Antimycobacterial Activity of Phorbol Esters from the Fruits of *Sapium indicum*

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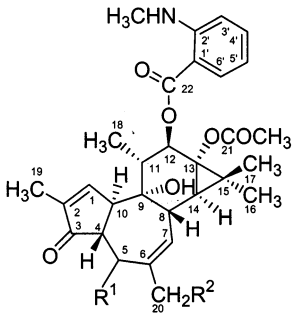
Three new phorbol esters, 12-(2-*N*-methylaminobenzoyl)-4β,5,20-trideoxyphorbol-13-acetate (**1**), 12-(2-*N*-methylaminobenzoyl)-4α,5,20-trideoxyphorbol-13-acetate (**2**), and 12-(2-*N*-methylaminobenzoyl)-4α,20-dideoxy-5-hydroxyphorbol-13-acetate (**6**), together with six known compounds (**3**−**5** and **7**−**9**), were isolated from the fruits of *Sapium indicum*. The chemical structures of **1**, **2**, and **6** were elucidated by analysis of their spectroscopic data. Compounds **1**−**3**, **5**, and **7**−**9** exhibited antimycobacterial activity with minimum inhibitory concentrations (MIC) between 3.12 and 200 μg/mL, but compounds **4** and **6** were inactive (MIC >200 μg/mL).

Sapium indicum L. is a mangrove plant belonging to the family Euphorbiaceae and is widely distributed in the coastal areas of countries of Southeast Asia bordering the Indian Ocean.[1] Previous phytochemical studies on *S. indicum* have resulted in the isolation of several phorbol esters.[2−6] Recently, several phorbol esters were found to inhibit HIV-1.[7] As part of our continuing chemical studies on Thai medicinal plants,[8−10] we describe herein the chromatographic separation of a hexane extract of the fruits of *S. indicum*, which resulted in the isolation of three new phorbol esters, 12-(2-*N*-methylaminobenzoyl)-4β,5,20-trideoxyphorbol-13-acetate (**1**), 12-(2-*N*-methylaminobenzoyl)-4α,5,20-trideoxyphorbol-13-acetate (**2**), and 12-(2-*N*-methylaminobenzoyl)-4α,20-dideoxy-5-hydroxyphorbol-13-acetate (**6**), along with six known phorbol esters. Compounds **1**−**9** were evaluated for their antimycobacterial activity against *Mycobacterium tuberculosis* H37Ra.[11]

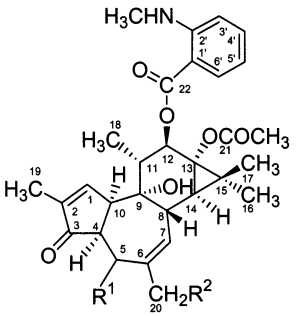
Six compounds of previously known structure were isolated from the hexane extract of the fruits of *S. indicum*, as described in the Experimental Section, and were identified, in turn, as sapintoxin A (**3**),[3] α-sapinine (**4**),[3] sapintoxin C (**5**),[4] sapintoxin B (**7**),[4] 12-(2′-*N*-methylaminobenzoyl)-4α-deoxy-5,20-dihydroxyphorbol-13-acetate (**8**),[2] and 12-(2-methylaminobenzoyl)-4-deoxyphorbaldehyde-13-acetae (**9**),[3] by comparison of their physical and spectral data with reported values. The ^{13}C NMR spectral data of these known isolates are reported herein for the first time.

Compound **1** was obtained as a yellow oil, and its molecular formula was determined as $C_{30}H_{37}NO_6$ by HRE-IMS (M^+ *m*/*z* 507.2628, calcd 507.2620). The IR spectrum showed the presence of carbonyls (1724, 1687 cm^{-1}), and the UV spectrum (λ_{max} 253, 360 nm) suggested the presence of a conjugated enone and benzoyl chromophores.[12] The ^{1}H and ^{13}C NMR spectra (Tables 1−3), analyzed by the aid of ^{1}H−^{1}H COSY and HMQC experiments, showed patterns similar to those of known compounds (**3**, **5**, and **7**)[3,4](Tables 1−3), with signals at δ 7.59 for H-1 (C-1 at δ 60.0), 5.25 for H-7 (C-7 at δ 125.7), and 1.05 for H-14 (C-14 at δ 35.8).

The multiplicity of signals in the ^{13}C NMR spectrum of **1**, as determined by DEPT experiments, indicated the presence of seven methyls, one methylene, 12 methines, and 10 quaternary carbons. The signals at δ 210.1, 173.7, and 168.1 in the ^{13}C NMR spectrum were attributed to carbonyl carbons. In addition, analysis of the HMBC spectrum showed that the proton H-12 (δ 5.65) correlated with the carbons C-11 (δ 42.5), C-13 (δ 65.6), C-15 (δ 25.4), C-18 (δ 15.1), and C-22 (δ 168.1), indicating an ester linkage at C-12. Other correlations are shown in Table 1 (Supporting Information). The proposed stereochemistry of this compound was supported from NOE correlations observed between H-8 (δ 2.40)/H-4 (δ 2.49)/H-11 (δ 1.71)



1 R^1 = H, R^2 = H
3 R^1 = H, R^2 = OH
5 R^1 = β-OH, R^2 = H
7 R^1 = β-OH, R^2 = OH
9 R^1 = H, R^2 = CHO



2 R^1 = H, R^2 = H
4 R^1 = H, R^2 = OH
6 R^1 = β-OH, R^2 = H
8 R^1 = β-OH, R^2 = OH

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Table 1. ^{1}H NMR Spectral Data for Compounds **1**−**5** (500 MHz in $CDCl_3$)

position	**1**	**2**	**3**	**4**
1	7.59 br s	7.05 s	7.56 br s	7.08 s
4	2.49 dt (4.5, 10.5)	2.70 m	2.52 dt (5, 9.5)	2.80 m
5β	2.87 dd (9, 18.5)	3.41 br d (15)	2.86 dd (9.5, 18)	3.45 dd (3.5, 16)
5α	2.04 dd (10.5, 18.5)	2.37 dd (4.5, 15)	2.17 dd (10, 18)	2.51 dd (5, 16)
7	5.25 m	4.83 br s	5.55 m	5.14 br s
8	2.40 br t (5)	1.95 br s	2.44 br t (5)	2.03 m
10	3.32 m	3.45 m	3.27 m	3.54 m
11	1.71 m	1.84 m	1.73 m	1.87 m
12	5.65 d (9.5)	5.71 d (10.5)	5.65 d (10)	5.72 d (10.5)
14	1.05 d (5.5)	0.83 d (5)	1.12 d (5)	0.84 d (5)
16	1.19 s	1.15 s	1.19 s	1.17 s
17	1.32 s	1.32 s	1.32 s	1.33 s
18	0.95 d (6.5)	1.09 d (6)	0.96 d (6.5)	1.12 d (6.5)
19	1.73 m	1.80 m	1.73 s	1.80 s
20	1.75 s	1.74 s	4.02 AB (13.5)	4.01 AB (12.5)
3′	6.70 br d (8)	6.70 dd (1.5, 8)	6.69 dd (1.5, 8.5)	6.70 d (8)
4′	7.42 dt (1.5, 8)	7.42 dt (1.5, 8)	7.40 dt (1.5, 8.5)	7.42 dt (2, 8)
5′	6.60 dt (1.5, 8)	6.61 dt (1.5, 8)	6.59 dt (1.5, 8.5)	6.62 t (8)
6′	7.83 dd (1.5, 8)	7.90 dd (1.5, 8)	7.81 dd (1.5, 8.5)	7.88 dd (1.5, 8)
NCH_3	2.94 d (4.5)	2.93 d (4.5)	2.93 s	2.93 br s
$COCH_3$	2.13 s	2.07 s	2.12 s	2.08 s

Table 2. ^{13}C NMR Spectral Data for Compounds **1**−**9** (125 MHz in $CDCl_3$)

carbon	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1	160.0	156.1	159.5	156.5	162.6	154.6	162.7	154.9	158.4
2	136.4	143.6	136.4	137.5	138.3	144.0	138.5	144.2	136.9
3	210.1	212.6	209.5	213.8	208.5	207.5	208.4	207.9	208.4
4	44.6	49.0	44.2	49.7	51.4	56.1	51.4	55.9	43.8
5	34.0	29.7	29.6	24.9	71.1	70.9	71.1	67.3	25.8
6	139.0	135.2	142.1	143.7	140.6	137.7	143.1	139.9	144.7
7	125.7	124.5	126.5	126.7	127.3	125.4	130.3	126.8	154.1
8	42.2	40.6	42.1	40.5	42.4	40.1	42.5	40.1	42.8
9	77.9	78.1	77.8	78.1	78.3	78.5	78.6	78.5	78.4
10	54.3	46.9	54.1	47.3	51.5	47.8	52.1	47.9	53.9
11	42.5	43.2	42.6	43.3	43.0	43.4	43.2	43.4	43.2
12	76.3	75.1	76.2	74.9	76.3	74.0	76.3	73.9	75.6
13	65.6	65.4	65.5	65.3	65.6	65.3	65.7	65.3	65.1
14	35.8	37.3	35.7	36.9	36.5	38.1	36.3	37.7	34.9
15	25.4	24.8	25.7	24.9	25.8	25.3	26.0	25.5	24.9
16	23.7	23.8	23.7	23.8	23.7	24.1	23.9	24.0	23.6
17	16.9	16.2	16.8	16.2	16.9	16.5	17.1	16.6	16.7
18	15.1	11.4	15.0	11.5	15.3	11.7	15.5	11.8	15.1
19	10.2	10.0	10.1	10.0	10.1	10.4	10.3	10.5	10.2
20	25.7	28.5	67.4	69.2	21.7	27.1	67.1	68.2	193.0
21	173.7	174.1	173.7	174.1	173.6	173.9	174.0	174.1	173.9
22	168.1	168.7	168.1	168.6	168.1	168.0	168.2	168.0	167.9
1′	152.3	152.8	152.3	152.8	152.3	152.4	152.6	152.4	152.3
2′	109.4	109.8	109.4	109.7	109.4	109.3	109.5	109.2	109.1
3′	110.8	111.0	110.8	111.0	110.8	110.9	111.1	110.9	110.9
4′	134.9	135.2	134.9	135.2	134.9	135.0	135.2	135.1	135.1
5′	114.4	114.5	114.4	114.5	114.4	114.3	114.7	114.4	114.5
6′	131.3	131.6	131.3	131.6	131.3	131.3	131.5	131.3	131.2
NCH_3	29.6	29.2	29.7	29.2	29.5	29.6	29.8	29.6	29.6
$COCH_3$	21.2	20.8	21.1	20.7	21.1	21.1	21.4	21.1	21.1

Table 3. ^{1}H NMR Spectral Data for Compounds **6**−**9** (500 MHz in $CDCl_3$)

position	**5**	**6**	**7**	**8**	**9**
1	7.70 br s	7.07 br s	7.71 br s	7.11 br s	7.51 br s
4	2.63 t (4.5)	3.12 dd (4.5, 6.5)	2.64 t (4.5)	3.21 m	2.53 m
5	4.87 br d (3.5)	4.45 br s	5.20 d (4.5)	4.57 br s	2.76 d (11)
7	5.33 m	4.88 br s	5.62 d (5)	5.21 d (1.5)	6.57 br s
8	2.34 br s	2.05 m	2.35 br t (5)	2.11 m	2.70 br t (6.5)
10	3.54 m	3.64 m	3.59 m	3.71 m	3.10 m
11	1.66 m	1.85 m	1.68 m	1.87 m	1.80 m
12	5.65 d (9.5)	5.70 d (10)	5.65 d (10)	5.72 d (10.5)	5.69 d (10)
14	1.09 d (5.5)	0.86 d (4.5)	1.13 d (5)	0.92 d (4.5)	1.25 d (4.5)
16	1.20 s	1.18 s	1.20 s	1.19 s	1.24 s
17	1.29 s	1.31 s	1.29 s	1.34 s	1.33 s
18	0.97 d (6.5)	1.12 d (6)	0.97 d (6)	1.16 d (6.5)	0.98 d (6.5)
19	1.75 m	1.81 br t (1.5)	1.75 m	1.82 m	1.73 m
20	1.88 s	1.88 br s	4.25 AB (13)	4.15 br s	9.45 s
3′	6.72 d (8)	6.72 d (8)	6.71 d (8)	6.74 d (8)	6.71 d (8)
4′	7.43 dt (1.5, 8)	7.43 dt (1.5, 8)	7.42 dt (1.5, 8)	7.45 dt (1.5, 8)	7.42 dt (2, 8)
5′	6.61 dt (1.5, 8)	6.61 dt (1.5, 8)	6.60 dt (1.5, 8)	6.63 dt (1.5, 8)	6.60 dt (2, 8)
6′	7.88 dd (1.5, 8)	7.88 dd (1.5, 8)	7.82 dd (1.5, 8)	7.89 dd (1.5, 8)	7.82 dd (2, 8)
NCH_3	2.93 s	2.94 d (4.5)	2.93 s	2.95 s	2.94 s
$COCH_3$	2.12 s	2.11s	2.13 s	2.11 s	2.16 s

and H-17 (δ 1.32) on the β-face and H-14 (δ 1.05)/H-16 (δ 1.19) and H-7 (δ 5.25) on the other side of the molecule (Figure 1, Supporting Information).

Compound **2**, isolated as a yellow oil, showed carbonyl bands at 1721 and 1687 cm^{-1} in the IR spectrum, and the UV spectrum indicated the presence of a conjugated enone

and benzoyl chromophores (λ_{max} 247, 357 nm). The molecular formula of **2** was determined as $C_{30}H_{37}NO_6$ from its HREIMS (M^+ *m/z* 507.2617, calcd 507.2620). The ^1H and ^{13}C NMR spectra of **2** were almost the same as those of **1**, except for signals at δ 7.05 for H-1 (C-1 at δ 156.1), 4.83 for H-7 (C-7 at δ 124.5), and 0.83 for H-14 (C-14 at δ 37.3) appeared at higher field, which can be explained in terms of shielding effects of the 1, 2- and 6, 7-double bonds. The signals of **1** at δ 2.04 for H_a-5 and δ 2.87 for H_b-5 (C-5 at δ 34.0) appeared at lower field because of the anisotropic effect of the carbonyl group, caused by the change of stereochemistry of the parent diterpene upon epimerization at C-4. The NOE interactions between H-4 and H-10 in **2** (Figure 2, Supporting Information) indicated that the protons positioned at C-4 and C-10 should be *syn* and were assigned arbitrarily as β-oriented. The HMBC correlations of **2** (Table 1, Supporting Information) were similar to those of compound **1**.

Compound **6** appeared as a yellow oil, whose molecular formula, $C_{30}H_{37}NO_7$, was inferred by HRFABMS [$(M + H)^+$ *m/z* 524.2652, calcd 524.2648]. The IR absorption bands at 1721 and 1687 cm^{-1} indicated the presence of carbonyls, and the UV spectrum showed absorption bands at 247 and 359 nm indicative of conjugated enone and benzoyl chromophores. The ^1H NMR spectrum of **6** was similar to those of 12-(2-*N*-methylaminobenzoyl)-4α,20-dideoxy-5-hydroxyphorbol[4] (Table 3) except for the appearance of an acetyl signal. In the HMBC spectrum an acetyl signal at δ 2.10 showed correlations to C-21 (δ 173.9) and C-13 (δ 65.3).

Compounds **1**−**3**, **5**, and **7**−**9** exhibited antimycobacterial activity with MIC values between 12.5 and 200 μg/mL (Table 4). It is interesting to note that the 4β-isomers showed higher activity than the 4α-isomers. Our result is in agreement with a previous literature report.[13]

Experimental Section

General Experimental Procedures. Specific rotations were determined with an Autopol II automatic polarimeter. UV spectra were measured with a UV-160A spectrophotometer (Shimadzu), and IR spectra were recorded on a Perkin-Elmer 1750 FTIR spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using a 500 MHz Varian Unity INOVA spectrometer. Chemical shifts are recorded in parts per million (δ) in $CDCl_3$. Mass spectra (EI or FAB) were recorded on a Finnigan-MAT 95 XL spectrometer. Column chromatography was carried out on silica gel 60 GF_{254} (Merck).

Plant Material. The fruits of *Sapium indicum* were collected in Sathing Phra, Songkhla, Thailand, in May 2000 and identified by Prof. Puangpen Sirirugsa. A voucher specimen (number 0012196) was deposited in the herbarium of the Department of Biology, Faculty of Science, Prince of Songkla University, Songkhla, Thailand.

Extraction and Isolation. Air-dried and powdered fruits (3.8 kg) were extracted with hexane at room temperature. The hexane extract was taken to dryness under reduced pressure to yield a yellow solid (2 g) and a yellow gum (17 g). The yellow solid (2 g) was partially separated by column chromatography on silica gel (100 g) and elution with 0−100% hexane−EtOAc to afford eight fractions. Fractions 3, 4, and 6 were further purified by preparative TLC with 30% hexane−EtOAc to give **1** (4.1 mg, R_f 0.53, 40% hexane−ether), **9** (4 mg, R_f 0.30, 20% hexane−ether), and **5** (6.6 mg, R_f 0.25, 40% hexane−ether), sequentially. Purification of fraction 7 (600 mg) was also performed by preparative TLC using the same conditions as described above to provide **3** (140 mg, R_f 0.16, 20% hexane−ether) and **4** (23.2 mg, R_f 0.21, 20% hexane−ether). The yellow gum (17 g) was partially separated by rapid column chromatography on silica gel (100 g), eluted with 0−100% EtOAc−hexane mixtures, to give 15 fractions. Fraction 6 (325 mg) was further purified by preparative TLC on silica gel plates, using 30% ether−hexane to afford **2** (9.3 mg, R_f 0.56, 40% hexane−ether). Fractions 10, 14, and 15 were also purified by preparative TLC using 50% ether−hexane to give **6** (10.4 mg, R_f 0.33, 40% hexane−ether), **7** (9.2 mg, R_f 0.06, 40% hexane−ether), and **8** (9.8 mg, R_f 0.13, 40% hexane−ether), respectively.

Table 4. Antimycobacterial Activities of Compounds **1**−**9**

compound	MIC (μg/mL)
1	50
2	200
3	3.12
4	>200
5	25
6	>200
7	12.5
8	25
9	25
isoniazide[a]	0.040−0.090
kanamycin sulfate[a]	2.0−5.0

[a] Positive control substance.

Compound 1: yellow oil; $[\alpha]_D^{28}$ +45.5° (*c* 0.0044, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 253 (5.32), 360 (5.01) nm; IR ($CHCl_3$) ν_{max} 3388 (OH), 1724, 1687 (C=O) cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS *m/z* 507 (3) $[M]^+$, 414 (3), 357 (7), 297 (14), 255 (4), 161 (8), 151 (100); HREIMS *m/z* 507.2628 $[M]^+$ (calcd for $C_{30}H_{37}NO_6$, 507.2620).

Compound 2: yellow oil; $[\alpha]_D^{28}$ −57.9° (*c* 0.0069, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 247 (5.03), 357 (4.57) nm; IR($CHCl_3$) ν_{max} 3388 (OH), 1721, 1687 (C=O) cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS *m/z* 507 (5) $[M]^+$, 414 (5), 357 (9), 297 (12), 255 (5), 161 (6), 151 (100); HREIMS *m/z* 507.2617 $[M]^+$ (calcd for $C_{30}H_{37}NO_6$, 507.2620).

Compound 3: yellow oil; $[\alpha]_D^{28}$ +18.5° (*c* 0.0054, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 252 (5.25), 360 (4.94) nm; IR ($CHCl_3$) ν_{max} 3389 (OH), 1720, 1687 (C=O) cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2.

Compound 4: yellow oil; $[\alpha]_D^{28}$ −52.6° (*c* 0.0057, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 252 (5.23), 360 (4.91) nm; IR ($CHCl_3$) ν_{max} 3388 (OH), 1721, 1687 (C=O) cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2.

Compound 5: yellow oil; $[\alpha]_D^{28}$ +36.4° (*c* 0.0055, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 253 (5.06), 360 (4.74) nm; IR ($CHCl_3$) ν_{max} 3388 (OH), 1721, 1687 (C=O) cm^{-1}; ^1H NMR, see Table 3; ^{13}C NMR, see Table 2.

Compound 6: yellow oil; $[\alpha]_D^{28}$ −33.3° (*c* 0.0030, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 247 (5.39), 359 (5.12) nm; IR ($CHCl_3$) ν_{max} 3388 (OH), 1721, 1687 (C=O) cm^{-1}; ^1H NMR, see Table 3; ^{13}C NMR, see Table 2; FABMS *m/z* 524 (4) $[M + H]^+$, 453 (6), 373 (7), 355 (11), 313 (13), 261 (15), 201 (85), 185 (33), 152 (47), 134 (100); HRFABMS *m/z* 524.2652 $[M + H]^+$ (calcd for $C_{30}H_{37}NO_7$, 524.2648).

Compound 7: yellow oil; $[\alpha]_D^{28}$ +13.5° (*c* 0.0074, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 252 (5.11), 360 (4.79) nm; IR ($CHCl_3$) ν_{max} 3388 (OH), 1724, 1687 (C=O) cm^{-1}; ^1H NMR, see Table 3; ^{13}C NMR, see Table 2.

Compound 8: yellow oil; $[\alpha]_D^{28}$ −31.9° (*c* 0.0094, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 252 (5.00), 361 (4.69) nm; IR ($CHCl_3$) ν_{max} 3387 (OH), 1721, 1687 (C=O) cm^{-1}; ^1H NMR, see Table 3; ^{13}C NMR, see Table 2.

Compound 9: yellow oil; $[\alpha]_D^{28}$ +55.6° (*c* 0.0018, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 252 (5.73), 360 (5.41) nm; IR ($CHCl_3$) ν_{max} 3387 (OH), 1724, 1687 (C=O) cm^{-1}; ^1H NMR, see Table 3; ^{13}C NMR, see Table 2.

Bioassay. The antimycobacterial activity was assessed against *Mycobacterium tuberculosis* H37Ra using the Microplate Alamar Blue Assay.[11] In this system, the standard drugs isoniazid and kanamycin sulfate were used as reference compounds (Table 4).

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Supporting Information Available: Table of HMBC NMR data for compounds **1**, **2**, and **6** and figures of NOE NMR interactions for compounds **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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