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Biogenetic-Type Total Synthesis of (±)-Farnesiferol A and (±)-Farnesiferol C

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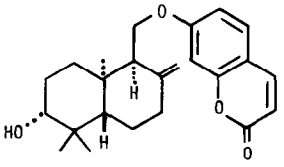
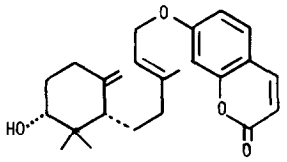
Biogenetic-type cyclization of *trans,trans*-umbelliprenin oxide **4** generates the natural occurring farnesiferol C (*dl*) (**3**), in addition to various other unnatural transformation products. Similar cyclization of the *cis,trans* counterpart (**34**) of **4** affords inter alia farnesiferol A (*dl*) (**1**). Bioorganic and physical organic aspects of these changes are discussed.

Elaborating on preliminary investigations by Casparis and Baumann three decades before (*1*), Caglioti *et al.* reported in 1958 (*2a*) the isolation from the highly odoriferous medicinal agent *Asa foetida* (*Umbelliferae*) of three well-defined isomers having the molecular formula $C_{24}H_{30}O_4$, designated as farnesiferols A, B, and C. Structural studies described in the latter publication permitted proposal of formula **1** for farnesiferol A, and in the succeeding year (*2b*) further degradative



1

and physical evidence were adduced in favor of structures **2** and **3** for farnesiferols B and C, respectively.



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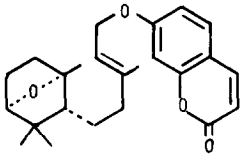

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The stereochemistry, both relative and absolute, of farnesiferol A was rigorously established at all centers with the exception of C-9, the cis relationship

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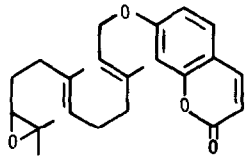
between the C-10 methyl and the C-9 hydrogen being inferred from hydrogenation experiments. A cis relationship between the C-3 and C-5 hydrogens in both farnesiferols B and C was suggested because of the presumed biogenetic relationship to farnesiferol A. The double bond geometry in the side chains of B and C was thought to be trans, again for biogenetic reasons.

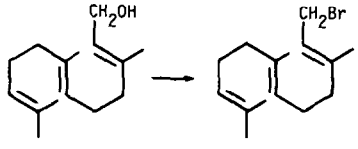
Because of the remarkably close resemblance of these systems to those which result when 10,11-oxidofarnesyl acetate or -farnesate is cyclized nonenzymatically (*3*), synthesis of the farnesiferols by parallel pathways seemed worthwhile, of interest, and eminently reasonable. We describe herein the simply executed total synthesis of farnesiferols A and C, achieved by acid-catalyzed cyclization of the (*dl*) terminal epoxide (**4**) of the naturally occurring umbelliprenin (*4*).



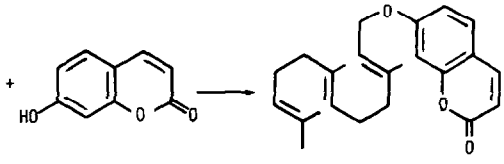
4

Biogenetic-type synthesis efforts in the farnesiferol area required first the preparation of umbelliprenin (**8**). This material was obtained from *trans,trans*-farnesol (**5**) in a manner similar to that employed by Baters and co-workers (*5*). Reaction of **5** with 48% aqueous hydrobromic acid in petroleum ether furnished *trans,trans*-farnesyl bromide (**6**), apparently contaminated with some residual alcohol. The unpurified bromide was treated with the sodium salt of umbelliferone (**7**) in dimethylformamide, and umbelliprenin (**8**) was isolated in 30% yield after chromatography and crystallization.

Despite being formed in somewhat low yield, this material may be safely assigned the trans,trans geometry on the basis of its nmr spectrum, which is dis-



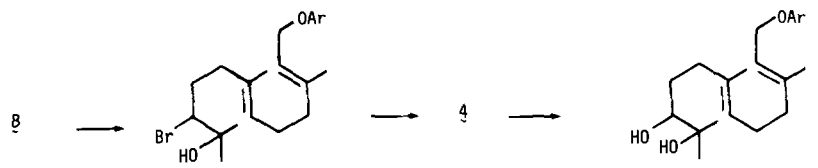
5 **6**



7 **8**

tinctly different from that of the isomer obtained from *cis,trans*-farnesol (*vide infra*). This observation reinforces the trans,trans assignment given to natural umbelliprenin by Bates and co-workers (*5*). The two allylic substitution reactions involved in the conversion of **5** to **8** must proceed with predominant retention of geometry, the lack of isomerization being attributed to a significant barrier to rotation about the allylic bond in an S_n1 process. Such retention in allylic replacement reactions has been observed in other systems (*5, 6*).

Trans,trans-umbelliprenin afforded the expected (*3, 7*) monobromohydrin **9** (53%) after reaction with *N*-bromosuccinimide in aqueous dimethoxyethane, followed by chromatography of crude product on silica gel. That nearly exclusive terminal attack had occurred is evident from the nmr spectrum of **9**, which contains two saturated methyl and two vinyl methyl signals—internal hypobromination would have produced a compound in which only one saturated methyl and three vinyl methyls remain. The terminal epoxide **4** was obtained (80%) by the

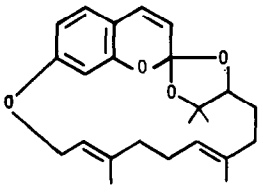


9 **10**

reaction of the bromohydrin with potassium carbonate in methanol. In spite of the rather broad mp range (47–52°) of **4**, the nmr spectrum of the compound showed no evidence of impurities and was in good accord with the indicated structure. Hydrolysis of the epoxide with 3% aqueous perchloric acid in dioxane gave rise to the corresponding glycol **10**.

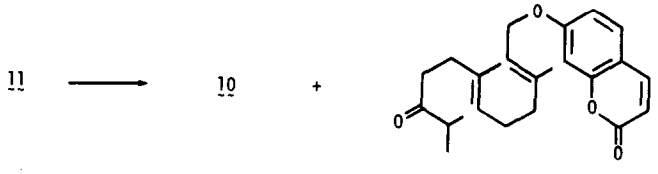
Initial cyclization experiments were performed with 0.1 equivalents of boron trifluoride etherate in anhydrous benzene for 30 min at room temperature. Analysis by thin-layer chromatography (TLC) showed the presence of at least five components in the product mixture, two less polar than the starting epoxide. The least polar product (12%), though crystalline, exhibited a very wide mp range (~125–175°) which could not be narrowed. The infrared spectrum of this material, while lacking the typical carbonyl absorption of the coumarins, displays the prominent fine structure expected of an aromatic nucleus. The ultraviolet spectrum had a principal maximum at 275 mμ (10,500) with shoulders at 227 (13,600), 235 (9500), 294 (6300), and 305 (5200), which contrasts with the ultraviolet absorption of the coumarins: λ_{max} 324 (16,000) and shoulders at 297 (9000), 252 (2500), and 242 (3500). It is evident that the coumarin nucleus is no longer present as such, even though the substance would appear to be aromatic in character. The conjecture that the strong Lewis acid conditions have effected some separate reaction of the benzopyrone moiety was discounted, since umbelliprenin appeared to be stable to boron trifluoride etherate in benzene. One is thereby forced to the conclusion that

both the epoxide function and the coumarin moiety must be present in order to form this product, for which the macrocyclic ortho ester structure **11** is proposed.



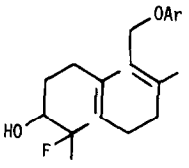
11

The analytical figures reveal an elemental composition identical to that of the starting epoxide **4**. The possibility of a dimer is excluded by the molecular weight, as determined by mass spectrometry (382) and osmometry (370). The ultraviolet spectral data correspond well to those reported for 7-methoxy-3-chromene: λ_{max} 222 mμ (17,000) and 279 mμ (7600) (*8*). Since structure **11** has two asymmetric centers, two diastereomers would be expected, consistent with the broad mp range and in keeping with the nmr spectrum. Molecular models indicate that both of the macrocyclic isomers are essentially strain-free. The concept of **11** being such a mixture helps to rationalize the nmr spectrum. There appear to be four saturated methyl groups (two superimposed) and four different vinyl methyl groups. The two unequal doublets at τ values of 4.72 and 4.61 ppm may be attributed to one of the two chromene vinyl protons (probably the proton at C-3) in each of the isomers of **11**. The presence of the masked coumarin in this compound was confirmed by hydrolysis with aqueous perchloric acid in dioxane, the two major products (34% each) being identified as the glycol **10** and the ketone **12** by direct comparison with authentic specimens.



12

It might at first seem surprising that the formation of **11** competes with the opening of the epoxide ring. Since the coumarin carbonyl certainly is the most basic site in **4**, however, the 0.1 equivalent of Lewis acid must be predominantly coordinated therewith, leaving very little free acid available to react with the epoxide group. The coordinated system then has ample opportunity to react intramolecularly with the epoxide unit to give **11**. An intermolecular analogy for this type of transformation is of course the reaction between an epoxide and a ketone in the presence of strong Lewis acids, to give the corresponding ketal.



13

Also isolated from the original reaction mixture was a substance (12.5%) identified as the fluorohydrin **13**, in that the nmr spectrum was very similar to that of the glycol **10**, except for the methyl group doublet (J_{HF} = 22 cps). The formation of **13** consumes the catalyst; and this factor must be responsible for the survival of **11** under the reaction conditions, since the macrocycle is itself destroyed by separate treatment with boron trifluoride etherate in benzene.

In order to suppress the production of **11**, further cyclizations were carried out with a 20% molar excess of the acid catalyst. Presumably the surplus boron trifluoride would be able to effect epoxide opening, even though the first equivalent probably remains coordinated with the coumarin carbonyl group. The formation of macrocycle **11** may still compete with other isomerizations, even with an excess of the Lewis acid, but **11** is not isolated owing to its lability to boron tribluoride.

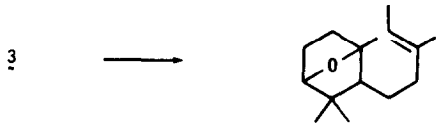
The mixture resulting from the modified cyclization was resolved into six compounds by a combination of chromatographic techniques. Once again the fluorohydrin **13** was observed (~7%) and was removed from mixtures with the nonhydroxylic products by conversion to the acid phthalate and extraction.

The least polar and major component (28%) proved to be the acyclic ketone **12**, the nmr spectrum of which revealed the presence of an isopropyl group, two allylic methyls, two vinyl hydrogens, and the allylic ether methylene protons in the molecule.

A third product was a bicyclic oxide (8%), identified as racemic farnesiferol C (**3**). The infrared and nmr spectra of the synthetic material were completely superimposable upon those of natural farnesiferol C isolated from asa foetida resin. The silica gel TLC mobilities of the two samples corresponded in three different solvent systems.

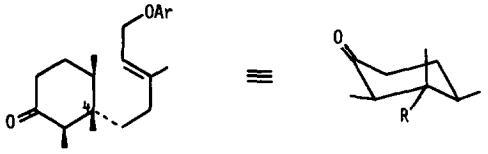
Both synthetic and natural **3** were reduced with lithium in ethylamine (*9*) to remove the allylic coumarin function, and vapor-phase chromatography (VPC) retention times and the infrared spectra of the sesquiterpenoid fragments **14** were found to be identical. Only a single product was obtained in this reductive cleavage, indicating that no geometrical isomerization had occurred, as observed in similar allylic reductions (*5, 10*). If the reaction mixture was allowed to stand overnight, however, a second peak appears in the chromatogram of the product, suggesting that the cis isomer of **14** results from base-catalyzed equilibration subsequent to reduction.

A second ketone **15** (4%) isolated from the mixture of products had a polarity on silica gel TLC which was very close to that of **3**. The former is slightly more polar with 40% ethyl acetate–petroleum ether and slightly less polar with 20% ethyl



14

acetate–benzene. The infrared spectrum of **15** shows, in addition to the usual fine structure common to these coumarin derivatives, a seemingly enhanced carbonyl absorption at about 5.85 μm (chloroform), indicative of a ketone group in either an acyclic environment or a six-membered (or higher) ring. The nmr spectrum of **15** revealed the presence of the same allylic side chain as in farnesiferol C. In addition there appeared two doublets indicating two secondary methyl groups and an unusually high-field unsplit methyl signal (9.40). The monocyclic structure **15**



15 15a

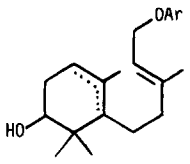
satisfies the structural requirements implicit in the preceding spectral data. In particular, the quaternary methyl group on position 4 is fixed in an axial orientation and lies within the shielding area of the carbonyl group (*11a*). The substitution of a carbonyl group at the 2, 4, or 6 position of the steroid nucleus does cause modest upfield shifts (0.025–0.05) in the resonance position of the similarly located C-10 methyl group (*12a*). The low magnitude of these shifts, however, necessitates the consideration of other factors. One of these is the general observation that axial substituents on a cyclohexane ring absorb at higher positions than their equatorial equivalents owing to the diamagnetic anisotropy of the annular carbon–carbon single bonds (*11b*). The juxtaposition of methyl groups in cyclic compounds may also be responsible for upfield shifts (*13*), probably because of the diamagnetic anisotropy of the additional carbon–carbon bonds. Thus, the signals of the methyl groups in 1,2,3-trimethylcyclopentane appear at higher field than that of the methyl in methyl cyclopentane. That one of the two secondary methyl groups is situated α to the ketone group was demonstrated by the double resonance technique carried out at 100 Hz. Irradiation in the region of the α protons (τ 7.5) caused the lower field doublet (9.06) to coalesce to a singlet, and saturation in the methyl area resulted in the collapse of a quartet in the α-proton region.

The relative stereochemistry depicted in formula **15** is assigned because it is the only formulation which keeps the C-4 methyl group locked in an axial configuration so as to maximize the shielding effects. With any of the alternative arrangements, the quaternary methyl group would be expected to spend one-half or more

of its time in an equatorial disposition; hence, the high-field methyl signal becomes even more difficult to rationalize. 3-Methyl-cyclohexanone gives a methyl signal at τ 8.96 (*14*). The triterpene ketone friedelin would seem to be a suitable model for **15**, and it also has a rather high-field methyl signal (9.30) (*15*), probably due to the C-5 methyl group.

The nmr spectrum of ketone **15** in benzene solution was also measured, for benzene shift data may provide information regarding the relative positions of methyl groups to a ketone function (*14*). The quaternary methyl group was found to move upfield (Δ = 0.17), while the methyl substituent α to the ketone was unaffected (Δ = 0). These shifts are in good agreement with the expected values for these positions, Δ = 0.11–0.16 and Δ = 0, respectively (*16*). The upfield shift of the other secondary methyl group (Δ = 0.30) corresponds rather well with that observed with 4-methylcyclohexanone (Δ = 0.34) (*14*), but it should be noted that an axial methyl group at this position experiences a similar shift (Δ = 0.32–0.37) (*16*). These benzene shift data are in good accord with structure **15**; however, it is possible that this correspondence is fortuitous, for the effect of the coumarin substituted side chain cannot be evaluated.

The remaining two components of the original reaction mixture are alcohols which are assigned the monocyclic and bicyclic skeletons **16** and **17**, respectively. The less polar monocyclic alcohol was isolated in 9% yield and is apparently a mixture of the two endocyclic double-bond isomers. The nmr spectrum of **16** shows, in addition to the typical absorptions from the allylic side chain, a second vinyl methyl group, two pairs of saturated methyls, and one proton on a carbon bearing a hydroxyl group. The vinyl proton region has an area corresponding to 1.3–1.4 protons (two different samples), including the vinyl hydrogen of the side chain. The mixture consists, therefore, of 30 to 40% of the trisubstituted double-bond isomer and 60–70% of the tetrasubstituted one. The areas of the saturated methyl groups are about equal.



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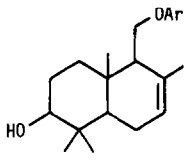

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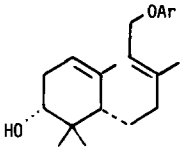


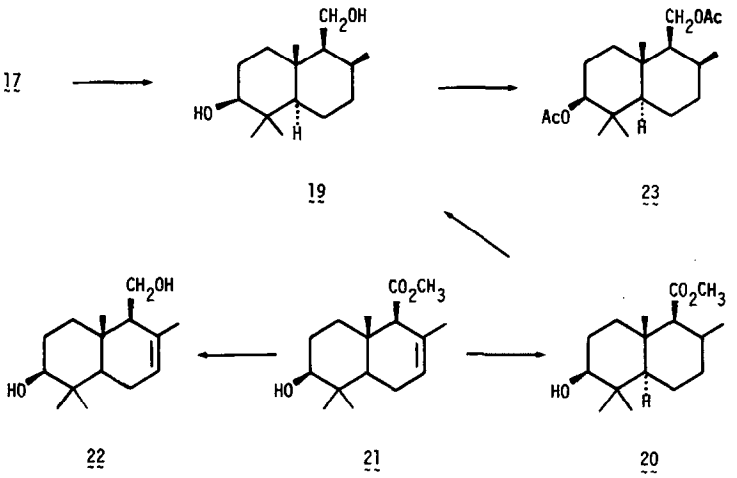
18

Farnesiferol D, recently isolated from Galbanum resin, was assigned structure **18**.[1] We compared the nmr spectrum of farnesiferol D with that of our synthetic mixture and found that the methyl signals of the natural product coincide with those of the less abundant component of the mixture in both chloroform-d and pyridine. Furthermore, **16** and **18** proved to be inseparable on silica gel TLC with

[1] Private communication from Professor D. Arigoni (Eidgenössische Technische Hochschule, Zürich, Switzerland), who kindly provided samples of farnesiferols A and D.

three different solvent combinations. While this comparison is not unequivocal, it seems likely that our synthetic mixture contains racemic farnesiferol D.

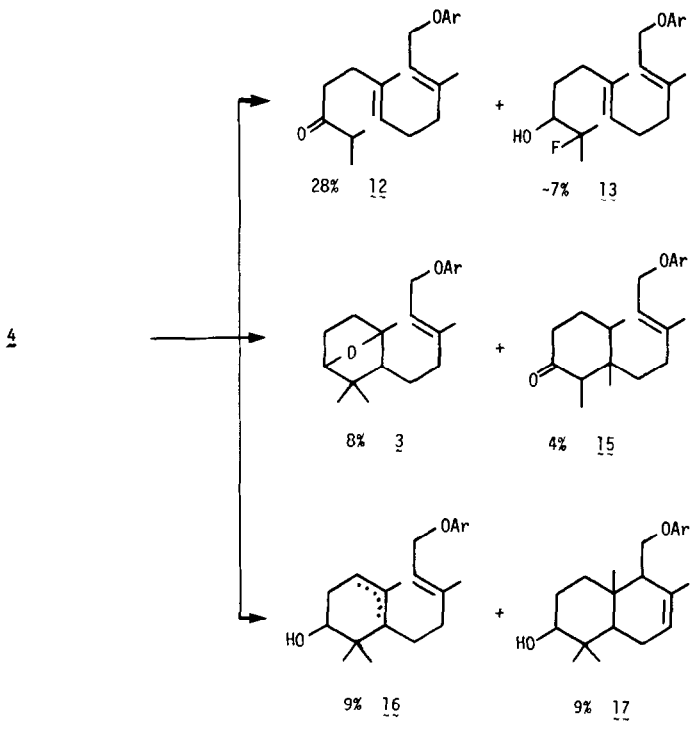
The nmr spectrum of the more polar alcohol **17** (9%) displays one particularly striking characteristic, different from all of the previous ones, i.e., the absence of the doublet from the allylic ether methylene group. Instead, there appears a complex two proton multiplet at higher field, suggesting that cyclization into the final double bond has indeed taken place and that this alcohol must be bicarbocyclic. The presence of three saturated methyl groups, one vinyl methyl group, one hydrogen on carbon-bearing hydroxyl, and one vinyl proton is in accord with structure **17**, a not unexpected product in light of earlier, model cyclization results (*3*).



Chemical proof for the bicyclic assignment **17**, including the indicated stereochemistry, was obtained by catalytic hydrogenation with platinum and acetic acid. In this reaction the coumarin moiety, probably first partially reduced, undergoes hydrogenolysis between the oxygen function and the aromatic ring (**1a**). The resulting saturated diol **19** was compared with the product from lithium aluminum hydride reduction of the hydroxy ester **20** (*3, 17*), the structure of the latter having been established by correlation of its precursor **21** with 3β-hydroxy drimenol **22** (*3, 17*). Comparison of the two diols by mp, mmp, and infrared spectroscopy established their identity. The corresponding diacetyl derivatives (**23**) possessed the same mp, undepressed mmp, and superimposable infrared spectra.

The results of this cyclization are summarized below. In all, 65% of the original mixture is accounted for in terms of purified, crystalline substances (except for the fluorohydrin **13**, which was impure and not regenerated from the acid phthalate derivative).

The synthesis of farnesiferol C from the *trans,trans*-epoxide **4** demonstrates that the allylic geometry of the natural product must be trans, as originally suggested (*2b*). The possibility of acid-catalyzed isomerization under the reaction

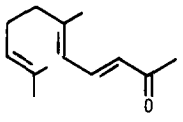


conditions is rendered unlikely on the basis of control experiments. Both *trans, trans*-farnesyl methyl ether and *trans,trans*-umbelliprenin **8** were not affected by 1-min exposure to boron trifluoride etherate in benzene. In the latter case, however, the recovery of pure material was only fair (55%). Also, the two bicyclic alcohols produced in the cyclization of the cis,trans epoxide (*vide infra*) are both different from **17**. Had complete equilibration occurred, the same product distribution would have been expected.

No firm evidence regarding the relative stereochemistry between positions 3 and 5 in the synthetic bridged oxide **3** and the monocyclic alcohols **16** was forthcoming. Regardless of whether the hydrogens are cis or trans, the relationship must be the same in both synthetic and natural **3**. The stereochemistry of the bicyclic alcohol **17**, however, was firmly established. Hence, if it be assumed here that the stereo relationship between C-3 and C-5 is fixed before the reaction path leading to **3, 16,** and **17** partitions, as is the case in similar systems (*17, 18*), then this stereochemistry must be the same in all three cases. In line with this view, it was shown that products **3, 12, 16,** and **17** are not interconverted under the original reaction conditions.

Although the cyclization described in the foregoing was successful in respect to the construction of the framework of farnesiferol A, the double bond in the observed bicyclic product (**17**) was found in the presumably more stable endocyclic position instead of the exocyclic location, as in the natural product. With the aim of exerting some control over the direction of elimination in the reaction, the

epoxide **4** was subjected to a different set of cyclization conditions. In the acid-catalyzed conversion of ψ-ionone (**24**) to the cyclic ionone isomers **25**, Ohloff and Schade had found that a concentrated, two-phase system consisting of petroleum ether, boron trifluoride etherate, dimethylformamide, and water gave rise to a relatively high proportion (40%) of γ-ionone, the exocyclic isomer (*19*). In the application of this procedure to **4** (with added benzene, for solubility reasons), the



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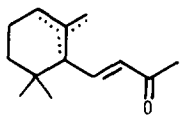


25

rather stringent conditions caused considerable decomposition; nevertheless, monocyclic (3%) and bicyclic (4%) alcohol fractions could be isolated. The nmr spectrum of the former was essentially the same as that of **16** except for the appearance of two additional signals (τ 8.98, 9.26) in the saturated methyl region (~20% of total). Although it is possible that this new component was the exocyclic isomer, farnesiferol B (**2**), the limited amount of material precluded further investigation. The nmr spectrum of the bicyclic alcohol fraction also revealed some previously unseen absorptions which pointed to the presence of the exocyclic isomer, but lack of material (0.8%) rendered complete characterization impossible. Nevertheless, the 100-Hz nmr spectrum did indicate three saturated methyl groups (poorly resolved); a proton on carbon-bearing acetate; and an exocyclic methylene group, evidenced by two broadened bands at τ 5.08 and 5.45. The infrared spectrum of the new bicycle displayed increased absorption in the 895-cm^{-1} region, compared to the acetate of **17**. Despite these indicators, the substance was, apart from its optical properties, different from natural farnesiferol A, in that chromatography (silica gel–silver nitrate) definitely separated the two acetates, the natural product being somewhat less polar. On the basis of these experiences, it would appear that farnesiferol A has the ψ-axial configuration at C-9, as originally put forward (*2a*).

Because of the similarity of product nature and distribution in the cyclization of epoxide **4** to that in related farnesol cases, there can be little doubt that the mechanistic pathways by which the products are formed are also, in general, parallel. On the basis of prior physical organic studies and conclusions (*18*), we can with confidence proffer the interpretation shown in Chart 1. Thus, epoxide **4** first monocyclizes, with participation of the neighboring π bond, to give the substituted cyclohexyl cation **26**, which subsequently partitions (1) by simple proton loss, to cyclohexene complex **16**, (2) by internal capture of hydroxyl oxygen, to bridged oxide **3** (farnesiferol C), (3) by further carbocyclization, to bicyclic cation **27**, the progenitor of the farnesiferol A isomer (**17**), and (4) by a series of hydrogen and methyl shifts, to cyclohexanone **15**. In regard to the last change, i.e., **26** → **15**, the stereoelectronic course probably involves a series of antiplanar shifts (**28**), the

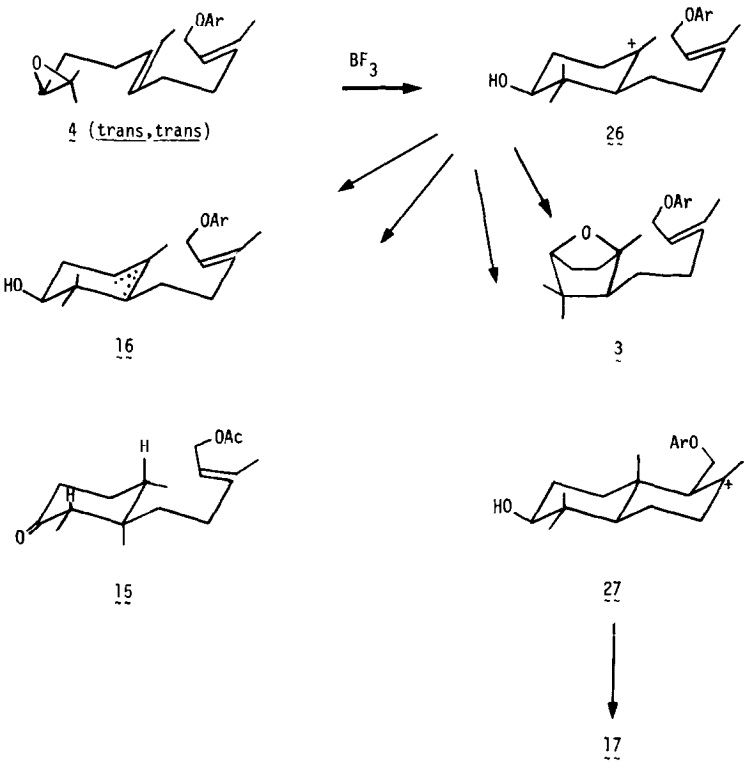
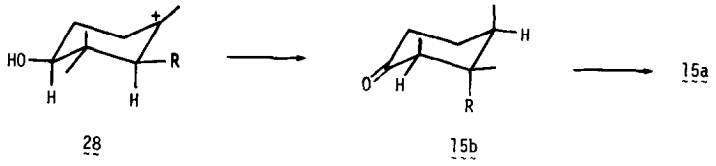
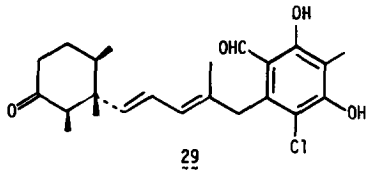


CHART 1



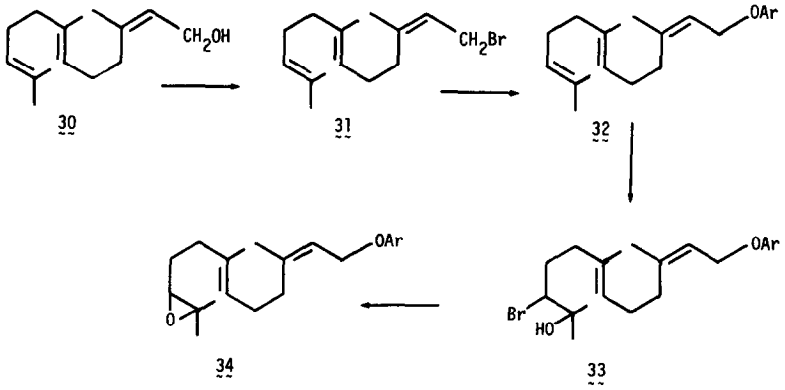
immediate result of which is conformational structure **29**, of greater energy than the 1,3-diequatorial dimethyl counterpart **15**. The stereochemistry predicted on the basis of this interpretation best accommodates the nmr data for this ketonic product. The same 2,3,4-trimethylcyclohexanone structure **15** has been assigned to the sesquiterpenoid antibiotic ascochlorin (**29**), a fungal metabolite isolated from cultures of an unidentified *Fusarium* species, *Ascochyta viciae*, and *Nectria coccinea* (*20*). The incorporation pattern of doubled-labeled [^{13}C]acetate into ascochlorin demonstrates that a rearrangement occurs during biosynthesis (*21*).

In facing the synthesis of structure **1** in another way, we turned to cyclization of the cis,trans epoxide corresponding to **4**. *cis,trans*-Farnesol **30** (~95% pure) was obtained from an enriched mixture by column chromatography on silica gel. Reac-



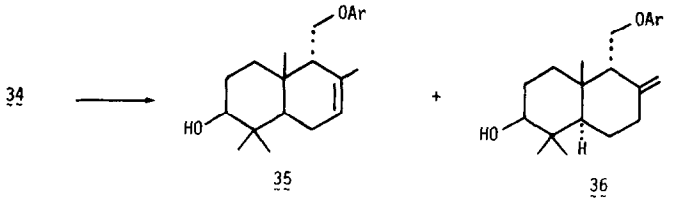
29

tion of **30** with phosphorous tribromide in petroleum ether furnished *cis,trans*-farnesyl bromide **31**, which without characterization was converted to the umbelliferone ether. The liquid *cis,trans*-umbelliprenin **32** (62% overall) was considered to be free from serious contamination by the trans,trans isomer by reason of the nmr spectrum, which differed significantly from that of **4** in both the vinyl methyl and methylene regions. The terminal bromohydrin **33** (54%) was produced by the action of *N*-bromosuccinimide in aqueous dimethoxyethane; and reaction of **33** with potassium carbonate in methanol afforded the *cis, trans*-epoxide **34**, (96%). The nmr spectrum of **34** also exhibited noticeable differences from that of its trans,trans equivalent.



30 31 32 34 33

The epoxide **34** was treated with 1.2 equivalents of boron trifluoride etherate in benzene for 1 min, after which the two most polar products were isolated by column and thin-layer chromatography. The less polar material (4%) was tentatively assigned structure **35**, the C-9 epimer of **17**. The nmr spectrum includes absorptions of three quaternary methyl groups, a vinyl methyl, one vinyl hydrogen, a hydrogen on carbon-bearing hydroxyl, and a complex multiplet for the homoallylic ether methylene group. This material is distinctly different from **17**, but no additional stereochemical evidence was sought. In view of the specificity of the previous cyclizations, it would be surprising if this substance is not the endocyclic double bond isomer of its companion, identified as (*dl*)-farnesiferol A (**36** + **1**) (2%) by direct comparison with natural material isolated from *Asa foetida*. The natural and synthetic samples displayed identical infrared spectra as well as TLC mobilities on both silica gel (three solvent systems) and silica gel–silver nitrate (the silver nitrate–silica gel adsorbent combination is a particularly sensitive test since **1**, **17**, and the exocyclic isomer of **17** are all separated from one another).

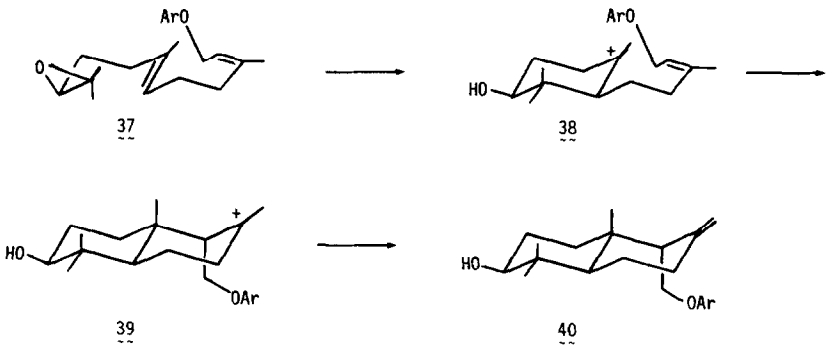


With the exception of a few minor peaks (e.g., τ 8.52, probably due to an impurity) the nmr spectra of the synthetic and natural farnesiferols A are completely superimposable. The exact coincidence of the well resolved, eight-line ABX pattern due to the ether methylene and the three sharp methyl signals adds weight to the positive nmr spectral comparison.

As an additional chemical confirmation of identity, the two bicyclic alcohols **1** and (**36** + **1**) were hydrogenated separately to the saturated diol stage (the natural diol has the opposite absolute configuration). The diols corresponded on TLC and furnished diacetates with identical infrared spectra.

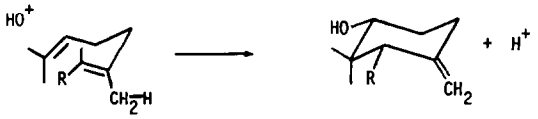
The successful synthesis of racemic farnesiferol A from the *cis,trans*-epoxide **34** provides strong reinforcement for the earlier axial C-9 designation (*2a*), especially since its apparent equatorial counterpart 29 was decidedly different. Although the *syn* stereochemical relationship between C-9 and C-10 is a rarity among the multitude of terpenoid natural products having a *trans*-decalin *A/B* ring system, farnesiferol A must now be considered a bona fide representative of this "abnormal" class, a notable early example of which is the triterpene derivative fusidic acid (*22*).

In regard to mechanistic interpretation, previous constructs (*18*) readily can be elaborated so as to embrace the present cis,trans case. It had already been demonstrated (*3*) that the BF_3-etherate catalyzed bicyclization of simple C_{10}-terpenoid types proceeded stereoselectively with respect to geometry of the starting material and relative stereochemistry of the product at all assymmetric centers; and this behavioral pattern applies to the trans,trans case (Chart 1). The same principles include the cis,trans system, implying that synthetic farnesiferol A arises by monocyclization (**37**) of epoxide to intermediary cation **38,** followed by a second cyclization to produce **39,** all proceeding in such ways as to reflect in the bicyclic



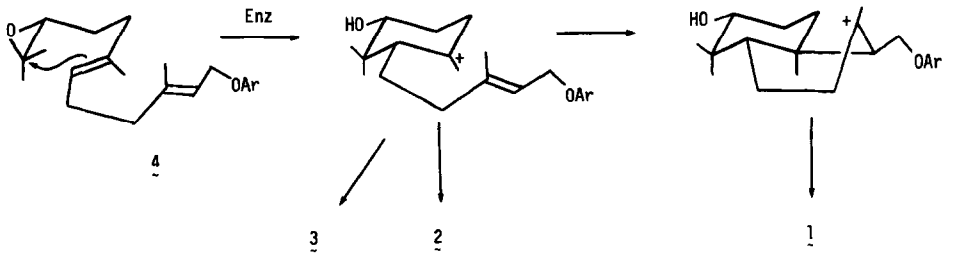
product the geometry and conformation as portrayed in **37**. The direct stereochemical consequence of these phenomena is the assignment shown in **39**, with a 9,10-cis arrangement of hydrogen and methyl, a direct consequence of the cisoid π-bond in the starting material. Termination of the overall bicyclization reaction involves proton loss, which although yielding a preponderance of endocycle **35**, does generate a significant proportion of the exo isomer (**36**), with assumed preferred conformation **40**.

In treating the matter of farnesiferol biogenesis, Caglioti *et al.* suggested that this natural product group "might arise biogenetically by oxidative cyclization of the known umbelliprenine" (**8**) (*2a*), and specifically directed attention (*2b*) to the plausibility of attack by hydroxonium ion coupled with cyclization (**41**), leading in the stereochemically preferred fashion to farnesiferol B (**2**). In light of recent advances in our understanding of the mechanism of lanosterol biosynthesis (*18*), this earlier view logically can be modified and expanded along lines illustrated in Chart 2. As in the nonenzymic counterpart, the biocyclization is preceded by



41 2

conversion of umbelliprenine to its terminal oxide (**4**), which is transformed in a separate step to monocyclic carbonium ion, the precursor of the three farnesiferols. In contrast to the abiological process, however, it seems likely that chair/boat folding of the oxide is involved, because, as in lanosterol biosynthesis (*23*), the 9,10-cis arrangement of hydrogen and methyl in farnesiferol A is thereby nicely accounted for. Obviously, lanosterol cyclase itself is not, by accident, the catalytic agent in farnesiferol biosynthesis, since entities of opposite chirality are involved throughout. On the other hand, since the enzymic and nonenzymic processes are closely similar with respect to product structures, involvement of the enzyme must be comparatively modest and may center on fixing the substrate in the chair/boat conformation, preparatory to cyclization. Although the chair/boat hypothesis most readily rationalizes the stereochemistry and therefore formation,



4 3 2 1

CHART 2

of farnesiferol A, it is supererogatory in respect to farnesiferols B and C, in which the allylic ether moiety remains intact. Yet, in the most economical interpretation, a single enzyme would initiate cyclization of the substrate, bringing it to the monocyclic stage, after which partitioning provides the various observed products. Again, one concludes on this basis that enzyme control during the stages ensuing monocyclization is not rigid, but permits termination of a biosynthetic process which is similar to the latter stage in the nonenzymic operation. In fact, in the formation of **2** and **3**, and even **1**, the changes following the formation of the monocyclic carbonium ion (or an equivalent) may well be in effect spontaneous, aside from maintenance of the chair/boat conformation in force at the outset.

Although, all things considered, oxide **4** production and cyclization seems the more likely course of events, an alternative such as proton promoted cyclization of umbelliprenin to members of the desoxy series, followed by enzymic introduction of hydroxyl at C-3, has not been ruled out experimentally. Each of the events in this possible combination has ample individual precedent, and tests similar to those employed in defining lanosterol biosynthesis could be employed to distinguish among the alternatives which can be conceived.

EXPERIMENTAL

Melting points were determined either with an oil bath or a Kofler block and are uncorrected. Petroleum ether refers to the fraction with a bp of 30 to 60°. H/D indicates the height to diameter ratio of the adsorbent column in the chromatographies. Preparative TLC separations were carried out on 20 × 20-cm plates having a 1-mm layer of the designated adsorbent.

trans,trans-Umbelliprenin (**8**)

Aqueous hydrobromic acid (15 ml, 48%) was added to a solution of *trans,trans*-farnesol (2.07 g, 9.33 mmol) (*24*) in 45 ml of petroleum ether. The mixture was stirred at room temperature for 2.5 hr then diluted with more petroleum ether. After three washes with water and one with saturated sodium chloride solution, the organic layer was dried (magnesium sulfate) and the solvent removed under reduced pressure. The residual, slightly yellow farnesyl bromide (~2.6 g) is best used immediately.

The sodium salt of umbelliferone (1.76 g, 10.9 mmol) (*25*) was prepared in 10 ml of dimethylformamide (distilled from calcium hydride) by cautious addition of 262 mg (10.9 mmol) of sodium hydride. The farnesyl bromide (2.58 g, 9.05 mmol) was transferred to the reaction vessel with 10 ml of solvent, and the mixture stirred overnight at room temperature under a nitrogen atmosphere. The orange solution was then diluted with water and extracted with four portions of 1 : 1 benzene–petroleum ether. The combined extracts were washed four times with water, dried, and concentrated to an orange oil (2.78 g).

This crude product was partially purified by percolation through an alumina column (15 g, activity III) with 1 : 1 ether–petroleum ether–petroleum ether and

TABLE 1

NMR SPECTRAL DATA AND ASSIGNMENTS[a]

Compound	Saturated methyl	Vinyl methyl	Ether methylene	Vinyl hydrogen	Other
3	9.02, 8.98 8.74	8.25	5.45 d (6.5)	4.57 t (6.5)	Bridgehead hydrogen 6.41 br d (4.5)
4	8.81, 8.77	8.39, 8.25	5.45 d (6.5)	4.92 br 4.59 t (6.5)	Epoxide ring hydrogen 7.49 t (6.5)
6		8.41, 8.41 8.34, 8.27		4.95, 4.95 br 4.52 t (8)	$-CH_2Br$ 6.10 d (8)
8		8.42, 8.42 8.34, 8.24	5.45 d (7)	4.93, 4.93 br 4.55 t (7)	
9	8.71, 8.68	8.40, 8.26	5.45 d (6.5)	4.88 br 4.60 t (6.5)	CHBr 6.15 m
10	8.87, 8.83	8.40, 8.22	5.43 d (6.5)	4.81 br 4.53 (6.5)	CHOH 6.63 m
11					C(O)H
Major	8.68, 8.59	8.40, 8.33	5.40 br d (~5)	4.72 d (9.5) 4.6–5.2 br, 3.44 d (9.5)	5.9–6.5 Aromatic 3.09 d (8)
Minor	8.91, 8.68	8.46, 8.22	5.40 br d (~5)	4.61 d (9.5)	3.55–3.84 m
12	8.95 d (7)	8.40, 8.24	5.43 d (6.5)	4.94 br 4.58 t (6.5)	α H 7.24–7.74 m
13	8.67 d (22)	8.37, 8.24	5.39 d (6.5)	4.86 br 4.53 t (6.5)	CHOH 6.49 br t (9.5)
15	9.40, 9.09 d (6.5) 9.06 d (6.5)	8.20	5.38 d (6.5)	4.48 t (6.5)	α H 7.6–7.9 m 7.52 q (6.5)
15 (benzene)	9.57, 9.39 d 9.06 d	8.45			
16					
60–70%	8.98, 8.92	8.38, 8.21	5.39 d (6.5)	4.49 t (6.5)	CHOH
30–40%	9.15, 9.03	8.38, 8.21	5.39 d (6.5)	4.74 br 4.49 t (6.5)	6.55 m
16 (pyridine)	8.75, 8.70 8.96, 8.82	8.36, 8.20 8.36, 8.20			
17	9.10, 9.10 8.99	8.36	5.75, 5.98 m	4.46 br	CHOH 6.71 m
19 (pyridine)	9.06, 8.97 8.92 d (7) 8.81		5.75–6.27		
29	9.10, 9.10		5.80 d (5)	5.08 br	$CHOCOCH_3$ 7.94
	9.10			5.45 br	5.45 m
32		8.42, 8.39 8.35, 8.20	5.47 d (6.5)	4.95, 4.95 br 4.55 t (6.5)	
34	8.78, 8.82	8.38, 8.21	5.47 d (6.5)	4.85, 4.85 br 4.56 t (6.5)	Epoxide ring hydrogen 7.48 t (6)
35	9.11, 9.02 8.98	8.46 or 8.23	6.09 m	4.48 br	CHOH 6.78 m
36	9.17, 9.00 8.93		5.55–6.13 m (8 line, ABX)	5.26 5.18	CHOH 6.73 m

[a] The chemical shift figures are τ values in parts per million with tetramethyl silane as internal standard. The solvent is chloroform d or carbon tetrachloride unless indicated to the contrary. The numbers enclosed in parentheses are coupling constants in c.p.s. The absorptions due to the coumarin moiety have been omitted. Abbreviations: br, broad; d, doublet; t, triplet; q, quartet; and m, multiplet.

ether. Several recrystallizations from both hexane and methanol furnished 464 mg of **8**, mp 60–62.5 (lit. mp 61–63°) (*26*).

The material recovered from the mother liquors was treated with 2 ml of pyridine and 0.6 ml of acetic anhydride to acetylate contaminating farnesol. The farnesyl acetate and other impurities were removed by chromatography on alu-

mina III (60 g, H/D 6.5). The purified umbelliprenin was eluted in seven fractions over the range of 10% (240 ml), 12.5% (360 ml), and 15% (60 ml) ether–petroleum ether. Recrystallization gave another 556 mg, mp 55–61° (total 1.02 g, 30%).

Anal. Calcd for $C_{24}H_{30}O_3$ (366.48): C, 78.65; H, 8.25. Found: C, 78.64; H, 8.29 (3807).

trans,trans-Bromohydrin (**9**)

N-Bromosuccinimide (4.23 g, 23.8 mmol) was added in portions to a stirred solution of 6.95 g (19.0 mmol) of **4** in 95 ml of dimethoxyethane and 25 ml of water at 15 ± 1°. After 5 min at 15° the solution was set aside (in the dark) for another 55 min. The solution was concentrated to about one-third volume under reduced pressure (temperature below 40°), diluted with 250 ml of water, and extracted twice with ether. The combined ether extracts were washed twice with water and then saturated sodium chloride solution, dried, and concentrated to a viscous oil.

Purified monobromohydrin was obtained by column chromatography on 485 g of silica gel–15% water (H/D 12). One-liter fractions were collected with ether–petroleum ether mixtures and analyzed by TLC (40% ethyl acetate–petroleum ether (60–68°) (Table 2). Fractions 10 and 11 contained 4.59 g of the pure bromohydrin. An additional 0.38 g was obtained by rechromatography of fractions 9, 12, and 13; yield 4.97 g (56.5%). Upon refrigeration the purified bromohydrin solidified; recrystallization from methanol at −20° gave a white powder, mp 44–46°.

Anal. Calcd for $C_{24}H_{31}O_4Br$ (463.41): C, 62.20; H, 6.74; Br, 17.25. Found: C, 61.96; H, 6.86; Br, 17.39.

trans,trans-Epoxide (**4**)

Anhydrous potassium carbonate (1.66 g, 12.0 mmol) was added to a solution of

TABLE 2

Fraction	Solvent (%)	Weight (est.) (g)
	Ether–petroleum ether	
1	0	0.02
2	5	0
3	10	0
4	15	0
5	20	0.16
6	3 × 25	1.56
7	2 × 27.5	0.28
8	30	0.06
9	30	0.06
10	3 × 32.5	2.62
11	2 × 35	1.90
12	35	0.40
13	2 × 50	0.44
14	2 × 100	1.46
15	Acetone	0.80

5.05 g (10.9 mmol) of the bromohydrin **9** in 135 ml of methanol, and the suspension was stirred under nitrogen for 20 min. The reaction mixture was diluted with water and extracted with ether. The aqueous phase was neutralized with ammonium chloride and extracted twice more with ether. The combined ether extracts were rinsed with saturated sodium chloride solution, dried, and evaporated. The residue was recrystallized from methanol at −20° to yield 3.62 g (87%). A portion of the recrystallized bromohydrin was similarly converted to the epoxide to obtain a sample for analysis, mp 47–52°.

Anal. Calcd for $C_{24}H_{30}O_4$ (382.48): C, 75.36; H, 7.91. Found: C, 75.28; H, 7.87.

trans,trans-Glycol (**10**)

Aqueous perchloric acid (1.5 ml, 3%) was added to a solution containing 201 mg (0.53 mmol) of the epoxide in 3 ml of dioxane. The reaction was stirred for 25 min at room temperature, diluted with water, and extracted with chloroform. The chloroform solution was washed twice with water, dried, and evaporated to dryness under reduced pressure. Some less polar impurities were separated by chromatography on 6 g of alumina III (H/D 11) by elution with 12-ml portions of 0, 10, 10, and 20% ethyl acetate–benzene mixtures. The glycol (180 mg, 85%) was eluted slowly with increases in eluent polarity, methanol being required to obtain the last traces of material. Further purification was effected by precipitation from ether at −20° or aqueous methanol at 0°, mp 82–94°.

Anal. Calcd for $C_{24}H_{32}O_5$ (400.50): C, 71.97; H, 8.05. Found: C, 72.16; H, 8.02.

Reaction of 4 with 0.1 Equivalents of Boron Trifluoride

Distilled boron trifluoride etherate (16 ± 1 μl, 0.13 mmol) was quickly introduced into a stirred solution of the epoxide **4** (508 mg, 1.33 mmol) in 25 ml of anhydrous benzene under nitrogen. After 30 min the yellow solution was poured into water and extracted with ether. The ethereal solution was rinsed twice with water, dried, and evaporated to dryness. The mixture was chromatographed on alumina III (15 g, H/D 14) according to the scheme (25 ml fractions) given in Table 3. Fractions 3 and 4 contained pure (by TLC) **11** (62 mg, 12%). This substance crystallizes from hexane or ethanol but without substantial improvement in the mp (125–175°). The infrared spectrum (carbon tetrachloride) has no hydroxyl or carbonyl absorptions but strong bands at 6.09, 6.17, and 6.67 μm; the ultraviolet absorption curve has λ_{max}^{EtOH} 275 mμ (10,500) with shoulders at 227 (13,600), 235 (9500), 294 (6300), and 305 (5200). Molecular weight: calcd 382; found 370 (osmometer), 382 (mass spectrum).

Anal. Calcd for $C_{24}H_{30}O_4$ (382.48): C, 75.36; H, 7.91. Found: C, 75.22, H, 7.99.

The fluorohydrin **13** (67 mg, 12.5% from **4**, 42% based on boron trifluoride) was isolated from fractions 7 and 8 by preparative TLC on silica gel GF developing with 50% ethyl acetate–petroleum ether 60–68°. Two minor impurities were separated by preparative TLC on alumina G with 35% ethyl acetate–petroleum ether 60–68°. The infrared spectrum of this material showed a modest hydroxyl band at 2.8 μm.

Anal. Calcd for $C_{24}H_{31}O_4F$ (402.49): C, 71.61; H, 7.76. Found: C, 71.75; H, 7.75.

TABLE 3

Fraction	Eluent (%)	Weight (mg)
	Benzene–petroleum ether	
1	0	0
2	30	0
3	30	15
4	2 × 50	47
5	50	0
6	100	48
7	100	32
	Ether–benzene	
8	2 × 5	60
9	2 × 10	69
10	2 × 15	41
11	2 × Methanol	136

The remaining products seemed to correspond to those obtained with 1.2 equivalents of acid, but were not extensively examined here.

Hydrolysis of **11**

The macrocyclic compound **11** (51 mg, 0.13 mmol) in 1.5 ml of dioxane was treated with 0.5 ml of 3% perchloric acid and then heated at steam bath temperature for 15 min. The hydrolysate was separated by chloroform extraction and the two major products isolated by preparative TLC on silica gel GF developing with 70% ethyl acetate–petroleum ether 60–68°.

The more polar component (18 mg, 34%) was recognized as the glycol **10** by its TLC mobility in 75% ethyl acetate–petroleum ether 60–68°, nmr spectrum, and solubility behavior. A recrystallized specimen had mp 80–93°, undepressed with the material obtained directly from **9**; the two had superimposable infrared spectra. The less polar component (18 mg, 35%) was shown to be **12** by nmr, TLC, and infrared comparison. After two recrystallizations the ketone exhibited mp 55–59°, mmp 55–59°.

Reactions of **4** *with 1.2 Equivalents of Boron Trifluoride*

Distilled boron trifluoride etherate (0.38 ml, 3.1 mmol) was quickly introduced into a stirred solution of the epoxide **4** (1.00 g, 2.62 mmol) in 50 ml of anhydrous benzene under a nitrogen atmosphere. After 40 sec the solution was poured into a mixture of ether (75 ml) and water (75 ml) and shaken until the bright yellow color faded (total time elapsed, 60–90 sec). Residual materials were then rinsed out of the flask. The ethereal layer was washed with water, dried, and evaporated to dryness. The mixture was chromatographed according to the method of Duncan (*27*) on a 700-g column of silica gel (H/D 15) eluting with 40% ethyl acetate–petroleum ether 60–68°. Fractions (40 ml) were taken at about 30-min intervals by means of an automatic fraction collector and analyzed by TLC (Table 4).

TABLE 4

Fractions	Weight (mg)	Remarks
1–30	0	—
31–42	12	Discarded
43–51	307	Crystalline
52–56	11	Discarded
57–68	239	Mixture
69–71	51	Mixture
72–83	49	Mixture
84–91	11	Discarded
92–110	115	Crystalline
111–129	34	Discarded
130–150	95	Crystalline
151–182	33	Discarded

Recrystallization of the material in fractions 43–51 from methanol (−20°) afforded 280 mg (28%) of **12**. The analytical sample had mp 57–59.5°.

Anal. Calcd for $C_{24}H_{30}O_4$ (382.48): C, 75.36; H, 7.91. Found: C, 75.08; H, 7.90 (4280).

The material in fractions 57–68 was heated on a steam bath with 292 mg (1.97 mmol) of phthalic anhydride in 2 ml of pyridine under nitrogen for 1 hr. The product was separated into neutral (192 mg) and acidic (96 mg, 7%) fractions by extraction with 5% sodium carbonate. The latter appeared (nmr spectrum) to consist mainly of the fluorohydrin acid phthalate but was not examined further.

The neutral fraction was further purified by chromatography on alumina II (H/D 12.5), carefully eluting with 50% and 67% benzene–petroleum ether. The crystalline fractions of **3** (97 mg) were combined and the later oily fractions (48 mg) purified by preparative TLC on alumina G. The least polar zone yielded another 6 mg of the oxide **3** and the second zone gave 12 mg of **15**. Recrystallization of the oxide fractions afforded 82 mg (8%) with mp 76.5–78.5°. Several crystallizations from methanol and ether–petroleum ether raised the mp to 85–87.5°. This material was shown to be identical with farnesiferol C by TLC (three solvent combinations on silica gel, one on alumina), infrared, and nmr comparisons.

Anal. Calcd for $C_{24}H_{30}O_4$ (382.48): C, 75.36; H, 7.91. Found: C, 75.08; H, 7.88.

Fractions 69–71 and 72–83 were purified separately by preparative TLC on silica gel GF using continuous (evaporative) development with 7.5% ethyl acetate–benzene for 4 hr. In each case five bands were observed, the third corresponding to **15**; combined yield 41 mg (4%). After recrystallization from ethanol this material had mp 141–143.5°. The infrared spectrum showed no hydroxyl absorption but a stronger carbonyl band (5.84–5.86 μm, chloroform) than usual for the coumarins.

Anal. Calcd for $C_{24}H_{30}O_4$ (382.48): C, 75.36; H, 7.91. Found: C, 74.98; H, 7.82.

Fractions 92–110 afforded the monocyclic alcohols **16** after recrystallization from ether–92 mg (9%). Further crystallization from methanol and ether–petroleum ether furnished the analytical specimen, mp 100–111°. This material has a TLC mobility on silica gel corresponding to farnesiferol D in three solvent systems

(40% ethyl acetate petroleum ether 60–68°, 20% ethyl acetate–benzene, and 10% methanol–benzene). The acetate of **16** showed one spot on silica gel 25% silver nitrate (*28*) which again corresponded to farnesiferol D acetate. The methyl signals in the nmr spectrum of **18** coincided with the high field pair from **16** in both chloroform-d and pyridine.

Anal. Calcd for $C_{24}H_{30}O_4$ (382.48): C, 75.36; H, 7.91. Found: C, 75.13; H, 7.91.

The material from fractions 130–150 crystallized upon contact with carbon tetrachloride–86 mg (9%). Recrystallization once each from ethanol and methanol furnished a sample of analytical purity, mp 91–109°.

Anal. Calcd for $C_{24}H_{30}O_4$ (382.48): C, 75.36; H, 7.91. Found: C, 75.09; H, 7.84.

Stability to boron trifluoride etherate in benzene

(*a*) *Cyclization products* **3, 12, 16,** and **17**. In each case 2.5 ± 0.05 mg (6.5 μ mol) of the product in 125 μl of benzene was treated with 1.0 μl of boron trifluoride etherate. Thin-layer chromatography analysis (all four products are well separated) at 20-sec intervals demonstrated that there was no significant interconversion of these materials after 60 sec.

(*b*) *trans,trans-Umbelliprenin* (**8**). *trans,trans*-Umbelliprenin (15.5 mg) was exposed to boron trifluoride etherate (6.0 μl) in 0.8 ml of benzene for 60 sec. Crystalline **8** (10 mg, mp 58–62°) was obtained after filtration over silica gel–15% water with 15% ether–petroleum ether and crystallization from methanol. Another recrystallization furnished 8.5 mg, mp 59–62°, mmp 59–62°.

(*c*) *trans,trans-Farnesyl methyl ether*. The ether (16.2 mg) was treated similarly and the material recovered by extraction (15 mg). Analysis by VPC (20% DEGS at 175°) showed that other than traces of elimination products there were no new peaks, and no increase in the small amount (2%) of the cis,trans ether present.

3β-Hydroxydihydrodrimenol ***19***

Lithium aluminum hydride (54 mg, 1.42 mmol) was added to a solution of the saturated hydroxy ester **20** (76 mg, 0.28 mmol) in 7 ml of tetrahydrofuran. The suspension was heated at reflux with stirring for 4 hr. The mixture was cooled, the excess hydride was destroyed by addition of 20% aqueous tetrahydrofuran, and the salt suspension was acidified with 10% sulfuric acid. Dilution with water and extraction with chloroform served to provide the product which was then sublimed (100–120°, 0.1 mm). The sublimate was recrystallized once from benzene; yield 54 mg (80%). A sharply melting specimen (158.5–160.5°) was obtained after additional recrystallizations from both benzene and aqueous methanol.

Anal. Calcd for $C_{15}H_{28}O_2$ (240.37): C, 74.95; H, 11.74. Found: C, 75.11; H, 11.82.

The diol (40 mg) was converted to the diacetate (**23**) by heating with 200 μl of acetic anhydride and 20 μl of pyridine at 75° for 1 hr. The excess reagents were removed under reduced pressure and the product was purified by sublimination (90–105°, 0.1 mm) and recrystallization (aqueous methanol) (mp 115–116°).

Anal. Calcd for $C_{19}H_{32}O_4$ (324.45): C, 70.33; H, 9.94. Found: C, 70.25; H, 9.88.

Hydrogenation of **17** *to* **19**

The bicyclic alcohol **17** (30 mg, 79 μmol) was hydrogenated in 15 ml of acetic acid with prereduced platinum oxide (62 mg) according to the procedure of Arigoni and co-workers for farnesiferol A (*2a*). The neutral residue (15 mg) was sublimed to give the crude diol (12 mg, 63%). A purified sample of **19** was obtained after several crystallizations from both benzene and aqueous methanol (mp 159–160°, mmp 158–160°). The infrared spectrum (potassium bromide pellet) of this material has a great deal of fine structure and is completely identical to a spectrum of **19** prepared from **20**. These two diols are indistinguishable on silica gel TLC in three different solvent systems.

A 5-mg portion of the diol was acetylated with acetic anhydride in pyridine as described above. The product was recrystallized four times from aqueous methanol, affording 4 mg of **23** with mp 114–115°, mmp 114–115.5°. The infrared spectrum of the two diacetates are superimposable.

Cyclization of **4** *according to Ohloff* (*19*)

Boron trifluoride etherate (0.71 ml, 5.8 mmol) was added with cooling to a solution of 14 μl of water in 115 μl of dimethylformamide under nitrogen. The epoxide **4** (568 mg, 1.49 mmol) in 0.5 ml of benzene and 1.0 ml of petroleum ether was quickly transferred in one portion to the cooled acid solution. The mixture was stirred vigorously at 25° for about 30 sec. The reaction was quenched with 5% sodium carbonate, and the product was separated by two ether extractions.

Initial purification was effected by chromatography on 15 g of alumina III (H/D 11), eluting with 25-ml portions of benzene–petroleum ether and ether–benzene mixtures. The second 10% ether–benzene fraction contained material corresponding to **16** on TLC. This and subsequent fractions, including a final 50-ml flushing with methanol, were combined (175 mg). This material was separated in a monocyclic alcohol fraction (17 mg) and a bicyclic alcohol fraction (21 mg) by a two-stage preparative TLC procedure. First a rough separation was accomplished with 5 plates developing in the usual fashion with 50% ethyl acetate–petroleum ether 60–68°, followed by repurification using the continuous development technique for four hours developing with 15% ethyl acetate–benzene.

The nmr spectrum of the monocyclic alcohol fraction shows one new methyl peak (9.26) and probably another superimposed on the signal at 8.98 due to **16** (approx 20% of the new component); otherwise the spectrum is the same as that of **16**. The bicyclic alcohol fraction exhibits in the nmr spectrum two additional methyl signals (9.15 and 9.18) as well as new absorption in the 5- to 6-τ region compared to **17**. This material was acetylated and by TLC analysis on silica gel-impregnated with 20 to 25% silver nitrate the acetate was found to be a mixture of two components, the acetate of **17** along with a more polar substance. The acetate of farnesiferol A **1** is of intermediate polarity and, therefore, different from either.

cis,trans-Farnesol (**30**)

The mother liquors remaining after the isolation of *trans,trans*-farnesyl diphenyl urethane (*24*) afforded after hydrolysis a farnesol mixture (25 g) enriched in **30**

(~1 : 1), but also containing diphenyl-amine. Chromatography on 750 g of silica gel–15% water (H/D 6) and elution with 8 liters of petroleum ether separated most of the amine. The next four 1-liter fractions (3 × 3% and 1 × 6% ether–petroleum ether) provided 13.3 g of a farnesol mixture enriched to about 3 : 1 in **30** (TLC analysis). This was combined with another 7.9 g of cis,trans-enriched farnesol (~5 : 1) similarly obtained and the total chromotographed on 1.2 kg of silica gel–15% water (H/D 10) taking 2-liter fractions (Table 5).

Fractions 5 and 6 were combined to give 9.0 g of **30** contaminated with some nerolidol and ethyl diphenyl urethane. This material was treated with 12.0 g of phthalic anhydride in 30 ml of pyridine for 2.5 hr at 25°. The solution was diluted with ether and the pyridine removed by extraction with 10% sulfuric acid. The acid phthalate of **30** was then separated by alternating extractions between 10% potassium carbonate (once) and water (twice). This sequence was repeated four times, the combined carbonate and water extracts were acidified, and the acid phthalate was obtained by ether extraction. The half ester (15.4 g) was hydrolyzed with potassium hydroxide (35 g) in 350 ml of methanol and 42 ml of water after 2.5 hr at reflux. The *cis,trans*-farnesol was extracted with petroleum ether and distilled (0.05 mm) to yield 7.03 g, $N_D^{25°}$ 1.4877 (lit. 1.4865) (*24*). The purity is estimated to be about 95% by vpc analysis (10% Apiezon L, programming 160–260°) of the corresponding methyl ether.

cis,trans-Umbelliprenin (**32**)

To a cooled (0°) solution of **30** (6.96 g, 31.3 mmol) in 150 ml of petroleum ether (60–68°) was added 1.50 ml (4.25 g, 15.7 mmol) of phosphorous tribromide. After 30 min the reaction mixture was diluted with water and extracted with petroleum ether. The organic phase was rinsed with 5% sodium bicarbonate and saturated sodium chloride then concentrated to the liquid *cis,trans*-farnesyl bromide **31** (8.7 g, 97%) under reduced pressure.

The cis,trans ether was prepared in the same manner as its trans,trans isomer with 7.4 g (45.8 mmol) of umbelliferone and 1.15 g (48 mmol) of sodium hydride in 120 ml of dimethylformamide. Chromatography of the product on 465 g of silica gel–15% water (H/D 8) and elution over the range of 10 to 15% ether–petroleum ether (750-ml fractions) afforded 7.38 g (64%) of **32**, homogeneous on TLC. Since

TABLE 5

Fraction	Eluent (%)	Weight (g)
	Ether–petroleum ether	
1	3 × 0	0.22
2	2 × 1	.05
3	4 × 2	.91
4	2 × 3	1.60
5	1 × 3	1.75
6	3 × 4	7.80
7	2 × 5	4.10
8	2 × 10	4.20

this material could not be induced to crystallize, a sample was purified for analysis by preparative TLC on silica gel GF developing with 32% ethyl acetate–petroleum ether 60–68°.

Anal. Calcd for $C_{24}H_{30}O_3$ (366.48): C, 78.65; H, 8.25. Found: C, 78.88; H, 7.79.

cis,trans-Bromohydrin (**33**)

The cis,trans ether (7.25 g, 19.8 mmol) was converted to the terminal bromohydrin by reaction with 4.23 g (23.8 mmol) of recrystallized *N*-bromosuccinimide in 100 ml of dimethoxyethane and 25 ml of water as described for the trans,trans isomer. The product was purified by chromatography on 500 g of silica gel–15% water (H/D 12) in a similar fashion; yield, 4.94 g (54%). The analytical specimen was obtained by preparative TLC on silica gel.

Anal. Calcd for $C_{24}H_{31}O_4Br$ (463.41): C, 62.20; H, 6.74; Br, 17.25. Found: C, 61.98; H, 6.56; Br, 17.39.

cis,trans-Epoxide (**34**)

The bromohydrin (4.81 g, 10.4 mmol) was stirred with 1.58 g (1.14 mmol) of anhydrous potassium carbonate in 130 ml of methanol for 30 min at 25°. The oily epoxide **34** was isolated by ether extraction and used without further purification: yield, 3.83 g (96%). Preparative TLC on silica gel afforded the analytical sample.

Anal. Calcd for $C_{24}H_{30}O_4$ (382.48): C, 75.36; H, 7.91. Found: C, 74.98; H, 7.60.

Reaction of **34** *with Boron Trifluoride Etherate*

Distilled boron trifluoride etherate (0.61 ml, 5.0 mmol) was added to a stirred solution of the epoxide (1.60 g, 4.19 mmol) in 90 ml of anhydrous benzene. After about 60 sec the reaction was quenched and the product isolated as before. The less polar products were separated by chromatography on 48 g of alumina III (H/D 6.5) after elution with 150 ml portions of 0, 10, 15, and 20% ether–benzene. The column was then stripped with 300 ml of methanol to give the crude bicyclic alcohol fraction (274 mg).

Further purification was accomplished by preparative TLC on silica gel (9 plates) using continuous development with 18% ethyl acetate–benzene for 2.5 hr. The two major and more polar zones were collected and purified again by preparative TLC. The less polar bicyclic alcohol **35** (66 mg, 4%) was recrystallized several times from methanol, mp 164–167°.

Anal. Calcd for $C_{24}H_{30}O_4$ (382.48): C, 75.36; H, 7.91. Found: C, 75.39; H, 7.96.

The more polar alcohol **36** (34 mg, 2%) after several crystallizations from methanol had mp 152–156°. The identity of this substance as the racemate of farnesiferol A was established by infrared and nmr spectral comparison. The natural and synthetic samples were also found to be indistinguishable by TLC on silica gel (three solvent systems) and silica gel–30% silver nitrate.

Anal. Calcd for $C_{24}H_{30}O_4$ (382.48): C, 75.36; H, 7.91. Found: C, 75.02; H, 8.10.

Synthetic farnesiferol A **36** (33 mg) was hydrogenated in 15 ml of acetic acid with 60 mg of platinum oxide in the same manner as **17**. The neutral product was

sublimed to give 13 mg of a white solid which was not separable by TLC from material similarly obtained from natural farnesiferol A. Recrystallization from benzene afforded the pure, racemic diol, mp 179–181°.

The diacetate was obtained from the diol (4 mg) with acetic anhydride-pyridine after heating on a steam bath for 45 min and standing overnight at room temperature. The product was recrystallized from aqueous methanol, mp 108–111°. The infrared spectrum of this material is identical to the spectrum of the diacetate derived from the natural product.

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