11.0, 1/2 H), 1.82-2.05 (m, 4 H), 1.62 (dd, J = 11.2, 8.3 Hz, 1/2 H), 1.51 (dd, J = 11.2, 8.3 Hz, 1/2 H), 1.30 (s, 3/2 H), 1.17 (s, 3/2 H). ^{13}C NMR ($CDCl_3$): δ 218.07, 218.00, 200.92, 173.34, 173.20, 59.79, 59.43, 54.62, 53.85, 51.73, 45.30, 33.85, 31.87, 31.22, 30.45, 30.38, 29.61, 29.51, 29.28, 28.01, 27.61, 21.34, 19.48. HRMS: m/e calcd for $C_{13}H_{21}NO_3S$ 271.1242, found 271.1243.

Methyl 3-[4-[2-(Thioacetoxy)ethyl]-2-methyl-1-oxocyclobut-2-yl]-propionate. To a solution of 110 mg (0.38 mmol) of **34**, a 4:1 mixture of diastereomers, in 15 mL of acetone was added 88 mg (0.77 mmol) of potassium thioacetate. The reaction mixture was stirred at reflux for 1 h and cooled to room temperature. The mixture was filtered, and the salts were washed with cold acetone. The acetone filtrate and washings were concentrated by rotary evaporation. The crude residue was taken up in water and extracted with ether. The ether fractions were combined, washed with water, dried (magnesium sulfate), and concentrated by rotary evaporation. Purification by flash chromatography through silica gel using 2:1 hexanes/ethyl acetate afforded 82 mg (80%) as a 4:1 mixture of diastereomers. IR (neat): 2960, 2880, 1765, 1735, 1690, 1440, 1140 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.67 (s, 3 H), 3.39 (dddd, J = 10.6, 8.9, 7.9, 6.4 Hz, 1 H), 2.91 (dd, J = 8.0, 6.9 Hz, 2 H), 2.23-2.45 (m, 2 H), 2.33 (s, 3 H), 2.16 (t, J = 10.9 Hz, 1 H, major), 1.84-2.05 (m, 3 H + 1 H, minor), 1.70-1.80 (m, 1 H), 1.61 (dd, J = 11.1, 7.8 Hz, 1 H, minor), 1.51 (dd, J = 11.4, 7.9 Hz, 1 H, major), 1.24 (s, 3 H, minor), 1.15 (s, 3 H, major). HRMS: m/e calcd for $[M^+ - OCH_3]$ $C_{12}H_{17}O_3S$ 241.0898, found 241.0893.

Methyl 3-[(1R*,5S*)-1-Hydroxy-7-methyl-2-thiabicyclo[3.2.0]hept-7-yl]propionate (39). To a solution of 79 mg (0.29 mmol) of the above thioacetate, a 4:1 mixture of diastereomers, in 10 mL of dry methanol was added 8 mg (0.35 mmol) of sodium. The reaction mixture was stirred for 30 min and quenched with hydrochloric acid. The aqueous solution was extracted with methylene chloride. The combined methylene chloride fractions were washed with brine, dried (magnesium sulfate), and concentrated by rotary evaporation. Purification by flash chromatography using 2:1 hexanes/ethyl acetate afforded 54 mg (81%) of **39** as a 2.5:1 mixture of diastereomers. IR (neat): 3460, 2960, 2880, 1740, 1442, 1275, 1210, 1180 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.69 (s, 3 H, major), 3.68 (s, 3 H, minor), 3.11-3.19 (m, 1 H), 3.01-3.09 (m, 1 H), 2.89-2.96 (m, 1 H), 2.48-2.64 (m, 1 H), 2.24-2.43 (m, 2 H), 1.85-2.19 (m, 3 H), 1.75-1.82 (ddd, J = 13.6, 9.7, 6.0 Hz, 1 H), 1.62 (dd, J = 11.6, 9.3 Hz, 1 H, minor), 1.57 (dd, J = 11.1, 9.0 Hz, 1 H, major), 1.28 (s, 3 H, major), 1.17 (s, 3 H, minor), 1.08 (dd, J = 11.2, 9.1 Hz, 1 H, major), 1.01 (dd, J = 11.7, 8.9 Hz, 1 H, minor). HRMS: m/e calcd for $[M^+ - H]$ $C_{11}H_{17}O_3S$ 229.0893, found 229.0896.

Methyl 3-[(1R*,5S*)-3-Methyl-2,8-dioxabicyclo[3.3.0]oct-3-yl]-propionate (40). A solution of 0.50 g (2.34 mmol) of **30**, a 3:1 mixture of diastereomers, in 500 mL of methylene chloride was degassed with nitrogen for 15 min. The solution was irradiated at 350 nm for 40 h. The reaction mixture was concentrated by rotary evaporation. Purification by flash chromatography using 1:1 hexanes/ethyl acetate afforded 0.40 g (80%) of a yellow oil as a 3:1 mixture of diastereomers. Further purification was achieved by Kugelrohr distillation, bp 90-95 °C (0.2 Torr). IR (neat): 2970, 2880, 2740, 1440, 1205, 1175, 1020 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.67 (d, J = 5.2 Hz, 1 H, minor), 5.63 (d, J = 5.2 Hz, 1 H, major), 3.85-3.97 (m, 2 H), 3.68 (s, 3 H), 2.95-2.99 (m, 1 H), 2.30-2.49 (m, 2 H), 2.11 (dd, J = 12.9, 9.8 Hz, 1 H, major), 1.62-2.08 (m, 4 H + 1 H, minor), 1.46 (dd, J = 13.0, 8.2 Hz, 1 H), 1.31, (s, 3 H, major), 1.15 (s, 3 H, minor). HRMS: m/e calcd for $[M^+ - CH_3]$ $C_{10}H_{15}O_4$ 199.0971, found 199.0970.

Methyl 3-[(1R*,5S*)-3-Methyl-2-oxa-8-thiabicyclo[3.3.0]oct-3-yl]-propionate (47). A solution of 50 mg (0.22 mmol) of **39**, a 2.5:1 mixture of diastereomers, in 22 mL of methylene chloride was degassed with nitrogen for 15 min. Triethylamine (2 μL, 6 mol %) was added by syringe. The reaction mixture was irradiated at 350 nm for 33 h and concentrated by rotary evaporation. The residue was purified by flash chromatography with 3:1 hexanes/ethyl acetate to yield 26 mg (52%) of a clear, colorless oil as a 2:1 mixture of diastereomers. IR (neat): 2950, 2870, 1735, 1440, 1175, 1030 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.86 (d, J = 6.5 Hz, 1 H, major), 5.78 (d, J = 6.5 Hz, 1 H, minor), 3.68 (s, 3 H, major), 3.67 (s, 3 H, minor), 3.18-3.31 (m, 1 H), 2.99-3.10 (m, 1 H), 2.75-2.82 (m, 1 H), 2.45-2.49 (m, 1 H), 2.33-2.42 (m, 1 H), 2.06-2.13 (m, 1 H), 1.96-2.02 (m, 2 H), 1.88-1.98 (m, 1 H, major), 1.81-1.86 (ddd, J = 12.5, 8.7, 1.3 Hz, 1 H), 1.63-1.71 (ddd, J = 14.0, 9.8, 5.9 Hz, 1 H, minor), 1.50 (dd, J = 12.5, 10.4 Hz, 1 H), 1.34 (s, 3 H, minor), 1.17 (s, 3 H, major). HRMS: m/e calcd for $C_{11}H_{18}O_3S$ 230.0976, found 230.0983.

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Supplementary Material Available: Experimental procedures for compounds **3**, **8**, **18/19**, **23-25**, **27-29**, **31-36**, and **41-46** and a description of kinetic experiments (14 pages). Ordering information is given on any current masthead page.

Kalmanol, a Pharmacologically Active Diterpenoid with a New Ring Skeleton from *Kalmia angustifolia* L.

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Abstract: Kalmanol (**4**), $C_{20}H_{34}O_6$, a hexahydroxy B-homo-C-nor grayanoid isolated from *Kalmia angustifolia* L. represents a new diterpenoid ring system and possesses cardiotoxic properties like those of the grayanotoxins. Its structure was determined by spectral methods: IR, MS, and ^1H and ^{13}C NMR, including 2D CH-correlation and COLOC. NOE difference established all stereochemical centers except for C-8 and C-16. Single-crystal X-ray analysis confirmed the derived structure and fixed the stereochemistry at the unknown centers.

The grayanoids, or grayanotoxins, such as grayanotoxin I (**1**), are a unique class of toxic diterpenoids with an A-nor-B-homo *ent*-kaurane skeleton that occur in the heath family (Ericaceae).[2] Alterations in that basic skeleton are also known as in the example leucothol A (**2**)[3] with the A-homo-B-nor grayanoid ring system and grayanol B (**3**)[4] with the 1,5-seco grayanoid system. We wish to report a third modification of that system as found in kalmanol

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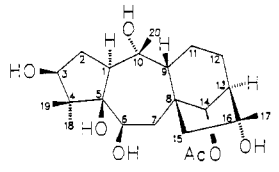
Table I. ^{13}C and ^{1}H NMR Spectral Data for Kalmanol[a]

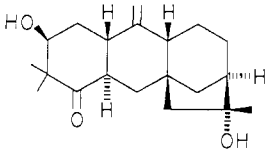
carbon	$\delta(^{13}C)$	$^{1}J_{CH}$	$\delta(^{1}H)$	J_{HH}
1	52.14 d	120.6	3.048	dd, 11.9, 3.0
2	35.61 t	128.6	2.702 β	dd, 15.0, 3.0
			2.401 α	ddd, 15.0, 11.9, 4.4
3	82.76 d	148.2	3.855	dd, 4.3, 4.3[b]
4	53.44 s			
5	86.25 s			
6	72.12 d	141.9	4.752	dd, 10.5, 9.3[c]
7	43.62 t	124.7	2.989 β	dd, 14.6, 10.5
			2.454 α	d, 14.6
8	82.94 s			
9	52.81 d	142.0	2.726	ddd (obs),[d] 11.5, 7.6, 7.6
10	75.68 s			
11	29.55 t	127.9	2.070	dddd,[d] 13.5, 11.5, 11.5, 5.7
			1.863	ddd,[d] 11.5, 6.0, 6.0
12	31.01 t	125.5	$\simeq$1.75	m (obs)
			0.957	dddd,[d] 12.9, 12.9, 12.3, 5.8
13	60.67 d	135.4	2.882	ddd,[d] 11.3, 9.1, 6.9
14	53.94 d	127.6	3.330	dd, 8.8, 8.8
15	53.44 t	127.5	1.946	s (2 H)
16	79.97 s			
17	23.53 q	124.7	1.371	s
18	24.13 q	125.4	1.236	s
19	20.96 q	125.7	1.758	s
20	25.12 q	125.1	1.925	s

[a] Taken at 67.9 MHz for ^{13}C and 500 MHz for ^{1}H in pyridine-d_5 on an IBM AF-270 and a Bruker AM-500 instrument, respectively. Multiplicities (obtained by SFORD for ^{13}C) are designated as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, and obs = obscured. The $^{1}J_{CH}$ values were obtained from the proton fully coupled ^{13}C NMR spectrum with data point resolution of 0.7 Hz. ^{1}H NMR spectrum data point resolution was 0.3 Hz. Chemical shifts are in ppm with solvent peaks taken as internal standards referenced to tetramethylsilane; the ^{1}H upfield peak for pyridine-d_4 was taken as 7.19 ppm, and the ^{13}C upfield peak for pyridine-d_5 was taken as 123.5 ppm. Methylene protons were designated α (below plane of drawing) and β (above plane). [b] Lost with D_2O and coupled to d at 6.447 ppm. [c] Lost with D_2O and coupled to d at 5.294 ppm. [d] Non-first-order pattern with separation values given solely from characterization.

(**4**), a minor constituent (1.2×10^{-3}% of dry weight) of the leaves of *Kalmia angustifolia* L.[5]



1



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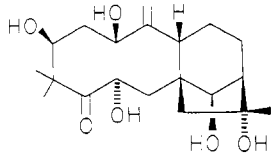

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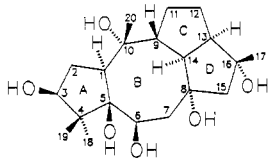

4

Kalmanol (**4**) with formula $C_{20}H_{34}O_6$ (MW 370), as supported by mass spectral data and by ^{13}C and ^{1}H NMR studies, has six D_2O-exchangeable protons,[6] and from the four double-bond equivalents required by the formula, it must be tetracyclic and possess six hydroxyls. Decoupling of the ^{1}H NMR spectral patterns (Table I) revealed two coupled systems that are found in grayanotoxin I (**1**): the four-spin system of protons of C-1, C-2, and C-3 and the three-spin system of protons of C-6 and C-7, in keeping with a grayanoid structure from at least C-1 to C-7. In addition, decoupling revealed a seven-proton coupled unit not part of a normal grayanoid skeleton, and this was found to be a 1,2,3-trisubstituted cyclopentane when CH-correlation results from a 2D NMR study[7] were taken into account. The remaining two protons (methyl groups excluded) were observed as a two-proton singlet at 1.946 ppm for a methylene in a symmetrical magnetic environment. Thus, kalmanol possesses a modified grayanoid system in which ring B is expanded to eight carbons and ring C contracted to five,[8] with the methylene singlet being the C-15 protons of the unaltered ring D.

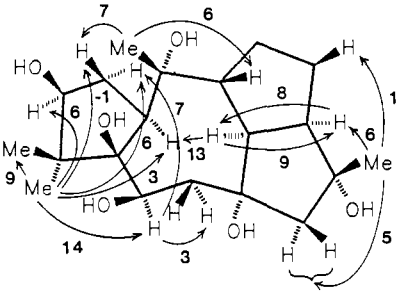

Figure 1. NOE enhancements from difference studies on kalmanol (**4**).

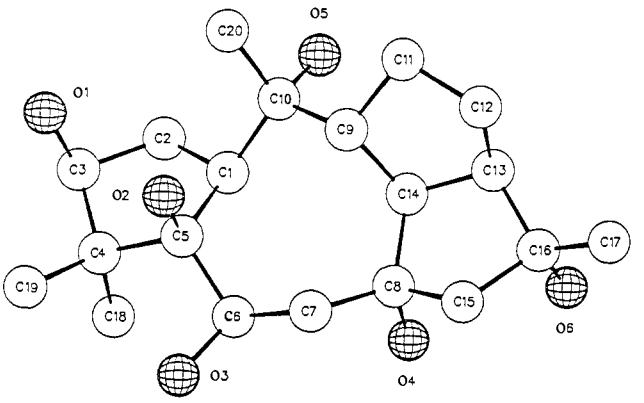

Figure 2. Computer-generated perspective drawing of kalmanol (**4**). Only one of the two independent and identical molecules is shown, hydrogens are omitted for clarity, and the absolute configuration shown was selected to agree with that of grayanotoxin (**1**).

Extensive NOE difference[9] studies (Figure 1) supported the modified ring skeleton, established the stereochemistry at the junction of rings C and D as cis, and confirmed those at C-1 and C-9 to be as in grayanotoxin I (**1**). The ^{1}H NMR spectral assignments (Table I) were also aided by these results,[10] but chirality at C-8 and C-16 remained unsupported.

^{13}C NMR assignments were made from a two-dimensional CH-correlation experiment with decoupling in the F_1 domain (^{1}H)[7] for proton-bearing carbons, and for quaternary carbons from a correlation via long-range coupling (COLOC)[11] experiment.[12]

(2) For X-ray structure analysis of grayanotoxin I: Kakisawa, H.; Kozima, T.; Yanai, M.; Nakanishi, K. *Tetrahedron* **1965**, *21*, 3091–104, and references cited therein. Narayanan, P.; Rohrl, M.; Zechmeister, K.; Hoppe, W. *Tetrahedron Lett.* **1970**, 3943–4.

(3) Furusaki, A.; Hamanaka, N.; Miyakoshi, H.; Okuno, T.; Matsumoto, T.; *Chem. Lett.* **1972**, 783–6.

(4) Fushiya, S.; Hikino, H.; Takemoto, T. *Tetrahedron Lett.* **1974**, 183–6.

(5) Collected in North Carolina by Prof. E. M. Croom, Jr., and authenticated by him. A voucher specimen is on file at the College of Pharmacy, OSU.

(6) The exchanged protons at 500 MHz in pyridine-d_5 were at 6.447 (d, 4.5), 6.435 (s), 6.290 (s), 5.294 (d, 9.3), 5.130 (s), and 4.447 ppm (s).

(7) Bax, A. *J. Magn. Reson.* **1983**, *53*, 517–20. Rutar, V. *J. Magn. Reson.* **1984**, *58*, 306–10. Wilde, J. A.; Bolton, P. H. *J. Magn. Reson.* **1984**, *59*, 343–46.

(8) The numbering system in kalmanol is based on that in grayanotoxin I, resulting in C-14 being placed in the eight-membered ring as a consequence of the B-ring expansion and C-ring contraction.

(9) Sanders, J. K. M.; Mersh, J. D. *Prog. Nucl. Magn. Reson. Spectrosc.* **1982**, *15*, 361–80.

(10) The negative NOE observed for H-2β when Me-18 was irradiated represents the third atom of a linear three-spin system (Me-18, H-2α, and H-2β) which is clearly seen in a Dreiding model. A description of this system is given in Noggle, J. H.; Schirmer, R. E. *The Nuclear Overhauser Effect*; Academic: New York, 1971; pp 59–64.

(11) Kessler, H.; Griesinger, C.; Zarbock, J.; Loosli, H. R. *J. Magn. Reson.* **1984**, *57*, 331–6.

Complete assignment of the ^{13}C NMR spectrum for kalmanol (**4**) is given in Table I along with the $^1J_{CH}$ values.

Single-crystal X-ray analysis of kalmanol (**4**) supported the new ring system proposed from the spectral data and established the chirality at the undesignated centers (particularly C-8 and C-16). A computer-generated perspective drawing of the final X-ray model of kalmanol (**4**) is shown in Figure 2. The actual X-ray structure encompassed two independent molecules which had identical configurations and essentially identical conformations. Only one molecule is shown for clarity. As can be readily seen, both C-8 and C-16 have α-hydroxyl groups. The overall conformation of kalmanol is interesting. Each of the five-membered rings has a C_2 or skew conformation. In the left-hand ring, the approximate two-fold axis runs through C-1 and bisects the C-3–C-4 bond. In the right-hand rings, the approximate twofolds run through C-14 and intersect the C-11–C-12 and C-15–C-16 bonds. The eight-membered ring also has an approximate twofold axis bisecting the C-5–C-6 and C-9–C-14 bonds. There is an apparent intramolecular hydrogen bond from O-4H to O-6 as well as a series of intermolecular hydrogen bonds in the solid state.

The likely biogenetic origin of kalmanol (**4**) is grayanotoxin I (**1**) or a related compound with an appropriate leaving group at C-14. The migration of the 8,9-bond to C-14 would enlarge ring B and contract ring C on loss of the leaving group at C-14. The carbocation center created at C-8 would then be neutralized with hydroxide (or H_2O with subsequent loss of proton). A concerted reaction would result in inversion of chirality of C-14, but since chirality has been maintained, the likely event is an enzymatic double-inversion process. With the characterization of kalmanol, a new tetracyclic diterpenoid ring skeleton can be added to the more than 20 recognized to date.[13]

The grayanoids are cardiotoxic and act by increasing the permeability of sodium ions in excitable membranes.[14] In a preliminary pharmacological evaluation, kalmanol (**4**) was compared to grayanotoxin I (**1**) in affecting the systolic tension in spontaneously beating isolated right atrium of the guinea pig.[15] Although less potent than grayanotoxin I (**1**), kalmanol (**4**) demonstrates that alterations in rings B and C can be tolerated without complete loss of activity. The structural features for activity in the grayanotoxins such as the 3β-OH (or 2β,3β-epoxy), 5β-OH, 6β-OH, and 10β-methyl, as established by Masutani et al.,[16] are still maintained in kalmanol. In comparison, leucothol A (**2**)[3] and grayanol B (**3**)[4] with alterations in rings A and B are reported to be nontoxic.

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were determined in pyridine-d_5 at 11.75 T on a Bruker AM-500 instrument and at 6.35 T on an IBM AF-270 instrument, with residual upfield pyridine peaks as internal standard set at 7.19 ppm for ^1H and 123.5 ppm for ^{13}C. Mass spectra were taken on a VG 70-250S instrument with glycerol as matrix for the fast atom bombardment (FAB) procedure. Optical rotations were obtained on a Perkin-Elmer 241 polarimeter, circular dichroism (CD) spectra on a Jasco J-500A spectropolarimeter, infrared spectra on a Beckman IR-4230, and ultraviolet spectra on a Beckman UV-5260 instrument.

Thin-layer chromatography (TLC) was performed on glass silica gel G60 plates (0.25 mm thick) and on reverse-phase RP-8 and RP-18 (both F-254) plates from E. Merck. Zone detection was by spraying with *p*-anisaldehyde–H_2SO_4–MeOH (1:1:18) and heating at 110–120 °C to yield purple-blue spots. Adsorbents for column chromatography were silica gel 60 (70–230 and 230–400 mesh) and reverse-phase LiChroprep RP-8 (40–63 μm as Lobar prepacked column) from E. Merck and Sephadex LH-20 from Pharmacia.

Solvents were of analytical grade and redistilled before use, except for spectral studies for which spectral-grade solvents were used.

Isolation of Kalmanol. The pulverized air-dried leaves (5.4 kg) on percolation to exhaustion at room temperature with ethanol gave 2.4 kg of extract, after removal of solvent at reduced pressure. The residue was partitioned between $CHCl_3$–H_2O, and the aqueous phase was extracted successively with EtOAc and *n*-BuOH. The EtOAc residue, 725 g, was chromatographed on Sephadex LH-20 with MeOH to give 49 g of terpenes as the fastest-moving components. TLC monitoring of column fractions was performed with $CHCl_3$–MeOH–H_2O (60:15:4 lower phase), and those fractions showing blue and purple zones after spraying were combined. Chromatography of the terpenes on 1.76 kg of silica gel and elution with $CHCl_3$ and increasing amounts of MeOH (0–20%) in $CHCl_3$ yielded nine pooled fractions containing components of similar mobility from TLC analysis. The sixth pooled fraction (4.8 g) was separated on silica gel columns, first with EtCOMe–$CHCl_3$–H_2O (16:4:0.5) and then with MeCN–$CHCl_3$–H_2O (14:6:0.5), to give a material of R_f 0.20 in the latter solvent system (two developments), which crystallized from EtCOMe–MeOH–Et_2O to give kalmanol (**4**).

Kalmanol (4): white needles; mp 255–6 °C; $[\alpha]^{25}_D$ +31° (MeOH); CD (c 1.4 × 10^{-3} M, MeOH) $[\phi]_{320-205}$ 0; IR (KBr) ν_{max} 3430 and 3280 (OH), 1470, 1451, 1420, 1390, 1308, 1205, 1140, 1089, 1070, 1012, 990, 901, 805, 690 cm^{-1} (see supplementary material); UV (MeOH) λ(end abs) 220 nm, log ϵ 1.77; MS (FAB, glycerol) m/z 371 (5% MH^+, $C_{20}H_{35}O_6$), 353 (4, MH – H_2O), 335.217 (45, MH – $2H_2O$, $C_{20}H_{31}O_4$ requires 335.222), 317.211 (90, MH – $3H_2O$, $C_{20}H_{29}O_3$ requires 317.212), 299.207 (82, MH – $4H_2O$, $C_{20}H_{27}O_2$ requires 299.201), 281 (24, MH – $5H_2O$), 177 (25), 101 (100).

Kalmanol crystallized in the orthorhombic space group $P2_12_12_1$ with a = 10.882 (3) Å, b = 15.382 (3) Å, and c = 23.045 (3) Å and *two* molecules of composition $C_{20}H_{34}O_6$ forming the asymmetric unit. A total of 2954 reflections were measured with Cu Kα radiation and 1° ω-scans. Of these, 2643 (89%) were judged observed [$|F_o| \geq 3\sigma(F_o)$] and used in subsequent calculations. The structure was phased with some difficulty and refined by block-diagonal least-squares techniques to a conventional crystallographic residual of 0.066 for the observed data. Additional crystallographic details are available and are described in supplementary material.

Acknowledgment. J.W.B. thanks the American Foundation for Pharmaceutical Education and the Johnson and Johnson Co. for the predoctoral fellowship and the OSU Graduate Student Alumni Research Award for some supplies, 1986–1987. We gratefully acknowledge Prof. E. M. Croom, Jr., for the plant collection. FT-NMR spectra at 500 MHz were obtained at the OSU Chemical Instrument Center on equipment funded in part by NIH Grant 1 S10 RR01458-01A1. We thank Professor A. M. Burkman for the pharmacological data, Dr. C. E. Cottrell for assistance concerning NMR operations, and C. R. Weisenberger and D. Chang for MS data. C.-Z.N. and J.C. acknowledge with thanks the support in part by NIH Grant CA24487.

Supplementary Material Available: Tables of atomic coordinates, thermal parameters, interatomic distances, interatomic angles, and torsional angles and the IR spectrum for kalmanol (**4**) (7 pages). Ordering information is given on any current masthead page.

(12) Specifically, the geminal dimethyls at 1.758 (H-19) and 1.236 (H-18) ppm showed two-bond coupling to C-4 (53.44 ppm) and three-bond coupling to C-5 (86.25 ppm), while the methyl at 1.925 ppm (H-20) gave two-bond coupling to C-10 (75.68 ppm) and three-bond coupling to methine carbons C-1 (52.14 ppm) and C-9 (52.81 ppm); and the remaining methyl at 1.371 ppm (H-17) exhibited two-bond coupling to C-16 and three-bond coupling to methine and methylene carbons C-13 (60.67 ppm) and C-15 (53.44 ppm). Also, the two-proton singlet at 1.946 (H-15) and 2.454 (H-7α) ppm showed two-bond coupling to C-8 (82.94 ppm) and three-bond coupling to C-14 (53.94 ppm).

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