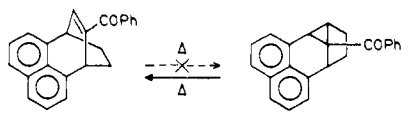
Acknowledgment. We thank Mrs. H. Matthäus for able technical assistance and Dr. H.-G. Heine, Bayer AG, for a generous gift of pleiadiene.

References and Notes

(1) Demuth, M.; Bender, C. O.; Braslavsky, S. E.; Görner, H.; Burger, U.; Amrein, W.; Schaffner, K. *Helv. Chim. Acta*, **1979**, *62*, 847–851.
(2) For leading references on di-π-methane photoreactions, cf.: Hixson, S. S.; Mariano, P. S.; Zimmerman, H. E. *Chem. Rev.* **1973**, *73*, 531–551. Zimmerman, H. E.; Steinmetz, M. G.; Kreil, C. L. *J. Am. Chem. Soc.* **1978**, *100*, 4146–4162.
(3) For a vinylogous di-π-methane-type thermal rearrangement of a bicyclo[4.4.1]undecatetraene to a *cis*-bicyclo[5.4.0]undecatetraene, see Sato, T.; Itô, S. *Tetrahedron Lett.* **1979**, 1051–1054. We thank Professor Itô for communicating these results prior to publication.
(4) (a) Woodward, R. B.; Hoffmann, R. "The Conservation of Orbital Symmetry"; Verlag Chemie: Weinheim, and Academic Press: New York, 1970. Zimmerman, H. E. *J. Am. Chem. Soc.* **1966**, *88*, 1565 and 1566; *Acc. Chem. Res.* **1971**, *4*, 272–280. (b) An analogous—photochemically forbidden—three-bridge mechanism has initially been considered by Zimmerman (Zimmerman, H. E.; Binkley, R. W.; Givens, R. S.; Sherwin, M. A. *J. Am. Chem. Soc.* **1967**, *89*, 3932–3933) for the photorearrangement of barrelene to semibullvalene, but it was ruled out experimentally in favor of the di-π-methane route. (c) The inclusion of a single formal double bond in lieu of the entire naphthalene π system in the orbital array of the transition state **3** (Scheme II) was chosen for simplicity and does not change the orbital symmetry argument. A six-electron process, which does not involve the naphthalene π electrons, is a formally equivalent alternative (however, see Hixson et al.[2] for arguments favoring the participation of the second double bond in di-π-methane photorearrangements).
(5) No rearrangement was observed with **1** and **2** at ≤180 °C (70 h). Quantitative analyses of the mixtures were obtained by GLC (glass capillary column, OV 101; experimental error ±5%). The low-percentage product **2** was additionally identified by GC–MS after thermolysis of a nondeuterated sample of **1**.
(6) The deuterium analyses were carried out either by 270-MHz ^{1}H NMR or 15.4-MHz FT ^{2}H NMR, or by a combination of both, depending on signal shifts and intensities.
(7) It is worthwhile to note in this connection that the dihydro compound **5** did not rearrange to **6** at 250 °C during 48 h. Only the reverse reaction, **6** →



5 **6**

5, was observed under these conditions (2 × 10^{-3} M solutions in toluene; no rearrangement of **6** occurred at ≤210 °C).
(8) For a review on energy storage in organic photoisomers, see Jones, G., II; Chiang, S.-H.; Xuan, P. T. *J. Photochem.* **1979**, *10*, 1–18.
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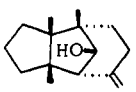
Stereoselective Synthesis of (±)-Gymnomitrol

Sir:

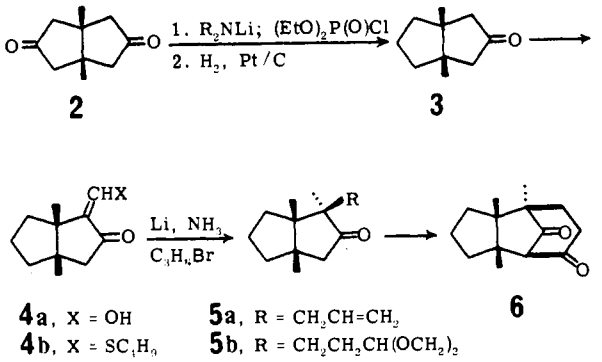
Gymnomitrol, one member of a group related sesquiterpenes isolated from the liverwort *Gymnomitrion obtusum* (Lindb.) Pears, has been assigned the novel tricyclic structure **1** on the



1

basis of degradative and spectroscopic evidence.[1] The presumed biogenetic parent, β-gymnomitrene,[2] co-occurs with gymnomitrol and has also been extracted from other species of liverwort.[3-5] Since the rare 4,8-methanoperhydroazulene nucleus[6] of gymnomitrol and cogeners most likely arises from cyclization of a bazzanenyl cation,[1,7] these compounds represent yet another biogenetic branch within the cuparene family of sesquiterpenes. In this communication we report a total synthesis of (±)-gymnomitrol which serves to confirm the structure of this interesting compound.[8]

Scheme I



The plan of the synthesis centered around the regio- and stereoselective geminal dialkylation of 3a,6a-dimethylhexahydro-2(1*H*)-pentalenone (**3**). This known compound[9] was conveniently prepared from the readily available diketone **2**[10] in the following manner (Scheme I). Addition of 1 equiv of the lithium derivative of hexamethyldisilazane to a tetrahydrofuran (THF) solution of **2** (−78 °C, 15 min) evidently produced the monoenolate anion which was phosphorylated with diethyl chlorophosphate (−78 to 25 °C, 2.5 h). Catalytic hydrogenation of the unpurified monoenol phosphate in ethyl acetate (5 atm, 5% Pt/C, 25 °C, 2.5 h)[11] provided monoketone **3** (mp 159–160 °C, sealed capillary) in 77% overall yield. The hydroxymethylene derivative **4** (mp 87–89 °C)[12] was prepared by condensation with ethyl formate (NaH, THF, 25 °C, 14 h, 83%) and converted into the *n*-butylthiomethylene ketone **5** by reaction with butanethiol (TsOH, C_6H_6, reflux, 18 h, 84%).[13] Reduction of **5** with lithium in liquid ammonia and 1,2-dimethoxyethane as cosolvent (2 equiv of H_2O, −78 to −33 °C, 0.5 h)[14] followed by addition of allyl bromide afforded a stereochemically homogeneous dialkylated ketone (**6**) in yields ranging from 26 to 49%.

Since the stereochemical outcome of the alkylation step in the reduction-alkylation **4a** → **5a** did not seem safely predictable, ketone **5a** was further converted into tricyclic diketone **6** to ascertain the stereochemistry. The allyl side chain was elaborated into an acetal-protected propionaldehyde substituent (**5b**) through a sequence of seven reactions.[15] Hydrolysis of the acetal (10% HCl, acetone, reflux) was accompanied by spontaneous aldol cyclization, and the resulting ketol was oxidized with Jones reagent to diketone **6** (55%; mp 214–216 °C; IR ν^{KBr} 1740, 1715 cm^{-1}). Although the IR and NMR spectral characteristics of **6** are very similar to those of nor diketone **14** previously prepared from natural gymnomitrol,[16] the larger chemical shifts for two of the three quaternary methyl groups in the former (δ^{CDCl_3} 1.04, 1.07, 1.10) provided convincing proof for the nonidentity of the two compounds.[17] Consequently the three-carbon bridge in diketone **6** is syn to the ring juncture methyl groups, and the alkylation of the methyl-substituted enolate anion from **4b** must have occurred exclusively on the convex surface of the bicyclic structure. It is also evident that the order of introduction of the methyl and three-carbon substituents at C-1 must be reversed in order to establish the correct stereochemistry for the synthesis of gymnomitrol. Cyano ketone **7** proved to be a suitable intermediate for this purpose (Scheme II).

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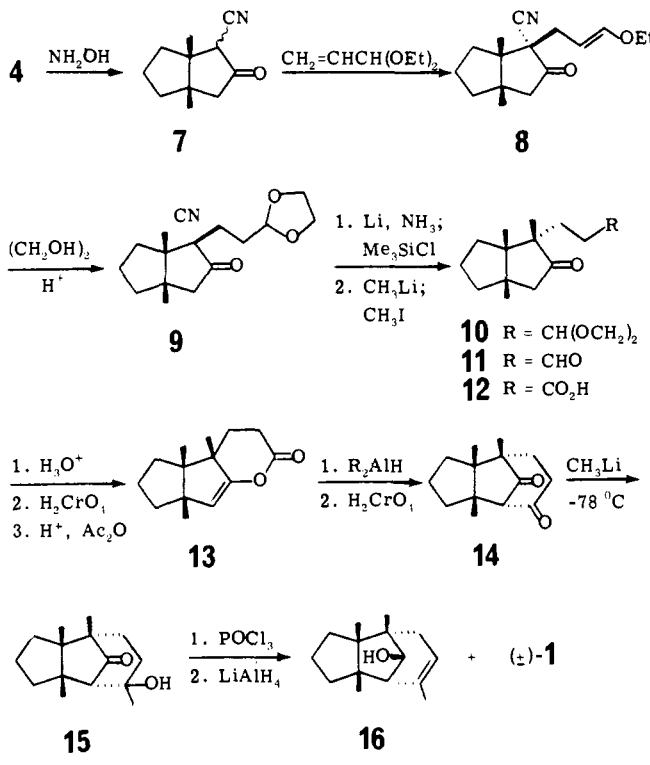
Scheme II



Reaction of hydroxymethylene ketone **4** with hydroxylamine in the presence of 5 equiv of sodium methoxide (CH_3OH, reflux, 20 h)[18] gave the crystalline cyano ketone **7** (mp 128–135 °C) as mixture epimers in 89% yield following column chromatography. When heated with 3 equiv of acrolein diethyl acetal in benzene at reflux for 22 h, **7** underwent alkylation affording the ethoxyallyl ketone **8** (76%)[19,20] as a yellow oil: NMR δ 4.6 (dt, 1 H, J = 7 and 13 Hz, vinyl H), 6.22 (d, 1 H, J = 13 Hz, vinyl H). The crystalline 1,3-dioxalane **9** (mp 79–80 °C), prepared by reaction with ethylene glycol in ether (concentrated HCl, 25 °C, 21 h, 92%), was subjected to reductive decyanation with lithium in liquid ammonia (THF, −78 °C, 20 min; 3-hexyne),[21] and the resulting enolate anion was trapped with chlorotrimethylsilane (86% distilled yield) after evaporating the ammonia. The lithium enolate was regenerated from the enolsilane by treatment with methyllithium (THF, 0 to 25 °C, 3 h) and alkylated with methyl iodide (25 °C, 17 h) to give keto acetal **10** (65% after column chromatography).

Keto aldehyde **11**, obtained by hydrolysis of the acetal protecting group (1.2 N HCl, acetone, reflux, 3 h), was remarkably resistant to aldol cyclization, evidently owing to steric hindrance from the opposing cyclopentane ring.[22] Consequently, the aldehyde was oxidized to keto acid **12** with Jones reagent (92%) and cyclized to the enol lactone **13** (mp 72.5–73 °C) with acetic anhydride ($HClO_4$, CH_2Cl_2, 0 °C, 20 min, 64%).[23] Reduction of **13** with diisobutyl aluminum hydride in THF (−78 to 0 °C, 6 h)[24] led to the bridged ketol which was oxidized with chromic acid directly to diketone **14**: mp 214–216 °C; 54%; NMR δ^{CDCl_3} 0.91, 1.01, 1.08 (3 s, 3 CH_3), 2.95 (s, bridgehead CH). The IR and NMR spectra of (±)-**14** are in good agreement with the corresponding spectra of the optically active nor diketone of the same structure obtained from gymnomitrol.[1,16]

The one remaining carbon atom was incorporated by regioselective addition of 1 equiv of methyllithium to the cyclohexanone carbonyl (ether, −78 °C, 4 h; aqueous NH_4Cl, −78 to 25 °C) of diketone **14** to give a 76% yield of ketol **15** as a single stereoisomer: IR ν 3400 (OH), 1730 (C=O) cm^{-1}. Dehydration of the latter with phosphorus oxychloride in pyridine (reflux, 2 h)[25] furnished a 1:1 mixture (64%) of (±)-gymnomitrone and its endocyclic isomer. The mixture of ketones was reduced with lithium aluminum hydride in THF at 0 °C, and the resulting alcohols then separated by preparative thin-layer chromatography on silica gel impregnated with silver nitrate (9:1 pentane–ether). The more polar component proved to be (±)-gymnomitrol ((±)-**1**, mp 107–109 °C) which had IR, NMR, and mass spectra identical with those of the natural product.[1,16]

Acknowledgments. We thank Professor John D. Connolly of the University of Glascow for donating the samples and spectra used for comparisons. This investigation was supported in part by research grants from the National Science Foundation (CHE 76-07513) and the National Cancer Institute (CA 20436). High resolution mass spectra were financed in part under a grant from the National Cancer Institute (CA 11388).

References and Notes

(1) Connolly, J. D.; Harding, A. E.; Thornton, I. M. S. *Chem. Commun.* **1970**, 1320–1321; *J. Chem. Soc., Perkin Trans. 1* **1974**, 2487–2493.
(2) The names β-barbatene[3] and β-pompene[4] have also been used in the literature.
(3) Andersen, N. H.; Huneck, S. *Phytochemistry* **1973**, *12*, 1818–1819. Andersen, N. H.; Costin, C. R.; Kramer, M., Jr.; Ohta, Y.; Huneck, S. *Ibid.* **1973**, *12*, 2709–2716.
(4) Matsuo, A.; Maeda, T.; Nakayama, M.; Hayashi, S. *Tetrahedron Lett.* **1973**, 4131–4134. Matsuo, A.; Nozaki, H.; Nakayama, M.; Kushi, Y.; Hayashi, S.; Kamijo, N. *Ibid.* **1975**, 241–244. Matsuo, A.; Uto, S.; Nakayama, M.; Hayashi, S. *Z. Naturforsch. C* **1976**, *31*, 401–402.
(5) Paknikar, S. K.; Kirtany, J. K.; Naik, C. G. *Ind. J. Chem.* **1975**, *13*, 1234.
(6) The only other naturally occurring sesquiterpene having this ring system of which we are aware is α-caryophyllene alcohol: Adams, D. R.; Bhatnagar, S. P.; Cookson, R. C. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1502–1506.
(7) Matsuo, A.; Hayashi, S. *J. Chem. Soc., Chem. Commun.* **1977**, 566–568.
(8) Independent syntheses of (±)-gymnomitrol have recently been achieved in the laboratories of G. Büchi, S. C. Welch, L. A. Paquette, and S. Itô. We wish to thank Professors Büchi and Welch for fruitful exchanges of information during the course of this work. See the two following communications.
(9) Borden, W. T.; Ravindranathen, T. *J. Org. Chem.* **1971**, *36*, 4125–4127.
(10) Weiss, U.; Edwards, J. M. *Tetrahedron Lett.* **1968**, 4885–4887.
(11) Jung, A.; Engel, R. *J. Org. Chem.* **1975**, *40*, 3652–3654.
(12) All compounds described in this paper gave IR and ^1H NMR spectra fully consistent with the structures shown in the schemes. Satisfactory combustion analyses were secured on the following compounds: **4a**, **5a**, **5b**, **6**, **7**, **9**, **10**, and **13**. The elemental composition of compounds **15**, **16**, and (±)-**1** was confirmed by high resolution mass spectrometry.
(13) Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1962**, *27*, 1615–1619.
(14) Coates, R. M.; Sowerby, R. L. *J. Am. Chem. Soc.* **1971**, *93*, 1027–1029; *Ibid.* **1972**, *94*, 5386–5396.
(15) The individual steps in the reaction sequence were performed with the following reagents and conditions: (a) $LiAlH_4$, THF (a 55:45 mixture of epimers was formed); (b) $PhCH_2Br$, KH, 1,2-dimethoxyethane; (c) BH_3, THF; H_2O_2, OH^-; (d) CrO_3-(Pyr)$_2$, CH_2Cl_2; (e) ethylene glycol, TsOH, C_6H_6, reflux; (f) Li, NH_3, THF, −33 °C; (g) CrO_3-(Pyr)$_2$, CH_2Cl_2. The overall yield was ~40%.
(16) Spectra of nor diketone **14** and (+)-gymnomitrol as well as authentic specimen of **14** and gymnomitryl acetate were kindly furnished by Professor Connolly.
(17) The configuration of the allyl group in **5a** was also supported by europium-induced NMR shifts for the methyl and allylic methylene substituents in the epimeric alcohols formed by reduction of **5a** with lithium aluminum hydride.
(18) Lapworth, A. *J. Chem. Soc.* **1900**, *77*, 1053–1071.
(19) An attractive mechanism for this novel variant of the Michael reaction is acetal exchange with the enol form of cyano ketone **7** followed by Claisen rearrangement. The scope of this and related reactions is currently under investigation in these laboratories. Precedent for this type of transformation may be found in the following references: (a) Dolby, L. J.; Elliger, C. A.; Esfandri, S.; Marshall, K. S. *J. Org. Chem.* **1968**, *33*, 4508–4511. (b) Clarke, D. G.; Cromble, L.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1007–1015. (c) Heyns, K.; Hohlweg, R. *Chem. Ber.* **1978**, *111*, 1632–1645.
(20) The orientation of the ethoxyallyl group in **8** is tentatively assigned as shown on the assumption that the steric factors responsible for the stereochemistry of the enolate alkylation reactions (**4b** → **5a** and **9** → **10**) will similarly affect the reaction of **7** with acrolein diethyl acetal, regardless of the exact mechanism.
(21) (a) The reductive decyanation of nitriles with metal–ammonia solutions has been reported previously: Arapakos, P. G.; Scott, M. K.; Huber, F. E., Jr. *J. Am. Chem. Soc.* **1969**, *91*, 2059–2062. Marshall, J. A.; Hagan, C. P.; Flynn, G. A. *J. Org. Chem.* **1975**, *40*, 1162–1166. (b) 3-Hexyne was added to destroy excess lithium.

(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.
(23) House, H. O.; Trost, B. M. *J. Org. Chem.* **1965**, *30*, 2502–2512. Boeckman, R. K., Jr.; Bershas, J. P.; Clardy, J.; Solheim, B. *Ibid.* **1977**, 3632–3633.
(24) Martin, J.; Parker, W.; Raphael, R. A. *J. Chem. Soc.* **1964**, 289–295. Colvin, E. W.; Malchenko, S.; Raphael, R. A.; Roberts, J. S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1989–1997. Welch, S. C.; Walters, R. L. *J. Org. Chem.* **1974**, *39*, 2665–2673.
(25) Johnson, W. S.; Krost, J. J.; Clement, R. A.; Dutta, J. *J. Am. Chem. Soc.* **1960**, *82*, 614–622.

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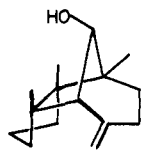
Synthesis of Gymnomitrol

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-



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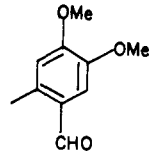
pene,[3] constituents of related liverwort species, were shown to be identical with gymnomitrene. To probe the generality of a new method for the preparation of bicyclo[3.2.1]octanes by acid-catalyzed addition of *p*-quinone ketals to olefins,[4] we pursued a synthesis of gymnomitrol (**1**), and the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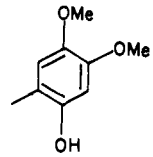

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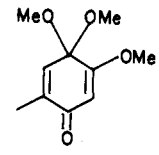

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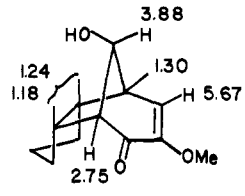

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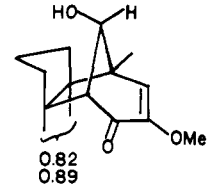
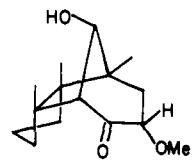


6

(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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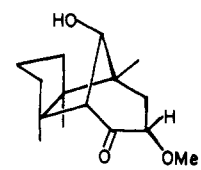

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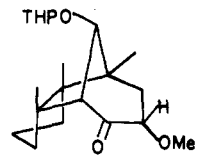

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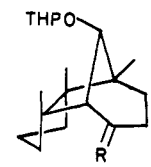

10 R = O

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]

Acknowledgments. We thank the National Institutes of Health (GM 09868) and the Hoffmann-La Roche Foundation for financial support. The high-field NMR experiments were performed at the facility for biomolecular research located at the F. Bitter National Magnet Laboratory, Massachusetts Institute of Technology, which is supported by the National Institutes of Health (RR 00995) and the National Science Foundation (Contract No. C-670). High resolution mass spectra were provided by the facility, supported by the National Institutes of Health (Grant RR 00317) (Principal Investigator, Professor K. Biemann) from the Biotechnology Resources Branch, Division of Research Resources.

References and Notes

(1) Connolly, J. D.; Harding, A. E.; Thornton, I. M. S. *Chem. Commun.* **1970**, 1320–1321; *J. Chem. Soc., Perkin Trans. 1* **1974**, 2487–2493.
(2) Andersen, N. H.; Huneck, S. *Phytochemistry* **1973**, *12*, 1818–1819. Andersen, N. H.; Costin, C. R.; Kramer, M., Jr.; Ohta, Y.; Huneck, S. *Ibid.* **1973**, *12*, 2709–2716.
(3) Matsuo, A.; Maeda, T.; Nakayama, M.; Hayashi, S. *Tetrahedron Lett.* **1973**, 4131–4134. Matsuo, A.; Nozaki, H.; Nakayama, M.; Kushi, Y.; Hayashi, S.; Kamijo, N. *Ibid.* **1975**, 241–244. Matsuo, A.; Uto, S.; Nakayama, M.; Hayashi, S. *Z. Naturforsch. C* **1976**, *31*, 401–402. Nozaki, H.; Matsuo, A.; Nakayama, M.; Kushi, Y.; Kamijo, N.; Hayashi, S. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 568–574.
(4) Büchi, G.; Mak, C.-P. *J. Am. Chem. Soc.* **1977**, *99*, 8073–8075. Büchi, G.; Chu, P.-S. *J. Org. Chem.* **1978**, *43*, 3717–3719.

0002-7863/79/1501-6767$01.00/0