Stereochemistry and Synthesis of α-Agarofuran

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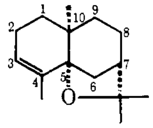
Abstract: A stereoselective total synthesis of α-agarofuran demonstrated that this and five other related furanoid sesquiterpenes have the relative and absolute stereochemistry indicated in structure **19**. Photooxygenation of the cyclohexadiene **10** yielded in addition to the anticipated *endo*-peroxide **11** a cross-conjugated ketone **13** presumably derived from the unstable doubly allylic hydroperoxide **12**.

Chemical examination of fungus infected agarwood (*Aquillaria agallocha* Roxb.) has led to the isolation of six closely related furanoid sesquiterpenes.[1,2] α- and β-agarofuran seem to be the major constituents and were used for degradative studies which led to structures **1** and **2**.[1] The arguments concerning the gross structures and the absolute configuration of the angular methyl group appear sound but the geometric disposition of the tetrahydrofuran ring rests on less secure grounds. It was deduced mainly from the optical rotatory dispersion curve of the nor ketone **3**, and because no closely related comparison compound was available we felt that this conclusion should be accepted with some reservation. In fact the known facile conversion of β-agarofuran to the alcohol **4** brought about by reduction with lithium in ethylenediamine seems to favor the alternate structure **6**. The geometry of this *trans* isomer **6** allows resonance stabilization of the developing carbanion by the adjacent double bond because the carbon–oxygen bond undergoing cleavage is orthogonal to the plane of the olefinic bond. In the corresponding *cis* isomer **5** however the allylic carbon–oxygen bond and the double bond are coplanar.



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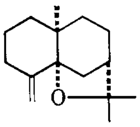

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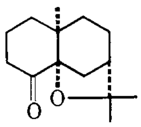

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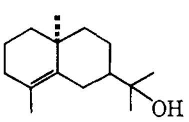

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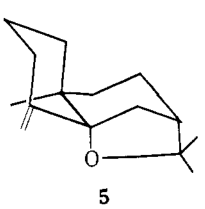

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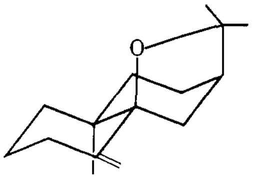

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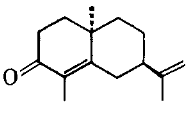
To settle this point we have prepared α-agarofuran by a stereoselective total synthesis which establishes the presence of a *trans*-decalin. The readily available (−)-epi-α-cyperone (**7**)[3,4] of known absolute configuration was chosen as starting material. Reduction with lithium aluminum hydride gave a mixture of epimeric alcohols **8**. The major isomer (80%) was obtained in crystalline form but no effort was made to determine its configuration. Dehydration of the mixture of epimers with phosphorus oxychloride in pyridine gave exclusively the undesired triene **9** with ultraviolet maxima at 233, 239, and 246 mμ (ε 11,300, 12,500, and 11,400) typical for heteroannular dienes. Pyrolytic dehydration of the crystalline alcohol or a mixture of both epimers over pyridine-treated alumina[5,6] furnished 75% of the desired triene **10** with an ultraviolet maximum at 277 mμ (ε 4600) and 25% of its isomer **9**. Pure olefins became available by gas chromatographic separation but the original mixture was equally suited for further transformation.



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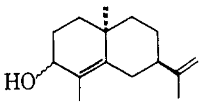

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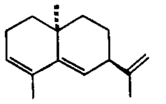

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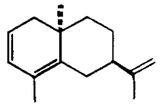

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Photosensitized oxygenation[7-10] in the presence of eosin yielded unchanged triene **9**, the crystalline *endo*-peroxide **11**, and minor amounts of the trienone **13**. The formation of the cross-conjugated ketone can be rationalized if we assume the intermediacy of the allylic hydroperoxide **12** resulting in turn from oxidation of the triene **10** with accompanying migration of the $\Delta^{2,3}$ double bond.[8-10] To our knowledge this is the first case in which photosensitized oxygenation has yielded both an *endo*-peroxide and a ketone seemingly derived from a hydroperoxide. Steric hindrance probably is the prime factor responsible for the production of a single endoperoxide and since the angular methyl group is in close proximity to the site undergoing reaction the peroxide bridge should have the β configuration.

Exposure of the peroxide **11** to basic alumina resulted in essentially quantitative conversion to a crystalline

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[1] M. L. Maheshwari, T. C. Jain, R. B. Bates, and S. C. Bhattacharyya, *Tetrahedron*, **19**, 1079 (1963).

[2] M. L. Maheshwari, K. R. Varma, and S. C. Bhattacharyya, *ibid.*, **19**, 1519 (1963).

[3] R. Howe and F. J. McQuillin, *J. Chem. Soc.*, 2423 (1955); 2670 (1956); 1194 (1958).

[4] R. B. Bates, G. Büchi, T. Matsuura, and R. R. Shaffer, *J. Am. Chem. Soc.*, **82**, 2327 (1960).

[5] E. von Rudloff, *Can. J. Chem.*, **39**, 1860 (1961).

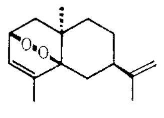
[6] E. J. Corey and A. G. Hortmann, *J. Am. Chem. Soc.*, **87**, 5736 (1965).

[7] G. O. Schenck, *Angew. Chem.*, **69**, 579 (1957), and references therein.

[8] K. Gollnick and G. O. Schenck in "Organic Photochemistry," Butterworth & Co. (Publishers), Ltd., London, 1964, p 507.

[9] A. Nickon and W. L. Mendelson, *J. Am. Chem. Soc.*, **87**, 17 (1965), and earlier papers.

[10] G. O. Schenck, K. Gollnick, G. Buchwald, S. Schroeter, and G. Ohloff, *Ann.*, **674**, 93 (1964).



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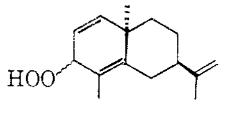

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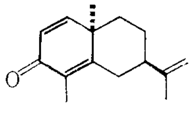

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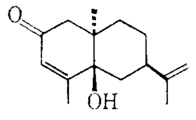
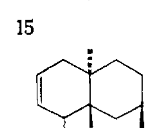


14

ketol whose spectral properties are in complete accord with structure **14**. Cyclization to the tetrahydrofuran turned out to be an unexpectedly facile process brought about readily by acid-washed alumina. The mild conditions employed leave little doubt that the chirality at C_7 is the same in both starting material **14** and product **15**. The final phase of the synthesis was concerned with reduction of the α,β-unsaturated ketone **15** to the corresponding olefin. Attempts to accomplish this by Wolff–Kishner reduction led to alcohols undoubtedly resulting from cleavage of the allylic carbon–oxygen bond and attempts to reduce the tosylhydrazone of **15** with either lithium aluminum hydride or sodium borohydride[11] led to no useful result. Direct reduction of the unsaturated ketone **15** with sodium borohydride gave minor amounts of the saturated axial alcohol **16** and approximately 90% of a mixture of epimeric allyl alcohols **17**. Consecutive treatments of **17** with thionyl chloride in ether and with lithium aluminum hydride in the same solvent produced an equal mixture of two olefins. Separation by adsorption chromatography gave a crystalline olefin **18** containing a *cis*-disubstituted double bond and a liquid isomer **19** whose infrared and nuclear magnetic resonance spectra were identical in detail with those of natural α-agarofuran.[1] Also the optical rotations of synthetic and natural material compared favorably and α-agarofuran consequently has the stereochemistry implied in structure **19**. Since the five other constituents[1,2] of agarwood oil (β-agarofuran, dihydroagarofuran, norketoagarofuran, 4-hydroxyagarofuran, and 3,4-dihydroxyagarofuran) have all been interrelated they also must contain a β-oriented oxido bridge. Finally, we note that the agarofurans now have the 7β-isopropyl configuration common to essentially all eudesmane-type sesquiterpenes.



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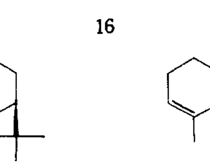

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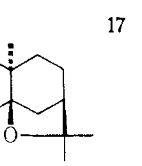

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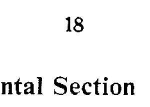

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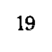

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Experimental Section

Microanalyses were performed by Dr. S. M. Nagy and associates of the Massachusetts Institute of Technology microchemical lab. Melting points were determined on a Kofler hot-stage microscope and are uncorrected. Ultraviolet spectra were recorded on a Cary Model 14 recording spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer Model 237 grating spectrometer; in general only bands characteristic of the functional groups present are listed. Optical rotations were measured in chloroform on a Zeiss photoelectric polarimeter and $[\alpha]$D was calculated from the observed α_{546} and α_{578} by means of the first approximation of Drude's formula for normal rotational dispersion. Nuclear magnetic resonance spectra were obtained on a Varian Associates A-60 instrument and are given in ppm from an internal tetramethylsilane standard. The abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively. Thin layer chromatograms (tlc) were made with Merck silica gel PF_{254} and developed with 50% ether in benzene. Merck silica gel 0.05–0.20 mm was used for preparing all column chromatograms. Anhydrous magnesium sulfate was used as the drying agent in working up reactions.

(−)-Epi-α-cyperone (7) was prepared according to the method of Howe and McQuillin;[3] bp 94° (0.05 mm); n^{25}D 1.5327; $[\alpha]^{25}$D −172° (*c* 7.1).

Lithium Aluminum Hydride Reduction of (−)-Epi-α-cyperone. A solution of 78.5 g (0.36 mole) of (−)-epi-α-cyperone in 2 l. of absolute diethyl ether was cooled to 0°, and then solid lithium aluminum hydride (13.7 g, 0.36 mole) was added gradually at such a rate as to maintain a gentle reflux. After stirring at room temperature for 7 hr, the mixture was again cooled in ice and excess hydride destroyed by the cautious addition of water (27.4 cc) and 10% sodium hydroxide solution (22.0 cc). To ensure complete hydrolysis the mixture was stirred for 12 additional hours, and then the salts were filtered and washed with ether. Evaporation of the solvent gave 79.0 g of a clear viscous oil which crystallized on addition of hexane to give 64.0 g (81%) of the alcohol **8** as needles, mp 66–68°. An analytical sample recrystallized from hexane had mp 67–68°; infrared spectrum (KBr): 3300, 1650, 1030, and 898 cm^{-1}; $[\alpha]^{25}$D −84.2° (*c* 6.1); nmr absorptions ($CDCl_3$) 1.08 (s, 3 H), 1.68 (s, 3 H), 1.1–2.6 (m, 12 H), 3.95 (t, *J* = 8 cps, 1 H), and 4.62 (s, 2 H).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.87; H, 10.93.

Dehydration of the Allylic Alcohol 8 with Phosphorus Oxychloride. Treatment of the allylic alcohol **8** (0.13 g, 0.59 mmole) with phosphorus oxychloride (1.43 cc) in excess dry pyridine (5.5 cc) followed by the addition of water and extraction with ether gave a yellow oil which was chromatographed on 3 g of silica gel. Elution with 30% benzene in hexane gave 80 mg (67%) of the heteroannular triene **9**; infrared absorptions (film) at 3100, 3040, 1650, 1612 (w), 895, and 805 cm^{-1}; ultraviolet maxima (ethanol) at 233, 239, and 246 mμ (ϵ 11,300, 12,500, and 11,400); nmr peaks ($CDCl_3$) at 0.94 (s, 3 H), 1.75 (broad s, 6 H), 1.15–2.50 (m, 9 H), 4.52 and 4.70 (2s, 2 H), and 5.38 (m, 2 H).

Pyrolytic Dehydration of the Allylic Alcohol 8. A finely ground mixture of **8** (6.6 g, 0.03 mole) and treated alumina (21 g; Woelm, neutral grade, activity I, mixed with 2% w/v of anhydrous pyridine), was pyrolyzed at 230° according to the procedure of Corey and Hortmann.[6] The resulting oil (5.4 g; 81%) was shown by glpc (125°; 6 ft, 15% silicone rubber column) to be a mixture of two trienes in the ratio 3:1. The major component, with an ultraviolet maximum (ethanol) at 277 mμ (ϵ 4600), was identified as the desired homoannular triene **10**; infrared maxima (film) at 3080, 3030, 1650, 1595, 900, and 720 cm^{-1}; nmr absorptions ($CDCl_3$) at 0.915 (s, 3 H), 1.68 (s, 6 H), 1.2–2.8 (m, 9 H), 4.70 (s, 2 H), 5.25–5.60 (m, 1 H), and 5.60 (s, 1 H).

The other component was identical in all respects with the heteroannular triene **9** obtained in the phosphorus oxychloride dehydration.

Photooxygenation of the Homannular Triene 10. A solution of 30.0 g of the crude trienes (22.5 g of homoannular triene; 0.112 mole) and 450 mg of eosin Y in 4 l. of a 1:1 mixture of benzene–absolute ethanol was irradiated with a 200-w photoflood lamp while a finely dispersed stream of purified oxygen was bubbled through the reaction mixture. The internal temperature could be maintained at 35° by monitoring a strong stream of air on the wall of the reaction vessel adjacent to the light source. At various times aliquots (3 cc) were withdrawn and analyzed by glpc. After 20 hr of irradiation the peak corresponding to the homoannular component had disappeared, while the corresponding peak for the heteroannular component had remained unchanged.

The bright orange solution was concentrated *in vacuo* to 1 l., filtered through a column of charcoal and Celite, and finally evaporated to give 32.5 g of a pale yellow oil. A 12.0-g portion was chromatographed on 300 g of silica gel using 25% hexane in benzene to give three separate components. The first to be eluted was a

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(11) L. Caglioti and M. Magi, *Tetrahedron*, 19, 1127 (1963).

hydrocarbon (2.6 g) which was identified as the unreacted heteroannular triene **9**. The next component was the desired *endo*-peroxide **11** (6.2 g; 62%) which crystallized from hexane in long white needles, mp 60–62°. The analytical sample had mp 62–63°; $[\alpha]^{24}\mathrm{D}$ −29.0° (*c* 5.5); infrared bands (KBr) were observed at 3080, 3050, 1650 (w), 1630, 1020, 875 (s), and 805 cm^{-1}; the nmr spectrum ($\mathrm{CDCl_3}$) showed proton resonances at 0.95 (s, 3 H), 1.78 (s, 3 H), 1.85 (d, *J* = 1.7 cps, 3 H), 1.1–2.5 (m, 9 H), 4.44 (m, *J* = 6.5, 2.5, and 2.5 cps, 1 H), 4.84 (s, 2 H), and 6.20 (d of q, *J* = 6.5 and 1.7 cps, 1 H).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.33; H, 9.29.

The final component to be eluted was the dienone **13** (2.0 g; 22%) which was obtained as a pale yellow oil; infrared maxima (film) at 3080, 1660, 1632, 1603, 870, and 750 cm^{-1}; ultraviolet maxima at 242 and 271 mμ (ϵ 12,000 and 8700); nmr absorptions at 1.25 (s, 3 H), 1.70 (s, 3 H), 1.94 (s, 3 H), 1.00–3.10 (m, 7 H), 4.60 and 4.75 (2s, 2 H), 6.20 (d, *J* = 10 cps, 1 H), and 6.75 (d, *J* = 10 cps, 1 H).

Rearrangement of 11 to the Hydroxy Ketone 14. A fine powder was prepared from the *endo*-peroxide **11** (1.0 g, 4.27 mmoles) and alumina (25.0 g; Woelm basic, activity I). The mixture was then placed in a column, saturated with diethyl ether, and stored at ambient temperature for 20 hr to ensure complete rearrangement. The now yellow alumina was placed in a porous thimble of a soxhlet extractor and continuously extracted with diethyl ether for 24 hr. Evaporation of the solvent gave 720 mg (72%) of the crystalline ketol **14**, mp 103–105°. Continued extraction for an additional 24 hr gave a further portion of ketol (115 mg, mp 102–105°), bringing the total yield to 84%. An analytical sample was recrystallized from hexane, mp 104–105°; $[\alpha]\mathrm{D}$ −71.5° (*c* 2.6); infrared absorptions (KBr) at 3410, 3085, 1650, 1620, 1405, 1020, and 878 cm^{-1}; ultraviolet maximum (ethanol) 233 mμ (ϵ 12,200); nmr absorptions ($\mathrm{CDCl_3}$) at 1.10 (s, 3 H), 1.94 (s, 3 H), 1.96 (d, *J* = 1.5 cps, 3 H), 0.90–2.6 (m, 8 H), 2.67 (s, 1 H), 2.97 (s, 1 H), 5.02 and 5.15 (2s, 2 H), and 5.75 (q, *J* = 1.5 cps, 1 H).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.39; H, 9.40.

Cyclization of 14 to the Ketofuran 15. A slurry of the hydroxy ketone **14** (800 mg, 3.42 mmoles) and alumina (25.0 g; Merck, acid washed) in 15.0 cc of dry benzene was heated at 75° for 10 hr, cooled, and then continuously washed with diethyl ether in a Soxhlet extractor for 6 hr. Evaporation of the solvent left 680 mg of a yellow oil which crystallized partially on storage. Thin layer chromatography of this oil showed (DNP spray) a major (R_f 0.46) and a minor (R_f 0.87) component, neither of which was the initial hydroxy ketone (R_f 0.41). The mixture was chromatographed on 34 g of silica gel using 8% ether in benzene as eluent. The first component to be eluted (70 mg; 9.0%) appeared to be a mixture of dehydration products as judged by its nmr spectrum. Further elution with 10% ether in benzene gave the crystalline ketofuran **15** (580 mg; 72%), mp 61–65°, which was homogeneous by tlc. The analytical sample was recrystallized from petroleum ether (bp 30–60°), mp 64.5–67°; infrared spectrum (KBr) 1675, 1625, 1408, 1145, 1090, 1070, 1005 (s), and 818 cm^{-1}; ultraviolet maximum (ethanol) at 230 mμ (ϵ 12,700); $[\alpha]^{24}\mathrm{D}$ −47.0° (*c* 0.6); nmr absorptions ($\mathrm{CDCl_3}$) at 1.04 (s, 3 H), 1.28 (s, 3 H), 1.41 (s, 3 H), 1.94 (d, *J* = 1.7 cps, 3 H), 1.1–3.1 (m, 9 H), and 5.84 (q, *J* = 1.7 cps, 1 H).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.55; H, 9.21.

Reduction of the Ketofuran 15 with Sodium Borohydride. To an ice-cold solution of sodium borohydride (82 mg, 2.14 mmoles) in 2.5 cc of absolute methanol there was added dropwise with stirring the ketofuran **15** (500 mg, 2.14 mmoles) dissolved in 2.5 cc of absolute methanol. After 3 hr at 0°, 6 cc of water was added and stirring continued for an additional 30 min. The methanol was removed *in vacuo*, and the aqueous layer was extracted with 2–6-cc portions of diethyl ether, which were washed with water, dried, and evaporated to give 510 mg of a clear viscous oil. Tlc revealed the presence of three components, none of which gave a positive test with DNP spray. The oil was placed on a column of silica gel (30 g) and eluted with 11% ether in benzene. The first component to be obtained in this manner was a crystalline solid (50 mg, 10%), mp 76–78°, identified as the axial dihydro alcohol **16**; $[\alpha]^{25}\mathrm{D}$ −50.7° (*c* 4.8); infrared maxima (Nujol) 3320, 1000, and 995 cm^{-1}; nmr peaks ($\mathrm{CDCl_3}$) at 0.92 (d, *J* = 7 cps, 3 H), 1.17 (s, 3 H), 1.22 (s, 3 H), 1.37 (s, 3 H), 1.0–2.35 (m, 13 H), and 4.05 (quintet, *J* = 3 cps, 1 H).

The second component eluted from the column was the desired allylic alcohol **17** which appeared as a mixture of the two epimers (R_f 0.17 and 0.20). The viscous oil (444 mg, 88%) had infrared bands (film) at 3400, 1650 (w), and 1000 cm^{-1}; the proton spectrum ($\mathrm{CDCl_3}$) substantiated the epimeric nature of the alcohols, 0.94 (s, 1.5 H), 1.04 (s, 1.5 H), 1.18 (broad s, 3 H), 1.33 (broad s, 3 H), 1.70 (broad s, 3 H), 1.0–2.6 (m, 10 H), 3.96 (m, 1 H), and 5.55 (m, 1 H).

Reduction of the Alcohol to Δ^2- and Δ^3-Agarofurans (18 and 19). A solution of the mixture of epimeric alcohols **17** (300 mg; 1.27 mmoles) in 4.0 cc of absolute diethyl ether was cooled to 0° and then 0.46 cc (0.76 g, 6.38 mmoles) of freshly distilled thionyl chloride was added slowly under a stream of nitrogen. After 30 min of stirring at 0°, excess thionyl chloride was destroyed by the cautious addition of 3.0 cc of water. The aqueous layer was extracted twice with ether (3-cc portions), and then the organic extracts were washed with 2 cc of water, dried, and evaporated to give 284 mg of a yellow oil. Thin layer chromatography showed no starting material and the presence of two new components at R_f's 0.65 and 0.75.

The crude allylic chlorides were dissolved in 4.0 cc of absolute ether, cooled to 0°, and immediately treated with 200 mg (5.3 mmoles) of lithium aluminum hydride. After stirring at room temperature for 10 hr, the mixture was cooled in ice and treated carefully with 0.4 cc of water and 0.322 cc of 10% sodium hydroxide solution. After an additional 2 hr, 2.0 g of anhydrous sodium sulfate was added and then the solid was filtered and washed with ether. Evaporation of the solvent gave 230 mg of an oil which was chromatographed on 10 g of silica gel with 30% benzene in hexane to give two pure components.

The first component was a crystalline solid (80 mg, 29%), mp 30–32°, which was assigned the structure **18** on the basis of the following measurements: bp 117° (1.5 mm); $[\alpha]^{24}\mathrm{D}$ +18.7° (*c* 6.7); $n^{20}\mathrm{D}$ 1.5055; infrared maxima (film) at 1650, 1150, 1082, 1070, 1020 (s), 895, and 720 (s) cm^{-1}; nmr absorptions ($\mathrm{CCl_4}$) at 0.95 (s, 3 H), 0.96 (d, *J* = 7 cps, 3 H), 1.13 (s, 3 H), 1.32 (s, 3 H), 1.10–2.40 (m, 10 H), and 5.27 (m, 2 H).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.30; H, 10.70.

The second component, **19** was a clear oil (80 mg; 29%) which was distilled *in vacuo* to give 70 mg of a clear oil homogeneous by glpc (140°; 2 ft, 20% silicone rubber column); bp 120° (2.3 mm); $n^{22}\mathrm{D}$ 1.5087; $[\alpha]^{24}\mathrm{D}$ +41.5° (*c* 3.6). The infrared and nmr spectra of this compound were totally superimposable on those of natural α-agarofuran; thus, the infrared spectrum (film) had maxima at 1653 (w), 1389, 1370, 1153, 1099, 1080, 1012, 887, and 838 cm^{-1}; the nmr spectrum ($\mathrm{CCl_4}$) showed absorptions at 0.89 (s, 3 H), 1.17 (s, 3 H), 1.30 (s, 3 H), 1.68 (d, *J* = 1.2 cps, 3 H), 1.90 (broad s, 2 H), 0.95–2.40 (m, 9 H), and 5.49 (broad s, 1 H).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.68; H, 11.17.

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