Registry No.—Copolystyrene–divinylbenzene, 9003-70-7; *p*-anisoyl chloride, 100-07-2; anisylformylaminomethane, 3400-22-4; anisylaminomethane, 5961-59-1; *p*-methoxybenzhydrylamine, 2538-34-3; *p*-methoxybenzhydrylamine HCl, 5267-46-9; *tert*-butyloxycarbonylalanine, 15761-38-3; alanylphenylalaninamide HF, 60195-80-4; Boc-Ala-Phe, 2448-58-0; Z-L-pyroglutamyl-N^{im}-tosyl-L-histidyl-L-prolyl, 60195-81-5; Boc-proline, 15761-39-4; Boc-N^{im}-tosyl-His, 35899-43-5; Z-<Glu, 32159-21-0; L-pyroglutamyl-L-histidyl-L-proline amide, 24305-27-9; Z-<Glu-N^{im}-tosyl-His-Pro-NH_2, 35899-45-7; Boc-L-isoleucyl-L-glutaminyl-L-asparagine, 52574-14-8; Boc-Asn-ONp, 4587-33-1; Boc-Gln-ONp, 15387-45-8; Boc-Gln-Asn-ONp, 60195-82-6; Boc-Ile, 13139-16-7; L-isoleucyl-L-glutaminyl-L-asparaginamide HF, 60195-83-7; Boc-L-isoleucyl-L-glutaminyl-L-asparaginamide, 60209-57-6; Boc-Ile-Gln-Asn-O-Bzl, 60209-58-7; Boc-Gly, 4530-20-5; Boc-Phe, 13734-34-4; Boc-Val, 13734-41-3; Boc-Glu(OBzl), 30924-93-7; Boc-Ala-Gly, 28782-78-7; Boc-Ala-Pro, 33300-72-0; Boc-Ala-Phe, 2448-58-0; Boc-Ala-Val, 60209-59-8; Boc-Ala-Glu(OBzl), 60209-60-1.

References and Notes

(1) This work was supported in part by USPHS Grant AM-18399. Nomenclature follows the tentative rules of the IUPAC-IUB Commission on Biochemical Nomenclature, *J. Biol. Chem.*, **247**, 977 (1972); **250**, 3215 (1975). Additional abbreviations used: Boc, *tert*-butyloxycarbonyl; Bzl, benzyl; DCCI, dicyclohexylcarbodiimide; ONp, *p*-nitrophenyl ester.
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Synthetic Approaches to 10-Epieudesmane Sesquiterpenes. A Synthesis of Intermedeol

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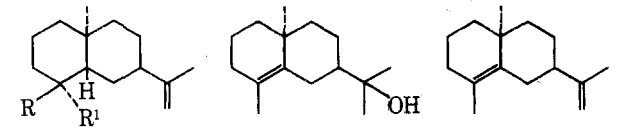
A number of synthetic approaches to the biosynthetically important 10-epieudesmane sesquiterpene intermedeol (1) have been explored. Reduction of epi-α-cyperone (**6**) with lithium–ammonia and oxidation of the intermediate enolate gave acetoxy ketone **9** as the major product. However, **9** could not be deoxygenated to intermedeol. Reduction of **6** with lithium in ammonia followed by trapping of the derived enolate with diethyl chlorophosphate gave enol phosphate ester **11**. Hydrogenolysis of **11** gave a mixture of three hydrocarbons, **3**, **4**, and **12**, while hydrogenolysis of the related enol phosphate **13** gave only one olefin (**15**) on reduction. The synthesis of **1** from α-agarofuran (**18**) was accomplished by the sequence conversion to the 3,4-oxide (**19**), reduction of **19** to 4β-hydroxydihydroagarofuran (**20**), and lithium–ethylenediamine reduction of **20** to diol **23**, which on partial dehydration afforded intermedeol (**1**). The C-4 epimer of intermedeol, **5**, was synthesized from 10-epieudesma-4,11-diene (**3**) by epoxidation to **24**, dissolving metal reduction of which gave **5**. The structure of **24** was confirmed by its conversion to 4α-hydroxydihydroagarofuran and that of **5** by reduction to the dihydro compound (**26**), which was synthesized by an alternate route.

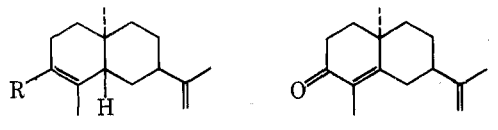
In the generally accepted biosynthetic scheme[1] for the nonisoprenoid nootkatone–valencene group of sesquiterpenes, 10-epieudesmanes, such as intermedeol (**1**),[2] 10-epi-γ-eudesmol (10-epieudesm-4-en-11-ol, **2**),[3] and the isomeric 10-epieudesmadienes (**3** and **4**)[4] play a key role. These compounds can all, at least in principle, undergo the carbonium ion type rearrangement suggested many years ago by Robinson for the biosynthesis of eremophilone from a eudesmane precursor.[5] In addition, at the time when this work was initiated, an additional sesquiterpenoid alcohol, "paradisiol" (**5**), the C-4 epimer of intermedeol, had been reported.[6] However, the infrared spectrum of "paradisiol" and intermedeol indicated that these compounds were identical, and subsequent synthetic and NMR studies showed that intermedeol was correctly represented by structure **1**,[2c] as originally suggested by Zalkow.[2a] Subsequent direct comparison showed that these compounds are in fact identical.[7]

The obvious starting point for a synthesis of either inter-

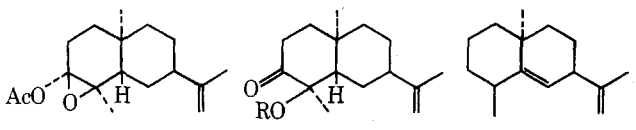
medeol (1) or "paradisiol" (5) is epi-α-cyperone (10-epieudesma-4,11-dien-3-one, 6), the well-known annelation product of dihydrocarvone and ethyl vinyl ketone.[8] This molecule contains all 15 carbon atoms present in the desired products, has the requisite stereochemistry at C-7 and C-10, and is functionalized in a manner which should facilitate the stereoselective synthesis of 1 and/or 5.



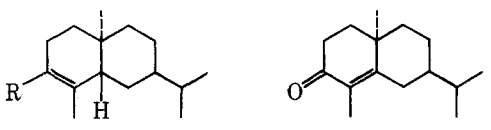
1, R = OH; R¹ = CH₃ 2 3
5, R = CH₃; R¹ = OH



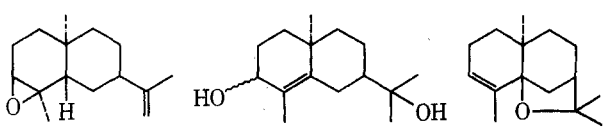
4, R = H 6
7, R = OAc
11, R = O₂P(OC₂H₅)₂



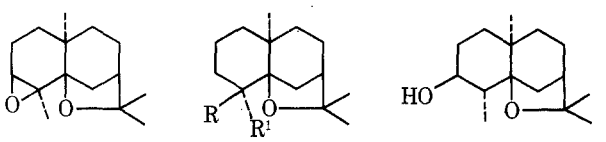
8 9, R = Ac 12
10, R = H



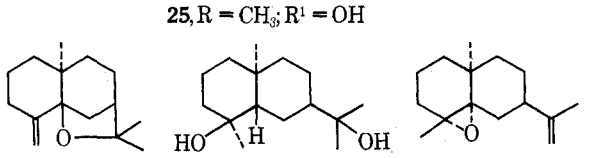
13, R = O₂P(OC₂H₅)₂ 14
15, R = H



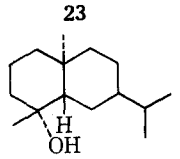
16 17 18



19 20, R = OH; R¹ = CH₃ 21
25, R = CH₃; R¹ = OH



22 23 24



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The initial approach to these sesquiterpenes introduced the correct stereochemistry at C-5 by lithium–ammonia reduction of enone 6 to the enolate anion. In an effort to effect oxygenation at C-4, the enolate was oxidized with lead tetraacetate[9] to give a mixture of products. Repeated chromatography of this mixture gave, in poor yield, a crystalline acetoxy ketone and a hydroxy ketone. The presence of relatively low field methyl singlets in their NMR spectra indicated that both compounds were oxygenated at C-4. They did not, however, have the same stereochemistry at this center since alkaline hydrolysis of the acetoxy ketone gave a ketol different from that obtained from the original reaction mixture. The stereochemistry of these compounds was resolved as follows: first, the same acetoxy ketone could be obtained in a three-step sequence by lithium–ammonia reduction of ketone 6 to the enolate and trapping this anion with acetic anhydride to give enol acetate 7. Treatment of 7 with *m*-chloroperbenzoic acid in ether[10] gave an unstable epoxy acetate, which on mild acid treatment gave the acetoxy ketone. By analogy with the acid-catalyzed rearrangement of the epoxy acetate derived from 3-acetoxy-2-cholestene,[11] the configuration of the C-4 acetate group in the acetoxy ketone should be opposite to that of the C-3 acetate in the precursor epoxide. Normal steric arguments lead to the conclusion that attack of peracid should occur from the less hindered β face of 7 leading to structure 8 for the epoxy acetate, and 9, 4β-acetoxy-5-epi-10-epieudesm-11-en-3-one, for the derived ketone.

A second factor indicating that 9 has the indicated stereochemistry follows from the observation that basic hydrolysis of the acetate gives a hydroxy ketone (10) in which the NMR signal for the angular methyl group appears at very slightly higher field (0.03 ppm) than that of the corresponding acetate (9). This is expected if the oxygen functionalities are both equatorial as they are in 9 and 10.[12] The hydroxy ketone obtained from the original lead tetracetate oxidation was different from 10, and on the basis of its spectral properties is probably the C-4 epimer of 10.

A number of attempts were made to remove the oxygen atom at C-3 in 9 and 10, including attempted formation of the ethylene thioketal of 9 and reduction of 9 and 10 to mixtures of diols followed by formation of the 3-tosylate or -mesylate. In all cases either no reaction occurred or gross mixtures were obtained.

In a second approach to intermedeol, enone 6 was converted to enol phosphate ester 11 in an attempt to prepare diene 4.[13] Hydrogenolysis of 11 with lithium–ethylamine led to partial reduction of the isolated double bond, while the use of lithium–ammonia gave a mixture of three dienes. The best results from the latter reductions were obtained using sodium–ammonia–*tert*-butyl alcohol for a short period of time, giving a mixture containing 42% of 4. Repeated preparative GLC gave pure 4, the properties of which agree with those reported for the natural product.[4] The major component of this mixture (46%) had spectral properties consistent with those reported for 10-epieudesma-4,11-diene (3).[4] The minor component of the mixture (12%) was assigned the structure 4-epi-10-epieudesma-5,11-diene (12) on the basis of its NMR spectrum, which shows a methyl doublet (J = 6 Hz) at δ 0.92, a methyl singlet at δ 1.00, the doubly allylic proton at C-7 as a multiplet at δ 2.52, and a one-proton vinyl quartet at δ 4.90. The stereochemistry at C-4 (equatorial methyl) is assigned on the basis of thermodynamic stability and the relatively small (6 Hz) coupling constant for the secondary methyl group.[14]

Although the lithium–ethylamine reduction of enol phosphate esters has been reported to proceed with virtually complete regiospecificity,[13] apparently the use of ammonia as a medium for these reactions leads to the equilibration of an intermediate carbanion. That the reduction is regiospecific in ethylamine was confirmed when it was found that the enol phosphate ester (13) derived from 10-epieudesm-4-en-3-one (14) was reduced cleanly with lithium–*tert*-butyl alcohol in this medium to give 5-epi-10-epieudesm-3-one (15).

Controlled oxidation of diene 4 gave 3β,4β-oxido-5-epi-10-epieudesm-11-ene (16) in good yield and greater than 70% purity;[15] however, following the disclosure by Zalkow[16] that a synthesis of intermedeol had been accomplished by the

lithium aluminum hydride reduction of epoxide **16**, this synthetic approach was abandoned.

In connection with some other work, the oxidation of 10-epieudesm-4-ene-3,11-diol (**17**)[17] with Jones reagent was attempted. However, rather than the expected ketone, the major product of this reaction was α-agarofuran (**18**).[17,18] Although the conversion of **17** and **18** by mild acid treatment has been reported,[18] the use of Jones reagent gives a product which is considerably cleaner than that obtained by the Canadian group.[19] Conversion of α-agarofuran to the 3β,4β-oxide (**19**),[20] followed by lithium aluminum hydride reduction, gave a 5:1 mixture of isomeric alcohols. The major product of the reduction was assigned the structure 4β-hydroxydihydroagarofuran (**20**) on the basis of its NMR spectrum (see Experimental Section), while the minor component of the mixture was assumed to be the 3β-hydroxy isomer (**21**) from similar considerations and its oxidation to the known 3-ketone.[18] The equatorial nature of the hydroxyl group in alcohol **20** was confirmed through its dehydration with thionyl chloride in pyridine to give β-agarofuran (**22**)[21] as the major product. It is noteworthy that reduction of epoxide **19** gives less than 20% of the product arising from normal trans diaxial opening of the oxide, while the epoxide which is a precursor to intermedeol gives ca. 60% of the axial secondary alcohol under similar conditions.[15]

Following the conditions used for the cleavage of the tetrahydrofuran ring of α-agarofuran,[20] reduction of alcohol **20** with lithium–ethylenediamine afforded as the major product a diol, assigned the structure 5-epi-10-epieudesma-4β,11-diol (**23**) on the basis of its NMR spectrum (see Experimental Section) and its preparation from natural intermedeol[2a,b,22] by oxidation with *m*-chloroperbenzoic acid and reduction of the resulting mixture of epimeric 11,12-epoxides with lithium aluminum hydride.

A number of attempts were made to selectively functionalize diol **23** in order to achieve a regioselective synthesis of intermedeol; unfortunately, this goal could not be achieved. However, dehydration of **23** using von Rudloff's procedure[23] gave a mixture of five compounds, of which intermedeol was the principal component. Pure intermedeol, identical in all respects with natural material, could be isolated from this mixture by careful chromatography.

As noted above, at the time these studies were initiated, the C-4 epimer of intermedeol, 5-epi-10-epieudesm-11-en-4α-ol (**5**), was considered to be a naturally occurring sesquiterpene.[6] Although this compound has subsequently been shown to be intermedeol,[2c,7] its synthesis remains of interest since a compound of this structure is a plausible natural product, because it is a substance having the structural and stereochemical features of a compound which could be found in nature. Also samples of **5** were needed for reference in connection with other work. Since alcohol **5** has an axial hydroxyl group, the obvious method of synthesis would involve reductive cleavage of an epoxide, either the 3α,4α-epoxide derived from diene **4**, or the 4α,5α-epoxide derived from diene **3**. In view of the problems encountered in preparing quantities of pure **4**, the latter approach was chosen.

10-Epieudesma-4,11-diene (**3**) occurs naturally and has been synthesized by desulfurization of the thioketal of enone **6**.[4] In an alternative approach, the mixture of epimeric alcohols obtained by reduction of enone **6**[17] was converted to the mixed acetates, which were then reduced to **3** by lithium in ammonia in an overall yield of 84% from enone **6**. Treatment of diene **3** with 1 equiv of *m*-chloroperbenzoic acid gave the desired epoxide (**24**). The α orentation of the oxirane ring is based on analogy with the reported epoxidation of the dihydro derivative of **3**,[24] and the conversion of **24** to 4α-hydroxydihydroagarofuran (**25**). This conversion was effected by reaction of epoxide **29** with *m*-chloroperbenzoic acid to give the bis epoxide and reduction under mild conditions to the 4α,5α-oxido-11-ol which on treatment with toluenesulfonic acid gave **25**.

Reduction of epoxide **24** with lithium–ammonia gave a single tertiary alcohol which on the basis of its NMR spectrum was either **5** or its C-5 epimer. That this alcohol was in fact **5** was confirmed by hydrogenation to 5-epi-10-epieudesman-4α-ol (**26**), a compound which had been synthesized earlier during the work leading to the confirmation of the identity of "paradisiol" and intermedeol.[2c] Alcohol **26** of known stereochemistry at both C-4 and C-5 was prepared from olefin **15** by conversion to the bromohydrin, a reaction known to occur by trans-diaxial addition of bromine and hydroxyl, and subsequent reduction with lithium aluminum hydride.[2c]

Experimental Section[25]

3-Acetoxy-5-epi-10-epieudesma-3,11-diene (7). A solution of 1.55 g of 10-epieudesma-4,11-dien-3-one (**6**)[8] in 20 ml of dry ether and 100 ml of liquid ammonia was reduced with lithium to the enolate of 5-epi-10-epieudesm-11-en-3-one as described below. The ammonia was replaced by 75 ml of dry benzene, and 30 ml of acetic anhydride was added slowly. The reaction mixture was stirred under nitrogen at room temperature for 1 h and poured into aqueous sodium bicarbonate, the aqueous layer was drawn off, washed with water and brine, and dried, and the solvent was removed at reduced pressure to give 1.343 g of yellow oil. This oil was dissolved in hexane-benzene (2:1) and chromatographed on Woelm silica gel. Elution with benzene gave 0.577 g of enol acetate **7** as a colorless liquid: ir 1755, 1687 cm^{-1}; NMR δ 0.91 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3C=), 1.72 (s, 3 H, CH_3C=), 2.10 (s, 3 H, CH_3CO), 4.84 (m, 2 H, CH_2=). For analysis, a small sample of this material was distilled at 130–140 °C (bath temperature, 0.1 mm).

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.93; H, 9.85.

4β-Acetoxy-5-epi-10-epieudesm-11-en-3-one (9). A. A solution of 0.725 g of 10-epieudesma-4,11-dien-3-one (**6**) in 15 ml of dry ether was added to ca. 50 ml of dry distilled liquid ammonia. Lithium ribbon, just sufficient to impart a permanent blue color, was added and the reaction mixture was stirred at reflux for 50 min. The ammonia was evaporated in a stream of dry nitrogen while 50 ml of dry benzene was added. Following the removal of the ammonia, 5.10 g of freshly dried lead tetraacetate was added in portions and the reaction mixture was stirred at room temperature in a nitrogen atmosphere for 1.5 h. The reaction mixture was filtered through Celite, washed with water and brine, and dried and the solvent was removed at reduced pressure to give 0.541 g of yellow oil. The crude product was dissolved in hexane–benzene (1:1) and chromatographed on 35 g of Woelm activity III neutral alumina. Elution with these solvents gave 0.173 g of a mixture of 4-epi-5-epi-10-epieudesm-11-en-3-one and the starting dienone, while elution with benzene afforded 0.106 g of crude acetoxy ketone. A total of 1.704 g of material obtained in this manner from three runs was combined, dissolved in benzene, and chromatographed on 75 g of Woelm activity I silica gel. Elution with benzene–ethyl acetate (9:1) gave 1.345 g of an oil, which although homogeneous to TLC (silica gel G, benzene–ethyl acetate, 8:1) was obviously a mixture from the NMR spectrum. This mixture was distilled, bp 150–160 °C (bath temperature, 0.15 mm) to give 0.661 g of a mixture of essentially the same composition, which was taken up in benzene–hexane (1:1) and chromatographed on 30 g of Woelm activity II neutral alumina. The first fractions eluted with these solvents gave mixtures of unreacted ketone and the desired acetoxy ketone, while later fractions afforded 0.065 g of pure material as a crystalline solid. Recrystallization from aqueous methanol gave the analytical sample: mp 90–91 °C; mass spectrum *m/e* (rel intensity) 278 (7), 236 (29), 235 (38), 219 (30), 218 (100); ir 1735, 1640, 879 cm^{-1}; NMR δ 1.22 (s, 3 H, CH_3), 1.40 [s, 3 H, $C(OCOCH_3)CH_3$], 1.72 (br s, 3 H, CH_3C=), 2.01 (s, 3 H, CH_3CO_2), 4.62, 4.72 (m, 1 H each, C=CH_2).

Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.51; H, 9.52.

The later benzene fractions and benzene–methylene chloride (4:1) gave 0.047 g of an oil, which on the basis of its spectral properties was identified as **4α-hydroxy-5-epi-10-epieudesm-11-en-3-one:** mass spectrum *m/e* (rel intensity) 236 (7), 219 (18), 218 (75), 203 (55), 193 (15), 190 (15), 179 (21), 175 (100), 162 (23), 161 (29), 149 (23), 148 (29), 147 (28); ir 3520, 1701, 1638 cm^{-1}; NMR δ 1.20 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3CO), 1.72 (br s, CH_3C=), 4.90 (br s, 2 H, CH_2=).

B. To a stirred solution of 0.538 g of 3-acetoxy-5-epi-10-epieudesma-3,11-diene (**7**) in 15 ml of ether at 0°C was added slowly a so-

lution of 0.496 g of *m*-chloroperbenzoic acid (72%) in 10 ml of ether. The reaction mixture was stirred at ambient temperature for 24 h, then shaken with successive portions of 10% aqueous sodium bisulfite, saturated sodium bicarbonate, water, and brine, and dried, and the solvent was removed at reduced pressure with gentle warming. The resulting yellow oil showed a carbonyl peak in the ir at 1755 cm^{-1}, and was, without purification, taken up in 15 ml of chloroform, treated with 0.025 g of toluenesulfonic acid, and stirred at room temperature for 18 h. The reaction mixture was washed with successive portions of saturated aqueous sodium bicarbonate and brine and dried and the solvent was removed to give 0.379 g of yellow oil, which was dissolved in benzene and chromatographed on Woelm silica gel. Elution with benzene–ethyl acetate (9:1) gave 0.140 g of acetoxy ketone **9**.

4β-Hydroxy-5-epi-10-epieudesm-11-en-3-one (10). A solution of 0.157 g of acetoxy ketone **9** in 10 ml of 1% methanolic potassium hydroxide was heated at reflux in a nitrogen atmosphere for 18 h. The reaction mixture was cooled, diluted with water, and extracted with methylene chloride. The extract was washed with water and brine and dried, and the solvent was removed to give 0.100 g of a yellow oil. TLC (silica gel G, benzene–ethyl acetate, 8:1) indicated that this material was almost exclusively one compound and it was purified by dissolving it in benzene–ethyl acetate (8:1) and filtering it through 3 g of Woelm silica gel to give 0.059 g of a pale yellow oil: ir 3636, 1712 cm^{-1}; mass spectrum *m/e* (rel intensity) 236 (17), 219 (58), 218 (75), 204 (25), 193 (100), 175 (75); NMR δ 1.22 (s, 6 H, CH_3), 1.75 (m, 3 H, CH_3C=), 4.82 (m, 2 H, CH_2=).

Deoxygenation of 10-Epieudesma-4,11-dien-3-one. To 125 ml of redistilled liquid ammonia was added a solution of 5.21 g of 10-epieudesma-4,11-dien-3-one (**6**) in 40 ml of dry ether. Sufficient lithium ribbon to impart a permanent blue color was added and the mixture stirred at reflux for 0.5 h. An additional 75 ml of dry ether was added and the ammonia was evaporated with gentle warming using a stream of dry nitrogen. During the evaporation of ammonia, sufficient ether was added to maintain a volume of ca. 100 ml. A solution of 10 ml of diethyl chlorophosphate in 75 ml of dry ether was added and the reaction mixture stirred at room temperature for 1 h. The phosphate ester was isolated by pouring the reaction mixture into water, drawing off the aqueous layer, washing the ethereal solution with successive portions of saturated aqueous sodium bicarbonate and brine, drying, and removing the solvent in vacuo with gentle warming. The crude phosphate ester showed characteristic infrared absorption at 1070 cm^{-1}; TLC indicated the presence of 5-epi-10-epieudesm-11-en-3-one as the only major impurity and this material was reduced without additional purification.

The crude phosphate ester was dissolved in a mixture of 75 ml of dry ether and 75 ml of dry *tert*-butyl alcohol and added to ca. 500 ml of redistilled liquid ammonia. To this solution was added 2.30 g of sodium and the reaction mixture stirred at reflux 8 min. The reaction was quenched by the addition of 100 ml of ethanol and the ammonia was removed in a stream of nitrogen. The residue was taken up in hexane and water, the aqueous phase drawn off, the hexane extracts washed with water and 10% hydrochloric acid and dried, and the solvent removed to give 3.66 g of yellow oil, which was dissolved in hexane and chromatographed on 110 g of Merck basic alumina. Elution with hexane gave 1.15 g of a mixture of hydrocarbons which upon GLC (OV-17, 200 °C) showed the presence of three compounds, in a ratio of 12:46:42 in order of increasing retention time. A small quantity of the mixture was separated by preparative GLC for characterization to give respectively **4-epi-10-epieudesma-5,11-diene (12),** NMR δ 0.92 (d, 3 H, J = 6 Hz, C**H**$_3$CH), 1.00 (s, 3 H, CH_3), 1.78 (d, 3 H, J = 1 Hz, CH_3C=), 2.52 (m, 1 H, H-7), 4.45 (m, 2 H, CH_2=), 4.90 (q, J = 4 Hz, H-6);[26] **10-epieudesma-4,11-diene (3),** identical with the material described below and the properties of which agree with those reported;[4] and **5-epi-10-epieudesma-3,11-diene (4),** the ir and NMR spectra of which agree with those reported by Klein,[4] mass spectrum *m/e* (rel intensity) 204 (47), 189 (67), 161 (100).

5-Epi-10-epieudesm-3-ene (15). 10-Epieudesm-4-en-3-one (**14**) was treated with lithium and liquid ammonia followed by diethyl chlorophosphate as described in the deoxygenation of 10-epieudesma-4,11-dien-3-one (vide supra). The crude enol phosphate ester derived from 4.51 g of ketone was taken up in 20 ml of dry ether and 40 ml of dry *tert*-butyl alcohol and added to ca. 150 ml of redistilled ethylamine. Sufficient lithium ribbon was added to impart a permanent blue color and the reaction mixture stirred at reflux for an additional 10 min. The reaction was quenched with ethanol and the ethylamine evaporated in a stream of nitrogen. The residue was taken up in hexane, washed with successive portions of water, 10% hydrochloric acid, and 10% sodium carbonate, and dried and the solvent was removed at reduced pressure to give 2.80 g of pale yellow oil. The crude reaction product was taken up in hexane and chromatographed on 90 g of Merck alumina. Elution with hexane gave 1.13 of olefin **15** as a colorless oil: mass spectrum *m/e* (rel intensity) 206 (50), 191 (100), 177 (17), 163 (29), 151 (12); NMR δ 0.85 (s, 3 H, CH_3), 0.90 (d, 6 H, J = 7 Hz, isopropyl), 1.60 (br s, 3 H, CH_3C=CH), 5.30 (m, 1 H, CH_3C=C**H**). GLC (OV-17, 190 °C) indicated that this material was contaminated with a small amount (total, 17%) of three other compounds. For analysis a small quantity of the olefin was rechromatographed on Merck alumina.

Anal. Calcd for $C_{15}H_{26}$: C, 87.30; H, 12.70. Found: C, 87.27; H, 12.68.

Further elution with hexane gave 0.35 g of 4-epi-5-epi-10-epieudesman-3-one as a waxy solid, mp 66–69 °C, after recrystallization from petroleum ether. The enantiomer is reported to melt at 66–67 °C.[27] The 2,4-dinitrophenylhydrazone had mp 224–226 °C after recrystallization from ethanol–ethyl acetate (lit. mp 222 °C for the enantiomer[27]).

3β,4β-Oxido-5-epi-10-epieudesm-11-ene (16). To a solution of 0.047 g of diene **4** in 3 ml of methylene chloride at 0 °C was added dropwise a solution of 0.049 g of *m*-chloroperbenzoic acid in 5 ml of the same solvent. The reaction mixture was stirred at 0 °C for 0.75 h and the excess peracid destroyed with 10% aqueous sodium bisulfite. The organic layer was drawn off and washed with successive portions of 5% aqueous sodium bicarbonate, water, and brine. After drying and removing the solvent at reduced pressure there was obtained 0.44 g of an oil which TLC (silica gel G, benzene–hexane, 1:1) showed to be contaminated with traces of another compound. No effort was made to purify this material. However, it had the expected spectral properties: mass spectrum *m/e* (rel intensity) 220 (10), 219 (52), 205 (100); NMR δ 0.80 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3CO), 1.68 (br s, CH_3C=), 2.77 (t, 1 H, J = 2 Hz, CHO), 4.55 (m, 2 H, CH_2=).

α-Agarofuran (18). To a solution of 10.6 g of 10-epieudesm-4-ene-3,11-diol[17] in 100 ml of permanganate stable acetone was added dropwise during 4 h 12 ml of Jones reagent. Dilution with water and extraction with ether gave 7.60 g of α-agarofuran, bp 69–72 °C (0.05 mm), the spectral properties of which were identical with those reported by Marshall.[17]

Lithium Aluminum Hydride Reduction of 3β,4β-Epoxydihydro-α-agarofuran. A solution of 4.80 g of epoxide **19**[20] in 100 ml of dry ether was added dropwise during 30 min to a stirred slurry of 1.20 g of lithium aluminum hydride in 100 ml of dry ether at −18 °C. The mixture was stirred for a further 4 h at this temperature and the product isolated in the usual manner. The oily crude material was found to be a 5:1 mixture of isomeric alcohols by GLC and was chromatographed on 50 g of neutral alumina. Elution with 5% benzene in pentane gave 3.0 g of **4β-hydroxydihydroagarofuran (20),** bp 90 °C (0.05 mm), as the major product: ir 3575 cm^{-1}; NMR δ 1.10 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.24 (3 H, CH_3), 1.38 (s, 3 H, CH_3).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.59; H, 10.98. Found: C, 75.82; H, 10.90.

Continued elution with benzene–pentane mixtures containing increasing proportions of benzene yielded eventually **3β-hydroxydihydroagarofuran (21):** bp 100 °C (0.05 mm); ir 3520 cm^{-1}; NMR δ 0.95 (d, 3 H, J = 5 Hz, C**H**$_3$CH), 1.05 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 3.58 (m, $W_{1/2}$ = 8 Hz, C**H**OH).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.59; H, 10.98. Found: C, 75.82; H, 10.90.

Oxidation of 0.025 g of alcohol **21** with Jones reagent and isolation of the product in the usual manner gave 0.014 g of 3-ketoagarofuran, mp 120–121 °C (lit. mp 124 °C[18]). The spectral properties are in agreement with those reported for this compound.[18]

β-Agarofuran (22). A solution of 0.240 g of 4β-hydroxydihydroagarofuran (**20**) in 5 ml of dry pyridine at 0 °C was treated with 0.65 ml of thionyl chloride. After 1.5 h the mixture was poured into ice–water and extracted with ether, and the product was isolated in the usual manner. The material so obtained was a mixture of β- and α-agarofuran in an 8:1 ratio by GLC. Chromatography on neutral alumina and elution with pentane gave β-agarofuran, bp 90 °C (0.05 mm), the spectral properties of which are consonant with those of authentic material.[20]

5-Epi-10-epieudesma-4β,11-diol (23). A. To a stirred solution of 0.300 g of 4β-alcohol **20** in 25 ml of dry, distilled ethylenediamine at 100 °C was added in portions, under nitrogen, 0.300 g of lithium metal. The mixture was heated at reflux for 1 h, cooled, poured into water, and extracted with ether. The residue was chromatographed on 30 g of neutral alumina. Elution with benzene gave a small amount of 10-epi-γ-eudesmol. Elution with ether gave a compound, presumably the 4β,5β-diol, which reacted readily with periodic acid: ir 3425 cm^{-1}; NMR δ 0.87 (d, 3 H, J = 6 Hz), 0.90 (d, 3 H, J = 6 Hz, isopropyl), 1.08 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3).

Finally, elution with ethyl acetate yielded 0.150 g of the desired

4β,11-diol (**23**) which crystallized from pentane in plates: mp 110–111 °C; ir (Nujol) 3455 cm^{-1}; NMR δ 0.90 (s, 3 H, CH_3), 1.09 (s, 3 H, CH_3), 1.29 [s, 6 H, $(CH_3)_2COH$]; (pyr) δ 0.93 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.40 [s, 6 H, $(CH_3)_2COH$].

Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.94; H, 11.76. Found: C, 75.10; H, 11.54.

B. A solution of 0.050 g of intermedeol (**1**), isolated from "I" strain *Bothriochloa intermedia*,[22] was stirred with 1 equiv of *m*-chloroperbenzoic acid in 10 ml of chloroform for 18 h at 0 °C. The reaction mixture was washed with cold 5% aqueous sodium hydroxide, water, and brine, dried, and concentrated under reduced pressure to give 0.040 g of crude epoxy alcohol: ir 3460 cm^{-1}; no olefinic absorbance. This material was dissolved in 5 ml of ether and added to a slurry of 0.075 g of lithium aluminum hydride in 10 ml of ether and added to a slurry of 0.075 g of lithium aluminum hydride in 10 ml of ether and stirred at room temperature for 18 h. The excess hydride was decomposed with water and the residue thoroughly extracted with ether. The combined ether extracts were dried and concentrated under reduced pressure to give 0.035 g of diol **23**. The spectral and chromatographic (GL, TLC) properties of this material were identical with those described in A above.

5-Epi-10-epieudesm-11-en-4β-ol (Intermedeol, 1). A mixture of 0.800 g of diol **23** and 3.2 g of 2% quinoline on alumina[23] was heated at a bath temperature of 192 °C for 2 h. Isolation of the products with ether gave 0.710 g of a viscous oil which GLC showed to be a mixture of five compounds. The retention time of the principal component (33%) of this mixture corresponded to that of intermedeol. The mixture was chromatographed on 25 g of activity I basic alumina and elution with benzene gave 0.160 g of a mixture enriched in intermedeol. Rechromatography of this mixture on 2.5 g of Woelm silica gel and elution with hexane–benzene (4:1) gave 0.045 g of intermedeol of ca. 90% purity. Evaporative distillation followed by chromatography on 1.0 g of Woelm silica gel (elution with hexane–benzene, 9:1) gave 0.020 g of material, homogeneous to GLC and TLC, and which had spectral and chromatographic properties identical with those of natural intermedeol (**1**).

3-Acetoxy-10-epieudesma-4,11-diene. A solution of 2.65 g of 10-epieudesma-4,11-dien-3-ol[17] in 25 ml of dry pyridine was treated with 3.4 ml of acetic anhydride and kept at ambient temperature under nitrogen for 18 h. Dilution with water and extraction with ether gave 2.90 g of acetate: bp 120 °C (bath, 0.05 mm); ir 1735, 1645, 1275, 885 cm^{-1}; NMR δ 1.10 (s, 3 H, CH_3), 1.57 (s, 3 H, $CH_3C{=}C$), 1.67 (s, 3 H, $CH_3C{=}C$), 2.20 (s, 3 H, CH_3CO), 4.70 (s, 2 H, $=CH_2$).

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.67; H, 10.06.

10-Epieudesma-4,11-diene (3). A solution of 1.84 g of the acetate mixture described above in 70 ml of dry ether was added dropwise during 10 min to a stirred solution of 0.35 g of lithium metal in 150 ml of liquid ammonia. After a further 20 min, ammonium chloride was added and the ammonia allowed to evaporate. Water was added and the diene isolated with ether. Distillation, bp 100 °C (bath, 0.05 mm), gave 1.29 g of material, the spectral data for which are in agreement with those reported.[4]

Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.14; H, 11.87.

4α,5α-Oxido-10-epieudesm-11-ene (24). *m*-Chloroperbenzoic acid (1 equiv) was added portionwise during 15 min to a stirred solution of 0.240 g of diene **3** in 20 ml of methylene chloride at 0 °C. Stirring was continued at room temperature for a further 45 min, and the solution was washed with cold 5% aqueous sodium hydroxide, water, and brine, dried, and concentrated. The oil residue was chromatographed on 8.0 g of Woelm activity III neutral alumina. Elution with hexane–benzene (9:1) gave 0.175 g of epoxide **24**: bp 95 °C (bath, 0.05 mm); ir 1641, 882 cm^{-1}; NMR δ 1.02 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3CO), 1.70 (s, 3 H, $CH_3C{=}$), 4.97 (s, 2 H, $CH_2{=}C$).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.83; H, 11.07.

4α-Hydroxydihydroagarofuran (25). To a solution of 0.220 g of epoxide **24** in 20 ml of methylene chloride was added a solution of 0.240 g of *m*-chloroperbenzoic acid in 20 ml of the same solvent and the mixture kept at room temperature for 18 h. The solution was washed with dilute alkali, brine, and water, then dried and concentrated to yield 0.225 g of diepoxide: NMR δ 1.00 (s, 3 H, CH_3), 1.27 [m, 6 H, $(CH_3)_2CO$]. The crude product in 5 ml of dry ether was treated with 0.100 g of lithium aluminum hydride in 10 ml of ether for 6 h at room temperature. Isolation of the product in the usual manner gave an oil which was dissolved in 10 ml of benzene, treated with a crystal of *p*-toluenesulfonic acid monohydrate, and stirred at room temperature for 5 days. Evaporation of the benzene in vacuo gave a semicrystalline mass which crystallized from hexane to give 0.075 g of material, mp 125–126 °C (lit. mp 130–131 °C[21]), alone or mixed with an authentic sample of 4α-hydroxydihydroagarofuran.

5-Epi-10-epieudesm-11-en-4α-ol (5). A solution of 0.300 g of epoxide **24** in 30 ml of dry ether was added during 10 min to a solution of 0.300 g of lithium metal in 100 ml of liquid ammonia and the mixture stirred for 2 h at reflux. Ammonium chloride was added and the ammonia allowed to evaporate. The residue was leached several times with ether and the extracts evaporated to yield 0.300 g of an oily residue which was chromatographed on 20 g of Woelm activity III neutral alumina. Elution with benzene afforded 0.175 g of alcohol **5**: bp 110 °C (bath, 0.05 mm); ir 3590, 1640, 885 cm^{-1}; NMR δ 1.05 (s, 3 H, CH_3), 1.13 (s, 3 H, CH_3COH), 1.72 (s, 3 H, $CH_3C{=}$), 4.90 (m, 2 H, $CH_2{=}$); NMR (pyr) δ 1.25 (s, 3 H), 1.73 (s, 3 H).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.07; H, 11.83.

5-Epi-10-epieudesman-4α-ol (26). A. A solution of 0.22 g of alcohol **5** in 50 ml of ethanol was shaken in hydrogen with 0.040 g of Adams catalyst at room temperature and pressure until absorption of hydrogen ceased. The suspension was filtered and the filtrate concentrated to leave 0.165 g of alcohol **26**: bp 100 °C (bath, 0.05 mm); mass spectrum *m/e* (rel intensity) 109 (100), 121 (59), 123 (36), 135 (44), 138 (69), 139 (62), 150 (33), 163 (79), 181 (95), 191 (72), 206 (23), 209 (72), 224 (10); NMR δ 0.85 (d, 6 H, J = 5.5 Hz, isopropyl), 1.10 (s, 3 H, CH_3COH); (pyr) δ 0.87 (d, J = 5.5 Hz), 1.25 (s, 3 H), 1.30 (s, 3 H).

Anal. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.31; H, 12.83.

B. To a chilled (0 °C) solution of 0.717 g of 5-epi-10-epieudesm-3-ene (**15**) in 25 ml of tetrahydrofuran containing 5 ml of water and 2.5 ml of 8% aqueous perchloric acid was added, with stirring, 1.40 g of *N*-bromosuccinimide. The reaction mixture was allowed to warm to room temperature, stirred for 3 h, and poured into water. The resulting suspension was extracted with ether, and the extracts were washed with successive portions of 10% aqueous sodium bisulfite, sodium carbonate, and brine. After drying, the solvent was removed at reduced pressure and 40 °C to give a yellow oil. TLC, IR, and NMR indicated the presence of unreacted olefin as well as bromohydrin, and the crude reaction mixture was reduced directly by dissolving it in 100 ml of dry ether, adding 0.7 g of lithium aluminum hydride, and stirring at room temperature for 18 h. The reaction mixture was cooled to 0 °C and the excess hydride was decomposed with ice water. The ethereal solution was decanted from the precipitated aluminum salts, washed with brine, and dried and the solvent removed at reduced pressure to give 0.763 g of an oil, which was dissolved in hexane and chromatographed on Merck alumina. Elution with hexane–benzene (7:2) gave 0.169 g of dihydroparadisiol as a colorless oil. Although this material was homogeneous to TLC and GLC (SE-30, 200 °C), the mass spectrum indicated that it was contaminated with unreduced bromohydrin. Pure material, identical with that described in part A above, was obtained by distillation at 130 °C (bath, 0.2 mm) and rechromatography.

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Registry No.—**1**, 6168-59-8; **3**, 28290-20-2; **4**, 60132-29-8; **5**, 29969-75-3; **6**, 2303-31-3; **7**, 60064-80-4; **9**, 60064-91-7; **10**, 60064-92-8; **10** 4α enantiomer, 60064-93-9; **12**, 60064-94-0; **14**, 22555-76-6; **15**, 41703-44-0; **16**, 28290-25-7; **17**, 15051-79-3; **18**, 5956-12-7; **19**, 60064-95-1; **20**, 60132-34-5; **21**, 60064-96-2; **22**, 6040-08-0; **23**, 60132-35-6; **24**, 60064-97-3; **25**, 15052-76-3; **26**, 29868-51-7; 4-epi-5-epi-10-epieudesma-3-one, 54030-91-0; 10-epieudesma-4β,5β-diol, 60064-98-4; 3-acetoxy-10-epieudesma-4,11-diene, 60064-99-5; 10-epieudesma-4,11-dien-3-ol, 17023-63-1.

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Synthesis of Intermedeol and Related Sesquiterpenoid Studies[1]

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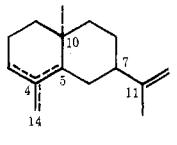
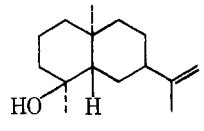
The 10-epieudesmanes (−)-7β,10α-selina-4,11-diene (I) and (+)-5βH,10α-selina-3,11-diene (II) were synthesized from 10α-selina-4,11-dien-3-one (VI) and natural (−)-7β,10β-selina-4,11-diene (I) was further converted into intermedeol (IV). Intermedeol (IV) was transformed into 5βH,10α-eudesmol (XI). On treatment with boron trifluoride etherate, neointermedeol (XV), a close relative of intermedeol, gave δ-selinene, while with thionyl chloride in benzene selina-4,11-diene was obtained.

The recent isolation of the dienes (−)-7β,10α-selina-4,11-diene (I) and (+)-5βH,7β,10α-selina-3,11-diene (II) from *Dipterocarpus alatus* Roxb.[3] and (−)-5β,7β,10α-selina-4(14),11-diene (III) from *Aristolochia indica* Linn.[4] are of particular interest since they can be visualized as arising biogenetically simply by dehydration of intermedeol (IV), the

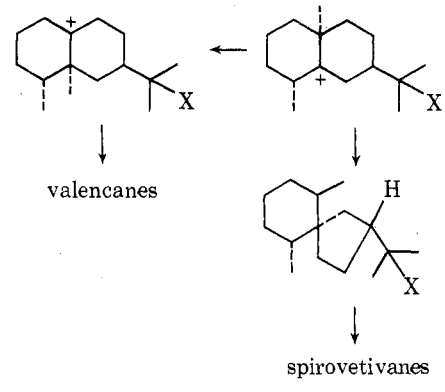


I, $\Delta^{4(5)}$
II, $\Delta^{3(4)}$, 5βH
III, $\Delta^{4(14)}$, 5βH



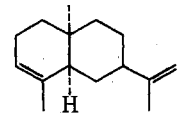
IV

first member of this family to be reported.[5] In fact, diene III was first prepared in 1962,[5b,6] by pyrolysis of intermedeol acetate, but was not recognized as such since, at that time, the configuration at C-7 was thought to be 7βH.[5a] The grapefruit constituent paradisol[7] is now known to be identical with intermedeol[8] and a direct comparison of the dehydration product of paradisol[7] with natural III has shown their identity.[4] Only a few other related 10-epieudesmanes have been reported,[9,10] but this group of sesquiterpenes appears to play an important role as biogenetic precursors to the valencanes and spirovetivanes.[11,12] Marshall and Andersen[12] have concluded from the literature on constituents of eudalene-yielding essential oils that (1) 10-epieudesmanes are more prone to rearrangement and (2) rearrangements always occur from a eudesmane with cis related methyl groupings. These observations were

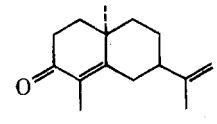


explained by postulating that relief of the strain associated with an axial isopropyl grouping and a 1,3-diaxial methyl interaction provides substantial driving force for the rearrangements.[12]

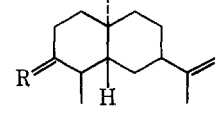
We now report the synthesis of I (21%) and II (13%) together with isomer V (37%) by a modified Wolff–Kishner reduction[13] of the previously reported dienone VI[14] and the further con-



V



VI



VII, R = O

VIII, R =