Physalins Possessing an Endoperoxy Structure from *Physalis alkekengi* var. *francheti*. Structural Revision of Physalin K

Bunsho Makino, Masao Kawai,* Yasushi Iwata, Hatsuo Yamamura, Yasuo Butsugan, Kiyoshi Ogawa,† and Mitsuo Hayashi†

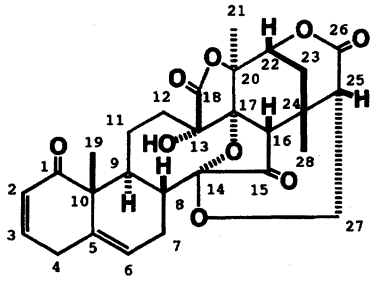
Department of Applied Chemistry, Nagoya Institute of Technology, Gokiso-cho, Showa-ku, Nagoya 466

†Institute for Life Science Research, Asahi Chemical Industry Co., Ltd., Ohito-cho, Shizuoka 410-23

(Received May 26, 1994)

Physalin K was isolated from *Physalis alkekengi* var. *francheti*. Spectroscopic studies and chemical correlations, however, revealed that the reported structure of physalin K at the AB ring moiety, namely, 4α, 5α-epoxy-6α-hydroxy-2-en-1-one, should be revised to 2α,5α-epidioxy-6β-hydroxy-3-en-1-one. A new physalin, named physalin Q, was also isolated and identified as the 2β,5β-epidioxy diastereomer of physalin K.

Physalins are steroidal constituents of *Physalis* and of closely related other genera belonging to *Solanaceae*.[1,2] Their highly oxygenated structures are characterized by the modified ergostane-type framework, namely, 13,14-seco-16,24-cyclosteroid. In the course of our study on the constituents of *P. alkekengi* var. *francheti* (Japanese name; Hôzuki), physalins A—C[3—5] and physalins L—P[6—9] were isolated and their structures were determined unambiguously. Row et al.[10—12] isolated physalin B (**1**) (Chart 1) and physalins D—K from *P. angulata* and *P. lancifolia* grown in India. Some of the physalins demonstrate cytotoxic activity against tumor cells *in vitro* and *in vivo*.[6,13—15] X-Ray crystallographic analyses in combination with ^{1}H NMR spectroscopy were also undertaken to study the unique heptacyclic[16] or octacyclic[17] structure of physalins. As a continuing study on the constituents of *P. alkekengi* var. *francheti*, we have isolated two physalins, **2** and **3**, which are stereoisomeric to each other. One of them (**2**) has been identified as known physalin K[12] by spectral and HPLC comparisons. A detailed spectroscopic study, however, has revealed that the reported structure of physalin K should be revised. This paper describes the structural elucidation of **2** and **3**.



Physalin B (1)

Chart 1.

Results and Discussion

From acetone extracts of the leaves of *P. alkekengi* var. *francheti*, two physalins, **2** and **3**, were isolated along with the known constituents of this plant, i.e., physalins A, B, F, N, and O.

Compound **2**, mp >300 °C, exhibited hydroxyl bands at 3645, 3550, and 3400 cm^{-1} and carbonyl bands at 1790, 1770, 1745, and 1725 cm^{-1}. The 400 MHz ^{1}H NMR spectra of **2** taken in DMSO-d_6 solution (Table 1) indicated the presence of three tertiary methyl groups (δ=1.03, 1.15, and 1.80), one tertiary and one secondary hydroxyl groups (δ=6.56, s and δ=5.71, d, J=5 Hz), a pair of mutually coupled olefinic hydrogens (δ=6.70, dd, J=8 and 6.5 Hz and δ=6.99, dd, J=8 and 1 Hz), and two methine groups each bearing an oxygen atom (δ=4.65, dd, J=6.5 and 1 Hz and δ=3.83, m, $W_{1/2}$=8 Hz). A pair of characteristic signals (δ=3.59, d, J=13 Hz and δ=4.26, dd, J=13 and 4 Hz) of the methylene group at C(27) revealed that **2** possesses the C(14)–O–C(27) bridge commonly found in **1** and other related physalins. These ^{1}H NMR spectral data closely resembled the reported data of physalin K isolated from *P. angulata* and *P. lancifolia*, which had been assumed as 4α,5α-epoxy-6α-hydroxy-5,6-dihydrophysalin B (**2'**) based on a ^{1}H NMR spectral analysis and a chemical correlation.[12] Actually, a direct comparison of **2** with the authentic sample of physalin K provided by Row's group using TLC, reversed-phase HPLC, and ^{1}H NMR analyses clearly demonstrated its identity to physalin K.

Table 1. 400 MHz ^{1}H NMR Spectral Data of Physalin B (**1**), 2,5-Epidioxy-6-hydroxy-3-en-1-ones (**2**, **3**, **12**, and **9**), and 4,5-Epoxy-6-hydroxy-2-en-1-ones (**4**, **8**, **2′**, and **7**) in DMSO-d_6 Solutions (chemical shift δ/ppm, spin multiplicity, and coupling constant/Hz)[a)]

Compound[b)]	**1**	**2** ($\alpha\beta$)	**3** ($\beta\beta$)	**12** ($\alpha\alpha$)	**9** ($\beta\alpha$)	**4** ($\alpha\beta$)	**8** ($\beta\beta$)	**2′** ($\alpha\alpha$)	**7** ($\beta\alpha$)
H-2	5.80 dd ($J_{2,3}$=10) ($J_{2,4\beta}$=2)	4.65 dd ($J_{2,3}$=6.5) ($J_{2,4}$=1)	4.69 dd ($J_{2,3}$=6) ($J_{2,4}$=1.5)	4.67 dd ($J_{2,3}$=6.5) ($J_{2,4}$=1.5)	4.70 d ($J_{2,3}$=6)	5.97 dd ($J_{2,3}$=10) ($J_{2,4}$=1.5)	5.96 dd ($J_{2,3}$=10) ($J_{2,4}$=1.5)	5.99 dd ($J_{2,3}$=10) ($J_{2,4}$=1.5)	6.00 dd ($J_{2,3}$=10) ($J_{2,4}$=1.5)
H-3	6.89 ddd ($J_{3,2}$=10) ($J_{3,4\alpha}$=5) ($J_{3,4\beta}$=2)	6.70 dd ($J_{3,4}$=8) ($J_{3,2}$=6.5)	6.68 dd ($J_{3,4}$=8) ($J_{3,2}$=6)	6.67 dd ($J_{3,4}$=8) ($J_{3,2}$=6.5)	6.73 dd ($J_{3,4}$=8) ($J_{3,2}$=6)	7.08 dd ($J_{3,2}$=10) ($J_{3,4}$=4)	7.10 dd ($J_{3,2}$=10) ($J_{3,4}$=4)	7.10 dd ($J_{3,2}$=10) ($J_{3,4}$=4)	7.16 dd ($J_{3,2}$=10) ($J_{3,4}$=4)
H-4	2.89 dd (α) ($J_{4\alpha,4\beta}$=20) ($J_{4\alpha,3}$=5)	6.99 dd ($J_{4,3}$=8) ($J_{4,2}$=1)	6.76 dd ($J_{4,3}$=8) ($J_{4,2}$=1.5)	6.98 dd ($J_{4,3}$=8) ($J_{4,2}$=1.5)	6.99 dd ($J_{4,3}$=8) ($J_{4,2}$=1)	3.49 dd ($J_{4,3}$=4) ($J_{4,2}$=1.5)	3.41 dd ($J_{4,3}$=4) ($J_{4,2}$=1.5)	3.66 dd ($J_{4,3}$=4) ($J_{4,2}$=1.5)	3.69 dd ($J_{4,3}$=4) ($J_{4,2}$=1.5)
	3.27 br d (β) ($J_{4\beta,4\alpha}$=20)								
H-6	5.59 br d ($J_{6,7\beta}$=6)	3.83 m ($W_{1/2}$=8)	4.00 m ($W_{1/2}$=7.5)	4.00 ddd ($J_{6,7\alpha}$=13) ($J_{6,OH}$=7) ($J_{6,7\beta}$=5)	3.88 ddd ($J_{6,7\alpha}$=12) ($J_{6,7\beta}$=5.5) ($J_{6,OH}$=5)	3.28 m ($W_{1/2}$=8)	3.49 m ($W_{1/2}$=8)	4.00 ddd ($J_{6,7\alpha}$=12) ($J_{6,OH}$=7.5) ($J_{6,7\beta}$=4)	3.98 dt ($J_{6,7\alpha}$=11.5) ($J_{6,OH}$=4) ($J_{6,7\beta}$=4)
		5.71 d (OH) ($J_{OH,6}$=5)	5.24 d (OH) ($J_{OH,5}$=3.5)	5.04 d (OH) ($J_{OH,6}$=7)	5.12 d (OH) ($J_{OH,6}$=5)	5.33 d (OH) ($J_{OH,6}$=3)	5.25 d (OH) ($J_{OH,6}$=3)	4.65 d (OH) ($J_{OH,6}$=7.5)	4.95 d (OH) ($J_{OH,6}$=4)
H-7	1.97 m (α)	1.60 dt (α) ($J_{7\alpha,7\beta}$=14) ($J_{7\alpha,8}$=14) ($J_{7\alpha,6}$=3)	1.74 m (α)	1.65 q (α) ($J_{7\alpha,7\beta}$=13) ($J_{7\alpha,8}$=13) ($J_{7\alpha,6}$=13)	1.44 q (α) ($J_{7\alpha,7\beta}$=12) ($J_{7\alpha,8}$=12) ($J_{7\alpha,6}$=12)	1.43 dt (α) ($J_{7\alpha,7\beta}$=11) ($J_{7\alpha,8}$=11) ($J_{7\alpha,6}$=2)	1.43 ddd (α) ($J_{7\alpha,7\beta}$=14) ($J_{7\alpha,8}$=10) ($J_{7\alpha,6}$=2)	1.27 m (α)	1.12 m (α)
	2.21 m (β)	1.99 dm (β) ($J_{7\beta,7\alpha}$=14)	2.10 m (β)	2.00 ddd (β) ($J_{7\beta,7\alpha}$=13) ($J_{7\beta,6}$=5) ($J_{7\beta,8}$=4)	2.20 dm (β) ($J_{7\beta,7\alpha}$=12)	2.14 m (β)	2.18 dt (β) ($J_{7\beta,7\alpha}$=14) ($J_{7\beta,6}$=2) ($J_{7\beta,8}$=2)	2.16 m (β)	2.31 ddd (β) ($J_{7\beta,7\alpha}$=12.5) ($J_{7\beta,6}$=4) ($J_{7\beta,8}$=3.5)
H-8	1.92 m	2.26 ddd ($J_{8,7\alpha}$=14) ($J_{8,9}$=10) ($J_{8,7\beta}$=3)	2.30 ddd ($J_{8,7\alpha}$=12.5) ($J_{8,9}$=10) ($J_{8,7\beta}$=3)	2.11 m	2.08 m	2.42 dt ($J_{8,7\alpha}$=11) ($J_{8,9}$=11) ($J_{8,7\beta}$=2)	2.31 dt ($J_{8,7\alpha}$=10) ($J_{8,9}$=10) ($J_{8,7\beta}$=2)	2.13 m	2.11 m
H-9	2.95 dd ($J_{9,8}$=11) ($J_{9,11\beta}$=9)	3.38 br t ($J_{9,8}$=10) ($J_{9,11\beta}$=10)	2.66 br t ($J_{9,8}$=10) ($J_{9,11\beta}$=10)	3.47 br t ($J_{9,8}$=10) ($J_{9,11\beta}$=10)	2.67 br t ($J_{9,8}$=9) ($J_{9,11\beta}$=9)	3.06 dd ($J_{9,8}$=11) ($J_{9,11\beta}$=8)	2.77 t ($J_{9,8}$=10) ($J_{9,11\beta}$=10)	3.04 dd ($J_{9,8}$=11) ($J_{9,11\beta}$=7.5)	2.81 br t ($J_{9,8}$=9.5) ($J_{9,11\beta}$=9.5)

Table 1. (Continued)

Compound[b)]	**1**	**2** ($\alpha\beta$)	**3** ($\beta\beta$)	**12** ($\alpha\alpha$)	**9** ($\beta\alpha$)	**4** ($\alpha\beta$)	**8** ($\beta\beta$)	**2′** ($\alpha\alpha$)	**7** ($\beta\alpha$)
H-11	2.18 m (α)	2.52 m (α)	2.77 tm (α) ($J_{11\alpha,11\beta}$=15) ($J_{11\alpha,12\alpha}$=15)	2.40 br t (α) ($J_{11\alpha,11\beta}$=14.5) ($J_{11\alpha,12\alpha}$=14.5)	2.69 m (α)	1.90 br dd (α) ($J_{11\alpha,11\beta}$=16)	1.56 br t (α) ($J_{11\alpha,11\beta}$=15) ($J_{11\alpha,12\alpha}$=12.5)	1.93 m (α)	1.50 br t (α) ($J_{11\alpha,11\beta}$=15) ($J_{11\alpha,12\alpha}$=15)
	1.10 m (β)	0.96 m (β)	1.03 m (β)	0.87 m (β)	0.92 m (β)	1.11 m (β)	0.95 m (β)	1.04 m (β)	0.88 m (β)
H-12	2.17 m (α)	1.92 m (α)	1.85 m (α)	1.90 m (α)	1.83 m (α)	2.14 m (α)	1.80 m (α)	2.15 m (α)	1.79 m (α)
	1.45 m (β)	1.37 br dd (β) ($J_{12\beta,12\alpha}$=16) ($J_{12\beta,11\beta}$=11)	1.37 dd (β) ($J_{12\beta,12\alpha}$=16.5) ($J_{12\beta,11\beta}$=10)	1.35 br dd (β) ($J_{12\beta,12\alpha}$=16) ($J_{12\beta,11\beta}$=10)	1.34 dd (β) ($J_{12\beta,12\alpha}$=16.5) ($J_{12\beta,11\beta}$=10.5)	1.46 dd (β) ($J_{12\beta,12\alpha}$=14.5) ($J_{12\beta,11\beta}$=11)	1.33 br dd (β) ($J_{12\beta,12\alpha}$=17) ($J_{12\beta,11\beta}$=11)	1.46 dd (β) ($J_{12\beta,12\alpha}$=16) ($J_{12\beta,11\beta}$=10)	1.30 br dd (β) ($J_{12\beta,12\alpha}$=17) ($J_{12\beta,11\beta}$=10)
H-13	6.28 s (OH)	6.56 s (OH)	6.43 s (OH)	6.59 s (OH)	6.48 s (OH)	6.24 s (OH)	6.43 s (OH)	6.15 s (OH)	6.45 s (OH)
H-16	2.86 s	2.83 s	2.83 s	2.82 s	2.83 s	2.86 s	2.83 s	2.86 s	2.83 s
H-19	1.09 s (Me)	1.03 s (Me)	1.31 s (Me)	0.88 s (Me)	1.09 s (Me)	1.20 s (Me)	1.21 s (Me)	1.06 s (Me)	1.02 s (Me)
H-21	1.78 s (Me)	1.80 s (Me)	1.75 s (Me)	1.82 s (Me)	1.76 s (Me)	1.80 s (Me)	1.76 s (Me)	1.81 s (Me)	1.76 s (Me)
H-22	4.56 dd ($J_{22,23R}$=3) ($J_{22,23S}$=2)	4.57 br s	4.55 m	4.57 br s	4.55 br s	4.58 br s	4.55 br s	4.58 br s	4.56 br s
H-23	2.14 m (R)	2.10 dd (R) ($J_{23R,23S}$=14) ($J_{23R,22}$=4)	2.08 m (R)	2.10 m (R)	2.09 dd (R) ($J_{23R,23S}$=14.5) ($J_{23R,22}$=3)	2.11 dd (R) ($J_{23R,23S}$=14) ($J_{23R,22}$=3)	2.09 dd (R) ($J_{23R,23S}$=14) ($J_{23R,22}$=3)	2.12 m (R)	2.09 dd (R) ($J_{23R,23S}$=15.5) ($J_{23R,22}$=3)
	1.96 m (S)	1.90 dd (S) ($J_{23S,23R}$=14) ($J_{23S,22}$=2)	1.89 dd (S) ($J_{23S,23R}$=15) ($J_{23S,22}$=2)	1.90 dd (S) ($J_{23S,23R}$=14) ($J_{23S,22}$=1.5)	1.89 br d (S) ($J_{23S,23R}$=14.5)	1.93 dd (S) ($J_{23S,23R}$=14) ($J_{23S,22}$=2)	1.89 dd (S) ($J_{23S,23R}$=14) ($J_{23S,22}$=1)	1.93 br d (S) ($J_{23S,23R}$=14)	1.89 br d (S) ($J_{23S,23R}$=15.5)
H-25	2.88 br d ($J_{25,27S}$=4)	2.90 d ($J_{25,27S}$=4)	2.89 d ($J_{25,27S}$=4)	2.91 d ($J_{25,27S}$=4)	2.90 d ($J_{25,27S}$=4)	2.91 d ($J_{25,27S}$=4)	2.90 d ($J_{25,27S}$=4)	2.92 d ($J_{25,27S}$=4)	2.92 d ($J_{25,27S}$=4)
H-27	3.60 dd (R) ($J_{27R,27S}$=14) ($J_{27R,25}$=1)	3.59 d (R) ($J_{27R,27S}$=13)	3.59 d (R) ($J_{27R,27S}$=13.5)	3.58 d (R) ($J_{27R,27S}$=13)	3.58 d (R) ($J_{27R,27S}$=13.5)	3.61 br d (R) ($J_{27R,27S}$=13)	3.60 d (R) ($J_{27R,27S}$=13)	3.61 d (R) ($J_{27R,27S}$=13)	3.59 d (R) ($J_{27R,27S}$=13.5)
	4.26 dd (S) ($J_{27S,27R}$=14) ($J_{27S,25}$=4)	4.26 dd (S) ($J_{27S,27R}$=13) ($J_{27S,25}$=4)	4.26 dd (S) ($J_{27S,27R}$=13.5) ($J_{27S,25}$=4)	4.27 dd (S) ($J_{27S,27R}$=13) ($J_{27S,25}$=4)	4.27 dd (S) ($J_{27S,27R}$=13.5) ($J_{27S,25}$=4)	4.28 dd (S) ($J_{27S,27R}$=13) ($J_{27S,25}$=4)	4.26 dd (S) ($J_{27S,27R}$=13) ($J_{27S,25}$=4)	4.29 dd (S) ($J_{27S,27R}$=13) ($J_{27S,25}$=4)	4.27 dd (S) ($J_{27S,27R}$=13.5) ($J_{27S,25}$=4)
H-28	1.16 s (Me)	1.15 s (Me)	1.15 s (Me)	1.15 s (Me)	1.14 s (Me)	1.18 s (Me)	1.15 s (Me)	1.17 s (Me)	1.14 s (Me)

a) $W_{1/2}$ refers to half width (/Hz). b) Configurations of 2,5-epidioxy or 4,5-epoxy group and 6-hydroxyl group are given in parentheses.

A detailed spectroscopic study, however, revealed that the reported structure **2′** was inconsistent with the spectral data of **2**. Out of the 28 carbon signals observed in the ^{13}C NMR spectra of **2** (Table 2), 17 signals which corresponded well to those of **1** were assigned easily, while the remaining 11 resonances assignable to C(1)–C(10) and C(19) atoms were incompatible to the proposed 4α,5α-epoxy-6α-hydroxy-2-en-1-one system at the AB ring moiety; i.e., two signals which could be assigned to the C(4) and C(5) in **2′** resonated at a considerably lower field (δ=77.6 and 83.4) than that expected for the epoxy enone structure. The C(1) carbonyl also resonated at a slightly lower field (δ=207.5), compared to the common conjugated 2-en-1-one system.[8,9] Detailed ^{1}H and ^{13}C NMR spectral analyses of **2** using ^{1}H–^{1}H, ^{13}C–^{1}H, and long-range ^{13}C–^{1}H COSY elucidated two partial structures consisting of 25 and 3 carbons, respectively, as shown in Fig. 1. A combination of these partial structures could form either a 2-en-1-one or a 3-en-1-one system as the possible structure of the A ring moiety of **2**. No apparent absorption maximum was observed in the UV spectrum of **2**, indicating that the A ring of **2** possesses a homoconjugated enone instead of the usual conjugated enone system.[18] The unusually deshielded resonances of the oxygen-carrying carbons described above suggested the presence of a peroxy bridge between C(2) and C(5), which was also supported by a positive starch-iodine test. In fact, the liquid secondary ion mass spectrum (SIMS) of **2** displayed a pseudomolecular ion peak $[M+H]^+$ at m/z 559, which corresponded to the molecular formula $C_{28}H_{30}O_{12}$, indicating an increment of one oxygen atom compared with the reported formula of physalin K.[12] With regard to the stereochemistry at C(6), the axial β-configuration was assigned to the secondary hydroxyl group considering the coupling constant (3 Hz) between H-6 and H-7α. For the purpose of determining the configuration of the peroxy bridge, **2** was treated with triphenylphosphine, since the stereochemistry of the deoxygenation of the unsaturated cyclic peroxides to epoxy alkenes was well elucidated.[19] The 4,5-epoxy-2-en-1-one **4**, obtained by the deoxygenation of **2**, was identical with one of the epoxidation products of 6-epiphysalin G (**5**) (Scheme 1). The epoxide **4** showed a negative Cotton effect ([θ] −12200) at 333 nm, reflecting the positive helicity of the 2-en-1-one moiety in the

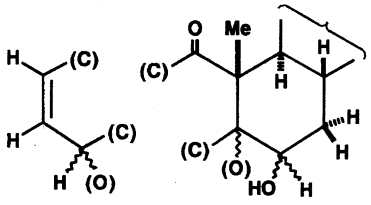
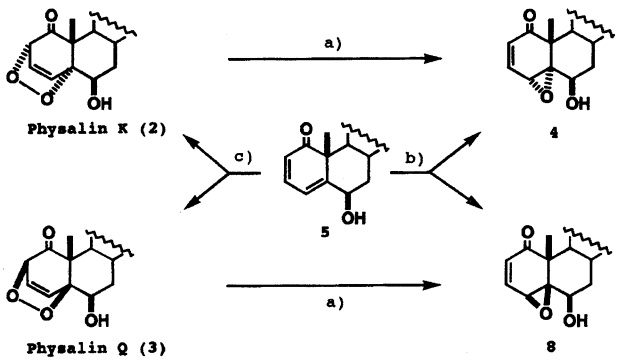


Fig. 1. Two partial structures in the AB ring moiety of **2**. The partial structure at C(11)–C(28) is the same as that of **1**.

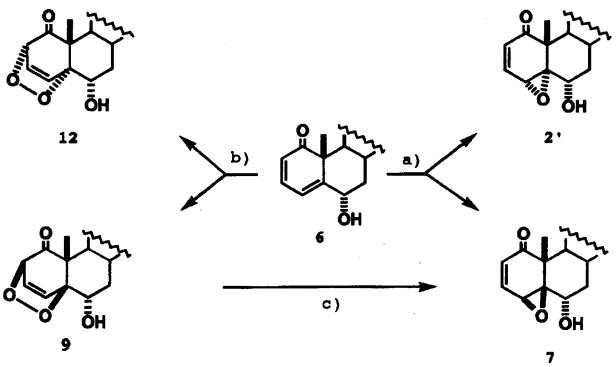


Scheme 1. a) Ph_3P, THF. b) mCPBA, $CHCl_3$. c) O_2, $h\nu$ (>480 nm), Rose Bengal, acetone.

trans A/B ring system.[20,21] Thus, the α-configuration of the epoxy function in **4**, and, therefore the α-configuration of the endoperoxy function in **2**, have been established. Accordingly, the structure of **2**, namely physalin K, has been determined unambiguously as being 2α,5α-epidioxy-6β-hydroxy-3,4-didehydro-2,3,5,6,-tetrahydrophysalin B.

The compound possessing structure **2′**, which had been erroneously assigned to physalin K, was independently synthesized from physalin G (**6**) along with the β-epoxy diastereomer **7** (Scheme 2). The synthetic **2′** showed different TLC and HPLC behaviors from the authentic **2** provided by Row's group. It is of interest that the epoxidation of these physalins, **5** and **6**, afforded both α- and β-epoxides with some β-predominance over α-isomer, while the corresponding withanolides are known to yield only β-epoxides, regardless of the configuration of the secondary hydroxyl group at C(6).[22,23] As shown in Tables 1 and 2, compound **2′** exhibited reasonable ^{1}H and ^{13}C NMR spectra which were clearly discernible from those of **2**, also confirming the validity of the structure **2** of physalin K.

The other component **3** (SIMS: m/z 559 [$C_{28}H_{30}O_{12}$ +H]$^+$), named physalin Q, is an isomer of **2**, which also gave positive peroxide test. As given in Tables 1 and 2, ^{1}H and ^{13}C NMR spectral data of **3** resembled those of **2**, which suggested a stereoisomeric relationship of



Scheme 2. a) mCPBA, $CHCl_3$. b) O_2, $h\nu$ (>480 nm), Rose Bengal, acetone. c) Ph_3P, THF.

Table 2. 100 MHz ^{13}C NMR Spectral Data of Physalin B (**1**), 2,5-Epidioxy-6-hydroxy-3-en-1-ones (**2**, **3**, **12**, and **9**), and 4,5-Epoxy-6-hydroxy-2-en-1-ones (**4**, **8**, **2′**, and **7**) in DMSO-d_6 Solutions (chemical shift δ/ppm)[a)]

Compound[b)]	**1**	**2** ($\alpha\beta$)	**3** ($\beta\beta$)	**12** ($\alpha\alpha$)	**9** ($\beta\alpha$)	**4** ($\alpha\beta$)	**8** ($\beta\beta$)	**2′** ($\alpha\alpha$)	**7** ($\beta\alpha$)
C(1)	202.4	207.5	206.4	207.0	205.4	200.2	200.1	200.7	199.7
C(2)	126.9	77.6	78.4	77.7	78.3	130.7	130.0	130.5	130.4
C(3)	146.1	126.6	125.2	127.0	125.8	140.8	140.9	141.7	141.7
C(4)	32.3	141.5	142.8	141.6	139.5	53.8	52.7	49.0	48.0
C(5)	135.5	83.4	84.1	84.5	86.6	63.8	64.9	66.4	67.3
C(6)	123.4	64.8	67.2	66.1	64.1	71.1	70.3	62.4	62.8
C(7)	24.4	28.1	28.6	27.6	29.7	29.4	31.2	30.6*1	32.5
C(8)	40.2	37.5	38.2	41.4	41.1	38.5	37.2	42.5	41.1
C(9)	33.1	32.4	39.1	31.8	38.5	33.9	36.9	33.6	36.7
C(10)	52.0	48.1	48.5	49.1	49.0	48.9	51.1	50.2	52.1
C(11)	24.1	20.2	21.4	19.9	20.8	24.7	20.5	24.6	20.4
C(12)	25.6	24.6	25.0	24.5	24.7	25.6	24.3	25.5	24.1
C(13)	78.2	78.1	78.0	78.2	78.1	78.4	78.2	78.5	78.2
C(14)	106.3	105.9	105.8	105.6	105.3	106.3	106.0	105.8	105.5
C(15)	209.3	209.2	209.3	209.0	208.9	209.7	209.1	209.4	208.8
C(16)	54.1	53.9	53.7	53.9	53.8	53.8	54.0	53.7	54.0
C(17)	80.7	80.5	80.6	80.5	80.6	80.9	80.4	81.0*2	80.5*3
C(18)	171.8	171.8	171.8	171.8	171.7	171.6	171.8	171.5	171.7
C(19)	16.8	18.4	14.9	17.6	12.9	15.7	12.9	15.3	11.5
C(20)	80.3	80.2	80.3	80.3	80.3	80.5	80.3	80.5*2	80.3*3
C(21)	21.7	21.6	21.7	21.6	21.6	21.7	21.5	21.7	21.5
C(22)	76.3	76.3	76.3	76.3	76.3	76.4	76.2	76.4	76.2
C(23)	31.4	31.3	31.2	31.2	31.2	31.3	31.2	31.3*1	31.1
C(24)	30.5	30.4	30.7	30.5	30.5	30.5	30.5	30.5	30.5
C(25)	49.4	49.3	49.2	49.2	49.2	49.3	49.2	49.3	49.1
C(26)	167.2	167.1	167.2	167.2	167.2	167.3	167.1	167.2	167.1
C(27)	60.6	60.6	60.7	60.7	60.8	60.7	60.8	60.8	60.9
C(28)	24.4	24.4	24.4	24.4	24.3	24.4	24.4	24.4	24.3

a) *1, *2, and *3 refer to interchangeable data. b) Configurations of 2,5-epidioxy or 4,5-epoxy group and 6-hydroxyl group are given in parentheses.

2 and **3**. The ^{13}C chemical shift differences between the corresponding carbons of **2** and **3** were less than 0.4 ppm for C(12)–C(28), except for C(19). Therefore, **3** was assumed to differ from **2** at the AB ring moiety. Significant differences were also observed for the proton resonances assignable to the AB ring moiety. For example, angular methyl C(19) of **3** (δ=1.31) resonated at a lower field than that of **2** (δ=1.03) and H-4 of **3** (δ=6.76) at higher field than that of **2** (δ=6.99). The secondary hydroxyl proton of **3** (δ=5.24) was observed at a considerably higher field than that of **2** (δ=5.71). The stereochemistry of the secondary hydroxyl group at C(6) of **3**, however, was assumed to have the same axial β-configuration as that of **2** based on a consideration of the half width (7.5 Hz) of the H-6 signal in **3**. Accordingly, **3** was deduced to be a diastereomer of **2** concerning the stereochemistry of the peroxy bridge. The remarkably deshielded H-9α of **2** (δ=3.38), compared with that of **3** (δ=2.66), also indicated the presence of α- and β-oriented oxygen functions in **2** and **3**, respectively. It is interesting that in the ^{13}C NMR spectra the C(9) resonance of **3** (δ=39.1), on the other hand, appears at a much lower field than that of **2** (δ=32.4). The deshielding of H-9 by a 5α-oxygen function and the deshielding of C(9) by a 5β-oxygen function are commonly observed in physalin derivatives.[24)] The 2β,5β-endoperoxy structure of **3** was confirmed by the deoxygenation of **3** with triphenylphosphine to give 4β,5β-epoxy-6β-hydroxy-2-en-1-one **8** ($[\theta]_{342}$ +14200). The β-epoxide **8** was also obtained by the epoxydation of **5** along with its α-epoxy diastereomer **4**, as shown in Scheme 1. Consequently, the structure of **3** has been established as being 2β,5β-epidioxy-6β-hydroxy-3,4-didehydro-2,3,5,6-tetrahydrophysalin B.

The diastereomeric peroxides, **2** and **3**, exhibited approximately antipodal CD spectra to each other (**2**: $[\theta]_{332}$ -33400_{sh}, $[\theta]_{326}$ -35200; **3**: $[\theta]_{331}$ $+26500_{sh}$, $[\theta]_{323}$ +29400). The octant rule is known to be applicable to β,γ-unsaturated ketones by considering the double bond as being a predominantly contributing group.[25)] It is interesting that, as shown in Fig. 2, compounds **2** and **3** follow this extended octant rule, despite the presence of the peroxy bridge.

The dienone alcohol **5**, namely 6-epiphysalin G, can be considered as being a precursor of physalins **2** and **3**, although **5** has not been known as a natural prod-

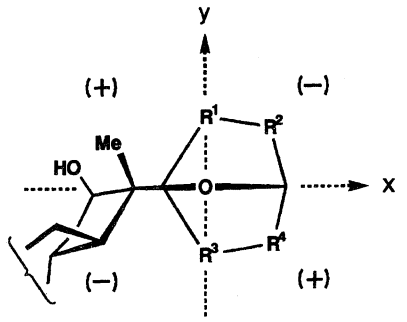
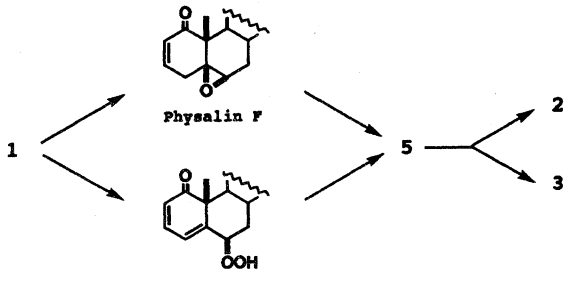
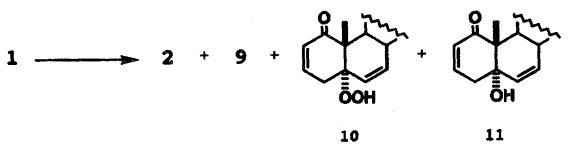


Fig. 2. Octant projection of **2** and **3** concerning the C(1) carbonyl group. The double bond is considered as a major contributor. **2**: $-R^1-R^2- = -CH=CH-$, $-R^3-R^4- = -O-O-$, **3**: $-R^1-R^2- = -O-O-$, $-R^3-R^4- = -CH=CH-$.

uct. Indeed, the photosensitized oxygenation of **5** using Rose Bengal as a sensitizer afforded **2** and **3** as cycloaddition products in 31 and 34% yields, respectively (Scheme 1). The hypothetical precursor **5** could be derived from the abundant congener, physalin B (**1**), via the 5β,6β-epoxide, physalin F, which is easily converted to **5** by the base-catalyzed isomerization.[22,23] The corresponding hydroperoxide, 6β-hydroperoxy-2,4-dien-1-one, a possible product of the reaction of **1** with singlet oxygen, could be an alternative candidate for the intermediate from **1** to **5** (Scheme 3). Therefore, **1** was subjected to photosensitized oxygenation in an attempt to convert **1** directly to **2** and **3**. Among the reaction products, the expected endoperoxide **2** (10%), namely physalin K, and its stereoisomer **9** (7%) were isolated along with a 5α-hydroperoxide **10** (10%) and the corresponding alcohol **11** (21%), while the other endoperoxide **3**, physalin Q, was not detected (Scheme 4). The stereochemistry of the hydroxyl function at C(6) of the endoperoxide **9**, which was a stereoisomer of **2** and **3**, was assumed to be α-equatorial, considering the coupling constant of H-6 ($J_{6,7\alpha}=12$ Hz). The assumption was also supported by the chemical shifts of H-8 ($\delta=2.08$) and C(8) ($\delta=41.1$) of **9** compared with those of **2** ($\delta=2.26$ and 37.5) and **3** ($\delta=2.30$ and 38.2) possessing 6β-hydroxyl group, since deshielding of H-8 and C(8) resonances caused by 6β-axial and 6α-equatorial oxygen functions, respectively, was commonly observed in physalin derivatives.[26] Positive Cotton effects ($[\theta]_{334}$ $+21000_{sh}$ and $[\theta]_{325}$ +23300) of **9** indicated β-orientation of the peroxy bridge. The structure of **9** was confirmed based on its formation from **6** accompanied by the 2α,5α-epidioxy diastereomer **12** and its conversion to 4β,5β-epoxy-6α-hydroxy-2-en-1-one **7**, as is also shown in Scheme 2. The structure of the hydroperoxide **10** was confirmed by its conversion to the 5α-alcohol **11** ($[\theta]_{333}$ -2300_{sh}), which gave the known conjugated trienone, 4,7-didehydrophysalin B, upon acid-induced dehydration. The isolation of unsaturated cyclic peroxides from plant extract is well precedented.[27]



Scheme 3. Possible mechanism of formation of physalin K (**2**) and physalin Q (**3**) from physalin B (**1**).



Scheme 4. Photosensitized oxygenation of physalin B (**1**).

Experimental

Mp's were determined on a hot-plate apparatus and are uncorrected. Column chromatography (CC) and TLC were performed using SiO_2 (Fuji Silysia, FL60D) and precoated SiO_2 plates (Merck, Silica Gel $60F_{254}$), respectively. HPLC were performed in the reversed-phase mode (Tosoh, TSK GEL ODS-80T_M, 4.6×150 mm, elution with MeOH–H_2O or CH_3CN–H_2O). IR spectra were measured using a JASCO A-102 spectrophotometer with a KBr disc, and UV spectra were recorded on a Hitachi 124 or Hitachi U-3500 spectrophotometer with a MeOH solution. Optical rotations in acetone and CD spectra in MeOH were recorded on a JASCO DIP-4 digital polarimeter and a J-600 spectropolarimeter, respectively. Mass spectra were measured on a Hitachi M-2000 spectrometer with electron impact ionization and SIMS were taken in glycerol matrices. NMR spectra were taken in DMSO-d_6 solution using JEOL JNM GSX-400, Varian UNITY 400 plus, or Varian Gemini-200 spectrometer.

Isolation of Physalins. Leaves of *P. alkekengi* var. *francheti* cultivated in Japan were air-dried (1.4 kg dry wt) and extracted with acetone in dark at room temperature. The extract (164 g) was defatted with heptane and the residue (88 g) was subjected to column chromatography repeatedly over silica gel using the solvent systems C_6H_6–EtOAc and $CHCl_3$–MeOH followed by recrystallizations to give physalins K (**2**; 88 mg) and Q (**3**; 106 mg) along with the known constituents, physalins A[4] (100 mg), B[4] (**1**; 4.98 g), F[11] (5.92 g), N[8] (230 mg), and O[8] (159 mg). **2**: Colorless fine needles from MeOH; mp >300 °C; $[\alpha]_D^{20}$ −224° (*c* 0.04); IR ν_{max} 3645, 3550, 3400, 1790, 1770, 1745, 1725, 1170, 1130, 1060 cm^{-1}; UV: no apparent absorption maximum above 210 nm; CD $[\theta]_{332}$ −33400(sh), $[\theta]_{326}$ −35200, $[\theta]_{222}$ −6400, $[\theta]_{208}$ +1400; SIMS *m/z* 559 $[M+H]^+$. Anal. Found: C, 58.38; H, 5.65%. Calcd for $C_{28}H_{30}O_{12}\cdot H_2O$: C, 58.33; H, 5.59%. **3**: Colorless fine needles from acetone; mp >300 °C; $[\alpha]_D^{20}$ +38° (*c* 0.06); IR ν_{max} 3425, 1800, 1780, 1770, 1740, 1725, 1705, 1170, 1140, 1090, 1060 cm^{-1}; UV: no apparent absorption maximum above 210 nm; CD $[\theta]_{331}$ +26500(sh), $[\theta]_{323}$ +29400,

$[\theta]_{235}$ −6600, $[\theta]_{225}$ −4000, $[\theta]_{206}$ −15700; SIMS m/z 559 $[M+H]^+$. Anal. Found: C, 59.18; H, 6.05%. Calcd for $C_{28}H_{30}O_{12}\cdot 1/2H_2O\cdot CH_3COCH_3$: C, 59.52; H, 5.96%.

Deoxygenation of Physalin K (2). To a solution of **2** (37 mg) in THF (1 ml) was added Ph_3P (53 mg); the mixture was stirred at room temperature for 19 h. The product was purified by silica-gel CC using solvent system $CHCl_3$–MeOH to afford 4α,5α-epoxy-6β-hydroxy-5,6-dihydrophysalin B (**4**) as colorless powder (11 mg); $[\alpha]_D^{15}$ −40° (c 0.09); IR ν_{max} 3430, 1770, 1730, 1670, 1165, 1130, 1055 cm^{-1}; UV λ_{max} 231 nm ($\log\varepsilon$ 3.45); CD $[\theta]_{333}$ −12200, $[\theta]_{250}$ +25500, $[\theta]_{213}$ −6300. HRMS Found: m/z 542.1844. Calcd for $C_{28}H_{30}O_{11}$: M, 542.1786.

Deoxygenation of Physalin Q (3). Using the same experimental procedure as mentioned above (Ph_3P 44 mg, THF 1.5 ml, 6 h), **3** (47 mg) was deoxygenated to afford 4β,5β-epoxy-6β-hydroxy-5,6-dihydrophysalin B (**8**) as colorless fine needles (21 mg) crystallized from MeOH/acetone (1 : 1); mp >300 °C; $[\alpha]_D^{18}$ −57° (c 0.05); IR ν_{max} 3570, 3395, 1770, 1735, 1665, 1170, 1080, 1060 cm^{-1}; UV λ_{max} 239 nm ($\log\varepsilon$ 3.52); CD $[\theta]_{350}$ +14000, $[\theta]_{342}$ +14200, $[\theta]_{244}$ −32700, $[\theta]_{204}$ +8100. HRMS Found: m/z 542.1843. Calcd for $C_{28}H_{30}O_{11}$: M, 542.1786. Anal. Found: C, 58.14; H, 5.85%. Calcd for $C_{28}H_{30}O_{11}\cdot 2H_2O$: C, 58.13; H, 5.92%.

Base-Catalyzed Isomerization of Physalin F. A solution of physalin F (1250 mg) in $CHCl_3$ (50 ml) containing Et_3N (0.3 ml) was refluxed for 35 h; the product, after the usual work-up, was chromatographed over silica gel using $CHCl_3$–MeOH (99 : 1) as an eluent. Crystallization from MeOH afforded 6-epiphysalin G (**5**) as colorless fine needles (973 mg), mp 285—287 °C; IR ν_{max} 3550, 3410, 1775, 1735, 1615, 1170, 1130, 1060 cm^{-1}; UV λ_{max} 311 nm ($\log\varepsilon$ 3.64); CD $[\theta]_{379}$ +5300, $[\theta]_{310}$ −25300, $[\theta]_{257}$ −2100, $[\theta]_{240}$ −6100; MS m/z 526 (M^+), 508 ($M-H_2O$), 498 ($M-CO$), 482 ($M-CO_2$), 454 ($M-CO-CO_2$); ^1H NMR (200 MHz) δ=0.98 (m, H-11β), 1.17 (s, CH_3-28), 1.22 (s, CH_3-19), 1.35 (dd, $J_{12\beta,12\alpha}$=16 and $J_{12\beta,11\beta}$=7 Hz, H-12β), 1.72 (s, CH_3-21), 1.89 (dd, $J_{23S,23R}$=15 and $J_{23S,22}$=1 Hz, H-23S), 2.09 (dd, $J_{23R,23S}$=15 $J_{23R,22}$=3.5 Hz, H-23R), 2.26 (dm, $J_{7\beta,7\alpha}$=14 Hz, H-7β), 2.69 (dd, $J_{9,8}$=11 and $J_{9,11\beta}$=8 Hz, H-9), 2.84 (s, H-16), 2.89 (d, $J_{25,27S}$=4 Hz, H-25), 3.61 (d, $J_{27R,27S}$=13 Hz, H-27R), 4.26 (dd, $J_{27S,27R}$=13 and $J_{27S,25}$=4 Hz, H-27S), 4.49 (br d, $J_{6,OH}$=2.5 Hz, H-6), 4.54 (br s, H-22), 5.13 (d, $J_{OH,6}$=2.5 Hz, HO-6), 5.93 (d, $J_{2,3}$=9 Hz, H-2), 6.17 (d, $J_{4,3}$=6 Hz, H-4), 6.41 (s, HO-13), 7.04 (dd, $J_{3,2}$=10 and $J_{3,4}$=6 Hz, H-3).

Epoxidation of 6-Epiphysalin G (5). To a solution of **5** (323 mg) and *m*-chloroperbenzoic acid (mCPBA) (80% purity, 322 mg) in $CHCl_3$ (70 ml) was added aq $NaHCO_3$ (54 mM, 70 ml); the mixture was stirred at room temperature for 64 h. After the usual work-up, the products were purified by repeated silica-gel CC (solvent systems: $CHCl_3$–MeOH, C_6H_6–EtOAc) to afford **4** (25 mg) and **8** (96 mg).

Photooxygenation of 6-Epiphysalin G (5). A solution of **5** (963 mg) containing Rose Bengal (30 mg) was irradiated by a tungsten–halogen lamp (150 W) through a colored glass filter (Toshiba, Y-50, 3 mm thickness) under O_2 bubbling at room temperature for 78.5 h. The products were purified by repeated silica-gel CC (solvent system: $CHCl_3$–MeOH) and recrystallizations from MeOH or acetone to give **2** (314 mg) and **3** (352 mg).

Photooxygenation of Physalin B (1). Using the same experimental procedure as mentioned above (Rose Bengal 73 mg, irradiation time 119 h), **1** (355 mg) was photooxygenated to afford **2** (40 mg), 2β,5β-epidioxy-6α-hydroxy-3,4-didehydro-2,3,5,6-tetrahydrophysalin B (**9**; 19 mg), 5α-hydroperoxy-6,7-didehydro-5,6-dihydrophysalin B (**10**; 39 mg), and 5α-hydroxy-6,7-didehydro-5,6-dihydrophysalin B (**11**; 77 mg). **9**: Colorless powder; $[\alpha]_D^{20}$ +29° (c 0.12); IR ν_{max} 3440, 1780, 1765, 1730, 1170, 1140, 1080, 1060 cm^{-1}; UV: no apparent absorption maximum above 210 nm; CD $[\theta]_{334}$ +21000(sh), $[\theta]_{325}$ +23300, $[\theta]_{238}$ −5500, $[\theta]_{225}$ −3000, $[\theta]_{207}$ −12000; SIMS m/z 559 $[M+H]^+$. **10**: Colorless cubes from acetone, mp 232—237 °C; IR ν_{max} 3420, 1785, 1765, 1710, 1655, 1170, 1135, 1060 cm^{-1}; ^1H NMR (200 MHz) δ=1.05 (s, CH_3-19), 1.17 (s, CH_3-28), 1.82 (s, CH_3-21), 1.94 (dd, $J_{23S,23R}$=14.5 and $J_{23S,22}$=2 Hz, H-23S), 2.83 (s, H-16), 2.95 (d, $J_{25,27S}$=4 Hz, H-25), 3.51 (dd, $J_{9,8}$=10.5 and $J_{9,11\beta}$=7 Hz, H-9), 3.66 (d, $J_{27R,27S}$=13 Hz, H-27R), 4.34 (dd, $J_{27S,27R}$=13 and $J_{27S,25}$=4 Hz, H-27S), 4.59 (br s, H-22), 5.76 (dd, $J_{2,3}$ or $J_{6,7}$=10 and $J_{2,4\beta}$ or $J_{6,8}$=2.5 Hz, H-2 or H-6), 5.78 (dd, $J_{6,7}$ or $J_{2,3}$=10 and $J_{6,8}$ or $J_{2,4\beta}$=3 Hz, H-6 or H-2), 5.99 (s, HO-13), 6.08 (dd, $J_{7,6}$=10 and $J_{7,8}$=2 Hz, H-7), 6.60 (ddd, $J_{3,2}$=10, $J_{3,4\alpha}$=4.5, and $J_{3,4\beta}$=1.5 Hz, H-3), 11.08 (s, HOO-5). **11**: Colorless powder, $[\alpha]_D^{20}$ −20° (c 0.07); IR ν_{max} 3480, 1780, 1765, 1735, 1665, 1170, 1135, 1060 cm^{-1}; UV λ_{max} 220.5 nm ($\log\varepsilon$ 3.84); CD $[\theta]_{345}$ −3000, $[\theta]_{333}$ −2300(sh), $[\theta]_{212}$ +4200. HRMS Found: m/z 508.1727. Calcd for $C_{28}H_{28}O_9$: M^+-H_2O, 508.1731; ^1H NMR (200 MHz) δ=0.99 (s, CH_3-19), 1.17 (s, CH_3-28), 1.81 (s, CH_3-21), 1.94 (dd, $J_{23S,23R}$=14.5 and $J_{23S,22}$=2 Hz, H-23S), 2.85 (s, H-16), 2.94 (d, $J_{25,27S}$=4 Hz, H-25), 3.47 (m, H-9), 3.65 (d, $J_{27R,27S}$=13 Hz, H-27R), 4.32 (dd, $J_{27S,27R}$=13 and $J_{27S,25}$=4 Hz, H-27S), 4.58 (br s, H-22), 4.82 (s, HO-5), 5.62 (dd, $J_{6,7}$=10 and $J_{6,8}$=2 Hz, H-6), 5.74 (dd, $J_{2,3}$=10 and $J_{2,4\beta}$=2 Hz, H-2), 5.77 (s, HO-13), 5.90 (dd, $J_{7,6}$=10 and $J_{7,8}$=2 Hz, H-7), 6.59 (ddd, $J_{3,2}$=10, $J_{3,4\alpha}$=5, and $J_{3,4\beta}$=2 Hz, H-3).

Deoxygenation of 9. To a solution of **9** (53 mg) in THF (1.5 ml) was added Ph_3P (77 mg, 3 equiv); the mixture was then stirred at room temperature for 3 h. The product was purified by silica-gel CC using the solvent system $CHCl_3$–MeOH and crystallization from acetone to afford 4β,5β-epoxy-6α-hydroxy-5,6-dihydrophysalin B (**7**; 26 mg). **7**: Colorless stout needles from acetone, mp 259—264 °C; $[\alpha]_D^{15}$ −39° (c 0.10); IR ν_{max} 3440, 1775, 1760, 1720, 1670, 1165, 1140, 1075 cm^{-1}; UV λ_{max} 237 nm ($\log\varepsilon$ 3.51); CD $[\theta]_{340}$ +13300, $[\theta]_{243}$ −32400, $[\theta]_{205}$ +13100; MS m/z 542 (M^+), 524 ($M-H_2O$), 496 ($M-H_2O-CO$).

Deoxygenation of 10. To a solution of **10** (23 mg) in EtOAc (5 ml) was added Ph_3P (41 mg); the mixture was stirred at room temperature for 3 h. The product was purified by silica-gel CC using $CHCl_3$ as an eluent to afford **11** (6 mg).

Acid-Induced Dehydration of 11 to 4,7-Didehydrophysalin B. A solution of **11** (6 mg) in AcOH (2 ml) was refluxed for 100 min; the product, after the usual work-up, was chromatographed over silica gel using $CHCl_3$ as an eluent to afford 4,7-didehydrophysalin B[8] (2 mg).

Base-Catalyzed Isomerization of Physalin J. A solution of physalin J[11] (427 mg), prepared from physalin B (**1**), in $CHCl_3$ (35 ml) containing Et_3N (2 ml) was refluxed for 45 h; the product, after the usual work-up, was purified

by silica-gel CC (solvent system: $CHCl_3$–MeOH) to afford physalin G (**6**; 337 mg).

Epoxidation of Physalin G (6). A solution of **6** (116 mg) and mCPBA (80% purity, 58 mg) in $CHCl_3$ (35 ml) was stirred at room temperature for 19.5 h. After the usual work-up, the products were purified by silica-gel CC using $CHCl_3$–MeOH as eluent to give 4α,5α-epoxy-6α-hydroxy-5,6-dihydrophysalin B (**2′**; 35 mg) and **7** (66 mg). **2′**: Colorless cubes from MeOH, mp >300 °C; $[\alpha]_D^{15}$ −39° (*c* 0.10); IR ν_{max} 3545, 3450, 1785, 1770, 1750, 1670, 1170, 1145, 1090, 1060 cm^{-1}; UV λ_{max} 233 nm ($\log\varepsilon$ 3.52); CD $[\theta]_{333}$ −11300, $[\theta]_{250}$ +19700, $[\theta]_{214}$ −8100. HRMS Found: *m/z* 542.1783. Calcd for $C_{28}H_{30}O_{11}$: M, 542.1786.

Photooxygenation of Physalin G (6). Using the same experimental procedure as that for **5**, **6** (613 mg) was photooxygenated using Rose Bengal (6 mg) as a sensitizing agent for 260 min. The products were purified by repeated silica-gel CC using the solvent system $CHCl_3$–MeOH and reversed-phase HPLC using 45% aqueous MeOH as eluent to afford **9** (493 mg) and 2α,5α-epidioxy-6α-hydroxy-3,4-didehydro-2,3,5,6-tetrahydrophysalin B (**12**; 13 mg). **12**: Colorless stout needles from MeOH; mp 293—297 °C; $[\alpha]_D^{15}$ −168° (*c* 0.08); IR ν_{max} 3525, 3280, 1790, 1755, 1725, 1170, 1130, 1060 cm^{-1}; UV: no apparent absorption maximum above 210 nm; CD $[\theta]_{332}$ −29300(sh), $[\theta]_{325}$ −30500, $[\theta]_{225}$ −7700, $[\theta]_{207}$ +7500; SIMS *m/z* 559 $[M+H]^+$.

The authors are grateful to Emeritus Professors L. Ramachandra Row and Teruo Matsuura for the generous gifts of samples of physalin K and related compounds.

References

1) O. E. Vasina, V. A. Maslennikova, and N. K. Abubakirov, *Khim. Prir. Soedin.*, **1986**, 263; *Chem. Nat. Compd.* (*Engl. Transl.*), **1986**, 243.
2) E. Glotter, *Nat. Prod. Rep.*, **8**, 415 (1991).
3) T. Matsuura, M. Kawai, R. Nakashima, and Y. Butsugan, *Tetrahedron Lett.*, **1969**, 1083.
4) T. Matsuura, M. Kawai, R. Nakashima, and Y. Butsugan, *J. Chem. Soc. C*, **1970**, 664.
5) M. Kawai and T. Matsuura, *Tetrahedron*, **26**, 1743 (1970).
6) M. Kawai, T. Matsuura, S. Kyuno, H. Matsuki, M. Takenaka, T. Katsuoka, Y. Butsugan, and K. Saito, *Phytochemistry*, **26**, 3313 (1987).
7) M. Kawai, T. Ogura, M. Nakanishi, T. Matsuura, Y. Butsugan, Y. Mori, K. Harada, and M. Suzuki, *Bull. Chem. Soc. Jpn.*, **61**, 2969 (1988).
8) M. Kawai, T. Ogura, B. Makino, A. Matsumoto, H. Yamamura, Y. Butsugan, and M. Hayashi, *Phytochemistry*, **31**, 4299 (1992).
9) M. Kawai, A. Matsumoto, B. Makino, H. Mori, T. Ogura, Y. Butsugan, K. Ogawa, and M. Hayashi, *Bull. Chem. Soc. Jpn.*, **66**, 1299 (1993).
10) L. R. Row, N. S. Sarma, T. Matsuura, and R. Nakashima, *Phytochemistry*, **17**, 1641 (1978).
11) L. R. Row, N. S. Sarma, K. S. Reddy, T. Matsuura, and R. Nakashima, *Phytochemistry*, **17**, 1647 (1978).
12) L. R. Row, K. S. Reddy, N. S. Sarma, T. Matsuura, and R. Nakashima, *Phytochemistry*, **19**, 1175 (1980).
13) M. D. Antoun, D. Abramson, R. L. Tyson, C. Chang, J. L. McLaughlin, G. Peck, and J. M. Cassady, *J. Nat. Prod.*, **44**, 579 (1981).
14) H. Chiang, S. Jaw, C. Chen, and W. Kan, *Anticancer Res.*, **12**, 837 (1992).
15) H. Chiang, S. Jaw, and P. Chen, *Anticancer Res.*, **12**, 1155 (1992).
16) M. Kawai, T. Taga, Y. Miwa, and Y. Butsugan, *J. Crystallogr. Spectrosc. Res.*, **22**, 131 (1992).
17) M. Kawai, B. Makino, T. Taga, Y. Miwa, T. Yamamoto, T. Furuta, H. Yamamura, Y. Butsugan, K. Ogawa, and M. Hayashi, *Bull. Chem. Soc. Jpn.*, **67**, 222 (1994).
18) The chemical shift values of the alkenic protons in **2** (δ=6.70 and 6.99) were also in conflict with the usual 2-en-1-one structure, which had been attributed to the distortion of the ring A due to the presence of the epoxide ring in Ref. 12.
19) M. Balci, *Chem. Rev.*, **81**, 91 (1981).
20) R. Tschesche, M. Baumgarth, and P. Welzel, *Tetrahedron*, **24**, 5169 (1968).
21) E. Glotter, I. Kirson, A. Abraham, P. D. Sethi, and S. S. Subramanian, *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1370.
22) M. Ishiguro, A. Kajikawa, T. Haruyama, Y. Ogura, M. Okubayashi, M. Morisaki, and N. Ikekawa, *J. Chem. Soc., Perkin Trans. 1*, **1975**, 2295.
23) E. Glotter, S. Kumar, M. Sahai, A. Goldman, I. Kirson, and M. Mendelovici, *J. Chem. Soc., Perkin Trans. 1*, **1991**, 739.
24) Comparison of the stereoisomeric pairs shown in Tables 1 and 2, namely **2′** vs. **7**, **4** vs. **8**, and **12** vs. **9**, also gives good examples of the effects of oxygen function at C(5) upon the chemical shifts of H-9 and C(9). The 5,6-epoxy pair of physalin F, β-epoxide (H-9: δ=2.49; C(9): δ=34.8) and physalin J, α-epoxide (H-9: δ=2.96; C(9): δ=28.2), constitutes another example.
25) A. Moscowitz, K. Mislow, M. A. W. Glass, and C. Djerassi, *J. Am. Chem. Soc.*, **84**, 1945 (1962).
26) The epimeric pairs found in Tables 1 and 2 (**2** vs. **12**, **3** vs. **9**, **4**, vs. **2′**, and **8** vs. **7**) also demonstrate the effects of oxygen function at C(6) upon the chemical shifts of H-8 and C(8).
27) (e.g.) J. A. Marco, J. F. Sanz, E. Falcó, J. Jakupovic, and J. Lex, *Tetrahedron*, **46**, 7941 (1990).