Phytochemistry, Vol. 26, No. 3, pp 687–696, 1987
Printed in Great Britain

0031 9422/87 $3.00 + 0.00

SYNTHESIS AND BIOLOGICAL ACTIVITY OF MIMICS OF PM-TOXINS, THE HOST-SPECIFIC CORN-PATHOTOXIN PRODUCED BY *PHYLLOSTICTA MAYDIS*

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(*Received for publication* 18 *August* 1986)

Key Word Index—*Phyllosticta maydis*; cms-T corn; yellow leaf blight; host-specific pathotoxin; PM-toxin A; synthesis; structure activity relationships; mitochondria; NADH oxidation; malate oxidation.

Abstract—To establish structure activity relationships, 12 mimics of PM-toxin A, a component of the host-specific corn pathotoxin produced by *Phyllosticta maydis*, have been synthesized as stereoisomeric mixtures. All the mimics synthesized have four β-ketol groups spaced by varying lengths of methylene chains or by a 1,3-diene chain. Mimics with the shorter methylene side-spacers or with the diene side-spacers are 30- to 300-fold less toxic than the native toxin, but the remaining compounds are equally or more toxic than the native toxin. These results can be accounted for by postulating that intramolecular associations at the β-ketol groups may yield two types of cage structure with active and less active conformations.

INTRODUCTION

PM-toxins [1–3], isolated from the cultured medium of *Phyllosticta maydis*, the causal fungus of yellow leaf blight disease of corn, consist of 10–12 components, of which the four main ones (C_{33} and C_{34}) have been purified and structurally determined to be a group of long carbon-chain polyketols (Fig. 1). Each component exhibits almost equal host-selective toxicity (10^{-8} to 10^{-9} M) toward susceptible corn with Texas-male sterile cytoplasm (cms-T corn), but none are toxic on resistant corn with normal fertile cytoplasm (N corn) at 10^{-5} M. PM-toxin closely

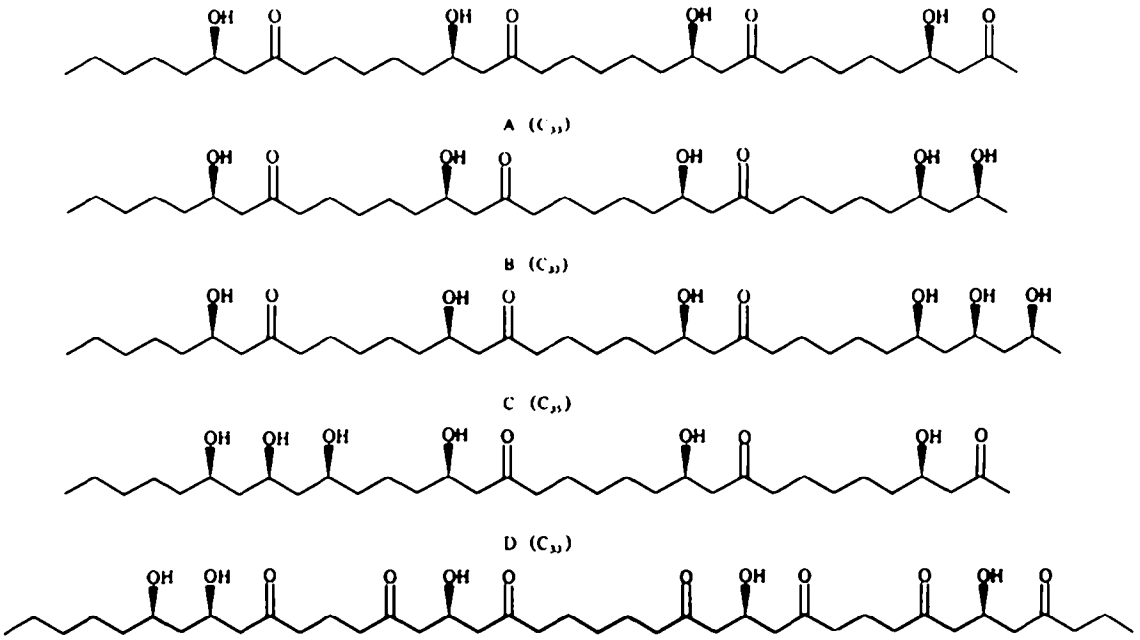


Fig. 1. Structures of PM-toxins (A, B, C, D) and HMT-toxin.

resembles HMT-toxin (C_{39} and C_{41}) [4–6] which has been isolated from the taxonomically unrelated corn pathogen, *Helminthosporium maydis*, Race T, in regard to chemical structure (Fig. 1) and biological activities.

Previous synthetic studies on PM-toxin B and synthetic analogues with shorter carbon chains (C_{16} and C_{24}) [7] suggested that the increase of oxygenic groups (β-ketol and β-diol groups) greatly enhances toxicity and that the stereoconfiguration at the hydroxyl functions may not contribute to toxicity.

To further clarify the structure–activity relationships for PM-toxin, we have prepared a series of PM-toxin A mimics which have four β-ketol groups spaced by varying lengths of methylene chains. Comparisons of their relative toxicities indicated structural requirements for the size of methylene spacer between the adjacent β-ketol and β-diol groups and also contribute to understanding the mode of action for the toxins. We report here the synthesis and biological activity of the 12 mimics of PM-toxin A (Fig. 2).

RESULTS AND DISCUSSION

The synthetic route for PM-toxin A mimics is shown in Scheme 1. All the mimics, which consist of stereoisomeric mixtures, were prepared by the application of the bis-addition [8, 9] of the Grignard reagent derived from the 1,ω-dibromoalkane (C_5, C_7 and C_9) to two equivalents of an aldehyde **1**. Each aldehyde **1** was prepared by the route shown in Schemes 2 (m = 1), 3 (m = 3), 4 (m = 5, 6, 7) or 5 (m = 5'). After conversion of the bis-adduct to the corresponding diketone **2**, removal of the protecting groups led to the PM-toxin A mimic (PM-XYX).

The structures of all the mimics were confirmed by means of their mass spectra (FD-MS), ^{13}C NMR (Table 3) and ^{1}H NMR spectra, and IR spectra as described in the Experimental section.

Biological activities of PM-toxin and mimics

As shown in Fig. 2, the mimics are identified by

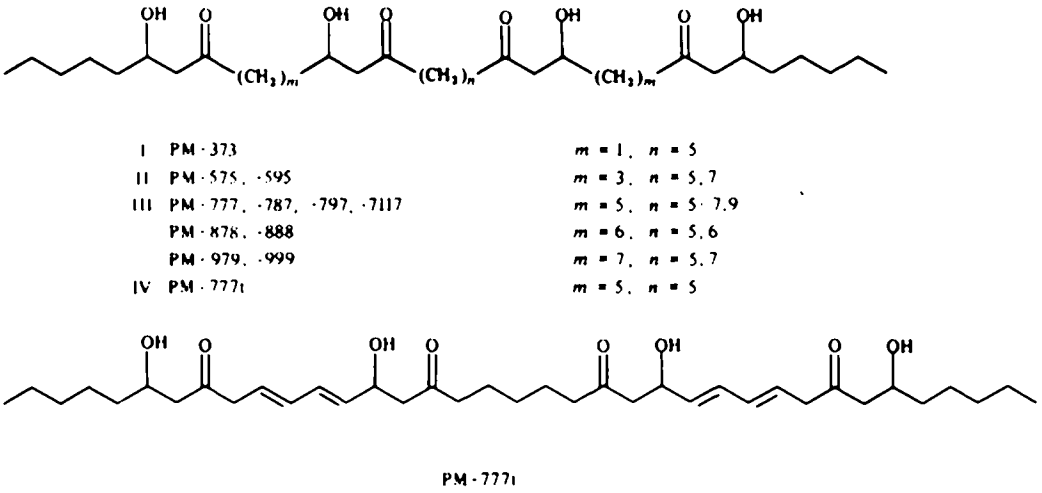


Fig. 2. Synthetic mimics of PM-toxin A.

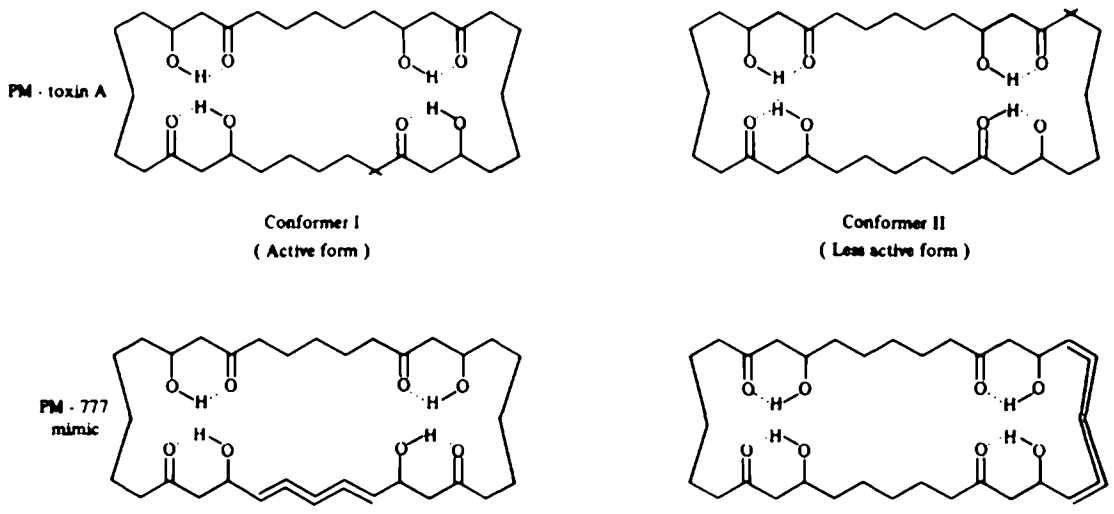
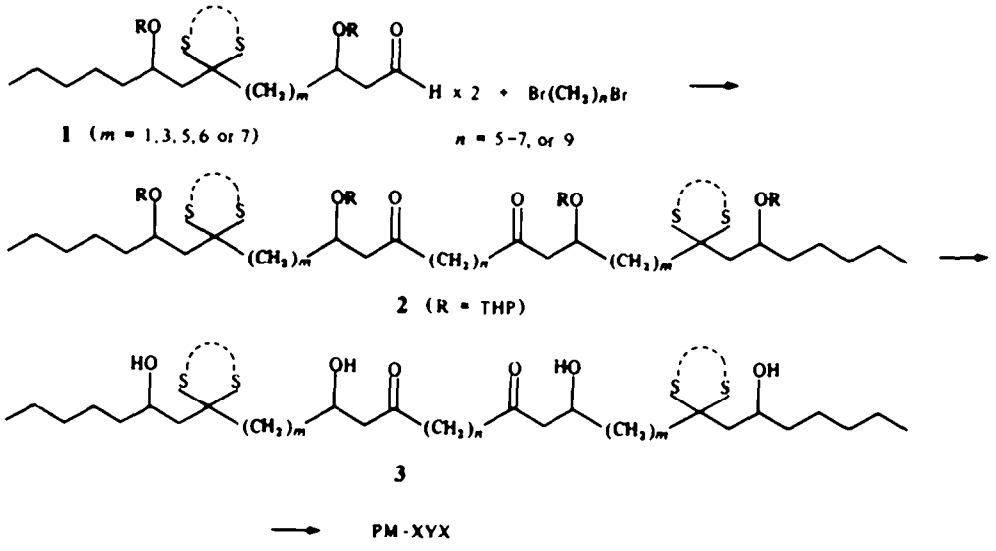
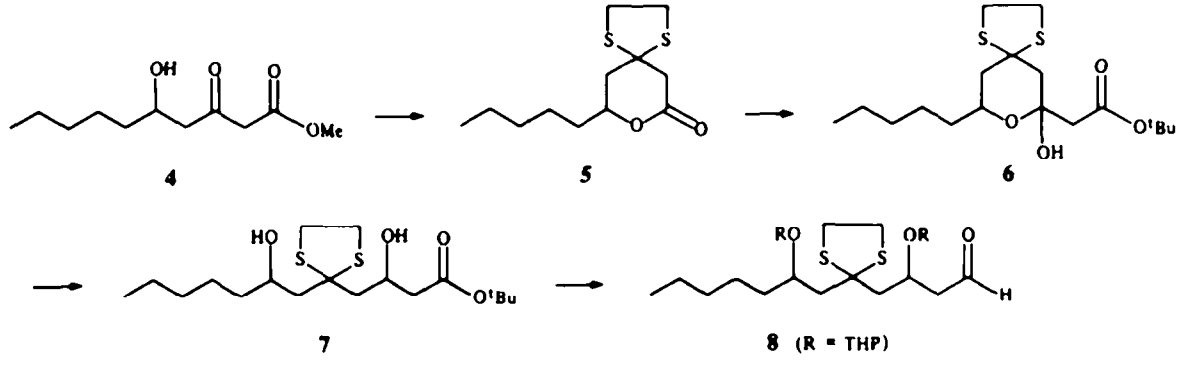


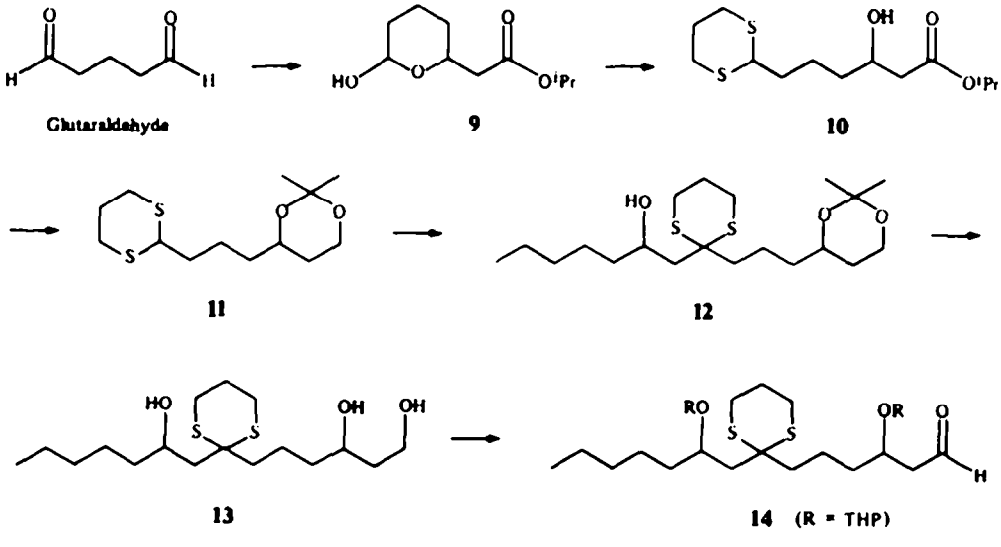
Fig. 3. Hypothetical cage conformations of PM-toxin A and synthetic mimics (PM-XYX).



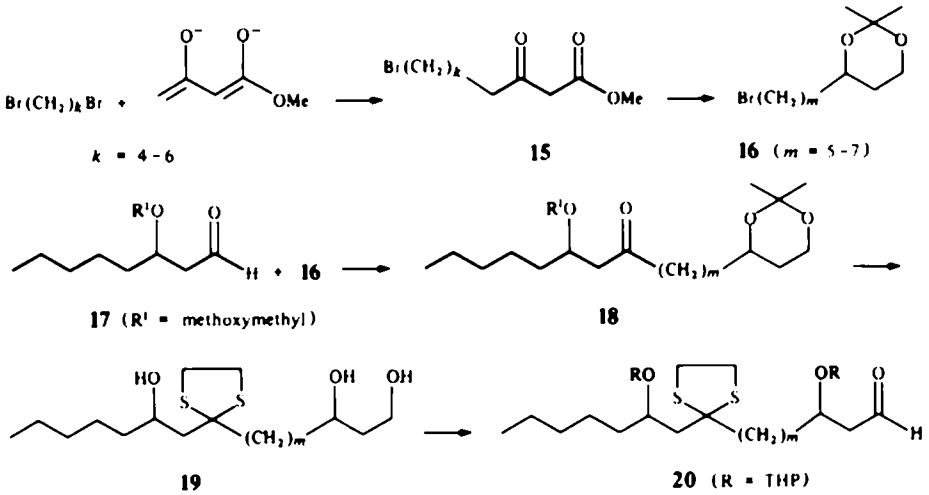
Scheme 1. Synthetic outline of PM-toxin A mimics (PM-XYX).



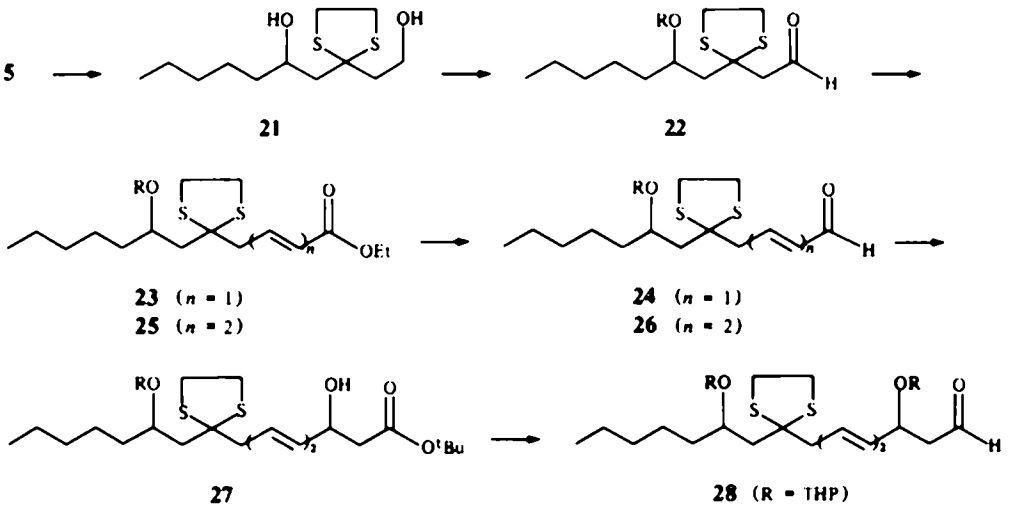
Scheme 2. Synthetic route of aldehyde **8** ($m = 1$).



Scheme 3. Synthetic route of aldehyde **14** ($m = 3$).



Scheme 4. Synthetic route of aldehyde **20** (m = 5–7).



Scheme 5. Synthetic route of aldehyde **28** (m = 5').

numbers which correspond to the length of spacer groups. A spacer group is the number of carbon atoms between the oxygen atoms of adjacent oxyoxo functions. Because of molecular symmetry, the first and third spacers are identical and have a value of $m + 2$ and that of the central spacers is $n + 2$.

If the numbering system were applied to PM-toxin A it would be 777. However, PM-toxin A does differ from the mimic PM-777. Going from left to right PM-toxin A has four consecutive oxyoxo groups, whereas PM-777 has two oxyoxo groups, then two oxooxy groups. Also, the mimics are stereoisomeric mixtures.

The biological activities of compounds were assayed using isolated mitochondria from susceptible (cms-T) corn. Stimulation of nicotinamide adenine dinucleotide (NADH) oxidation and inhibition of malate oxidation were measured by oxygen electrode and dye reduction methods, respectively. At the concentrations tested, PM-777 showed activities that were virtually equivalent to PM-toxin A (Tables 1 and 2). In the malate oxidation assay, PM-777 appeared to have slightly higher activities than PM-toxin A, but the reverse was observed in the NADH oxidation assay. However, considering the standard deviation of the assays, these differences were not significant. Thus, the order of oxyoxo groups and the stereoisomeric configurations are not important determinants of toxicity towards susceptible mitochondria.

The effect of the lengths of the outside spacers may be seen by comparing the activities of PM-373, 575, 777, 878 and 979. PM-373 and 575 exhibited similar activities, but both were significantly less active than PM-777, whereas the activities of PM-777, 878 and 979 were nearly equivalent. Double bonds in the outside spacers lowered activity as shown by comparing PM-777t with PM-777. Presumably the low activity is due to an increased rigidity of the molecule. PM-777, 787, 797 and 7117 showed similar activities, perhaps with PM-7117 being slightly lower. The effect of having middle spacers with lengths less than seven was not tested.

In general, if the spacers were equal to or greater than

Table 1. Effects of synthetic mimics of PM-toxin on malate oxidation by cms-T-corn mitochondria

Concentration (ng/ml)	PM A	PM-mimics											
		777	373	575	777t	878	979	595	797	7117	787	888	999
0.0	100	100	100	100	100	100	100	100	100	100	100	100	100
0.1	100	67	100	—	–	91	76	–	58	96	65	96	90
0.3	77	42	98	100	106	63	46	106	31	67	44	66	74
1.0	49	25	102	106	110	35	25	102	22	38	24	36	42
3.0	28	15	99	104	104	26	15	90	11	24	14	21	28
10.0	15	10	96	98	94	15	9	67	8	16	10	14	17
30.0	11	7	77	88	104	9	9	49	6	15	8	12	31
100.0	—	—	—	79	102			45					—
300.0	—	—	—	55	49			41					–

Values are expressed as a percentage of the amount of 2,6-dichlorophenol indolphenol (DCPIP) reduced by toxin-treated cms-T mitochondria relative to the control. The control was cms-T mitochondria treated with 3 μl dimethylsulphoxide. The average amount of DCPIP reduced by the control was 1.1 nmol DCPIP per μg mitochondrial protein. The values are an average of three replications with an average standard deviation of 26%. Assays were not conducted at the concentrations for which numerical values are missing.

Table 2. Effects of synthetic mimics of PM-toxin on NADH oxidation by cms-T corn mitochondria

Concentration (ng/ml)	PM A	PM-mimics							
		777	373	575	777t	595	797	787	999
0.3	90	87					94	92	102
1.0	142	141		–			175	220	139
3.0	180	166			—		138	229	137
10.0	233	180	5	42	4	82	173	220	159
30.0			47	66	19	96			–
100			42	67	51	91			-
1000			90	111	127	135	-	—	—

Values represent the percentage change in the state four rates of NADH oxidation after the addition of toxin. Control mitochondria were treated with 3 μl dimethyl sulphoxide which had no effect on the rate of NADH oxidation. The values are the average of three replications with an average standard error of 35%. Assays were not conducted at concentrations for which numerical values are missing.

those in PM-toxin A, the mimic showed activities comparable to the native toxin. None of the oxyoxo groups of PM-888 will align with the groups in PM-toxin A or PM-777, yet it shows equal toxicity. PPM-797 appeared to be the most potent of the mimics and slightly more active than PM-toxin A. The toxicity of all mimics were specific since N-corn mitochondria were not affected at any of the concentrations tested.

Apparent structure–activity relationships can be accounted for by postulating that the molecules may form two types of circular (cage) conformations, with distinguishable hydrophilic and hydrophobic domains [10], Fig. 3. Conformer I is formed by hydrogen bonding between the two sets of adjacent oxyoxo groups. Conformer II has the two internal oxyoxo groups as one set and the two outside groups as the second set of hydrogen-bonded groups. PM-toxin A and all the potent mimics can form both conformers, but PM-373, 575, 595 and 777t, the less active mimics, can only form conformer II by molecular models. Although both conformers have similar overall geometry, conformer I may be the more active form. These results, along with similar studies with HMT-toxin, indicate that channel formation may be involved in the mode of action for PM-toxin [10].

EXPERIMENTAL

IR spectra were obtained with films on NaCl plates or with KBr discs. All compounds obtained were racemic.

5-Hydroxy-3-oxodecanoic lactone-3-ethlenedithioketal (5). Boron trifluoride etherate (BF_3-etherate, 8 ml) was added to 4 (33.0 g, 152 mM) and 1,2-ethanedithiol (21.3 g, 228 mM) in dry dichloromethane (CH_2Cl_2, *ca* 400 ml) at 0° [11]. After 18 hr of stirring at 25°, the mixture was conc. at room temp. The residue was passed through a short silica gel column. Elution with EtOAc–hexane (40:60) gave an oil of 5 (30.86 g, 78.4% yield), ^{1}H NMR (90 MHz, $CDCl_3$): δ0.89 (3H, *br t*, 10-H), 2.10 (1H, *dd*, J = 14, 4 Hz, 4-H_{ax}) 2.38 (1H, *ddd*, J = 14, 4, 2 Hz, 4-H_{eq}), 2.92 (1H, *d*, J = 18 Hz, 2-H_{ax}), 3.20 (1H, *dd*, J = 18, 2 Hz, 2-H_{eq}), 3.40 (4H, *s*, $-S(CH_2)_2S-$), 4.44 (1H, *m*, 5-H). IR ν_{max} cm^{-1} (film): 1730 (δ-lactone). HR-MS: *m/z* 260.0884 [M]$^+$; calc. for $C_{12}H_{20}O_2S_2$: 260.0903.

t-Butyl, 3,7-dihydroxy-5-oxododecanoate-5-ethylenedithioketal (7). A soln of lithium diisopropylamide (LDA), which was generated at 0° from diisopropylamine (3.03 g, 30 mM) and *n*-butyllithium (*n*-BuLi, 1.6 M hexane soln, 25 mM) in dry tetrahydrofuran (THF, 13 ml), was cooled to −78°. *t*-BuOAc (4.04 ml, 30 mM) dissolved in dry THF (10 ml) was added dropwise for over 45 min. To this ester enolate, a soln of 5 (6.50 g,

Table 3. ^{13}C NMR spectral data of PM-toxin A mimics (PM-XYX) (22.5 MHz, C_5D_5N δ ppm)

PM		373	575	595	777	777t	787	797	7117	878	888	979	999
	CH_3	14.1	14.1	14.1	14.1	14.1	14.1	14.1	14.1	14.1	14.1	14.1	14.1
	CH_2	22.8	22.8	22.8	22.8	22.8	22.8	22.8	22.8	22.8	22.8	22.8	22.8
	CH_2	31.9	32.0	32.0	32.0	32.0	32.0	32.0	32.0	31.9	32.0	32.0	31.9
	CH_2	25.7	25.7	25.7	25.9	25.7	25.9	25.9	25.9	25.9	25.9	26.0	26.0
	CH_2	38.1	38.2	38.2	38.2	38.2	38.2	38.2	38.1	38.2	38.2	38.2	38.2
	CHOH	67.7	67.8	67.7	67.7	67.6	67.7	67.7	67.7	67.7	67.7	67.7	67.7
	CH_2	51.1	51.0	51.0	51.1	50.8	51.1	51.1	51.1	51.1	51.1	51.1	51.1
	C=O	N.D.	210.3	210.3	210.2	209.0	210.2	210.2	N.D.	N.D.	N.D.	210.2	N.D.
	CH_2	50.5*	43.7	43.7	43.7	47.5	43.7	43.6	43.7	43.7	43.7	43.7	43.7
	CH_2		20.2	20.3	23.8	126.4†	23.7	23.7	23.8	23.7	23.7	23.7	23.7
CH=	CH_2		37.6	37.6	29.4	129.3†	29.4	29.4	29.4	29.4	29.4	29.7	29.7
CH	CH_2				25.7	133.6†	25.7	25.7	25.7	29.7	29.7	29.3	29.3
=CH	CH_2				38.1	136.7†	38.1	38.2	38.1	25.7	25.7	29.7	29.7
	CH_2									38.2	38.2	25.7	25.7
	CH_2											38.2	38.2
	CHOH	64.3	67.5	67.5	67.7	68.2	67.7	67.7	67.7	67.7	67.7	67.7	67.7
	CH_2	52.0*	50.9	50.9	51.1	50.8	51.1	51.1	51.1	51.1	51.1	51.1	51.1
	C=O	N.D.	209.9	210.0	210.2	207.9	210.2	210.2	N.D.	N.D.	N.D.	210.2	N.D.
	CH_2	43.3	43.5	43.7	43.5	43.5	43.7	43.6	43.7	43.5	43.7	43.5	43.7
	CH_2	23.4	23.5	23.6	23.6	23.5	23.6	23.7	23.8	23.5	23.6	23.5	23.7
	CH_2	28.8	28.9	29.1	28.9	28.8	29.1	29.1	29.4	28.8	29.1	28.8	29.2
	CH_2			29.4				29.4	29.6				29.4
	CH_2								29.4				

*Tentative assignment.
†No assignment.

25 mM) in dry THF (10 ml) was added dropwise. After 2 hr at −78° [12], the mixture was quenched with EtOH (5 ml) and extracted with Et_2O. The extract was washed with water, dried over $MgSO_4$, and conc. to produce an oil of **6** (8.9 g). ^1H NMR (90 MHz, $CDCl_3$): δ0.87 (3H, *br s*, 12-H), 1.46 (9H, *s*, $-C(CH_3)_3$), 1.6–2.4 (4H, *m*, 4,6-H), 2.49 (2H, *s*, 2-H), 3.28 (4H, *s*, $-S(CH_2)_2S-$), 4.1 (1H, *m*, 7-H), 5.22 (1H, *d*, J = 2 Hz, OH). IR ν_{max} cm^{-1} (film): 1705 (ester), 3430 (OH).

Sodium borohydride ($NaBH_4$, 910 mg, 24 mM) was added to a soln of **6** (8.9 g) in EtOH (150 ml) at 0°. Stirring was continued for 18 hr at 25°. Water was added and the mixture was extracted with EtOAc. The extract was washed with satd brine and dried. Evaporation of the solvent and subsequent column chromatography on silica gel with EtOAc–hexane (1:3) gave an oil of **7** (4.66 g, 49.7% yield). ^1H NMR (90 MHz, $CDCl_3$): δ0.89 (3H, *br t*, 12-H), 1.46 (9H, *s*, $C(CH_3)_3$), 2.0–2.3 (4H, *m*, 4,6-H), 2.42 (2H, *d*, J = 6 Hz, 2-H), 3.12 and 3.48 (each 1H, *d*, J = 3 Hz, OH), 4.00 and 4.32 (each 1H, *m*, 3,7-H). IR ν_{max} cm^{-1} (film): 1720 (ester), 3430 (OH). HR-MS: *m/z* 378.1910 [M]$^+$; calc. for $C_{18}H_{34}O_4S_2$: 378.1897.

3,7-Di (tetrahydropyranyl)oxy-5-oxododecanal-5-ethylenedithioketal (**8**). Dihydropyran (DHP, 5 ml) was added dropwise to a mixture of **7** (3.0 g, 7.93 mM) and *p*-toluenesulphonic acid (*p*-TsOH, 119 mg) in dry dioxane (17 ml) at 20°. After 7 min, aq. $NaHCO_3$ soln was added and the mixture was extracted with EtOAc. The EtOAc extract was washed with satd brine, dried and conc. to give an oil of the crude bis-THP derivative (5.0 g), which was used in the next step without purification. Lithium aluminium hydride ($LiAlH_4$, 580 mg, 12.3 mM) was added to a soln of the above product in dry THF (*ca* 100 ml) with ice-cooling. After 18 hr of stirring at room temp., water (0.6 ml), 15% aq. NaOH soln (0.6 ml) and water (1.8 ml) were added successively. Evaporation of the solvent of the filtrate gave an oil of the crude alcohol compound (3.94 g).

A soln of the above product (3.94 g) in dry pyridine (50 ml) was added in one portion to a slurry of chromic anhydride (CrO_3, 4.07 g, 40.7 mM) in dry pyridine (*ca* 200 ml). The mixture was stirred at room temp. for 7 hr. Et_2O was added, the mixture was filtered and the residue was washed with Et_2O. The extract was then washed with water and conc. CC on silica gel with EtOAc–hexane (1:9) gave an oil of **8** (2.19 g, 58.3% yield). ^1H NMR (90 MHz, $CDCl_3$): δ0.89 (3H, *br t*, 12-H), 2.6–2.8 (2H, *m*, 2-H), 3.25 (4H, *s*, $S(CH_2)_2S-$), 9.81 (1H, *t*, J = 2 Hz, 1-H). IR ν_{max} cm^{-1} (film): 1720 and 2720 (aldehyde). HR-MS: *m/z* 474.2459 [M]$^+$; calc. for $C_{24}H_{42}O_5S_2$: 474.2470.

Isopropyl, 2'-hydroxy-6'-tetrahydropyranylacetate (**9**). Glutaralehyde (20 g, 200 mM) dissolved in dry THF (80 ml) was added in one portion to a cold soln (−78°) of the enolate anion of *iso*-PrOAc (200 mM) which was prepared in a similar manner as described previously for that of *t*-BuOAc. After 15 min, the mixture was worked up as described previously gave a mixture of the mono- and bis-adduct which on CC (silica gel) produced an oil of the mono-adduct **9** (21.1 g, 52.0% yield). ^1H NMR (90 MHz, $CDCl_3$): δ1.24 (6H, *d*, J = 6 Hz, $CH(CH_3)_2$), 2.2–2.8 (2H, *m*, 2-H), 4.0 and 4.5 (each 0.5H, *m*, 6'-H), 4.80 and 5.36 (each 0.5H, *m* and *br s*, 2'-H), 5.10 (1H, quintet like, J = 6 Hz, $-CH(CH_3)_2$). IR ν_{max} cm^{-1} (film): 1720 (ester), 3400 (OH). HR-MS: *m/z* 184.1059 [M − H_2O]$^+$; calc. for $C_{10}H_{16}O_3$: 184.1098.

Isopropyl, 3-hydroxy-7-oxoheptanoate-7-propylenedithioacetal (**10**). **9** (21.1 g, 104 mM) was reacted with 1,3-propanedithiol (16.8 g, 156 mM) and BF_3-etherate (5.6 ml) in dry CH_2Cl_2 (*ca* 500 ml). After 18 hr of stirring, water was added and the mixture was extracted with CH_2Cl_2. The organic extract was washed with water and conc. CC of this crude product on silica gel with EtOAc–hexane (4:6) gave an oil of **10** (20.85 g, 68.5% yield). ^1H NMR (90 MHz, $CDCl_3$): δ1.25 (6H, *d*, J = 6 Hz, $-CH(CH_3)_2$), 2.41 and 2.43 (each 1H, ABX, J = 12, 8, 4 Hz, 2-H), 2.7–3.0 (6H, *m*, $-S(CH_2)_3S-$), 3.02 (1H, *d*, J = 2 Hz, OH), 4.0 (1H, *m*, 3-H), 4.05 (1H, *t*, J = 6 Hz, 7-H), 5.05 (1H, quintet, J = 6 Hz, $-CH(CH_3)_2$). IR ν_{max} cm^{-1} (film): 1720 (ester), 3450 (OH). HR-MS: *m/z* 292.1154 [M]$^+$; calc. for $C_{13}H_{24}O_3S_2$: 292.1165.

5,7-Dihydroxy-1-heptanal-5,7-isopropylideneketal-1-propylenedithioacetal (**11**). Reduction of **10** with $LiAlH_4$ in a similar manner as described for **8** gave an oil of the crude dialcohol compound (16.4 g). A soln of this compound and *p*-TsOH (750 mg) in 2,2-dimethoxypropane, Me_2CO (each 75 ml) and dry dioxane (150 ml) was stirred at 20° for 1 hr. Powdered $NaHCO_3$ was added and the solvent was removed. The residue dissolved in EtOAc was washed with satd brine and dried. Evaporation of the solvent followed by distillation (126 to 130°/0.2 mmHg) gave an oil of **11** (13.86 g, 70.5% yield). ^1H NMR (90 MHz, $CDCl_3$): δ1.37 and 1.44 (each 3H, *s*, $C(CH_3)_2$), 2.7–3.0 (6H, *m*, $-S(CH_2)_3S-$), 3.6–4.0 (3H, *m*, 5,7-H), 4.05 (1H, *t*, J = 6 Hz, 1-H). HR-MS *m/z*: 276.1194 [M]$^+$; calc. for $C_{13}H_{24}O_2S_2$: 276.1216.

1,3,9-Trihydroxy-7-oxotetradecane-1,3-isopropylideneketal-7-propylenedithioketal (**12**). *n*-BuLi (28.9 mM) was added dropwise to a soln of **11** (9.96 g, 27.5 mM) in dry THF (100 ml) at −40°. After 2 hr at −40°, 1-hepteneoxide (2.85 g, 25 mM) dissolved in dry THF (5 ml) was added to the above anion solution at −20°. The reaction vessel was closed under positive N_2 gas pressure and stored for 3 days at −20° and then for another 3 days at 0° [13]. The mixture was poured into ice-water. Extraction with EtOAc furnished an organic soln which was washed with water and dried. The residue obtained after solvent removal gave an oil of **12** (5.71 g, 58.5% yield) that was purified by CC on silica gel with EtOAc–hexane (1:4). ^1H NMR (90 MHz, $CDCl_3$): δ0.89 (3H, *br t*, 14-H), 1.37 and 1.50 (each 3H, *s*, $C(CH_3)_2$), 2.6–3.2 (6H, *m*, $-S(CH_2)_3S-$), 3.40 and 3.44 (each 0.5H, *d*, J = 2 Hz, OH), 3.6–4.1 (4H, *m*, 1,3,9-H). IR ν_{max} cm^{-1} (film): 3450 (OH). HR-MS: *m/z* 390.2272 [M]$^+$; calc. for $C_{20}H_{38}O_3S_2$: 390.2261.

3,9-Di (tetrahydropyranyl)oxy-7-oxotetradecanal-7-propylenedithioketal (**14**). A soln of **12** (5.71 g, 14.6 mM) in 80% aq. AcOH (50 ml) was stirred at 25° for 2 hr and then conc. at room temp., giving an oil of **13** (5.55 g). ^1H NMR (90 MHz, $CDCl_3$): δ0.89 (3H, *br t*, 14-H), 2.5–3.0 (2H, *m*, OH), 2.6–3.0 (6H, *m*, $-S(CH_2)_3S-$), 3.32 (1H, *br s*, OH), 3.6–4.1 (4H, *m*, 1,3,9-H). IR ν_{max} cm^{-1} (film): 3400 (OH). HR-MS: *m/z* 350.1963 [M]$^+$; calc. for $C_{17}H_{34}O_3S_2$: 350.1948.

Pivaloyl chloride (1.76 g, 14.6 mM) was added dropwise at −20° to the stirred soln of **13** (5.55 g) in dry pyridine (25 ml). After 1 hr at −20°, water was added and the mixture was extracted with EtOAc. The organic layer was washed with water and then conc., giving an oil of the crude acylated compound (6.11 g), which was converted to the corresponding bis-THP ether derivative as described for **8**. A mixture of the bis-THP ether derivative and NaOH (5.3 g) in 15% aq. MeOH (40 ml) and THF (20 ml) was stirred at room temp. for 18 hr. Water was added to this mixture, which was extracted with Et_2O. The extract was washed with water, dried and conc. to an oil of the crude alcohol (6.85 g), which was converted by oxidation to an oil of **14** (4.20 g, 51.5% yield), as described for **8**.

14, ^1H NMR (90 MHz, $CDCl_3$): δ0.89 (3H, *br t*, 14-H), 2.5–2.7 (2H, *m*, 2-H), 2.7–3.0 (6H, *m*, $-S(CH_2)_3S-$), 4.70 (2H, *br s*, $-OCHO-$), 9.80 (1H, *t*, J = 2 Hz, 1-H). IR ν_{max} cm^{-1} (film): 1720 and 2720 (aldehyde). HR-MS: *m/z* 516.2919 [M]$^+$; calc. for $C_{27}H_{48}O_5S_2$: 516.2939.

Preparation of the trialcohols (**19**) *via the ketones* (**18**). **18b** and **18c** (m = 6,7) and then **19b** and **19c** (m = 6,7) were obtained by the same method as previously described for **18a** and **19a** (m = 5).

Refluxing a soln of **16** and Mg metal in THF for 20 min, with aldehyde **17** in THF at −10° for 45 min, followed by oxidation of the resulting alcohol mixture with pyridinium dichromate in

dimethylformamide at room temp. for 18 hr gave a crude ketone product **18**. Without purification, **18** was treated with 1,2-ethanedithiol (3.5 equiv.) and BF_3-etherate for 18 hr and produced an oil of **19** after CC on silica gel. **19b**, an oil (m = 6, 60.4 % yield), ^{1}H NMR (90 MHz, $CDCl_3$): δ0.89 (3H, *br t*, 17-H), 2.22 (2H, *br s*, OH), 3.31 (4H, *s*, $-S(CH_2)_2S-$), 3.46 (1H, *d*, J = 2 Hz, OH), 3.7–4.1 (4H, *m*, 1,3,12-H). IR ν_{max} cm^{-1} (film): 3350 (OH). HR-MS: m/z 378.2242 [M]$^+$; calc. for $C_{19}H_{38}O_3S_2$: 378.2259. **19c**, an oil (m = 7, 39.2 % yield), ^{1}H NMR (90 MHz, $CDCl_3$): δ0.89 (3H, *br t*, 18-H), 2.40 (2H, *br s*, OH), 3.32 (4H, *s*, $-S(CH_2)_2S-$), 3.48 (1H, *s*, OH), 3.7–4.1 (4H, *m*, 1,3,13-H). IR ν_{max} cm^{-1} (film): 3400 (OH). HR-MS: m/z 392.2421 [M]$^+$; calc. for $C_{20}H_{40}O_3S_2$: 392.2416.

Preparation of the bromo-acetonides (**16**) *via the corresponding bromo β-ketoesters* (**15**). **15b** and **15c** (k = 5, 6), and then **16b** and **16c** (m = 6, 7) were obtained in the manner reported previously for **15a** (k = 4) and **16a** (m = 5). **15b**, an oil (k = 5, 58.7 % yield), ^{1}H NMR (90 MHz, $CDCl_3$): δ2.55 (2H, *t*, J = 7 Hz, 4-H), 3.40 (2H, *t*, J = 6 Hz, 9-H), 3.44 (2H, *s*, 2-H), 3.73 (3H, *s*, $-OCH_3$). HR-MS: m/z 264.0350 [M$^+$]; calc. for $C_{10}H_{17}O_3Br$: 264.0360. **15c**, an oil (k = 6, 59.1 % yield), ^{1}H NMR (90 MHz, $CDCl_3$): δ2.54 (2H, *t*, J = 7 Hz, 4-H), 3.40 (2H, *t*, J = 6 Hz, 10-H), 3.44 (2H, *s*, 2-H), 3.73 (3H, *s*, OCH_3). HR-MS: m/z 278.0511 [M$^+$]; calc. for $C_{11}H_{19}O_3Br$: 278.0517. **16b**, an oil (m = 6, 56.5 % yield, 89–93°/0.5 mmHg), ^{1}H NMR (90 MHz, $CDCl_3$): δ1.39 and 1.45 (each 3H, *s*, $C(CH_3)_2$), 3.41 (2H, *t*, J = 7 Hz, 9-H), 3.6–4.1 (3H, *m*, 1,3-H). HR-MS: m/z 263.0626 [M $-$ CH_3]; calc. for $C_{11}H_{20}O_2Br$: 263.0646. **16c**, an oil (m = 7, 60.7 % yield, 105–109°/0.15 mmHg). ^{1}H NMR (90 MHz, $CDCl_3$): δ1.39 and 1.45 (each 3H, *s*, $C(CH_3)_2$), 3.41 (2H, *t*, J = 7 Hz, 10-H), 3.6–4.1 (3H, *m*, 1,3-H). HR-MS: m/z 292.1016 [M$^+$]; calc. for $C_{13}H_{25}O_2Br$: 292.1036.

Preparation of the aldehydes (**20**). The aldehydes **20** were prepared from the corresponding trialcohols **19** in the same method as described above for **14**. **20a**, an oil (m = 5, 48.8 % overall yield), ^{1}H NMR (90 MHz, $CDCl_3$): δ0.89 (3H, *br t*, 16-H), 2.4–2.7 (2H, *m*, 2-H), 3.26 (4H, *s*, $-S(CH)_2S-$), 4.1 (2H, *m*, 3,11-H), 4.67 (2H, *br s*, $-OCHO$), 9.80 (1H, *t*, J = 2 Hz, 1-H). IR ν_{max} cm^{-1} (film): 1725 and 2720 (aldehyde). HR-MS: m/z 530.3088 [M]$^+$, calc. for $C_{28}H_{50}O_5S_2$: 530.3096. **20b** an oil (m = 6, 48.0 % overall yield), ^{1}H NMR (90 MHz, $CDCl_3$): δ0.89 (3H, *br t*, 17-H), 2.4–2.7 (2H, *m*, 2-H), 3.26 (4H, *s*, $-S(CH_2)_2S-$), 4.1 (2H, *m*, 3,12-H), 4.67 (2H, *br s*, $OCHO-$), 9.80 (1H, *m*, 1-H). IR ν_{max} cm^{-1} (film): 1725 and 2720 (aldehyde). HR-MS: m/z 544.3278 [M]$^+$; calc. for $C_{29}H_{52}O_5S_2$: 544.3253. **20c**, an oil (m = 7, 53.0 % overall yield), ^{1}H NMR (90 MHz, $CDCl_3$): δ0.88 (3H, *br t*, 18-H), 2.4–2.7 (2H, *m*, 2-H), 3.26 (4H, *s*, $S(CH_2)_2S-$), 4.1 (2H, *m*, 3,13-H), 4.67 (2H, *br s*, $OCHO-$), 9.80 (1H, *m*, 1-H). IR ν_{max} cm^{-1} (film): 1725 and 2720 (aldehyde). HR-MS: m/z 558.3383 [M]$^+$; calc. for $C_{30}H_{54}O_5S_2$: 558.3409.

1,5-*Dihydroxy*-3-*oxodecane*-3-*ethylenedithioketal* (**21**). The dithiolane lactone **5** (30.86 g, 118 mM) was reacted with $LiAlH_4$ (4.50 g, 118 mM) in dry THF (200 ml) at 0° for 1 hr and the mixture was worked up, giving an oil of **21** (38.9 g), ^{1}H NMR (90 MHz, $CDCl_3$): δ0.89 (3H, *br t*, 10-H), 2.0–2.4 (4H, *m*, 2,4-H), 3.36 (4H, *s*, $S(CH_2)_2S-$), 3.94 (3H, *m*, 1,5-H). IR ν_{max} cm^{-1} (film): 3350 (OH). HR-MS: m/z 264.1211 [M$^+$]; calc. for $C_{12}H_{24}O_2S_2$: 264.1215.

5-(*Tetrahydropyranyl*)*oxy*-3-*oxodecanal*-3-*ethylenedithioketal* (**22**). Compound **21** was converted to the corresponding aldehyde **22** (22.9 g, 56.0 % yield) in a similar manner as that described previously for **14**. **22**, ^{1}H NMR (90 MHz, $CDCl_3$): δ0.89 (3H, *br t*, 10-H), 3.02 and 3.26 (total 2H, *d*, J = 2 Hz, 2-H), 3.31 and 3.34 (total 4H, *s*, $S(CH_2)_2S-$), 4.56 and 4.68 (total 1H, *m*, 5-H), 9.78 (1H, *t*, J = 2 Hz, 1-H). IR ν_{max} cm^{-1} (film): 1720 and 2720 (aldehyde). HR-MS: m/z 346.1632 [M$^+$]; calc. for $C_{17}H_{30}O_3S_2$: 346.1633.

Ethyl, 7-(*tetrahydropyranyl*)*oxy*-5-*oxo*-2(E)-*dodecenoate*-5-*ethylenedithioketal* (**23**). The ylide soln was prepared from triethyl phosphonoacetate (14.8 g, 69.5 mM), sodium hydride (60 % NaH, 2.65 g, 66.2 mM) in dry dimethoxyethane (DME, 40 ml). Compound **22** (22.9 g, 66.2 mM) dissolved in dry DME (40 ml) was added dropwise at room temp. to the above ylide soln. The mixture was stirred for 18 hr [14], poured into water and extracted with EtOAc. The extract was washed with water, dried, and conc., and produced an oil of the stereochemically pure product **23** (28.5 g) [8], ^{1}H NMR (90 MHz, $CDCl_3$): δ0.88 (3H, *br t*, 12-H), 1.29 (3H, *t*, J = 7 Hz, $-OCH_2CH_3$), 2.0–2.5 (2H, *m*, 6-H), 2.84 and 3.06 (each *ca* 1H, *dd*, J = 7,1 Hz, 4-H), 3.27 and 3.28 (total 4H, *s*, $-S(CH_2)_2S-$), 4.0 (1H, *m*, 7-H), 4.26 (2H, *q*, J = 7 Hz, OCH_2CH_3), 4.70 (1H, *br s*, $-OCHO-$), 5.95 and 5.96 (each *ca* 0.5H, *dd*, J = 14,1 Hz, 2-H), 7.04 and 7.08 (each *ca* 0.5H, *dt*, J = 14,7 Hz, 3-H). IR ν_{max} cm^{-1} (film): 1650 and 1720 (α,β-unsaturated ester). HR-MS: m/z 416.2026 [M]$^+$; calc. for $C_{21}H_{36}O_4S_2$: 416.2052.

7-(*Tetrahydropyranyl*)*oxy*-5-*oxo*-2(E)-*dodecenal*-5-*ethylenedithioketal* (**24**). Diisobutylaluminium hydride (DIBALH, 73 mM) was added to the mixture of **23** (28.5 g) in dry THF (100 ml) at −20°. After the stirring for 1 hr, water and then 5 % aq. NaOH was added and the mixture was extracted with Et_2O. The usual work-up gave an oil of the crude allylic alcohol (25.4 g), which was then oxidized with CrO_3 in pyridine. The reaction proceeded for 2 hr and produced an oil of **24** (19.05 g, 77.4 % yield) after being passed through a short column of silica gel. ^{1}H NMR (90 MHz, $CDCl_3$): δ0.89 (3H, *br t*, 12-H), 2.0–2.5 (2H, *m*, 6-H), 3.02 and 3.24 (each 1H, *d*, J = 7 Hz, 4-H), 3.30 and 3.31 (total 4H, *s*, $S(CH_2)_2S$), 6.20 (1H, *dd*, J = 14,8 Hz, 2H), 7.00 and 7.04 (each *ca* 0.5H, *dt*, J = 14,7 Hz, 3-H), 9.54 (1H, *d*, J = 8 Hz, 1-H). IR ν_{max} cm^{-1} (film): 1635, 1690 and 2720 (α,β-unsaturated aldehyde). FD-MS: m/z 372 [M$^+$].

9-(*Tetrahydropyranyl*)*oxy*-7-*oxotetradeca*-2(E),4(E)-*dienal*-7-*ethylenedithioketal* (**26**). **26** (10.70 g, 82.0 % overall yield) was obtained from **24** via the diene ester **25**, as described previously. **25**, an oil, ^{1}H NMR (90 MHz, $CDCl_3$): δ0.88 (3H, *br t*, 14-H), 1.29 (3H, *t*, J = 7 Hz, $-OCH_2CH_3$), 1.9–2.5 (2H, *m*, 8-H), 2.7–3.1 (2H, *m*, 6-H), 3.27 and 3.28 (total 4H, *s*, $-S(CH_2)_2S-$), 4.20 (2H, *q*, J = 7 Hz, $-OCH_2CH_3$), 4.68 (1H, *m*, $-OCHO-$), 5.86 (1H, *dd*, J = 16,1 Hz, 2-H), 6.2–6.5 (2H, *m*, 4,5-H), 7.2–7.5 (1H, *m*, 3-H). IR ν_{max} cm^{-1} (film): 1615, 1640 and 1710 (α,β,γ,δ-unsaturated ester). HR-MS: m/z 358.1594 [M$^+$ $-$ C_5H_8O]; calc. for $C_{18}H_{30}O_3S_2$: 358.1634. **26**, an oil, ^{1}H NMR (90 MHz, $CDCl_3$): δ0.88 (3H, *br t*, 14-H), 2.2–2.5 (2H, *m*, 8-H), 2.8–3.2 (2H, *m*, 6-H), 3.28 (4H, *s*, $-S(CH_2)_2S-$), 4.64 (1H, *m*, $OCHO-$), 6.08 (1H, *dd*, J = 16,8 Hz, 2-H), 6.3–6.6 (2H, *m*, 4,5-H), 7.0–7.3 (1H, *m*, 3-H), 9.55 (1H, *d*, J = 8 Hz, 1-H). IR ν_{max} cm^{-1} (film): 1595, 1640, 1680 and 2720 (α,β,γ,δ-unsaturated aldehyde). HR-MS: m/z 314.1354 [M $-$ C_5H_8O]$^+$; calc. for $C_{16}H_{26}O_2S_2$: 314.1372.

t-*Butyl*, 3-*hydroxy*-11-(*tetrahydropyranyl*)*oxy*-9-*oxohexadeca*-4(E),6(E)-*dienenoate*-9-*ethylenedithioketal* (**27**). **27** (12.3 g, 95.2 % overall yield) was obtained by the aldol condensation of the anion of t-BuOAc with **26**, as described previously. **27**, an oil, ^{1}H NMR (90 MHz, $CDCl_3$): 0.88 (3H, *br t*, 16-H), 1.46 (9H, *s*, $C(CH_3)_3$), 2.0–2.4 (2H, *m*, 10-H), 2.4–2.6 (2H, *m*, 2-H), 2.7–3.1 (2H, *m*, 8-H), 3.26 (4H, *s*, $S(CH_2)_2S-$), 4.52 (1H, *m*, 3-H), 4.72 (1H, *m*, $OCHO-$), 5.70 (1H, *dd*, J = 14.6 Hz, 4-H), 5.9–6.6 (3H, *m*, 5,6,7-H). IR ν_{max} cm^{-1} (film): 1720 (ester), 3450 (OH). HR-MS: m/z 412.2083 [M $-$ $C_5H_{10}O_2$]$^+$; calc. for $C_{22}H_{36}O_3S_2$: 412.2083.

3,11-*Di*(*tetrahydropyranyl*)*oxy*-9-*oxohexadeca*-4(E),6(E)-*dienal*-9-*ethylenedithioketal* (**28**). **28** (4.40 g, 40.9 % overall yield) was obtained from **27** as described previously. **28**, an oil, ^{1}H NMR (90 MHz, $CDCl_3$): δ0.88 (3H, *br t*, 16-H), 2.0–2.4 (2H, *m*, 10-H), 2.5–3.0 (4H, *m*, 2,8-H), 3.26 (4H, *s*, $S(CH_2)_2S-$), 5.2–6.4 (4H, *m*, 4,5,6,7-H), 9.80 (1H, *m*, 1-H). IR ν_{max} cm^{-1}: 990 (double

bond), 1725 (aldehyde). FD-MS: *m/z* 526 [M$^+$].

Preparation of the tetraalcohols (3) *via the diketones* (2). A mixture of Mg turnings (200 mg, 8.25 mg atoms), 1,5-dibromopentane (950 mg, 4.13 mM) and a crystal of I_2 in dry THF (15 ml) was refluxed for 20 min. A soln of 1 (1.5 mM) in dry THF (3 ml) was added dropwise at −10° to a part of the above Grignard reagent (3 ml). The mixture was quenched by addition of satd NH_4Cl soln after 45 min of stirring at 25° and extracted with EtOAc. After the extract was washed with water, dried and conc., the residual oil was oxidized with CrO_3 (900 mg, 9 mM) in pyridine (50 ml) for 18 hr. The usual working up gave a mixture of the mono- and bis-adduct 2.

This mixture was dissolved in EtOH (20 ml) and 0.1 N HCl (0.2 ml), and was heated under reflux for 13 min [15], and extracted with $CHCl_3$. The extract was washed with satd brine, dried and conc. CC on silica gel with EtOH–$CHCl_3$ (1:9) gave an oil of 3-777 ($m = n = 5$, 30.8% yield). The remaining tetraalcohols were prepared in a similar manner. 3-373, an oil (30.4% yield), ^{1}H NMR (90 MHz, $CDCl_3$): δ0.89 (6H, *br t*, 1.29-H), 2.44 (4H, *t*, J = 7 Hz, 13, 17-H), 2.1–2.3 (8H, *m*, 7,9,21,23-H), 2.6 (4H, *m*, 11,19-H), 3.35 (8H, *s*, $-S(CH_2)_2S-$), 3.4 and 3.5 (each 2H, *br m*, OH), 4.00 (2H, *br m*, 6,24-H), 4.44 (2H, *br m*, 10,20-H). IR ν_{max} cm^{-1} (film): 1705 (C=O), 3430 (OH). FD-MS: *m/z* 703 [M + Na]$^+$, 681 [M + H]$^+$, 680 [M]$^+$, 662 [M − H_2O]$^+$. 3-575, an oil (19.7% yield), ^{1}H NMR (90 MHz, $CDCl_3$): δ0.89 (6H, *br t*, 1,33-H), 2.42 (4H, *t*, J = 7 Hz, 15,19-H), 2.53 (4H, *m*, 13,21-H), 2.6–3.0 (12H, *m*, $S(CH_2)_2S$), 3.1 (2H, *br m*, OH), 3.3 (2H, *br m*, OH), 4.0 (4H, *br m*, 6,12,22,28-H). IR ν_{max} cm^{-1} (film): 1705 (C=O), 3400 (OH). FD-MS: *m/z* 764 [M]$^+$. 3-595, an oil (42.0% yield), ^{1}H NMR (90 MHz, $CDCl_3$): δ0.89 (6H, *br t*, 1,35-H), 2.43 (4H, *t*, J = 7 Hz, 15,21-H), 2.53 (4H, *m*, 13,23-H), 2.6–3.0 (12H, *m*, $S(CH_2)_3S$), 3.1 (2H, *br m*, OH), 3.3 (2H, *br m*, OH), 4.0 (4H, *br s*, 6,12,24,30-H). IR ν_{max} cm^{-1} (film): 1705 (C=O), 3400 (OH). FD-MS: *m/z* 792 [M]$^+$. 3-777, an oil (30.8% yield), ^{1}H NMR (90 MHz, $CDCl_3$): δ0.89 (6H, *br t*, 1,37-H), 2.43 (4H, *t*, J = 7 Hz, 17,21-H), 2.30 and 2.60 (each 2H, ABX, J = 12,7,5 Hz, 15,23-H), 3.0 (2H, *br s*, OH), 3.31 (8H, *s*, $-S(CH_2)_2S-$), 3.4 (2H, *br s*, OH), 4.0 (4H, *br m*, 6,14,24,32-H). IR ν_{max} cm^{-1} (film): 1705 (C=O), 3430 (OH). FD-MS: *m/z* 792 [M]$^+$, 774 [M − H_2O]$^+$. 3-777t, an oil (6.4% yield), ^{1}H NMR (90 MHz), $CDCl_3$): δ0.89 (6H, *br t*, 1,37-H), 1.96 (4H, *d*, J = 6 Hz, 7,31-H), 2.42 (4H, *t*, J = 7 Hz, 17,21-H), 2.5–2.8 (8H, *m*, 9,15,23,29-H), 3.0 (2H, *m*, OH), 3.3 (2H, *m*, OH), 3.31 (8H, *s*, $S(CH_2)_2S$), 4.0 (2H, *m*, 6,32-H), 4.6 (2H, *m*, 14,24-H), 5.5–6.5 (8H, *m*, 10,11,12,13,25,26,27,28-H). IR ν_{max} cm^{-1} (film): 990 (double bond), 1705 (C=O), 3400 (OH). FD-MS: *m/z* 748 [M − H_2O × 2]$^+$. 3-787, an oil (36.3% yield), ^{1}H NMR (90 MHz, $CDCl_3$): δ0.89 (6H, *br t*, 1,38-H), 2.43 (4H, *t*, J = 7 Hz, 17,22-H), 2.40 and 2.64 (each 2H, ABX, J = 12,7,5 Hz, 15,24-H), 3.02 (2H, *d*, J = 2 Hz, OH), 3.31 (8H, *s*, $S(CH_2)_2S-$), 3.45 (2H, *d*, J = 1 Hz, OH), 4.0 (4H, *br m*, 6,14,25,33-H). IR ν_{max} cm^{-1} (film): 1705 (C=O), 3430 (OH). FD-MS: *m/z* 806 [M]$^+$. 3-797, an oil (40.6% yield), ^{1}H NMR (90 MHz, $CDCl_3$): δ0.89 (6H, *br t*, 1,39-H), 2.43 (4H, *t*, J = 7 Hz, 17,23-H), 2.40 and 2.64 (each 2H, ABX, J = 12,7,5 Hz, 15,25-H), 3.02 (2H, *d*, J = 2 Hz, OH), 3.31 (8H, *s*, $S(CH_2)_2S$), 3.44 (2H, *d*, J = 1 Hz, OH), 4.0 (4H, *br m*, 6,14,26,34-H). IR ν_{max} cm^{-1} (film): 1705 (C=O), 3430 (OH). FD-MS: *m/z* 820 [M]$^+$. 3-7117, an oil (25.1% yield), ^{1}H NMR (90 MHz, $CDCl_3$): δ0.89 (6H, *br t*, 1,41-H), 2.42 (4H, *t*, J = 7 Hz, 17,25-H), 2.40 and 2.64 (each 2H, ABX, J = 12,7,5 Hz, 15,27-H), 3.06 (2H, *d*, J = 2 Hz, OH), 3.32 (8H, *s*, $S(CH_2)_2S$), 3.46 (2H, *d*, J = 1 Hz, OH), 4.0 (4H, *br m*, 6,14,28,36-H). IR ν_{max} cm^{-1} (film): 1705 (C=O), 3430 (OH). FD-MS: *m/z* 848 [M]$^+$. 3-878, an oil (17.7% yield), ^{1}H NMR (90 MHz, $CDCl_3$): δ0.89 (6H, *br t*, 1,39-H), 2.43 (4H, *t*, J = 7 Hz, 18,22-H), 2.40 and 2.64 (each 2H, ABX, J = 12,7,5 Hz, 16,24-H), 3.0 (2H, *d*, J = 2 Hz, OH), 3.32 (8H, *s*, $-S(CH_2)_2S$), 3.46 (2H, *d*, J = 1 Hz, OH), 4.0 (4H, *br m*, 6,15,25,34-H). IR ν_{max} cm^{-1} (film): 1705 (C=O), 3430 (OH). FD-MS: *m/z* 820 [M]$^+$. 3-888, an oil (27.9% yield), ^{1}H NMR (90 MHz, $CDCl_3$): δ0.89 (6H, *br t*, 1,40-H), 2.43 (4H, *t*, J = 7 Hz, 18,23-H), 2.40 and 2.64 (each 2H, ABX, J = 12,7,5 Hz, 16,25-H), 3.02 (2H, *d*, J = 2 Hz, OH), 3.32 (8H, *s*, $-S(CH_2)_2S-$), 3.46 (2H, *d*, J = 1 Hz, OH), 4.0 (4H, *br m*, 6,16,26,35-H). IR ν_{max} cm^{-1} (film): 1705 (C=O), 3430 (OH). FD-MS: *m/z* 834 [M]$^+$. 3-979, an oil (25.1% yield), ^{1}H NMR (90 MHz, $CDCl_3$): δ0.89 (6H, *br t*, 1,41-H), 2.43 (4H, *t*, J = 7 Hz, 19,23-H), 2.40 and 2.64 (each 2H, ABX, J = 12,7,5 Hz, 17,25-H), 2.96 (2H, *d*, J = 2 Hz, OH), 3.31 (8H, *s*, $-S(CH_2)_2S-$), 3.46 (2H, *d*, J = 1 Hz, OH), 4.0 (4H, *br m*, 6,16,26,36-H). IR ν_{max} cm^{-1} (film): 1705 (C=O), 3430 (OH). FD-MS: *m/z* 848 [M]$^+$. 3-999, an oil (27.4% yield), ^{1}H NMR (90 MHz, $CDCl_3$): δ0.89 (6H, *br t*, 1,43-H), 2.42 (4H, *t*, J = 7 Hz, 19,25-H), 2.40 and 2.64 (each 2H, ABX, J = 12,7,5 Hz, 17,27-H), 3.00 (2H, *d*, J = 2 Hz, OH), 3.31 (8H, *s*, $-S(CH_2)_2S$), 3.45 (2H, *d*, J = 1 Hz, OH), 4.0 (4H, *br m*, 6,16,28,38-H). IR ν_{max} cm^{-1} (film): 1705 (C=O), 3430 (OH). FD-MS: *m/z* 876 [M]$^+$.

Preparation of the PM-toxin A mimics. A mixture of 3 ($m = n = 5$, 320 mg, 0.403 mM), mercuric chloride (470 mg), mercuric oxide (145 mg) in water (0.5 ml) and acetonitrile (10 ml) was stirred for 4 hr at room temp. The filtrate of the cold mixture was extracted with $CHCl_3$. The extract was washed with satd NH_4Cl soln and dried over $MgSO_4$. Evaporation of the solvent followed by precipitation from MeOH gave a colourless powder of PM-777. The other mimics were prepared in a similar manner.

PM-373, a slightly yellowish powder (ppt. from Et_2O–EtOAc, 5% yield), ^{1}H NMR (90 MHz, C_5D_5N): δ0.82 (6H, *br t*, 1,29-H), 2.45 (4H, *t*, J = 7 Hz, 13,17-H), 2.6–3.3 (12H, *m*, 7,9,11,19,21,23-H), 4.50 (2H, *br m*, 6,24-H), 5.16 (2H, *br m*, 10,20-H). IR ν_{max} cm^{-1} (KBr): 1705 (C=O), 3400 (OH). FD-MS: *m/z* 551 [M + Na]$^+$, 529 [M + H]$^+$.

PM-575, a colourless powder (ppt. from Me_2CO, 40.6% yield), ^{1}H NMR (90 MHz, C_5D_5N): δ0.83 (6H, *br t*, 1,33-H), 1.8–2.2 (4H, sextet like, J = 7 Hz, 10,24-H), 2.48 (4H, *t*, J = 7 Hz, 15,19-H), 2.67 (4H, *t*, J = 7 Hz, 9,25-H), 2.5–3.0 (8H, *m*, 7,13,21,27-H), 4.45 (4H, *m*, 6,12,22,28-H). IR ν_{max} cm^{-1} (KBr): 1700 (C=O), 3350 (OH). FD-MS: *m/z* 607 [M + Na]$^+$, 589 [M + Na − H_2O]$^+$.

PM-595, a colourless powder (ppt. from MeOH, 45.1% yield), ^{1}H NMR (90 MHz, C_5D_5N): δ0.83 (6H, *br t*, 1,35-H), 1.8–2.2 (4H, sextet like, J = 7 Hz, 10,26-H), 2.50 (4H, *t*, J = 7 Hz, 15,21-H), 2.68 (4H, *t*, J = 7 Hz, 9,27-H), 2.5–3.0 (8H, *m*, 7,13,23,29-H), 4.44 (4H, *br m*, 6,12,24,30-H). IR ν_{max} cm^{-1} (KBr): 1700 (C=O), 3350 (OH). FD-MS: *m/z* 635 [M + Na]$^+$, 617 [M + Na − H_2O]$^+$.

PM-777, a colourless powder (ppt. from MeOH, 28.1% yield), ^{1}H NMR (90 MHz, C_5D_5N): δ0.83 (6H, *br t*, 1,37-H), 2.53 and 2.57 (each 4H, *t*, J = 7 Hz, 9,17,21,29-H), 2.6–3.0 (8H, *m*, 7,15,23,31-H), 4.44 (4H, *m*, 6,14,24,32-H). IR ν_{max} cm^{-1} (KBr): 1700 (C=O), 3250 and 3300 (OH). FD-MS: 663 [M + Na]$^+$.

PM-777t, a slightly brownish powder (ppt. from Me_2CO, 23.2% yield), ^{1}H NMR (90 MHz, C_5D_5N): δ0.83 (6H, *br t*, 1,37-H), 2.52 (4H, *t*, J = 7 Hz, 17,21-H), 2.6–3.1 (8H, *m*, 7,15,23,31-H), 3.50 (4H, *d*, J = 6 Hz, 9,29-H), 4.44 (2H, *m*, 6,32-H), 5.08 (2H, *m*, 14,24-H), 6.00 (2H, *dt*, J = 16,6 Hz, 10,28-H), 6.00 (2H, *dd*, J = 16,7 Hz, 13,25-H), 6.30 (2H, *dd*, J = 16,9 Hz, 11,27-H or 12,26-H), 6.65 (2H, *dd*, J = 16,9 Hz, 12,26-H or 11,27-H). IR ν_{max} cm^{-1} (KBr): 980 (double bond), 1700 (C=O), 3350 (OH). FD-MS: *m/z* 655 [M + Na]$^+$, 637 [M + Na − H_2O]$^+$.

PM-787, a colourless powder (ppt. from $CHCl_3$–MeOH, 64.0% yield), ^{1}H NMR (90 MHz, C_5D_5N): δ0.83 (6H, *br t*, 1,38-H), 2.53 (4H, *t*, J = 7 Hz, 17,22-H), 2.57 (4H, *t*, J = 7 Hz, 9,30-H), 2.6–3.0 (8H, *m*, 7,15,24,32-H), 4.44 (4H, *m*, 6,14,25,33-H). IR ν_{max} cm^{-1} (KBr): 1700 (C=O), 3350 (OH). FD-MS: *m/z* 677

$[M + Na]^+$, 659 $[M + Na - H_2O]^+$.

PM-797, a colourless powder (ppt. from $CHCl_3$–MeOH, 40.8% yield), ^1H NMR (90 MHz, C_5D_5N): δ0.83 (6H, *br t*, 1,39-H), 2.55 (8H, *t*, J = 7 Hz, 9,17,23,31-H), 2.6–3.0 (8H, *m*, 7,15,25,33-H), 4.44 (4H, *br m*, 6,14,26,34-H). IR ν_{max} cm^{-1} (KBr): 1700 (C=O), 3250 (OH). FD-MS: *m/z* 692 $[M + Na + H]^+$, 691 $[M + Na]^+$, 669 $[M + H]^+$.

PM-7117, a colourless powder (ppt. from $CHCl_3$–EtOH, 54.0% yield), ^1H NMR (90 MHz, C_5D_5N): δ0.83 (6H, *br t*, 1,41-H), 2.57 (8H, *t*, J = 7 Hz, 9,16,25,33-H), 2.4–3.0 (8H, *m*, 7,15,27,35-H), 4.46 (4H, *br m*, 6,14,28,36-H). IR ν_{max} cm^{-1} (KBr): 1700 (C=O), 3400 (OH). FD-MS: *m/z* 719 $[M + Na]^+$, 701 $[M + Na - H_2O]^+$, 697 $[M + H]^+$.

PM-878, a colourless powder (ppt. from MeOH, 30.8% yield), ^1H NMR (90 MHz, C_5D_5N): δ0.83 (6H, *br t*, 1,39-H), 2.57 (8H, *t*, J = 7 Hz, 9,18,22,31-H), 2.5–3.0 (8H, *m*, 7,16,24,33-H), 4.48 (4H, *br s*, 6,15,25,34-H). IR ν_{max} cm^{-1} (KBr): 1700 (C=O), 3350 (OH). FD-MS: *m/z* 669 $[M + H]^+$, 651 $[M + H - H_2O]^+$.

PM-888, a colourless powder (ppt. from MeOH, 41.2% yield), ^1H NMR (90 MHz, C_5D_5N): δ0.83 (6H, *br t*, 1,40-H), 2.55 (8H, *t*, J = 7 Hz, 9,18,23,32-H), 2.4–3.0 (8H, *m*, 7,16,25,34-H), 4.48 (4H, *br m*, 6,15,26,35-H). IR ν_{max} cm^{-1} (KBr): 1700 (C=O), 3350 (OH). FD-MS: *m/z* 683 $[M + H]^+$, 665 $[M + H - H_2O]^+$.

PM-979, a colourless powder (ppt. from $CHCl_3$–MeOH, 22.6% yield), ^1H NMR (90 MHz, C_5D_5N): δ0.83 (6H, *br t*, 1,41-H), 2.56 (8H, *t*, J = 7 Hz, 9,19,23,33-H), 2.6–3.0 (8H, *m*, 7,17,25,35-H), 4.44 (4H, *br m*, 6,16,26,36-H). IR ν_{max} cm^{-1} (KBr): 1700 (C=O), 3350 (OH). FD-MS: *m/z* 720 $[M + Na + H]^+$, 697 $[M + H]^+$, 679 $[M + H - H_2O]^+$.

PM-999, a colourless powder (ppt. from $CHCl_3$–MeOH, 64.9% yield), ^1H NMR (90 MHz, C_5D_5N): δ0.83 (6H, *br t*, 1,43-H), 2.56 (8H, *t*, J = 7 Hz, 9,19,25,35-H), 2.6–3.0 (8H, *m*, 7,17,27,37-H), 4.44 (4H, *br m*, 6,16,28,38-H). IR ν_{max} cm^{-1} (KBr): 1700 (C=O), 3350 (OH). FD-MS: *m/z* 747 $[M + Na]^+$, 725 $[M + H]^+$, 707 $[M + H - H_2O]^+$.

Isolation of mitochondria and bioassays. Methods for the isolation of mitochondria and NADH oxidation assays have been reported previously [16]. Malate oxidation was followed by the reduction of 2,6-dichlorophenol indophenol (DCPIP). A decrease in the absorbance of DCPIP at 610 nm was recorded when mitochondrial respiration was measured by a modification of the method of Flavel [17]. A standard reaction mixture contained assay buffer (pH 7.5, 10 ml), 4.8 mM DCPIP (200 μl), 1M KCN (100 μl) and 3 M malate (pH 7.5, 200 μl). The reaction mixture was warmed to 37° in a water bath, and 5–10 μl of a mitochondrial suspension was added to 1 ml of the reaction mixture. One to 1.5 min after the addition of the mitochondria to the substrate-containing reaction mixture, either DMSO or toxin was added to the suspension and the decrease in absorbance was followed until there was no longer any change. In DMSO treated mitochondria, the DCPIP was completely reduced in 8–10 min. All experiments were repeated at least three times.

Toxin solutions. A dilution series for each compound tested was prepared in DMSO. Dilutions were made so that a 1000-fold dilution of the DMSO solution with the reaction mixture would yield the concentration reported.

Acknowledgements The authors thank Mr. Y. Esumi (The Institute of Physical and Chemical Research, Wako-shi, Saitama, Japan) for FD-MS and HR-MS. This work was supported by USDA, Grant No. 85-CRCR-1-1542.

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