Structure and Absolute Configuration of Malyngolide, an Antibiotic from the Marine Blue-Green Alga *Lyngbya majuscula* Gomont

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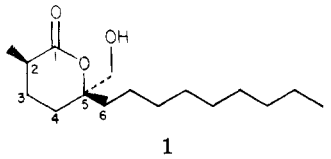
The δ-lactone malyngolide, an antibiotic effective against *Mycobacterium smegmatis* and *Streptococcus pyogenes*, was isolated from the dichloromethane extract of a shallow-water variety of the blue-green alga *Lyngbya majuscula* Gomont. Its skeletal structure and relative stereochemistry were established by spectral analysis, chemical degradation, and a lanthanide-induced proton chemical shift study. The absolute configuration was determined by a circular dichroism study and by converting malyngolide to levorotatory methyl 2-methyl-5-oxotetradecanoate which had an optical rotation comparable with that of methyl 2(*R*)-methyl-5-oxoheptanoate. The structure was verified by X-ray crystallographic analysis of the levorotatory saponification product, (2*R*,5*S*)-5-hydroxy-5-(hydroxymethyl)-2-methyltetradecanoic acid.

The methanolic extract of Hawaiian *Lyngbya majuscula* has been reported[1] to be active against *Micrococcus pyogenes* var. *aureus*,[2] *Mycobacterium smegmatis*, and *Pseudomonas fluorescens* but inactive toward *Escherichia coli*[3] and *P. aeruginosa*. We report here the isolation and structure determination of malyngolide (1), the major antibiotic in the lipid extract of a shallow-water variety of *L. majuscula* from Kahala Beach, Oahu, which is active against *M. smegmatis* and *Streptococcus pyogenes*, less active against *Staphylococcus aureus* and *Bacillus subtilis*, and inactive against *Enterobacter aerogenes*, *E. coli*, *P. aeruginosa*, *Salmonella enteritidis*, and *Staphylococcus marcescens*.



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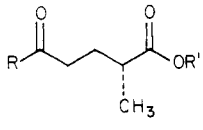
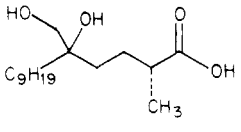
Successive extraction of the freeze-dried alga with petroleum ether and dichloromethane followed by gel filtration of the dichloromethane extract led to malyngolide. The electron-impact mass spectrum failed to give a molecular ion but showed a large fragment ion at *m/e* 239 for $C_{15}H_{27}O_2$. The ^{13}C NMR spectrum, however, indicated the presence of 16 carbon atoms, including an ester carbonyl (δ 175.0), two carbons singly bonded to oxygen, one a methylene (δ 67.4) and the other a quaternary carbon (δ 86.4), two methyl groups (δ 17.0 and 14.1), and one methine carbon (δ 35.2). The remaining 10 carbons were all methylenes. The molecular formula of malyngolide, therefore, was $C_{16}H_{30}O_3$. The ^1H NMR spectrum revealed a pair of doublets (δ 3.71 and 3.47) for an isolated, oxygen-bearing methylene group, a doublet (δ 1.27) for a methyl group attached to the methine, and a broad multiplet for a single proton adjacent to the carbonyl group (δ 2.40). Since no C=C bonds were present, a δ-, or larger, lactone (~1735 cm^{-1}) seemed the logical choice to satisfy both sites of unsaturation and the positions of the carbonyl absorptions in the IR and ^{13}C NMR spectra. A hydroxyl group (3410 cm^{-1}) had to be attached to the isolated methylene since the signals for the isolated methylene were shifted downfield to a single peak at δ 4.10 in the ^1H NMR spectrum of malyngolide acetate. The lactone oxygen was therefore attached to the quaternary carbon along with the hydroxymethyl group and the alkyl chain. The methine bearing the methyl group was adjacent to the lactone carbonyl since irradiation of the 1 H multiplet at δ 2.40 reduced the methyl doublet to a singlet.

The size of the lactone ring was determined by chemical degradation. Mild base hydrolysis gave a crystalline 1,2-dihydroxy acid which was converted to a keto acid by oxidation with lead tetraacetate. The mass spectral fragmentation of the keto acid indicated that the generated oxo group was on the δ carbon and that its structure was **2**. This meant that the hydroxy and hydroxymethyl groups of the 1,2-dihydroxy acid were also on the δ carbon and that its structure was **3a**. Malyngolide was therefore a δ-lactone.



2, R = C_9H_{19}
4, R = C_2H_5



3a

Since the optical rotations of **2**, $[\alpha]_D$ −8.4° in chloroform, and its methyl ester, $[\alpha]_D$ −7.5° in chloroform, had the same sign as that of methyl 2(*R*)-methyl-5-oxoheptanoate[4] (**4**), $[\alpha]_D$ −16.2° in chloroform, the *R* configuration was assigned to C-2 in **2** and **3a**.

The relative stereochemistry and absolute configuration of malyngolide were established by a lanthanide-induced proton chemical shift (LIS) study. In order to initiate this study it was first necessary to establish the conformation of the δ-lactone ring. X-ray crystallographic studies of δ-lactones had revealed that the C–CO–O–C portion of the ring is planar[5] and that the conformation of the ring is either boat or half-chair.[6] In the case of malyngolide we

(1) Starr, T. J.; Dieg, E. F.; Church, K. K.; Allen M. B. *Tex. Rep. Biol. Med.* **1962**, *20*, 271.
(2) The origin of this name is unclear.
(3) *Lyngbya majuscula* from La Parguera, Puerto Rico, showed good activity against *E. coli* but only a trace or no activity against *M. smegmatis* and *S. aureus*. Burkholder, P. R.; Burkholder, L. M.; Almodovar, L. R. *Bot. Mar.* **1960**, *2*, 149.
(4) Biellman, J. F.; Wenning, R. *Bull. Soc. Chim. Fr.* **1971**, 1676.
(5) McConnell, J. F.; Mathieson, A. McL.; Schoenborn, B. P. *Tetrahedron Lett.* **1962**, 445.
(6) Cheung, K. K.; Overton, K. H.; Sim, G. A. *Chem. Commun.* **1965**, 634.

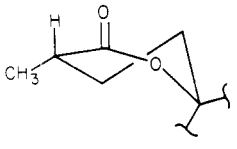
0022-3263/79/1944-4039$01.00/0

Table I. Lanthanide-Induced Shifts and Calculated and Measured Europium-Proton Distances for Malyngolide

assignment[a]	$\Delta\delta$, ppm	r_{calcd}, Å	r_{measd}, Å
H_a on C-2	3.48	4.7	4.9
H_a on C-3	2.24	6.2	5.6
H_e on C-3	2.82	6.1	5.3
H_a on C-4	5.05	4.2	4.3
H_e on C-4	1.96	5.5	5.9
1 H on C-6[b]	2.00	5.7	5.9
2 H on C-7	1.67	6.4	6.3
3 H on C-15	1.51	6.8	6.5

[a] Based on spin-spin decoupling experiments at 220 MHz. [b] Signal becomes a doublet ($|J_{gem}| = 12$ Hz) on irradiation of the C-7 methylene signal.

suspected that the half-chair conformation would be strongly favored because of the 1,4 interactions between the substituents on C-2 and C-5. The position of the lactone carbonyl absorption (~1735 cm^{-1}) in the IR spectrum[6,7] and the presence of a single band at 222 nm in the circular dichroism (CD) curve[8,9] confirmed this assignment. Moreover, the sign of the Cotton effect,[10] $[\theta]_{222}$ −3900, in the CD spectrum indicated that the δ-lactone ring had the absolute stereochemistry shown in **1a** where the methyl group on C-2 was pseudoequatorial. In **1a** the configuration at C-2 was therefore *R* and this determination agreed nicely with the one obtained by chemical degradation.



1a

The induced shifts of the various protons in malyngolide were measured by a stepwise addition of $Eu(fod)_3$ to a deuteriochloroform solution. A 220-MHz ^1H NMR analysis of the solution containing 0.3 equiv of $Eu(fod)_3$ permitted assignments for all the ring-proton signals. Two of these signals, one of them the multiplet for the C-2 methine and the other a doublet of doublets of doublets ($|J| \approx 14$, 12, and 3 Hz) for the axial C-4 proton, underwent the largest shifts. Irradiation of the methyl doublet showed that the C-2 methine was coupled to the two C-3 protons by 11 and 5 Hz, confirming that the C-2 proton was axially oriented. Irradiation of the C-2 methine revealed the positions of the C-3 proton signals; in the decoupled spectrum the signal that had become a broad triplet[11] with $|J| \approx 11$–14 Hz was attributed to the axial C-3 proton. The assignments for the C-3 protons were confirmed by irradiation of the axial C-4 proton. The latter double-resonance experiment also located the signal for the equatorial C-4 proton.

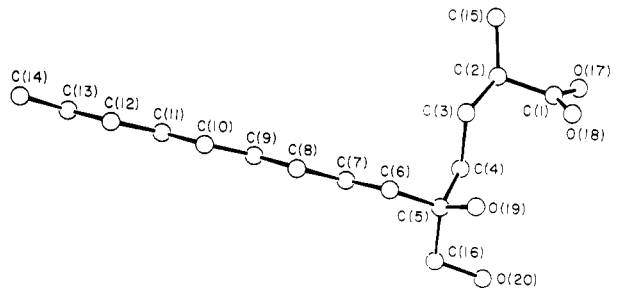
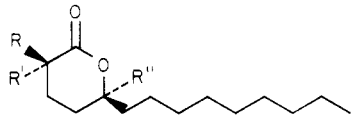


Figure 1. Computer-generated perspective view of 5-hydroxy-5-(hydroxymethyl)-2-methyltetradecanoic acid (**3**). Hydrogens are omitted for clarity.

A graph of chemical shift vs. added $Eu(fod)_3$ was used to determine the shifts induced by 1 equiv of $Eu(fod)_3$, $\Delta\delta$. In order to find the best location for the europium atom, we plotted log $\Delta\delta$ vs. log r_{meas},[12] where r_{meas} is the measured distance between the europium and the proton as determined from a molecular model. The axial protons on C-2 and C-4 exhibited the largest induced shifts for the ring protons, indicating that the europium was on the same side of the lactone ring and that the hydroxymethyl group on C-5 was pseudoequatorial. When the europium was 2.8 Å from the hydroxyl oxygen and above the ring at a distance of 3.0 Å from the ring oxygen, the points fell closest to a straight line of slope −3. A comparison of the measured europium–proton distances with those calculated from the graphical plot of log $\Delta\delta$ and log r_{meas} is given in Table I. From these data it is clear that malyngolide has the *S* configuration at C-5 and the absolute stereochemistry depicted in **1**.

Malyngolide is the most stable C-2 epimer since epimerization at C-2 apparently does not occur during the saponification of **1** to **3**. The related acid **5**, obtained by



5, R = CH_3; R′ = H; R″ = CO_2H
6, R = H; R′ = CH_3; R″ = CO_2H
7, R = CH_3; R′ = H; R″ = CO_2Me
8, R = H; R′ = CH_3; R″ = CO_2Me
9, R = CH_3; R′ = H; R″ = CHO
10, R = H; R′ = CH_3; R″ = CHO

Jones oxidation of **1**, equilibrated to a mixture of **5** and **6** (characterized as the methyl ester **7** and **8**) during either the oxidation or workup. Aldehyde **9**, which was obtained by Moffatt oxidation of **1**, epimerized to a mixture of **9** and **10** upon chromatography on silica gel.

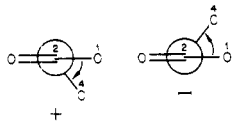
The relative stereochemistry was supported further by a X-ray crystallographic analysis of **3**. A computer-generated perspective drawing of **3** is shown in Figure 1. The X-ray experiment defined only the relative configuration, and the absolute configuration shown conforms to the *R*

(7) Carbonyl absorptions (in CCl_4) between 1730 and 1750 cm^{-1} are typical of half-chair conformations for δ-lactones; absorptions in the 1758–1765 cm^{-1} range are characteristic of boat conformations.[6]

(8) Korver, O. *Tetrahedron* **1970**, *26*, 2391.

(9) CD studies show that the half-chair conformation is more stable than the boat conformation. (+)-5-Decanolide, for example, exists completely in the half-chair conformation at −185 °C, and the CD curve exhibits a negative maximum at 222 nm. At room temperature, however, (+)-5-decanolide exists in both the boat and half-chair conformations, and the CD spectrum displays two maxima, a positive one at 210 nm for the boat and a negative one at 240 nm for the half-chair. The presence of the positive band between 210 and 220 nm for the boat conformation produces a red shift in the negative maximum at temperatures above −185 °C.

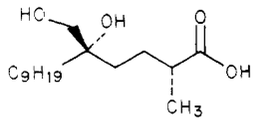
(10) The sign of the Cotton effect of the lactone chromophore is opposite to the sign of the dihedral angle between O(1)C(2)C(3) and C(2)-C(3)C(4). Looking down the C(2)–C(3) bond (Newman projection) of the δ-lactone, a positive dihedral angle is defined as one which requires a clockwise rotation of the C(2)–O(1) bond (in front) to eclipse the C(3)–C(4) bond (in back); conversely, a negative dihedral angle requires a counterclockwise rotation.



(11) This signal is actually an unresolved doublet ($J_{ae} \approx 3$ Hz) of doublets of doublets (J_{aa} and $|J_{gem}| \approx 11$–14 Hz).

(12) (a) Hinckley, C. C. *J. Am. Chem. Soc.* **1969**, *91*, 5160. (b) Hinckley, C. C.; Klotz, M. R.; Patil, F. *Ibid.* **1971**, *93*, 2417. (c) Cockerill, A. F.; Davies, G. L. O.; Harden, R. C.; Rackham, D. M. *Chem. Rev.* **1973**, *73*, 553.

absolute stereochemistry at C-2. The configuration at C-5 is then *S*. In general, bond distances and angles agree well with generally accepted values except for apparent bond shortening toward the methyl terminus of the chain. Such apparent bond shortening can be corrected if the bond distances are corrected with the riding model[13] and is not unusual in structures of this type. The alkyl chain from carbons 5 to 14 is in the fully extended conformation. There is another fully extended portion from carbons 16 to 15 at right angles to this. The "kink" in the structure



3

has the effect of clustering all of the oxygen atoms in the same general area. There is an intermolecular contact of 2.62 Å between O-19 and O-20 which appears to be a hydrogen bond.

Experimental Section

NMR spectra were determined at 100 MHz unless noted otherwise; chemical shifts are expressed as δ units relative to Me_4Si. Optical rotations were recorded on an ETL-NPL (Ericsson Telephone Unlimited) automatic polarimeter. Melting points are uncorrected. Mass spectra were obtained at 70 eV. Elemental analyses were performed by Chemical Analytical Services, University of California, Berkeley.

Isolation. *Lyngbya majuscula* was collected at Kahala Beach, Oahu, in January, 1976. The freeze-dried alga (1.2 kg) was extracted successively with petroleum ether and dichloromethane to give 1.5 and 12.0 g of extract, respectively. A portion (1.1 g) of the dichloromethane extract was applied to a 180 × 2.5 cm column of Sephadex LH-20; elution with hexane–dichloromethane (1:4) gave four fractions. Fraction 4 (128 mg) was passed twice through a column (105 × 2 cm) of Bio-Beads S-X8 with benzene to give 54 mg (0.05% of dried alga) of malyngolide (**1**) as a colorless oil: $[\alpha]_D$ −13° (*c* 2, $CHCl_3$); CD (EtOH) $[\theta]_{220}$ −3900; UV (EtOH) end absorption; IR (CCl_4) 3616, 3428, 1739 sh, 1726 cm^{-1}; IR (neat) 3410, 1730, sh 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.71 (1 H, d, *J* = −12 Hz), 3.47 (1 H, d, *J* = −12 Hz), 3.20 (1 H, br s), 2.40 (1 H, m), 1.45–2.15 (4 H, m), 1.27 (3 H, d, *J* = 6.5 Hz), 1.27 (16 H, br), 0.88 (3 H, br t); ^{13}C NMR (C_6D_6) δ 175.0 (C=O), 86.4 (C—O), 67.4 (CH_2—O), 37.2 (CH_2), 35.2 (CH), 32.0 (CH_2), 29.7 (4 CH_2),[14] 26.3 (CH_2), 25.3 (CH_2), 23.5 (CH_2), 22.7 (CH_2), 17.0 (CH_3), 14.1 (CH_3); MS *m/e* (rel intensity) 239 (100), 223 (10), 211 (95), 155 (69), 143 (80), 115 (28), 111 (31), 95 (47); high-resolution MS *m/e* 239.2020 ($C_{15}H_{27}O_2$ requires 239.2011).

Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.0; H, 11.2. Found: C, 69.6; H, 11.0.

Acetylation of 1. A solution of 42 mg of malyngolide and 15 mg of 4-(*N*,*N*-dimethylamino)pyridine in 1.5 mL of Ac_2O was warmed to 60 °C for 30 min and then allowed to stand at room temperature for 19 h. Workup gave 42 mg of a brown oil which was chromatographed on Bio-Beads S-X8 with benzene to give 35 mg of malyngolide acetate as a colorless oil: $[\alpha]^{29}_D$ −17° (*c* 1, $CHCl_3$); IR (CCl_4) 1742 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.10 (2 H, br s), 2.41 (1 H, m), 2.09 (3 H, s), 1.95–1.55 (5 H, m), 1.30 (3 H, d, *J* = 7 Hz), 1.28 (15 H, br), 0.88 (3 H, br t); MS *m/e* (rel intensity) 269 (<1), 252 (2), 239 (30), 211 (14), 155 (15), 143 (10), 125 (11), 97 (7), 95 (7); high-resolution MS *m/e* 269.2149 ($C_{16}H_{29}O_3$ requires 269.2117), 252.2093 ($C_{16}H_{28}O_2$ requires 252.2089).

Hydrolysis of 1. A solution of 26 mg of malyngolide and 35 g of $Ba(OH)_2$ in 10 mL of 20% aqueous methanol was allowed to stand at 5 °C for 72 h. The methanol was evaporated, and the aqueous suspension was acidified to pH 4 with dilute HCl. Extraction with $CHCl_3$ gave 26 mg of an oily solid. Recrystallization from hexane–acetone gave 13 mg of the dihydroxy acid **3** as fine white needles: mp 70–71 °C; $[\alpha]_D$ −14.6° (*c* 1, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 6.15 (3 H, br), 3.63 (2 H, br s), 2.49 (1 H, m), 2.10–1.50 (6 H, m), 1.26 (14 H, br), 1.23 (3 H, d, *J* = 6.5 Hz), 0.90 (3 H, br t);

Anal. Calcd for $C_{16}H_{32}O_4$: C, 66.6; H, 11.2. Found: C, 66.7; H, 11.1.

Lead Tetraacetate Oxidation of 3. To a solution of crude **3** (44 mg) in dry benzene was added 66 mg of lead tetraacetate. The mixture was stirred at room temperature for 14 h. Filtration and evaporation gave 45 mg of a crude oil. Purification on Sephadex LH-20 ($CHCl_3$–MeOH, 1:1) and recrystallization from hexane gave 12.6 mg of **2** (32%) as fine, colorless needles: mp 59.5–60.5 °C; $[\alpha]_D$ −8.4° (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.41 (5 H, m), 1.83 (2 H, m), 1.52 (2 H, m), 1.25 (12 H, br), 1.18 (3 H, d, *J* = 6.5 Hz), 0.86 (3 H, br t); MS *m/e* (rel intensity) 256 (2), 239 (2), 211 (3), 210 (10), 183 (19), 155 (54), 144 (68), 129 (55), 127 (20), 126 (100), 111 (35), 101 (100), 99 (100); high-resolution MS *m/e* 256.2009 ($C_{15}H_{28}O_3$ requires 256.2039), 238.1929 ($C_{15}H_{26}O_2$ requires 238.1933), 155.1431 ($C_{10}H_{19}O$ requires 155.1436), 101.0591 ($C_5H_9O_2$ requires 101.0603).

Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.3; H, 11.0. Found: C, 70.1; H, 11.1.

The corresponding methyl ester, which was produced during the gel filtration of **3** on Sephadex LH-20 with $CHCl_3$–MeOH, was a colorless oil, $[\alpha]_D$ −7.5° (*c* 1.7, $CHCl_3$).

Jones Oxidation of 1. Malyngolide (39 mg) was dissolved in 5 mL of acetone, and 2.3 mL of Jones reagent[15] was added in five portions to the stirred mixture over 2.5 h. After the mixture was stirred an additional 30 min, methanol was added to consume excess reagent. The mixture was concentrated, diluted with water, and extracted with $CHCl_3$ to give 36 mg of the two epimeric acids **5** and **6** as a colorless oil. Treatment with excess ethereal diazomethane gave 39 mg of a light yellow oil which was subjected to gel filtration on Sephadex LH-20 with $CHCl_3$–MeOH (3:2) to give 29 mg of the two epimeric carbomethoxy lactones **7** and **8** as a colorless oil: IR (CCl_4) 1763, 1745 cm^{-1}; ^1H NMR ($CDCl_3$, several signals doubled) δ 3.79 and 3.67 (3 H, s), 2.70–2.15 (3 H, m), 2.15–1.40 (6 H, m), 1.25 and 1.15 (3 H, d, *J* = 7 Hz), 1.24 (12 H, br), 0.86 (3 H, br t); high-resolution MS *m/e* 298.2151 ($C_{17}H_{30}O_4$ requires 298.2144), 239.2018 ($C_{15}H_{27}O_2$ requires 239.2011).

Moffatt Oxidation of 1. To a stirred solution of 29 mg of malyngolide in 3 mL of benzene and 3 mL of dimethyl sulfoxide was added successively 0.04 mL of pyridine, 0.02 mL of trifluoroacetic acid, and 265 mg of dicyclohexylcarbodiimide.[16] The reaction vessel was sealed and allowed to stand at room temperature for 2.5 h. The mixture was diluted with 15 mL of benzene, and the benzene layer was washed with H_2O (3 × 10 mL) and evaporated to give 59 mg of oily solid which contained only **9** by ^1H NMR analysis. Chromatography on silica gel (10 g, 200–400 mesh) with hexane–$CHCl_3$ (1:9) as the eluant gave 10.5 mg of a mixture of the epimeric aldehydes as a pale yellow oil: ^1H NMR of major epimer **9** ($CDCl_3$) δ 9.60 (1 H, s), 2.40 (1 H, m), 2.12 (1 H, m), 2.00–1.45 (4 H, m), 1.27 (3 H, d, *J* = 7 Hz), 1.25 (15 H, br), 0.87 (3 H, br t); ^1H NMR of minor epimer **10** ($CDCl_3$) δ 9.50 (1 H, s).

X-ray Analysis of 3. Compound **3** crystallized as thin needles by slow evaporation of acetone–isooctane solutions, and preliminary X-ray photographs indicated monoclinic symmetry. Accurate lattice constants, *a* = 19.457 (7), *b* = 5.222 (2), and *c* = 18.263 Å and β = 90.98 (3)°, were obtained from a least-squares fitting of 15 moderate 2θ values. Systematic absences of *hkl* values (missing if *h* + *k* = 2*n*), the known chirality, and a rough density of 1.0 g cm^{-3} were consistent with the space group *C*2 with one molecule of **3** ($C_{16}H_{32}O_4$) per asymmetric unit. All unique diffraction maxima with $2\theta \leq 45°$ were surveyed by using graphite-monochromated Mo Kα radiation (0.71069 Å) and a variable-speed ω-scan technique. Of the 1355 reflections measured in this way, 927 (60%) were judged observed after correcting for Lorentz, polarization, and background effects ($F_o \geq 3\sigma(F_o)$).

The angular dependence of the scattering was removed, and the intensity data were converted to normalized structure factors.[17]

(13) Busing, B. W. R.; Levy, H. A. *Acta Crystallogr.* **1964**, *17*, 142.
(14) Number of carbons obtained by integration of proton noise-decoupled spectrum (decoupler off during delay, no NOE).
(15) Pasto, D. J.; Johnson, C. R. "Organic Structure Determination"; Prentice-Hall: Englewood Cliffs, NJ, 1969; p 362.
(16) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. I, p 305.

A crude phasing model was achieved by a multisolution weighted tangent formula approach. There was some difficulty in deducing a reasonable molecular fragment using these early E syntheses. The scattering is dominated by the long hydrocarbon chain. The two largest normalized structure factors are the 402 (5.00) which defines the orientation of the long alkyl chain and the $80\bar{1}2$ (4.04) which defines the spacing along the chain. All attempts at deducing phases led to E syntheses with infinite alkyl chains and little else. With the aid of model building we were able to select a correct fragment of this chain, and this eventually led to the correct structure. The important consideration turned out to be putting a "kink" in the structure which clustered all of the hydroxyl and carboxyl groups about a crystallographic twofold axis. Full-matrix least-squares refinements have currently converged to a standard crystallographic R value of 0.074 for the observed data. Additional crystallographic material is available as supplementary material.

(17) All crystallographic calculations were done on a Prime 400 computer operated by the Materials Science Center and the Department of Chemistry, Cornell University. The principal programs used were as follows: REDUCE and UNIQUE, data reduction programs, M. E. Leonowicz, Cornell University, 1978; BLS, block-diagonal least-squares refinement, K. Hirotsu, Cornell University, 1978; ORFLS (modified), full-matrix least-squares, W. R. Busing, K. O. Martin, and H. S. Levy, Oak Ridge National Laboratory, Report ORNL-TM-305; ORTEP, crystallographic illustration program, C. Johnson, Oak Ridge National Laboratory, Report ORNL-3794; BOND, structural parameters and errors, K. Hirotsu, Cornell University, 1978; MULTAN-76, direct methods and fast fourier transform, G. Germain, P. Main, and M. Woolfson, University of York.

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Registry No. 1, 71582-80-4; 1 acetate, 71582-81-5; 2 (R′ = H), 71582-82-6; 2 (R′ = CH_3), 71582-83-7; 3, 71582-84-8; 5, 71582-85-9; 6, 71582-86-0; 7, 71582-87-1; 8, 71582-88-2; 9, 71582-89-3; 10, 71582-90-6; Ac_2O, 108-24-7.

Supplementary Material Available: Tables of atomic coordinates, thermal parameters, bond distances, bond angles (4 pages). Ordering information is given on any current masthead page.

Acylation–Cycloalkylation. A New Annelation Route to Eudesmanes

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Condensation of vinylacetyl chloride (3) with 9-chloro-1-*p*-menthene (1) followed by distillation and chromatography gave 4*H*-7-(2′-chloro-1′-methylethyl)-4a,5,6,7,8,8a-hexahydro-4a-methyl-1-naphthalenone (4) (38% yield) and 2*H*-7-(2′-chloro-1′-methylethyl)-3,4,5,6,7,8-hexahydro-4-methyl-1-naphthalenone (9) (33% yield). Catalytic hydrogenation of 4, followed by ketalization, elimination of hydrogen chloride with potassium *tert*-butoxide in Me_2SO, and hydrolysis afforded 7-isopropenyl-4a-methyloctahydro-1-naphthalenone (16). Condensation of 16 with methylenetriphenylphosphorane afforded (+)-β-selinene (17) while reaction with methylmagnesium iodide yielded neointermedeol (18). The structure of ketone 9 was shown by conversion to occidol (22).

Acylation–cycloalkylation[1] provides an annelation route which, unlike the traditional Robinson synthesis,[2] yields a reactive carbonyl function adjacent to a newly created bridgehead position. Herein we illustrate the use of this annelation in the synthesis of the eudesmanes, β-selinene, and neointermedeol. The eudesmane sesquiterpenes are widely distributed in nature,[3] and their synthesis[4] and role in biosynthesis[5] have received considerable attention in recent years.

Our synthetic approach begins with chloride 1,[6] prepared from (+)-limonene (2) by hydroboration[7] followed by treatment of the resulting alcohol with triphenylphosphine and carbon tetrachloride.[8] Condensation of vinylacetyl chloride (3) with chloride 1 by using stannic chloride or aluminum chloride in methylene chloride under a variety of conditions gave negligible amounts of the desired conjugated ketone 4. By contrast, the reaction of 3 with 1-methylcyclohexene, 2,3-dimethyl-2-butene, and 2-methyl-2-butene under comparable conditions afforded ketones 5, 6, and 7 and 8, respectively, in moderate yield.

When the annelation was conducted in nitromethane with aluminum chloride, there was isolated by distillation and chromatography a 38% yield of ketone 4 and a 33%

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