Antitumor Agents, 119. Kansuiphorins A and B, Two Novel Antileukemic Diterpene Esters from Euphorbia kansui

Tian-Shung Wu, Yuh-Meei Lin, Mitsumasa Haruna, De-Ji Pan, Tetsuro Shingu, Yuh-pan Chen, Hong-Yen Hsu, Tatsuhiko Nakano, and Kuo-Hsiung Lee

J. Nat. Prod., **1991**, 54 (3), 823-829• DOI: 10.1021/np50075a011 • Publication Date (Web): 01 July 2004

Journal of Natural Products
Vol. 54, No. 3, pp. 823-829, May-Jun 1991

ANTITUMOR AGENTS, 119[1]. KANSUIPHORINS A AND B, TWO NOVEL ANTILEUKEMIC DITERPENE ESTERS FROM *EUPHORBIA KANSUI*

TIAN-SHUNG WU, YUH-MEEI LIN, MITSUMASA HARUNA, DE-JI PAN, TETSURO SHINGU,

Natural Products Laboratory, Division of Medicinal Chemistry and Natural Products, School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27599

YUH-PAN CHEN, HONG-YEN HSU,

Brion Research Institute of Taiwan, 116 Chung-Ching S. Road, Section 3, Taipei, Taiwan

TATSUHIKO NAKANO, and KUO-HSIUNG LEE*

Natural Products Laboratory, Division of Medicinal Chemistry and Natural Products, School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27599

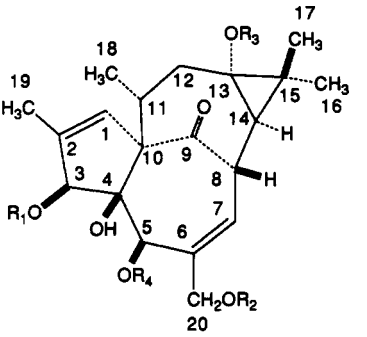
ABSTRACT.—The extract of the roots of *Euphorbia kansui*, which has been widely used in Chinese folk medicine for the treatment of cancer, demonstrated antileukemic activity against the P-388 lymphocytic leukemia in mice. Bioassay-directed fractionation of the active extract led to the isolation and characterization of two novel antileukemic diterpene esters, kansuiphorin A [**1**] [13-hydroxyingenol-3-(2,3-dimethylbutanoate)-13-dodecanoate-20-hexadecanoate] and kansuiphorin B [**2**] [6,7-epoxy-13-hydroxyingenol-3-(2,3-dimethylbutanoate)-13-dodecanoate-20-hexadecanoate], whose structures were established from spectral evidence and chemical transformation. Kansuiphorins A and B demonstrated potent antileukemic activity with T/C≥176 and 177% at 0.1 and 0.5 mg/kg, respectively. The selectivity of kansuiphorin A, which inhibits the growth of particular cell types within the disease-oriented human cancer cell line panels, is discussed.

The dried roots of *Euphorbia kansui* Liou (Euphorbiaceae) are known as "kan sui" in Chinese folklore. Kan sui was recorded in *Sheng Nung's Herbal* as a low-grade drug (2) and has been used as a herbal remedy for edema, ascites (3,4), and cancer (5) in China. Previous investigations on kan sui have yielded tirucallol, α-euphorbol, α-euphol (2), the analgesic and anti-writhing kansuinine A, kansuinine B, 20-deoxyingenol-3-benzoate, 20-deoxyingenol-5-benzoate, ingenol-3-(2,4-decadienoate)-20-acetate, and 13-oxyingenol-13-dodecanoate-20-hexanoate (6–8). In addition, kansuiphorins C and D were recently isolated as two new cytotoxic diterpenes from this same plant by our laboratory (9). Further bioassay-directed fractionation of an EtOH extract, which showed significant (T/C≥125%) (10) inhibitory activity in vivo against P-388 lymphocytic leukemia growth in BDF_1 mice, has led to the isolation and characterization of two novel diterpene esters, kansuiphorins A [**1**] and B [**2**]. Compounds **1** and **2** exhibited potent in vivo antileukemic (P-388) activity with T/C≥176 and 177% at 0.1 and 0.5 mg/kg, respectively. Kansuiphorin A is also selectively cytotoxic to certain human cancer cell lines, including leukemia, non-small-cell lung cancer, colon cancer, melanoma, and renal cancer cells.

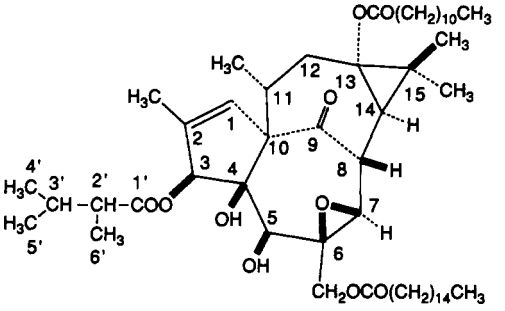
RESULTS AND DISCUSSION

The ground roots of *E. kansui* were extracted with 95% EtOH. Guided by an in vivo (P-388) assay, the active EtOH extract was further extracted with Et_2O. Cc of the active Et_2O extract yielded kansuiphorin A [**1**] [13-hydroxyingenol-3-(2,3-dimethylbutanoate)-13-dodecanoate-20-hexadecanoate] and kansuiphorin B [**2**] [6,7-epoxy-

[1]For part 118, see Toyota *et al.* (1).



1 R_1=COCH(Me)CH(Me)$_2$, R_2=CO(CH$_2$)$_{14}$Me, R_3=CO(CH$_2$)$_{10}$Me, R_4=H
3 R_1=COCH(Me)CH(Me)$_2$, R_2=CO(CH$_2$)$_{14}$Me, R_3=CO(CH$_2$)$_{10}$Me, R_4=Ac
4 R_1=R_2=R_4=H, R_3=CO(CH$_2$)$_{10}$Me
5 R_1=R_2=R_4=Ac, R_3=CO(CH$_2$)$_{10}$Me



2

13-hydroxyingenol-3-(2,3-dimethylbutanoate)-13-dodecanoate-20-hexadecanoate] in 0.001% and 0.0003% yield, respectively.

Kansuiphorin A [**1**], $C_{54}H_{90}O_9$, obtained as a colorless oil, displayed ir absorptions at 3480 (OH), 1740, 1725, 1710 (CO), and 1650 (C=C) cm^{-1}. The ^{1}H-nmr spectrum of **1** was very similar to those of 13-hydroxyingenol derivatives (7), but some differences were observed. In the case of 13-hydroxyingenol-13-dodecanoate-20-hexanoate, H-3 appeared at δ 4.43 (s), but in **1** the corresponding proton resonated as a singlet at the lower field of δ 5.45. A broad singlet at δ 1.26, due to methylene protons, appeared in greater intensity, and the methyl region (δ 1.15–0.85) presented more complexity. The mass spectrum showed that the three ester groups consisted of a 2,3-dimethylbutanoate $[MH - 116]^+$, a dodecanoate $[MH - 116 - 200]^+$, and a hexadecanoate $[MH - 116 - 200 - 256]^+$ unit. The presence of the 2,3-dimethylbutanoate moiety was confirmed by double resonance experiments. On irradiation at δ 2.31 (H-2′) the signals at δ 1.92 (H-3′) and 1.15 (Me-6′) changed from a multiplet to a quintet and from a doublet to a singlet, respectively. Irradiation at δ 1.92 (H-3′) induced a multiplet at δ 2.31 (H-2′) and two doublets at δ 0.95 and 0.93 (H-4′ and -5′) to a quartet and two singlets, respectively. When irradiated at δ 0.93 and 0.95, a multiplet at δ 1.92 (H-3′) collapsed to a doublet (J = 6.7 Hz).

Acetylation of **1** afforded a monoacetate **3**. The ^{1}H-nmr spectrum showed a signal for an acetyl group (δ 2.22). The singlets at δ 3.87 (H-5) and 5.45 (H-3) observed in the spectrum of **1** now shifted to δ 5.38 and 4.97, respectively. The upfield shift of H-3 by 0.48 ppm on acetylation of H-5 in **1** is due to the anisotropic effect of the acetyl carbonyl group.

Mild alkaline hydrolysis of **1** with 0.5 M KOH in MeOH at room temperature afforded a tetrahydroxy derivative **4**. The mass spectrum showed a fragment ion $[M-200]^+$, indicating that the dodecanoate ester did not undergo hydrolysis and hence is attached to the tertiary OH at C-13. The ir spectrum showed the presence of two carbonyl groups (1735 and 1720 cm^{-1}). In the ^1H-nmr spectrum, the two-proton signal (H_2-20) and the one-proton signal (H-3) now resonated at δ 4.16 and 4.43, respectively, which were upfield relative to **1**. Acetylation of **4** afforded a triacetate **5** whose ^1H-nmr spectrum exhibited signals for three acetyl groups (δ 2.01, 2.12, and 2.22) (Table 1).

From the foregoing results, it is clear that the remaining two ester groups, 2,3-dimethylbutanoate and hexadecanoate, in **1**, are located at C-3 and C-20. The position of the 2,3-dimethylbutanoate ester group was determined by the ^{13}C-^1H long range COSY spectrum of **1**. This ester carbonyl carbon resonated at the lower field of δ 177.44 than the carbonyl carbons (δ 174.08) of the dodecanoate and hexadecanoate moieties; it is known that branched alkyl ester carbonyl carbons are more deshielded than those of *n*-alkyl ester carbonyl carbons (11). A long range CH coupling between this carbonyl carbon and H-3 was observed (Figure 1). This was taken as evidence that 2,3-dimethylbutanoate is connected to C-3; hence hexadecanoate is attached to C-20. The ^{13}C-nmr spectral data which confirmed the structural assignment of **1** for kansuiphorin A are listed in Table 2.

Kansuiphorin B [**2**], $C_{54}H_{90}O_{10}$, obtained as a colorless oil, showed the ir absorptions at 3460 (OH), 1732 and 1720 (CO) cm^{-1}. In the ^1H-nmr spectrum four signals at δ 6.09 (H-7), 4.06 (H-8), 4.47 (H-20), and 4.74 (H-20) in **1** shifted upfield to δ 3.47, 3.17, 4.13, and 4.29, respectively. This suggested the presence of an epoxide instead of a double bond between C-6 and C-7 in **1**. Because the coupling constant between H-7 and H-8 is 6 Hz, this epoxide ring is β-oriented (Table 1). Kansuiphorin B is not an artifact of kansuiphorin A as a result of using Et_2O for extraction, as the former was not formed when a known amount of the latter was subjected to the same extraction and isolation procedure using peroxide-free Et_2O as the extraction solvent.

The potent antileukemic activity demonstrated by **1** and **2**, as mentioned above, prompted us to examine further their possible tumor specificity in the disease-oriented human cancer cell line panels that have recently been established by the National

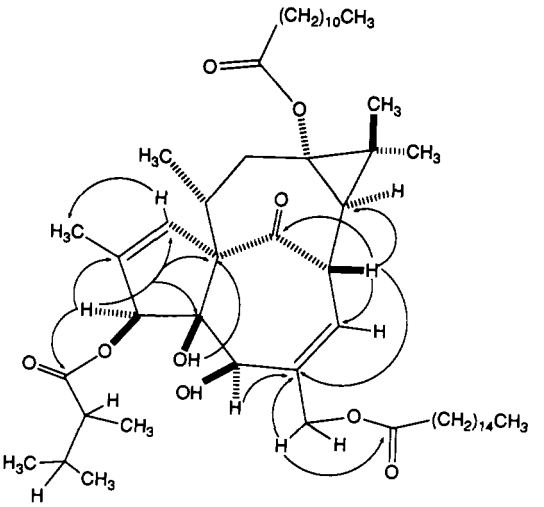


FIGURE 1. Long-range ^{13}C-^1H COSY spectrum of kansuiphorin A [**1**].

TABLE 1. ^{1}H-nmr Spectra of Kansuiphorin A [**1**], Its Derivatives **3**, **4**, and **5**, and Kansuiphorin B [**2**].[a]

Proton	Compound				
	1	**2**	**3**	**4**	**5**
H-1	6.02 d, J = 1.5	6.05 d, J = 1.0	6.08	5.93 d, d, J = 1.5	6.08, J = 0.9
H-3	5.45 s	5.40 s	4.97 s	4.43 s	4.97 s
H-5	3.87 s	3.72 d, J = 8.1	5.38 b	3.82 s	5.40 s
H-7	6.09 d, J = 3.7	3.47 d, J = 6.0	6.21 d	6.03 d, J = 4.4	6.21 d, J = 4.2
H-8	4.06 dd, J = 3.7, 13	3.17 dd, J = 6, 12.2	4.21 d	4.06 dd, J = 4.4, 12.3	4.20 dd, J = 4.2, 12
H-11	2.59 m	2.43 m		2.43 m	2.60 m
H_2-12	2.23 dd, J = 5.5, 16	2.25 dd, J = 4.2, 17	2.68 m	2.24 dd, J = 6.9, 11.7	2.28 dd, J = 4.6, 16
	2.71 dd, J = 3.5, 16	2.61 dd, J = 3, 17	2.78	2.72 dd, J = 4, 11.7	2.69 dd, J = 3.5, 16
H-14	1.29 d, J = 13	1.2 d, J = 12.2	1.30	1.14 d, J = 12.3	1.21 d, J = 12
Me-16	1.06 s	1.08 s	1.07 s	1.07 s	1.07 s
Me-17	1.18 s	1.28 s	1.19 s	1.22 s	1.19 s
Me-18	0.98 d, J = 8.4	0.94 d, J = 6.7	1.01 d	0.92 d, J = 7.2	1.00 d, J = 7.2
Me-19	1.78 d, J = 1.5	1.79 d, J = 1.0	1.77 d	1.86 d, J = 1.5	1.79 d, J = 0.9
H_2-20	4.47 d, J = 12.8	4.13 d, J = 12	4.22 d	4.16 ABq, J = 4.3	4.19 d, J = 12
	4.74 d, J = 12.8	4.22 d, J = 12	4.58 d	4.16 ABq	4.58 d, J = 12
4-OH	3.50 s	3.30 s	3.30 bs	3.33 br	3.29 bs
5-OR_4	3.61 s (OH)	3.35 d, J = 8.1 (OH)	2.22 s (Ac)	3.35 br (OH)	2.22 s, 3H (Ac)
R_1	2.31 m, 1H	2.31 m	2.31 m	4.12 s (OH)	2.12 s, 3H (Ac)
	1.92 m, J = 6.7, 1H	1.89 m, J = 6.7, 1H	1.89 m		
	1.15 d, J = 6.5, 3H	1.13 d, J = 7.1, 3H	1.14 d		
	0.93 d, J = 6.7, 3H	0.94 d, J = 6.7, 3H	0.94 d		
	0.95 d, J = 6.7, 3H	0.92 d, J = 6.7, 3H	0.91 d		
R_2	2.30 t, J = 7.6, 2H	2.30 t, J = 7.3, 2H	2.29 t, 2H	3.67 s (OH)	2.01 s, 3H (Ac)
	1.25 s, -$(CH_2)_{13}$-	1.26 s, -$(CH_2)_{13}$-	1.26 s, 26H		
	0.88 t, J = 7.0	0.88 t, J = 7.0, 3H	0.88 t, 3H		
R_3	2.21 t, J = 7.0, 2H	2.20 t, J = 9.0, 2H	2.21 t, 2H	2.20 t, J = 7.5	2.21 t, 2H
	1.25 s, -$(CH_2)_9$-	1.26 s, -$(CH_2)_9$-	1.26 s, 18H	1.25 s, 18H	1.25 s, 18H
	0.88 t, J = 7.0, 3H	0.88 t, J = 7.0, 3H	0.88 t, 3H	0.88 t, 3H	0.88 t, 3H

[a]The assignment of the signals in **1** was confirmed by double resonance experiments. J is in Hertz.

TABLE 2. ^{13}C-nmr Data of Kansuiphorin A [**1**] ($CDCl_3$).

Carbon		Carbon		Carbon	
C-1	131.65 (d)	C-1′	177.33 (s)	C-1‴	173.86 (s)
C-2	136.26 (s)	C-2′	44.50 (t)	C-2‴	34.45 (t)
C-3	82.80 (d)	C-3′	31.09 (d)	C-3‴	24.68 (t)
C-4	84.73 (s)	C-4′	20.67 (q)[a]	C-4‴	29.70 (t)[a]
C-5	74.95 (d)	C-5′	19.19 (q)[a]	C-5‴	29.67 (t)[a]
C-6	136.60 (s)	C-6′	14.10 (q)	C-6‴	29.60 (t)[a]
C-7	128.38 (d)	C-1″	174.05 (s)	C-7‴	29.32 (t)[a]
C-8	42.85 (d)	C-2″	34.32 (t)	C-8‴	29.15 (t)[a]
C-9	205.17 (s)	C-3″	24.97 (t)	C-9‴	29.47 (t)[a]
C-10	71.97 (s)	C-4″	29.70 (t)[a]	C-10‴	31.93 (t)
C-11	37.67 (d)	C-5″	29.70 (t)[a]	C-11‴	22.70 (t)
C-12	35.15 (t)	C-6″	29.67 (t)[a]	C-12‴	14.10 (q)
C-13	69.08 (s)	C-7″	29.67 (t)[a]		
C-14	28.39 (d)	C-8″	29.60 (t)[a]		
C-15	30.42 (s)	C-9″	29.60 (t)[a]		
C-16	22.49 (q)	C-10″	29.32 (t)[a]		
C-17	16.71 (q)	C-11″	29.29 (t)[a]		
C-18	18.19 (q)	C-12″	29.15 (t)[a]		
C-19	15.52 (q)	C-13″	29.47 (t)[a]		
C-20	66.34 (t)	C-14″	31.93 (t)		
		C-15″	22.70 (t)		
		C-16″	14.10 (q)		

[a]Assignments may be interchanged.

Cancer Institute (12). As shown in Table 3, compound **1** is more sensitive to leukemia MOLT-4, HL-60 TB, and K-562, non-small-cell lung cancer H-322 and HOP-62, colon cancer SW-620, melanoma SK-MEL-5, RPMI-7951, and Maime-3M, and renal cancer A-498, A-704, and SN-12 K1. However, it is not sensitive to leukemia P388/ADR, non-small-cell lung cancer H-522, H-125, H-23, and EKVX, small cell lung cancer H-82, H-524, H-69, and H-146, colon cancer DLD-1 and HCC-2998, breast cancer MCF-7 and MCF-7/ADR, CNS cancer U-251, SNB-19, SNB-44, and SNB-75, melanoma SK-MEL-2, ovarian cancer OVCAR-8 and OVCAR-5, and renal cancer

TABLE 3. Cytotoxicity of Kansuiphorin A [**1**] Against the Panels of Human Cancer Cell Lines.

Disease Type	Cell Line[a]	IC_{50} (μg/ml)
Leukemia	MOLT-4	0.13
	HL-60 TB	0.03
	K-562	0.03
Non-small cell lung cancer	H-322	0.33
	HOP-62	0.06
Colon cancer	SW-620	0.08
Melanoma	SK-MEL-5	0.14
	RPMI-7951	0.05
	Maime-3M	0.32
Renal cancer	A-498	0.02
	A-704	0.03
	SN-12 K1	0.07

[a]The cell lines listed in this table are those which are more sensitive to **1** based on a pattern of sensitivity study.

UO-31. Compounds **1** and **2** deserve further development as potentially useful antitumor agents.

It is noteworthy that **1** and **2** belong to the ingenol-type diterpene esters. The ingenol-3-esters are known to possess irritant and tumor-promoting activities, while ingenol-20-esters are inactive (13,14). Thus, **1** and **2** are unlikely to show irritant and tumor-promoting properties unless they are metabolized in vivo into C-20 free alcohols. It has also been observed that C-20 esterification tends to abolish the tumor-promoting activity while keeping the antileukemic activity intact. Presumably such modification in structures would change these compounds into protein kinase C inhibitors rather than activators which are required for carcinogenicity (15, K.H. Lee and H.C. Lin, unpublished observations).

EXPERIMENTAL

PLANT MATERIAL.—The roots of *E. kansui* (4) used in this investigation were obtained from the Ho-Cheng Herb Store, Taipei, in spring 1985. A voucher specimen was kept at the Herbarium of Brion Research Institute of Taiwan, Taipei, Taiwan.

GENERAL EXPERIMENTAL PROCEDURES.—^{1}H- and ^{13}C-nmr spectra were recorded at 400 MHz and 100.06 MHz, respectively, using a JEOL FX-400 instrument. The usual pulse sequences of JEOL were used in ^{1}H-^{1}H COSY and ^{1}H-^{13}C COSY experiments; for the heteronuclear correlations, coupling constants of 140 Hz (one-bond), 5 Hz, and 10 Hz (long-range) were employed in measurements. Eims and fabms were determined on a V.G. Micromass 70-70 instrument at 70 eV with a direct inlet system. Si gel (Merck 70-230 mesh) was used for cc, and precoated Si gel (Merck 60 f-254) plates were employed for tlc. Detection of components was performed by spraying with 1% $Ce(SO_4)_2$ or 10% H_2SO_4 solution, followed by heating or by use of a uv lamp.

ISOLATION OF KANSUIPHORINS A [**1**] AND B [**2**].—The dried roots of *E. kansui* (1 kg) were extracted exhaustively with 95% EtOH. The EtOH extract (165 g) was further extracted with Et_2O. Cc of the resulting Et_2O extract [T/C (P-388) = 150% at 24 mg/kg] on Si gel with *n*-hexane–EtOAc (5:1) as eluent yielded an active fraction a [2.1 g, T/C (P-388) = 165% at 5 mg/kg]. Further cc [Si gel, $CHCl_3$-EtOAc (7:1)] of this active fraction a gave a fraction b, which showed an enhanced activity [T/C (P-388) = 151% at 0.5 mg/kg]. Subsequent repeated preparative tlc of fraction b [Si gel, $CHCl_3$-Me_2CO (20:1) and then C_6H_6-Me_2CO (39:1)] afforded kansuiphorins A [**1**] (10 mg) and B [**2**] (0.3 mg).

KANSUIPHORIN A [**1**].—Kansuiphorin A was isolated as a colorless oil: $[\alpha]^{20}D$ −27.8° (c = 0.1, $CHCl_3$); uv λ max (EtOH) 275, 281 nm; ir (neat) 3480, 1740, 1725, 1710, 1650, 1460, 1380, 1370 cm^{-1}; fabms (thioglycerol) *m/z* $[M+H+TG]^+$ 991, $[M+H]^+$ 883, $[M+H-28]^+$ 855, $[M+H-116]^+$ 768, $[768-H_2O]^+$ 750, 675, 657, 629, 619, 583, $[M+H-116-200]^+$ 567, 549, $[M+H-116-256]^+$ 511, 493, 483, 465, $[M+H-200-256]^+$ 427, 419, 409, 391, 359, 345, $[M+H-200-256-(Me)_2CHCH(Me)CO+H]^+$ 329, $[M+H-116-200-256]^+$ 311, 293, 283, 265, 255, 241, 227, 213); fabms (thioglycerol + NaOAc) *m/z* $[M+Na+TG]^+$ 1013, $[M+Na]^+$ 905; fabms (glyerol) *m/z* $[M+H]^+$ 833.

ACETYLATION OF KANSUIPHORIN A [**1**]. Compound **1** was acetylated with Ac_2O-pyridine at room temperature overnight. The product was purified by preparative tlc [Si gel, $CHCl_3$-Me_2CO (20:1)] to yield **3** as a colorless oil.

ALKALINE HYDROLYSIS OF KANSUIPHORIN A [**1**].—A solution of **1** (6 mg) in 0.5 M KOH/MeOH (2 ml) was allowed to stand at room temperature for 40 min. After the solution was neutralized with 2% HCl/MeOH (pH 4–5), it was filtered and the filtrate was evaporated. The product was dissolved in $CHCl_3$, washed wtih 2% $NaHCO_3$ and H_2O, dried over $MgSO_4$, and evaporated to give a residue. Purification of the residue by preparative tlc [Si gel, $CHCl_3$-MeOH (9:1)] furnished a tetrahydroxy derivative **4** (1.9 mg) as a colorless oil: ir (neat) 3455, 1735, 1720, 1460, 1380 cm^{-1}; fabms (thioglycerol) *m/z* $[M+Na+TG]^+$ 677, $[M+H+TG]^+$ 655, $[M+K]^+$ 585, $[M+Na]^+$ 569, 555, 541, 529, 511, 493, 479, 447, 471, 455, 437, 419, 403, 387, $[M+K-200]^+$ 385, 371, $[M+Na-200]^+$ 369, 347, 329, 327, 311, 299, 283, 255, 239, 227, 215, 213; eims *m/z* $[M-18]^+$ 528, 511, 510, 498, 492, 482, 467, 453, 441, 424, 413, 401, 384, 360 $[M-200]^+$ 346, 328, 310, 292, 282, 264.

ACETYLATION OF THE TETRAHYDROXY DERIVATIVE **4**.—Compound **4** was acetylated to yield **5** by a method analogous to that described above for the acetylation of **1** to give **3**. Compound **5** was obtained as a colorless oil: ir 3460, 1740, 1730, 1715, 1460, 1375, 1370 cm^{-1}

KANSUIPHORIN B [**2**].—Kansuiphorin B was obtained as a colorless oil: $[\alpha]^{20}D$ +54.3 (c = 0.03, $CHCl_3$); ir (neat) 3460, 1732, 1720, 1455, 1378, 1365 cm^{-1}; fabms (thioglycerol) *m/z* $[M+NH_4]^+$ 916, 783, 511, 327, 311, 293, 281, 269, 257, 232, 215. It exhibited no uv absorption above 200 nm.

BIOLOGICAL ACTIVITY.—In vivo antileukemic assay was carried out according to standard National Cancer Institute procedures described in the literature (10). Kansuiphorins A [**1**] and B [**2**] demonstrated potent antileukemic activity in P-388 lymphocytic leukemia with T/C≥176 and 177% at 0.1 and 0.5 mg/kg, respectively. The in vitro cytotoxicity (Table 3) against the disease-oriented human cancer cell line panels was assayed under the auspices of the Natural Products Branch, Division of Cancer Treatment, National Cancer Institute, by procedures described in the literature (12).

ACKNOWLEDGMENTS

This investigation was supported by a grant from the National Cancer Institute (CA 17625) awarded to K.H. Lee. The authors thank Dr. Yung-Chi Cheng and Mr. Michael H. Fisher of the Cancer Research Center, University of North Carolina at Chapel Hill, for biological assays. Thanks are also due to Drs. M. Suffness, G.M. Cragg, T. Otani, and B.J. Abbott of the National Cancer Institute for the human cancer cell line panels assay.

LITERATURE CITED

1. T. Toyota, N. Fukamiya, M. Okano, K. Tagahara, J.J. Chang, and K.H. Lee, *J. Nat. Prod.*, **53**, 1526 (1990).
2. H.Y. Hsu, *Formosan Sci.* **40**, 1 (1986), and literature cited therein.
3. "Chung Kuo Yao Dian" (Chinese Pharmacopoeia), People's Health Press, Beijing, 1985, p. 68.
4. "Chung Yao Da Tzu Dian" (Dictionary of Chinese Drugs), Shanghai Science and Technology Press, Shanghai, 1977, Vol. 1, p. 573.
5. K. Kondo and M. Sugi, "Cancer Therapy in Modern China," Shi Zen Sha, Tokyo, Japan, 1977, p. 254.
6. D. Uemura, H. Ohwaki, Y. Hirata, Y.P. Chen, and H.Y. Hsu, *Tetrahedron Lett.*, 2527 (1974).
7. D. Uemura, Y. Hirata, Y.P. Chen, and H.Y. Hsu, *Tetrahedron Lett.*, 2529 (1974).
8. D. Uemura and Y. Hirata, *Tetrahedron Lett.*, 1701 (1975), and literature cited therein.
9. D.J. Pan, C.Q. Hu, J.J. Chang, T.T. Lee, Y.P. Chen, H.Y. Hsu, D.R. McPhail, A.T. McPhail, and K.H. Lee, *Phytochemistry*, **30**, 1018 (1991).
10. R.I. Geran, N.H. Greenberg, M.M. MacDonald, A.M. Schumacher, and B.J. Abbott, *Cancer Chemother. Rep.*, **3**, 1 (1972).
11. J.B. Stothers, "Carbon-13 NMR Spectroscopy," Academic Press, New York, 1972, p. 296.
12. R.H. Shoemaker, A. Monks, M.C. Alley, D.A. Scudiero, D.L. Fine, T.L. McLemore, B.J. Abbott, K.D. Paul, J.G. Mayo, and M.R. Boyd, in: "Prediction of Response to Cancer Therapy." Liss, New York, 1988, pp. 265–286, and literature cited therein.
13. L.A.C. Pieters and A.J. Vlietinck, *J. Nat. Prod.*, **52**, 186 (1989), and literature cited therein.
14. H.J. Opferkuch and E. Hecker, *J. Cancer Res. Clin. Oncol.*, **103**, 255 (1982), and literature cited therein.
15. H.C. Lin, "Glycerol Derivatives as Potential Anticancer Agents," Ph.D. Dissertation, University of North Carolina at Chapel Hill, 1988.

Received 1 October 1990