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Biogenetic-Type Synthesis of Hydroxylated Tricyclic Diterpenes in the Pimarane Class

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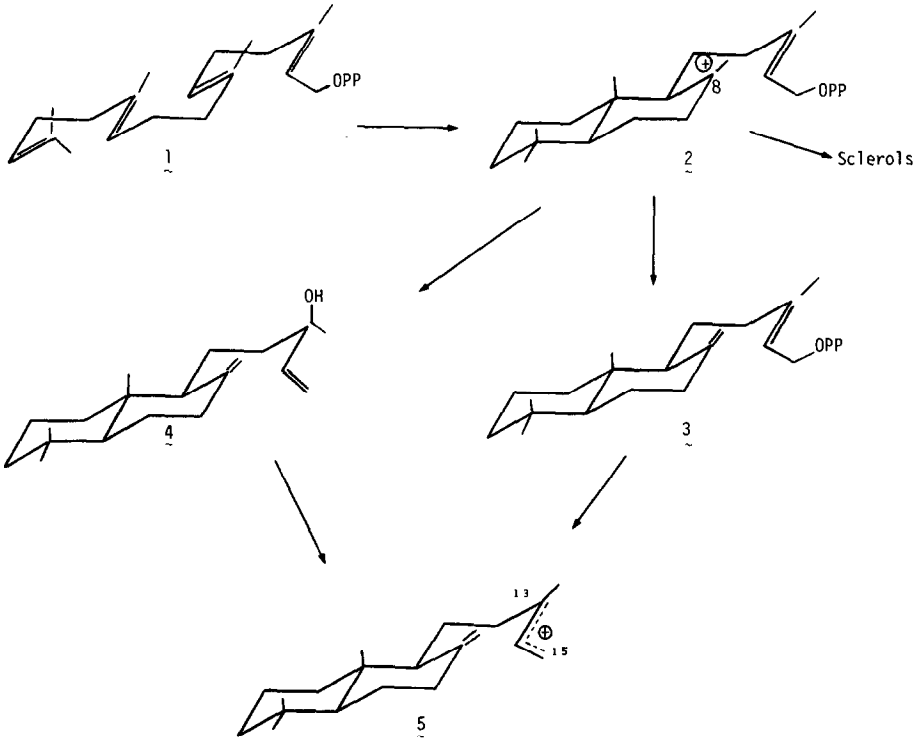
The biogenetic-type synthesis of various diterpenoids (in the racemic form) possessing the pimarane backbone was achieved through nonenzymic cyclization of the oxide of methyl geranylgeranyl carbonate (**46**). Treatment of oxide **46** with $BF_3 \cdot Et_2O$ in CH_3NO_2 effected formation of pimaradienol **36**, isopimaradienol **39**, and the naturally occurring tricycle **40**. Acid treatment of either **39** or **40** led to an equilibrium mixture which includes isomer **41**, also of natural origin. Side-chain oxidation of dienol **40** afforded araucarol (**16**), a third plant product. Other substances formed in the cyclization of oxide **46** are described, and a mechanistic interpretation of the overall reaction course is presented.

Chart 1 portrays the biogenetic pathway by which many polycyclic diterpenes are believed to be formed. Initial cyclization of geranylgeranyl pyrophosphate **1**



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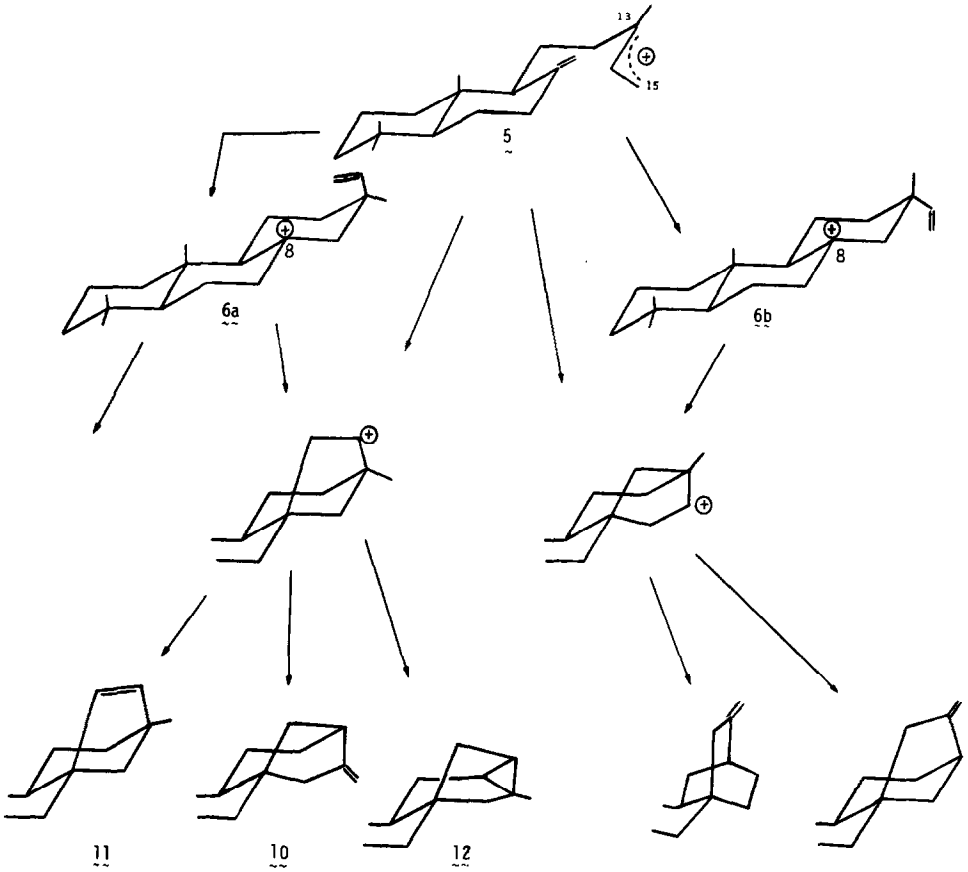
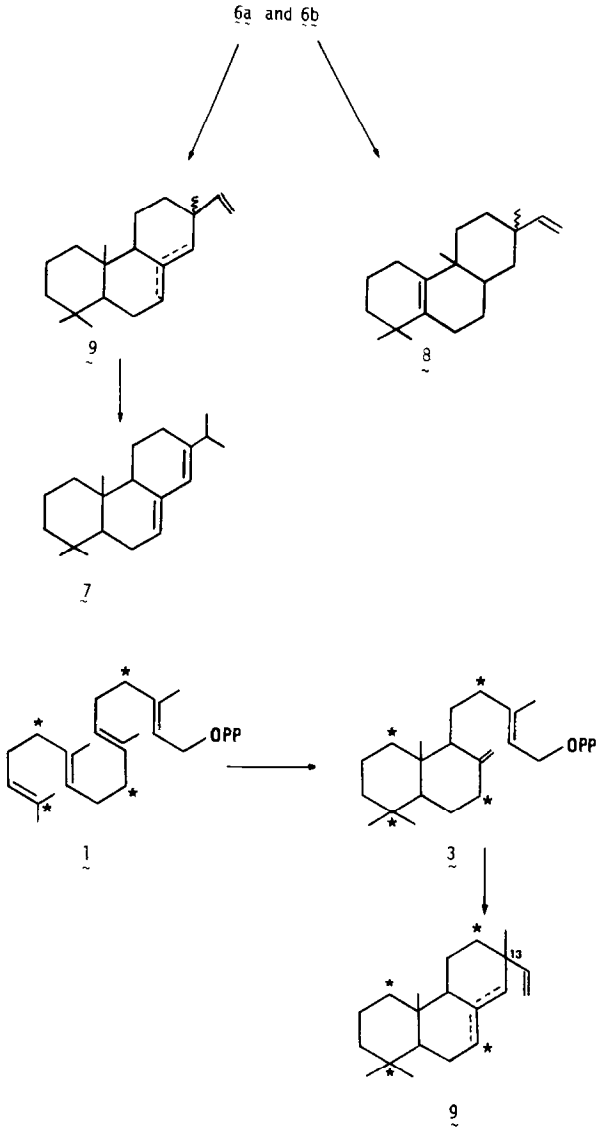
leads via bicyclic intermediate **2** to copalyl pyrophosphate **3**, which has been isolated (*1*) and implicated in further biosynthetic transformations. Reaction of carbonium ion **2** is considered to give rise to the sclerols, manoöl (**4**), and backbone rearranged labdanes. Subsequent to formation of the allylic carbonium ion **5**, generated by solvolysis of copalyl pyrophosphate **3**, cyclization in an alternate fashion can occur, yielding the C-13 epimeric pimarane carbonium ions **6a** and **6b** (Chart 2). Backbone rearrangements lead to the abietadiene (**7**) and rosadiene (**8**) skeleta, while elimination provides the pimaradiene skeleton (**9**) (Chart 3). Carbonium ion species **6a** and **6b** can also cyclize further, affording tetracyclic systems, as indicated in Chart 2.



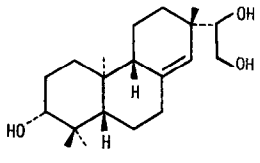
As early as 1958, Birch *et al.* (*2*) established that the biosynthetic pathway to gibberellic acid GA3 proceeds from geranylgeranyl pyrophosphate (**1**) through bicyclic intermediate **3** and thence to a pimaradiene-type species **9** (Chart 4); and later experiments by Cross *et al.* (*3*) and Graebe *et al.* (*4*) showed that (−)-kaurene (**10**) is also a precursor of the gibberellins. Recently West and Fall (*5*), Hanson and White (*6*), and West and Robinson (*7*) corroborated the above find-



ings and also established the intermediacy of geranylgeranyl pyrophosphate in the biosynthesis of beyerene (**11**) and trachylobane (**12**).

The role of **5** and **6** as biological intermediates has prompted several groups (*8–11*) to initiate nonenzymic experiments starting with bicyclic or tricyclic compounds, in order to determine the further disposition of these species. The work outlined in this paper is concerned, however, with the abiological production of 3-hydroxylated tricyclic material from the terminal epoxide of geranylgeranyl esters. A number of natural products having the 3-hydroxypimaradiene-type structure have been isolated and characterized. Darutigenol (**13**) is present in *Siegesbeckia orientalis L.*, which is found in Madagascar (*12*). Ent-isopimara-

8(14),15-diene-3-β-ol (**14a**) (*13*) as well as its antipode (**14**) (*14*) have been isolated from *Cleistanthus Schlechteri var.* Schlechteri heartwood and *Xylia dolabriformis* (Pynkado) heartwood, respectively. The 7(8) double-bond isomer, deoxyoblongifoliol (**15a**) (*15*) has been found in the bark of *Croton oblongifolius,* and its antipode (**15**) appears in the New Zealand kauri heartwood (*16*) (*Agathis australis*). Kauri resin contains large amounts of araucarol (**16**) and araucarone (**17**). These substances may well arise by enzymic cyclization of 14,15-oxidogeranylgeraniol (**18,** X = OH) (or its pyrophosphate, **18,** X = OPP), a reasonable precursor and a natural product in its own right. Realization of the same cyclization course by nonenzymic means, and when necessary followed by appropriate oxidation of the resulting tricyclic products, would permit the total synthesis of the above natural products. In such a plan, timing of the various chemical events ($k_1 : k_2 : k_3$) is crucial—starting material **18** and anticipated, unisolated intermedi-



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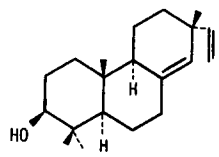

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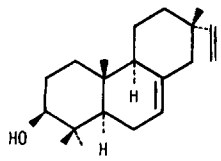

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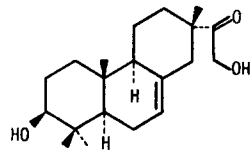

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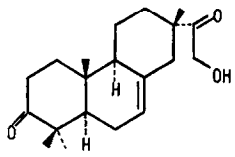

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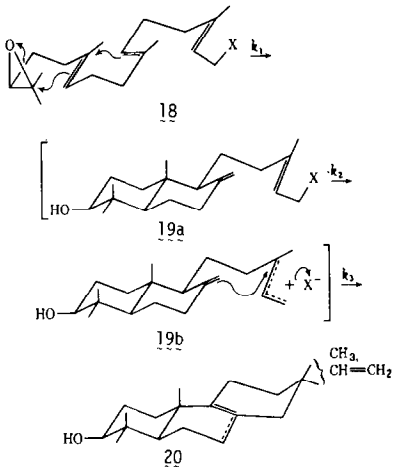
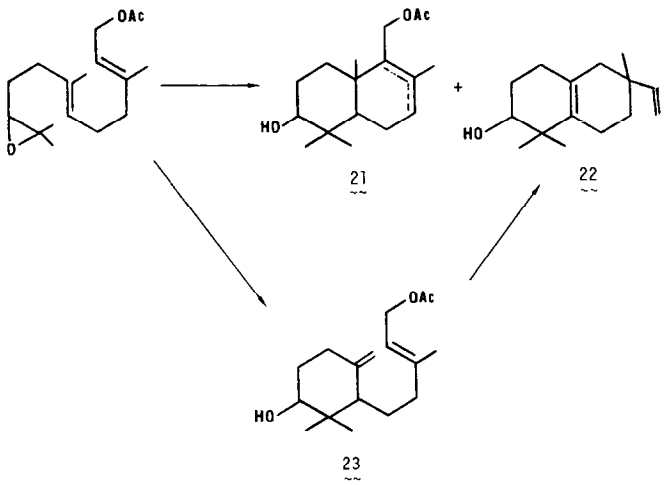
ates **19a** and **19b** are subject to a number of side reactions, many of which have been observed in similar systems, and all of which must be minimized in order that significant amounts of **20** be produced in one reaction vessel. For example, if loss of X occurs (a) much more rapidly from **18** than k_1 or (b) much more slowly from **19a** than $k_2 - k_3$, undesired cyclizations or other phenomena could prevail. Furthermore, the single catalyst and solvent combination utilized obviously must be suitable for all three reactions. Opportunity for control is offered in the choice of catalyst, solvent, and leaving group X.

A precedent for the pathway by which such a cyclization sequence could occur

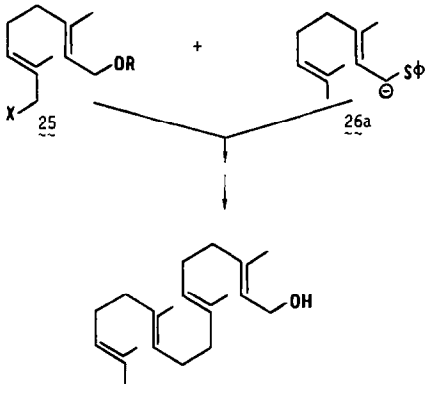


is the finding in this laboratory (*17*) that phosphoric acid cyclization of farnesyl acetate terminal epoxide produced, in addition to the expected product **21,** a substance assigned the structure **22.** Such a product necessitates the intermediacy of **23,** a manoöl-type compound possessing an exocyclic methylene group. Subsequent work by van Tamelen and Nadeau (*18*) revealed that although geranylgeranyl acetate terminal epoxide (**18**) (R = OAc) under similar conditions failed to produce any identifiable product, the use of stannic chloride in benzene afforded a small amount of a tricycle arising via the "normal" cyclization mode. This present endeavor represents a thorough reinvestigation and extension of this earlier assay.



Despite a number of published syntheses (*18, 19*) of geranylgeraniol (**24**), certain advances in selenium dioxide oxidation methodology (*20*) motivated us to embark upon a new stereoselective synthesis, utilizing the coupling of two C_{10}

units, both derived from the inexpensive, commercially available geraniol.[1] Alkylation (*21*) of geranyl thioether (**26**) anion (**26a**) by an allylic halide **25**, followed by reductive cleavage of the allylic carbon–sulfur bond, would afford the desired head-to-tail linkage of the two geranyl moieties.



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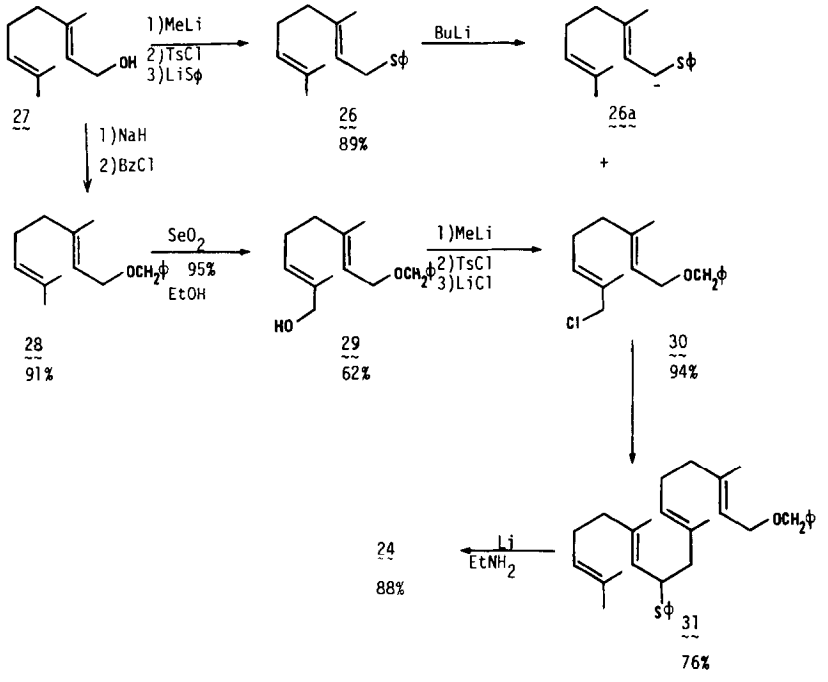
geranylgeraniol

In practice, titration of geraniol (99.9% trans) (**27**) in an ether : hexamethyl phosphoric triamide mixture with methyllithium at 0°C followed by immediate quenching with *p*-toluenesulfonyl chloride afforded the allylic tosylate which, in the same reaction vessel, was subjected to displacement by thiophenoxide anion. Chromatographic purification on silica gel afforded the desired geranyl thiophenyl ether (**26**) in 89% yield. Similar alkoxide formation followed by addition of benzyl chloride afforded 91% of the benzyl ether **28** after chromatographic purification of the reaction mixture. The benzyl ether was then subjected to selenium dioxide oxidation in refluxing 95% ethanol for 1.5 hr. Allylic alcohol **29** of 99.9% purity was obtained after calcium chloride complexation under highly controlled conditions.

Through the method of Stork *et al.* (*22*), allylic alcohol **29** was converted to the corresponding chloride **30** by titration with methyllithium followed by addition of *p*-toluenesulfonyl chloride and then lithium chloride, providing a 94% yield of the pure trans product. A Biellmann-type coupling (*21*) was then executed on the two fragments **26** and **30** to afford the desired C_{20} skeleton. The thiophenyl ether **26** was treated with butyllithium in tetrahydrofuran to produce the anion **26a**. Freshly purified chloride **30** was added, after which quenching, work-up, and chromatographic purification afforded the coupled product **31** in 76% yield. Geranylgeraniol was unmasked by simultaneous reduction (*23*) of both the thiophenyl and benzyl moieties with lithium in ethylamine, the desired crude product being afforded in 88% yield. Gas chromatographic analysis revealed 90% all *trans*-geranylgeraniol

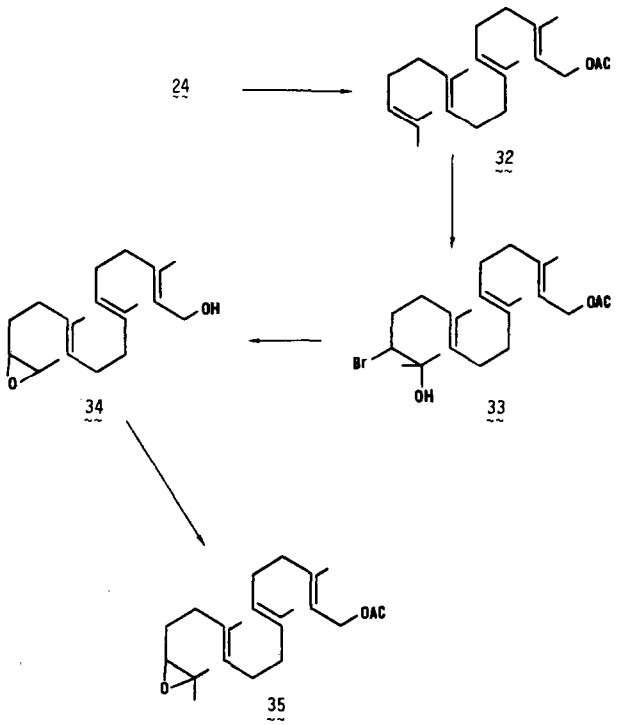
[1] Primary sources utilized for geraniol were Givadaun (France) and Fluka (Switzerland) whose American distributor is Columbia Organics.



contaminated by one other component presumed to be the product from conjugate reduction of the thiophenyl ether moiety (3,7,11,15-tetramethyl-2,6,9,14-hexadecatetraen-1-ol). Material of 99% all trans purity was obtained by fractional recrystallization of the corresponding diphenyl carbamate from methanol.

Conversion of geranylgeraniol to the various potential cyclization substrates entails terminal epoxidation and appropriate acylation of the hydroxy group. Acetylation with acetic anhydride in pyridine afforded a quantitative yield of geranylgeranyl acetate (**32**), treatment of which with 1 mole equivalent of *N*-bromosuccinimide in a tetrahydrofuran–water mixture gave a crude product which was chromatographically purified to yield 60% of the desired bromohydrin **33**. Conversion to the epoxide, accompanied by saponification, was accomplished by treatment of the bromohydrin with potassium carbonate in methanol at room temperature, yielding **34**. Reacetylation with acetic anhydride in pyridine was nearly quantitative, affording all *trans*-geranylgeranyl acetate terminal epoxide **35**. Although purification can be carried out at various stages between geranylgeranyl acetate **32** and geranylgeranyl acetate terminal epoxide **35**, a 60% overall yield of the acetoxy terminal epoxide involving utilization of crude intermediates can be realized. The epoxide was generally stored as the acetate, which was found to be more stable than the geranylgeraniol terminal epoxide **34**. The acetyl unit can be quantitatively excised from the molecule with potassium carbonate in methanol, thus allowing ready access to the other acylated species used in attempted cyclizations.

The possible products possessing the pimarane backbone are shown in Charts 5 and 6. Depending on the conformation of the allylic carbonium ion side chain,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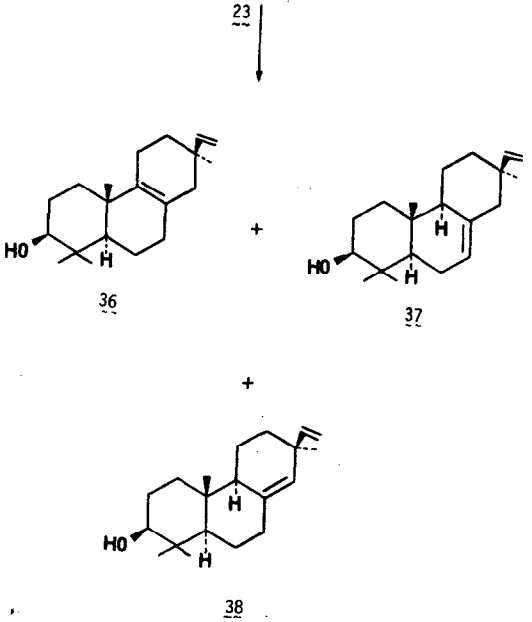
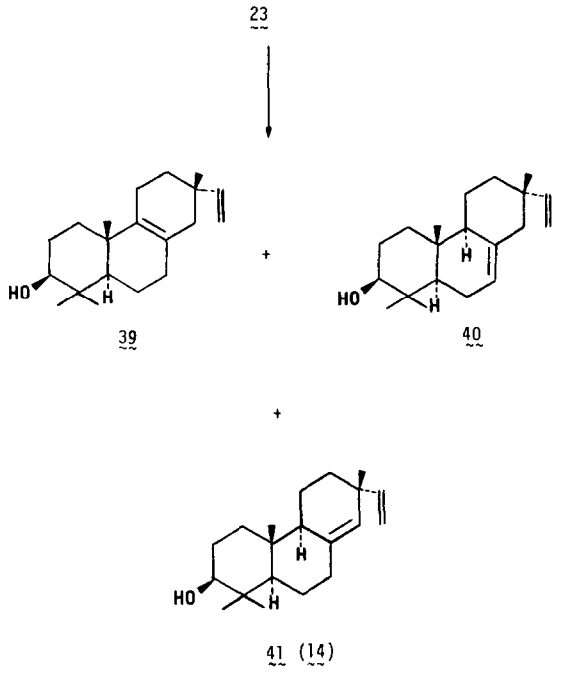
OAc
32
OAc
Br
OH
33
OH
O
34
OAc
O
35

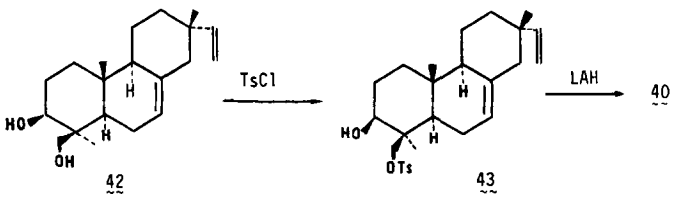

23
HO
H
36
+
HO
H
H
37
+
HO
H
H
38



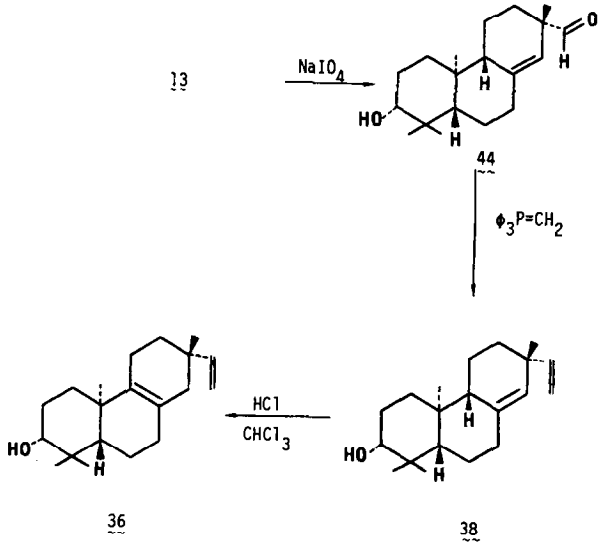
formation of C-13 epimers, each collapsing by three possible modes of proton loss, is permitted. Thus, one may envision production of the 8(9), 7(8), or 8(14) double-bond isomers **36, 37,** or **38,** each having a beta vinyl group in the C ring, exemplified by darutigenol **13** (*12*). In addition, one may equally expect production of the 8(9), 7(8), or 8(14) double-bond isomers **39, 40,** or **41** in which the C-ring vinyl group is alpha. Both **40** and **41** as well as their corresponding antipodes, are found in nature (*13–16*), and the natural products araucarol **16** and araucarone **17** (*16*) are derivable from these intermediates.

From natural sources it was possible for us to obtain material which could be transformed into five of the six possible 3-hydroxypimaradienes, expected to be useful as reference compounds. Treatment of a chloroform solution of the naturally occurring isopimara-8(14),15-diene-3β-ol **41** with hydrogen chloride gas, the method of Wenkert and Kumazawa (*9c*), established an equilibrium mixture of the three isomers **39, 40, 41,** with a predominance of the 8(9) isomer **39.** A convenient method for obtaining larger amounts of the 7(8) isomer **40** involves transformation of virescenol B (**42**) (*24*)[2] to the mono *p*-toluene-sulfonate **43,** which was then reduced to the diene **40** by the action of lithium aluminum hydride, a conversion identical to that previously performed (*24*) on iso-Virescenol B, the 8(9) isomer. Acid treatment of **40** afforded the same isomeric mixture obtained from **41,** as did authentic natural product **40,** obtained by acetone extraction of *Agathis australis* heartwood from New Zealand.

[2] A sample of Virescenol B was supplied to us by Mme. Polonski, Institut de Chimie des Substance Naturelles, CNRS, Gif-sur-Yvette, France.



Periodate cleavage of darutigenol, as described by Diara *et al.* (*12c*), quantitatively afforded the aldehyde **44,** which when treated with methylene triphenyl phosphine ylid, gave the desired ent-pimara-8(14),-15-diene-3β-ol **38.** By treatment in chloroform with dry HCl gas, an equilibrium mixture was established containing predominantly the 8(9) isomer **36.** A third entity, possibly the 7(8)



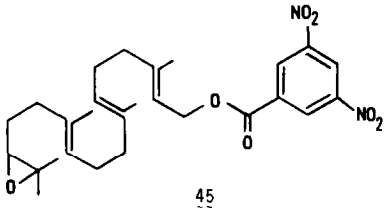
isomer **37,** was also formed low yield; but since it neither existed in the cyclization mixtures nor had any intrinsic value of its own, isolation and characterization were not pursued.

Cyclization studies were initiated on the acetate of geranylgeraniol terminal epoxide (**35**). The presence or absence of the acetate function in product served as a convenient criterion for pimarane production, since by necessity, acetate must be lost in order to effect ring-C closure in a manner which can produce the pimarane cation. The presence of acetate may be easily discerned in the nmr by reason of its downfield methyl resonance at δ = 1.94 ppm (carbon tetrachloride).

In an effort to utilize conditions similar to those employed in farnesylacetate epoxide cyclization experiments (*17*), we carried out initial cyclization studies with cold 85% phosphoric acid. Thus, acetate epoxide **35** was added to vigorously vibrating phosphoric acid at approximately −35°C under nitrogen. After 1 hr, work-up revealed a mixture of products, some of which had thin-layer chromato-

graphic (TLC) mobility expected for the desired 3-hydroxypimaradienes. Isolation by preparative TLC and analysis by nmr spectroscopy revealed, however, that this material had not fully cyclized. The other products were also purified and analogously were shown not to have fully cyclized. Other acid catalysts were therefore auditioned in an effort to effect the desired transformations.

Stannic chloride in polar media had been successfully utilized previously for epoxide polyene cyclizations (*17, 18, 25*). In this study, variations were introduced by changing solvent, temperature, and reaction time. Nitromethane, acetonitrile, benzene, and ether as well as times from 1 min to many hours were employed at temperatures ranging from 0°C to room temperature. Appropriate TLC areas were purified and examined, revealing no material possessing the pimarane backbone. In all cases, the acetate function had not solvolyzed. It seemed logical, therefore, to replace the acetate with a more labile group which could still serve as a useful nmr probe, and toward that end the 3,5-dinitrobenzoate **45** and the methyl carbonate **46** were investigated. The dinitrobenzoate group possesses ring protons well downfield at δ = 9.08 ppm (carbon tetrachloride), quite divorced from all other nmr signals of interest. Similarly, the methyl carbonate function imparts a strong singlet at δ = 3.66 ppm (carbon tetrachloride).



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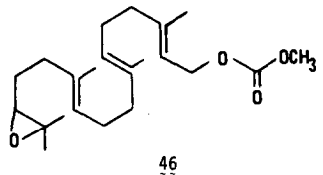

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Geranylgeranyl 3,5-dinitrobenzoate terminal epoxide (**45**) was conveniently prepared by acylation of geranylgeraniol terminal epoxide with an excess of 3,5-dinitrobenzoyl chloride in pyridine at room temperature. Similarly, geranylgeranyl methyl carbonate terminal epoxide (**46**) may be prepared within hours by the action of distilled methyl chloroformate on geranylgeraniol terminal epoxide in pyridine. Both esters may be purified chromatographically.

Cyclization experiments showed the dinitrobenzoate **45** to be quite resistant to solvolysis. Phosphoric acid treatment at various temperatures produced material showing no signs of benzoate loss or C-ring formation. Concurrently, investigation of the carbonate cyclization met with success; and thus further experimentation with the dinitrobenzoate was curtailed.

Methyl geranylgeranyl carbonate terminal epoxide **46** was introduced into vibrating phosphoric acid at 0°C under argon. Upon work-up, the crude reaction mixture was found to possess material having the same broad chromatographic mobility as that of the 3-hydroxypimaradienes. This material was isolated but proved to be a complex mixture, as shown by gas chromatography. The major component, though not identical to the 3-hydroxypimaradienes **36** or **38**, had a

retention time which appeared reasonable for tricyclic material. Once isolated, the major component was shown not to possess the carbonate group but did have the requisite vinyl group as well as a pimarane C ring, as evidenced by its nmr spectrum. This compound, formed in very low yield, was subsequently identified as isopimara-8(9),15-diene-3β-ol (**39**). These results encouraged us to initiate cyclizations of methyl carbonate **46** with other Lewis acids.

Although neither stannic chloride nor picric acid afforded material possessing the desired pimarane backbone, boron trifluoride etherate in nitromethane gave not only isopimara-8(9),15-diene-3β-ol **39** but also an equal amount of pimara-8(9),15-diene-3β-ol **36** and, in low yield, the natural product (*19, 20*) isopimara-7(8),15-diene-3β-ol **40.** Other solvents such as benzene or acetonitrile resulted in poorer yields of these products in the same distribution. In addition, efforts were made to quench the reaction before completion in order to investigate the possible intermediacy of the other double-bond isomers, colder temperatures, and shorter reaction times being employed. It was found, however, that even at $-20°C$, in 15 sec all the starting material had been consumed, and the same product distribution was apparent on workup. Typically, therefore, the starting material was added neat to a stirred solution of distilled boron trifluoride etherate in distilled dry nitromethane at 0°C under dry nitrogen. The reaction was then quenched after 30 min by addition to a 50:50 mixture of saturated sodium hydrogen carbonate and diethyl ether. The crude reaction mixture appeared as four major segments by TLC. The percentages of each component (*A*, *B*, *C*, and *D*), including the remaining plate extracts are shown in Table 1.

As analyzed by gas chromatography (OV 225 and OV 17), 65% of the least polar section, *A*, was composed of a mixture of equal amounts of material having the same retention times as isopimara-8(9),15-diene-3β-ol **39** and pimara-8(9),15-diene-3β-ol **36,** its C-13 epimer. In addition, 5% of *A* exhibited gas chromatographic behavior identical to that of the natural product isopimara-7(8),15-diene-3β-ol **40.** Various analytical systems were developed to cope with the difficult separation of these similar double-bond isomers. Initial separation of components was effected by multiple elution TLC on silver-nitrate-impregnated silica gel, with small percentages (0.1–0.5%) of isopropanol in benzene as the eluent serving

TABLE 1

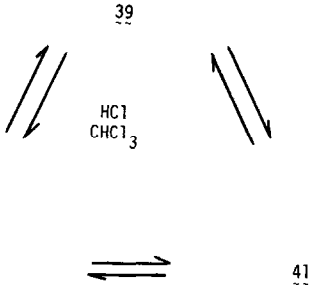
CYCLIZATION OF GERANYLGERANYL METHYL CARBONATE TERMINAL EPOXIDE IN NITROMETHANE AT 0°C WITH BORON TRIFLUORIDE ETHERATE CATALYSIS

Fraction	%	R_f (25% ethyl acetate : hexane)
A	19.3	0.44
B	10.6	0.40
C	36.2	0.28
D	17.4	0.23
Remainder[a]	16.4	—

[a] Excluding solvent front and origin.

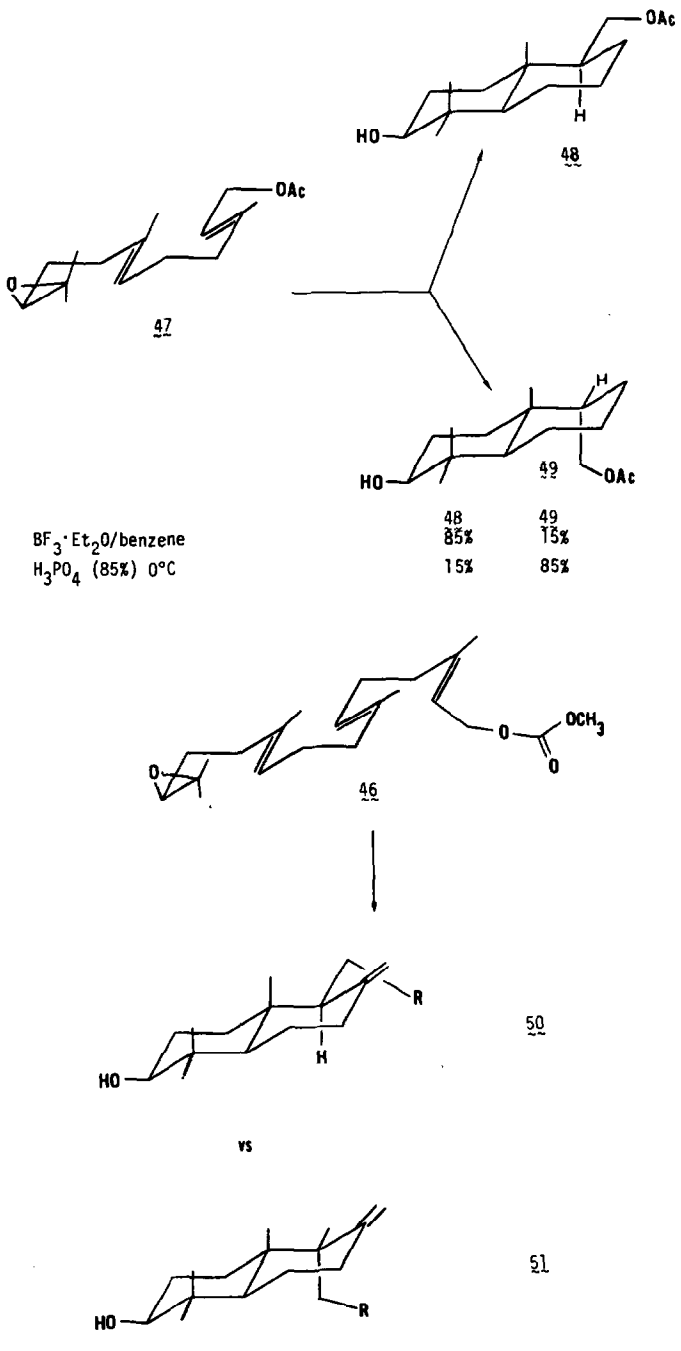
admirably. The enriched fractions were then subjected to high-pressure liquid chromatographic (HPLC) procedures and finally purified by preparative gas chromatography with 3% OV 225 on Gas Chrom Q. Comparison of chromatographic and spectral data of the three compounds and their corresponding previously prepared standards confirmed their structures. Considering the mechanistic complexity necessary for the production of these compounds, the production of a significant amount of any such product is remarkable. The isolation of the natural product isopimara-7(8),15-diene-3β-ol **40** from this cyclization formally constitutes its total synthesis.

By means of the procedure of Wenkert and Kumazawa (*9c*), an equilibrium was established between the three isopimadiene structures **39, 40,** and **41.** In this



method, a solution of each isomer in dry chloroform at 0°C was treated for 2 to 4 hr with dry gaseous hydrogen chloride, thereby producing the equilibrium mixture of all three isomers. Since both **39** and **40** were formed by the cyclization of methyl geranylgeranyl carbonate terminal epoxide **46,** this isomerization formally constitutes the total synthesis of the two antipodal natural products isopimara-8(14),15-diene-3β-ol **14** and ent-isopimara-8(14),15-diene-3β-ol **14b.** These structures were confirmed by comparison of their chromatographic and spectral characteristics with those of authentic specimens.

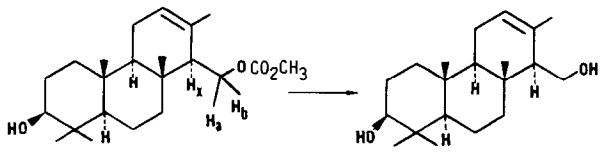
One might ask, at this point, why both C-13 epimeric 8(9) isomers, **36** and **39,** are formed in the boron trifluoride etherate cyclization of the methyl carbonate **46** while only one epimer, **39,** is formed during phosphoric acid cyclization of the same substrate. Earlier work in these laboratories on the cyclization of *trans, trans*-farnesyl-acetate terminal epoxide **47** (Chart 7) had shown that boron trifluoride etherate afforded a product (**48**) requiring a chair–chair transition state conformation for cyclization. Interestingly, the primary product (**49**) of phosphoric acid cyclization possessed a pseudo-axial acetoxymethylene, suggesting a chair–boat conformation for cyclization. Mediation of phosphoric acid (the solvent as well as initiator) in determining the conformation of the transition state could account for the observed difference. Similarly, one may speculate that the initial bicyclic intermediate **51** is produced during phosphoric acid cyclization, whereas **50** is produced during boron trifluoride etherate cyclization. The equatorially disposed side chain of **50** has no great rotomeric preference, as indicated in numerous manoöl cyclizations. Examination of models of **51** indicates steric inter-



actions of the axially disposed side chain which could cause a conformational preference leading to the single product observed. Likewise, C-ring formation (as in the previous B-ring formation) may be subject to solvent effects causing a preferred conformation in the transition state. The problem is further compounded

by the C-9 proton loss in the formation of final products. A combination of the above effects may contribute to single-epimer production observed in phosphoric acid.

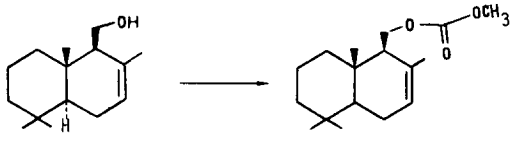
The nature of the remaining products formed in the boron trifluoride etherate cyclization of methyl carbonate **46** warrants some discussion. Component *C* (Table 1) of the semipurified reaction mixture was a solid, shown to be almost homogeneous by multiple elution TLC using silver-nitrate-impregnated silica gel plates. Further purification with this chromatographic system produced homogeneous material. An nmr spectrum of this compound revealed (a) that the methyl carbonate had maintained its integrity and (b) the allylic-ether methylene (H_{ab}) doublet centered at $\delta = 4.67$, $J = 7$ Hz (d_6-benzene) was absent, and in its stead was an ABX pattern centered at $\delta = 4.32$ (d_6-benzene) indicating C-ring formation. Other salient features of the nmr spectrum such as the C-3 axial hydrogen doublet of



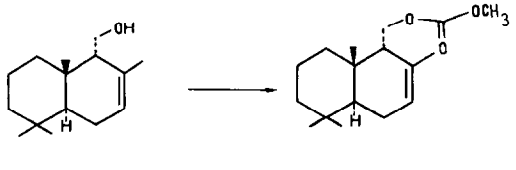
52 57

doublets centered at $\delta = 3.02$ (d_6-benzene) and the single remaining olefin proton (H_c) at $\delta = 5.45$ (d_6-benzene) indicated **52** as the structure. Double-resonance experiments in the methine (H_b) region ($\delta = 2.08$) cleanly collapsed the eight-line ABX pattern to a four-line AB pattern.

To be certain of the stereochemistry at C-14 in ring C, model compounds **55** and **56** were synthesized from drimenol **53** and epidrimenol **54** by treatment with methyl chlorofomate in pyridine. The nmr spectrum of methyl drimenyl carbonate **55** contains the eight-line ABX methylene (H_{ab}), carbonate methyl, and olefin



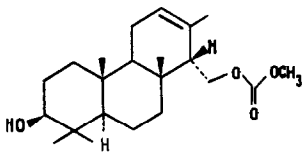
53 55



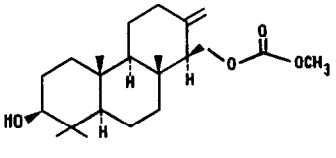
54 56

proton (H_c) which are superimposable on those observed for **52.** Methyl epidrimenyl carbonate **56,** however, produced a distorted ABX pattern, the doublet-like absorption centered at $\delta = 4.29$ being distinctly different from that of **52.** The structure of **52,** however, was corroborated by hydrolysis to the corresponding diol **57,** the mass spectral properties of which are in accord with those published.

Component *D* (Table 1) of the semipurified reaction mixture was shown by multiple elution TLC on silver-nitrate-impregnated silica gel to consist of two compounds which were separated by this chromatographic system into a higher R_f component DH and a lower R_f component DL. Nuclear magnetic resonance examination of compound DH revealed a carbonate methyl, a distorted ABX pattern, and olefin protons identical to those found for methyl epidrimenyl carbonate **56.** All other features were similar to those of **52.** Thus, DH appeared to be the C-14



58



59

epimer of **52** and was assigned structure **58.** The nmr spectrum of compound DL, though maintaining the general backbone properties of its cogeners, distinctly displayed an exomethylene pattern of two doublets at $\delta = 4.79$, $J = 1$ Hz and $\delta = 4.96$, $J = 1$ Hz (d_6-benzene) and other olefin signals. In addition, the vinyl methyl resonance, apparent in both **52** and **58,** was completely missing. DL was assigned structure **59,** the exocyclic methylene counterpart of **52.** The stereochemistry at C-14 was designated as beta due to the clean ABX pattern, which was similar, but not identical, to that observed for **52.**

The remaining material, component *B* (Table 1), appeared to be a complex mixture, as indicated by silver-nitrate-impregnated silica gel chromatography. In addition, examination of the nmr spectrum of the mixture indicated no material possessing the 3 beta-hydroxy function, as evidenced by the absence of the doublet of doublets at $\delta = 3.02$ (d_6-benzene). Isolation and characterization were therefore abrogated.

Oxidation of the vinyl side chain of isopimara-7(8),15-diene-3β-ol **40** with potassium permanganate in a dimethoxyethane : acetic anhydride mixture followed by basic hydrolysis of the acetates afforded the racemic version of araucarol, a naturally occurring diterpenoid. The structure was confirmed by nmr and mass spectral comparison with authentic material. Since isopimara-7(8),15-diene-3β-ol **40** was produced during the cyclization of geranylgeranyl methyl carbonate terminal epoxide, the final transformation completes the total synthesis of *dl*-araucarol.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope and are un-

corrected as are the boiling points. Nuclear magnetic resonance spectra (nmr) were taken on a Varian T-60 spectrometer for 60-MHz spectra and the Varian XL-100 pulsed Fourier transform spectrometers for 100-MHz spectra at Stanford University. Tetramethylsilane was used as an internal standard with chloroform-*d* and carbon tetrachloride, while residual benzene was used in d_6-benzene. All chemical shifts are reported in parts per million (ppm) on the δ scale. Microanalyses were performed at Stanford University by E. Meier and J. Consul. Low-resolution mass spectra were obtained at 20 eV on an Atlas CH-7 mass spectrometer interfaced with a Varian Aerograph 2100 gas chromatograph by J. Trudell at the Stanford Medical Center. High-resolution mass spectra were determined at 70 eV on an AEI MS-9 spectrometer or on a Varian MAT 711 spectrometer under the supervision of Annemarie Wegmann.

Analytical TLC was carried out on commercially available (Analtech) 2.5 × 9-cm plates or 5 × 20-cm plates precoated with Merck silica gel GF (0.25-mm thickness). Compounds were detected by spraying the developed plate with a 15% phosphomolybdic acid : methanol solution followed by heating. Preparative TLC was performed on 20 × 20-cm plates coated with Merck silica gel HF-254 (0.5-, 1-, and 2-mm thickness; 75-g silica gel/165 ml water will produce three 1-mm plates). Silver-nitrate-impregnated TLC plates were prepared by addition of a solution of 7.5 g silver nitrate in 160 ml of water to 75 g of silica gel. Material was removed from preparative TLC plates by washing the silica with diethyl ether. When a dilute methanolic Rhodamine 6-G spray was used for visualization, small amounts of extracted Rhodamine were removed by passage of the ether through either an appropriate quantity of magnesium sulfate or Florisil (60–100 *M*). The silica gel employed for column chromatography was nondeactivated Merck (70–325 *M*). All solvents were reagent grade or were distilled prior to use.

Gas–liquid phase chromatographic analyses were performed on a Varian Aerograph 2100 instrument employing flame-ionization detection. Analytical work was done on 6-ft × 2-mm glass columns while preparative work was accomplished through the utilization of 5-ft × 4-mm glass columns with a 10 : 1 glass splitter. All column supports employed were purchased from Applied Science Laboratories.

Geranyl Thiophenyl Ether **26** *(3,7-Dimethyl-2,6-octadiene-1-thiophenyl Ether)*

A solution of pure geraniol (15 g, 0.097 mol) in 3 : 1 dry ether : hexamethyl phosphoric triamide (620 ml) was titrated with methyllithium to a triphenyl methane endpoint at 0°C under a dry nitrogen atmosphere. *p*-Toluenesulfonyl chloride (22.2 g, 0.113 mol) in hexamethyl phosphoric triamide (75 ml) was added while stirring. After an additional 2.5 hr at 0°C, lithium thiophenoxide (12.6 g, 0.113 mol) in hexamethyl phosphoric triamide (400 ml) was added and the solution brought to room temperature for 2 hr. The reaction was quenched by addition of water followed by extraction with 3 portions of hexane. The combined organic layers were washed with saturated sodium hydrogen carbonate solution and brine, dried over magnesium sulfate, and evaporated under reduced pressure to afford crude product as a yellow oil. Chromatographic purification on silica gel (100 g/g) utiliz-

ing dichloromethane as the eluent afforded a clear oil homogeneous by TLC (R_f 0.78 in 8% ether : hexane; 0.27 in hexane). Yield: 21.8 g (89%). (See Table 2.)

Anal. Calcd for $C_{16}H_{33}S$: C, 78.01; H, 9.00; S, 13.01. Obsd: C, 78.19; H, 9.25; S, 13.18.

Preparation of Geranyl Benzyl Ether 28

Pure geraniol **27** (61.6 g; 0.40 mol) was slowly added to a suspension of sodium hydride (17.6 g, 0.40 mol based upon 57% disperion) in anhydrous tetrahydrofuran (800 ml). After refluxing for 1 hr, the solution was cooled to room temperature whereupon benzyl chloride (60.0 g, 0.475 mol) was introduced. After 4 hr at reflux, the reaction mixture was diluted with hexane (800 ml), washed with water and brine, dried by the action of anhydrous magnesium sulfate, and evaporated under reduced pressure leaving a slightly yellow oil. Distillation through a 40-cm vigreaux column under vacuum afforded a main fraction (bp 122–124 at 0.3 mm) which was homogeneous by gas chromatography (OV 225). Yield: 69.7 g (91%).

8-Hydroxy-3,7-dimethyl-2,6-octadienyl Benzyl Ether 29

Selenium dioxide (5.5 g, 0.05 mol) was added to geranyl benzyl ether **28** (24.5 g, 0.10 mol) in 95% ethanol (150 ml) and the solution brought to reflux for 1.5 hr. The initial fine red precipitate turned granular and black during the course of reaction. After cooling to 10°C and filtration through Celite, the ethanol was evaporated under reduced pressure leaving an orange oil which was triturated in ether (1000 ml) and filtered. The solution was washed with water, twice with saturated sodium hydrogen carbonate and brine, dried over magnesium sulfate, filtered, and evaporated under reduced pressure to afford a yellow oil. Chromatography on silica gel (25 g/g) with gradient elution from 5 to 50% ethyl acetate : hexane recovered starting material (13.8 g) and allowed isolation of the desired benzyl ether **29** homogeneous by TLC (R_f 0.54 in 50% ethyl acetate : hexane). Yield: 9.0 g (62% yield based upon reacted starting material). Material of 99.9% purity was obtained by calcium chloride complexation in hexane under a dry, inert atmosphere, in the same manner previously described for the purification of geraniol. (See Table 3.)

Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Obsd: C, 78.38; H, 9.26.

TABLE 2

^{1}H-nmr ($CDCl_3$) δ (ppm)	Assignment
7.20 (m, 5H)	Aromatic
5.45–4.76 (br m, 2H)	Vinyl
3.47 (d, 2H), J = 7 Hz	=C—CH_2—S
2.0 (br m, 4H)	Methylene
1.65 (s, 3H)	Allylic methyl
1.53 (s, 6H)	$(CH_3)_2$C=C

TABLE 3

^{1}H-nmr ($CDCl_3$) δ (ppm)	Assignment
7.20 (s, 5H)	Aromatic
5.35 (br t, 2H), J = 7 Hz	Vinyl H
4.40 (s, 2H)	C_6H_6—CH_2—O
3.92 (d, 2H), J = 7 Hz	=CH—CH_2—O—CH_2—C_6H_6
3.86 (s, 2H)	HOCH_2
2.02 (br m, 4H)	Methylene
1.57 (s, 6HO)	Methyl

8-Chloro-3,7-dimethyl-2,6-octadienyl Benzyl Ether ***30***

Utilizing the method of Stork *et al.* (*22*), the allylic alcohol **29** (5.20 g, 20 mmol) in a dry 2:1 ether:hexamethyl phosphoric triamide solution (15 ml) was titrated with methyllithium to a triphenylmethane endpoint under dry nitrogen at 0°C. After warming to room temperature, *p*-toluenesulfonyl chloride (4.36 g, 23 mmol) in a like solvent system (15 ml) was slowly added immediately followed by dry lithium chloride (2.45 g, 60 mmol). The suspension was stirred for 17 hr and became quite viscous with a fine white precipitate. Addition of water (50 ml) was followed by extraction with ether. The combined ethereal layers were washed with water and brine, dried over magnesium sulfate, filtered, and evaporated under reduced pressure to afford a slightly yellow oil. Very fast chromatography through silica gel (70 g/g) utilizing dichloromethane as the eluent afforded the desired allylic chloride **30** homogeneous by TLC (R_f 0.76 in methylene chloride; 0.48 in 8% ether:hexane). Yield: 5.14 g (94%). (See Table 4.)

Anal. Calcd for $C_{17}H_{23}OCl$: C, 73.22; H, 8.33; Cl, 12.71. Obsd: C, 73.12; H, 8.22; Cl, 12.69.

3,7,11,15-Tetramethyl-9-phenylthio-2,6,10,14-hexadecatetraenyl Benzyl Ether ***31***

A Biellmann coupling (*21*) was executed on the two C-10 fragments **26** and **30** to

TABLE 4

^{1}H-nmr ($CDCl_3$) δ (ppm)	Assignment
7.20 (s, 5H)	Aromatic
5.40 (br q, 2H), J = 7 Hz	Vinyl H
4.40 (s, 2H)	C_6H_5—CH_2—O
3.94 (d, 2H)	=CH—CH_2—O—CH_2—C_6H_5
3.89 (s, 2H)	CH_2Cl
2.03 (br m, 4H)	Methylene
1.68 (s, 3H)	$CH_3(ClCH_2)C$=
1.57 (s, 3H)	Methyl

afford the desired C-20 backbone. A solution of geranyl thiophenyl ether **26** (1.14 g, 4.60 mmol) in freshly distilled tetrahydrofuran (30 ml) at −78°C was treated with butyllithium (4.18 mmol), resulting in a yellow solution. After 2.5 hr under a dry argon atmosphere, freshly purified allylic chloride **30** (1.0 g, 3.67 mmol) in dry tetrahydrofuran (5 ml) was added and the solution allowed to stir an additional 1.5 hr. The system was quenched at −78°C with a 1 : 1 methanol : ether mixture (3 ml), whereupon the yellow color was dissipated. The solution was allowed to attain room temperature at which point equal portions of water and ether were added. Separation of the phases followed by additional extraction of the aqueous layer with ether afforded a combined organic mixture which was washed with water and brine, dried over magnesium sulfate, filtered, and evaporated under reduced pressure, affording a colorless oil (1.92 g). Chromatography on silica gel (100 g/g) utilizing dichloromethane as the eluent afforded material homogeneous by TLC (R_f 0.59 in 8% ether : hexane; 0.85 in dichloromethane). Yield: 1.37 g (76%). (See Table 5.)

Anal. Calcd for $C_{33}H_{44}OS$: C, 81.08; H, 9.09; S, 6.56. Obsd: C, 80.76; H, 9.05; S, 6.65.

Geranylgeraniol ***24***

Reduction of both the thiophenyl and benzyl moieties was performed in a modification of the procedure established by van Tamelen *et al.* (*23*). To dry ethylamine (75 ml), distilled from lithium wire into the reaction vessel, at −78°C was added lithium wire (with 1% sodium; 423 mg, 50.0 g-atom) as small pieces. The temperature of the blue solution was brought to 0°C for 1.5 hr to ensure dissolution and then decreased to −78°C. The coupled product (**31**; 978 mg, 2.0 mmol) in tetrahydrofuran (20 ml) was added slowly and the resulting solution allowed to stir an additional 15 min. Maintaining the temperature at −78°C, 3-hexyne was added until the blue color was totally dissipated and the resulting yellow solution then quenched with methanol until colorless. After attaining room temperature, water was added until all the solids dissolved, and the volatiles were carefully evaporated under reduced pressure. The resulting cloudy solution was extracted four times with ether and the combined organic layers washed with water and brine, dried over magnesium sulfate, filtered, and evaporated under reduced pressure

TABLE 5

^{1}H-nmr ($CDCl_3$) δ (ppm)	Assignment
7.20 (br m, 10H)	Aromatic
4.40–4.80 (br m, 4H)	Vinyl H
4.40 (s, 2H)	C_6H_5—CH_2—O
3.94 (m, 3H)	C_6H_5—S—CH and =CH—CH_2—O
2.47–1.80 (br m, 10H)	Methylene
1.55 (br s, 12H)	Methyl
1.33 (s, 3H)	Methyl

affording a clear oil (700 mg). Chromatography on silica gel (100 g/g) with 40% ether in hexane as eluent afforded a clear oil homogeneous by TLC (R_f 0.41 in 50% ether/hexane). Yield: 505 mg (88%).

Gas chromatographic analysis on OV 225 and OV 17 (both 3% on 80/100 mesh Gas Ghrom Q) revealed 90% all *trans*-geranylgeraniol **24** contaminated by one other component presumed to be the product from conjugate reduction of the thiophenyl ether moiety (3,7,11,15-tetramethyl-2,6,9,14-hexadecatetraen-1β-ol). The structure of geranylgeraniol **24** was confirmed by comparison with authentic material (*21–23*) (gas chromatography, nmr, and ir). Geranylgeraniol of 99+% all trans purity was obtained by fraction recrystallization of the corresponding diphenyl carbamate (mp 47.8–48.5°C) from methanol.

Preparation of Geranylgeranyl Acetate (3,7,11,15-Tetramethyl-2,6,10,14-hexadecatetraenyl Acetate) ***32***

To a solution of geranylgeraniol (350 mg, 1.22 mmol) **24,** in dry, freshly distilled pyridine (8 ml), under dry argon cover, was added distilled acetic anhydride (0.7 ml) and the solution allowed to stir at room temperature overnight. After the addition of water (25 ml) and hexane (50 ml) the organic layer was separated and washed with 5% hydrochloric acid, water, saturated sodium hydrogen carbonate, and brine. Upon filtration through anhydrous magnesium sulfate and evaporation under reduced pressure, a clear oil was obtained (584 mg). Chromatography on silica gel (40 g/g) with initial elution utilizing 1.5% ether : hexane and subsequently 8% ether : hexane afforded the desired acetate **32** homogeneous by TLC (R_f 0.39 in 8% ether : hexane; 0.71 in 50% ether : hexane). Yield: 406 mg (100%).

Spectral data were identical to those reported (*18*) for this compound.

Preparation of Geranylgeranyl Acetate Terminal Bromohydrin (3,5,11,15-Tetramethyl-14-bromo-15-hydroxy-2,6,10-hexadecatrienyl Acetate) ***33***

A solution of geranylgeranyl acetate **32** (1.65 g, 4.95 mmol) in freshly distilled tetrahydrofuran (150 ml) at 0°C under argon was titrated with distilled water to the cloud point. Just enough tetrahydrofuran was added to clear the solution. Recrystallized *N*-bromosuccinimide (950 mg, 5.4 mmol) was added in small portions over a 45-min period. The solution was allowed to stir for 3.5 hr at 0°C, whereupon most of the tetrahydrofuran was evaporated under reduced pressure. Care must be taken not to exceed room temperature. Water (100 ml) and brine (50 ml) were added and the mixture extracted with hexane (3 × 125 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution, dried over magnesium sulfate, filtered, and evaporated under reduced pressure to afford a clear oil (2.32 g). Chromatography on silica gel (100 g/g) with gradient elution from 10 to 20% ethyl acetate : hexane afforded a clear oil homogeneous by TLC (R_f 0.39 in 25% ethyl acetate : hexane). Yield: 1.26 g (60%).

Spectral data were identical to those reported (*18*) for this compound.

Preparation of Geranylgeraniol Terminal Epoxide 34

(a) *From geranylgeranyl acetate terminal bromohydrin* **33.** Potassium carbonate (3 g, 21.8 mmol) was added to a solution of geranylgeranyl acetate terminal bromohydrin **33** (1.25 g, 2.91 mmol) in freshly distilled methanol (100 ml) at room temperature under argon. The granular material was soon replaced by a fine white precipitate and the suspension allowed to stir overnight. Water (200 ml) was added and the solution extracted with hexane (3 × 150 ml). The combined organic layers were washed with brine, evaporated under reduced pressure, and dried under vacuum yielding an oil (918 mg). Chromatography on silica gel (100 g/g) with 50% ethyl acetate : hexane as the eluent afforded a colorless oil homogeneous by TLC (R_f 0.31 in 25% ethyl acetate : hexane; 0.58 in 50% ethyl acetate : hexane). Yield: 888 mg (99%).

(b) *From geranylgeranyl acetate terminal epoxide* **35.** Potassium carbonate (400 mg, 3.62 mmol) was added to a solution of geranylgeranyl acetate terminal epoxide **35** (175 mg, 0.50 mmol) in freshly distilled methanol (30 ml) at room temperature under a nitrogen cover. The granular suspension was soon replaced by a fine white precipitate and the reaction allowed to stir at room temperature for 1 hr. Water (60 ml) was added and the solution extracted with hexane (4 × 50 ml). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure affording, after drying under vacuum, a clear oil homogeneous by TLC (R_f 0.31 in 25% ethyl acetate : hexane; 0.58 in 50% ethyl acetate : hexane). Yield: 149 mg (97%). Spectral data were identical to those reported (*21a*) for this compound.

Preparation of Geranylgeranyl Acetate Terminal Epoxide 35

Excess acetic anhydride (1 ml) was added to a solution of geranylgeraniol terminal epoxide (255 mg, 0.83 mmol) **34** in freshly distilled pyridine (20 ml) at room temperature under a nitrogen cover. The solution was allowed to stir overnight whereupon it was added to water (75 ml) and extracted with hexane (3 × 75 ml). The combined organic layers were washed with copper sulfate solution until the blue color persisted, then with water, saturated sodium hydrogen carbonate, and brine. Upon evaporation under reduced pressure and drying under vacuum a clear oil was obtained, homogeneous by TLC (R_f 0.61 in 25% ethyl acetate : hexane). Yield: 277 mg (96%).

Preparation of Geranylgeranyl 3,5-Dinitrobenzoate Terminal Epoxide 45

To a solution of geranylgeraniol terminal epoxide **34** (278 mg, 0.91 mmol) in freshly distilled dry pyridine (20 ml) was added 3,5-dinitrobenzoyl chloride (415 mg, 1.80 mmol assay at 98%) as a powder. The solution was stirred at room temperature under dry nitrogen overnight whereupon water (75 ml) was introduced and the reaction mixture extracted with hexane (3 × 75 ml) and ether (3 × 75 ml). The combined organic layers were washed with aqueous copper sulfate until the blue color persisted and then with saturated sodium hydrogen carbonate and brine. The organic volatiles were removed by evaporation under reduced pressure

leaving crude product as a yellow oil (425 mg). Chromatography on silica gel (100 g/g) with 25% ethyl acetate as the eluent afforded the dinitrobenzoate **59** as a clear oil homogeneous by TLC (R_f 0.59 in 25% ethyl acetate : hexane). Yield: 370 mg (87%).

Anal. Calcd for $C_{27}H_{36}N_2O_7$ *m/e* M^+: 500.2522. Obsd: 500.2492.

Preparation of Geranylgeranyl Methyl Carbonate Terminal Epoxide ***46***

Freshly distilled methyl chloroformate (0.3 ml, 367 mg, 3.88 mmol) was slowly added via syringe into a solution of geranylgeraniol terminal epoxide **34** (90 mg, 0.29 mmol) in freshly distilled dry pyridine (15 ml) at 0°C under dry nitrogen. A large amount of white solid is formed upon addition. While the solution was allowed to attain room temperature a number of color changes were observed, ending with a slight yellow tint which disappears after 1 hr. Most of the solid also disappears. After 2.5 hr, the reaction was added to a 50% hexane : water mixture (80 ml) and the aqueous layer extracted with hexane (2 × 50 ml additional). The organic layers were combined and washed with aqueous copper sulfate until the blue color persisted, then with water, saturated sodium hydrogen carbonate, and brine. Upon evaporation of the hexane under reduced pressure and drying under vacuum, a clear oil was obtained (104 mg). Preparative TLC (2-mm × 20-cm × 20-cm silica gel PF plate) with 3.5 hr of continuous elution with 10% ethyl acetate : hexane afforded the desired methyl carbonate **60** homogeneous by TLC (R_f 0.59 in ethyl acetate : hexane). Yield: 96 mg (90%).

Anal. Calcd for $C_{22}H_{36}O_4$ *m/e* ($M^+-C_2H_4O_3$): 288.2453. Obsd: 288.2451.

Preparation of 17-nor-15-aldehydo-darutigenol ***44****; Periodate cleavage of Darutigenol*

Following the procedure of Lederer *et al.* (*12a*), sodium periodate (19.0 mg, 90 mol) was added to a solution of darutigenol (7.5 mg, 25.3 μmol) in a mixture of freshly distilled tetrahydrofuran (0.6 ml) and water (1 ml) at room temperature. The solution was allowed to stir for 0.5 hr, whereupon it was poured into a 50% ether : water mixture (20 ml) and the aqueous layer extracted with ether (10 ml additional). The combined ethereal layers were washed with brine, separated, and evaporated under a stream of nitrogen to afford the aldehyde as a white solid which was homogeneous by TLC (R_f 0.28 in 25% ethyl acetate : hexane). Yield: 7.3 mg (100%).

mp 119–120°C (lit. (*12a*) 120°C).

Preparation of Ent-pimara-8(14),15-diene-3β-ol ***38***

Methyl lithium in ether (140 μl at 1.8 *M*, 250 μmol) was added to a suspension of triphenyl methyl phosphonium bromide (120 mg, 340 μmol) in anhydrous ether (3 ml) at 0°C under a nitrogen cover. After being allowed to attain and remain at room temperature 0.5 hr, the yellow suspension was returned to 0°C. After introduction of 17-nor-16-aldehydo-darutigenol **44** (3 mg, 10.4 mol) in freshly distilled dry tetrahydrofuran (100 liters) the solution was allowed to stir at room tempera-

ture for 1.5 hr whereupon the reaction was quenched with water, dissipating the yellow color. Addition of the reaction to a 50% water : ether mixture (30 ml) was followed by extraction with ether (2 × 15 ml additional). The combined ethereal layers were washed with brine, filtered through anhydrous magnesium sulfate, and evaporated under a stream of nitrogen leaving a clear oil. Preparative TLC purification (250 × 10-cm × 20-cm silica gel GF plate) with 25% ethyl acetate : hexane as the eluent afforded the diene **38** as a white solid, homogeneous by TLC (R_f 0.43 in 25% ethyl acetate : hexane). Yield: 2 mg (66%). Mass spectral data were identical to that published by Fetizon *et al.* (*26*) for this compound.

mp 113–115°C.

mass spec. *m/e* M^+ 288, 273 (5%), 270 (8%), 255 (12%), 153 (6%), 135 (100%).

Preparation of Ent-pimara-8(9),15-diene-3β-ol **36**

Through a solution of ent-pimara-8(14),15-diene-3β-ol **38** (1 mg, 3.5 mmol) in dry chloroform (0.75 ml) at 0°C under a dry nitrogen cover was bubbled dry hydrogen chloride gas. After 1.5 hr, the reaction was quenched by addition of 50% saturated sodium hydrogen carbonate : ether (4 ml) followed by additional extraction of the aqueous layer with ether (2 ml). The combined organic layers were washed again with saturated hydrogen carbonate, separated, and evaporated under a stream of nitrogen affording a white solid homogenous by TLC (R_f 0.45 in 25% ethyl acetate : hexane). Yield: 1 mg (100%). Gas chromatographic analysis (OV 225) showed almost complete conversion to a single different peak. This material was chromatographically and spectrally identical to the compound isolated from the boron trifluoride etherate catalyzed cyclization of geranylgeranyl methyl carbonate terminal epoxide **46.**

mp 91–93°C

Anal. Calcd for $C_{20}H_{32}O$ *m/e* M^+: 288.2453. Obsd: 288.2451.

mass spec. *m/e* M^+ 288, 273 (42%), 270 (26%), 255 (100%), 119 (81%), 107 (68%), 105 (75%).

Preparation of 19-Tosyl-Virescenol B **43**

To a solution of Virescenol B (5 mg, 15 μmol) in freshly distilled dry pyridine (0.240 ml) under dry nitrogen cover, was added *p*-toluenesulfonyl chloride (3.9 mg, 20 mol) and the solution was stirred overnight. Almost no reaction had occurred and there was no indication that any acylating agent remained by TLC analysis. Thus, small portions of *p*-toluenesulfonyl chloride were added while the reaction progress monitored by TLC. When almost all the starting material had been consumed, an approximately equal mixture of two components were observable. A 50% ether : water mixture (4 ml) was introduced into the reaction and the aqueous layer extracted with ether (2 × 3 ml additional). The combined organic layers were washed with aqueous copper sulfate until the blue color persisted and then with brine. Evaporation of the ether under a stream of nitrogen afforded an oil which was purified by preparative TLC (250-μm × 20-cm × 10-cm silica gel GF plate) utilizing 25% ethyl acetate : benzene as the eluent. This afforded starting material as a white solid, 0.4 mg (R_f 0.38 in 50% ether : benzene); a highly mobile

component as an oil (3.3 mg, R_f 0.84 in 50% ether : benzene) presumed to be the ditosylate, which may be recycled, and the desired monotosylate **56** as a white solid (3.4 mg, R_f 0.59 in 50% ether : benzene). Yield: 3.4 mg (95% based upon recoverable starting material).

mp 119–121°C.

*Preparation of Isopimara-7(8),15-diene-3β-ol **40** from 19-Tosyl-Virescenol B*

To a suspension of excess lithium aluminum hydride in freshly distilled dry tetrahydrofuran (5 ml) at room temperature under nitrogen cover was added 19-tosyl-Virescenol B **43** (3 mg, 7.01 mol) in freshly distilled dry tetrahydrofuran (250 μl). The suspension was brought to reflux for 1 hr and then allowed to stir an additional 2 hr at room temperature, at which point all the starting material had been consumed as evidenced by TLC. Wet ether was added to quench unreacted lithium aluminum hydride and the solvents decanted from the white amorphous material. Tetrahydrofuran was utilized to extract any remaining compounds from this solid. The organic layers were combined and evaporated under reduced pressure. The remaining material was extracted into benzene and the solution was filtered to divorce the particulate matter. Evaporation of the benzene under a stream of nitrogen afforded an oil (2.1 mg) which immediately solidified. Purification by preparative TLC (250-μm × 20-cm × 5-cm silica gel GF plate) utilizing 20% ethyl acetate : hexane as the eluent afforded pure diene **40** as a white solid homogeneous by TLC (R_f 0.49 in 25% ethyl acetate : hexane). Yield: 1.3 mg (65%).

It should be noted that preparative TLC on small amounts of material causes severe percentage losses. In addition, lithium aluminum hydride reductions on small amounts of material leave significant amounts unavoidably occluded in the white powder produced in work-up. These may be the reasons for the yield reduction observed. Material obtained in this manner had an impurity which was present from the initial sample of Virescenol B. Ultimate purification was effected by HPLC on a Waters 25-cm × 4-mm μPorasil column with 0.08% isopropanol : hexane as the eluent. This pure compound was identical in all respects both to that obtained by isomerization of isopimara-8(14),15-diene-3β-ol and to the natural product extracted from *Agathis australis* (*16*).

mp 140–141°C (lit. (*16*) 146–147°C).

mmp 140–141°C.

mass spec. *m/e* M^+ 288, 273 (4%), 270 (3%), 255 (22%), 148 (16%), 133 (34%), 133 (34%), 105 (72%), 55 (100%).

*Cyclization of Geranylgeranyl Methyl Carbonate Terminal Epoxide **46***

(a) *With boron trifluoride etherate : nitromethane.* Geranylgeranyl methyl carbonate terminal epoxide **46** (1 eq) was added to a solution of distilled boron trifluoride etherate (10 eq) in nitromethane (1 mg substrate/0.04 ml) at either −20 or 0°C under a nitrogen cover. The solution was allowed to stir for various lengths of time (at −20°C: 15, 30 sec, 1, 2, 3, 5, 10, 20, 40, and 80 min; at 0°C: 10, 30, 60, 120

min), whereupon it was quenched with a 50% saturated sodium hydrogen carbonate: ether mixture. The aqueous layer was separated and extracted twice with additional ether. The combined organic layers were washed with saturated sodium hydrogen carbonate, water, and brine, then dried over magnesium sulfate, filtered, and evaporated under reduced pressure, affording a clear oil. Reaction at 0°C for 30 min was used for preparative runs. The crude product was initially purified by preparative TLC (1-mm × 20-cm × 15-cm silica gel plates) utilizing continuous elution for 2 hr with 10% ethyl acetate: hexane as the eluent affording the four major sections illustrated in Table 1.

The least polar fraction *A*, comprising 19.3% of the recovered material, was shown by gas chromatography (OV 225 and OV 17) to contain two peaks (65%) which had retention times identical to naturally derived isopimara-8(9),15-diene-3β-ol **39** and pimara-8(9),15-diene-3β-ol **36.** An additional peak (5%) corresponding to isopimara-7(8),15-diene-3β-ol **40** (*15a*) was also observed. Enrichment of these three components was accomplished by HPLC (0.1–0.2% isopropanol: hexane as the eluent) on a 25-cm μPorasil column with a flow rate of 1 ml/min, followed by multiple elution (6 passes) preparative TLC on 10% silver-nitrate-impregnated silica gel plates using 0.2% isopropanol: benzene as the eluent. Various bands were isolated over the desired region and showed significant enrichment of the three desired compounds in different fractions. Table 6 shows the relative mobilities of the various three hydroxy pimaradienes on 10% silver nitrate silica gel plates.

Final purification was effected by preparative gas chromatography (24-ft × 4-mm i.d., 3% OV 225 on 80/100 mesh Gas Chrom Q; carrier gas at 60 ml/min) utilizing a 10: 1 splitter affording the pure components pimara-8(9),15-diene-3β-ol **36,** isopimara-8(9),15-diene-3β-ol **39,** and the natural product (*16*) isopimara-7(8),15-diene-3β-ol **40.** These samples co-injected with their naturally derived standards producing single sharp peaks on both OV 225 (5, 6, and 24 ft) and OV 17 (6 ft) gas chromatographic columns. Each compound and its respective standard produced superimposable nmr and mass spectra.

Fraction *C*, of the initial chromatography, comprised 36.2% of the recovered material. It was shown to be nearly homogeneous by TLC on silver-nitrate-impregnated silica gel. Final purification on this system utilizing two passes with

TABLE 6

	R_f	
	0.1% ipro/C_6H_6 2-hr cont. elution	0.2% ipro/C_6H_6 6 elutions
Pimara-8(14),15-diene-3β-ol	0.26	0.39
Pimara-8(9),15-diene-3β-ol	0.23	—
Isopimara-8(14),15-diene-3β-ol	0.22	—
Isopimara-7(8),15-diene-3β-ol	0.20	—
Isopimara-8(9),15-diene-3β-ol	0.14	0.25

25% ethyl acetate : hexane afforded a white solid homogeneous by TLC (R_f 0.28 in 25% ethyl acetate : hexane on silica gel; 0.43 in two passes with 25% ethyl acetate : hexane on 10% silver-nitrate-impregnated silica gel). Comparison by nmr, as previously indicated, between drimenol methyl carbonate **55** and this isolated compound allowed the assignment of **52** as its structure. A small amount **52** was dissolved in methanol followed by addition of 5% potassium hydroxide in aqueous methanol. After 18 hr, the reaction was quenched by the concurrent addition of water and ether and the aqueous layer extracted with additional ether. The combined organic layers were evaporated under a stream of nitrogen and the remaining oil purified by preparative TLC (250-μm × 20-cm × 10-cm silica gel plate eluted three times with 25% ethyl acetate : hexane) to afford a small amount of white solid (R_f 0.19 in 25% ethyl acetate : hexane). The nmr revealed the loss of the carbonate moiety. The solid was assigned the structure **57,** a known (*18*) compound whose spectrum was in accord with that observed for this material.

Fraction *D* comprising 17.4% of the initial isolation was further purified by multiple elution preparative TLC on 10% silver-nitrate-impregnated silica gel (250-μm × 20-cm × 10-cm plate), eluted first with 10% ethyl acetate : benzene and then three times with 25% ethyl acetate : hexane with 0.1% isopropanol added. This enabled isolation of a more mobile compound DH (R_f 0.61 in system above) and a less mobile compound DL (R_f 0.55 in the system above). As previously discussed, comparison of DH with epidrimenol methyl carbonate **56** indicated its structure to be **58,** the C-14 epimer of **52.** The other component DL clearly showed exomethylene protons in the nmr spectrum. As previously discussed, it was assigned structure **59.**

Fraction *B* comprising 10.6% of the initial purification was found to be a complex mixture of components by analysis on TLC on silver-nitrate-impregnated silica gel. The nmr revealed no appreciable 3-hydroxy components, and it was therefore decided not to pursue further purification.

Boron trifluoride Etherate/Benzene

Geranylgeranyl methyl carbonate terminal epoxide **46** (1 eq) was added to a solution of boron trifluoride etherate (10 eq) in dry distilled benzene (1 mg substrate/0.04 ml) at 5–7°C under a dry nitrogen atmosphere. The solution was allowed to stir for various times (5, 10, 20, 40 and 80 min), whereupon it was quenched and partitioned with a 50% saturated sodium hydrogen carbonate : ether mixture. After additional extraction with two portions of ether, the organic layers were combined and evaporated under a stream of nitrogen. The remaining oil was separated by preparative TLC (250 × 20-mm × 5-mm silica gel plate) utilizing 25% ethyl acetate : hexane as the eluent and the band in the desired 3-hydroxypimarane region was eluted. The resulting oil showed the same product distribution as noted in the nitromethane cyclization by gas chromatographic analysis (OV 225). The yield of product, however, was lower.

Boron trifluoride etherate : acetonitrile

The identical procedure as that applied for benzene was followed except that

the temperature used was −20°C. The only products observed were more polar than the desired region. Isolation was therefore not pursued.

(b) *With phosphoric acid.* To vibrating 85% phosphoric acid (1 mg substrate/0.12 ml) at 0°C under an argon cover, geranylgeranyl methyl carbonate terminal epoxide **60** was added slowly via syringe. The yellow solution was vibrated an additional hour at 0°C, whereupon it was added to a 50% ice water : ether mixture. The aqueous layer was extracted with three additional portions of ether. The combined organic layers were washed with water, saturated sodium hydrogen carbonate, and brine, then dried over magnesium sulfate, filtered, and evaporated under reduced pressure to afford the crude product as an oil. Chromatographic purification on silica gel (150 g/g) utilizing 10% ethyl acetate : hexane as the eluent produced a fraction which had the same mobility on TLC (R_f 0.48 in 25% ethyl acetate : hexane) as the desired 3β-hydroxy pimaradienes. Analysis by nmr indicated the loss of the carbonate functionality. Gas chromatographic analysis revealed a component possessing a retention time indicative of tricyclic material. Purification by preparative TLC on silver-nitrate-impregnated silica gel utilizing 50% ethyl acetate : hexane as the eluent, HPLC on a 25-cm micropac column utilizing 0.1% isopropanol : hexane as the eluent, followed by preparative gas chromatography on both 5-ft and 24-ft preparative (OV 225) columns afforded material which had identical chromatographic and spectral properties to isopimara-8(9),15-diene-3β-ol **39.**

(c) *With stannic chloride.* Geranylgeranyl methyl carbonate terminal epoxide **46** (1 eq) was added via syringe to a solution of distilled stannic chloride (10 eq) in dry distilled nitromethane (1 mg substrate/0.04 ml) at 0°C under a dry nitrogen cover. The solution was allowed to stir for 30 min whereupon saturated sodium hydrogen carbonate was added (equal volume) and the reaction mixture extracted with four portions of ether. The combined ethereal layers were evaporated under a stream of nitrogen and the resulting oil was separated by preparative TLC (250-μm × 20-cm × 5-cm silica gel plate) utilizing 25% ethyl acetate : hexane as the eluent. The band in the desired 3-hydroxypimarandiene region was eluted, and the resulting oil was analyzed by both gas chromatography and nmr to reveal no tricyclic material.

(d) *With picric acid.* To geranylgeranyl methyl carbonate terminal expoxide **46** (1 eq) in dry distilled nitromethane at room temperature under a dry nitrogen cover was added dry picric acid (10 eq) and the yellow solution allowed to stir for 1.5 hr. The reaction was quenched by the addition of a 50% saturated sodium hydrogen carbonate : ether mixture followed by extraction of the aqueous phase thrice with additional ether. The combined organic layers were evaporated under a stream of nitrogen affording an oil which was separated by preparative TLC (250-μm × 20-mm × 5-mm silica gel plate) utilizing 25% ethyl acetate : hexane as the eluent. The band corresponding to the 3-hydroxypimaradienes was eluted and found to be devoid of tricyclic material. No further work was therefore pursued.

Preparation of Drimenyl Methyl Carbonate **55**

To a solution of optically active drimenol (**53**) (17 mg; 7.66 mol) in dry freshly

distilled pyridine (1 ml) at 0°C under a dry nitrogen cover, methyl chloroformate (30 μl; excess) was added via syringe. An immediate white precipitate is formed which slowly dissolves as the reaction is allowed to attain room temperature. The reaction was incomplete after 5 hr. Small portions of additional methyl chloroformate were added at 0°C until all the starting material was consumed while progress was carefully monitored by TLC. Water was added and the reaction mixture extracted with hexane (5 × 5 ml). The combined organic layers were washed with copper sulfate solution until the blue color persisted and the volatiles evaporated under a stream of nitrogen leaving an oil. Purification by preparative TLC (250-μm × 20-cm × 20-cm silica gel plate) utilizing 10% ethyl acetate : hexane as the eluent afforded chromatographically homogeneous material (R_f 0.66 in 25% ethyl acetate : hexane). Yield: 18 mg (86%).

Anal. Calcd for $C_{17}H_{28}O_3$ *m/e* ($M^+-C_2H_4O_3$): 204.1882. Obsd: 204.1893.

Preparation of Epidrimenol Methyl Carbonate **56**

To a solution of epidrimenol (**54**) (1 mg; 0.45 mol) in dry, freshly distilled pyridine (0.5 ml) at 0°C under a dry nitrogen cover, methyl chloroformate (30 μl; excess) was added via syringe. An immediate white precipitate is formed which slowly dissolves as the reaction is allowed to attain room temperature. The reaction was incomplete after 5 hr. Small portions of additional methyl chloroformate were added at 0°C until all of the starting material was consumed while progress was carefully monitored by TLC. Water was then added and the reaction mixture extracted with hexane (5 × 2 ml). The combined organic layers were washed with copper sulfate solution until the blue color persisted, and the hexane evaporated under a stream of nitrogen leaving a small amount of oil. Purification by preparative TLC (250-μm × 20-cm × 5-cm silica gel plate) utilizing 10% ethyl acetate : hexane as the eluent afforded chromatographically homogeneous material (R_f 0.65 in 25% ethyl acetate : hexane).

Anal. Calcd for $C_{17}H_{28}O_3$ *m/e* ($M^+-C_2H_4O_3$): 204.1882. Obsd: 204.1880.

Preparation of d,l-Araucarol

Excess anhydrous potassium carbonate (7 mg) was added to a solution of *d,l*-isopimara-7(8),15-diene-3β-ol **40** (400 g) in dry 3 : 4 dimethoxy ethane : acetic anhydride (350 μl) and stirred for 1 hr at room temperature under nitrogen. Excess potassium permangenate (10 mg) was then added and allowed to react for 1.5 hr at room temperature. Quenching with a 1 : 1 mixture of 12.5% sodium bisulfite : ethyl acetate (2 ml) followed by additional extraction with ethyl acetate (1 ml) afforded an organic layer which was evaporated under a stream of nitrogen. Thin-layer chromatography revealed almost total consumption of starting material and the production of two major components (R_f 0.63; 0.53 in 90% ether : hexane). The acetates were hydrolyzed by brief treatment with 10% methanolic potassium hydroxide (0.5 ml; for 5 min) and the solution partitioned between ether : water followed by additional ether extraction (4 × 1 ml). The combined organic layers were washed with brine and evaporated under a stream of nitrogen leaving an oil which was primarily material having the same mobility on silica gel as naturally

derived araucarol **16.** Preparative TLC (250-μm × 4-cm × 20-cm silica gel plates) utilizing multiple elution with 50% ether : hexane affords homogeneous material (R_f 0.42 in 90% ether : hexane; 0.32 in 90% chloroform : acetone) whose structure was confirmed by nmr and mass spectral comparison with naturally occurring (*20*) optically active araucarol **16.**

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