This description of the Asp–His pair requires the existence at the active site of α-chymotrypsin of an electrostatic interaction of *variable* strength between the carboxylate anion of Asp-102 and protonated His-57. That the active sites of the serine proteinases may indeed be flexible with respect to the relative positions of Asp-102 and His-57 is attested to by recently refined crystallographic data for the serine proteinase *Streptomyces griseus* protease A (SGPA). Although the extent of sequence homology between this bacterial enzyme and the pancreatic serine proteinases is small,[39] the geometries of the active-site residues Asp-102, His-57, Ser-195, and Ser-214 are almost identical in SGPA, β-trypsin, and α-chymotrypsin[39,40] (the numbering scheme used here is that of bovine chymotrypsinogen A[41]). The specific tetrapeptide aldehyde inhibitor Ac-L-Pro-L-Ala-L-Pro-L-Phe-H forms a stable covalent tetrahedral adduct with Ser-195 of SGPA, with a K_i of 2×10^{-6} M at pH 4.0.[42] X-ray crystallographic analysis of the complex crystallized at pH 4.1 shows that a major change in the position of the side chain of His-57 is associated with the binding of the inhibitor. Further, the hydrogen bond which has been proposed between $O^{\delta 1}$ of Asp-102 and $N^{\delta 1}$ of His-57 in the native enzyme is not able to be formed when His-57 occupies this altered position. Our results provide independent evidence which suggests the absence of a significant electrostatic interaction between Asp-102 and His-57 in an acyl-enzyme derived from a specific substrate (Ac–Trp–OEt) and in two relatively stable acyl-enzymes. Thus, the "charge-relay" as originally represented serves no useful catalytic purpose in any of these acyl-enzymes.

It is noteworthy that James' group has also reported that in SGPA, trypsin, α-chymotrypsin,[39,40] and α-lytic protease[43] the active-site aspartyl residue is situated in a polar environment. In earlier interpretations of crystallographic data for the serine proteinases,[9] the environment of the residue was described as hydrophobic, and it was on this basis that a pK_a' of ~7 for the aspartic acid residue in α-lytic protease was rationalized by Hunkapiller et al.[10] In the present work we find that in several acyl-enzymes the ionizing group controlling deacylation has some zwitterion character. If the zwitterion is, as we have assumed, the (Asp-anion)–(His-57 cation) pair, then Asp-102 must have a lower pK_a' than His-57 in these acyl-enzymes.

Acknowledgment. This work was supported in part by the Australian Research Grants Committee. The skilled technical assistance of Mr. Allen Tripp is gratefully acknowledged.

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A Vinylsilane Route of (±)-Gymnomitrol

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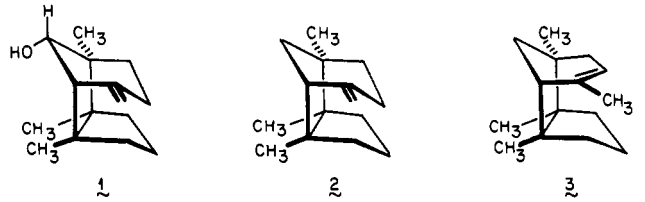
Abstract: Gymnomitrol, a sesquiterpenic alcohol of unusual structure, has been synthesized in an efficient and stereoselective manner. Selective ketalization of the bicyclo[3.3.0]octanedione (**4**), followed by Wolff–Kishner reduction and deketalization, afforded the C_s symmetric ketone **5**. Methylenation with paraformaldehyde and *N*-methylanilinium trifluoroacetate gave the exocyclic methylene derivative (**6**) which entered into copper-catalyzed 1,4 addition with the Grignard reagent from (*E*)-2-(bromovinyl)trimethylsilane and subsequent in situ methylation to deliver **12** in 66% yield. Epoxidation and dilute acid hydrolysis of this intermediate furnished hydroxy ketone **15** directly. The coproducts **14a** and **14b** could also be converted to **15** which was oxidized to diketone **16**. The final stages of the synthesis involved regioselective addition of methyllithium to **16**, dehydration of the tertiary carbinol functionality, and ultimate lithium aluminum hydride reduction.

Background

The liverwort *Gymnomitrion obtusum* (hindb) Pears has been shown by Connolly and co-workers[1] to be a rich source of sesquiterpenoids possessing the otherwise rare 4,8-methanoperhydroazulene carbocyclic framework.[2] The major metabolite, in alcohol called gymnomitrol, was assigned the interesting structure **1** on the basis of convincing spectroscopic and chemical evidence. Additional support for this formulation materialized later in the form of an *x*-ray crystal structure analysis of a derivative of two closely related hydrocarbons **2** and **3** with which it cooccurs.[3-5] The ring system of these molecules can also be regarded to be constructed of a diquinane[6] part structure which is further embellished by incorporation of one of the cyclopentane rings into a stereochemically well-defined functionalized bicyclo[3.2.1]octane network.



1 **2** **3**

(1) Connolly, J. D.; Harding, A. E.; Thorton, I. M. S. *J. Chem. Soc., Chem. Commun.* **1970**, 1320. *J. Chem Soc., Perkin Trans. 1* **1974**, 2487.
(2) α-Caryophyllene alcohol happens to be the only known derivative: (a) Adams, D. R.; Bhatnagar, S. P.; Cookson, R. C. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1502. (b) Corey, E. J.; Nozoe, S. *J. Am. Chem. Soc.* **1964**, *86*, 1652.
(3) Hydrocarbon **2** has been variously called gymnomitrene,[1] β-pompene,[4] and β-barbatene,[5] whereas **3** is known as isogymnomitrene,[1] α-pompene,[4] and α-barbatene.[5]
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(5) (a) Andersen, N. H.; Tseng, C. W.; Moore, A.; Ohta, Y. *Tetrahedron* **1978**, *34*, 47. (b) Andersen, N. H.; Costin, C. R.; Kramer, M., Jr.; Ohta, Y.; Huneck, S. *Phytochemistry*, **1973**, *12*, 1709; (c) Andersen, N. H.; Huneck, S. *Ibid.* **1973**, *12*, 1818.
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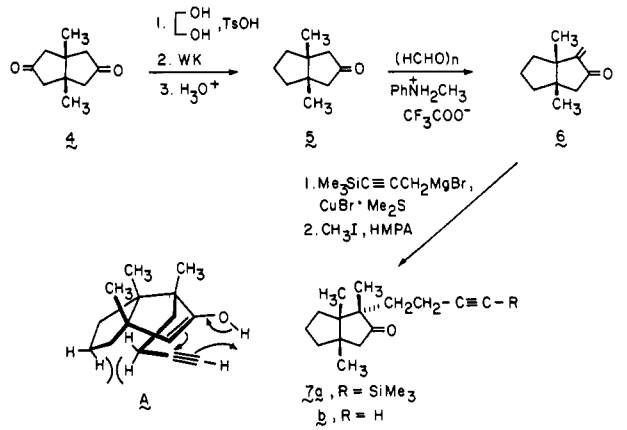
Scheme I



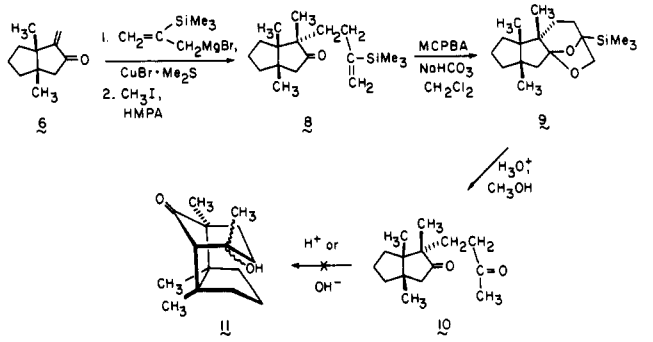
While it appears likely that **1** is elaborated in nature by cyclization of a bazzanenyl cation,[1,7] the known successful strategies for the synthesis of gymnomitrol have not followed this biogenetic rationale but have made use of alternate cyclization procedures.[8-12] Recently, we communicated[11] a convenient stereoselective synthesis of (±)-gymnomitrol. Herein, we detail our preparation of (±)-**1** which is based on vinylsilane chemistry and discuss factors which gain importance in the proper assembly of carbon atoms as demanded by this sesquiterpenic alcohol.

Synthetic Strategy

From the outset, we established gymnomitrone, the oxidized form of **1**, as the most operationally acceptable target molecule, since sodium borohydride reduction of this ketone was known to deliver **1** exclusively.[1] Further, the direct incorporation of all requisite carbon atoms was initially considered for reasons of expediency. Our first thought was that thermal activation of bicyclic ketone **7b** might allow for operation of an ene reaction,[13] provided that the rather substantial steric congestion would allow for proper alignment of the triple bond and enol segments (see A). Consequently, provision for the required endo orientation of the acetylenic sidechain in **7** became the immediate focus of attention. It is instantly recognized that the configurational features of this intermediate correspond to placement of the more highly functionalized alicyclic unit on the more hindered, concave face of the diquinane ring system. Accordingly, recourse was made to kinetic control of the geminal dialkylation sequence.

Proper elaboration of the three contiguous quaternary carbons in **7** with their all-cis methyl substitution plan was rapidly achieved beginning with the readily available diketone **4**.[14] This substrate was efficiently monoketalized and reduced to **5** by the Wolff–Kishner technique on a large scale without difficulty (Scheme I). Bicyclo[3.3.0]octane derivatives such as **4** and **5** are rather conformationally rigid rooftop-shaped molecules. For this reason, it was felt that alkylation of the enolate anion derived from **5** would occur from the convex (β) face, the presence of methyl groups at the angular positions notwithstanding. This conclusion is founded on the reasonable assumption that two freely rotating methyl groups are less sterically demanding than a fused cyclopentane ring. In the event, a problem of some seriousness now emerges since the enolate anion center in **5** (two equivalent sites) is neopentyl in character and consequently sterically disadvantaged. Attempted alkylation of this species with a 1-(trimethylsilyl)-1-butyn-4-yl halide or sulfonate ester would result inexorably in elimination.

Scheme II



To bypass such complications, we converted **5** to **6** with paraformaldehyde (not *s*-trioxane)[15,16] and *N*-methylanilinium trifluoroacetate in dioxane solution. With the availability of **6**, conjugate additions could now be performed at a relatively uncongested methylenic carbon. Since the methyl group is to be introduced last, the ideal situation develops where the smallest substituent, itself incapable of succumbing to E_2 chemistry, is to become bonded to the carbon atom of the regiospecifically generated enolate. The reaction of **6** with (1-trimethylsilyl)-propargyl)magnesium bromide[17] and the cuprous bromide–dimethyl sulfide complex,[18] followed by methyl iodide in hexamethylphosphoramide, afforded the stereochemically homogeneous **7a** in 40% yield after chromatography. The stereochemical assignment to **7a** was originally inferred from the close similarity of its methyl chemical shifts (δ 1.11, 1.03, and 0.95 in $CDCl_3$, $\Delta\delta = 0.16$). In our experience,[19] the ^1H NMR spectra (in $CDCl_3$ solution) of *exo*-2,*cis*-1,5-trimethylbicyclo[3.3.0]octan-3-ones are characterized by a more narrow triad of methyl singlets ($\Delta\delta \approx 0.2$) than their endo-2,cis-1,5 isomers ($\Delta\delta \approx 0.4$). While exposure of **7a** to potassium fluoride in aqueous dimethylformamide delivered the desired acetylenic ketone, conditions were not found to cause **7b** to enter into ene reaction. Evidently, numerous nonbonded steric interactions seriously impede this reaction.

We were next led to consider diketone **10** as a reasonable alternative precursor. The carbonyl groups within **10** are seen to be properly predisposed for conversion to **11** under aldol conditions (Scheme II). Somewhat lessened electronic requirements relative to the thermal ene cyclization were expected. To gain access to the diketone, **6** was treated with (2-(trimethylsilyl)-2-propenyl)magnesium bromide and methyl iodide as previously described. Catalysis of the conjugate addition by the cuprous bromide–dimethyl sulfide complex proved more effective than that provided by cuprous iodide–tri-*n*-butylphosphine.[20] The yield of **8** was 37%. Because of efficient carbonyl participation,[21] the peracid oxidation of **8** under buffered ($NaHCO_3$) conditions led directly to an epimeric mixture of cyclic ketals **9** (99%). When subjected to hydrolysis with dilute sulfuric acid in methanol, this product provided the target diketone **10** ($\Delta\delta_{CH_3} = 0.21$) in 97.5% yield.

Julia,[22] as well as Marshall and Schaefer,[23] have previously examined the intramolecular aldol condensation of diketones of

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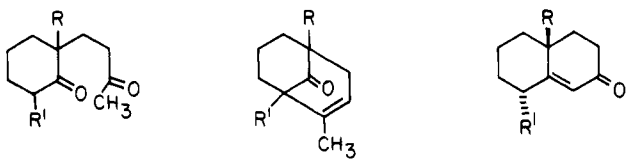
general formula B and have noted that bicyclo[3.3.1]nonane (C)



B C D

formation is significantly favored over the conversion to octalones D. In our hands, numerous attempts to effect the cyclization of **10** under a wide variety of acidic and alkaline conditions proved unsuccessful. Because independently synthesized **11** (see below) did not prove exceptionally prone to ring opening, the difficulties associated with the intended **10** → **11** conversion appear to be of kinetic origin.

Because **10** proved to be a rather inert substance, we turned to ketoaldehyde **14a**, a molecule which benefits from a reduction in steric congestion at the projected electrophilic carbonyl site. Treatment of **6** with the Grignard reagent from ((*E*)-2-bromovinyl)trimethylsilane[24] under conditions of the copper-catalyzed 1,4-addition–methylation procedure described above gave **12** as a colorless oil in 66% yield ($\Delta\delta_{CH_3}$ = 0.21) (Scheme III). Due to the shortened length of the vinylsilane side chain in **12**, epoxidation delivered silyl epoxide **13** without involvement of the neighboring ketone carbonyl. Direct hydrolysis in 20% sufuric acid–methanol (1:1) at the reflux temperature and preparative layer silica gel chromatography of the mixture gave two fractions consisting of **14a**/**14b** (45:55, 74%) and **15** (22%). Hydrolysis of the first fraction in aqueous acetic acid led to isolation of pure **14a** (74%, $\Delta\delta_{CH_3}$ = 0.20).

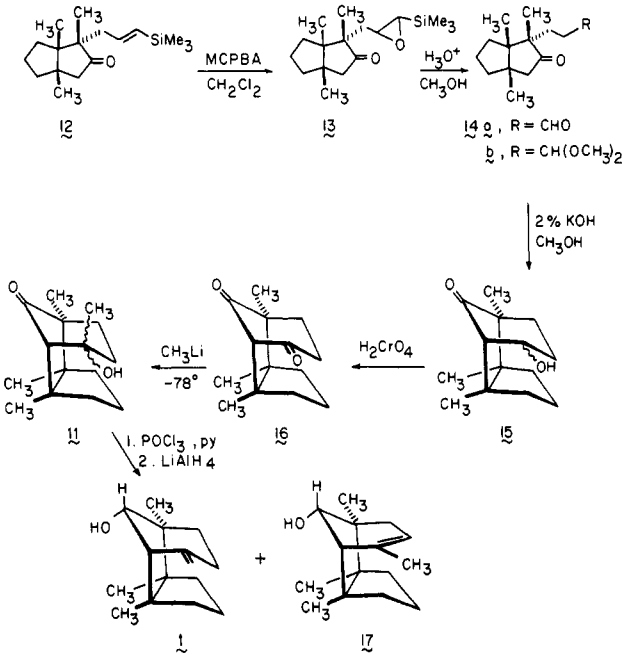
It was now necessary to achieve the base-induced cyclization of the keto aldehyde. Fortunately, this proved possible with 2% potassium hydroxide in methanol *at room temperature*. Thin-layer chromatographic assay of the progress of reaction suggested that equilibrium between **14a** and **15** had been reached after 2.5 days. Chromatographic separation of the two compounds showed that the extent of conversion to **15** was 43%; the yield of tricyclic ketol was 61%, based upon recovered **14a**.

With **15** in hand, introduction of the final carbon atom could be readily accomplished by sequential oxidation with Jones' reagent (89%) and regioselective reaction with methyllithium (1 equiv) at −78 °C (70%). The IR and ^{1}H NMR spectra of diketone **16** were in excellent agreement with those reported for the optically active ozonolysis product of gymnomitrone.[1] In addition, **11** proved to be stereochemically homogeneous.

The dehydration of **11** was achieved by treatment with phosphorus oxychloride in pyridine and gave a 1:1 mixture of gymnomitrone and its double-bond isomer in 70% yield. without purification, these ketones were reduced with lithium aluminum hydride in tetrahydrofuran. Preparative layer chromatography on silver nitrate impregnated silica gel led to the isolation of (±)-gymnomitrol (**1**) and (±)-isogymnomitrol (**2**). The spectral (IR, ^{1}H NMR) features of our sample were superimposable upon those of the authentic natural product[1].

During the course of this total synthesis, Gras' methylenation procedure was deployed for the purpose of stereocontrolled creation of a quaternary carbon atom which itself is flanking two fully substituted carbons. Furthermore, vinylsilane sidechains were efficiently affixed via cuprate chemistry as latent ketone and aldehyde precursors whose unmasking was achieved in the presence of other carbonyl groups without the need for blocking procedures.[25] Finally, in view of the demonstrated feasibility of the **14a** → **15** intramolecular cyclization under sterically demanding circumstances, aldol condensations between a ketone and an aldehyde may well have greater general value in synthesis than heretofore appreciated.

Scheme III



12 13 14a, R = CHO; b, R = CH(OCH3)2 11 16 15 1 17

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 467 spectrometer. The ^{1}H NMR spectra were determined with Varian T-60 or EM-360 instrument, and apparent splittings are given in all cases. Mass spectra were measured on an AEI-MS9 spectrometer at an ionizing energy of 70 eV. Microanalytical determinations were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

***cis*-1,5-Dimethylbicyclo[3.3.0]octane-3,7-dione Monoethylene Ketal.** A mixture of **4** (8.3 g, 0.05 mmol),[14] ethylene glylcol (7.2 g, 0.116 mol), benzene (40 mL), and a catalytic quantity of *p*-toluenesulfonic acid was heated at the reflux temperature under a Dean–Stark trap for 2 days. The cooled reaction mixture was washed with 10% sodium hydroxide solution (20 mL) and distilled water (5 × 20 mL) prior to drying. Solvent evaporation and vacuum distillation of the residue gave 11.5 g (90.5%) of the bis(ketal) as a colorless oil: bp 92–94 °C (0.15 torr); ^{1}H NMR (δ, $CDCl_3$) 3.80 (s, 8 H), 2.20 (d, J = 12 Hz, 4 H), 1.77 (d, J = 12 Hz, 4 H), 1.03 (s, 6 H); *m/e* calcd 254.1513, obsd 254.1525.

A mixture of **4** (6.64 g, 0.04 mol) and the bis(ketal) (10.16 g, 0.04 mol) in 100 mL of benzene containing a catalytic quantity of *p*-toluenesulfonic acid was heated at the reflux temperature for 5 h, cooled, and treated with 6 drops of pyridine. The solution was washed with saturated sodium bicarbonate solution and brine before drying and solvent removal. VPC analysis (2 ft × 0.25 in. 10% SE-30, 150 °C) of the residue showed the diketone:monoketal:bis(ketal) ratio to be approximately 1:2:1. Chromatography on alumina (elution with hexane–ether mixtures) gave 7.15 g of monoketal. The fractions containing the other two components were combined and recycled twice to provide a total of 13.6 g (80.95%) of colorless crystalline product: ^{1}H NMR (δ, $CDCl_3$) 3.83 (s, 4 H), 2.40 (s, 2 H), 2.26 (s, 2 H), 2.06 (s, 4 H), 1.13 (s, 6 H); *m/e* calcd 210.1256, obsd 210.1254.

***cis*-1,5-Dimethylbicyclo[3.3.0]octan-3-one (5).** A solution of the monoketal (7.43 g, 0.035 mol), potassium hydroxide (6.5 g), and hydrazine hydrate (4.7 mL) in 50 mL of triethylene glycol was heated at the reflux temperature for 1 h. Water and excess hydrazine were then removed by distillation until the temperature of the reaction mixture reached ~240 °C. Heating was continued overnight. The cooled contents were diluted with water and extracted with ether (3×). The combined organic layers were washed with brine, dried, and evaporated to leave the unpurified ketal: ^{1}H NMR (δ, $CDCl_3$) 3.83 (s, 4 H), 1.83 (s, 4 H), 1.60 (m, 6 H), 1.03 (s, 6 H). This material was heated with 250 mL of 2 N sulfuric acid for 6 h, cooled, and extracted with ether. The combined organic phases were washed with saturated sodium bicarbonate solution and brine, dried, and evaporated to leave 4.41 g (82%) of **5**, sublimation of which at 60 °C (0.3 torr) provided colorless crystals: mp 159–160 °C (lit.[8] mp 159–160 °C); IR (KBr, cm^{-1}) 1740; ^{1}H NMR (δ, $CDCl_3$) 2.13 (AB_q, 4 H), 1.70 (m, 6 H), 1.03 (s, 6 H); *m/e* calcd 152.1201, obsd 152.1205.

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2-Methylene-*cis*-1,5-dimethylbicyclo[3.3.0]octan-3-one (6). To a refluxing solution of **5** (625 mg, 4.0 mmol) in dry dioxane (20 Ml) was added portinwise a mixture of paraformaldehyde (450 mg, 5.0 mmol) and *N*-methylamilinium trifluoroacetate (2.55 g, 11.5 mmol) over a 3-day period. The progress of reaction was monitored by VPC analysis. The cooled reaction mixture was diluted with water and extracted with ether. The combined organic layers were washed with water and sodium bicarbonate solution prior to drying and evaporation. Chromatography on silica gel (elution with pentane–ether, 4:1) gave 50% of **6**, 5% of dimethylene ketone, and 45% of unreacted **5**. The desired product (90% based on recovered **5**) was generally utilized soon after isolation: ^{1}H NMR (δ, $CDCl_3$) 6.00 (s, 1 H), 5.20 (s, 1 H), 2.30 (d, J = 2 Hz, 2 H), 1.70 (m, 6 H), 1.12, (s, 3 H), 1.03 (s, 3 H).

***cis*,*cis*-1,2,5-Trimethyl-2-(4-(trimethylsilyl)-3-butynyl)bicyclo[3.3.0]-octan-3-one (7a).** One equivalent of bromine was added to a solution of triphenylphosphine (13.1 g, 0.05 mol) in 50 mL of dry dichloromethane at 0 °C. 1-(Trimethylsilyl)propargyl alcohol (5.08 g, 0.04 mol)[26] was introduced in one portion at 0 °C, and the reaction mixture was stirred at room temperature for 2 days. The solvent was removed under reduced pressure, and the residue was passed through a short silica gel column (ether elution). Distillation afforded 5.72 g (75.2%) of the bromide: bp 85 °C (43 torr); ^{1}H NMR (δ, $CDCl_3$) 3.84 (s, 2 H), 0.16 (s, 9 H).

The magnesium powder was generated under nitrogen from anhydrous magnesium dichloride (0.88 g, 9.3 mmol) and potassium metal (0.65 g, 16.7 mg-at) in tetrahydrofuran (20 mL) as described more fully below. To the resulting suspension at room temperature was added 1.61 g (8.4 mmol) of 1-(trimethylsilyl)-3-bromo-1-propyne dissolved in ether (10 mL) during 1 h. After 20 min of stirring, the bromide was determined to be entirely consumed by VPC analysis. The reaction mixture was cooled to −78 °C, and a solution of the cuprous bromide–dimethyl sulfide complex (924 mg) in 7 mL of dimethyl sulfide was added dropwise during 20 min. The mixture was stirred for an additional hour at −78 °C before a solution of **6** (270 mg, 1.65 mmol) in 6 mL of anhydrous tetrahydrofuran was introduced over a 1-h period. After being stirred for 5 h at −78 °C, the reaction mixture was allowed to warm to 0 °C during 2 h, stirring at 0 °C for 15 min, and transferred via canula into a solution of methyl iodide (9 mL) in hexamethylphosphoramide at room temperature. The mixture was stirred overnight, worked up as described below, and finally chromatographed on silica gel (elution with pentane–ether, 9:1). Further purification of **7a** was achieved by VPC (2 ft × 0.25 in. 5% SE-130 °C). There was obtained 80 mg (16.7%) of **7a**: IR (neat, cm^{-1}) 2960, 2870, 2180, 1735, 1250, 840; ^{1}H NMR (δ, $CDCl_3$) 2.39 (m, 2 H), 2.18 (d, J = 1 Hz, 2 H), 1.60 (m, 8 H), 1.10 (s, 3 H), 0.99 (s, 3 H), 0.91 (s, 3 H), 0.08 (s, 9 H); m/e calcd 290.2065, obsd 290.2071.

***cis*,*cis*-1,2,5-Trimethyl-2-(3-butynyl)bicyclo[3.3.0]octan-3-one (7b).** Potassium fluoride dihydrate (188 mg, 2.0 mmol) was added in one portion to a solution of **7b** (56.8 mg, 0.196 mmol) and water (282 mg, 15.7 mmol) in 1.5 mL of dimethylformamide at room temperature. The reaction mixture was stirred for 1 day, diluted with water (5 mL), and extracted with ether–pentane (1:2, 7 × 10 mL). The combined organic phases were washed with water and brine, dried, and evaporated. There was obtained 418 mg (97.9%) of **7b** which was purified for analysis by preparative VPC (2 ft × 0.25 in. 5% SE-30, 115 °C) and obtained as a white solid: mp 70–71 °C; ^{1}H NMR (δ, $CDCl_3$) 2.37–2.20 (m, 5 H), 1.87 (m, 2 H), 1.63 (m, 6 H), 1.12 (s, 3 H), 1.01 (s, 3 H), 0.92 (s, 3 H); m/e calcd 218.1671, obsd 218.1674.

Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.44; H, 10.23.

***cis*,*cis*-1,2,5-Trimethyl-2-(3-(trimethylsilyl)-3-butenyl)bicyclo[3.3.0]-octan-3-one (8). (A) CuBr·Me_2S Catalysis.** Following the procedure described above, 3.9 g (0.03 mmol) of 2-(trimethylsilyl)-2-propen-1-ol[27] was treated with 11.8 g (0.053 mol) of triphenylphosphine and 1 equiv of bromine in 50 mL of dichloromethane. The usual workup afforded 4.98 g (86%) of the bromide as a colorless oil: IR (neat, cm^{-1}) 3060, 1600, 1250, 930, 835; ^{1}H NMR (δ, $CDCl_3$) 5.87 (m, 1 H), 5.43 (m, 1 H), 4.8 (m, 2 H), 0.13 (s, 9 H).

Into a three-necked flask equipped with reflux condenser, addition funnel, septum, and magnetic stirrer was placed 1.47 g (15.6 mmol) of anhydrous magnesium dichloride and 1.08 g (27.7 mg-at) of freshly cut potassium in 20 mL of anhydrous tetrahydrofuran, and the mixture was heated to reflux under nitrogen for 2 h.,2,8 To the cooled dark gray suspension was added dropwise a solution of 2-(trimethylsilyl)-3-bromopropene (2.51 g, 13.1 mmol) in 15 mL of anhydrous ether over 1 h. After 20 min, VPC analysis (5% SE-30, 90 °C) indicated that the bromide was completely consumed. The mixture was cooled to −78 °C, and a solution of cuprous bromide–dimethyl sulfide complex[18] (1.43 g, 7.1 mmol) in 10 mL of anhydrous dimethyl sulfide was added during 20 min. After 1 h at −78 °C, a solution of **6** (0.40 g, 2.4 mmol) in 6 mL of tetrahydrofuran was added during 1 h to the rapidly stirred reaction mixture. Upon completion of the addition, stirring was maintained for 5 h at −78 °C and for 2 h at 0 °C. At this point, the contents were transferred under nitrogen to a solution containing 9 mL or methyl iodide and 4 mL of hexamethylphosphoramide. This mixture was stirred overnight at room temperature, treated with saturated ammonium chloride solution, and extracted three time with ether. The combined ether phases were diluted with an equal volume of pentane and washed three times with water and once with brine prior to drying. Solvent evaporation and silica gel chromatography of the residue (elution with ether–pentane, 1:9) gave 260 mg (37.1%) of **8** as a colorless oil; ^{1}H NMR (δ, $CDCl_3$) 5.45 (m, 1 H), 5.22 (m, 1 H), 2.20 (s, 2 H), 2.12 (m, 2 H), 1.62 (br m, 8 H), 1.11 (s, 3 H), 1.03 (s, 3 H), 0.95 (s, 3 H), 0.09 (s, 9 H); m/e calcd 292.2222, obsd 292.2229.

Anal. Calcd for $C_{18}H_{32}OSi$: C, 73.90; H, 11.02. Found: C, 73.73; H, 11.07.

(B) CuI·Bu_3P Catalysis. Into a three-necked flask fitted with a mechanical stirrer was introduced under nitrogen an ethereal solution (11 mL) containing 5.3 mmol of the Grignard reagent from 2-(trimethylsilyl)-3-bromopropene which was cooled to −78 °C. A solution of the cuprous iodide–tri-*n*-butylphosphine complex[20] (2.0 g) in anhydrous ether (6 mL) was next added, followed 30 min later by a solution of **6** in 3 mL of ether. The reaction mixture was stirred at −78 °C for 1 h and at 0 °C for 1.5 h. Methyl iodide (4.73 g) in 5 mL of hexamethyl phosphoramide was added in one portion, and the reaction mixture was stirred overnight at room temperature. Workup as described in the preceeding section gave 56 mg (18.2%) of **8**.

Epoxidation of 8. To a cold (0 °C) solution of **8** (98 mg, 0.34 mmol) in dry dichloromethane (5 ml) was added 74.3 mg of *m*-chloroperbenzoic acid (80% purity) and 66.6 mg of dried sodium bicarbonate. The mixture was stirred at 0 °C for 2 h and at room temperature for 20 h. VPC analysis (5% SE-30, 130 °C) of progress of the reaction showed **8** to be totally consumed at this point. The reaction mixture was washed twice with saturated sodium bicarbonate solution and once with brine. Drying and solvent removal left 1.02 g (99%) of pure **9**. In the absence of buffer, the yield of **9** was only 77.4%: IR (neat, cm^{-1}) 2940, 2860, 1380, 1365, 1300, 1030, 830; ^{1}H NMR (δ, $CDCl_3$) 3.56 (br s, 2 H), 2.59–1.12 (series of m, 12 H), 0.97, 0.91, 0.80, 0.76 (all s, total 9 H), 0.02 and −0.01 (both s, total 9 H); m/e calcd 308.2171, obsd 308.2179.

Anal. Calcd for $C_{18}H_{32}O_2Si$: C, 70.07; H, 10.45. Found: C, 69.68; H, 10.30.

***cis*,*cis*-1,2,5-Trimethyl-2-(3-oxobutyl)bicyclo[3.3.0]octan-3-one (10).** Ketal **9** (109 mg) was heated at reflux with 5 mL of 20% sulfuric acid and 5 mL of methanol under nitrogen overnight. The cooled reaction mixture was diluted with water and extracted with ether (3×). The combined organic phases were wahed with water, saturated sodium bicarbonate solution, and brine prior to drying and solvent evaporation. The residue was purified by preparative layer chromatography on silica gel to give 78 mg (97.5%) of **10**: IR (neat, cm^{-1}) 2950, 2920, 2865, 1730, 1720; ^{1}H NMR (δ, $CDCl_3$) 2.52 (m, 2 H), 2.22 (m, 2 H), 2.08 (s, 3 H), 1.62 (m, 8 H), 1.13 (s, 3 H), 0.98 (s, 3 H), 0.92 (s, 3 H); m/e calcd 236.1776, obsd 236.1782.

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: c, 76.18; H, 10.22.

***cis*,*cis*-1,2,5-Trimethyl-2(3-(trimethylsilyl)-2-propenyl)bicyclo-[3.3.0]octan-3-one (12).** ((*E*)-2-bromovinyl)trimethylsilane (5.15 g, 28.8 mmol)[24] dissolved in anhydrous tetrahydrofuran (20 mL) was added to a rapidly stirred slurry of magnesium turnings (770 mg, 31.7 mg-at) and tetrahydrofuran (7 mL) at a rate which maintained gentle reflux. Upon completion of the addition, the mixture was heated at reflux for 20 min, cooled to −78 °C, and treated dropwise during 5 min with a solution of cuprous bromide–dimethyl aulfide complex (1.87 g) in 14 mL of dimethyl sulfide. A solution of **6** (859 mg, 5.24 mmol) in anhydrous tetrahydrofuran (20 mL) was next introduced slowly over a 2-h period. The reaction mixture was stirred at −78 °C for 18 h, allowed to warm to 0 °C during 4 h, and transferred via canula into a solution of methyl iodide (20 mL) in hexamethylphosphoramide (15 mL) at room temperature. Following an additional 24 h of stirring, saturated ammonium chloride solution was added and the product was extracted into ether. The combined organic layers were diluted with an equal volume of pentane, washed with water (3×) and brine, dried, and evaporated. Chromatography of the residue on silica gel (elution with hexane–ether, 93:7) gave 956 mg (65.7%) of **12** as a colorless solid: mp 34.5–35.5 °C; IR (neat, cm^{-1}) 2960, 2880, 1740, 1620, 1250, 995, 860, 836; ^{1}H NMR (δ, $CDCl_3$) 6.25 (m, 1 H), 5.68 (d, J = 19 Hz, 1 H), 2.33 (m, 4 H), 1.73 (br s, 6

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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]

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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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