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Cyclization Studies with 14,15-Oxidogeranylgeranyl Acetate

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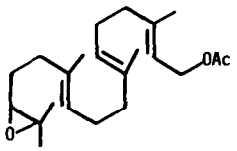
As a model for more elaborate biogenetic-type syntheses of naturally occurring 3-hydroxylated tetra- and pentacyclic terpenoids, the acid-induced cyclization of 14,15-oxidogeranylgeranyl acetate (**1**) was studied. Through stannic chloride catalysis, the epoxide **1** was transformed into the tricyclic diol monoacetate **12**, along with monocyclic ketone **29**, acyclic chlorohydrin **32**, and bridged 1,4-oxide **33**. The structure and stereochemistry assigned to the tricycle **12** were confirmed by conversion to a reduction product, monoacetate **26**, which was indistinguishable on spectral grounds from a substance obtained by an independent synthesis starting from manoöl (**17**).

Investigations into the reactivity of 6,7-oxidofarnesyl acetate and methyl 6,7-oxidofarnesate revealed that models for the *A–B* portion of many polycyclic terpenoids, including four relevant asymmetric centers, can be produced stereoselectively when nonenzymic, biogenetic-type cyclizations of these epoxides occur (*1*). It was of interest to us to inquire whether this reaction mode is applicable to higher terpenoid cases, especially since such extension would bode well for the successful development of biogenetic-type total synthesis of various naturally occurring tetra- and pentacyclic triterpenoids, including e.g. lanosterol. In particular, in the generation of more than two new rings and any additional attendant chiral centers, would the process continue to enjoy overall the stereospecificity characteristic of the simpler model reactions? Toward this end, we elected to study the cyclization of *dl*-14,15-oxidogeranylgeranyl acetate (**1**) which, it was hoped, would be transformed into a hydrophenanthrene with up to six asymmetric



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centers. This case is especially biologically pertinent, in that the terminal epoxide of geranylgeraniol is a natural product and may be the progenitor of various 3-hydroxylated polycyclic diterpenoids, such as darutigenol and araucarol.

Of prime importance in planning a synthesis of epoxide **1** was consideration of methods which would ultimately yield a pure isomer with the desired geometry,

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namely, all trans. The problem involving the geometry of two of the three olefinic bonds was solved by using as a starting material the available *trans,trans*-farnesol (**2**). The synthetic sequence leading from farnesol to the desired diterpene terminal epoxide (**1**) involved 10 steps, and is outlined in Chart 1.

Farnesyl bromide (**3**) can be made by either of two commonly used methods. A procedure used previously in our laboratories for this transformation involved treatment of **2** with 48% hydrobromic acid in hexane at 0°. Since this method, however, was suspected of producing at least a small amount of isomerization, the phosphorous tribromide method for making bromides was assyed (*2*). Farnesyl bromide samples originating from each of the two procedures were then converted

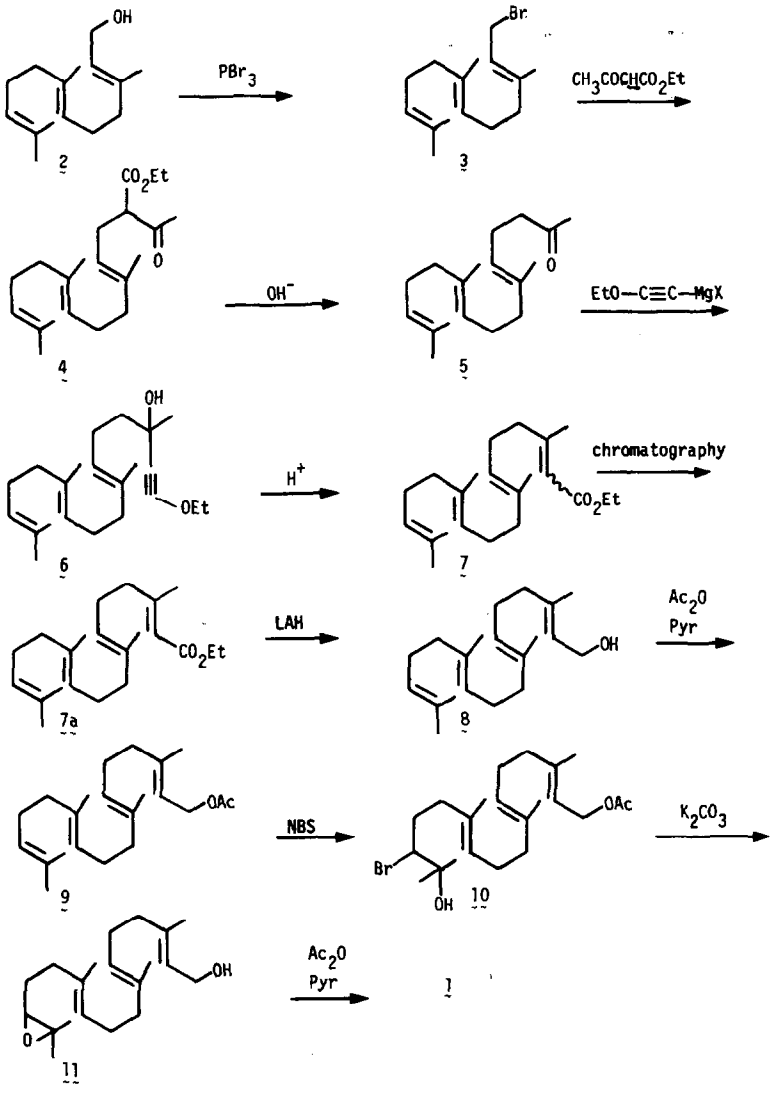
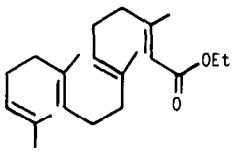


CHART 1

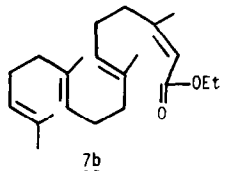
to methyl ethers and analyzed by gas–liquid chromatography (GLC). The hydrobromic acid product was contaminated with about 5% of an impurity presumed to have resulted from isomerization. Although the phosphorus tribromide product also contained this impurity, it was present only in trace quantity (<1%).

With pure farnesyl bromide in hand, we proceeded to the next step, one which involved introduction of three of the five new carbon atoms necessary to produce the C_{20} geranylgeraniol system. Acetoacetic ester anion displacement on farnesyl bromide, essentially the same method used previously to synthesize farnesyl acetone (**5**) as a mixture of geometrical isomers (*2*), proceeded in the expected yield of only about 50%. Instead of performing both steps (displacement followed by alkaline hydrolysis) without isolation of intermediates as published, we evaluated execution of the two steps separately, isolation and purification of the ketoester **4** and its subsequent hydrolysis. Each step proceeded in better than 90% yield, and an overall yield of 80% was realized. Samples of ketone **5** were checked for homogeneity and found to be at least 95% pure trans,trans. The retention time of the cis,trans isomer was shown to be shorter than that of the trans,trans by a GLC study of products from a parallel synthesis starting with a mixture of farnesol isomers.

The next synthetic step, a Grignard addition of ethoxyacetylene to **5**, gave an intermediate acetylenic ether (**6**) which was difficult to isolate in a highly pure state because of its facile isomerization during workup to the desired α,β-unsaturated ester, ethyl geranylgeranate (**7**). To complete the synthesis of the latter, crude **6** was stirred in ethyl alcohol containing 10% sulfuric acid. The two-step transformation (**5** → **7**) proceeded in an overall yield of 75%, the product being a mixture of equal parts of esters **7a** and **7b**, the cis,trans isomers. By preparative TLC it was possible to resolve the mixture into the two components (**7a** and **7b**). The problem of ascertaining which was the trans and which the cis isomer was solved by means of nmr spectroscopy. The protons in the methyl group on the



7a



7b

conjugated double bond in systems such as **7a** and **7b** exhibit nmr signals at different values which are characteristic of the geometry of the olefinic bond (*3*). For isomer **7a** the protons in question appear at 7.86 τ, and for **7b** at 8.13 τ. In each case the signal is a doublet with J = 1.5 cps. These data allow assignment of the trans configuration to ester **7a** and cis to ester **7b**, in excellent agreement with published values.

Lithium aluminum hydride reduction of ester **7a** provided in 95% yield *trans, trans*-geranylgeraniol (**8**). Geometric homogeneity was confirmed by GLC analysis, while nmr and ir analyses served to verify the structure. Acetylation of **8** produced a nearly quantitative yield of the corresponding acetate (**9**).

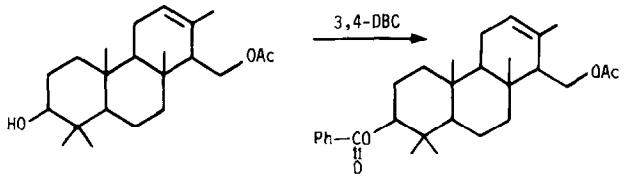
Treatment of ester **9** with 1 mole equivalent of *N*-bromosuccinimide (NBS) in a mixed solvent of tetrahydrofuran–water gave a crude product, which after purification by column chromatography yielded 48% of the desired bromohydrin, **10.** Since other work had already demonstrated the high selectivity of terminal attack by NBS in this reaction (*1*), there was little likelihood that appreciable amounts of internal bromohydrin had been formed. A significant amount of internal attack would have been revealed by the nmr spectrum of the product. The two saturated methyl groups on the carbon bearing the hydroxyl group of **10** would appear as a singlet at 8.73 τ; internal bromohydrin would possess only one such methyl group. Careful integration of the nmr spectrum of the bromohydrin product revealed that, relative to the three acetate protons at 8.06 τ and the three vinyl protons at 4.5–5.2 τ, the peak at 8.73 τ integrated for the full value of 6.0 protons.

Conversion of bromohydrin **10** to epoxide was accomplished by treatment with potassium carbonate in methanol. This reaction also hydrolyzed the acetate function, and the product isolated was *trans,trans,trans*-geranylgeraniol terminal epoxide **(11).** Reacetylation of **11** with acetic anhydride in pyridine afforded, in quantitative yield, geranylgeranyl acetate terminal epoxide **(1).**

Initial cyclization experiments were conducted with epoxide **1** in cold phosphoric acid. After 1 hr of vigorous stirring at 0°, cold water was added, and the mixture was extracted with hexane. A crude hydroxyacetate fraction (30%) could then be isolated by column chromatography. Analytical TLC showed that this fraction could be resolved into three spots, and preparative TLC made it possible to separate these three subfractions. By GLC it became evident that each of the subfractions was still a mixture. Furthermore, through nmr analysis of each subfraction, it was possible to show that none of the hydroxyacetate components of the mixtures was tricyclic.

When epoxide **1** was treated with stannic chloride in benzene near 0°, a complex mixture of products resulted which by TLC seemed similar to the mixture which resulted from the phosphoric acid reaction. Isolation of the hydroxyacetate fraction by column chromatography was followed by further refinement of this fraction by preparative TLC. Two subfractions, *E*-1 (R_f 0.32) and *E*-2 (R_f 0.30) were thus obtained. Analysis by GLC of *E*-1 indicated a complex mixture of six compounds while *E*-2 exhibited only three peaks, the major component of which had a longer retention time than any product yet encountered in this series of experiments. Analysis by nmr indicated that fraction *E*-1 was devoid of tricyclic products; however, *E*-2, though obviously a mixture, showed a distinct multiplet at 5.85–6.02 τ, indicative of *nonallylic* methylene bearing acetate, a structural unit ascribable to tricycle of the nonallylic acetate type **(12).**

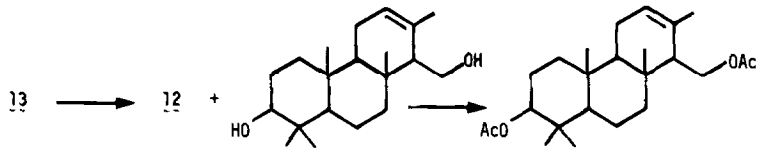
Purification of fraction *E*-2 was accomplished by conversion to a corresponding mixture of mixed 3,5-dinitrobenzoate acetates. The new diester mixture was then purified by preparative silver nitrate TLC, the 3,5-dinitrobenzoate function providing a method for detection (uv light) of the bands on the plate. Since it was expected that silver nitrate would complex more strongly with the noncyclized components in the mixture, the front running component would therefore most likely contain the compound of interest. In fact, two uv active bands appeared, *E*-2a (less polar) and *E*-2b (more polar). The nmr spectrum of *E*-2b still featured



12 13

absorption in the vinyl and vinyl methyl regions of such magnitude as to indicate a mono- or bicyclic structure. Base hydrolysis of *E*-2b followed by GLC analysis revealed a mixture of two short retention time products, identity of which was not proven.

Fraction *E*-2a from the silver nitrate purification was a crystalline diester, the nmr spectrum of which seemed consistent with the assignment of structure **13** (Table 1). Reaction of the diester with 1 mole equivalent of potassium carbonate gave mostly diol monoacetate **12** but also some of the crystalline diol **14.** Acetylation of **14** gave an oily but pure (GLC) diacetate (**15**).



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Mass spectral analysis of tricycle **14** provided at the outset good evidence for its structure. It had been shown in the resin acid series that compounds such as **16** undergo a characteristic retro-Diels fragmentation in the C ring (*4*). In addition to

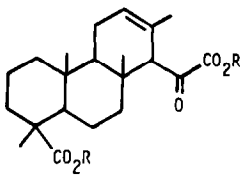

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TABLE 1

Peak (τ)		Assignment
1.78	3H	3 Phenyl hydrogens
4.59	1H	1 Vinyl hydrogen
5.18	1H	1 Benzoate ether hydrogen
5.88	2H	2 Acetate ether hydrogens
7.98	3H	3 Acetate hydrogens
8.98		
9.02	12.5H	4 Saturated methyls
9.05		

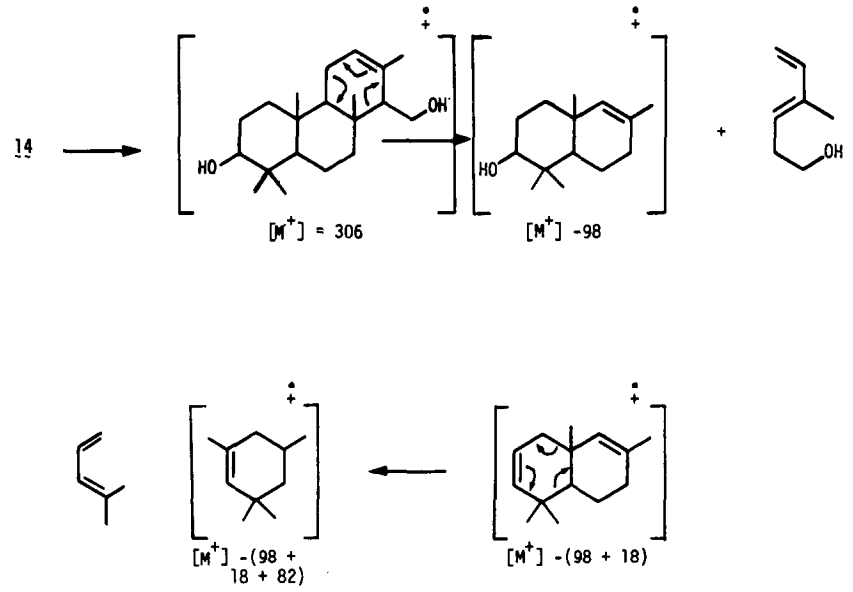


CHART 2

other peaks which are in agreement with the structure assigned, diol gave rise to a large peak corresponding to the retro-Diels fragmentation (Chart 2).

It is difficult to imagine any other structures which would fit the nmr and mass spectral evidence cited above. Since these data provide no clues as to the stereostructure of the tricyclic system, however, we set about to produce a stereochemically authentic compound for direct comparison (Chart 3). The rearranged bromide (**18**), produced by reaction of commercially available manoöl (**17**) with phosphorus tribromide, is converted, through a procedure previously described (*5*), to the corresponding acetate (**19**). Spectral data and physical constants for these compounds were in good agreement with those cited in the literature. On base hydrolysis **19** is converted to the allylic isomer of manoöl (**20**), the nmr and ir spectral characteristics of which are all consistent with the assigned structure. Chromium trioxide in pyridine was used to transform alcohol **20** to the α,β-unsaturated aldehyde, **21**, nmr and ir spectroscopy being employed to show that the aldehyde function is α,β unsaturated, as well as to demonstrate that the exocyclic double bond is still intact. Treatment of aldehyde **21** with silver oxide in ethanol gave the α,β unsaturated acid (**22**), the methyl ester (**23**) of which was then generated by reaction with diazomethane. Preparative TLC of ester **23** gave two fractions (**23a** and **23b**) in a ratio of about 2: 1. The major fraction (**23a**) was shown by its nmr behavior to consist mainly of the desired trans isomer (Table 2).

Treatment of the ester (**23a**) under strongly acidic conditions (formic–sulfuric acid) previously employed for the closely analogous cyclization of agathic ester gave a complex mixture of products (*4*). The desired tricyclic product, however, was easily separated from the mixture by selective alkaline hydrolysis, the ester function of **24** being so sterically hindered that its rate of hydrolysis is very slow. Thus, hydrolysis followed by extraction with alkali of the acidic materials left the

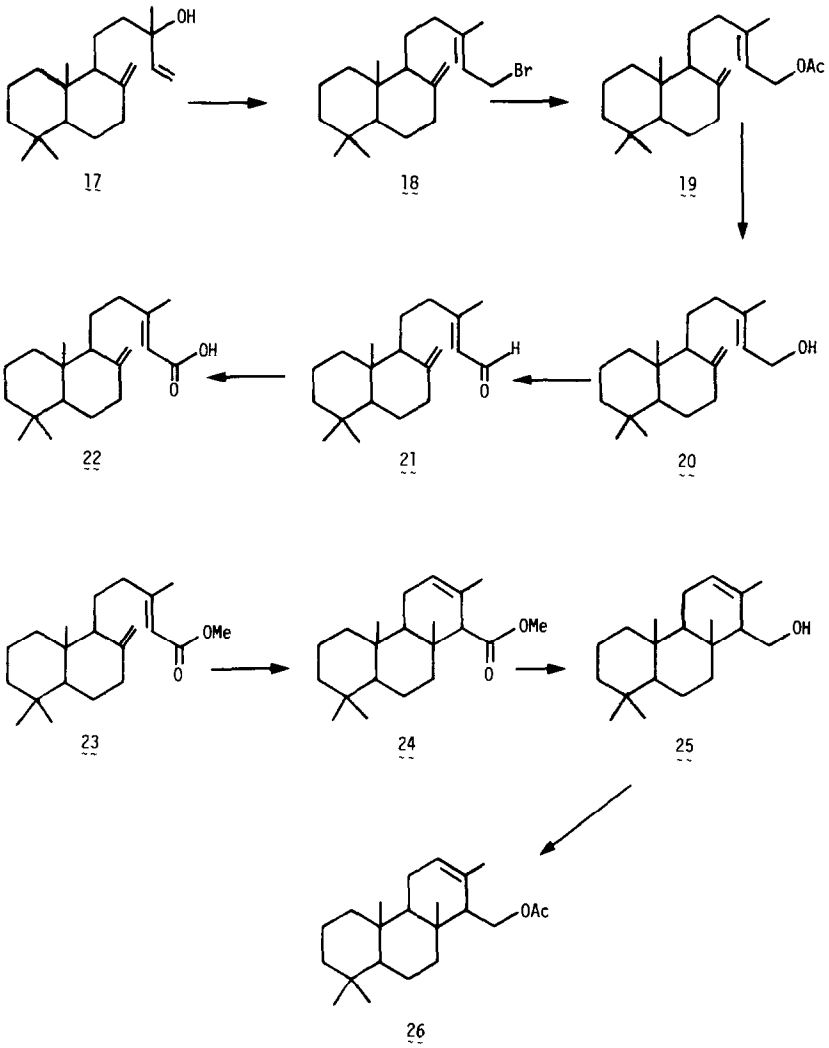


CHART 3

neutral tricyclic ester (**24**). This material was further purified by preparative TLC, and by GLC analysis was shown to be homogeneous. Infrared and nmr spectra of ester **24** were all in order (Table 3).

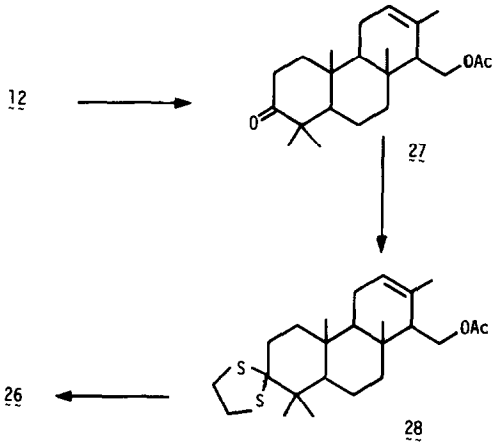
Lithium aluminum hydride reduction of **24** and subsequent treatment of the resulting alcohol (**25**) with acetic anhydride in pyridine gave a homogeneous acetate (**26**), the ir and nmr spectra of which were entirely consonant with the expected structure. Mass spectral analysis showed only a trace of the molecular ion presumably because of the facile loss of acetic acid. It should be noted that this loss results in the base peak and that the fragment left does not, unlike the parent, undergo a retro-Diels reaction.

For direct comparison with the tricyclic product (**12**) from the epoxide cyclization, the hydroxyl group was removed by conversion of **12** to the thioketal (**28**),

TABLE 2

Peak (τ)	Assignment
4.42 1H	Olefinic H_α to carbonyl
5.20	
5.52 2H	Exocyclic methylene H's
6.40 3H	O-Methyl
7.85 3H	Olefinic methyl β to carbonyl
9.13	
9.20 9H	3 Saturated methyls
9.32	

via ketone **27**, followed by Raney nickel desulfurization. After preparative TLC purification, the desulfurized product was found to be homogeneous by GLC.



Furthermore, coinjection of synthetic and cyclization derived tricycle **26**, on two different GLC systems (Apiezon-L and SE-30) resulted in appearance of a single sharp peak. Also, nmr and ir spectra of both samples were identical.

In addition to the crude hydroxyacetates (33%), a number of other fractions were isolated and classified (Table 4). For example, a ketonic fraction (28%) was identified by ir and nmr means. The nmr spectrum showed the presence of two

TABLE 3

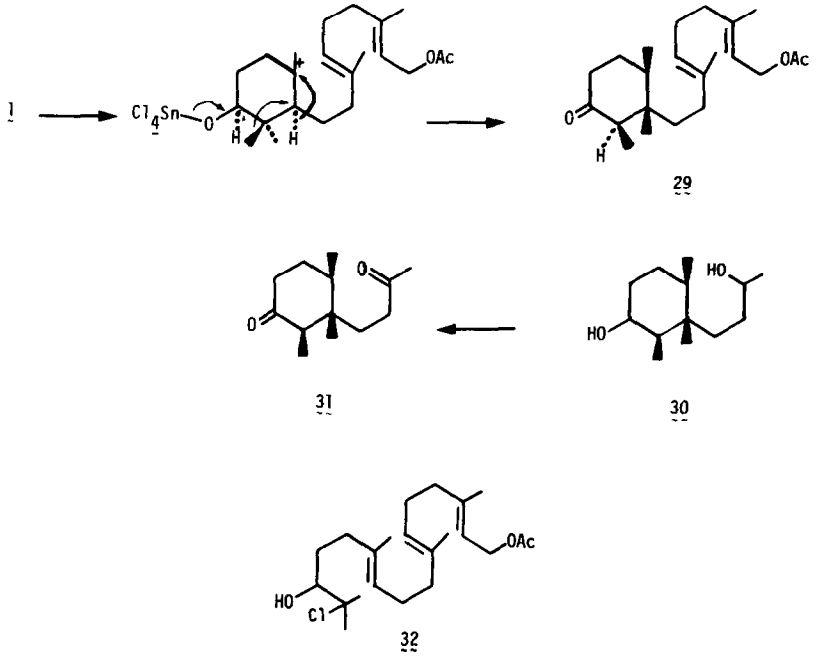
Peak (τ)	Assignment
4.50 1H	Vinyl proton
6.40 3H	O-Methyl
7.18 1H	H_α to carbonyl
9.10	
9.15 12H	4 Saturated methyls
9.17	

TABLE 4

PRODUCT YIELDS FROM $SnCl_4$ CYCLIZATION OF 1

Fraction	Yield (%)
Hydroxyacetates	33
Ketones (monocyclic)	28
Monocyclic ether	8
Chlorohydrin	20
Hydrocarbon	8
Other	4

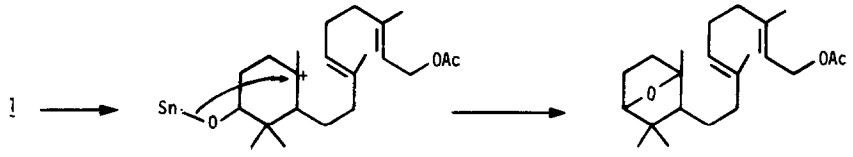
tertiary and one secondary methyl group, as well as two vinyl hydrogens, data fitting a ketonic-type structure already precedented in cyclizations in the sesquiterpene series (*6*). Further work involving degradation of this ketone (**29**) served to prove its structure. Ozonolysis of **29**, followed by reductive cleavage gave the diol **30** in good yield. Oxidation of **30** with Jones' reagent produced a diketone (**31**), the ir and nmr spectra of which were in excellent agreement with theory. The oily diketone **31** was converted to the crystalline bis-semicarbazone, which gave elementary analysis data confirming the empirical formula.



The chlorohydrin (**32**) was one of the major products arising from simple nucleophilic displacement on the oxide ring by chloride ion. Nuclear magnetic resonance and ir spectra readily revealed the structure of **32** from which the starting

epoxide (**1**) could be regenerated by treatment with potassium carbonate in methanol.

The fraction consisting of monocyclic bridged ether was not easily characterized. Although elemental analysis was in harmony with structure **33**, GLC analysis indicated a complex mixture of isomers. The nmr spectrum, although indicating the predominance of **33**, also showed that the sample was a mixture.



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A substantial amount of hydrocarbon was also produced in the stannic chloride cyclization. Gas–liquid chromatography showed this fraction to be a very complex mixture, probably of secondary products arising from loss of water and acetic acid by hydroxyacetates initially formed. Because of the complexity of this mixture, no attempts were made to identify its components.

EXPERIMENTAL

trans,trans-Farnesyl bromide (**3**). The experiment described here is an adaptation of the one used by Ruzicka for the synthesis of **3** as a mixture of isomers (*2*). To 15.0 g (0.068 mol) of farnesol (**2**) (*7*) in 30 ml hexane at 0° was slowly added with constant stirring, 9.20 g (0.034 mol) phosphorus tribromide. After the addition had been completed (15 min), the reaction was checked by TLC and found to be over. Methanol (2 ml) was added, followed by extraction with 2 × 10 ml water, 10 ml 10% sodium bicarbonate solution, and 10 ml water. The hexane layer was dried over anhydrous sodium sulfate and then evaporated, leaving 19.2 g (95%) **3**.

A portion of the above product (100 mg) was treated with 100 mg sodium methoxide in anhydrous methanol. The methyl ether thus formed was purified by chromatography on silica gel (eluent = 7: 93 ethyl acetate: hexane) and checked for homogeneity by GLC analysis (Apiezon-L, 3 ft. × ¼ in., t = 160°). Only one large peak (8.5 min) was observed, except for a small peak (<2%) at 7.2 min.

trans,trans-Farnesyl acetone (**5**). The two-step procedure described below is a modification of one used by Ruzicka for the synthesis of **5** of a mixture of isomers (*2*). To 125 ml absolute methanol was added 5.40 g (0.100 mol) powdered sodium methoxide (Aldrich Chemicals). The solution, under nitrogen cover, was cooled to 0°, and to it was added 15.0 g (0.120 mol) freshly distilled ethyl acetoacetate, followed by 11.2 g (0.041 mol) of farnesyl bromide (**3**). The mixture was stirred at 0° for 3 hr and 1 hr more at room temperature. Isolation was accomplished by addition of enough dilute hydrochloric acid to neutralize the base, and extraction

with a 200-ml volume of hexane. The hexane layer was thoroughly washed with water to remove unreacted ethyl acetoacetate, and then with saturated sodium sulfate solution. After evaporation of the hexane, there remained 12.9 g (94%) of a nearly colorless oil (**4**). The ir spectrum contained two carbonyl bands, one at 1745 cm^{-1} (ester) and one at 1720 cm^{-1} (ketone). A small portion was filtered through grade IV alumina with benzene and prepared for combustion analysis.

Anal. Calcd for $C_{21}H_{34}O_3$: C, 74.40; H, 10.25. Found: C, 74.41; H, 10.11.

Decarbethoxylation of **4** proceeded smoothly by alkaline hydrolysis in refluxing ethanol. To a solution made by adding 6.0 g potassium hydroxide to 50 ml 95% ethanol was added 12.00 g (0.036 mol) **4**. The mixture was refluxed under cover of nitrogen for 4 hr, then cooled and evaporated to a small volume (~25 ml). After dilution with 50 ml water the mixture was extracted with 2 × 100 ml 5% hydrochloric acid and 2 × 100 ml water. The organic layer was dried over anhydrous sodium sulfate, and the hexane was evaporated. This procedure provided 8.95 g (95%) of a colorless oil which by TLC (25:75 ethyl acetate:hexane) appeared as one major spot (R_f 0.61) with minor contaminants at R_f 0.23, 0.70. Gas–liquid chromatographic analysis (Apiezon-L) indicated >90% purity. After column chromatography on silica gel (10% water) the compound was completely homogeneous.

Anal. Calcd for $C_{18}H_{30}O$: C, 82.38; H, 11.52. Found: C, 82.64; H, 11.43.

trans,trans,trans and trans,trans,cis-Ethyl geranylgeranate (**7a** *and* **7b**). The title compounds were prepared as a mixture from ketone **5** via the -alkyne-ol **6**, according to the two-step procedure described by Nazarov for the synthesis of similar compounds (*8*). To a solution of 4.26 g (0.031 mol) methyl iodide in 50 ml dry ether at 0° was added 0.61 g (0.025 mol) magnesium. When all the metal had reacted, the solution was cooled and 2.00 g (0.029 mol) freshly distilled ethoxyacetylene in 25 ml ether was slowly added. Then the mixture was refluxed for 10 min. After cooling the solution to 0°, 5.00 g (0.019 mol) farnesyl acetone (**5**) was slowly added dropwise. The mixture gradually became yellow; and when the addition of **5** was complete, stirring was continued at reflux temperature for 0.5 hr. At the end of this time, the TLC of a small aliquot (hydrolyzed with 10% ammonium chloride solution) indicated the complete disappearance of ketone **5**.

The reaction mixture was poured onto ice and 10% ammonium chloride, and extracted with hexane. The layers were separated, and the organic portion was washed with 2 × 35 ml water. The combined water layer was backextracted with 2 × 50 ml hexane, and the total organic portion was washed with water until clear and then with saturated sodium chloride solution. The organic solution was dried over powdered anhydrous potassium carbonate and evaporated, leaving 5.80 g (91%) of the ethoxyacetylene adduct **6**. The ir spectrum contained a strong band at 2270 cm^{-1} (alkyne) and a weak ester carbonyl band at 1720 cm^{-1}, indicating the major presence of -yne-ol **6** and minor amounts of its rearrangement product (**7**). To complete the isomerization (**6** → **7**) 5.60 g (0.017 mol) **6** was added to a solution of 10 ml 15% sulfuric acid in 40 ml ethanol, and stirred at 50° for 4 hr. Addition of 75 ml water was followed by extraction with hexane. The organic layer was washed with 2 × 30 ml 10% potassium bicarbonate solution and 2 × 30 ml water, then dried over anhydrous magnesium sulfate. The yield of crude product (mix-

ture of **7a** and **7b**) was 5.21 g (93%). Infrared analysis confirmed the completeness of the reaction by the total disappearance of the 2270 cm^{-1} alkyne band. Thin-layer chromatography of the product indicated two equal-intensity spots in the ester region and GLC (Apiezon-L, 250°) of the same material produced two equal-intensity peaks at 12.4 and 14.3 min.

Preparative TLC made possible the clean separation of ester isomers **7a** and **7b**. Two silica gel GF plates (0.5 mm, 20 × 20 cm) were spotted with 20 mg of the ester mixture and run in 25 : 75 ethyl acetate : hexane solvent. Examination of the plates with uv light revealed two narrowly separated bands of $R_f \simeq 0.65$. These bands were scraped from the plates, eluted, and then resubjected to the same preparative TLC purification. This resulted in the isolation of samples of **7a** (15 mg) and **7b** (14 mg) which were homogeneous by GLC. Isomer **7b**, which was less polar on TLC, had the shorter (12.4 min) retention time, while the more polar TLC isomer (**7a**) had the longer (14.3 min) retention time.

Separation of **7a** and **7b** was accomplished more conveniently and on a larger scale by column chromatography of silica gel (10% water). To purify 3.00 g crude ester, 300 g silica gel (10% water) and a 4.50 × 60-cm column were used. The elution was begun with 7 × 150-ml fractions hexane, then graduated to 6 × 150-ml fractions 7 : 93 benzene : hexane, and to 4 × 150-ml fractions 10 : 90 benzene : hexane. At this point the less polar isomer (**7b**) started coming through in a pure state (the fractions were examined by GLC during the chromatography). The latter solvent was retained until the weight per fraction ratio began to decrease. The solvent had just been changed to 12 : 88 benzene : hexane when isomer **7a** came into evidence. The chromatography was continued until no more ester came through. In this way 750 mg of *trans,trans,cis* (**7b**) and 615 mg of *trans,trans, trans*-ethyl geranylgeranate (**7a**) were obtained pure. The middle fractions (total 1495 mg) contained both isomers in varying ratios, and were later purified in the same way. The nmr spectra of **7a** and **7b** were identical except for the doublet arising from the vinyl methyl group on the α,β-unsaturated olefin bond (see Table 5). The combustion analyses data for the isomers were:

Anal. Calcd for $C_{22}H_{36}O_2$;C, 79.46; H, 10.91. (**7a**) Found: C, 79.13; H, 10.77. (**7b**) Found: C, 79.76; H, 10.84.

trans,trans,trans-Geranylgeraniol (**8**). To 500 mg (1.50 mmol) **7a** in dry ether at

TABLE 5

Peak		Assignment
4.43 τ		Proton on α, unsaturated double bond
4.80–5.18		3 other vinyl protons
5.95 τ,	quartet (J = 7.0 cps)	Ether methylenes
7.87 τ (**7a**),	doublet (J = 1.5 cps)	Vinyl methyl on α, β unsaturated double bond
8.13 τ (**7b**),		
8.75 τ,	triplet (J = 7.0 cps)	Ester methyl group

0° under cover of nitrogen was added 114 mg (3.00 mmol) lithium aluminum hydride. The reaction was stirred for 2 hr at room temperature and for 15 min at reflux temperature. Excess hydride and the complex were decomposed by dropwise addition of saturated sodium sulfate to the cooled mixture. The aluminum oxide was collected by filtration and washed thoroughly with ether and methanol. The organic portions were combined, washed with 3 × 25 ml water, 2 × 25 ml saturated sodium chloride, and then dried over anhydrous sodium sulfate. The yield of alcohol **8** was 410 mg (95%). The ir and nmr spectra of **8** closely resemble those of farnesol. A small portion of **8** was filtered through silica gel with ether and submitted for analysis:

Anal. Calcd for $C_{20}H_{34}O$: C, 82.69; H, 11.80. Found: C, 82.83; H, 11.67.

trans,trans,trans-Geranylgeranyl acetate (**9**). To 750 mg alcohol **8** in 10 ml anhydrous pyridine was added 1.5 ml freshly distilled acetic anhydride. The mixture was stirred overnight, under nitrogen cover at room temperature. Isolation of the acetate was accomplished by diluting the mixture with 50 ml water and extraction with hexane. The hexane fraction was washed with 5% hydrochloric acid until the pyridine odor no longer persisted and then with water and saturated sodium chloride. The yield of **9** was 835 mg (97%). Homogeneity was indicated by the presence of only one peak on GLC. A portion was flushed with ether through grade IV alumina and submitted for analysis:

Anal. Calcd for $C_{22}H_{36}O_2$: C, 79.46; H, 10.91. Found: C, 79.36; H, 10.90.

trans,trans,trans-Geranylgeranyl acetate terminal bromohydrin (**10**). Acetate **9** (500 mg, 1.51 mmol) was dissolved in 75 ml tetrahydrofuran (THF) and then "titrated" with water until the solution became cloudy. Just enough THF to remove the cloudiness was then added and the solution was flushed with nitrogen and brought to 0°. *N*-Bromosuccinimide, 284 mg (1.60 mmol) was slowly introduced, and the reaction was stirred at 0° for 1 hr. The product was isolated by adding 100 ml water and extracting with 3 × 50 ml hexane. After being washed with water and dried over sodium sulfate, the organic layer was evaporated, leaving 606 mg (94%) crude bromohydrin.

The crude product was purified by column chromatography on 40 g deactivated silica gel (10% water). The nonpolar impurities were removed by 4 × 30-ml fractions hexane, 5 × 30-ml fractions 5:95 ether:hexane, and 4 × 30-ml fractions

TABLE 6

Peak	Assignment
4.10–5.10 τ	3 Vinyl protons
5.50 τ, doublet (J = 7.0 cps)	Methylene ether protons
6.25 τ, multiplet	Proton on carbon bearing bromine
8.06 τ, singlet	Acetyl methyl
8.30, 8.41 τ	3 Vinyl methyl groups
8.72, one peak	Bromohydrin methyls

10:90 ether:hexane. Pure bromohydrin (**10**) was eluted by 5 × 30-ml fractions 15:85 ether:hexane. This procedure netted 310 mg **10**, for an overall yield from **9** of 48%. The TLC of **10** exhibited only one spot. The nmr spectrum in carbon tetrachloride contained peaks assigned as shown in Table 6. A sample of **10** gave the following analytical data.

Anal. Calcd for $C_{22}H_{37}O_3Br$: C, 61.53; H, 8.69; Br, 18.61. Found: C, 61.28; H, 8.75; Br, 18.41.

trans,trans,trans-Geranylgeraniol terminal epoxide (**11**). A solution of the bromohydrin (**10**), 400 mg (0.93 mmol) in 35 ml methanol containing 1.0 g potassium carbonate was stirred at room temperature for 12 hr. Water (50 ml) was added and the mixture was extracted with 3 × 50 ml hexane. Washing of the hexane layer with water and saturated sodium sulfate was followed by drying over anhydrous sodium sulfate. Evaporation of the hexane left 232 mg (95%) **11**. A sample of **11** was filtered through deactivated silica gel with ether and submitted for analysis.

Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.37; H, 11.18. Found: C, 78.27; H, 11.01.

trans,trans,trans-Geranylgeranyl acetate terminal epoxide (**1**). The hydroxylic epoxide (**11**), 300 mg (1.04 mmol), was dissolved in 15 ml anhydrous pyridine to which solution was then added 1.0 ml acetic anhydride. After being stirred for 8 hr, the mixture was diluted with 50 ml water and extracted with 3 × 30 ml hexane. The organic layer was washed with 4 × 30 ml 5% hydrochloric acid solution, 2 × 30 ml water, and finally 2 × 30 ml saturated sodium chloride solution. The residue remaining after evaporation was a pale yellow oil weighing 332 mg (97%). This material appeared as a single spot on TLC, but was flushed through a short column of grade V alumina to ensure purity. The peaks in the nmr spectrum (carbon tetrachloride) of **1** were assigned as given in Table 7.

Anal. Calcd for $C_{22}H_{36}O_3$; C, 75.81; H, 10.41. Found: C, 75.62; H, 10.28.

Phosphoric Acid Catalyzed Cyclization of trans,trans,trans-Geranylgeranyl Acetate Terminal Epoxide (**1**)

Cyclization procedure. To 20 ml cold phosphoric acid in a 50-ml Vibromischer flask (under nitrogen cover) was added 300 mg epoxy acetate (**1**). The mixture was vigorously vibrated for 1 hr at 0°. The viscous mixture was poured onto ice and water and extracted with 3 × 50 ml hexane. The combined organic portions were

TABLE 7

Peak	Assignment
4.60–5.10 τ	3 Vinyl protons
5.50 τ, doublet (J = 7.0 cps)	Ether methylene protons
7.49 τ, triplet (J = 6.0 cps)	Epoxide ring proton
8.06 τ, singlet	Acetyl methyl
8.30, 8.40 τ	3 Vinyl methyl groups
8.79, 8.81 τ	Epoxide ring methyls

washed with water and 2 × 50 ml sodium bicarbonate solution and 2 × 50 ml saturated sodium chloride solution. Evaporation of the hexane left 290 mg pale yellow viscous oil.

Isolation of hydroxyacetate compounds. The crude cyclization product was separated into its major components by column chromatography using 20 g silica gel (10% water). The elution was conducted with 25-ml fractions hexane; 50:50 hexane:benzene; benzene, to remove less polar products; and 10:90 ether:benzene, to remove hydroxy acetates (Table 8). Infrared analysis of the fractions indicated that only group *D* contained hydroxyacetates (acetate carbonyl, 1740 cm^{-1}; —OH, 3400 cm^{-1}). The analytical TLC of *D* exhibited three spots very close together. This material (87 mg) was separated into three fractions (*x*, *y*, *z*) by preparative TLC on two plates (20 × 20 cm, 1.0 mm, silica gel G) using 30:70 ethyl acetate:hexane solvent. The fractions, in order of increasing polarity, weighed: *x*, 20 mg; *y*, 31 mg; *z*, 25 mg. Examination by nmr showed that none of them contained tricyclic compound. Groups *B* and *C* of the chromatography were examined by ir and GLC. Both were complex mixtures which showed little promise and therefore the stannic chloride cyclization, described below, was investigated.

Stannic Chloride Catalyzed Cyclization of trans,trans,trans-Geranylgeranyl Acetate Terminal Epoxide (**1**)

Cyclization procedure. To 500 mg (1.42 mmol) of the epoxide (**1**) in 10 ml cold anhydrous benzene (under nitrogen cover) was added 74 mg (0.28 mmol) stannic chloride. After 10 min of stirring the mixture was poured onto ice and 10% potassium bicarbonate solution, and was extracted with 3 × 30 ml hexane. The hexane layer was washed with 2 × 30 ml water and 30 ml saturated sodium chloride solution. Evaporation left 490 mg crude product.

Column chromatography of the cyclization mixture. The crude cyclization mixture was column chromatographed using 30 g silica gel (10% water) and a 1.2 × 25-cm column. In this way the mixture was separated into give main groups including *E*, which by ir and TLC was broadly identified as containing hydroxyacetates (Table 9).

Thin-layer chromatographic purification of fraction E (hydroxyacetates). Fraction *E* (162 mg) was purified by TLC on four plates (20 × 20 cm, 1.0 mm, silica gel G) using 25:75 ethyl acetate:hexane solvent. Two main bands, very close together, were detected by developing a small portion of each plate with iodine

TABLE 8

Fraction	Eluent	Weight (mg)	% (weight/290 mg)
1–5 (*A*)	Hexane	5	1.5
6–11 (*B*)	50:50 Hexane:benzene	58	20
12–26 (*C*)	Benzene	105	36
27–30 (*D*)	10:90 Ether:benzene	87	30
31–33 (*E*)	Ether	10	3.0

TABLE 9

Fraction	Eluent	Weight (mg)	% (weight/490 mg)
1–6 (*A*)	10:90 Benzene : hexane	39	8
7–11 (*B*)	50:50 Benzene : hexane	40	8
12–18 (*C*)	Benzene	138	28
19–27 (*D*)	Benzene	98	20
28–33 (*E*)	10:90 Ether : benzene	162	33

vapor. The less polar ($R_f \sim 0.32$) band contained a total of 105 mg (*E*-1). The other ($R_f \sim 0.30$) contained 35 mg (*E*-2). The GLC scan of *E*-1 displayed six major peaks and several smaller ones, all with retention times shorter than we expected for tricyclic isomers (<20 min; Apiezon-L, 250°). Fraction *E*-1 was carefully examined by nmr and found to be void of tricyclic compounds.

On the other hand, *E*-2 was characterized by only three peaks, at 18.5 (~10%), 19.5 (~10%), and 24.2 min (~80%). Furthermore, inspection of the nmr spectrum of *E*-2 indicated the probable presence of a tricyclic structure: a new multiplet at 5.85–6.02 τ; the almost complete disappearance of the 5.50 τ doublet; low intensity vinyl hydrogen and vinyl methyl absorption. Hence further purification of *E*-2 was undertaken.

Preparation of silver nitrate impregnated silica gel (GF) preparative TLC plates. Three silver nitrate silica gel (GF) plates (20 × 20 cm, 1.0 mm) were made at one time. Silver nitrate, 6.5 g, was dissolved in 125 ml water. The solution was added to 65 g silica gel (GF) and the mixture was shaken for 1 min. The mixture was spread in the usual way and the plates were dried in an 80° oven. They were stored in the dark until ready for use.

Silver nitrate preparative TLC purification of the 3,5-dinitrobenzoates derived from fraction E-2. Fraction *E*-2 (30 mg) was dissolved in 2.0 ml pyridine to which was added 150 mg recrystallized 3,5-dinitrobenzoyl chloride. The mixture, under nitrogen cover, was stirred at 50° for 8 hr. The diester was isolated by diluting the reaction mixture with 5 ml water and extracting with ether. The ether layer was washed repeatedly with water and 10% potassium bicarbonate solution to remove pyridine and 3,5-dinitrobenzoic acid. This was followed by washing with 3 × 10 ml 5% hydrochloric acid, 2 × 10 ml water, and 10 ml saturated sodium chloride. The ether layer was dried over anhydrous sodium sulfate and, after evaporation, gave 33 mg (70%) of a semisolid mass.

The crude diester was dissolved in benzene and spotted on two silver nitrate–silica gel (GF) plates. The solvent used was 50:50 ethyl acetate : hexane. By uv light two well-separated bands were evidenced: *E*-2a (R_f 0.80) and *E*-2b (R_f 0.60). The compounds were scraped from the plate and washed from the silica gel with ether and ethyl acetate. Fraction *E*-2b, a thick yellow oil, weighed 4.2 mg; *E*-2a, also an oil, weighed 20 mg. Addition of a small amount of hexane to the latter produced pale yellow crystals, mp 108–113°, but various attempts to crystallize *E*-2b were unsuccessful.

The nmr spectrum of *E*-2a was consistent with the assignment of tricyclic

structure **13.** Fraction *E*-2b, however, was obviously not tricyclic by nmr (strong doublet at 5.50 τ and no absorption at 5.80–6.10 τ).

Hydrolysis of diester **13.** To 0.5 ml ethanol in a 10-ml test tube (under nitrogen cover) was added 19.2 mg (0.035 mmol) diester **13.** Potassium carbonate (6.00 mg, 0.043 mmol, 1.23 mole equivalents) was then added; the mixture immediately turned pink. The reaction was allowed to stand for 2 hr and was then diluted with 1.0 ml water. Extraction with ether and washing of the ether with 2 × 1 ml potassium bicarbonate solution was followed by drying of the organic layer over anhydrous sodium sulfate. Evaporation left 11.8 mg of a pale yellow oil. Thin-layer chromatography showed the absence of starting diester **13** and the appearance of two products. Preparative TLC on a 20 × 20-cm, 0.5-mm silica gel plate using 35 : 65 ethyl acetate : hexane easily separated the two components (R_f 0.32 and 0.15). The weights and yields (based on starting compound **13**) were: hydroxyacetate **12,** 8.20 mg (67%), and diol **14,** 1.60 mg (15%). Although various efforts to induce **12** to crystallize failed, diol **14** was found to be white amorphous solid, mp 138–141° (methanol). The only notable ir absorption for **14** (in carbon tetrachloride) was found at 3450 cm^{-1} (—OH).

Removal of the 38-Hydroxyl Group of Tricyclic Hydroxyacetate **12**

Conversion of **12** *to ketoacetate* **27.** To 7.05 mg **12** in 0.5 ml reagent grade acetone at 0° under nitrogen cover was added 5 drops (excess) Jones' reagent. The orange mixture was shaken for 1 min, and then 10 drops methanol was added. Dilution with 1.0 ml water was followed by extraction with 4 × 1 ml hexane. The hexane was washed with water and dried over anhydrous sodium sulfate. Evaporation left an oily residue weighing 6.90 mg (98%) which appeared as one spot on TLC. The ir spectrum of **27** revealed two strong carbonyl bands, one at 1720 cm^{-1} (ketone) and another at 1745 cm^{-1} (acetate). Gas–liquid chromatographic analysis of **27** indicated the presence of only one compound.

Preparation of the dithioketal **(28)** *of ketoacetate* **27.** The ketone **(27),** 6.90 mg, was dissolved in 0.30 ml ethanedithiol (excess) in a 10-ml test tube. One drop 100% acetic acid and 10 μl boron trifluoride etherate were then added and the mixture was allowed to stand at room temperature for 3 hr. The product was isolated by adding 2.0 ml hexane to the mixture and washing first with 5 × 1 ml 15% potassium hydroxide to remove excess acid and thiol, and then with water. The hexane layer was dried over anhydrous sodium sulfate and evaporated. The crude product, 6.90 mg (85%), was mainly one spot on TLC, but was contaminated with a small amount of starting compound **(27).** Purification by preparative TLC on silica gel (G) (20 × 20 cm, 0.5 mm) using 25 : 75 ethyl acetate : hexane, gave 6.10 mg pure dithioketal **(28),** R_f 0.75. The ir spectrum contained acetate absorption at 1745 cm^{-1} and no ketone carbonyl (1720 cm^{-1}).

Preparation of acetate **26** *by desulfurization of dithioketal* **28.** The dithioketal **(28),** 6.10 mg, was dissolved in 1.0 ml anhydrous ethanol contained in a 5-ml round-bottom flask. Freshly prepared Raney nickel (W2) was added (70 mg), and the mixture was heated at 70° with stirring for 12 hr. A check of the reaction by TLC showed that a small amount of unreacted **28** still remained. Therefore, the

Raney nickel was filtered off and washed with hot ethanol; the ethanol was evaporated to a volume of 1 ml, 70 mg more Raney nickel was added, and the reaction was heated for 8 hr more. Thin-layer chromatography showed the reaction was then complete. The Raney nickel was filtered off, and the filtrate was evaporated with a stream of nitrogen. The residue was flushed through a small column of grade IV alumina with ether. Evaporation of the ether left 3.7 mg viscous oil. The ir spectrum contained a band at 1745 cm^{-1} (acetate carbonyl). In the mass spectrum of **26,** the base peak was that fragment resulting from loss of acetic acid (*m/e* 272); the molecular ion (*m/e* 332) was not detected. The 100-mc nmr of **26** contained peaks assigned as indicated in Table 10.

Synthesis of Acetate **26** *from Manoöl* **(17)**

Isomanoöl bromide **(18).** Manoöl **(17)** (900 mg, 4.09 mmol) was allowed to react with 730 mg (4.09 mmol) freshly distilled phosphorus tribromide. The yield of the bromide **(18)** was 790 mg (69%).

Isomanoöl acetate **(19).** The synthesis of acetate **19** has been described (*9*). To 780 mg (2.76 mmol) of the bromide **(18)** in ethanol was added 2.0 g silver acetate. The yield was low because of the competing elimination reaction: 130 mg (18%).

Isomanoöl **(20).** To 130 mg (0.49 mmol) of the acetate in 20 ml anhydrous ether under cover of nitrogen was added 100 mg (2.64 mmol) lithium aluminum hydride. The solution was stirred under cover of nitrogen for 2 hr. Addition of saturated sodium sulfate solution and filtration of the precipitate was followed by washing of the ether with 10% hydrochloric acid and water. The organic solution was dried over sodium sulfate and evaporated, leaving 92.5 mg (93%) of the alcohol **(20).** The ir spectrum of **20** contains absorptions at 3350 cm^{-1} (OH) and at 895 cm^{-1} (*gem*-disubstituted olefin).

Anal. Calcd for $C_{20}H_{34}O$: C, 82.69; H, 11.80. Found: C, 82.61; H, 11.66.

Oxidation of isomanoöl to the bicyclic acid **22.** The method of Poos *et al.* (*10*) was used to prepare the crude aldehyde **21** which was used in the next step in reaction with silver oxide to produce the desired acid **(22).** To 1.0 ml anhydrous pyridine at room temperature was carefully added 63.0 mg (0.63 mmol) chromium trioxide. The alcohol **(20),** 92.0 mg (0.42 mmol), was dissolved in 0.5 ml pyridine and the solution was added under a stream of nitrogen to the chromium trioxide–pyridine mixture. The flash was flushed with nitrogen and stoppered, and the

TABLE 10

Peak	Assignment
4.60 τ, broad	Vinyl protons
5.90 τ, multiplet	Methylene ether protons
7.98 τ, singlet	Acetyl methyl
9.09	
9.15	4 Tertiary methyls
9.18	

solution was vigorously shaken for 45 min. A 0.5-ml portion of methanol was added and the mixture was diluted with 5.0 ml 10% phosphoric acid. After extracting the solution with 3 × 10 ml hexane, the combined hexane portions were washed with 3 × 10 ml 10% phosphoric acid, 3 × 10 ml water, and 10 ml saturated sodium chloride. The solution was dried over sodium sulfate and evaporated, leaving 66 mg crude aldehyde (**21**). Analytical TLC inspection of the product indicated two minor contaminants, including a small amount of unreacted **20**. The ir spectrum in carbon tetrachloride exhibited an aldehyde hydrogen absorption at 2760 cm^{-1}, a strong carbonyl band at 1680 cm^{-1}, a conjugated double bond at 1630 cm^{-1}, and a band for a geminal disubstituted double bond at 895 cm^{-1}.

The crude aldehyde (**21**), 66 mg (0.25 mmol), was dissolved in 7 ml 50:50 ethanol: water. To the mixture was added 135 mg (0.50 mmol) silver nitrate and 85 mg (3.0 mmol) potassium hydroxide. The mixture was stirred, under nitrogen cover, for 5 hr at room temperature and for 2 hr more at 60°. The reaction was cooled, diluted with 10 ml water, and extracted with hexane to remove nonacidic material. The aqueous fraction was evaporated to a volume of 5 ml and 30% acetic acid was added until the solution was acidic to litmus. Ether was used to extract the aqueous mixture and the combined ether portions was washed with water and saturated sodium chloride. Drying over sodium sulfate and evaporation of the solvent left 32 mg (45% from **21**). The ir spectrum (in carbon tetrachloride) of the acid (**22**) shows a broad band for hydroxyl (3500–3100 cm^{-1}), a broad carbonyl band (1745–1680 cm^{-1}), a conjugated olefin band (1630 cm^{-1}), and a band for geminal disubstituted olefin (895 cm^{-1}). The nmr spectrum (in carbon tetrachloride) of **22** contained peaks assigned as shown in Table 11.

Bicyclic methyl ester (**23**). The bicyclic acid (**22**), 32 mg, was dissolved in 3 ml anhydrous ether. To this solution was added 2 ml (large excess) of a solution of diazomethane in ether. The mixture was allowed to stand for 1 hr, and acetic acid was added until the yellow color disappeared. The ether solution was washed with 2 × 5 ml 10% sodium bicarbonate and 2 × 5 ml water, then dried over anhydrous magnesium sulfate. Evaporation left 33 mg (97%) methyl ester (**23**). The TLC of **23** showed two spots in the ester region and the GLC scan (Apiezon-L, 200°) exhibited two narrowly separated peaks, **23a** (12.8 min) and **23b** (11.4 min) in a ratio **23a : 23b** = 1 : 2. Preparative TLC purification of **23** (20 × 20 cm, 0.5 mm, silica gel (GF)) using 25 : 75 ethyl acetate : hexane gave two fractions which by GLC were shown to be pure **23a** (22.5 mg) and **23b** (6.0 mg). The ir spectra of **23a** and **23b** contained bands at 1720 cm^{-1} (conjugated carbonyl), 1650 cm^{-1} (conjugated double bond), 1150 cm^{-1} (ether stretch), and 895 cm^{-1} (geminal disubstituted double bond). The nmr spectrum of **23a** in carbon tetrachloride contained a doublet at

TABLE 11

Peak	Assignment
4.30 τ	Vinyl proton adjacent to carboxyl
5.20, 5.52 τ	Geminal disubstituted olefin
9.12, 9.20, 9.32 τ	3 Tertiary methyls

7.85 τ for the methyl group attached to the conjugated olefin bond, thus proving the trans geometry of **23a**. A sample of **23** was analyzed.

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.14; H, 10.82.

Tricyclization of bicyclic ester **23a**. To a 10-ml round-bottom flask equipped with a small condenser and containing 22.0 mg **23a** was added 2.0 ml 98% formic acid. The mixture was stirred for 1 hr at 70° at the end of which time the formic acid was evaporated (under vacuum). To the remaining oily mixture was added 3 ml of 80% ethanol which was 1.0 normal in potassium hydroxide. The reaction proceeded at reflux temperature for 3 hr (under nitrogen cover). The mixture was diluted with 8 ml water and extracted with 3 × 10 ml hexane to remove unsaponified ester product, tricyclic **24**. The hexane solution was washed with 2 × 10 ml 10% potassium bicarbonate solution, 2 × 10 ml water, and 10 ml saturated sodium chloride solution. Drying over sodium sulfate and evaporation of the hexane lefl 6.5 mg yellow oil. This crude product was mainly one spot (R_f 0.75, 20:80 ethyl acetate:hexane) on TLC, but was contaminated with several minor impurities. Preparative TLC purification on silica gel (GF) (10 × 20 cm, 0.5 mm, 20:80 ethyl acetate:hexane) made possible the isolation of pure tricyclic **24**, white crystals (from methanol), mp 112–114°, 4.3 mg (20%). The ir spectrum of **24** contains absorptions at 1745 cm^{-1} (ester carbonyl stretch), 1160 cm^{-1} (ether stretch), and no absorption at 895 cm^{-1} (**23a**). Gas–liquid chromatographic analysis on Apiezon-L showed the compound was pure. The nmr spectrum is in perfect agreement with the structure assignment. Another sample of **24**, prepared in the same way as described, was prepared for analysis.

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.01; H, 10.75.

Conversion of **24** *to the tricyclic comparison compound, acetate* **26**. To 2 ml anhydrous ether and 4.2 mg ester (**24**) was added 15 mg lithium aluminum hydride. The mixture was let stand at room temperature for 1 hr under cover of nitrogen. Isolation was achieved by first adding 2 ml hexane, then 3 drops water and 0.5 ml 10% hydrochloric acid. This was followed by separation of the layers and further extraction of the aqueous phase with hexane. The combined hexane volume was washed with water and dried with anhydrous sodium sulfate. Evaporation of the hexane left 3.2 mg (85%) of an oil (**25**) which was one sharp spot on TLC.

The alcohol (**25**), 3.2 mg, was then converted to its acetate (**26**) by treatment with 0.25 ml acetic anhydride in 2 ml pyridine. The product, 3.4 mg (95%), was

TABLE 12

Peak	Assignment
4.60–5.12 τ	2 Vinyl hydrogens
5.50, doublet (J = 7.0 cps)	Methylene ether hydrogens
8.04, singlet	Acetyl methyl
8.41	Vinyl methyls
9.12, doublet (J = 7.0 cps)	Secondary methyl
9.14, doublet (J = 6.0 cps)	Secondary methyl
9.45, singlet	Tertiary methyl

TABLE 13

Peak	Assignment
7.90 τ, singlet	Methyl ketone
9.11 τ, doublet (J = 6.0 cps)	Secondary methyl
9.14 τ, doublet (J = 6.5 cps)	Secondary methyl
9.40 τ, singlet	Tertiary methyl

isolated by the standard procedure described above for the acetylation reactions.

The ir and nmr spectra of **26**, as derived from the stannic chloride cyclization of epoxide **1** and from manoöl were identical. Both acetate samples had identical retention times on Apiezon-L (200°, 18.4 min) and SE-30 (210°, 24.4 min).

Other Products from the Stannic Chloride Catalyzed Cyclization of Epoxide **1**

Monocyclic ketone (**29**). The initial column chromatographic purification of the cyclization mixture gave a substance, fraction *C* (R_f 0.40) which was loosely identified as a ketoacetate by its ir spectrum. This material (130 mg) was further purified by another column chromatography on silica gel to remove minor impurities. This resulted in 114 mg of a ketoacetate which is homogeneous by TLC and GLC. The ir spectrum contains two carbonyl bands: 1745 cm^{-1} (acetate) and 1720 (ketone). The nmr spectrum in carbon tetrachloride exhibited assigned peaks as shown in Table 12.

Ozonolysis of ketoacetate (**29**). The ketoacetate (**29**), 100 mg (0.29 mmol), was dissolved in 25 ml chloroform and ozone was passed through until a potassium iodide trap indicated that reaction was complete. The chloroform was evaporated leaving a glassy residue (ozonide), 108 mg. Ethanol (10 ml) was added to the flask, and the ozonide was reductively cleaved with 100 mg (excess) sodium borohydride according to the method of Sousa and Bluhm (*11*). Dilution of the ethanol solution with 10 ml saturated sodium chloride and extraction with 3 × 10 ml ether was followed by washing the ether extract with 2 × 10 ml water and 2 × 10 ml saturated sodium chloride. The ether solution was dried over sodium sulfate and evaporated, leaving 52 mg (85%) diol **30**.

The diol, 50 mg (0.23 mmol), was dissolved in 2 ml reagent grade acetone at 0°. Jones' reagent was then added dropwise until the orange color persisted. A few drops of methanol was added to destroy excess reagent, and the mixture was diluted with 4 ml water. The aqueous solution was extracted with ether and the ether phase was washed with water and saturated sodium chloride. Evaporation of the ether left 45 mg (90%) diketone (**31**). The ir spectrum (carbon tetrachloride) of **31** contains a strong ketone carbonyl absorption at 1725 cm^{-1}. The nmr spectrum of **31** (carbon tetrachloride) contained absorptions assigned as shown in Table 13. The oily diketone was converted to its disemicarbazone and recrystallized with ethanol. The white crystals have mp 223–225°.

Anal. Calcd for $C_{15}H_{28}N_6O_2$: C, 55.53; H, 8.70; N, 25.90. Found: C, 55.41; H, 8.70; N, 25.71.

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