H), 1.22 (s, 3 H), 1.11 (s, 3 H), 1.01 (s, 3 H), 0.09 (s, 9 H); *m/e* calcd 278.2066, obsd 278.2073.

Anal. Calcd for $C_{17}H_{30}OSi$: C, 73.31; H, 10.86. Found: C, 73.36, H, 10.90.

Epoxidation of 12. A solution of *m*-chloroperbenzoic acid (776 mg of 85% purity, 4.5 mmol) in 10 mL of dichloromethane was added dropwise to a solution of **12** (825 mg, 2.97 mmol) in 10 mL of the same solvent cooled to 0 °C. The mixture was stirred at 0 °C for 30 min and at room temperature for 35 h. Washing with saturated sodium sulfite (2×) and sodium bicarbonate solutions (1×) as well as brine, followed by drying and solvent evaporation, left a residue which was purified by silica gel chromatography (elution with hexane–ether, 9:1). There was isolated 612 mg of **13** (74.3% based on recovered **12**) and 126 mg (15.3%) of unreacted **12**. The epoxide was utilized without further purification: ^{1}H NMR (δ, $CDCl_3$) 3.08 (m, 1 H), 2.25 (m, 2H), 1.91 (d, J = 4 Hz, 1 H), 1.67 (br m, 8 H), 1.20 (s, 3 H), 1.14 (s, 3 H), 1.00 (s, 3 H), 0.93 (s, 9 H).

Acid-Catalyzed Rearrangement of 13. A solution of **13** (531 mg, 1.8 mmol) in 25 mL of 20% sulfuric acid and 20 mL of methanol was heated at the reflux temperature for 24 h. After being cooled, the reaction mixture was diluted with water and extracted with ether. The combined ether layers were washed with water, saturated sodium bicarbonate solution, and brine before drying. Removal of solvent in vacuo left 0.43 g of a residue which was chromatographed on silica gel (hexane–ethyl acetate, 83:17). There was obtained 328 mg (74%) of a mixture of **14a** and **14b** (ratio 45:55) and 86 mg (22%) of **15**.

The **14a–14b** mixture was hydrolyzed with 50% aqueous acetic acid (30 mL) at room temperature for 12 h. Dilution with an equal part of water and ether extraction provided a solution which was washed with water, saturated sodium bicarconate solution, and brine. Drying and solvent evaporation gave 295 mg (73.8%) of **14a**.

For **14a**: IR (neat, cm^{-1}) 2966, 2880, 2720, 1730; ^{1}H NMR (δ, $CDCl_3$) 9.85 (t, J = 2 Hz, 1 H), 2.70 (m, 2 H), 2.32 (s, 1 H), 2.28 (s, 1 H), 1.70 (br m, 8 H), 1.20 (s, 3 H), 1.06 (s, 3 H), 1.00 (s, 3 H); *m/e* calcd 222.1620, obsd 222.1624.

For **14b**: 1H NMR (δ, $CDCl_3$) 4.28 (m, 1 H), 3.28 (s, 6 H), 2.25 (s, 1 H), 2.22 (s, 1 H), 1.64 (br m, 10 H), 1.13 (s, 3 H), 1.03 (s, 3 H), 0.95 (s, 3 H); *m/e* calcd 268.2038, obsd 268.2045.

Cyclization of 14a. A 61.5 mg (0.27 mmol) sample of **14a** was dissolved in 2% methanolic potassium hydroxide (10 mL) and stirred at room temperature for 2.5 days. Continual TLC analysis showed that **14a** was no longer being consumed. After the usual workup, the residue was purified by preparative TLC (silica gel, hexane–ethyl acetate (80:17) elution). There was obtained 18.5 mg (43% conversion, 61% based on recovered **14a**) of **15** and 31.2 mg of unreacted **14a**. For **15**: ^{1}H NMR (δ, $CDCl_3$) 1.43 (m, 1 H), 2.67–1.33 (series of m, 12 H), 0.95 (s, 3 H), 0.90 (s, 3 H), 0.80 (s, 3 H); IR (neat, cm^{-1}) 3480, 2960, 2875, 1740, 1040.

Oxidation of 15. The alcohol from above was treated directly with 1.3 equiv of Jones' reagent in acetone solution (5 mL). After being stirred for 3 h, the product was isolated in the usual fashion and purified by TLC on silic gel (elution with hexane–ethyl acetate, 83:17). There was isolated 16.5 g (89.1%) of **16**: IR (neat, cm^{-1}) 2960, 2880, 1750, 1710, 1460; ^{1}H NMR (δ, $CDCl_3$) 2.93 (s, 1 H), 2.37 (m, 2 H), 1.70 (br m, 8 H), 1.07 (s, 3 H), 1.01 (s, 3 H), 0.90 (s, 3 H).

Gymnomitrone and Isogymnomitrone. A solution of methyllithium in ether (0.24 mL of 1.54 M, 0.37 mmol) was added to a cold (−78 °C) solution of **16** (70 mg, 0.32 mmol) in anhydrous ether (5 mL). After 4 h of stirring at this temperature, the reaction mixture was treated with 2 mL of saturated ammonium chloride solution and extracted with ether. The combined organic layers were washed with brine, dried, and evaporated to give 72 mg of ketol **11**: IR (neat, cm^{-1}) 3460 and 1740.

This material was dissolved in pyridine (5 mL) under an argon atmosphere, and 150 mg of phosphorus oxychloride was slowly introduced by syringe at room temperature. The reaction mixture was heated at 90–100 °C for 2 h, cooled to 20 °C, and poured slowly into ice-cold 4 N hydrochloric acid. Extraction with dichloromethane, followed by drying and solvent removal, left 48.7 mg (70.2%) of a mixture of gymnomitrone and isogymnomitrone which was reduced directly.

Gymnomitrol (1) and Isogymnomitrol (17). The preceding mixture of ketones (48.7 mg) dissolved in 2 mL of anhydrous tetrahydrofuran was added under nitrogen at 0 °C to a stirred slurry of lithium aluminum hydride (9.7 mg) in 2 mL of the same solvent. After 2 h at 0 °C, the stirred reaction mixture was quenched by addition of saturated ammonium chloride solution, neutralized with 4 N hydrochloric acid, and extracted with ether. The combined organic phases were dried and evaporated, and the residue (42.2 mg) was separated into its two components by preparative TLC on silica gel impregnated with 5% silver nitrate (elution with pentane–ether, 9:1). The more rapidly eluted product (R_f = 0.37) proved to be **17** (15 mg) whose ^{1}H NMR spectrum was identical with that of the authentic sample.[1]

The slower component was **1** (15.3 mg) whose spectral properties proved in all respects identical with those of the natural product.[1]

Acknowledgment. This investigation was supported in part by research grants from the National Cancer Institute (Grant CA-12115) and Eli Lilly and Co. The authors wish to thank Professor Joseph D. Connolly (University of Glasgow) for generously providing the requisite comparison spectra.

Total Synthesis of (±)-Isocomene, a Naturally Occurring Triquinane

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Abstract: Isocomene, a sesquiterpene hydrocarbon of unusual structure, has been synthesized in an efficient and stereospecific manner. Cuprous bromide promoted conjugate addition of the Grignard reagent derived from β-bromopropionaldehyde ethylene ketal to the bicyclo[3.3.0]octenone **7**, followed by treatment with methyllithium and dehydration, afforded the unsaturated ketal **9**. Mild aqueous acetic acid hydrolysis of **9** proceeded without skeletal rearrangement to give a mixture of aldehyde **10** (62%) and tricyclic alcohol **11** (19%), which were readily separated by chromatography. The independent conversion of **10** to **11** with stannic chloride in benzene was essentially quantitative. Sequential oxidation of **11** with Jones' reagent and phenylselenyl chloride–*m*-chloroperbenzoic acid delivered dienone **13**. The final stages of the synthesis entailed the addition of lithium dimethylcuprate and Wolff–Kishner reduction. Comparison of the spectra of the resultant colorless solid with those of the natural product showed them to be identical.

When one considers the almost inexhaustible prodigality of Nature in its production of cyclic terpenes which possess bewilderingly varied structures,[1] it is not suprising that substances possessing the tricyclo[6.3.0.$0^{4,8}$]undecane ring system have been isolated from natural sources. Perhaps less expected is the relatively late timing of these discoveries. Thus, no example of this class was known prior to 1972. In contrast, the last few years have been witness to the characterization of a remarkably broad range of such unusual triquinanes[2] which now includes **1–6**.

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(2) Paquette, L. A. *Forschr. Chem. Forsch.* **1979**, *79*, 41.

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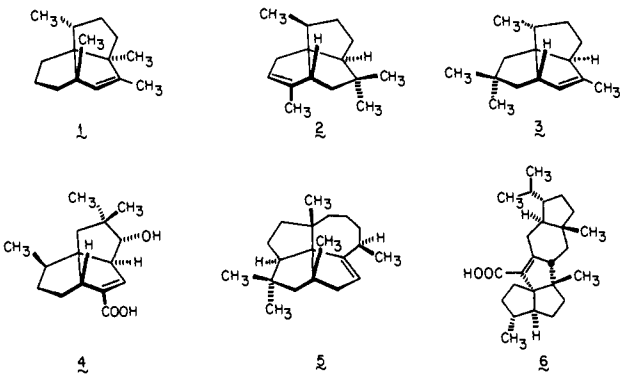
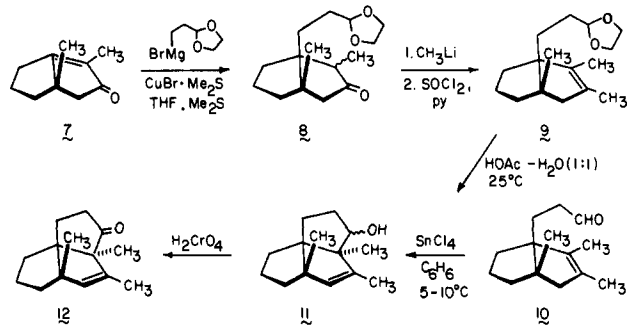


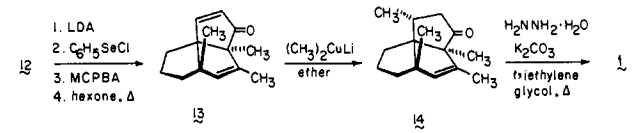
Several tricyclic lactones in which one of the five-membered rings has been expanded by insertion of an oxygen atom are also known.[3] Isocomene (**1**) was isolated in 1977 simultaneously by Zalkow from *Isocoma wrightii*, rayless goldenrod toxic to cattle and sheep (**1** is not the toxic principle),[4] and by Bohlmann from *Berkheya radula*, a plant native to South Africa.[5] The sesquiterpene hydrocarbon **2** was successfully characterized by Bohlmann and Zdero in 1979[6] and assigned the common name senoxydene to denote its occurrence in *Senecio oxyodontus*. The isomeric triquinane **3**, obtained by Ohfune and co-workers from solvolysis mixtures of protoilludyl cation precursors,[7] is herein designated as pentalenene. Its possible involvement in the biosynthesis of pentalenolactone requires additional clarification.[8] Pentalenic acid (**4**), which has been isolated from the culture broths of those strains of *Streptomyces* which produce pentalenolactone, appears to be of mevalonoid origin and may be a link in the biosynthetic pathway.[9] In 1979, Corbett et al. disclosed the fact that laurenene, the fascinating tetracyclic molecule **5**, is a principal diterpenoid constituent of the volatile oil of *Dacridium cupressinium*.[10] Finally, retigeranic acid (**6**), a pentacyclic sesterterpene produced by the lichen *Lobaria retigera*, was shown in 1972 to contain the characteristic bridged spirane arrangement of three cyclopentane rings in a segment of its carbon skeleton.[11]

This class of molecules has appealed to us as challenging synthetic targets. We were attracted initially to isocomene (**1**) because of its unusual sterically crowded tricyclopentanoid framework wherein three vicinal quaternary carbon atoms comprise the central core. Herein are reported the complete details of a total synthesis of **1** by an efficient and presumably general route involving a useful cyclopentanone annulation scheme. Since our preliminary communication on this subject,[12] two additional syntheses of **1** have been published. The ene reaction pathway deployed by Oppolzer, Bättig, and Hudlicky[13] and the intramolecular [2 + 2] photocycloaddition methodology utilized by Pirrung[14] are nicely complementary to the strategem which follows. A fourth report by Chatterjee[15] is so laden with tactical improbabilities and stereochemical impossibilities as to be considered specious.

Scheme I



Scheme II



Results and Discussion

In planning the synthesis of isocomene, we quite naturally focused attention on its four contiguous asymmetric centers. The thought was that three of them are so intricately linked to the triquinane framework as to present little difficulty. Furthermore, since the nonangular methyl group is in the more thermodynamically favored orientation, the restriction that it not be introduced by catalytic hydrogenation of an exocyclic methylene substituent was apparent.

Bicyclic enone **7** could be easily obtained from 2-methylcyclopentanone on a relatively large scale by the procedure of Yoshikoshi and co-workers.[16] Treatment of **7** with the Grignard reagent of β-bromopropionaldehyde ethylene ketal[17] in the presence of the cuprous bromide–dimethyl sulfide complex[18] resulted in smooth conjugate addition to give **8** in 68% yield (Scheme I). The stereochemical homogeneity of the substituted α-carbonyl site was inconsequential since this asymmetry was to be lost in the subsequent steps. The assumption that the all-important configuration of the β carbon is cis to the angular methyl substituent rests on the large thermodynamic advantage generally enjoyed by *cis*-bicyclo[3.3.0]octanes relative to their trans forms[19] and steric approach factors. This assignment receives confirmation by the subsequent series of reactions.

With the acquisition of **8**, the decision was made to exploit the acetal function as the initiator of the required cyclization.[20] Not unexpectedly, the reaction of **8** with methyllithium resulted in high

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levels of enolization. Repeated exposure to the organometallic reagent was necessary to attain the desired tertiary alcohol in respectable yield (see Experimental Section). Without purification of this intermediate, dehydration was achieved with thionyl chloride in pyridine at room temperature. That the elements of water had been lost to give exclusively the more highly substituted double bond isomer **9** was clearly apparent from the ^{1}H NMR spectrum.

During the intramolecular cyclization of **9**, the new five-membered ring bond must form on the exo face of the molecule for steric reasons. In this connection, direct stannic chloride promoted closure to the expected β-hydroxyethyl derivative of **11** could be readily accomplished in 72% yield. However, subsequent reactions of this substituent led to formation of complex mixtures, seemingly because of facile Wagner–Meerwein shifts. For this reason, **9** was subjected instead to mild hydrolysis in aqueous acetic acid at room temperature. It was gratifying to see that such mild conditions furnished a mixture of aldehyde **10** (62%) and the tricyclic alcohol **11** (19%). The two components were easily separated by chromatography. The independent closure of **10** to **11** with stannic chloride in benzene at 5–10 °C was particularly efficient (95%). Subsequent Jones' oxidation of **11** delivered ketone **12**, the IR, ^{1}H NMR, and ^{13}C NMR spectra of which showed that formation of the third five-membered ring in this manner had proceeded with exceptionally good regiochemical control to produce uniquely the internal double bond isomer.[21]

Introduction of the remaining methyl group was achieved by first subjecting **12** to selenation via its enolate, followed by selenoxide elimination,[22] which very cleanly produced the dienone **13** in ca. 50% overall yield (Scheme II). In total agreement with the anticipated high rigidity of the triquinane framework within **13** and the consequent approximate planarity of the cyclopentenone ring, the α and β protons associated with the unsaturated ketone moiety appeared at widely different chemical shifts (δ 5.94 and 7.31, respectively), much as in cyclopentenone itself. Condensation of **13** with lithium dimethylcuprate gave a single C_{15} ketone (**14**), which, without purification, was subjected directly to Wolff–Kishner reduction with hydrazine hydrate and potassium carbonate in triethylene glycol[23] at 200 °C. The resulting hydrocarbon was isolated by preparative vapor phase chromatography in 80% overall yield for the two steps. Its IR and ^{1}H NMR spectra were identical with those of the natural product obtained from two sources.[4,5]

In the strictest sense, the endo surface of the conjugated π bond in **13** is so much more sterically encumbered than the exo that the stereochemistry of cuprate addition can be predicted with full confidence. With delivery of a methyl group from the exterior, the present strategy ultimately provides an independent proof of the structure and the stereochemistry of isocomene.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 467 spectrophotometer. The ^{1}H NMR spectra were determined with Varian T-60 and Bruker HX-90 instruments and apparent splittings are given in all cases. Mass spectra were measured with an AEI MS9 spectrometer at an ionization energy of 70 eV. Preparative-scale VPC purifications were carried out on a Varian Aerograph Model A-90-P3 instrument equipped with thermal conductivity detectors. Microanalytical determinations were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

2,5-Dimethyl-1-[3-(ethylenedioxy)propyl]bicyclo[3.3.0]octan-3-one (8). Finely divided magnesium was generated under argon by heating anhydrous magnesium chloride (2.72 g, 28.6 mmol) with potassium metal (2.0 g, 51.2 mmol) in 40 mL of dry tetrahydrofuran at the reflux temperature for 2 h. The suspension was cooled to room temperature and treated with β-bromopropionaldehyde ethylene ketal (4.56 g, 25 mmol) during 10 min. After an additional 20 min, the reaction mixture was cooled to −78 °C and a solution of the cuprous bromide–dimethyl sulfide complex[18] (2.64 g, 12.8 mmol) in dimethyl sulfide (24 mL) was introduced over a 10-min period. This mixture was stirred at −78 °C for 1 h, at which time a solution of **7**[16] (1.07 g, 7.18 mmol) in 15 mL of anhydrous ether was added dropwise during 1.5 h. Stirring was continued at −78 °C for 12 h, whereupon the mixture was allowed to warm to −5 °C over 2.5 h. A saturated solution of ammonium chloride whose pH was adjusted to 8 with aqueous ammonium hydroxide was introduced and the product was isolated by ether extraction. Adduct **8** was separated from starting enone by silica gel chromatography on a Waters Prep 500 liquid chromatograph (petroleum ether–ethyl acetate, 82.5:17.5). There were obtained 0.99 g (68.4%) of **8** and 0.21 g (20%) of recovered **7**.

For **8**: IR (neat, cm^{-1}) 2945, 2865, 1735, 1450, 1408, 1130, 1025, 935; ^{1}H NMR ($CDCl_3$, δ) 4.82 (t, J = 4 Hz, 1 H), 3.89 (m, 4 H), 2.27 (m, 1 H), 2.13 (s, 2 H), 1.97–1.37 (m, 10 H), 1.10 and 0.98 (pair of s, total 6 H); m/e calcd for $C_{15}H_{24}O_3$ 252.1725, obsd 252.1731.

1-[3-(Ethylenedioxy)propyl]-2,3,5-trimethylbicyclo[3.3.0]oct-2-ene (9). Methyllithium (1.4 mL of a 1.5 M solution, 2.1 mmol) in ether was added dropwise to a cold (0 °C) stirred solution of **8** (351 mg, 1.39 mmol) in ether (5 mL) under nitrogen. After 15 min, methanol (85 μL) was introduced, followed by an additional 2.1 mmol of CH_3Li. This procedure was repeated a total of nine times, at which point saturated ammonium chloride solution was added. The layers were separated and the aqueous phase was extracted with ether. The combined organic layers were washed with brine, dried, and evaporated to give 442 mg of alcohol, which was directly dehydrated.

Thionyl chloride (0.93 mL) was added slowly to a cold (0 °C) solution of the above alcohol in pyridine (15 mL) under nitrogen and stirring was maintained at 0 °C for 1 h and at room temperature for 3 h. The reaction mixture was diluted with ether, washed with saturated sodium bicarbonate solution, dried, and evaporated. The crude product was purified by TLC on silica gel (elution with hexane–ether, 4:1). There were isolated 246 mg of **9** (79.2% based on recovered starting material) and 40 mg (11.4%) of **8**.

For **9**: IR (neat, cm^{-1}) 2950, 2870, 1445, 1140, 1040; ^{1}H NMR ($CDCl_3$, δ) 4.98–4.65 (m, 1 H), 4.05–3.72 (m, 4 H), 2.1 (br s, 2 H), 1.95–1.11 (m, 10 H), 1.48 (br s, 6 H), 1.02 (s, 3 H); m/e calcd 250.1933, obsd 250.1939.

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.73; H, 10.43.

Hydrolysis of 9. A solution of **9** (490 mg, 1.96 mmol) in acetic acid (35 mL) and water (35 mL) was stirred at room temperature under nitrogen for 21 h. The reaction mixture was diluted with water, saturated with sodium chloride, and extracted with ether. The combined organic layers were washed with water, saturated sodium bicarbonate solution, and brine prior to drying. Removal of solvent left a residue (372 mg) which was separated into its components by preparative layer chromatography on silica gel (hexane–ether, 9:1). There were isolated 251 mg (62.2%) of aldehyde **10** and 74.5 mg (18.5%) of alcohol **11**.

For **10**: ^{1}H NMR ($CDCl_3$, δ) 9.77 (t, J = 2 Hz, 1 H), 2.33 (m, 2 H), 2.13 (m, 2 H), 2.00–1.10 (br m, 14 H), 1.03 (s, 3 H); m/e calcd for $C_{14}H_{22}O$ 206.1671, obsd 206.1675.

Cyclization of 10. A benzene solution 0.25 M in stannic chloride (8.5 mL, 2.13 mmol) was added dropwise to a solution of **10** (229 mg, 1.11 mmol) in 30 mL of benzene at 5 °C under nitrogen. A pink coloration was observed. The reaction mixture was stirred at 5–10 °C for 2 h, during which time a pink precipitate had formed. Following the addition of saturated ammonium chloride solution, the product was extracted into ether and the combined organic layers were washed with saturated sodium bicarbonate solution, dried, and evaporated. There was obtained 219 mg (95.6%) of **11**: IR (neat, cm^{-1}) 3390, 2940, 2860, 1440, 1370, 1050; ^{1}H NMR ($CDCl_3$, δ) 5.23 (m, $W_{1/2}$ = 3 Hz, 1 H), 3.70 (t, J = 4 Hz, 1 H), 2.33–1.1 (series of m, 10 H), 1.07 (s, 6 H).

Oxidation of 11. A 218-mg sample of **11** in acetone (20 mL) was treated with a slight excess of Jones' reagent and stirred at room temperature for 2 h. The solution was decanted from the green precipitate and evaporated under reduced pressure. The residue and precipitate were triturated with ether and water. The combined organic layers were washed with water, saturated sodium bicarbonate solution, and brine prior to drying. Following solvent removal and TLC silica gel purification (hexane–ether, 9:1), there was obtained 166 mg (77%) of ketone **12**: IR (neat, cm^{-1}) 2960, 2870, 1735, 1445, 1070, 850, 835; ^{1}H NMR ($CDCl_3$, δ) 5.10 (m, 1 H), 2.6–1.0 (series of m, 10 H), 1.60 (d, J = 2 Hz, 3 H), 1.17 (s, 3 H), 1.05 (s, 3 H); ^{13}C NMR ($CDCl_3$, ppm) 220.12, 13 .24, 65.37, 59.94, 56.59, 42.24, 38.57, 36.99, 28.71, 23.97, 22.39, 15.50, 12.40; m/e calcd 204.1514, obsd 204.1518.

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.35; H, 9.94.

1,3,4-Trimethyltricyclo[6.3.0.0^{4,8}]undeca-2,6-dien-5-one (13). n-Butyllithium in hexane (0.72 mL of a 1.48 M solution, 1.066 mmol) was added to a solution of diisopropylamine (112 mg) in 10 mL of tetrahydrofuran cooled to −78 °C under argon. After 30 min at this tem-

(21) Compare: Andersen, N. H.; Ladner, D. W. *Synth. Commun.* **1978**, *8*, 449.

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perature, the stirred reaction mixture was treated dropwise with 170 mg (0.833 mmol) of **12** dissolved in 8 mL of tetrahydrofuran. After an additional hour, phenylselenyl chloride (0.20 g, 1.093 mmol) in 5 mL of tetrahydrofuran was introduced in dropwise fashion. Stirring was maintained at −78 °C for 3 h prior to warming to room temperature. Following the addition of saturated ammonium chloride solution, the product was extracted into dichloromethane and the combined organic layers were washed with water, dried, and evaporated. The product was purified by preparative layer chromatography on silica gel (hexane–ether, 95:5). There were obtained 188 mg (88.3%) of the α-phenylseleno ketone and 49 mg of unreacted **12**.

A solution of 85% *m*-chloroperbenzoic acid (121 mg, 0.7 mmol) in dichloromethane (18 mL) was added to a solution of the α-phenylseleno ketone (187.5 mg) in 10 mL of the same solvent at −78 °C under nitrogen. The reaction mixture was stirred at −78 °C for 2 h, allowed to warm to −5 °C, and treated with 0.34 mL of triethylamine. After 1.5 h, room temperature was attained and a yellow solution was observed. This solution was transferred into 30 mL of hexane and heated at the reflux temperature for 2.5 h. Dichloromethane (100 mL) was added and this solution was washed with saturated sodium bicarbonate and brine solutions. The organic phase was dried and evaporated, and the crude product was purified by TLC on silica gel. There was obtained 95 mg of **13**: IR (neat, cm^{-1}) 2960, 2870, 1700, 1590, 1448; ^1H NMR ($CDCl_3$, δ) 7.31 (d, J = 6 Hz, 1 H), 5.94 (d, J = 6 Hz, 1 h), 4.93 (m, 1 H), 1.70 (d, J = 2 Hz, 3 H), 1.63 (br m, 6 H), 1.10 (s, 3 H), 0.97 (s, 3 H); *m/e* calcd 202.1358, obsd 202.1361.

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.90; H, 8.98.

1,3,4,7-Tetramethyltricyclo[6.3.0.0^{4,8}]undec-2-en-5-one (14). Lithium dimethylcuprate was prepared by adding slightly more than 2 equiv of methyllithium to 438 mg of cuprous iodide slurried in 1 mL of anhydrous ether. Subsequent to cooling to −20 °C, a solution of **13** (90 mg) of 4 mL of anhydrous ether was added dropwise and the mixture was stirred for 1 h at −20 °C and for 2 h at 0 °C. The usual workup afforded 122 mg of crude product which was used directly for the next step. For **14**: IR (neat, cm^{-1}) 2950, 2880, 1735, 1450, 845; ^1H NMR ($CDCl_3$, δ) 5.03 (br s, $W_{1/2}$ = 3 Hz, 1 H), 2.75 (q, J = 17 Hz, 1 H), 2.27 (q, J = 17 Hz, 1 H), 1.55 (d, J= 7 Hz, 3 H), 1.40 (br m, 7 H), 1.18 (s, 3 H), 1.10 (s, 3 H), 0.87 (d, J = 7 H , 3 H); *m/e* calcd 218.1671, obsd 218.1674.

(±)-Isocomene (1). A mixture of unpurified **14** (122 mg), potassium carbonate (252 mg), hydrazine hydrate (0.23 mL), and triethylene glycol (2 mL) was heated at reflux for 1.5 h. A small distillation head was placed atop the flask in place of the condenser and the pot temperature was increased to 200 °C. After 1.5 h, the collected distillate was taken up in ether and washed with 10% hydrochloric acid. The pot residue was heated at 250 °C for 3 h, cooled, diluted with water, and extracted with ether. The combined ether phases were washed with 10% hydrochloric acid, water, and brine prior to drying and concentration. Dissolution in pentane followed by passage through a short silica gel column and VPC purification (2 ft × 0.25 in. 5% SE-30 on Chromosorb W, 100 °C) gave 70 mg (77%) of isocomene whose IR and ^1H NMR spectra were identical with those of the natural product. On standing, the colorless oil slowly crystallized: mp 59–62 °C; *m/e* calcd 204.1878, obsd 204.1882.

Acknowledgment. This research was generously financed by the National Cancer Institute (Grant CA-12115) and the Eli Lilly Co. The cooperation of Professors Bohlmann and Zalkow in making copies of the spectra of isocomene available to us is gratefully acknowledged.

Stereochemical Studies of Isoprenoid Biosynthesis. Biosynthesis of Pentalenolactone from [U-$^{13}C_6$]Glucose and [6-$^2H_2$]Glucose

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Abstract: The biosynthesis of pentalenolactone (**1**) from mevalonate has been established by feeding [U-$^{13}C_6$]glucose to cultures of *Streptomyces* UC5319. The uniformly labeled glucose serves as an in vivo precursor of [1,2-$^{13}C_2$]acetyl-CoA. The ^{13}C NMR spectrum of the derived pentalenic acid (**5**) and pentalenolactone methyl esters show a pattern of enhancements and couplings consistent with a biosynthetic pathway involving cyclization of farnesyl pyrophosphate to humulene followed by further cyclization to a tricyclic intermediate pentalenene (**7**) and subsequent oxidative cleavage and rearrangment. The results of feeding [6-^2H]glucose, a potential precursor of [2-$^2H_2$]acetyl-CoA, were less clear-cut with label derived from both D-3′ and D-5 of mevalonate appearing in the methyl esters of **1**, **5**, and **6**. A stereochemical analysis establishes that the cyclization of farnesyl pyrophosphate involves electrophilic attack on the *si* face of the 10,11 double bond and suggests that humulene formation and cyclization may take place at the same active site.

The sesquiterpene *Streptomyces* antibiotic pentalenolactone (**1**) was isolated in 1970 by an Upjohn group as part of a screening program for antimetabolites having potential antitumor activity.[2] The same substance was independently isolated by Takeuchi et al. while screening for substances inhibitory against nucleic acid synthesis in bacterial cells.[3] The acidic lipophilic antibiotic proved to be identical with PA 132, first isolated by researchers at Chas. Pfizer and shown to be active against a variety of microorganisms including gram-negative and gram-positive bacteria, pathogenic and saprophytic fungi, and protozoan species.[4] Most recently pentalenolactone was also shown to be identical with arenaemycin E and found to block glycolysis in target organisms by selective inhibition of glyceraldehyde-3-phosphate dehydrogenase.[5]

The structure and absolute configuration of pentalenolactone were firmly established by X-ray diffracton analysis of the bromohydrin derived from tetrahydropentalenolactone[2] and corre-

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