tetracyclic level, with provision for apperance of hydroxyl at C-3; (3) stereochemical facets of the cyclization process; and (4) the generation of lanosterol from a polycyclic precursor by means of hydrogen and methyl migrations. With regard to (1), we utilized the previously described (**8**) selective oxidation of polyenes in order to prepare the terpenoid terminal epoxides needed for the polycyclization studies. In the present paper, such polycyclizations are restricted to formation of mono- and bicarbocyclic products and serve as model reactions for biogenetic-type natural product syntheses, which are described in later papers in this series. In these model annelation reactions, several new asymmetric centers can be generated in a single laboratory step, and therefore stereochemical aspects will be described and discussed. Hydrogen and methyl migrations are rare in the simple, sesqui- and diterpenoid models employed, but gain more significance in synthetic endeavors at the triterpene level, taken up elsewhere (*10*).

In the earliest proposals for the biosynthetic conversion of squalene to lanosterol, a notable, obligatory feature is attack by an oxidizing species selectively on a terminal double bond, which must be viewed as a special event in either the biochemical or nonenzymatic sense. As part of our overall aim of chemically simulating to as great a degree as possible the biogenesis of naturally occurring 3-hydroxy polycyclic terpenoids, nonenzymic realization of such a selective oxidation of squalene emerged as the first challenge in our bioorganic program. This problem was solved with dispatch, and the solution is recorded and discussed elsewhere (*8*). For present purposes, it may be noted at the outset that, perhaps surprisingly, the reaction utilized to effect a highly selective terminal oxidation of squalene, namely formation of 2,3-bromohydrin by the action of *N*-bromosuccinimide (NBS) in the presence of water and a suitable organic solvent, also serves generally to convert many lower acyclic terpenes and their derivatives to terminal bromohydrins. Thus, farnesol and geranylgeraniol derivatives can be conveniently converted to the corresponding 10,11- and 14,15-bromohydrins (**5**, **6**), which on treatment with base provide the 10,11- and 14,15-oxides, respectively.



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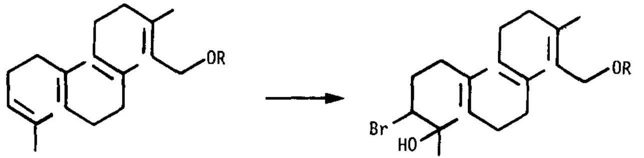

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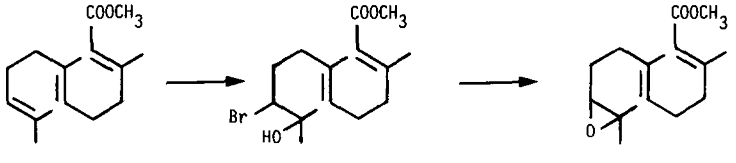
At this point, special mention should be made of one particular case, the conversion of methyl *trans,trans*-farnesate (**7**) via **8** to the 10,11-oxide (**9**), first reported in 1963 in connection with our survey of sesquiterpenoid terminal epoxide cyclization (*9*). Several years later, the first isolated "juvenile hormone" (JH)



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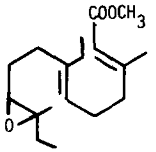
was reported (*11*, *12*) to be the higher homolog **10**, after which the second JH example proved to possess structure **11**, (*13*). More recently, the original, synthetic methyl 10,11-oxidofarnesate was itself also shown to be a naturally occurring JH.



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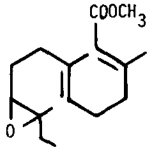

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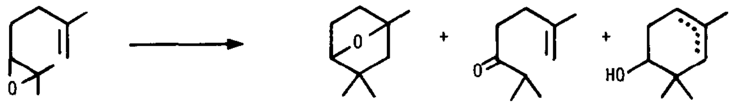
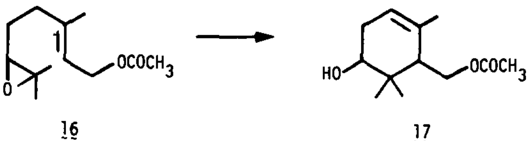
In preparation for cyclization studies, the selective NBS/$H_2O$ oxidation was attempted first with pure *trans,trans*-farnesyl acetate, and later with methyl *trans,trans*-farnesate. In all cases, highly selective (95%) (*14*) attack at the terminal, dimethyl olefinic site was observed. The reactions were usually run in aqueous tetrahydrofuran at 0° and proceeded in yields which fell, after chromatography, within the range 50–75% of material in a state of purity acceptable for conversion to the corresponding oxide in essentially quantitative yield.

With the terminal epoxides of naturally occurring terpenoids readily available, attention was directed to cyclization behavior. Monoterpenoids were suitable for use in the simplest version, viz., monocarbocyclization; and this level was sounded in 1962, primarily by Goldsmith but also by ourselves, in experiments preliminary to polycarbocyclization assays. Goldsmith treated the 5,6-oxidogeraniolene case (**12**), which on boron trifluoride ($BF_3$)-etherate catalyzed cyclization in benzene gave products **13–15** (*15*). In our laboratory, 6,7-oxidogeranyl acetate



12 13 14 15

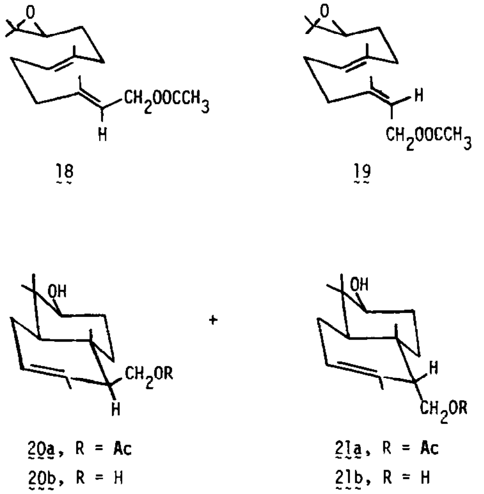
(**16**) was exposed to the action of cold 85% phosphoric acid, which induced formation of *inter alia* a product which nmr analysis revealed to be the cyclohexene **17**. Encouraged by such results, we began to probe lower depths, viz., the bicarbocyclization level. The initial, successful survey was carried out in the farnesol series, which involved, however, only low yields of bicarbocyclic and other materials. Conversions were found to be considerably higher in the farnesic acid series, and more systematic and successful development with produce analysis was carried out therein (*vide infra*).



16 17

In the case of *trans,trans*-farnesyl acetate terminal epoxide, although one can imagine various conformations which would permit epoxide ring-opening-carbocyclization reactions, the three-dimensional arrangement depicted in **18** seemed particularly attractive. In this conformation, the epoxide unit is so oriented that $S_n2$-like attack by the neighboring $\pi$ electrons, coupled with epoxide ring-opening, is favorable and would generate a cyclohexanol ring with the C-3 equatorial hydroxyl trans to the C-5 hydrogen. Assuming interaction of the developing cyclohexyl cation with the second olefinic center—all occurring with preservation of the trans relationship of methyl and hydrogen on the first olefinic bond—there should evolve a trans-fused bicyclic cation which would solvate or deprotonate to final product.

In the most stereoselective result, boron trifluoride (BF$_3$) etherate in benzene catalyzed in ~10% yield cyclization of the pure trans,trans isomer to a mixture of bicyclic diol monoacetates, 15% **21a** and 85% **20a**, the latter featuring, at the four asymmetric centers, stereochemistry characteristic of the usual 3-hydroxylated *A*/*B* ring system of polycyclic terpenoids (Chart 1). The constitution and stereochemistry of product **21a** was proved by (1) chromic anhydride oxidation to the acetoxy ketone **22** and lithium aluminum hydride reduction to the same diol (**21b**) (mp 150–151°) produced by hydrolysis of **21a**, thus indicating the equatorial nature of the hydroxyl group, and (2) conversion, by means of Raney nickel desulfurization of **22** ethylene dithio ketal, to *dl*-epidrimenol (mp 65.5–66.5°), an authentic sample of which was prepared by lithium aluminum hydride reduction of the methyl ester of the known corresponding acid (mp 138°) (*16*). In parallel experiments, the diol monoacetate **20a** was (1) oxidized to ketone **23** and reduced to authentic **20b** (mp 113–114°) and (2) converted to monohydric alcohol identical with *dl*-drimenol (mp 61–62°). When a mixture (65% trans; 35% cis) of farnesyl acetate was subjected to the oxidation–cyclization sequence just described, a mixture of 55% **20a** and 45% **21a** (by vapor-phase chromatography VPC)) was



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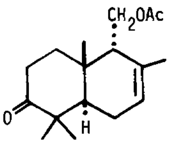
20a, R = Ac
20b, R = H

21a, R = Ac
21b, R = H

CHART 1. (a) BF$_3$ · Et$_2$O-benzene on *trans,trans*-acetate: 85% **20**, 15% **21**. (b) BF$_3$ · Et$_2$O-benzene on 65% *trans,trans*-35% *trans,cis*-acetate: 55% **20**, 45% **21**.



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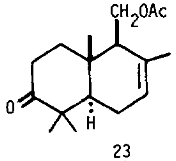

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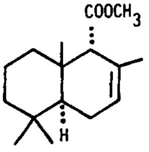
generated, thus indicating that, under the specified conditions and to the extent that **20a** and **21a** are formed, geometry determines stereochemistry of product, at least at the sites under consideration.

If cyclization is conducted with cold 85% $H_3PO_4$ instead of $BF_3$ etherate in benzene, there is generated, again in ~10% yield, a mixture of **20a** and **21a**, but in the ratio of 15 : 85. The same distribution is observed when the $H_3PO_4$ cyclization is carried out on the same 65 : 35 mixture of farnesyl acetate geometrical isomers employed in the aforementioned $BF_3$ experiment.

Isomer **21**, bearing a pseudo-axial acetoxymethylene substituent, is of special interest because it features in the unsaturated ring the uncommon cis 9,10-methyl–hydrogen relationship, invoked to rationalize the methyl–hydrogen migration–elimination sequence leading in nature to lanosterol (*2*, *17*). Despite the pseudo-axial substituent, but by reason of decreased steric interaction with both neighboring angular and olefinic methyls, this isomer is judged to be the more stable in the **20–21** pair. Although this point cannot be readily verified by equilibration experiments in the bicyclic diol series, base-promoted epimerization experiments with the closely related methyl bicyclofarnesates established the equilibrium ratio 70 : 16 : 14 for the detectable components **24**, **25**, and **26**. On the basis



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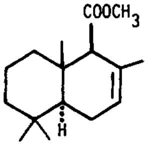

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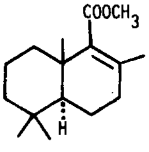

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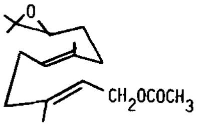
of work described elsewhere (*18*), a similar situation obtains for the corresponding 3-oxygenated methyl bicyclofarnesates, which are even more closely related to the hydroxydrimenols.

By reason of the foregoing observations and arguments, it is clear that, even though the yields of bicyclic materials are lower than those from the acyclic esters, the $BF_3$ catalyzed cyclization of 10,11-oxidofarnesyl acetate is not complicated by prior cis–trans isomerization of starting material, highly stereoselective with reference to emergence of the new hydroxyl group and the ring juncture, and less, but still reasonably stereoselective with respect to the relative configuration at the chiral center bearing the acetoxymethylene group. In addition, it has been demonstrated that bicyclic product of $BF_3$/epoxide cyclizations is not stereochemically modified under the conditions of the cyclization (*19*). For all of these reasons, we believe the $BF_3$ cyclizaiton involves, at one point in time or another, contributing conformational elements as shown in the representation **18** for the trans,trans case, and **19** for the trans,cis isomer.

Although the $H_3PO_4$ promoted reaction seems also to be highly stereoselective in the development of three asymmetric centers, the stereochemistry at C-9 is randomized, as shown by the experiments in the trans,trans and trans,cis starting materials, which both afford the same ratio of the two isomers **20** and **21a**, with the more thermodynamically stable one **(21a)** predominating. The reason for this behavior is not known, although it, like that observed in the oxidofarnesate series, may depend on the solvent-dependent conformation of the epoxide in the transition state during which the second ring is formed (*19*). Thus, whereas (transition state) "chair–chair" conformations **18–19** seem to be preferred in the benzene medium used for the $BF_3$ cyclization of the trans,trans and trans,cis cases respectively, **19** and "chair–boat" **27** may be controlling conformations in 85% $H_3PO_4$, the solvent and catalyst in the alternative cyclization mode. The significance of the foregoing and other results for the mechanism of acyclic terpenoid terminal epoxide cyclizations has previously been taken up elsewhere (*19*).



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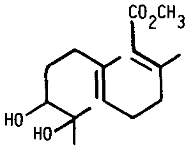
For preparative purposes, the cyclizaiton of 10,11-oxidofarnesates was more promising, and attention was therefore refocused on this version of the basic scheme. Toward that end, methyl *trans,trans*-farnesate (prepared by stepwise oxidation of farnesol to farnesic acid, followed by treatment with diazomethane) was subjected to the action of NBS under conditions already described herein. After purificaiton by column chromatography, the sole monobromohydrin isolated was obtained reproducibly in yields of 74 to 76%. The nmr spectral properties of this product were entirely consistent with the assigned structure **8**, and incompatible with isomeric bromohydrin possibilities. Similarly, chemical and spectral behavior clearly defined the structure of the derived epoxide as **9**. Nuclear magnetic resonance analysis confirmed that the epoxide unit is positioned at the terminal site: signals at $\tau$ 8.78 and 8.81 (3 hydrogens each) correspond to the *gem*-dimethyls attached to the carbon in the epoxide ring, which differ in that one is cis to a hydrogen atom and the other is cis to the alkyl chain. Chemical degradation of the epoxide **9** offered further proof for the position of the epoxide group. Treatment of **9** with dilute aqueous perchloric acid resulted in a nearly quantitative yield of glycol **28**. Periodate cleavage of the glycol led to the following results: (1) 115% of periodate was consumed, (2) a 70% yield of crude acetone-2,4-dinitrophenylhydrazone was isolated, and (3) after chromatography and vacuum distillation, a yield of 85.6% of aldehyde **29** was obtained.



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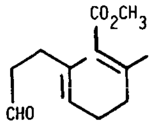

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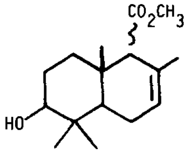

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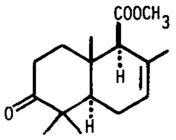
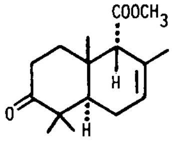
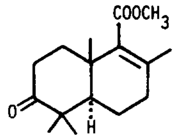
and catalyst. The bicyclic hydroxyester mixture (**30**) was isolated by column chromatography, oxidized to the ketoester, and subjected to saponification conditions. The ketoester (~10% yield), which is nonsaponifiable, showed two vpc peaks in the ratio of 62:38. Reduction of the ketoester mixture with lithium aluminum hydride afforded *inter alia*, a crystalline compound which was identical to *dl*-3-hydroxy-epidrimenol (**21b**), obtained previously through cyclization in the epoxyfarnesol series. This result demonstrates that cyclization of the farnesic ester affords, at least in part, the desired trans-fused decalin nucleus and also indicates that the major component of the ketoester mixture possesses structure **32**, the other constituent possibly being **31** and/or **33**. A second mixture of keto bicyclic esters (from oxidation of the bicyclic ester fraction resulting from $BF_3$ cyclization, as described below) was separated by preparative vpc into three pure components, stereoisomers **31** and **32**, accompanied by a much smaller amount of **33** (*18*). Lithium aluminum hydride reduction of one of the $\beta,\gamma$-unsaturated stereomers (**31**) afforded the previously described (*vide supra*) *dl*-3-hydroxydrimenol (**20b**), a result which, taken together with the formation of *dl*-3-hydroxyepidrimenol by similar reduction of the second $\beta,\gamma$-unsaturated component in the ketoester mixture, defines the structure of the two ketoester stereoisomers, as shown.



**31**

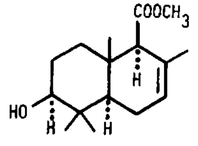


**32**

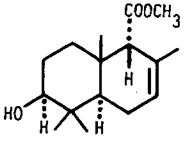


**33**

In that lithium aluminum hydride converts either a ketoester or its parent hydroxyester to the same hydroxydrimenol isomer, the relative configuration at C-3 in the original hydroxyester must correspond to that in the drimenol. On the basis of such considerations, the stereoformulas **34** and **35** emerge. These assignments parallel those in the oxidofarnesyl acetate series and are corroborated by their successful use as starting materials for the synthesis of more complex natural products of known structure (*18*).



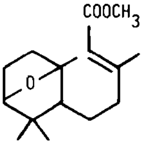
**34**



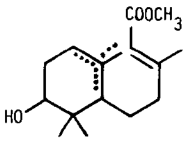
**35**

Inadvertantly, it was discovered that under phosphoric acid cyclization conditions identical to those ordinarily used, except that especially slow stirring was involved, the yield of hydroxybicyclic ester increased markedly; and in subsequent runs, yields of 20 to 28% could be realized when stirring was maintained at a sluggish rate. More remarkably, in this subtle modification the proportion of isomers **34** : **35** formed shifted from 62 : 38 to 13 : 87! The explanation for this change seems to depend on the physical nature of $N_3PO_4$ and the epoxy ester liquids, which are not entirely miscible but, when being stirred together, exist as a cloudy mixture. During more vigorous stirring, the epoxide and its products experience more contact with the acid; while with slower stirring, the epoxy ester constitutes a clear-cut single phase, exposed for the most part only to that acid which is dissolved therein. The lower yield version could be associated with increased, unfavorable contact of product with $H_3PO_4$, and in fact only 50% of hydroxybicyclic ester survived when exposed separately to the action of the rapidly stirred reagent. The shift in isomer ratios possibly results from an effect of medium change, caused by the factors cited, on the stereochemical courses of the cyclization, or from an acid-promoted isomerization of equatorial to axial ester.

In addition to bicarbocyclic esters **34** and **35**, other products were isolated from the phosphoric acid-catalyzed reactions of 2,3-oxidofarnesic ester. Detectable by thin-layer chromatography (TLC) analysis and isolable by preparative TLC, two uv active substances were purified and subjected to elemental and spectral analysis. Isolated in pure form in 6 to 10% yield, one noncrystalline product, isomeric with starting material, exhibited uv, ir, and nmr spectral properties entirely in accord with the assigned structure **36.** A second isomer, obtained only as an impure product in 11% yield, was provisionally allocated structure **37**, an assignment confirmed by positive comparisons with purer material isolated from cyclizations promoted by boron trifluoride etherate, to which we not turn.



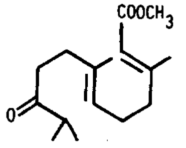
**36**



**37**

Like $H_3PO_4$, $BF_3$ etherate causes conversion of oxidofarnesate to bicarbocyclic products, but with a greater degree of stereocontrol and stereoselectivity. In reactions with 99% *trans,trans*-oxidofarnesate, carried out with 1 molar equivalent of $BF_3$ etherate in benzene at room temperature, there was regularly formed a 22–25% yield of a bicyclic ester complex which was shown by VPC analysis of the corresponding ketoesters to consist of 91% **34**, 2% **35**, a trace of the $\alpha,\beta$-unsaturated isomer, and 6.5% of a new hydroxyester, not studied but suspected of being the bicyclic $\beta,\gamma$-unsaturated ester with an exocyclic double bond.

By-products formed in the $BF_3$-induced reaction and isolated by chromatographic means include the bridged oxide (**36**) (32%), the monocarbocyclic hydroxyester (**37**) (7%), and in addition, a simple rearrangement product, the acyclic ketoester **38** (9%), apparently not generated when phosphoric acid acts on starting epoxyester. Assignment of structure in the last case rests on sodium borohydride



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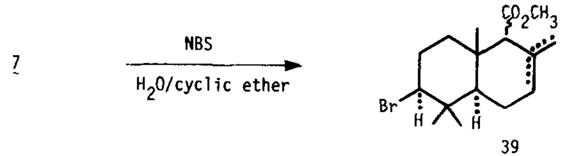
reduction to the corresponding hydroxyester as well as ir (carbonyl) and nmr (2 olefinic protons, 2 allylic methyls, and an isopropyl) spectral properties. When the $BF_3$ reaction was carried out on a 90.5 : 9.5 mixture of *trans,trans* and $\Delta^2$-*cis*, $\Delta^6$-*trans*-oxidofarnesate, there was formed a 90.5 : 9.5 mixture of acyclic ketoesters, regarded as the corresponding trans,trans and cis,trans materials. This result signifies retention of geometry in this case and strongly suggests that double bonds remaining in other $BF_3$ reaction products geometrically correspond to those in the starting material, i.e., all are trans. Since the bridged oxide and monocarbocyclic ester formed in the $BF_3$ reaction are indistinguishable from the corresponding products from the $H_3PO_4$ reaction, the double bonds in these latter products (**36** and **37**) can be assigned, with the same degree of assurance, the trans stereochemistry.

One fraction isolated from the $BF_3$ reaction consisted of a mixture of bicyclic ester and a second component suspected of being the monocyclic hydroxyester **37**. In that the bicyclic ester cannot be saponified readily, the mixture could be separated by base-promoted selective hydrolysis of the monocyclic material to the corresponding acid, which was reconverted to the methyl ester with diazomethane. Infrared, uv, and nmr spectral analysis of the reconstituted ester revealed it to be a mixture of monocarbocyclic olefin isomers corresponding to structure **37**.

The above compounds generated in the $BF_3$ reaction account for 73% of total product. In addition to a certain amount of material which could not be recovered, two additional fractions were obtained in the chromatographic procedures. Seemingly, $\alpha,\beta$-unsaturated esters, these materials gave rise to confusing nmr spectra and were not examined further. Despite these minor shortcomings, the $BF_3$-promoted cyclization of methyl 10,11-oxidofarnesate remains, in terms of product identificaiton and material balance, one of our better studied polyolefin oxide cyclizations.

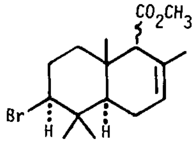
In terminating this summary of experiments with the main model cyclizations in the sesquiterpene series, we append a brief account of an unusual cyclization mode (*20*) encountered while carrying through a relatively large scale reaction of NBS/water with methyl farnesate, described earlier in this paper. Concurrent with acyclic bromohydrin formation, there are produced the bicyclic bromoesters **39**, arising by *direct* terminal oxidation and cyclization of the acyclic terpene, a process akin to that previously, but erroneously presumed to operate in the biogenesis of 3-hydroxylated polycyclic terpenes and steroids.

By chromatographic means, a fraction (12–15% of total), consisting mainly of bromocyclized material, was isolated as a product of the NBS reaction on farnesic ester (**7**). Separation into bromomonocyclic and bromobicyclic ester was achieved by selective saponification, the more hindered ester group of the bicyclic compo-



39

nents (4–5% of the cyclized material) remaining intact. When subjected to preparative TLC, this nonsaponified fraction was further separated into two major components in equal amount. Chemical and spectral observations permit the assignments of structures **40** and **41** to these compounds (*20*).



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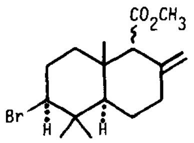
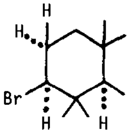


41

The general nature of these bromoesters was revealed by lithium aluminum hydride reduction, which, in the case of **40**, gave rise to roughly equivalent amounts of the known epimeric (±)-drimenols. Although ester **40** remained liquid, the exocyclic isomer **41** was crystalline (mp 82.5–82.6°). The nmr spectra of **40** and **41** were completely consistent with the assigned structures.



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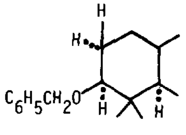

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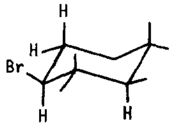

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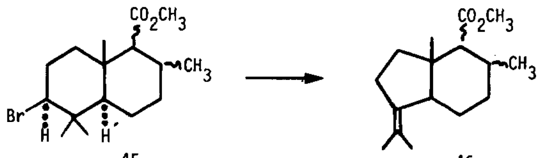
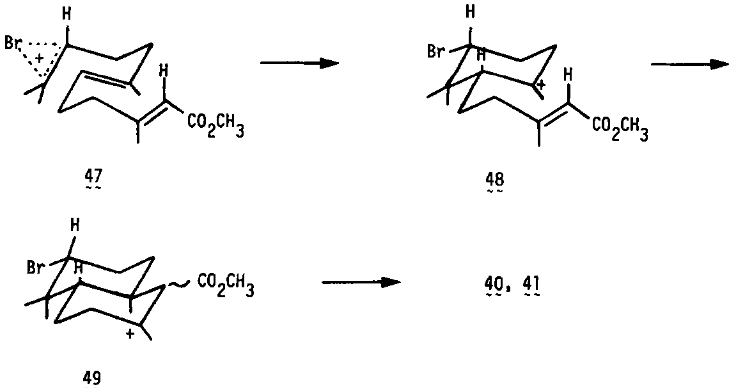
The position and stereochemistry of halogen were confirmed by means of the following observations. A 100-Mc/sec nmr spectrum displayed a clear-cut quartet for the CHBr unit (**42**), with $J = 6.0$ and 10.5 Hz. This splitting pattern, similar to that (4.5 and 11.0 Hz) of the corresponding proton in (±)-β-onocerin dibenzyl ether (**43**), signifies *axial* hydrogen interacting with two protons, one axial and one equatorial, on adjacent carbon (**44**). On the chemical side, catalytic reduction (Pt/acetic acid) of **40** provided the dihydrobromoester **5**, which was subjected to the action of anhydrous silver fluoroborate in benzene. On the basis of nmr data, structure **46** can be assigned to the (noncrystalline) product, an outcome quite consistent with the anticipated behavior of halogen in the assigned position (cf. the corresponding ring contractions undergone by naturally occurring terpenes during dehydration of the *A* ring).



45 46

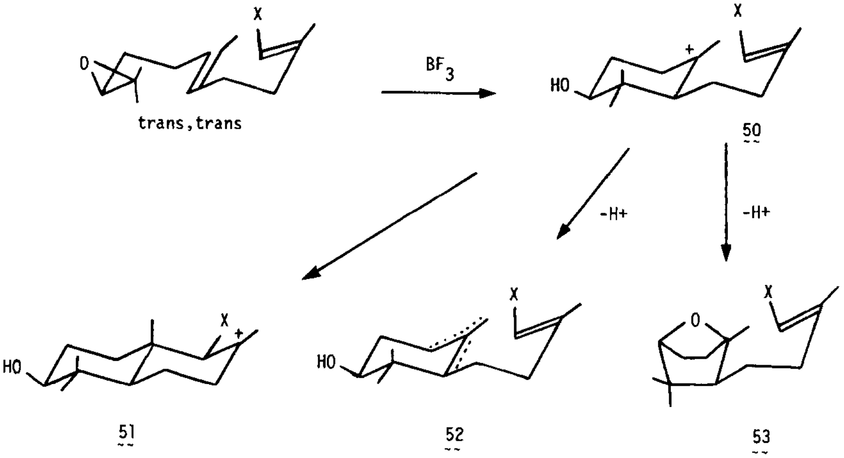
Although the intimate aspects of the bromination–cyclization mechanism remain obscure, the broad outlines are somewhat clearer. That the bromobicyclic esters do not arise in a secondary process from methyl farnesate terminal bromohydrin (**8**) is suggested by the observation that no cyclized product was detectably formed when **8** was subjected to the approximate conditions of the original NBS reaction, including the presence of a halogen acceptor (farnesol). Also, in view of the mild conditions of pH and temperature employed in the NBS reaction, further cyclization of bromomonocyclic diene is unlikely. Thus the most likely interpretation of the cyclization course involves (1) formation of an initially produced terminal bromonium ion **47**, followed by (2) conversion of this terminal bromonium ion into a monocyclic carbonium (**48**), part of which does not suffer proton loss but proceeds, classically or nonclassically, to bicyclic cation **49**. This interpretation is consistent with, and based in part on, mechanistic information and conclusions regarding the polycyclization of polyene oxides, a subject treated elsewhere and applied in the following paragraphs to the terpenoid terminal epoxide cyclizations already described in this contribution.



47 48

49 40, 41

Recent studies (*21*) have led to the generalized view that the mechanism of epoxide-triggered polycyclizations involves an initial, acid-promoted epoxide ring-opening with participation of the neighboring olefinic bond, affording a conformationally rigid cyclohexyl cation, followed by successive carbocation/π-bond interactions which lead to a series of conformationally rigid polycyclic cations, the last in the series usually suffering proton loss to generate final, stable product. In the application to the cases at hand, 10,11-oxidofarnesylacetate or -farnesate is thought to be first converted to monocyclic cation (**50**) (or solvated species), a genuine but highly reactive intermediate having initially a conformation in which the spatial relationships of substituents on the double bond in the starting material are generally preserved. During the formation of bicarbocycle (**51**) the second $\pi$-bond interacts, in a second step, with the available cationic center before any significant conformational change in the first-formed ring occurs, but only when, by reason of e.g. propitious solvent effects or statistical distribution of conformers, the side chain is suitably oriented for such interaction. When such is not the case, the monocyclic cation has other reaction outlets. On the basis of structures actually generated, these include simple proton loss to give monocyclic diene (**52**) and internal "trapping" of the cyclohexyl cation by the hydroxyl in the same ring, a reaction necessitating a conformational flip to the boat system required by the bridged ether product (**53**). These interpretations are applied to the $BF_3$-catalyzed reactions in Chart 2 and to certain of the $H_3PO_4$ reactions, in Chart 3. Thus, such



$X = CH_2OCOCH_3$ or $COOCH_3$

CHART 2.

product development is nicely interpretable in terms of the mechanistic picture previously advanced (*21*), and the construct in fact constitutes good support for the proposed cyclization mechanism. For additional information and discussion bearing on mechanistic and stereochemical aspects of the overall cyclization process, the reader is referred to earlier publications from this laboratory (*19, 22*).

In regard to a comparison of the $BF_3$- with the $H_3PO_4$-catalyzed reaction, the extent of cyclization varies markedly. In the former case, acyclic ketone is formed, and the proportion of monocarbocyclic to bicarbocyclic product is distinctly greater than in the latter reaction. This divergence can be ascribed to one or more of a number of effects, including possibly e.g. the greater effectiveness of the $BF_3$ etherate in catalyzing the rearrangement of epoxide to ketone, or of $H_3PO_4$ in

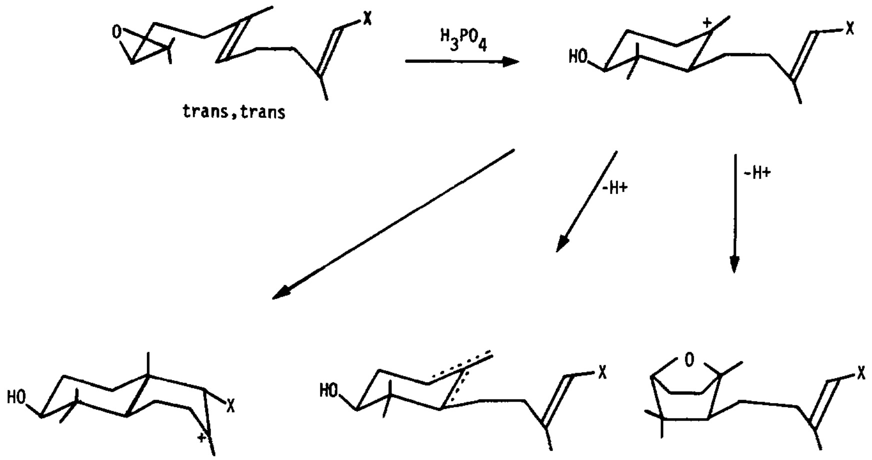


CHART 3.

catalyzing cyclization; the greater population in $H_3PO_4$ of conformers suitable for cyclization; or faster destruction of acyclic ketone and/or monocarbocyclic materials as they form in the $H_3PO_4$ reaction. In the absence of additional data, selection of the correct explanation(s) is not possible.

## EXPERIMENTAL

Melting points were measured on a microscope hot stage or in a capillary tube and are uncorrected. Infrared spectra were determined using Perkin–Elmer Infracord or Model 421 recording infrared spectrophotometers. Nuclear magnetic resonance spectra were recorded on a Varian A-60 or HR-100 spectrometer, using tetramethylsilane as an internal standard; all chemical shifts are reported in parts per million using the α scale, with tetramethylsilane set at zero. Microanalyses were carried out by E. Meier and J. Consul at Stanford University.

Column chromatographies were performed using Merck alumina or Davison 60–200 mesh silica gel, and all solvents were distilled. Petroleum ether used was the commercial hydrocarbon solvent, bp 60–68°, unless otherwise specified. Gas chromatographic analyses were carried out on a Perkin–Elmer Model 154 or F&M Model 700 gas chromatograph, using 6-ft 0.25-in. columns unless otherwise noted.

*Farnesol.* The starting farnesol (from Fluka A.G., Buchs, Switzerland) was shown by vpc to consist roughly of 60% *trans,trans-* and 40% *trans,cis*-farnesol. Isolation of the trans,trans geometrical isomer from the mixture was carried out via the diphenylurethane-derivative according to the procedure of Bates *et al.* (*23*).

*trans,trans-Farnesyl acetate.* Farnesol (4.8 g) was mixed with 10 ml $Ac_2O$ and 20 ml Py and left at room temperature for 2 hr. Ice water was added and the mixture extracted with petroleum ether 60–68. The organic layer was shaken three times with ice water, three times with saturated $KHCO_3$ solution, three times with 2 *N* $H_3PO_4$, and again with water until neutral. After drying over $MgSO_4$ and evaporation of the solvent, 5.6 g (100%) *rans,trans*-farnesyl acetate was obtained.

*Farnesyl acetate 10,11-monobromohydrin* (**5**, R = $COCH_3$). To a solution of 5.0 g (0.019 mol) of farnesyl acetate in 92 ml of glyme (1,2-dimethoxyethane) was added 28 ml of water. The resulting cloudy solution was stirred at 10°, and 3.74 g (0.021 mol) of *N*-bromosuccinimide was added in small portions. The homogeneous mixture was left at room temperature in the dark for 16 hr. Partial removal of the solvent was effected by distillation under reduced pressure at 40°, and the residue was poured into ether and water. The ether layer was washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated under reduced pressure.

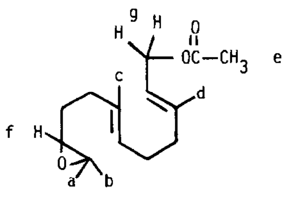
The resulting yellow liquid (6.9 g) was chromatographed on 140 g of silica gel–15% water. Elution with benzene afforded 4.5 g (0.012 mol, 65%) of pure monobromohydrin, one spot on TLC (benzene–2% methanol); infrared (liquid film): 2.88, 5.80, 6.02 (weak), 8.12, 8.72, 9.00, 9.84, 10.6, 11.1, and 13.1 $\mu$.

*Anal.* Calcd for $C_{17}H_{29}O_3Br$ (361.3): C, 56.51; H, 8.09; Br, 22.12. Found: C, 56.61; H, 8.14; Br, 21.98.

(±)-*10,11-Oxidofarnesyl acetate* (**18**). A mixture of 4.4 g (0.012 mol) of farnesyl acetate monobromohydrin and 2.0 g (0.05 mol) of sodium hydroxide in 130 ml of methanol–10% water was stirred for 4 hr at room temperature. The solution was neutralized with dilute hydrochloric acid, and the solvent was removed under reduced pressure. Ether and water were added; the ether layer was washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated to yield 3.0 g of a yellow oil. The infrared spectrum indicated that the acetate function had undergone hydrolysis.

The crude epoxyalcohol was dissolved in a mixture of 4.5 ml of acetic anhydride and 9.0 ml of pyridine and left at −10° for 24 hr. Ice water and ether were added, and the ether layer was washed with cold water, dilute phosphoric acid, water, saturated potassium bicarbonate solution, water, and saturated sodium chloride solution. Drying over anhydrous sodium sulfate and evaporation afforded 3.3 g of a yellow oil.

Chromatography on 66 g of silica gel–15% water, and elution with benzene, afforded 2.84 g (0.010 mol, 85%) of epoxide **18**, one spot on TLC (benzene–3% methanol). An analytical sample was prepared by microdistillation under high vacuum; infrared (chloroform): 5.80, 6.01, 8.19, 9.00, 9.86, 10.6, 11.2, and 11.6 $\mu$; nmr (carbon tetrachloride):



| Shift | Integration | Assignment |
|---|---|---|
| 1.19, 1.22 | 6H | a,b |
| 1.62, 1.70 | 6H | c,d |
| 1.95 | 3H | e |
| 2.10 (m) | 6H | allylic H |
| 2.52 (t, $J$ = 6) | 1H | f |
| 4.48 (d, $J$ = 7.5) | 2H | g |
| 5.27 (m) | 2H | vinyl H |

*Anal.* Calcd for $C_{17}H_{28}O_3$ (280.4): C, 72.82; H, 10.06. Found: C, 72.93; H, 10.28.

*(±)-Drimenol.* α-Bicyclofarnesic acid, mp 131–131.8°, was prepared according to the procedure of Stork and Burgstahler (*1*). Esterification of 223 mg (0.945 mmol) of α-bicyclofarnesic acid with diazomethane afforded 236 mg (0.944 mmol, 100%) of a colorless oil which crystallized upon standing, mp 43–47°; infrared (chloroform): 5.80, 8.42, and 8.61 μ.

A solution of 138 mg (0.552 mmol) of the ester in 15 ml of anhydrous ether was treated with excess lithium aluminum hydride, and the mixture was stirred at room temperature for 2.5 hr. The excess lithium aluminum hydride was decomposed with water, and the aqueous layer was acidified with dilute sulfuric acid and extracted with ether. The ether layer, upon washing with water, drying with anhydrous sodium sulfate, and evaporation, yielded 127 mg of a colorless oil. The oil crystallized upon treatment with pentane to yield 91 mg (0.410 mmol, 74%) of *dl*-drimenol (**16**), mp 62–64°. Sublimation at 50% (0.05 mm) and recrystallization from pentane afforded 57 mg, melting point unchanged; infrared (chloroform): 2.79, 2.92, 9.00, 9.30, 9.73, 10.06, 10.19, 10.41, and 11.91 μ, identical with the spectrum of authentic drimenol.

*(±)-Epidrimenol.* Methyl α-bicyclofarnesate was epimerized according to the procedure of Stork and Burgstahler (*1*). The resulting mixture of epimeric acids could not be separated by fractional crystallization. It was therefore esterified with diazomethane and separated by preparative vpc on a diethylene glycol succinate (DEGS) column at 200°. The resulting of epi-methyl α-bicyclofarnesate was 92% pure by vpc (DEGS).

To a solution of 10 mg (0.040 mmol) of the ester in anhydrous ether was added excess lithium aluminum hydride, and the mixture was stirred at room temperature for 5 hr. Decomposition of excess hydride with a saturated aqueous solution of sodium potassium tartrate, filtration, and evporation of the ether afforded 11 mg of a colorless oil. Chromatography on 1.5 g of alumina (Merck, acid-washed) and elution with pentane–10% ether afforded 6 mg (0.027 mmol, 67%) of *dl*-epidrimenol) (**16**), which crystallized upon standing, mp 56–63°; infrared (chloroform): 2.85, 9.27, 9.61, 10.00, 10.39, and 11.80 μ. Sublimation at 43°/0.05 mm) afforded material with mp 59–64°.

*Phosphoric acid cyclization of* **18**. To 40 ml of 85% phosphoric acid, agitated vigorously at −10°, was added 2.5 g (8.9 mmol) of oxide **18** over a period of 1 hr. Agitation was continued for 3 hr at −10°, and the resulting dark brown mixture was poured into ice water and extracted with ether. The ether layer was washed with saturated potassium bicarbonate solution, water, and saturated sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated to yield 1.6 g of a viscous yellow oil. The product exhibited four major and many minor spots of TLC (benzene–3% methanol).

Chromatography on 50 g of silica gel–15% water, and elution with benzene–5% ether and –10% ether, afforded 482 mg of material enriched in the desired hydroxyacetate **21a.** This material was rechromatographed on 15 g of alumina and eluted with benzene–5% ether to yield 427 mg of crude bicyclic material. The infrared spectrum (chloroform) confirmed the presence of hydroxyl (2.78 and 2.89 $\mu$) and acetate (5.80 and 8.02 $\mu$) functions.

A solution of 280 mg (1.00 mmol) of the crude bicyclic hydroxyacetate **21a** in 10 ml of 2% potassium hydroxide in 95% methanol was refluxed for 2 hr, cooled, and poured into ether and ice water. The aqueous layer was saturated with sodium chloride and extracted with ether. The ether layer was washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated to yield 230 mg of a yellow oil. The oil showed one major and several less polar minor spots of TLC (benzene–4% methanol). Chromatography on 6.9 g of silica gel–15% water afforded 87 mg of partially crystalline material, upon elution with benzene–20% ether and –50% ether. Recrystallization from methylene chloride–petroleum ether gave 34 mg of bicyclic diol **21b,** mp 148–150°; infrared (KBr pellet): 3.05 (OH) and 6.15 $\mu$ (c═c, very weak).

Crude diol-monoacetate **21c** (163 mg) was dissolved in 10 ml acetone, cooled to 0–5°, and treated with 0.5 ml of Jones reagent for 30 min. Usual work-up afforded 153 mg crude ketoacetate **22.** Vapor-phase chromatography (column Z SE-30, $t$ = 200°, $p$ = 10 psig, $h$ = 3.5) showed the following composition: ~83% ketoacetate **22** (retention time 20½ min). ~17% ketoacetate **23** (retention time 15 min). Thus the cyclization of pure trans,trans **18** with conc. $H_3PO_4$ gave exactly the same results as the $H_3PO_4$-cyclization of the mixture of geometrical isomers (*vide supra*).

*Boron trifluoride cyclization of* **18.** To a three-neck flask (rubber cap, $N_2$ inlet, drying tube) was added a solution of 1.48 g of oxide **18** in 16 ml dry benzene (distributed over NaH). The solution was cooled to 8°, and under stirring 0.25 ml $Bf_3 \cdot Et_2O$ (freshly distributed) was added with a syringe through the rubber cap (addition time 1 min). The reaction mixture was then stirred at room temperature for 1¼ hr. The resulting solution was taken up in ether, the ether layer washed with cold water, dried over $MgSO_4$ and evaporated to dryness; 1.43 g crude cyclization product was obtained, which was chromatographed on 60 g silica gel (15% $H_2O$). (See Table 1.) Fractions 14–18 containing the impure bicyclic diolmonoacetate were recombined and divided into 2 crops: ($A$) (224 mg) and ($B$) (237 mg).

In order to purify further the highly contaminated diol-monoacetate present in cuts 14–18, crop $A$ was submitted to a selective saponification. It could be shown in separate experiments that under the following conditions acyclic acetate is completely saponified, whereas bicyclic acetate remains unchanged. Cyclization material $A$ (224 mg, ½ of fractions 14–18) was dissolved in 2.5 ml MeOH and treated during 15 min at room temperature with 25 ml of a saturated $K_2CO_3$ solution in 90% MeOH/10% $H_2O$. After neutralization with diluted $H_3PO_4$ and usual work-up, 212 mg selective saponified material was obtained. Thin-layer chromatography (benzene/3% MeOH) showed essentially two spots: bicyclic diolmonoacetate with high $R_f$ value and acyclic material (diol) with low $R_f$ value.

TABLE 1

| Fraction | Eluent (ml) | | Weight (mg) | Total weight (mg) |
|---|---|---|---|---|
| 1 | Petroleum ether | 250 | 9 | 9 |
| 2 | | | 2 | 11 |
| 3 | | | 2 | 13 |
| 4 | Petroleum ether/50% benzene | 200 | 45 | 58 |
| 5 | | | 24 | 82 |
| 6 | | | 22 | 104 |
| 7 | Benzene | 200 | 163 | 267 |
| 8 | | | 149 | 416 |
| 9 | | | 105 | 521 |
| 10 | | | 87 | 608 |
| 11 | | | 70 | 678 |
| 12 | | | 47 | 725 |
| 13 | | | 37 | 762 |
| 14 | Benzene/5% ether | 200 | 152 | 914 |
| 15 | | | 157 | 1071 |
| 16 | | | 95 | 1166 |
| 17 | | | 43 | 1209 |
| 18 | | | 26 | 1235 |
| 19 | Benzene/10% ether | 500 | 99 | 1334 |

The isolation of the desired diol-monoacetate was accomplished by preparative TLC on three 20 × 20-cm plates, using 0.75-mm-thick silica gel G layers and benzene/3% MeOH as developing solvent; 81 mg of the fraction containing the bicyclic diol-monoacetate were obtained.

This material was saponified over night at room temperature with 5 ml of a 2% KOH solution in 95% MeOH. Usual work-up afforded 38 mg crude diol. After standing over night, 17 mg crystallized. Two recrystallizations from $CH_2Cl_2$/hexane afforded diol **20b**, mp 113–114°.

The analytical sample was dried over night at room temperature under high vacuum:

*Anal.* Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.26; H, 10.77.

Cyclization material *B* (237 mg, ½ of fractions 14–18) was dissolved in 15 ml acetone and cooled to 0–5°. Under stirring, 0.5 ml of a standard Jones reagent (1.7 m in $CrO_3$) was added dropwise within a few minutes. The resulting solution was stirred at 0° during 30 min. Usual work-up afforded 227 mg crude ketoacetate **23**.

For further purification of the ketoacetate the crude material was submitted to a selective saponification. Crude **23** (227 mg) was dissolved in 2.5 ml MeOH and treated during 15 min at room temperature with 25 ml of a solution (saturated) ($K_2CO_3$ in 90% MeOH–10% $H_2O$). Usual work-up after neutralization yielded 201 mg selectively saponified ketoacetate. Thin-layer chromatography (benzene/2% MeOH) showed two spots: bicyclic ketoacetate with a higher $R_f$ value and acyclic ketol with a lower $R_f$ value. Separation was realized by preparative TLC on three 20 × 20-cm plates, using 0.75-mm-thick silica gel layers and benzene/3% MeOH as developing solvent. Ketoacetate **23** (47 mg) was obtained. Vapor-phase chromatography (column Z SE-30, $t = 200°$, $p = 10$ psig, $h = 3.3$) showed the following composition: ~85% ketoacetate **23** (retention time 20 min) and ~15% ketoacetate **22** (retention time 14½ min).

*Reduction of ketoacetate* **23** *with* $NaBH_4$. To a solution of 47 mg of **23** in 2 ml MeOH and 2 drops with $H_2O$ 20 mg of $NaBH_4$ were added. The resulting solution was left at room temperature overnight. Usual work-up afforded 42 mg diol-monoacetate **20a.** The crude diol-monoacetate was left for 8 hr at room temperature in 3 ml of a 2% KOH solution in 95% MeOH. Usual work-up yielded 37 mg crude diol **20b,** which crystallized partially after standing; mp 111–112°; mix mp with diol obtained under *A*, 111–112.5°. The ir spectra of the two diols were superimposable.

*Correlation of ketoacetate* **23** *with drimenol.* To a solution of 35 mg ketoacetate **23** in 0.2 ethane-dithiol and 4 drops of AcOH 20 μl $BF_3 \cdot Et_2O$ was added. The reaction mixture was left for 1 hr at room temperature. The resulting solution was taken up in ether, the ether layer washed three times with 2*N* NaOH solution and then with $H_2O$ until neutral, dried over $MgSO_4$, and evaporated to dryness, giving 45 mg of crude thioketal. The latter was dissolved in 6 ml abs. EtOH and heated under reflux over night with ~500 mg freshly prepared W2 Raney-Ni. Filtration from the catalyst and evaporation of the EtOH afforded 28 mg crude drimenol-acetate.

Twenty-eight milligrams of the crude desulfurization product was left over night at room temperature in 2 ml of a 2% KOH solution in 95% MeOH. Usual work-up afforded 24 mg crude drimenol. This material was purified by preparative TLC on one 20 × 20-cm plate, using a 0.75-mm-thick silica gel G layer and benzene/4% MeOH as developing solvent; 14 mg purified noncrystalline drimenol resulted which showed only a single spot on TLC. Vapor-phase chromatographic analysis using column Z SE-30, $t = 190°$, $p = 10$ psig, showed the following composition: ~85% drimenol (retention time 10 min) and ~15% epidrimenol (retention time 7½ min).

*Drimenyl p-nitrobenzoate*. Five milligrams of the above mixture in a few drops of pyridine was treated for 2 hr at room temperature with 5 mg *p*-nitrobenzoylchloride. The resulting reaction mixture was taken up in ether, the ether layer shaken subsequently two times with saturated $NaHCO_3$ solution, 2 *N* $H_3PO_4$ and $H_2O$ until neutral. After drying over $MgSO_4$ and evaporation of the ether, 10 mg crude, oily *p*-nitrobenzoate resulted. Purification was carried out by preparative TLC (one 10 × 20-cm plate, 0.75-mm-thick silica gel G layer, benzene/2% MeOH as developing solvent); 7.5 mg purified drimenyl *p*-nitrobenzoate was obtained; 2.5 mg could be obtained crystalline. After two recrystallizations from petroleum ether 60–68°, 0.5 mg derivative of mp 99–101° was obtained. A mp with authentic drimenyl *p*-nitrobenzoate was 99–102°.

*Drimenyl allophanate*. Three milligrams of the above mixture was treated at room temperature over night with 0.1 ml of a cyanic acid solution in ether. After evaporation of the ether, the residue was heated under reflux for 10 min with 0.5 ml benzene. Filtration from the insoluble polymeric products of cyanic acid and evaporation of the solvent afforded ~3 mg of crude, crystalline allophanate. Three recrystallizations from MeOH gave <0.1 mg drimenyl allophanate of mp 176.5–178.5°; mp with authentic drimenyl allophanate, 178–180°.

*Cyclization of a mixture of trans,trans oxide* **18** *and trans,cis oxide* **19.** Commercial FLUKA-farnesol (~60% trans,trans, ~40% trans,cis) was carried through the same steps as described for the *trans,trans*-farnesol. Although the oxide mixture could not be analyzed by VPC, it is safe to assume that it has the same ratio of geometrical isomers as the farnesol mixture used as starting material.

*Cyclization with $BF_3 \cdot Et_2O$ in benzene.* The cyclization of 270 mg of oxide mixture **18–19** in 10 ml anhydrous benzene with 0.025 ml $BF_3 \cdot Et_2O$ as well as the purification of the crude cyclization product until the ketoacetate stage was carried out in the same way as described above. Ketoacetate (18 mg) **22–23,** purified by selective saponification, was obtained. Vapor-phase chromatography (column Z SE-30, $t = 200°$, $p = 10$ psig, $h = 3.3$) showed the following composition: ~55% ketoacetate **23** (retention time 20 min) and ~45% ketoacetate **22** (retention time 14½ min).

This mixture of epimeric ketoacetates was taken through the thioketal, desulfurization followed by saponification steps to a mixture of drimenol and epi-drimenol. Vapor-phase chromatographic analysis (column Z SE-30, $t = 190°$, $p = 10$ psig, $h = 3.5$) gave the following relative ratio for the two epimers: ~58% drimenol (retention time 10½ min) and ~42% epi-drimenol (retention time 7½ min).

*Cyclization with $H_3PO_4$.* The oxide **18–19** mixture (1.396 g) was cyclized in 40 ml conc. $H_3PO_4$ as described for the pure trans,trans oxide **18.** Crude, yellow oily cyclization product (1.05 g) was obtained which was consequently chromatographed on 40 g silica gel (15% $H_2O$). The single cuts were checked by TLC, and the whole chromatogram was divided into four fractions:

Fraction I: petroleum ether/benzene 1 : 1 and benzene cuts 3–10, 285 mg.

Fraction II: benzene/5% ether and early benzene/10% ether cuts 11–15, 294 mg.

Fraction III: late benzene/10% ether and benzene/20% ether cuts 16–19, 221 mg.

Fraction IV: benzene/ether 1 : 1 and ether cuts 20 and 21, 72 mg.

Fraction II, containing the bicyclic diol-monoacetate Vb was rechromatographed on 10 g alumina I/n. (See Table 2.) The benzene/5% ether cuts (85 mg) containing the bicyclic diol-monoacetate were recombined.

TABLE 2

| Fraction | Eluent (ml) | | Weight (mg) | Total weight (mg) |
|---|---|---|---|---|
| 1 | Benzene | 20 | 0 | 0 |
| 2 | | | 2 | 2 |
| 3 | Benzene/5% ether | 20 | 9 | 11 |
| 4 | | | 5 | 16 |
| 5 | | | 23 | 39 |
| 6 | | | 48 | 87 |
| 7 | | 50 | 101 | 108 |
| 8 | Benzene/5% ether | 50 | 36 | 224 |
| 9 | Benzene/10% ether | 50 | 5 | 229 |
| 10 | | | 6 | 235 |
| 11 | Ether | 50 | — | — |

*Diol* **21b** *by direct saponification of* **21a.** Bicyclic diol monoacetate (85 mg, cuts 3–6 of the above chromatography) was saponified over night in 5 ml of a 2% KOH solution in 95% MeOH. Usual work-up afforded 81 mg crude diol, which was filtered through a short alumina II column. The crystalline diol (18 mg) was eluted with benzene/15% ether. An additional crop of 44 mg diol was obtained from fraction I going through the same purification procedures as described above. After two recrystallizations from methylenechloride/hexane, the diol melted at 150–151°, mp with diol **20b:** 100–110°. The analytical sample was dried overnight at room temperature under high vacuum (0.001 mm Hg): IR No. 160.

*Anal.* Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.42; H, 11.06.

*Diol* **21b** *via ketoacetate* **22.** A second cyclization of oxide **18–19** mixture conc. $H_3PO_4$ was carried through the same purification procedures as described. Vapor-phase chromatographic analysis using column Z SE-30 ($t = 200°$, $p = 10$ psig, $h = 3.5$) showed the following composition: ~85% ketoacetate **22** (retention time 14½ min) and ~15% ketoacetate **23** (retention time 20 min).

To a solution of 8.5 mg ketoacetate **22** in 4 ml anhydrous ether 50 mg $LiAlH_4$ was added, and the resulting reaction mixture was heated (under $N_2$) under reflux for 2 hr. Usual work-up afforded 7.5 mg crude crystalline diol **21b,** which after one recrystallization from $CH_2Cl_2$ had mp 150–151°. Mix mp with diol obtained by direct saponification of **21a** showed no depression (mp 150–151°).

*Correlation of ketoacetate* **22** *with epi-drimenol.* Ketoacetate **22** (108 mg) was saponified at room temperature overnight in 10 ml of a 2% KOH solution in 95% MeOH. Usual work-up afforded 86 mg of the corresponding ketol. The ketol was dissolved in 15 ml diethylene glycol, 5 ml hydrazine (distributed over KOH) and 5 ml EtOH and heated under reflux for 1½ hr. Three grams of KOH was then added, and EtOH and excess hydrazine were distilled out of the reaction flask until the temperature of the reaction mixture reached 190°. The resulting solution was kept at 180–190° for 6 hr. Usual work-up afforded 72 mg crude reduction product, which was chromatographed on 3.5 g alumina I/n. The benzene and benzene/5% ether fractions eluted 15 mg of oily epi-drimenol, which crystallized after standing overnight (mp 59–62°) and was sublimed at 55–57°/0.08 mm Hg.

*Anal.* Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.82; H, 11.69.

The ir spectrum was identical with that of authentic epi-drimenol. A mixture mp with authentic material gave no depression, while a mmp with drimenol melted at room temperature.

*trans,trans-Farnesic acid.* A mixture of farnesic acid geometrical isomers (*24*) (75.3 g, 0.32 mol) was dissolved in 800 ml of 95% ethanol and 320 ml (0.32 mol) of 1 *N* aqueous sodium hydroxide. To this solution were added 2000 ml of distilled water and a solution of *S*-benzyl thiouronium hydrochloride (64.5 g, 0.32 mol) in 800 ml of distilled water. A white precipitate formed immediately. After storage at 0° overnight the precipitate was filtered and partially dried. It was then dissolved in 3000 ml of reagent methanol and 300 ml of distilled water, warmed to 50°, and slowly cooled to 0°. After 24 hr at 0°, the ivory-colored crystals were filtered and dried on high vacuum. This product was dissolved in 800 ml of hot reagent methanol, filtered with Norit, diluted with 100 ml of distilled water, and cooled slowly to 0°. After 2 days storage at 0° the fine white platelets were filtered off, and dried at

0.03 mm, yielding 24.5 g (19%) of *S*-benzyl thiouronium *trans,trans*-farnesate, mp 131.5–132.0°. (reported (*23*) mp 130–131°. The acid was regenerated from its salt by the method of Eschenmoser and co-workers (*16*), using 24.5 g (0.061 mol) of *S*-benzyl thiouronium *trans,trans*-farnesate, 2 × 700 ml of trisodium phosphate–hydrochloric acid buffer, and 3 × 100 ml of ethyl ether. The yield of pure *trans, trans*-III, a clear colorless oil, was 14.6 g (98%).

*Methyl farnesate.* To a solution of *trans,trans*-farnesic acid (14.10 g, 60 mmol) in 25 ml of distilled ethyl ether and 25 ml of reagent methanol cooled to 0°, excess distilled ethereal diazomethane was added. After storage for 15 hr at room temperature, the yellow solution was warmed slightly and the color disappeared. It was then concentrated under reduced pressure to a colorless oil which was flushed through a column of activity III neutral alumina (140 g, 3.1 × 18 cm) in 1200 ml of distilled petroleum ether (bp 30–60°) yielding a colorless oil, 14.60 g (98%) after concentration under reduced pressure. A vpc of this oil revealed a trace at 21.3 min, 1% cis,trans and a peak at 26.6 min, 99% trans,trans isomer. The ultraviolet max (95% ethanol) was 218 m$\mu$ ($\epsilon$ = 14,800). The liquid film infrared spectrum showed a carbonyl peak at 1718 $cm^{-1}$, a conjugated carbon–carbon double bond peak at 1644 $cm^{-1}$, and carbon-oxygen stretching peaks at 1220 and 1144 $cm^{-1}$. The nmr spectrum in carbon tetrachloride contained peaks assigned as shown in Table 3. A small portion was microdistilled for analysis, bp 90–100° (0.02 mm).

*Anal.* Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.54; H, 10.34.

*N-Bromosuccinimide oxidation of methyl farnesate. trans,trans*-Farnesic acid (14.60 g, 58.4 mmol) was dissolved in 250 ml of distilled tetrahydrofuran and 50 ml of distilled water. The solution was cooled to 0°, *N*-bromosuccinimide (11.45 g, 64.4 mmol) was added, and the mixture was swirled. The resultant colorless solution was stored at 0° for 2 days. The solution was evaporated under reduced pressure to about 60 ml at room temperature, and the residue was poured into 200 ml of ethyl ether, extracted first with 2 × 500 ml of distilled water, and then with 50 ml of 25% aqueous sodium chloride. The combined aqueous solution was reextracted with 2 × 50 ml of ethyl ether. The total ethyl ether (~300 ml) was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to dryness. The residue was purified by chromatography on silica gel · 10% water (1000 g, 6 × 48 cm). The column was eluted with 7000 ml of petroleum ether (bp 30–60°): ethyl ether 90 : 10; 3000 ml of 85 : 15; and 2000 ml of 80 : 20 of the same solvents. These three fractions were combined and evaporated to dryness under reduced pressure, yielding 3.17 g, a yellow oil, labeled fraction *A*.

TABLE 3

| Peak | Assignment |
|---|---|
| 4.42 $\tau$, 1H | Olefinic hydrogen $\alpha$ to the ester |
| 4.95 $\tau$, 2H | Olefinic hydrogens in the two double bonds |
| 6.42 $\tau$, 3H | Methyl ester hydrogens |
| 7.87 $\tau$, doublet, $J$ = 1.7 cps | Allylic methyl group $\beta$ to the ester |
| 8.04 $\tau$ | Allylic methylene |
| 8.35 and 8.42 $\tau$ | Three allylic methyl groups |

Elution of the column with 10,000 ml of petroleum ether (bp 30–60°): ethyl ether 70:30, and subsequent evaporation under reduced pressure to dryness gave 15,346 g of a colorless oil, designed fraction *B* and consisting of 10,11-bromohydrin. Elution of the column with 4000 ml of ethyl ether and evaporation under reduced pressure to dryness gave 3.054 g of a yellow oil which was not investigated.

*Fraction A.* Thin-layer chromatography with benzene: ethyl acetate 50:10 showed a main spot at $R_f$ 0.66, and a trace at $R_f$ 0.35. Methyl farnesate also showed one spot at $R_f$ 0.66. Fraction *A* was analyzed by vpc with a 2-m ¼-in. Perkin–Elmer P column at 190° and 15 lb helium pressure with a flame ionization detector. The largest peak at 26.3 min (~50%) corresponded to methyl farnesate; however, several other peaks were present: 14.6, 21.2, 24.5, 28.8, 32.0, 38.2, and 43.6 min.

*Fraction B: Methyl farnesate-monobromohydrin* (**8**). Thin-layer chromatography with benzene: ethyl acetate 50:10 showed only one spot, $R_f$ 0.36. The ultraviolet maximum (95% ethanol) was 217.5 m$\mu$ ($\epsilon$ = 21,500). The liquid film ir spectrum showed hydroxyl absorption at 3490 cm$^{-1}$; conjugated ester absorption at 1700–1720 cm$^{-1}$; carbon–oxygen stretching bands at 1220 and 1145 cm$^{-1}$; and conjugated carbon–carbon double bond absorption at 1645 cm$^{-1}$. The nmr spectrum of Fraction *B* in carbon tetrachloride contained peaks assigned as given in Table 4. If $X$ is the percent of the bromohydrin at the central double bond and $Y$ the percent of the bromohydrin at the terminal double bond, then $3X + 6Y = 5.82$; $X + Y = 100$; therefore $X = 6\%$ and $Y = 94\%$. Thus by nmr it is concluded that the monobromohydrin is at least 94% in the terminal position. A small portion of fraction *B* was dried at 0.03 mm at room temperature for 18 hr and analyzed.

*Anal.* Calcd for $C_{16}H_{27}O_3Br$: C, 55.33; H, 7.84; Br, 23.01. Found: C, 55.42; H, 7.62; Br, 23.09.

The analytical data of fraction *B* are all consistent for methyl farnesate monobromohydrin (**8**). The best yield from methyl farnesate was 76%; other runs gave 62–76%.

*Isolation of methyl 3-bromobicyclofarnesates from the selective saponification of fraction A.* Crude fraction *A* (3.165 g), after being flushed through activity III

TABLE 4

| Peak | Assignment |
|---|---|
| 4.40 $\tau$, 1H | Olefinic hydrogen of the conjugated ester |
| 4.86 $\tau$, 1H | Olefinic hydrogen of the central double bond |
| 6.25 and 6.49 t, 4H | Hydrogen on carbon bound to bromine, and methyl ester hydrogens |
| 7.33 $\tau$, 1H | Hydroxyl hydrogen |
| 7.87 $\tau$, multiplet, 10H | Methylenes and allylic methyl group on conjugated double bond |
| 8.41 $\tau$, 3.4H | Allylic methyl group in the central double bond |
| 8.72 $\tau$, singlet, 5.82H | *gem*-Dimethyl group attached to carbon bound to oxygen |

neutral alumina with petroleum ether (bp 40–50°) and isolated by evaporation, was added to a mixture of 50 ml of reagent methanol, 5 ml of distilled water, and 6.1 g of potassium hydroxide. After refluxing for 2 hr on the steam bath the yellow solution was diluted with 10 ml of distilled water and evaporated under reduced pressure to about 10 ml. The residue was added to 100 ml of ethyl ether and extracted with 400 ml, then 200 ml of 10% aqueous potassium carbonate. The aqueous layers were reextracted with 100 ml of ethyl ether. The total ether (200 ml) was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness under reduced pressure affording 61.3 mg (0.42%) of a yellow oil. This oil was purified by preparative TLC, one plate (20 × 20 cm), silica gel GF (1 mm), using benzene: ethyl acetate 50: 10. The area of $R_f$ 0.6–0.75 was eluted with 5 × 20 ml of acetone : methanol 3 : 2. Upon evaporation under reduced pressure 31 mg (0.21%) of a pale yellow oil was obtained. A Beilstein test performed on this material was positive for halogen. The nmr spectrum of this material in carbon tetrachloride contained peaks assigned as shown in Table 5. The material was microdistilled for analysis; from 31 mg was obtained 27.3 mg of clear, colorless oil, bp 90–100° (0.02 mm).

*Anal.* Calcd for $C_{16}H_{25}O_2Br$: C, 58.36; H, 7.65; Br, 24.27. Found: C, 57.95; H, 8.13; Br, 23.09.

*Reduction of methyl 3-bromobicyclofarnesate to drimenol and epidrimenol.* A mixture of bromoester (9.2 mg, 0.028 mmol) in 5.0 ml of freshly distilled anhydrous tetrahydrofuran and lithium aluminum hydride (29.8 mg, 0.784 mmol) was refluxed for 18 hr with stirring. The mixture was cooled to room temperature, and saturated aqueous sodium potassium tartrate (~1 ml) was cautiously added. The mixture was poured into 25 ml of 25% aqueous sodium chloride and 10 ml of 10% phosphoric acid, and extracted first with 50 ml, then with 10 ml of ethyl ether. The total ethyl ether solution (70 ml) was dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to dryness, giving 10.8 mg of oily residue. Three separate Beilstein tests on this material were negative for halogen. The residue was purified by preparative TLC, one plate (20 × 20 cm), silica gel GF (1 mm), using benzene : ethyl acetate 50: 10. In order to locate the desired material, authentic drimenol was spotted on either side of the residue. The drimenol was developed with iodine vapor and showed $R_f$ 0.45–0.29. The area of the residue, $R_f$ 0.25–0.53, was scraped away and eluted with 7 × 10 ml of reagent methanol giving 1.0 mg (16%) of a yellow oil. Analysis of this product was accom-

TABLE 5

| Peak | Assignment |
|---|---|
| 4.55 $\tau$, 0.8H | Olefinic hydrogen |
| 6.10 $\tau$, triplet, $J$ = 8 cps, 1.2H | Hydrogen on carbon bearing bromine |
| 6.38, 6.40, 6.42 $\tau$, 3H | Three different methyl ester hydrogens |
| 7.92 $\tau$, 4H | Allylic methylene hydrogens |
| 8.42 $\tau$, 3.8H | Allylic methyl group |
| 8.80 $\tau$, ~1H | Homoallylic methyl group |
| 8.95 and 9.04 $\tau$, 8H | Saturated methyl groups |

plished with vpc using a 150-ft 0.02-in Perkin–Elmer # Z Golay column at 200° and 15 lb helium pressure and a flame ionization detector. Authentic drimenol gave one peak at 17.0 min while authentic epidrimenol gave a peak at 13.6 min. The reaction product gave three peaks totaling about 60%; 14.0, 17.4, and 19.9 min in the ratio 40 : 55 : 5; in addition, there were impurities to the extent of about 40%. A mixture of drimenol and the reaction product gave a sharp peak at 17.2 min in addition to the other peaks from the reaction product. The peaks at 14.0 min and 17.4 min are ascribed to epidrimenol and drimenol.

*Separation and isolation of bromobicycloesters.* Fraction *A* was saponified as described above. The crude nonsaponified ester was purified by preparative continuous TLC using two plates, 20 × 20 cm, with a 1.0-mm layer of silica gel GF and with benzene : hexane 60 : 40 for 2 hr. The crude ester was separated into three different and well-resolved components:

band 1: pseudo $R_f$ 0.6–0.5, 39.0 mg;
band 2: pseudo $R_f$ 0.7–0.6, 6.5 mg (uv absorbing);
band 3: pseudo $R_f$ 0.8–0.7, 17.0 mg.

Band 1 represents the bromobicyclic ester **40**, while band 2 was assumed to be due to the α,β-unsaturated ester isomer. The nmr spectrum of band-3 material in carbon tetrachloride permitted structure assignment **41.** (See Table 6.) It was observed that band-3 material solidified upon standing at −20° and therefore it was sublimed at 60–70° (0.03 mm). The resultant solid, mp 78–81°, was crystallized from hot reagent methanol (0.40 ml). The crystals were collected, washed with 0.10 ml of cold methanol and dried on high vacuum. After one recrystallizaiton the mp was 82.5–82.6°.

*Anal.* Calcd for $C_{16}H_{25}O_2Br$: C, 58.36; H, 7.65; Br, 24.27. Found: C, 58.50; H, 7.81; Br, 24.6.

*Hydrogenation of methyl 3-bromobicyclofarnesate.* A mixture of 3 ml of glacial acetic acid and 22 mg of platinum oxide was stirred under hydrogen for 1 hr until the catalyst and hydrogen had equilibrated. A solution of the bromobicycloester (29.8 mg, 0.09 mmol) in 2 ml of acetic acid was added to the hydrogenation flask, and the mixture was stirred under hydrogen for 1 hr. The mixture was stirred under hydrogen for 1 hr. The mixture was filtered; the acetic acid was evaporated

TABLE 6

| Peak | Assignment |
|---|---|
| 5.2 and 5.37 τ, 2H | Two olefinic hydrogens on an exocyclic double bond |
| 6.11 τ, quartet, 1H; from a 100-mc nmr, $J$ = 10.5 cps and $J$ = 6 cps | Axial hydrogen on carbon attached to bromine |
| 6.41 τ, 3H | Methyl ester hydrogens |
| 7.34 τ, 0.95H | Hydrogen on carbon α- to the carbomethoxy group |
| 8.93 and 9.03 τ, 9.1H | Angular methyl and *gem*-dimethyl groups |

to dryness; the residue was dissolved in hexane and refiltered, then evaporated to dryness giving 30.1 mg of pale yellow oil, assigned structure **45.**

*Silver fluoroborate-promoted hydrogen bromide elimination of the dihydrobromoester* **45.** (*Note:* All manipulations of this reaction were carried out in a portable drybox under dry nitrogen.) The bromoester **45** (30.1 mg, 0.091 mmol) was added to 1.5 ml of anhydrous benzene and stirred vigorously. Silver fluoroborate (21.7 mg, 0.111 mmol) was quickly added and the mixture stirred further for 1.5 hr. During this time a precipitate appeared which gradually darkened. The mixture was diluted with 25 ml of 5% aqueous phosphoric acid, and extracted with 2 × 10 ml of ethyl ether. The ether was dried over anhydrous magnesium sulfate and evaporated to dryness. The yellow residue (20.2 mg) had a fragrant aroma. The product was purified by preparative TLC, one plate, 20 × 20 cm, 1.0 mm of silica gel GF using benzene as eluent. Material corresponding to the least polar spot was isolated, 12.8 mg (50%), assigned as **46.** Its vpc using a capillary Golay column 0.02 in. × 150 ft at 180° and 10 lb helium pressure with a flame ionization detector showed a major peak at 19.0 min, 89%; and three impurity peaks at 18.0 min, 5%; 16.3 min, 2.8%; and 13.7 min, 2.5%. The nmr spectrum was measured in carbon tetrachloride (Table 7).

*Methyl 10,11-oxidofarnesate* (**9**). A solution of the monobromohydrin **8** (13.974 g, 40.3 mmol) in 250 ml of reagent methanol was stirred for 15 min at room temperature with anhydrous potassium carbonate (15.0 g, 109 mmol). Thin-layer chromatography showed that the reaction was complete in 1 min. After filtration, 200 ml of petroleum ether (bp 30–60°) was added to the filtrate, and the solution was extracted with 1250 ml of distilled water, then with 250 ml of 25% aqueous sodium chloride. The aqueous layers were each reextracted with 2 × 100 ml of light petroleum. The total petroleum fractions (~400 ml) were dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to dryness. The pale yellow residue was dissolved in 100 ml of light petroleum and added to 20 g of activity VI neutral alumina. This mixture was filtered, and the alumina was washed with 6 × 25 ml of light petroleum. The petroleum extract (~250 ml) was evaporated to dryness, yielding 9.579 g (90%) of a nearly colorless oil. Its TLC with benzene : ethyl acetate 50 : 10 showed one spot, $R_f$ 0.475. A small portion was microdistilled for analytical data, bp 80–90° (0.01 mm). The ultraviolet maximum (95% ethanol) was 218 m$\mu$ ($\epsilon$ = 14,600). The liquid film infrared spectrum showed the $\alpha,\beta$-unsaturated ester moiety at 1720 and 1646 cm$^{-1}$, and carbon–oxygen stretching vibrations at 1220 and 1140 cm$^{-1}$. The nmr spectrum in carbon tetrachloride contained peaks assigned as shown in Table 8.

TABLE 7

| Peak | Assignment |
|---|---|
| 6.41 $\tau$ | Methyl ester hydrogens |
| 7.55 $\tau$, doublet, $J$ = 4 cps | Hydrogen on carbon $\alpha$- to the carbomethoxy group |
| 8.33 and 8.45 $\tau$ | Allylic *gem*-dimethyl group |
| 9.17 $\tau$, doublet, $J$ = 7 cps | Secondary methyl group |
| 9.25 $\tau$ | Angular methyl group |

TABLE 8

| Peak | Assignment |
|---|---|
| 4.43 τ, 1H | Olefinic hydrogen in the conjugated ester |
| 4.88 τ, 1H | Olefinic hydrogen on the central carbon–carbon double bond |
| 6.41 τ, 3H | Methyl ester hydrogens |
| 7.51 τ, triplet, $J$ = 6 cps, 1.2H | Hydrogen on the carbon in the epoxide |
| 7.87 τ, doublet, $J$ = 1.3 cps, 8.7H | Allylic methyl group in the conjugated ester and allylic methylenes |
| 8.38 τ, doublet, $J$ = 1.2 cps, 4.5H | Allylic methyl group of the central carbon–carbon double bond |
| 8.78 and 8.81 τ, 6.0H | *gem*-Dimethyl group attached to carbon which is in the epoxide |

*Anal.* Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 71.86; H, 9.80.

*Conversion of oxide* **9** *to the glycol* **28.** Oxide **9** (1.017 g, 3.3 mmol) was dissolved in 20 ml of distilled tetrahydrofuran and 10 ml of 3% aqueous perchloric acid at 3°. After being stirred at 0° for 24 hr, the mixture was poured into 50 ml of ethyl ether and extracted with 400 ml of 12%, then 100 ml of 25% aqueous sodium chloride. The aqueous layers were re-extracted with 50 ml of ethyl ether. The total ethyl ether (~100 ml) was dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to dryness, giving 1.087 g of crude glycol. Upon chromatography on silica gel · 10% water (170 g, 3.4 × 27 cm) by flushing with 500 ml of petroleum ether (bp 30–60°) : ethyl ether 70 : 30; 300 ml of 60 : 40; 300 ml of 50 : 50; 300 ml of 40 : 60; and 1400 ml of 100% ethyl ether, the fraction obtained with 100% ethyl ether gave 1.005 g of colorless oil (93%), which showed only one spot ($R_f$ 0.6) by TLC with ethyl acetate. The hygroscopic oil decomposed upon attempted distillation, so analysis was performed on a portion which was dried overnight at room temperature (0.01 mm). The ultraviolet maximum (95% ethanol) was 218 mμ ($\epsilon$ = 12,500). The liquid film infrared spectrum showed strong hydroxyl absorption at 3400–3500 $cm^{-1}$, and the $\alpha,\beta$-unsaturated ester absorption at 1715 and 1645 $cm^{-1}$.

*Anal.* Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92. Found: C, 66.67; H, 9.76.

*Periodate cleavage of glycol* **28.** Sodium metaperiodate (2.8011 g, 13.096 mmol) was added to a solution of glycol **28** (932.5 mg, 3.28 mmol) in 60 ml of spectroquality methanol and 60 ml of distilled water. The mixture was sealed and a stream of nitrogen gas bubbled into it below the liquid surface. The nitrogen was then passed into a tower of a solution of 2,4-dinitrophenylhydrazine (1.0695 g, 5.4 mmol) in 3 ml of concentrated hydrochloric acid and 120 ml of methanol. This solution is designated as fraction *C*. After 6 hr of stirring at room temperature with a slow flow of nitrogen, the mixture developed a white water-soluble precipitate. The mixture was poured into 400 ml of ethyl ether and the reaction flask rinsed with 4 × 5 ml of distilled water, which was added to the ether. After separation the aqueous layer was extracted with 3 × 100 ml of ethyl ether. The total ethyl ether (700 ml) designated fraction *B*, was extracted with 2 × 50 ml of distilled water. The total aqueous extracts were added to a 500-ml volumetric flask; a stream of nitrogen passed through for 15 min to remove the residual ether; and the solution was diluted to 500.0 ml with distilled water. The solution was designated fraction *A*.

*Fraction A: Periodate titration.* Titrations were carried out in quadruplicate to determine the excess periodate. To a 20.00-ml aliquot were added in the following order: 10.00 ml of 0.06204 *M* sodium arsenite standard solution, 0.2 g of potassium bicarbonate, 0.2 of potassium iodide, and 2 ml of 2% aqueous starch solution. The resulting solution was titrated with a potassium iodide–iodine solution, the molarity (0.0500 *M*) of which had been determined about 2 hr before use. The four aliquots required 5.42, 5.45, 5.42, and 5.42 ml of the iodine solution (5.43 ml average). A control reaction performed in the same way but without glycol consumed 4.38% of the total periodate.

Calculations: (10.00 ml × 0.06204 *M*) − (5.43 ml × 0.0500 *M*) = 0.3489 mmol; 0.3489 mmol of arsenite is equivalent to the millimoles of excess periodate; 0.3489 × 500/20 (aliquot factor) = 8.723 mmol of excess periodate; 13.091 (total millimole of periodate) × 0.0438 = 0.574; 13.096 − (8.723 + 0.574) = 3.799 mmol of periodate consumed by the glycol (theoretical 3.28 mmol); 100 × 3.799/3.28 = 115% complete.

Three other experiments performed in the same way gave 76, 109, and 78%. Thus the reaction is 75–100% complete, on the basis of periodate titrations.

*Fraction B: Methyl 3,7-dimethyl-deca-2,6-dien-10-onoate* (**29**). The ethereal portion (700 ml) was dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to dryness, giving 738 mg (106% recovery) of a pale yellow oil. A portion (164.2 mg) was flushed through a column of silica gel (16 g, 1.5 × 15 cm) in 250 ml of benzene : ethyl ether 80 : 20, which, when evaporated under reduced pressure, gaven 146.8 mg (89.5% of theoretical). A portion of the chromatographed aldehyde **29** (126.2 mg) was microdistilled for analytical data, yielding 120.8 mg (85.6% of theoretical) of a clear colorless oil, bp 95–105° (0.02 mm). The ultraviolet maximum (95% ethanol) was 218 m$\mu$ ($\epsilon$ = 14,300). The liquid

TABLE 9

| Peak | Assignment |
|---|---|
| 0.35 $\tau$, triplet, $J$ = 1.7 cps, 0.9H | Aldehyde hydrogen |
| 4.44 $\tau$, 1.0H | Olefinic hydrogen in the conjugated ester |
| 4.90 $\tau$, 1.0H | Olefinic hydrogen in the central carbon–carbon double bond |
| 6.40 $\tau$, 3.0H | Methyl ester hydrogens |
| 7.64 $\tau$, triplet, $J$ = 5 cps, and doublet, $J$ = 1.7 cps, 3.7H | Two hydrogens on the carbon $\beta$ to the aldehyde, and allylic methylene hydrogens |
| 7.89 $\tau$, doublet, $J$ = 1.4 cps, 6.8H | Allylic methyl group hydrogens in the conjugated ester and allylic methylenes |
| 8.40 $\tau$, doublet, $J$ = 2 cps, 3.0H | Allylic methyl group hydrogens in the central double bond |

film infrared spectrum showed the following: an aldehyde hydrogen peak at 2720 cm$^{-1}$; a single carbonyl peak at 1718 cm$^{-1}$; conjugated carbon–carbon double-bond peak at 1641 cm$^{-1}$; carbon–oxygen stretching vibrations at 1220 and 1142 cm$^{-1}$. The nmr spectrum in carbon tetrachloride contained peaks assigned as indicated in Table 9.

*Anal.* Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.39; H, 8.96.

*Fraction C: Acetone-2,4-dinitrophenylhydrazone*. The methanolic 2,4-dinitrophenylhydrazine was diluted with 25 ml of distilled water and evaporated under reduced pressure to about 30 ml. This residue was diluted with 300 ml of ethyl ether and extracted with 2 × 50 ml of 25% aqueous sodium chloride. A reddish solid obtained from the ether layer was flushed with 300 ml of benzene through a column of silicic acid (100 g, 1.3 × 27 cm) eluting 550 mg (70% crude) of orange solid, the 2,4-dinitrophenylhydrazone. In three other runs of the reaction crude yields of 57 to 99% were obtained. The material isolated in 57% yield was recrystallized twice. Its mp 121.5–122.5° and mixed mp 120.5–123° with authentic acetone-2,4-dinitrophenylhydrazone, mp 120.5–124° were identidal and undepressed.

### *Phosphoric Acid Catalyzed Cyclization of Methyl 10,11-Oxidofarnesate* (**9**)

*Cyclization procedure A (fast stir)*. Over a period of 5 min *trans,trans*-epoxide **9** (1.442 g, 5.42 mmol) was added dropwise to 25 ml of vigorously stirring 85% phosphoric acid at 0°. The ice bath was removed, and the red mixture was stirred rapidly at room temperature for 105 min. The mixture was poured into 300 ml of distilled water, and extracted with 200 ml, then 50 ml of ethyl ether. The total ethyl ether solution (~250 ml) was dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to dryness, yielding 1.372 g of yellow oil.

*Isolation of methyl 3-ketobicyclofarnesates* (**31–33**). The crude cyclization product (1.372 g) was chromatographed on silica gel · 10% water (110 g, 2.6 × 29 cm). The column was eluted with pentane : ethyl ether 95 : 5 (500 ml); 90 : 10 (500 ml); 85 : 15 (500 ml); and 80 : 20 (500 ml). These fractions were discarded. Elution with 1000 ml of pentane : ethyl ether 70 : 30 yielded after evaporation under reduced pressure to dryness 701 mg (50% crude) of hydroxyester $XIX_P$. To a solution of this material (701 mg, 2.65 mmol) in 30 ml of glacial acetic acid, a solution of chromium trioxide (295 mg, 2.95 mmol) in 15 ml of glacial acetic acid was added over a period of 10 min. After being stirred for 3.5 hr at room temperature, the mixture was diluted with 2 ml of methanol, and the resulting solution was evaporated under reduced pressure to dryness. The green residue was added to 50 ml of ethyl ether and extracted with 50 ml of dilute aqueous sodium chloride and then with 50 ml of distilled water. The combined aqueous layers were reextracted with 10 ml of ethyl ether. The total ethyl ether (~60 ml) was dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to dryness, yielding 606 mg of yellow oil. A solution of this material (606 mg, 2.29 mmol) in 10 ml of methanol, 1 ml of distilled water, and sodium hydroxide (700 mg, 17.5 mmol) were refluxed for 2 hr. The reaction mixture was then diluted with 50 ml of ethyl ether and extracted with 3 × 100 ml of 10% aqueous potassium carbonate and 100 ml of 25% aqueous sodium chloride. The combined aqueous layers were reextracted with 50 ml of ethyl ether. The total ethyl ether (~100 ml) was dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to dryness, yielding 144 mg (10%) of yellow oil. On a vpc using a 2-m ¼-in. Perkin–Elmer #Z column at 200° and 15 lb helium pressure with a flame ionization detector, this material showed two peaks: 5.7 min (61.8%) assigned the α-axial isomer **32**; and 7.4 min (38.2%), assigned a mixture of the α-equatorial isomer **31** and the β-isomer **33**.

*Reduction of methyl 3-ketobicyclofarnesate* **32** *to 3-hydroxy-epidrimenol* (**21b**). A solution of methyl 3-ketobicyclofarnesate (137 mg, 0.52 mmol) of isomer ratio **32**: **31–32** 62: 38 in 10 ml of dry ethyl ether cooled to 15° was mixed with lithium aluminum hydride (151.6 mg, 4.0 mmol). After the mixture had been stirred at room temperature for 12 hr, 3 ml of saturated aqueous sodium potassium tartrate was added, and the ether was decanted. After extraction with a small amount of water, the ether solution was dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to dryness, yielding 111 mg of viscous oil. The oil was dissolved in 3 ml of methylene chloride and 6 ml of hexane and stored at −10° overnight. The crystals which had deposited were filtered off, affording 19 mg, mp 142–147°. After one recrystallization 10.0 mg of crystals, mp 149.5–150°, were obtained. A mixed mp 148.5–149.5° of this compound with authentic diol **21b**, mp 144.0–148.5°, was undepressed. The infrared spectra of these compounds were identical in every respect.

*Cyclization procedure B* (*slow stir*). To 50 ml of very slowly stirring 85% phosphoric acid at 0° was added *trans,trans*-epoxide **9** (2.012 g, 7.56 mmol) dropwise over a period of 35 min. The resulting pale red mixture was stored at 0° for 30 min without stirring. The ice bath was removed, and the mixture was stirred slowly at room temperature for 2 hr. The dark mixture was poured into 550 ml of distilled water and extracted with 3 × 100 ml of ethyl ether. The total ethyl ether (~300 ml) was dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to dryness leaving 1.990 g of oily yellow residue.

*Isolation of methyl 3-hydroxybicyclofarnesate* **34** and **35**. A portion of the crude cyclization product (519.6 mg, 1.96 mmol) was dissolved in 25 ml of reagent methanol and 10 drops of water. After addition of potassium hydroxide (1.030 g, 18.4 mmol), the mixture was refluxed for 3 hr. The yellow solution was diluted with 10 ml of distilled water and evaporated under reduced pressure to 10 ml. The residue was poured into 50 ml of ethyl ether and extracted with 2 × 100 ml of 10% aqueous potassium carbonate and 25 ml of 25% aqueous sodium chloride. The aqueous portions were reextracted with an additional 50 ml of ethyl ether. The total ethyl ether extract (~100 ml) was dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to dryness, yielding 183.7 mg of nonsafonified ester. A portion of this residue (73.2 mg) was purified by preparative TLC, one plate (20 × 20 cm), silica gel GF (1 mm), with benzene : ethyl acetate 40: 10. After detection in bright light the opaque band at $R_f$ 0.20–0.05 was removed and eluted with 5 × 25 ml of methanol, to yield 41.2 mg (20%) of purified hydroxybicycloester. The yield from several runs varied within the range 20–28%.

*Methyl 3-ketobicyclofarnesate.* The mixture of hydroxyesters **34** and **35** (41.2 mg, 0.156 mmol) was dissolved in 1.5 ml of acetone, cooled to 0°, treated with 10 drops of Jones reagent, and stirred at 0° for 15 min. The mixture was poured into 50 ml of ethyl ether and extracted with 2 × 100 ml of 10% aqueous sodium chloride. The aqueous layers were reextracted with 50 ml of ethyl ether. The total ethyl ether (~100 ml) was dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to dryness. The residue was flushed through a column of activity VI neutral alumina (1.5 g, 7 × 31 mm) with 25 ml of pentane, yielding 38.1 mg of oil. Microdistillation afforded 36.8 mg (89.5%) of clear colorless oil, bp 95–100° (0.02 mm). A vpc of the oil using a 2-m ¼-in. Perkin–Elmer FS-1265 column at 200° and 15 lb of helium pressure with a flame ionization detector showed two peaks and a shoulder: 32.2 min (13%), assigned the $\alpha$-axial isomer **32**; 40.0 min (72.5%), assigned the $\alpha$-equatorial isomer **31**; and 44.2 min (~14.5%), assigned the $\beta$-isomer **33**.

*Isolation of the major by-products of the cyclization.* A portion of the crude cyclization product (868 mg) was chromatographed on silica gel · 10% water (45 g, 1.9 × 23 cm) and eluted as given in Table 10. The TLC of fractions A–D using one plate (5 × 20 cm), silica gel GF (0.25 mm), benzene : ethyl acetate 50 : 10 showed the following:

*A* one spot, $R_f$ 0.76–0.65, uv active, dark spot with iodine.

*B* three spots: $R_f$ 0.73–0.67, uv active, faint spot with iodine; $R_f$ 0.61–0.56, faint spot with iodine; $R_f$ 0.46–0.39, uv active, faint spot with iodine.

*C* two main spots, $R_f$ 0.36–0.26, uv active, dark spot with iodine and $R_f$ 0.26–0.10, dark spot with iodine; traces at $R_f$ 0.63–0.53, 0.46–0.39.

*D* one spot, $R_f$ 0.26–0.10, faintly uv active, dark spot with iodine; trace at origin.

Fractions *A* and *D* were not identified.

*Fraction B: 2,2,4-Trimethyl-3-(trans-4-carbomethoxy-3-methyl-1-but-3-enyl)-1,4-endoxycyclohexane* (**36**). Fraction *B* (121 mg) was purified by preparative TLC, two plates (20 × 20 cm), silica gel GF (1 mm), using benzene : ethyl acetate 100 : 18. The uv active band at $R_f$ 0.50–0.39 was eluted with 5 × 20 ml of methanol yielding 49.5 mg (6%) of clear colorless oil. The nmr spectrum of this material in carbon tetrachloride was identical to the nmr of fraction *C* from the boron trifluoride cyclization (*vide infra*), and is therefore the bridged oxide **36**. Yields in two runs were 6 and 10%.

*Fraction C: 2,2,4-Trimethyl-3-(trans-4-carbomethoxy-3-methyl-1-but-3-enyl)-1-hydroxycyclohex-3-ene* (**37**). Fraction *C* (95.5 mg) was purified by continuous

TABLE 10

| Fraction | Solvent | | Weight (mg) | % (weight/8.68 mg) |
|---|---|---|---|---|
| *A* | Benzene | 500 | 176 | 20.4 |
| *B* | Benzene : ethyl ether 1% | 600 | 121 | 14.0 |
| *C* | Benzene : ethyl ether 4% | 600 | 246 | 28.4 |
| *D* | Ethyl ether | 500 | 317 | 36.7 |

preparative TLC, two plates (20 × 20 cm), silica gel GF (1 mm), using benzene : ethyl acetate 50 : 5 for 3 hr. The uv active band, pseudo-$R_f$ 0.40–0.27, was carefully scraped away, yielding 37.3 mg after elution with 7 × 15 ml of methanol. This corresponds to a yield of 11% of hydroxymonocycloester **37**. A continuous TLC using benzene : ethyl acetate 50 : 1 for 30 hr gave one uv active spot, pseudo-$R_f$ 0.94–0.78, and a trace at $R_f$ 0.62–0.53, detected with iodine vapor. The ultraviolet maximum (95% ethanol) was 215 m$\mu$ ($\epsilon = 7640$), indicating that the monocyclic alcohol **37** (total yield ~6%) was about 50% pure (see section below).

### *Boron Trifluoride-etherate Catalyzed Cyclization of Methyl 10,11-Oxidofarnesate* **9**

*Cyclization procedure.* A solution of *trans,trans*-epoxide **9** (2.045 g, 7.69 mmol) in 160 m of anhydrous distilled benzene was stirred for 23 hr at room temperature with anhydrous distilled, but pale yellow, boron trifluoride-etherate (1.09 g, 7.69 mmol). The yellow solution was poured into 50 ml of ethyl ether and extracted with 200 ml of 10%, then 100 ml of 25% aqueous sodium chloride. The total ethyl ether (260 ml) was dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to dryness yielding 2.079 g of a pale yellow oil. Its TLC (benzene : ethyl acetate 50 : 10) showed six distinct spots: $R_f$ 0.65, 0.56, 0.42, 0.26, 0.22, 0.18.

*Isolation of methyl 3-hydroxybicyclofarnesates* **34** and **35**. A portion (514 mg) of the crude product was dissolved in 25 ml of reagent methanol and 10 drops of distilled water. After addition of potassium hydroxide (846 mg) the mixture was refluxed 2 hr. The solution was then diluted with 10 ml of distilled water and evaporated under reduced pressure to about 10 ml. The residue was poured into 50 ml of ethyl ether and extracted with 2 × 100 ml of 10% aqueous potassium carbonate and 25 ml of 25% aqueous sodium chloride. The aqueous portions were reextracted with a second 50 ml of ethyl ether. The total ethyl ether (~100 ml) was dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to dryness yielding 182.9 of unsaponified ester. A comparison of this ester with the crude cyclization product by TLC suggested that saponification was incomplete. Therefore the ester (182.9 mg) was dissolved in 10 ml of reagent methanol and 5 drops of distilled water. This solution was refluxed for 1 hr with potassium hydroxide (396 mg) and extracted as before to yield 155.4 mg (30.2%) of nonsaponifiable ester. Thin-layer chromatography with benzene : ethyl acetate 50 : 10 showed one main spot, $R_f$ 0.21, and three traces, $R_f$ 0.68, 0.49, and 0.30. That the main spot contained a hydroxyl group was ascertained by a thin-layer experiment in which two spots of the nonsaponifiable ester were placed on the same plate about 2 cm apart. On one of the spots were added 2 drops of acetyl chloride. The other spot was untreated. The plate was placed at 90° for 5 min and developed in benzene : ethyl acetate 50 : 10. Iodine vapor detection showed the acetylated spot, $R_f$ 0.42, to be less polar than the nonacetylated spot, $R_f$ 0.21. A portion (70.9 mg) of the nonsaponifiable ester was purified by preparative TLC, one plate (20 × 20 cm), silica gel GF (1 mm), using benzene : ethyl acetate 50 : 10. After detection in bright light the opaque band at $R_f$ 0.1–0.3 was removed and eluted with 5 × 25 ml of reagent methanol to yield a colorless oil (53 mg, which corresponds to an overall yield of hydroxybicycloester of 22.6%). A TLC of this material with benzene : ethyl acetate 50 : 10 showed one spot, $R_f$ 0.21.

*Reduction of methyl 3-hydroxybicyclofarnesate* **34** *to 3-hydroxydrimenol* **(20b)**. A portion of the hydroxyester mixture **34–35** (48 mg, 0.018 mmol) was dissolved in 20 ml of dry ethyl ether, and lithium aluminum hydride (74 mg, 1.95 mmol) was added. The mixture was stirred at room temperature for 8 hr; 10 drops of saturated aqueous sodium potassium tartrate were added; and the mixture was filtered. The ether was evaporated under reduced pressure to dryness, giving 33.8 mg of a glassy residue, which was dissolved in 0.20 ml of benzene and stored at room temperature for 5 days. The crystalline rosettes were filtered off and dried on high vacuum for 24 hr, giving 16 mg (33%), mp 110–111°. After one recrystallization 11.7 mg gave 10.0 mg of crystals, mp 112.5–113°. A mixed mp 111.5–112° of this compound with authentic 3-hydroxydrimenol, mp 113–114°, was undepressed, Infrared spectra of the two compounds using potassium bromide pellets were identical in every respect.

*Methyl 3-ketobicyclofarnesate.* To a solution of hydroxyester **34** (53 mg, 0.020 mmol) in 1.5 ml of reagent acetone stirring at 0° was added 10 drops of Jones reagent. The mixture was stirred at 0° for 15 min, poured into 50 ml of ethyl ether, and extracted with 2 × 100 ml of 10% aqueous sodium chloride. The aqueous layers were reextracted with 50 ml of ethyl ether. The total ethyl ether extract (~100 ml) was dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to dryness. The residue was flushed through a column of activity VI neutral alumina (1.5 g, 7 × 30 mm) and eluted with 25 ml of distilled pentane, yielding 53 mg of a pale yellow oil. This product was microdistilled, bp 90–100° (0.01 mm), yielding 46.9 mg (88.5%) of clear colorless oil. Thin-layer chromatography with benzene : ethyl acetate 50 : 10 showed one spot, $R_f$ 0.42. Analysis by vpc using a 2-m $\frac{1}{4}$-in. Perkin–Elmer FS-1265 column at 200° and 15 lb helium pressure with a flame ionization detector showed the following: a trace peak at 18 min (unidentified); a trace peak at 22.0 min (unidentified); a peak (6.6%) at 24.5 min (unidentified); a peak (2.2%), the α-axial isomer **32**; a peak (91.2%) at 38.9 min, the α-equatorial isomer **31**; and a shoulder at 44 min, the β-isomer **33.**

*Anal.* Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.23; H, 8.82.

In a separate experiment a mixture of the ketobicycloesters were separated by preparative vpc using a 20-ft $\frac{1}{2}$-in. 20% SE-30 column on the Aerograph A-90 at 210° and 40 lb helium pressure. Before separation the ratio of **32 : 31 : 33** was to 31 : 62 : 7. The isomers (413 mg total) were separated and collected yielding 159 mg of pure methyl α-equatorial-3-ketobicyclofarnesate **31**, mp 74.8–75.2°, and 89 mg of pure methyl α-axial-3-ketobicyclofarnesate **32**, mp 106.8–107.5°. The liquid film infrared spectrum of ketoester **31** showed a shoulder at 1715 $cm^{-1}$ and a peak at 1700 $cm^{-1}$, while the liquid film infrared spectrum of ketoester **32** showed peaks at 1718 and 1698 $cm^{-1}$. The nmr spectra in carbon tetrachloride contained peaks assigned as shown in Table 11.

*Reduction of methyl 3-ketobicyclofarnesate* **31** *to 3-hydroxydrimenol* **(20b)**. A mixture of ketoester **31** (14.8 mg, 0.056 mmol) and lithium aluminum hydride (23 mg, 0.61 mmol) in 10 ml of dry ethyl ether was stirred at room temperature for 5.5

TABLE 11

| Peak | Assignment |
|---|---|
| Ketoester **31** | |
| 4.48 τ, 0.9H | Olefinic hydrogen |
| 6.36 τ, 3.0H | Methyl ester hydrogens |
| 7.14 τ, 1.0H | Hydrogen on the carbon α to the carbomethoxy group |
| 8.40 τ, 4.9H | Allylic methyl group and methylene hydrogens |
| 8.87, 8.92, 8.98 τ, 9.3H | *gem*-Dimethyl and angular methyl groups |
| Ketoester **32** | |
| 4.47 τ, 0.9H | Olefinic hydrogen |
| 6.40 τ, 3.0H | Methyl ester hydrogens |
| 7.50 τ, 1.0H | Hydrogen on the carbon α to the carbomethoxy group |
| 8.38 τ, 3.5H | Allylic methyl group |
| 8.88 and 8.96 τ, 9.1H | *gem*-Dimethyl and angular methyl groups |

hr, after which 3 drops of saturated aqueous sodium potassium tartrate were added. The mixture was filtered and evaporated under reduced pressure to dryness, affording 12 mg of a viscous oil. This oil was dissolved in 0.10 ml of benzene and stored at room temperature, yielding crystalline rosettes after 2 days. The crystals were filtered and dried on high vacuum giving 8 mg (54%), mp 110–110.5°. A mixed mp 110.5–112° of this compound with 3-hydroxydrimenol, mp 112–114°, was undepressed. The infrared spectra of the two compounds in potassium bromide pellets were identical in every respect.

*Isolation of the major by-products of the boron trifluoride-etherate catalyzed cyclization.* The remainder of the boron trifluoride catalyzed cyclization product (1.557 g) was chromatographed on silica gel · 10% water (80 g, 2.2 × 28.5 cm). The fraction size was 125 ml and five separate weight peaks were eluted (see Table 12). The TLC of fractions *A*–*E* using one plate (5 × 20 cm), silica gel GF (0.25 mm), benzene : ethyl acetate 50 : 10 (iodine vapor) showed the following:

*A* one spot, $R_f$ 0.53, uv active (unidentified).

*B* main spot, $R_f$ 0.44, uv active; minor spot, $R_f$ 0.29.

TABLE 12

| Fraction | Solvent | Weight (mg) | % (weight/15.57 mg) |
|---|---|---|---|
| 1–5 (*A*) | Benzene | 108 | 7.0 |
| 6–13 (*B*) | Benzene | 263 | 17.0 |
| 14–23 (*C*) | Benzene : ethyl ether 0.9% | 471 | 30.0 |
| 27–36 (*D*) | Benzene : ethyl ether 2–3% | 357 | 23.0 |
| 45–63 (*E*) | Benzene : ethyl ether 4–25% | 189 | 12.0 |

*C* one spot, $R_f$ 0.28, uv active; trace at $R_f$ 0.22, uv active.
*D* two spots, $R_f$ 0.22, uv active and $R_f$ 0.18, not uv active.
*E* one spot, $R_f$ 0.15, partially uv active (unidentified).

*Fraction B: Methyl trans-trans-3,7,11-Trimethyldodecan-2,6-dien-10-on-oate* (**38**). Fraction *B* (263 mg) was purified by preparative TLC, four plates (20 × 20 cm), silica gel GF (1 mm), using benzene : ethyl acetate = 100 : 25. Three uv active bands were collected: Fraction B-1, $R_f$ = 0.83–0.71, 31 mg; Fraction B-2, $R_f$ = 0.70–0.63, 145 mg; Fraction B-3, $R_f$ = 0.61–0.50, 72 mg. Comparison of Fractions A and B-1 using TLC suggested that they were identical and both (total yield = 9%) were discarded.

Fraction *B-2* was microdistilled, yielding 134 mg of clear colorless oil, bp 90–100° (0.02 mm). A vpc of the distillate using a 2 m, ⅛-in Perkin–Elmer FS-1265 column at 200° and 15 lb helium pressure with a flame ionization detector showed one peak at 32.4 min. In an earlier experiment methyl farnesate of isomer ratio *cis,trans* : *trans,trans* 9.5 : 90.5 was converted to the monoepoxide and cyclized by the same procedure as pure *trans,trans*-methyl farnesate. By chromatography, material corresponding to fraction *B*-2 was isolated. A vpc of this material using conditions identical to those used for fraction *B*-2 showed two peaks: 27.8 min (9.4%) and 32.4 min (90.6%). Therefore the single peak corresponding to fraction *B*-2 is the *trans,trans* compound. The ultraviolet maximum (95% ethanol) was 218 m$\mu$ ($\epsilon$ = 15,200). The liquid film infrared spectrum revealed the following: no hydroxyl absorption, a single carbonyl peak at 1710 cm$^{-1}$, and a conjugated carbon–carbon double bond peak at 1642 cm$^{-1}$. The nmr spectrum in carbon tetrachloride contained peaks assigned as shown in Table 13.

*Anal.* Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 71.76; H, 9.70.

The presence of a ketone was further demonstrated by sodium borohydride reduction of fraction *B*-2. A mixture of fraction *B*-2 (16.5 mg, 0.062 mmol) and sodium borohydride (15.7 mg, 0.51 mmol) in 1.0 ml of reagent methanol and one drop of water was stirred for 1 hr at room temperature. By TLC using benzene : ethyl acetate 50 : 10 the reaction mixture showed one uv active spot, $R_f$ 0.40–

TABLE 13

| Peak | Assignment |
|---|---|
| 4.41 $\tau$, 1H | Olefinic hydrogen on the conjugated ester |
| 4.92 $\tau$, 1H | Olefinic hydrogen in the central carbon–carbon double bond |
| 6.39 $\tau$, 3H | Methyl ester hydrogens |
| 7.4–7.75 $\tau$, ~6H | Hydrogens on carbon $\beta$ to a ketone and allylic methylene hydrogens |
| 7.88 $\tau$, doublet, $J$ = 2 cps, ~5H | Allylic methyl hydrogens on the conjugated ester |
| 8.40 $\tau$, 3H | Allylic methyl hydrogens of the central carbon–carbon double bond |
| 8.95 $\tau$, doublet, $J$ = 7 cps, 7H | Isopropyl methyl hydrogens |

0.32, and fraction *B*-2 showed one uv active spot, $R_f$ 0.65–0.53. The reaction mixture was poured into 20 ml of ethyl ether and extracted with 25 ml of 25% aqueous sodium chloride. The ether layer was dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to dryness, yielding 16 mg of a colorless oil. The liquid film infrared spectrum of this oil showed a hydroxyl band at 3400 $cm^{-1}$, and the $\alpha,\beta$-unsaturated ester absorption at 1720 and 1640 $cm^{-1}$. The above data prove that fraction *B*-2 is *trans,trans*-methyl 3,7,11-trimethyl-10-keto-dodeca-2,6-dienoate (**38**). This compound was isoalted in a total yield of 145 mg, 9.4%.

*Fraction C: 2,2,4-Trimethyl-3-(trans-4-carbomethoxy-3-methyl-1-but-3-enyl)-1,4-endoxycyclohexane* (**36**). Fraction *C* (471 mg) was purified by preparative TLC, seven plates (20 × 20 cm), silica gel GF (1 mm), using benzene: ethyl acetate 100: 40. The main uv active band, $R_f$ 0.65–0.44, was collected yielding a colorless oil (429 mg) after elution from the silica gel with 6 × 40 ml of methanol. This oil was microdistilled, yielding 318 mg, bp 95–105° (0.02 mm). The vpc of the distillate using a 2-m ¼-in. Perkin–Elmer FS-1265 column at 200° and 15 lb helium pressure with a flame ionization detector showed one peak at 21.4 min. Material corresponding to fraction *C* and starting from methyl farnesate of isomer ratio *cis,trans* : *trans,trans* 9.5 : 90.5 was isolated previously (*vide supra*). A vpc of this material using conditions identical to those used for fraction *C* showed two peaks: 14.7 min (9.6%) and 21.4 min (90.4%). Therefore fraction *C* corresponds to the trans compound. The ultraviolet maximum (95% ethanol) was 219 mμ ($\epsilon$ = 14,500). The liquid film infrared spectrum displayed: no hydroxyl absorption; a carbonyl peak at 1714 $cm^{-1}$, and conjugated carbon–carbon double-bond absorption at 1641 $cm^{-1}$; a broad band at 1000 $cm^{-1}$. This band is not present in any other compound in these studies and may be attributed to a bridged oxide system. The nmr spectrum in carbon tetrachloride contained peaks assigned as indicated in Table 14.

*Anal.* Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.01; H, 9.76.

The isolated amounts of **36** are 72 mg of fraction *B*-3 and 429 mg of fraction *C*, corrsponding to a total yield of 32.3%.

*Fraction D: 2,2,4-Trimethyl-3-(trans-4-carbomethoxy-3-methyl-1-but-3-enyl)-1-hydroxycyclohex-3-ene* (**37**). Fraction *D* (357 mg) was dissolved in 10 ml of reagent methanol and 10 drops of water; potassium hydroxide (750 mg) was added, and

TABLE 14

| Peak | Assignment |
|---|---|
| 4.41 τ, 1H | Olefinic hydrogen in the conjugated ester |
| 6.38 τ, 4H | Methyl ester hydrogens and 1H due to the hydrogen on carbon bearing oxygen |
| 7.87 τ, ~4H, doublet, $J$ = 1.6 cps | Allylic methyl hydrogens on the conjugated carbon–carbon double bond |
| 8.73 τ, 2.8H | Methyl group attached to carbon bearing oxygen |
| 8.95 and 9.01 τ, 6H | *gem*-Dimethyl group |

TABLE 15

| Peak | Assignment |
|---|---|
| 4.42 $\tau$, 0.5H | Olefinic hydrogen in the conjugated ester |
| 4.80 $\tau$, 0.7H | Olefinic hydrogen in the ring |
| 5.17 $\tau$, 0.5H | Unknown; perhaps exocyclic olefinic hydrogen |
| 6.39 $\tau$, 3H | Methyl ester hydrogens |
| 6.67 $\tau$, 0.8H, triplet, $J = 7$ cps | Hydrogen on carbon bearing oxygen |
| 7.01 $\tau$, 0.9H | Hydroxyl hydrogen |
| 7.84 $\tau$, 4.3H | Allylic methyl group in the conjugated ester |
| 8.30 and 8.40 $\tau$, 4.3H | Allylic methyl group in ring, perhaps two isomers |
| 8.96 and 9.06 $\tau$, 4.7H | *gem*-dimethyl group |
| 9.2 $\tau$, 0.9H | Unknown |

the mixture was refluxed for 1 hr. It was evaporated to ~1 ml, dissolved in 50 ml of ethyl ether, and extracted with 2 × 100 ml of 10% aqueous potassium carbonate. The aqueous layers were combined and reextracted with 30 ml of ethyl ether. The total ethyl ether (~80 ml) was dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to dryness, yielding 246 mg of nonsaponifiable ester, identified as methyl 3-hydroxybicyclofarnesate. The aqueous layer was acidified to pH 1 with 35 ml of 85% phosphoric acid and extracted with 2 × 50 ml of ethyl ether. The ether was dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure, yielding 93 mg of acid. The product was dissolved in 2 ml of methanol and 2 ml of ethyl ether, cooled to 0°, and treated with excess ethereal diazomethane. After 4 hr at room temperature the yellow solution was evaporated to dryness, yielding 102 mg (6.6%) of ester, which was purified by preparative TLC, two plates (20 × 20 cm), silica gel GF (1 mm), using benzene : ethyl acetate 60 : 40. The uv active band, $R_f$ 0.53–0.43, was eluted with 5 × 25 ml of methanol, and subsequent evaporation under reduced pressure yielded 70 mg. This material (63 mg) was microdistilled, yielding 59.5 mg (7%) of clear colorless oil, bp 90–100° (0.02 mm). The ultraviolet spectrum (95% ethanol) shows only continuous absorption: at 218 m$\mu$, $\epsilon = 6900$. The liquid film infrared spectrum shows strong hydroxyl absorption at 3400–3500 cm$^{-1}$, and the $\alpha,\beta$-unsaturated ester absorption at 1720 and 1640 cm$^{-1}$. The nmr spectrum in carbon tetrachloride contains peaks assigned as shown in Table 15.

*Anal.* Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 71.83; H, 9.75.

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