THE MOLECULAR STRUCTURE OF MELAMPODININ-A

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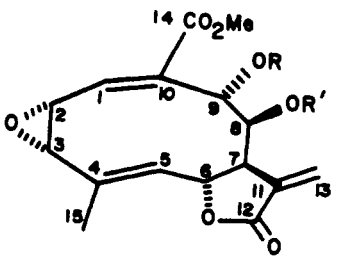
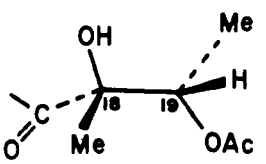
ABSTRACT.—The molecular structure of melampodinin-A (**3**) was determined by single crystal x-ray diffraction. Previous tentative assignments related to the attachment of the 2-hydroxy-2-methyl-3-acetoxybutyrate to C8 as well as the chiralities of the two asymmetric centers of the above ester group, C18(R) and C19(S), were confirmed by the crystallographic study.

Melampodinin-A (**3**) is a common constituent of several *Melampodium* species (1,2) and exhibits considerable *in vivo* inhibitory activity against lymphocytic leukemia (P-388) (2). The structure of melampodinin-A had been previously assigned on the basis of ^{1}H nmr correlations with melampodin-A acetate (**2**) (3,4), a compound with known absolute configuration (5) as determined by chemical



	R	R'
1,	H	Epoxyangelate
2,	Ac	Epoxyangelate
3,	Ac	**A**



A

correlation with melampodin-A (**1**) (4). Previous structural assignments of compound **3** with respect to the sites of attachment of the 2-hydroxy-2-methyl-3-acetoxybutyrate and the acetate moieties to C8 and C9, respectively, were based on ^{1}H nmr shift comparisons with **2** (4). The chirality of the two asymmetric centers of the 2-hydroxy-2-methyl-3-acetoxybutyrate had been tentatively assigned on mechanistic arguments (4). Because of the distinct increased biological activity of melampodinin-A in comparison with melampodin-A acetate (**2**), single crystal x-ray data on melampodinin-A were obtained to eliminate structural uncertainties.

The structure of the basic skeletal arrangement of melampodinin-A closely resembles that of melampodin-A (**1**), as determined by x-ray (5) and neutron diffraction (6). As the absolute configuration of melampodin-A is known (5), our determination establishes the absolute configuration of the two asymmetric centers of the substituent at C8. As seen in figure 1, the configuration at C18

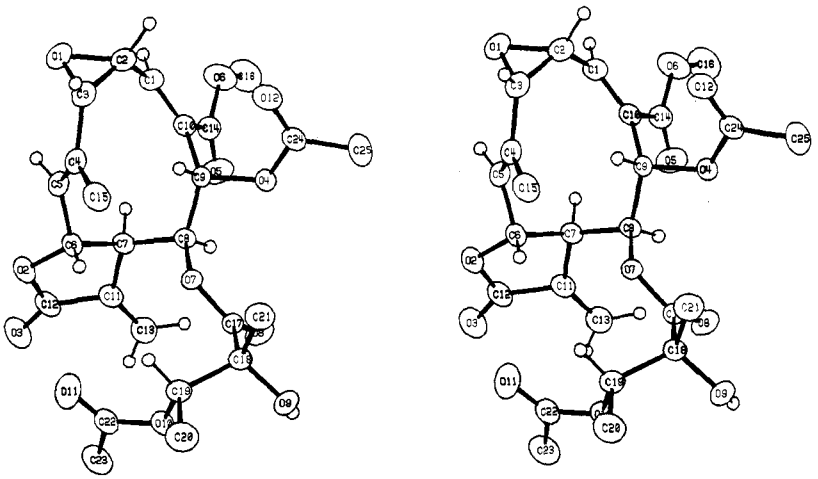


FIG. 1. Stereoscopic representation of the melampodinin-A molecule. Hydrogen atoms of methyl groups have been omitted for clarity.

is R, and that at C19 is S. The bond distances (table 3) and angles (table 2) exhibit excellent agreement with both the x-ray and neutron diffraction determinations of melampodin-A and will not be discussed further here. It is quite striking that the torsion angles (table 4) of the two molecules also agree excellently. The largest difference in an endocyclic torsion angle found by comparing the present structure and the neutron diffraction study (6) is only 4.4° (C10–C1–C2–C3), and the mean difference is 1.7°. That the two molecules exhibit quite different packing and yet nearly identical endocyclic torsion angles attests to the conformational rigidity of the melampolide skeleton.

The most notable intermolecular interaction is a hydrogen bond involving the hydroxyl group O9 as donor and the carbonyl oxygen atom O12 of an acetate

TABLE 1. Coordinates for nonhydrogen atoms.

Atom	X	Y	Z	Atom	X	Y	Z
O1	0.3969(2)	0.5862(0)	0.5151(2)	C7	0.3721(2)	0.2236(4)	0.2556(2)
O2	0.5648(2)	0.3070(3)	0.2738(2)	C8	0.2279(2)	0.2241(3)	0.1925(2)
O3	0.6545(2)	0.1277(3)	0.2476(2)	C9	0.1655(2)	0.3079(3)	0.2548(2)
O4	0.0344(1)	0.2616(2)	0.1958(1)	C10	0.2200(2)	0.2917(4)	0.3907(2)
O5	0.2294(2)	0.0601(3)	0.3838(2)	C11	0.4369(2)	0.1228(4)	0.2149(2)
O6	0.1999(2)	0.1514(3)	0.5309(2)	C12	0.5628(2)	0.1789(4)	0.2447(2)
O7	0.1829(1)	0.2793(2)	0.0719(1)	C13	0.3997(3)	0.0088(4)	0.1628(3)
O8	0.0932(2)	0.0892(2)	−0.0187(2)	C14	0.2173(3)	0.1561(4)	0.4327(2)
O9	−0.0182(2)	0.2018(2)	−0.2383(2)	C15	0.2759(3)	0.6001(4)	0.1741(3)
O10	0.2500(2)	0.2211(3)	−0.1524(2)	C16	0.1915(4)	0.0242(6)	0.5761(3)
O11	0.4275(2)	0.3293(4)	−0.0347(3)	C17	0.1129(2)	0.2022(3)	−0.0240(2)
O12	−0.0245(2)	0.4373(3)	0.2656(2)	C18	0.0609(2)	0.2820(3)	−0.1418(2)
				C19	0.1722(2)	0.3345(4)	−0.1609(2)
C1	0.2643(3)	0.3892(4)	0.4710(2)	C20	0.1323(3)	0.3990(5)	−0.2816(3)
C2	0.2701(3)	0.5338(4)	0.4596(3)	C21	−0.0199(3)	0.3928(4)	−0.1337(3)
C3	0.3196(3)	0.6109(4)	0.3893(3)	C22	0.3750(2)	0.2336(4)	−0.0916(2)
C4	0.3540(3)	0.5477(4)	0.2999(3)	C23	0.4420(3)	0.1140(6)	−0.1020(3)
C5	0.4350(2)	0.4497(4)	0.3319(2)	C24	−0.0525(2)	0.3394(4)	0.2052(2)
C6	0.4364(2)	0.3504(3)	0.2455(2)	C25	−0.1829(3)	0.2864(5)	0.1343(3)

TABLE 2. Selected bond angles of melampodinin-A.

Atoms	Angle (°)	Atoms	Angle (°)
C2–O1–C3	62.0(2)	C8–C9–C10	115.7(2)
C6–O2–C12	109.7(2)	C1–C10–C9	124.8(3)
C2–C1–C10	133.7(3)	C1–C10–C14	120.1(3)
O1–C2–C1	114.0(3)	C9–C10–C14	115.1(2)
O1–C2–C3	58.4(2)	C7–C11–C12	105.1(3)
C1–C2–C3	129.2(3)	C7–C11–C13	131.9(3)
O1–C3–C2	59.6(2)	C12–C11–C13	123.0(3)
O1–C3–C4	118.5(3)	O2–C12–O3	120.7(3)
C2–C3–C4	121.4(3)	O2–C12–C11	109.6(2)
C3–C4–C5	120.9(3)	O3–C12–C11	129.7(3)
C3–C4–C15	111.5(3)	O7–C17–O8	125.3(2)
C5–C4–C15	127.2(3)	O7–C17–C18	110.3(2)
C4–C5–C6	123.3(2)	O8–C17–C18	124.5(2)
O2–C6–C5	112.6(2)	O9–C18–C17	108.9(2)
O2–C6–C7	103.0(2)	O9–C18–C19	111.3(2)
C5–C6–C7	110.5(2)	O9–C18–C21	107.2(2)
C6–C7–C8	116.0(2)	C17–C18–C19	109.1(2)
C6–C7–C11	101.7(2)	C17–C18–C21	109.2(2)
C8–C7–C11	117.1(2)	C19–C18–C21	111.1(3)
O7–C8–C7	109.4(2)	O10–C19–C18	105.7(2)
O7–C8–C9	105.2(2)	O10–C19–C20	109.9(2)
C7–C8–C9	115.2(2)	C18–C19–C20	113.7(2)
O4–C9–C8	102.2(2)		

TABLE 3. Bond distances in melampodinin-A.

Atoms	Distance (Å)	Atoms	Distance (Å)
O1–C2	1.444(3)	C2–C3	1.479(5)
O1–C3	1.427(3)	C3–C4	1.490(4)
O2–C6	1.468(3)	C4–C5	1.320(4)
O2–C12	1.357(4)	C4–C15	1.505(4)
O3–C12	1.193(3)	C5–C6	1.481(4)
O4–C9	1.465(2)	C6–C7	1.540(4)
O4–C24	1.348(3)	C7–C8	1.524(3)
O5–C14	1.196(4)	C7–C11	1.504(4)
O6–C14	1.323(3)	C8–C9	1.547(3)
O6–C16	1.438(5)	C9–C10	1.514(3)
O7–C8	1.453(3)	C10–C14	1.486(4)
O7–C17	1.352(3)	C11–C12	1.483(4)
O8–C17	1.187(3)	C11–C13	1.309(4)
O9–C18	1.402(3)	C17–C18	1.536(3)
O10–C19	1.457(3)	C18–C19	1.539(3)
O10–C22	1.331(3)	C18–C21	1.517(4)
O11–C22	1.202(4)	C19–C20	1.501(4)
O12–C24	1.203(3)	C22–C23	1.496(5)
C1–C2	1.491(5)	C24–C25	1.492(4)
C1–C10	1.336(4)		

substituent as acceptor. The hydrogen bond links molecules related by a screw axis in the b direction. It is nonlinear, having an O · · · O distance of 2.802(3) Å, and an O–H · · · O angle of approximately 154°. The epoxy oxygen atom O1 forms a close contact (O1 · · · C12 2.947(3) Å) with the lactone ring of an adjoining molecule.

EXPERIMENTAL

Crystals of melampodinin-A were grown from dichloromethane solution. A fragment of dimensions 0.40 x 0.44 x 0.72 mm, cut from a large single crystal, was used for data collection. Intensity measurements were made by use of MoKα radiation on an Enraf-Nonius CAD4 automatic diffractometer equipped with a graphite monochromator. *Crystal Data:* $C_{25}H_{30}O_{12}$, MW=522.5, monoclinic space group $P2_1$, $a=11.862(3)$, $b=10.232(3)$, $c=12.382(2)$ Å, $\beta=116.95(2)°$, $Z=2$, $d_c=1.295$ g cm^{-3}, $\lambda=0.71073$ Å, μ(MoKα)=1.12 cm^{-1}. Data were collected

TABLE 4. Selected torsion angles for melampodinin-A.

Atom 1	Atom 2	Atom 3	Atom 4	Angle (°)
C10	C1	C2	C3	− 51.5
C1	C2	C3	C4	10.2
C2	C3	C4	C5	− 54.9
C3	C4	C5	C6	154.8
C4	C5	C6	C7	−101.2
C5	C6	C7	C8	78.9
C6	C7	C8	C9	− 72.5
C7	C8	C9	C10	− 45.7
C8	C9	C10	C1	124.7
C9	C10	C1	C2	3.6
O2	C6	C7	C11	− 32.4
C6	C7	C11	C12	27.2
C7	C11	C12	O2	− 12.1
C11	C12	O2	C6	− 9.7
C12	O2	C6	C7	26.9

by ω-2θ scans of variable speed designed to yield $I \simeq 50\sigma(I)$ for all significant reflections. Background measurements were made for each reflection, and intensities were corrected for background. Periodic remeasurement of standard reflections indicated no crystal decay during data collection. Of the 3246 data in one quadrant having $2 \leq 2\theta \leq 53°$, 1979 had $I > 3\sigma(I)$, and were used in the refinement.

The structure was solved by direct methods program MULTAN78 (7), completed by Fourier techniques, and refined by least squares methods to $R = 0.035$. Hydrogen atoms were located in difference maps but were not refined. Coordinates for nonhydrogen atoms are listed in table 1; hydrogen atom coordinates and anisotropic thermal parameters can be obtained from the authors.

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