Crystal and Molecular Structure of Melampodin B, a 4,5-*cis*-9,10-*trans*-Germacranolide Sesquiterpene Dilactone

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The crystal and molecular structure of melampodin B, $C_{17}H_{18}O_7$, has been determined by single crystal *X*-ray diffraction. Crystals are monoclinic, $P2_1$, a = 9.714(4), b = 6.922(1), c = 12.503(1) Å, β = 106.76(1)°, Z = 2. The structure was refined to an R value of 3.0% over 1 871 total reflections. The cyclodeca-4,5-*cis*-9,10-*trans*-diene ring is in a conformation theoretically derivable from a cyclodeca-4,5-*cis*-1,10-*cis*-diene precursor, as determined by empirical force field calculations. Lactone rings are fused to the cyclodecadiene at C(6)–C(7) and at C(8)–C(10). Intermolecular hydrogen bonds between the hydroxy group and a lactone carbonyl oxygen atom link molecules in the solid.

MEMBERS of the white-rayed daisy complex of the genus *Melampodium* (Compositae, Heliantheae) have been a rich source of various configurational types of germacranolide sesquiterpene lactones.[1] Investigations of *Melampodium leucanthum*, *M. cinereum*, and *M. argophyllum* have led to the isolation of melampolides,[2-7] 1(10)-*cis*-4,5-*cis*-germacranolides and their biogenetic derivatives[8,9] as well as biomodified germacranolide dilactones of the melampodin B type.[10,11]

Our previous structural studies of the melampodin B skeleton (Figure 1) were based mainly on n.m.r. spectral

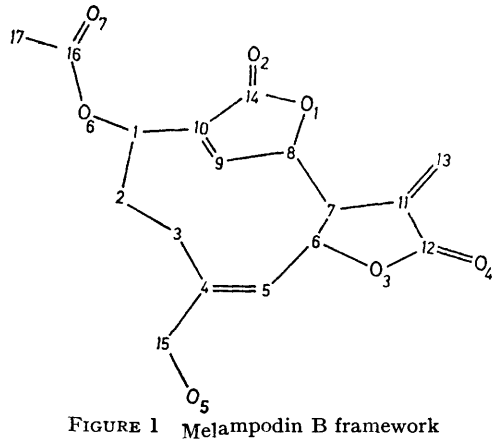

FIGURE 1 Melampodin B framework

assignments. Whereas the basic skeletal arrangement of melampodin B could be clearly established from n.m.r. parameters, the stereochemistry of the 4,5-double bond could not be unambiguously determined. It was tentatively assigned a *trans*-configuration on the basis of its co-occurrence with melampodin A, a melampolide of known absolute configuration.[2] However, Herz's empirical criterion,[12] applied to the 15-H absorption at δ 9.49 p.p.m. in the aldehyde derivative of melampodin B, indicated a 4,5-*cis*-configuration. The *X*-ray structure determination of melampodin B was carried out to resolve this ambiguity.

EXPERIMENTAL

Crystals of melampodin B were grown by slow cooling of an acetonitrile solution. A well formed crystal of approximate dimensions 0.3 × 0.3 × 0.2 mm was mounted on a glass fibre in random orientation on an Enraf–Nonius CAD-4 diffractometer. The *X*-ray source was set at a take-off angle of 3.8° with respect to the graphite monochromator. Lattice parameters and orientation were determined at 22 ± 2 °C from least-squares refinement of 15 accurately centred reflections having $2\theta > 19°$.

Crystal Data.—$C_{17}H_{18}O_7$, M = 334. Monoclinic, a = 9.714(4), b = 6.922(1), c = 12.503(1) Å, β = 106.76(1)°, Z = 2, D_c = 1.38 g cm^{-3}, U = 805.0 Å^3. Mo-K_α radiation, λ = 0.710 73 Å, μ = 1.16 cm^{-1}. Space group $P2_1$ or $P2_{1/m}$ from systematic absences $0k0$, k odd. Final solution dictates $P2_1$.

The intensities of 2 297 unique reflections in two octants of reciprocal space ($4° < 2\theta < 58°$) were measured using the ω—2θ scan described elsewhere.[8] Two reflections were remeasured periodically throughout data collection, and since these intensities decreased uniformly to *ca.* 95% of their initial values a linear decay correction was applied to all data. The variance of each intensity was estimated as $\sigma(I)^2 = I_t + I_b + (0.02I_t)^2$, where I_t is the total count and I_b is the estimated background. Lorentz and polarization corrections were applied, but no absorption correction was made.

Structure Solution and Refinement.—The structure was solved by the direct phasing procedure of MULTAN74.[13] Use of 3 500 Σ_2 relationships over 400 highest E values led to 64 phase sets. The set with the highest combined figure of merit (f.o.m.) yielded an E map showing 21 of the 23 non-hydrogen atoms. It is worthy of note that the high value of the combined f.o.m. was due to the very low value of ψ_0,[14] whereas the correct phase set ranked seventh in terms of the residual, and fiftieth in terms of the absolute f.o.m.

Combinations of least-squares refinement,† difference Fourier synthesis, and positional calculations were used to locate all atoms in the molecule. The matrix of the final model was partitioned into two blocks, one containing the positional parameters of all 42 atoms and the other containing the thermal parameters (H isotropic, C and O anisotropic) and scale factor. In addition to the 1 305 reflections for which $I > 3\sigma(I)$, 566 low intensity reflections were included in the final refinement since their calculated F values were greater than observed. Refinement converged to R 0.030 and R_w 0.020, with goodness-of-fit parameter of 0.71.

† Least-squares minimizes the function $\Sigma w\Delta^2$ where $\Delta = ||F_o| - |F_c||$ and $w = \sigma(F_o)^{-2}$. The residual factors are $R = \Sigma\Delta/\Sigma|F_o|$ and $R_w = (\Sigma w\Delta^2/\Sigma w|F_o|^2)^{\frac{1}{2}}$. The goodness-of-fit parameter is $[\Sigma w\Delta^2/(N_o - N_v)]^{\frac{1}{2}}$ where N_o is the number of reflections and N_v the number of adjustable parameters. All sums are over the N_o reflections.

RESULTS AND DISCUSSION

Atomic parameters are listed in Table 1, crystal and molecular structural parameters in Table 2, and torsion angles in Table 3. Observed and calculated structure

TABLE 1

Atomic positional ($\times 10^4$) and thermal parameters (H $\times 10^3$ and $\times 10^2$)

Atom	X	Y	Z	U
C(1)	3 636(2)	586(5)	1 093(2)	
C(2)	3 562(3)	1 990(5)	2 018(2)	
C(3)	4 950(3)	3 280(5)	2 419(2)	
C(4)	5 813(2)	2 885(4)	3 624(2)	
C(5)	7 081(2)	2 008(5)	3 975(2)	
C(6)	7 994(2)	1 226(5)	3 289(2)	
C(7)	8 212(2)	−997(5)	3 328(2)	
C(8)	7 125(3)	−2 048(5)	2 374(2)	
C(9)	5 613(2)	−1 509(5)	2 334(2)	
C(10)	5 017(2)	−526(4)	1 411(2)	
C(11)	9 770(2)	−1 189(5)	3 333(2)	
C(12)	10 472(3)	685(5)	3 745(2)	
C(13)	10 424(3)	−2 634(6)	2 994(3)	
C(14)	6 038(2)	−441(5)	740(2)	
C(15)	5 075(3)	3 624(5)	4 451(2)	
C(16)	1 839(2)	−1 476(5)	−91(2)	
C(17)	707(3)	−2 972(6)	−76(3)	
O(1)	7 280(2)	−1 377 [a]	1 314(1)	
O(2)	5 924(2)	306(4)	−151(1)	
O(3)	9 468(2)	2 014(4)	3 771(1)	
O(4)	11 743(2)	1 074(4)	4 057(1)	
O(5)	5 892(2)	3 471(4)	5 593(1)	
O(6)	2 430(2)	−750(4)	951(1)	
O(7)	2 192(2)	−988(4)	−895(1)	
H(1)	352(2)	125(3)	33(1)	24(6)
H(21)	259(2)	294(4)	172(2)	58(8)
H(22)	340(2)	126(3)	265(1)	30(6)
H(31)	557(2)	301(3)	191(2)	40(7)
H(32)	456(2)	477(4)	235(2)	63(8)
H(5)	756(2)	186(3)	479(2)	34(6)
H(6)	766(2)	174(3)	253(1)	20(5)
H(7)	808(2)	−147(3)	411(2)	36(6)
H(8)	728(2)	−346(3)	238(2)	45(7)
H(9)	520(2)	−178(3)	300(1)	28(6)
H(131)	991(2)	−391(4)	270(2)	78(9)
H(132)	1 152(2)	−244(4)	302(2)	66(8)
H(151)	474(2)	499(4)	423(2)	46(7)
H(152)	404(3)	291(4)	438(2)	82(9)
H(171)	−10(4)	−232(6)	53(3)	188(16)
H(172)	0(4)	−308(7)	−94(3)	200(17)
H(173)	105(3)	−409(5)	29(3)	128(13)
H(50)	666(2)	416(4)	574(2)	102(11)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	37(1)	39(2)	29(1)	−10(1)	3(1)	−1(1)
C(2)	32(1)	42(2)	42(2)	−1(1)	7(1)	−2(1)
C(3)	38(1)	32(2)	35(1)	0(1)	5(1)	−1(1)
C(4)	35(1)	27(2)	31(1)	−8(1)	8(1)	−5(1)
C(5)	34(1)	41(2)	25(1)	−2(1)	5(1)	−6(1)
C(6)	28(1)	41(2)	32(1)	−2(1)	5(1)	−5(1)
C(7)	34(1)	41(2)	31(1)	1(1)	11(1)	−3(1)
C(8)	44(2)	32(2)	40(2)	−3(1)	13(1)	−2(1)
C(9)	34(1)	32(2)	41(1)	−8(1)	14(1)	−7(1)
C(10)	33(1)	31(2)	28(1)	−8(1)	8(1)	−6(1)
C(11)	38(1)	50(2)	32(1)	5(2)	7(1)	−3(1)
C(12)	41(2)	54(2)	38(2)	0(2)	13(1)	−3(2)
C(13)	47(2)	65(2)	66(2)	8(2)	12(2)	−17(2)
C(14)	41(2)	41(2)	32(1)	−11(1)	7(1)	−14(1)
C(15)	39(1)	41(2)	41(1)	1(1)	10(1)	−6(2)
C(16)	39(2)	39(2)	50(2)	4(2)	−2(1)	−7(2)
C(17)	47(2)	57(2)	88(2)	−21(2)	9(2)	−14(2)
O(1)	45(1)	47(1)	33(1)	−3(1)	16(1)	−11(1)
O(2)	58(1)	69(1)	30(1)	−8(1)	14(1)	0(1)
O(3)	31(1)	46(1)	54(1)	−5(1)	11(1)	−12(1)
O(4)	30(1)	70(2)	73(1)	−5(1)	12(1)	−6(1)
O(5)	47(1)	53(1)	34(1)	−5(1)	16(1)	−9(1)
O(6)	37(1)	48(1)	40(1)	−12(1)	6(1)	−7(1)
O(7)	88(1)	57(2)	41(1)	−12(1)	7(1)	−8(1)

[a] Fixed to define the origin of the unit cell.

TABLE 2

Interatomic distances (Å) and angles (°)

(*a*) Distances

C(1)–C(2)	1.528(4)	C(8)–O(1)	1.453(4)
C(1)–C(10)	1.498(5)	C(9)–C(10)	1.321(6)
C(1)–O(6)	1.463(4)	C(10)–C(14)	1.473(7)
C(2)–C(3)	1.574(6)	C(11)–C(12)	1.487(5)
C(3)–C(4)	1.523(9)	C(11)–C(13)	1.319(4)
C(4)–C(5)	1.329(5)	C(12)–O(3)	1.348(4)
C(4)–C(15)	1.507(6)	C(12)–O(4)	1.213(5)
C(5)–C(6)	1.501(6)	C(14)–O(1)	1.375(7)
C(6)–C(7)	1.552(5)	C(14)–O(2)	1.204(3)
C(6)–O(3)	1.488(7)	C(15)–O(5)	1.423(8)
C(7)–C(8)	1.530(9)	C(16)–C(17)	1.515(5)
C(7)–C(11)	1.517(4)	C(16)–O(6)	1.359(6)
C(8)–C(9)	1.502(4)	C(16)–O(7)	1.200(5)

(*b*) Angles

C(2)–C(1)–C(10)	111.1(2)	C(1)–C(10)–C(9)	129.1(2)
C(2)–C(1)–O(6)	106.4(2)	C(1)–C(10)–C(14)	121.8(2)
C(10)–C(1)–O(6)	109.4(2)	C(9)–C(10)–C(14)	108.7(2)
C(1)–C(2)–C(3)	112.3(2)	C(7)–C(11)–C(12)	106.4(2)
C(2)–C(3)–C(4)	113.0(2)	C(7)–C(11)–C(13)	129.6(3)
C(3)–C(4)–C(5)	127.0(2)	C(12)–C(11)–C(13)	123.9(2)
C(3)–C(4)–C(15)	112.5(2)	C(11)–C(12)–O(3)	109.9(2)
C(5)–C(4)–C(15)	120.5(2)	C(11)–C(12)–O(4)	128.9(3)
C(4)–C(5)–C(6)	128.3(2)	O(3)–C(12)–O(4)	121.1(3)
C(5)–C(6)–C(7)	115.9(2)	C(10)–C(14)–O(1)	108.5(2)
C(5)–C(6)–O(3)	107.1(2)	C(10)–C(14)–O(2)	130.3(2)
C(7)–C(6)–O(3)	104.1(2)	O(1)–C(14)–O(2)	121.1(2)
C(6)–C(7)–C(8)	112.9(2)	C(4)–C(15)–O(5)	115.1(2)
C(6)–C(7)–C(11)	102.3(2)	C(17)–C(16)–O(6)	110.4(3)
C(8)–C(7)–C(11)	115.1(2)	C(17)–C(16)–O(7)	125.9(3)
C(7)–C(8)–C(9)	110.9(2)	O(6)–C(16)–O(7)	123.7(3)
C(7)–C(8)–O(1)	109.2(2)	C(8)–O(1)–C(14)	108.7(2)
C(9)–C(8)–O(1)	104.3(2)	C(6)–O(3)–C(12)	111.0(2)
C(8)–C(9)–C(10)	109.6(2)	C(1)–O(6)–C(16)	116.9(2)

(*c*) Intermolecular contacts (H $\cdots$ H < 2.4 Å, H $\cdots$ O < 2.6 Å) [a]

O(5) $\cdots$ O(4)^{I}	2.851(4)	H(152) $\cdots$ O(4)^{III}	2.493(8)
H(50) $\cdots$ O(4)^{I}	2.003(6)	H(151) $\cdots$ O(5)^{IV}	2.516(10)
H(50) $\cdots$ H(132)^{I}	2.292(12)	H(1) $\cdots$ O(1)^{V}	2.570(6)
H(9) $\cdots$ O(5)^{II}	2.357(8)		

[a] Symmetry operations are: (I) $2-x, y+\frac{1}{2}, 1-z$; (II) $1-x, y-\frac{1}{2}, 1-z$; (III) $x-1, y, z$; (IV) $1-x, y+\frac{1}{2}, 1-z$; (V) $1-x, y+\frac{1}{2}, -z$.

TABLE 3

Torsion angles (°)

C(10)–C(1)–C(2)–C(3)	51	C(11)–C(7)–C(8)–O(1)	−56
O(6)–C(1)–C(2)–C(3)	170	C(6)–C(7)–C(11)–C(12)	22
C(2)–C(1)–C(10)–C(9)	51	C(6)–C(7)–C(11)–C(13)	−155
C(2)–C(1)–C(10)–C(14)	−120	C(8)–C(7)–C(11)–C(12)	145
O(6)–C(1)–C(10)–C(9)	−66	C(8)–C(7)–C(11)–C(13)	−32
O(6)–C(1)–C(10)–C(14)	122	C(7)–C(8)–C(9)–C(10)	113
C(2)–C(1)–O(6)–C(16)	149	O(1)–C(8)–C(9)–C(10)	−4
C(10)–C(1)–O(6)–C(16)	−91	C(7)–C(8)–O(1)–C(14)	−115
C(1)–C(2)–C(3)–C(4)	−115	C(9)–C(8)–O(1)–C(14)	3
C(2)–C(3)–C(4)–C(5)	109	C(8)–C(9)–C(10)–C(1)	−169
C(2)–C(3)–C(4)–C(15)	−71	C(8)–C(9)–C(10)–C(14)	3
C(3)–C(4)–C(5)–C(6)	1	C(1)–C(10)–C(14)–O(1)	172
C(15)–C(4)–C(5)–C(6)	−178	C(1)–C(10)–C(14)–O(2)	−7
C(3)–C(14)–C(15)–O(5)	−174	C(9)–C(10)–C(14)–O(1)	−1
C(5)–C(4)–C(15)–O(5)	6	C(9)–C(10)–C(14)–O(2)	180
C(4)–C(5)–C(6)–C(7)	−115	C(7)–C(11)–C(12)–O(3)	−12
C(4)–C(5)–C(6)–O(3)	129	C(7)–C(11)–C(12)–O(4)	167
C(5)–C(6)–C(7)–C(8)	94	C(13)–C(11)–C(12)–O(3)	165
C(5)–C(6)–C(7)–C(11)	−142	C(13)–C(11)–C(12)–O(4)	−17
O(3)–C(6)–C(7)–C(8)	149	C(11)–C(12)–O(3)–C(6)	−5
O(3)–C(6)–C(7)–C(11)	−24	O(4)–C(12)–O(3)–C(6)	177
C(5)–C(6)–O(3)–C(12)	142	C(10)–C(14)–O(1)–C(8)	−1
C(7)–C(6)–O(3)–C(12)	19	O(2)–C(14)–O(1)–C(8)	177
C(6)–C(7)–C(8)–C(9)	−54	C(17)–C(16)–O(6)–C(1)	176
C(6)–C(7)–C(8)–O(1)	61	O(7)–C(16)–O(6)–C(1)	−5
C(11)–C(7)–C(8)–C(9)	−171		

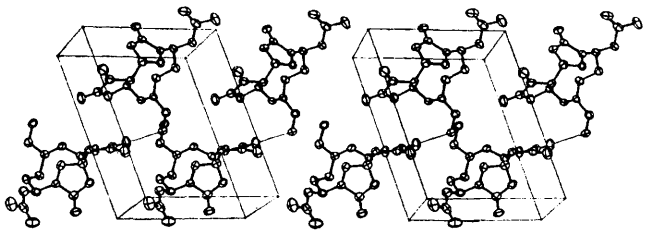

FIGURE 2 Stereoscopic diagram of the packing of melampodin B molecules in the unit cell

factors (×10) are given in Supplementary Publication No. SUP 22819 (28 pp.).*

The unit cell (Figure 2) contains two discrete molecules related by the screw axis, and each molecule (Figure 3) consists of a cyclodecadiene ring (A), a five-membered α-methylene-γ-lactone (B) *trans*-fused to ring A at C(6) and C(7), and a five-membered αβ-unsaturated γ-lactone ring (C) condensed at C(8) and C(10) and oriented axially towards the β-face of ring A. While the absolute configuration was not determined experimentally, we believe the stereochemistry shown in Figure 3 is correct, as discussed below.

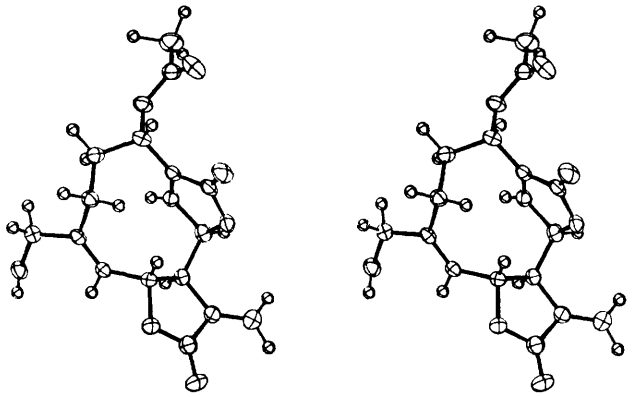

FIGURE 3 Stereoscopic diagram of the β-face of melampodin B

Ring A.—The cyclodeca-1-*cis*,6-*trans*-diene ring differs from the usual germacra-1,5-diene ring system, from which we assume melampodin B to be derived. Indeed, the endocyclic torsion angle pattern of melampodin B resembles that of eupaformonin, a germacra-1(10)-*trans*-4,5-*cis*-diene of the heliangolide type.[15] The greatest deviations involve C(1) and C(9), and consideration of Figure 4 suggests that shift of the *trans*-double bond between the 9,10 and 10,1 positions, with appropriate adjustment of C(9) and C(1), could bring the two cyclodecadiene rings into greater coincidence. Thus, since the absolute configuration of eupaformonin has been determined experimentally and is as shown in Figure 4, by analogy we believe the absolute stereochemistry of melampodin B to be 1*S*,6*R*,7*S*,8*R*. In addition, this arrangement places the C(7) substituent in the β-orientation, in universal agreement with all other germacranolides.

* See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1979, Index Issue.

By the foregoing argument we do not suggest that the biogenetic precursor to melampodin B is a helianogolide, but merely a germacranolide of some type. In fact, assuming the energetically favoured pathway necessitates minimum intramolecular rearrangement so that the precursor and product conformations closely resemble one another, the melampodin B precursor may well be a *cis-cis*-germacradiene. While the existence of this type of germacranolide has not been demonstrated as yet by

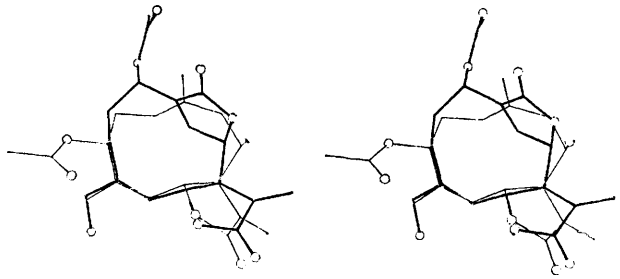

FIGURE 4 Melampodin B (heavy lines) and eupaformonin fitted by least squared distances between C(2)—(7) and C(10)

X-ray analysis, n.m.r. evidence has been presented.[7] We have found a minimum energy conformer of cyclodeca-1-*cis*,5-*cis*-diene from empirical force field calculations † which closely resembles melampodin B: the root-mean-square deviation of endocyclic torsion angles $\Delta\Omega$ $(=[\Sigma(\Delta\omega)^2/10]^{\frac{1}{2}})$ averages 27° (Table 4). By the same measure, eupaformonin differs from melampodin B by 67°.

TABLE 4

Endocylic torsion angles (°): I, melampodin B; II, eupaformonin; III, cyclodeca-1-*cis*,5-*cis*-diene by MMI; IV cyclodeca-1-*cis*,5-*cis*-diene by QCFF; V, tamaulipin A

	Ring A			
ω	I	II	III	IV
10,1	51	168	−1	−1
1,2	51	−80	91	96
2,3	−115	−58	−106	−112
3,4	109	92	91	96
4,5	1	4	−1	−1
5,6	−115	−124	−126	−119
6,7	94	135	99	103
7,8	−54	−80	−47	−59
8,9	113	61	99	103
9,10	−169	−96	−126	−119

	Ring B			Ring C	
ω	I	II	V	ω	I
6,7	−24	14	−24	8,9	−4
7,11	22	−12	21	9,10	3
11,12	−12	6	−10	10,14	−1
12,O	−5	4	−6	14,O	−1
O,6	19	−12	19	O,8	3
C=C–C=O	−17	+9	−10		
C.d.	−277	+264	−260		

† The conformation according to Allinger's (MMI) program [16] differs slightly from that of Warshel and Levitt's (QCFF) [17] with $\Delta\Omega$ 6°. White considered two dissimilar conformers of cyclodeca-1-*cis*,5-*cis*-diene (ref. 18, Figures 6g and f). Both MMI and QCFF agree that conformation (6g) is lowest in energy. The relative energy (kcal mol^{-1}) of (6f) is: 0.05 (White), 0.36 (MMI), 1.15 (QCFF). The relative energy of the melampodin B conformer is: 1.52 (MMI), 0.83 (QCFF).

Ring B.—The five-membered lactone ring at C(6) and C(7) is a highly non-planar ($\Sigma|\omega|$ 82°) twist-envelope with significant torsional asymmetry (ΔC_2 5.4°). Atom C(6) is at the flap and is elevated above the mean plane of the other four atoms toward the β face. This stereochemistry is almost identical to that of the lactone ring in tamaulipin A,[19] but just opposite that observed in eupaformonin (Table 4). Since the chirality of the C=C–C=O chromophore determines the sign of the Cotton effect for the n–π* transition, these measures are also shown in Table 4, and are consistent with the assigned stereochemistry of melampodin B.

Ring C.—The conformation of this lactone is similar to that of ring B but much flatter ($\Sigma|\omega|$ 12°) and more symmetric (ΔC_2 0°). The chromophore is maximally conjugated (ω 180°), and while the bond length of C(10)–C(14) [1.473(7) Å] is slightly shorter than the corresponding C(11)–C(12) [1.486(5) Å], suggestive of this conjugation, the difference is not statistically significant. All other bonds in the molecule are normal except for the bond angles imposed on the 9,10 double bond by ring C.

Hydrogen Bonding.—In the solid state, molecules of melampodin B are linked in spiral chains by hydrogen bonds between the hydroxy group on C(15) and the carbonyl oxygen O(4) of lactone ring B.

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