(22) Reaction of keto aldehyde **11** with 0.25% sodium carbonate in 4:3 water–methanol for 3 days at room temperature, the best of many conditions tried, produced a 2–3:1 equilibrium mixture of **11** (40–55%) and the bridged ketol (18–20%). Also isolated in one run was ~15% trimethyl ketone from a retro-Michael reaction of **11**. In contrast, the epimeric keto aldehyde from hydrolysis of **5b** cyclized very readily.
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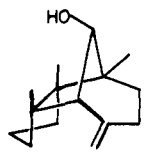
Synthesis of Gymnomitrol

Sir:

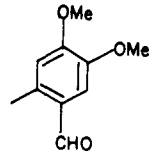
Gymnomitrol, one of the latest finds in Nature's seemingly inexhaustible reservoir of sesquiterpenes, was isolated from *Gymnomitrion obtusum* (Lindb.) Pears. Chemical studies[1] revealed the novel structure **1**, and both barbatene[2] and pom-



1

pene,[3] constituents of related liverwort species, were shown to be identical with gymnomitrene. To probe the generality of a new method for the preparation of bicyclo[3.2.1]octanes by acid-catalyzed addition of *p*-quinone ketals to olefins,[4] we pursued a synthesis of gymnomitrol (**1**), and the results are described in this communication.[5]

Aldehyde **2**[6] was transformed to phenol **3**, mp 87–88 °C (85%), by treatment with *m*-chloroperbenzoic acid in methylene chloride, followed by hydrolysis with potassium hydroxide. Oxidation of **3** with DDQ[7] in methanol at 0 °C afforded the *p*-quinone ketal **4** (63%): mp 103–104 °C; UV max



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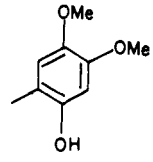

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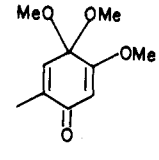

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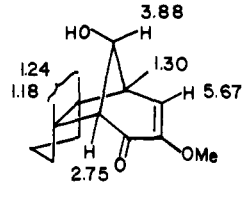

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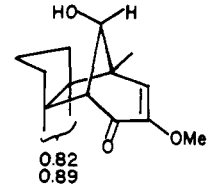

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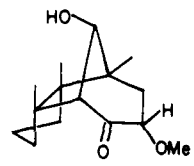
(95% C_2H_5OH) 234 nm (ε 12 400), 293 (3500). Condensation of the ketal **4** with 1,2-dimethylcyclopentene[8] in the presence of 1 equiv of stannic chloride in CH_3NO_2–CH_2Cl_2 (−20 °C, 10 min) gave a mixture of two diastereomeric adducts that was immediately reduced with sodium borohydride in CH_3OH (−20 °C, 10 min). The major alcohol **5** (10% overall yield; mp 175.5–177.5 °C; UV max (95% C_2H_5OH) 267 nm (ε 6700); IR ($CHCl_3$) 3670, 3450, 1680, 1620 cm^{-1}) was separated from its diastereomer **6** by crystallization from ether. The NMR data (270 MHz) indicated in formulae **5** and **6** were used to assign configurations. In addition to these cycloadducts the reaction mixture contained 30–45% phenol **3** and an undetermined amount of the quinone derived from ketal **4**. Catalytic hydrogenation of **5** and **6** over 10% Pd/C in ethanol produced the stereochemically homogeneous dihydro derivatives **7** and **8**, respectively (77%). These were found to be easily separable by flash chromatography.[9] In preparative runs we took advantage of this finding by hydrogenating the mixture of **5** and **6** prior to separation. Isomers **7** and **8** (both unstable oils) were



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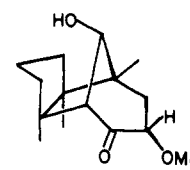

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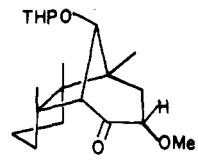

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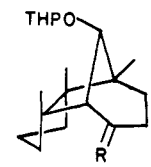

10 R = O

11 R = CH_2

thus obtained in a ratio of 3.3:1. The remaining steps in the synthesis could only be accomplished after the hydroxy group in **7** had been protected. The tetrahydropyranyl ether **9** (dihydropyran, CH_2Cl_2, catalytic amount of camphorsulfonic acid, 20 °C, 1 h) was reduced with calcium (liquid ammonia, THF, 10 min),[10] and the resulting product (78% for two steps) was condensed with methyltriphenylphosphonium bromide (2:1 THF–Me_2SO, *n*-BuLi, 80 °C, 3.5 h) to afford olefin **11**. Deprotection (3:2:2 AcOH–H_2O–THF, 60 °C, 7 h) gave racemic gymnomitrol (**1**) (76% for two steps), mp 105–108 °C, which had IR and NMR spectra identical with those of the natural product.[11]

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A Stereoselective Total Synthesis of (±)-Gymnomitrol

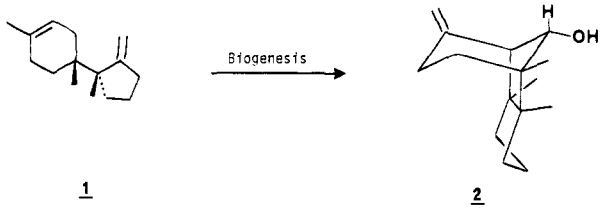
Sir:

The tricyclic sesquiterpenoid gymnomitrol (**2**) was isolated as a major metabolite from liverwort *Gymnomitrion obtusum* (Lindb.) Pears.[1] The corresponding hydrocarbon, gymnomitrene (previously known as β-barbatene[2] or β-pompene[3]), also occurs with **2**. The structure and stereochemistry of **2** were determined by degradation and spectroscopy in conjunction with biogenetic considerations.[1] The unique carbon framework of this cyclotrichothecane is thought to arise, biogenetically, from bazzanene (**1**, Scheme I).[1,4] We report in this communication an efficient and stereoselective total synthesis of (±)-gymnomitrol (**2**).[5,26]

The starting material chosen for the synthesis of **2** is 2-methylcyclopentanone (**3**). Normally, cyclopentanones are difficult to alkylate because of the relative ease of enolization, aldol condensation, and polyalkylation.[6] A number of methods for the regioselective synthesis of unsymmetrical ketones such as **3** have been developed.[7-9] In practice, however, we found that generation of the enolate anion of **3** with 0.95 equiv of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C, equilibration to the thermodynamically more stable enolate anion[10] at room temperature for 4–5 h, and then quenching with 2,3-dibromopropene at 0 °C afford after chromatography on silica gel ketone **4** in 79% yield (Scheme II). Hydrolysis of vinyl bromide **4** with 90% sulfuric acid at 0 °C proceeds smoothly in 91% yield on small scale (200 mg) to give diketone **5**; however, the yields decrease dramatically in larger scale runs. To circumvent this troublesome step an alternative method was selected. Vinyl bromide **4** is conveniently hydrolyzed to diketone **5** in 91% yield using mercury(II) acetate in 88% formic acid at room temperature.[11] Cyclization of diketone **5** to bicyclic enone **6**[12] is accomplished in 84% yield with potassium hydroxide in ethanol at reflux.

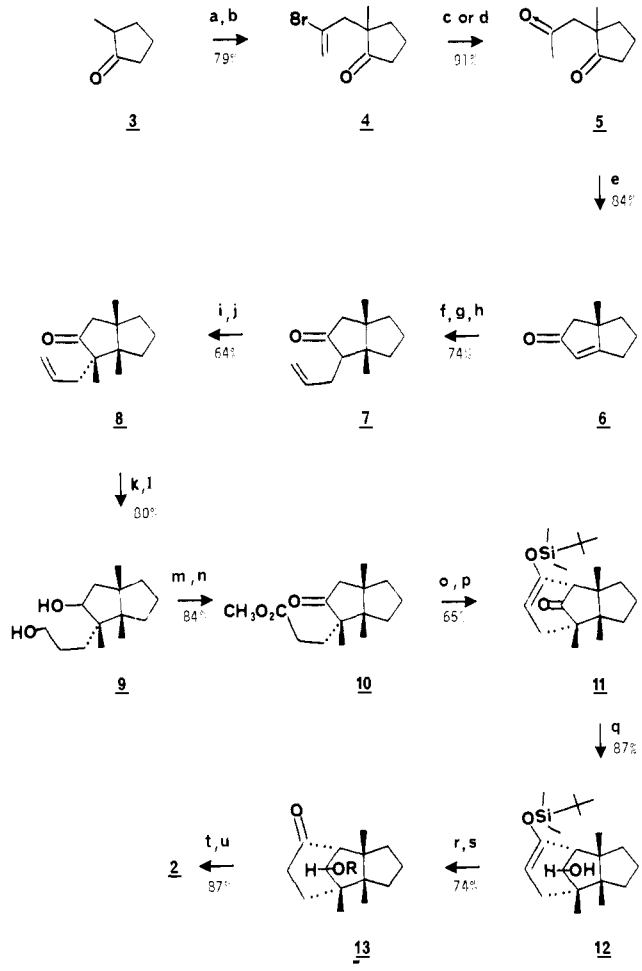
Addition of enone **6** to a solution of lithium dimethylcopper in THF at −78 °C, followed by quenching with allyl chloride in hexamethylphosphoric triamide (HMPT) at room temperature and an aqueous hydrochloric acid workup, affords bicyclic ketone **7** in 74% yield as a 60:40 ratio of diastereomers.[13] Alkylation of ketone **6** using sodium hydride in 1,2-dimethoxyethane (DME), followed by addition of methyl iodide, produces ketone **8** in 64% yield as a single diastereomer.[14,15] This alkylation takes place with the alkylating agent, methyl iodide, approaching the less hindered convex side of the thermodynamically more stable enolate anion. The stereochemical assignment of this methylation product **8** is confirmed by analysis of the europium-induced NMR shifts[16] for the three quarternary methyl groups in the two isomeric alcohols formed by reduction of ketone **8** with sodium borohydride in 100% ethanol. This reduction affords a 79:21 ratio of diastereomeric alcohols which are separated by chromatography on silica gel. The magnitudes for the europium-induced NMR shifts for the methyl groups in these two isomers are quite different. In the major isomer (β-OH) the C-1 methyl group moves at a faster rate than the two bridge methyl groups; however, in the minor isomer (α-OH) all three methyl groups move at similar rates upon increasing the concentration of Eu(DPM)$_3$. The europium-induced NMR shifts of these isomers are in agreement with those shifts observed by Connolly

Scheme I



1 2

Scheme II[a]



[a] (a) 0.95 × LDA, THF, −78 °C to room temperature, 4–5 h; (b) CH_2=$CBrCH_2Br$; (c) 90% H_2SO_4, 0 °C; (d) $Hg(OAc)_2$, 88% HCO_2H; (e) KOH, EtOH, heat; (f) $LiMe_2Cu$, THF; (g) CH_2=$CHCH_2Cl$, HMPT; (h) H_3O^+; (i) NaH, DME; (j) CH_3I; (k) Sia_2BH, THF; (l) H_2O_2, NaOH, H_2O; (m) CrO_3, H_2SO_4, H_2O, acetone; (n) CH_2N_2, Et_2O (small scale) or CH_3I, K_2CO_3, acetone (large scale); (o) 2.0 × $LiN(SiMe_3)_2$, THF, reflux, 2 h and 35 min; (p) HMPT, *t*-$BuMe_2$-SiCl, 0 °C; (q) $NaBH_4$, 100% ethanol, 0 °C to room temperature, 6 h; (r) CH_2=$C(OCH_3)CH_3$, $POCl_3$ catalyst (R = $-C(CH_3)_2OCH_3$; (s) *n*-Bu_4F, THF; (t) $(C_6H_5)_3P$=CH_2, Me_2SO, 75 °C, 16 h; (u) MeOH, 5% HCl catalyst, room temperature, 0.5 h.

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