

## A Novel 1 : 1 Complex of Potassium Mikanin-3-*O*-sulfate with Methanol

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**Mikanin-3-*O*-sulfate (1), in the form of its potassium salt, together with mikanin (2) and alpinetin (3) were isolated from *Mikania micrantha*. The crystal structures of  $K(1) \cdot CH_3OH$ , 2 and  $3 \cdot H_2O$  were established by X-ray crystallography. The potassium ions in  $K(1) \cdot CH_3OH$  are bridged by O5, O7 and O8 to form a chain of face-sharing  $KO_8$  coordination polyhedra, from which the aglycon units are outstretched to form a polymeric molecular column. Adjacent molecular columns are linked by  $\pi$ - $\pi$  stacking between parallel, intercalating aglycon units to form layers matching the (10 $\bar{1}$ ) family of planes, which are further interconnected into a three-dimensional supramolecular assembly. Sulfation at 3-OH induced better co-planarity and conjugation of the rings.**

**Key words** potassium mikanin-3-*O*-sulfate methanol complex; mikanin; alpinetin; X-ray diffraction

Flavonoid sulfates are characterized by a flavone skeleton covalently linked to one or more inorganic sulfate groups. They occur commonly in a large number of plant species,<sup>1,2)</sup> and are also found in the metabolites of microorganisms<sup>3)</sup> and animals.<sup>4)</sup> This kind of compounds occupy an important position in the field of natural products chemistry since they provide a structural link between organic and inorganic components in nature. The pharmacological assay of flavonoid sulfates has revealed an enhancement of antioxidant activity and aldose reductase inhibitory activity as compared with the corresponding parent flavonoids.<sup>5,6)</sup> It is worthy of note that while a wide variety of flavonoid sulfates are known to occur in nature, their crystal structures and stereochemistry have not been described.

Mikanin-3-*O*-sulfate (1) was first isolated from *Brickellia longifolia* and reported as its sodium salt based on mass spectrometry.<sup>7)</sup> During the course of systematic screening for antiviral agents, the potassium salt of 1 together with

mikanin (2)<sup>8)</sup> and alpinetin (3)<sup>9)</sup> were isolated from *Mikania micrantha*, a weedy vine of the family Compositae. All three compounds were first isolated from this plant, but their molecular structures have not been reported. Herein, single-crystal X-ray crystallographic studies of 1—3 were undertaken to establish their structural characteristics, which are important for an understanding of their biosynthesis pathway and biological activities.

### Results and Discussion

Potassium mikanin-3-*O*-sulfate, K(1), was obtained from a hot 95% EtOH extract of the dried aerial parts of the plant by filtration after cooling to room temperature, followed by recrystallization from methanol as its 1 : 1 solvate. The presence of elemental S and K was unequivocally established from an energy dispersive X-ray fluorescence spectrum. Single-crystal analysis of  $K(1) \cdot CH_3OH$  revealed a novel stable complex constructed from two fundamental units: the

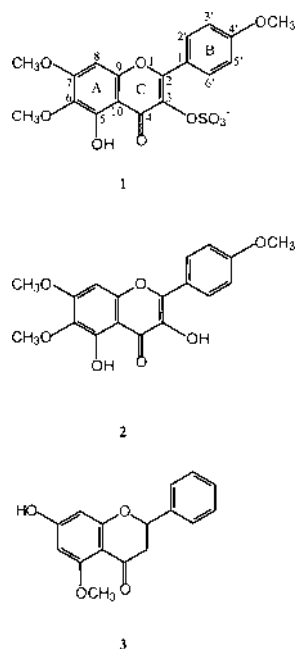


Chart 1. Chemical Formulae of Mikanin-3-*O*-sulfate (1), Mikanin (2) and Alpinetin (3)

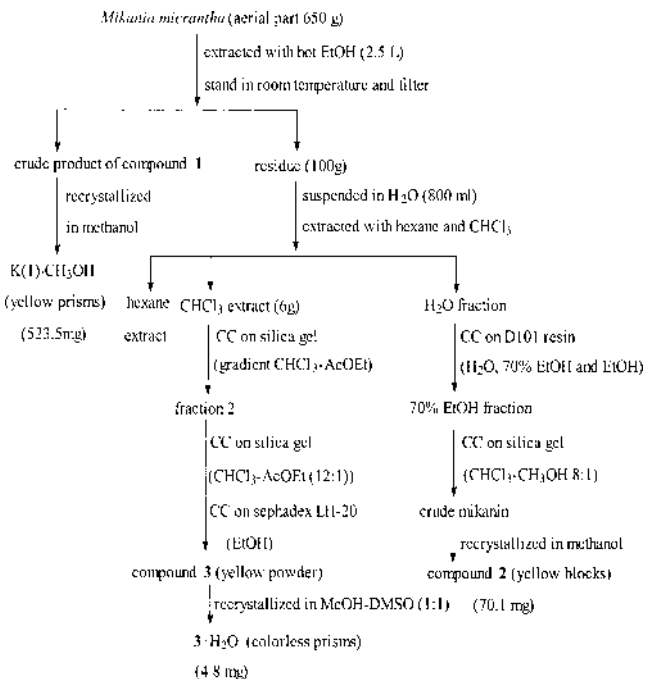


Chart 2. Isolation and Crystallization of Compounds 1, 2 and 3

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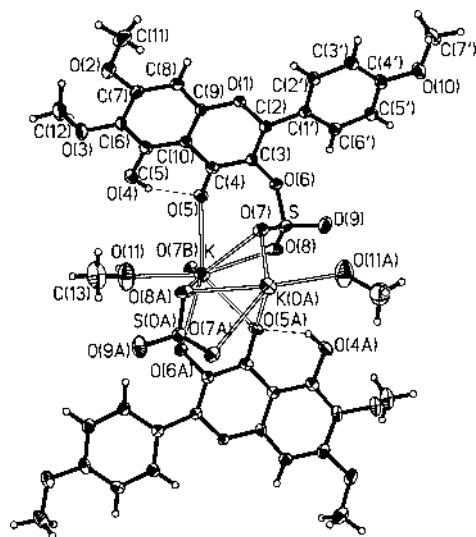


Fig. 1. ORTEP View of  $K(1) \cdot CH_3OH$

Atoms are shown as 30% thermal ellipsoids. Selected interatomic distances (Å) and angles (°): S–O6 1.659(2), S–O7 1.443(2), S–O8 1.442(2), S–O9 1.429(2), K–O5 2.898(2), K–O5a 2.843(2), K–O6a 3.019(2), K–O7 2.906(2), K–O7b 2.849(2), K–O8 2.881(3), K–O8a 2.872(2), K–O11 2.679(3), K–S 3.405(1), K–K0a 4.128(1), O8–S–O7 113.7(1), O9–S–O8 115.0(1), O9–S–O7 115.1(1), O5–K–O8 69.2(1), O8–K–O7, 49.3(1), O10–K–O5a 73.9(1), O5a–K–O8a 70.1(1), O8a–K–O6a 48.2(1), O6a–K–O11 76.8(1), O11–K–O7b 77.9(1), O7b–K–O5 73.9(1), K–O7–K0a 91.6(1), K–O5a–K0a 91.9(1), K–O8a–K0a 91.7(1). Symmetry codes: (a)  $-x+3/2, y-1/2, -z+3/2$ ; (b)  $-x+3/2, y+1/2, -z+3/2$ .

mikanin-3-*O*-sulfate monoanion **1** and a potassium cation coordinated by methanol (Fig. 1).

Compound **1** is composed of a benzopyranone moiety, a phenyl moiety and a sulfate monoanion. The benzopyranone moiety is nearly planar and the mean deviation of the atoms from the least-squares plane is 0.053(3) Å. The methoxy group at C6 is nearly orthogonal to the benzopyranone moiety, as indicated by the torsion angle C12–O3–C6–C7 = 89.0(4)°. The methoxy group at C7 is slightly twisted out of the benzene ring with torsion angle C11–O2–C7–C8 = 5.0(5)°, whereas the methoxy group at C4' is nearly coplanar with the phenyl ring and the torsion angle C3'–C4'–O10–C7' is 0.7(4)°. The two rigid ring systems, the phenyl and the benzopyrone moieties, make a dihedral angle of 4.8(2)°. An intramolecular hydrogen bond between O4 and O5 (with distances of O4–O5, 2.628 Å; O4–H4a, 0.820 Å; H4a–O5, 1.904 Å, and angle of O4–H4a–O5, 146.5°), leads to formation of a six-membered ring. The S–O6 distance [1.659(2) Å], which corresponds well to a single bond, is significantly longer than S–O7, S–O8 and S–O9 [1.443(2), 1.442(2), 1.429(2) Å, respectively], which are consistent with some degree of double bond character. The similar S–O bond distances and O–S–O bond angles involving O7, O8 and O9 [115.0(1)°, 115.1(1)°, 113.7(1)°, respectively] indicate that the negative charge is delocalized over all three oxygen atoms.

The potassium cation is coordinated by eight oxygen atoms, *i.e.* O11 from the methanol ligand, O6a from the hydroxyl group at C3, O5 and O5a from the carbonyl group, and the other four oxygen atoms from the sulfate monoanion (O7, O7b, O8, O8a). The dative bond from methanol to  $K^+$  is slightly shorter (K–O11 = 2.679(3) Å) and the distance between  $K^+$  and O6a is slightly longer (3.019(2) Å). The other distances are in the range of 2.843–2.906 Å. The

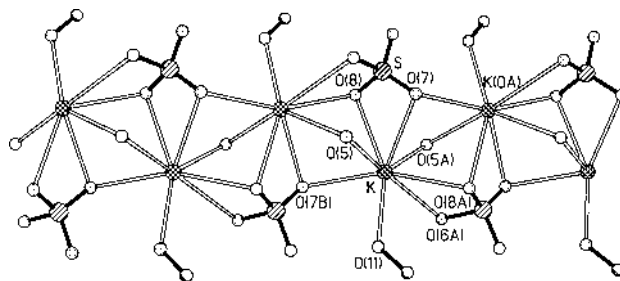


Fig. 2. A Chain of Face-Sharing  $KO_8$  Coordination Polyhedra along the *b*-Axis in  $K(1) \cdot CH_3OH$

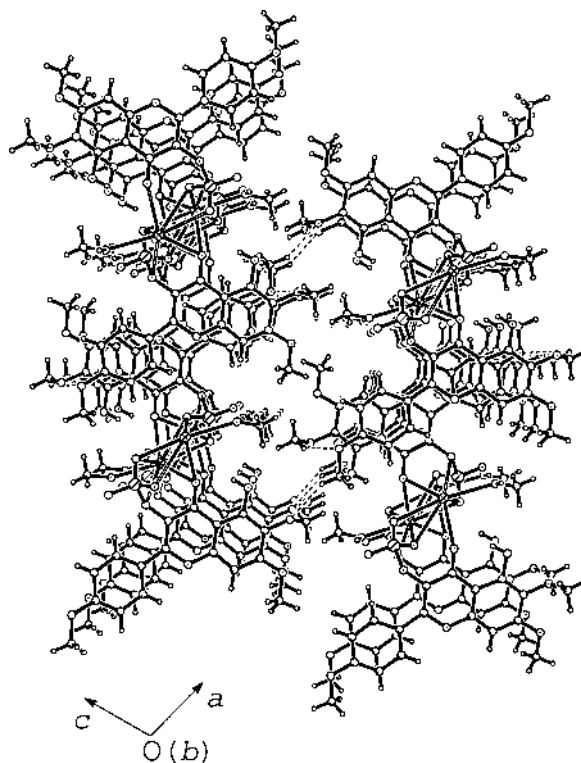


Fig. 3. Packing Diagram of  $K(1) \cdot CH_3OH$  Viewed Down the *b*-Axis, Showing the Molecular Columns (End-on View),  $\pi$ - $\pi$  Stacking of Intercalating Aglycon Units, and Layers Matching the (101) Family of Planes

The dashed lines indicate the intermolecular C–H...O interactions that connect the layers into a three-dimensional supramolecular assembly.

K–O distances found in the complex  $K(1) \cdot CH_3OH$  are comparable with those of *p*-MeC<sub>6</sub>H<sub>4</sub>S(CH<sub>2</sub>)O<sub>2</sub>–K(18-crown-6),<sup>10</sup> in which  $K^+$  is coordinated by 18-crown-6 and sulfone, and slightly longer than those of [(Ph(Me)C:N:C(H)Ph)K((*t*BuOK)<sub>2</sub>·(thf)<sub>2</sub>)<sub>∞</sub>], in which  $K^+$  is surrounded by ligands composed of an aza-allylic unit, *t*BuO<sup>−</sup> and THF.<sup>11</sup> Two adjacent potassium nuclei (K and K0a) in the complex  $K(1) \cdot CH_3OH$ , separated by 4.128 Å, are bridged by O5, O7 and O8 to form a chain of face-sharing  $KO_8$  coordination polyhedra along the (010) direction (Fig. 2).

In the solid state, the aglycon (5-hydroxy-6,7,4'-trimethoxyflavone) units of **1** are extended, at the junctions of O5 and O6, on both sides of each coordination polyhedral chain to form a polymeric molecular column running in the (010) direction. Adjacent molecular columns, related by  $\bar{1}$  symmetry, are linked by  $\pi$ - $\pi$  stacking between parallel, intercalating aglycon units at an interplanar separation of

3.50 Å (nearly half of the *b*-axis) and an intermolecular C–H···O interaction (C12–H···O10, 3.452 Å, 1–*x*, 1–*y*, 1–*z*) to form layers matching the (10 $\bar{1}$ ) family of planes. Such layers are further interconnected into a three-dimensional supramolecular assembly through interlayer C–H···O interactions (C7'–H···O3, 3.412 Å, *x*–1, *y*, *z*)<sup>12,13</sup> (Fig. 3).

Compound **2** is the parent flavonoid of **1**, and its molecular structure is similar to the aglycon unit. However, the major difference between **2** and **1** appears to be the orientation of the methoxy groups and the dihedral angle between the benzopyrone and the phenyl moieties. The corresponding torsion angles for the methoxy groups at C6, C7 and C4' are –98.7(2)°, 0.1(2)° and 4.5(2)°, respectively. The dihedral angle for **2** is 9.2(2)° which shows that **1** and **2** differ by a rotation of 4.4° of ring B around the C1'–C4' axis. An increase

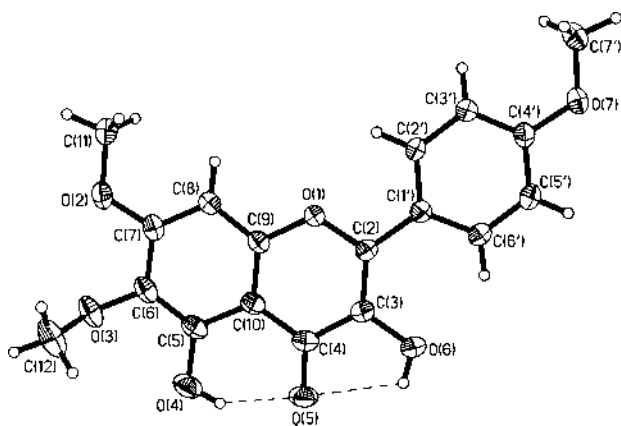


Fig. 4. Molecular Structure of Mikanin (**2**) with Atom Labeling Scheme

The C and O atoms are drawn as 30% thermal ellipsoids. The dashed lines represent intramolecular hydrogen bonds.

of the dihedral angle means a decrease in the degree of conjugation between the C2–C1' bond and the  $\pi$  electrons of the pyrone ring and the phenyl group (Fig. 4).

Compound **3** is a flavanone with a single bond between C2 and C3, which disrupts the planarity and conjugation of the rings and produces a larger dihedral angle of 70.8°. The crystal structure of the monohydrate of **3** is shown in Fig. 5.

It is well known that the introduction of substituents at the essentially single bond that connects the chromophores results in steric inhibition of their co-planarity. The degree of co-planarity decreases as the bulk of the substituents increases. The sulfate group of **1** is bigger than the hydroxyl group of **2**. However, examination of the crystal structure of

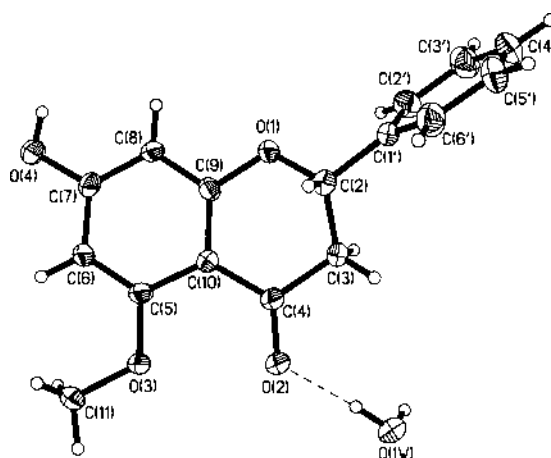


Fig. 5. Molecular Structure of Alpinetin Monohydrate (**3**) with Atom Labeling Scheme

The C and O atoms are drawn as 30% thermal ellipsoids. The intermolecular hydrogen bond in the asymmetric unit is indicated by a dashed line.

Table 1. Crystal Data and Structure Refinement for Compounds K(**1**)·CH<sub>3</sub>OH, **2** and **3**·H<sub>2</sub>O

Compound	K( <b>1</b> )·CH <sub>3</sub> OH	<b>2</b>	<b>3</b> ·H <sub>2</sub> O
CCDC deposit no.	162405	162406	162407
Color/shape	Yellow/prism	Yellow/block	Colorless/prism
Chemical formula	C <sub>19</sub> H <sub>19</sub> O <sub>11</sub> KS	C <sub>18</sub> H <sub>16</sub> O <sub>7</sub>	C <sub>16</sub> H <sub>14</sub> O <sub>4</sub> ·H <sub>2</sub> O
Formula weight	494.50	344.31	288.29
Temperature, K	293(2)	293(2)	293(2)
Crystal system	Monoclinic	Triclinic	Monoclinic
Space group	<i>P</i> 2 <sub>1</sub> / <i>n</i> (No. 14)	<i>P</i> $\bar{1}$ (No. 2)	<i>P</i> 2 <sub>1</sub> / <i>c</i> (No. 14)
Unit cell dimensions	<i>a</i> = 15.529(1) Å <i>b</i> = 7.0953(5) Å <i>c</i> = 18.944(1) Å $\beta$ = 99.350(2)°	<i>a</i> = 7.6856(9) Å <i>b</i> = 7.983(1) Å <i>c</i> = 13.197(1) Å $\alpha$ = 86.409(2)° $\beta$ = 77.395(2)° $\gamma$ = 85.358(2)°	<i>a</i> = 5.188(1) Å <i>b</i> = 9.237(1) Å <i>c</i> = 29.243(6) Å $\beta$ = 93.421(5)°
Volume, Å <sup>3</sup>	2059.6(2)	786.8(1)	1399.2(5)
<i>Z</i>	4	2	4
Density (calculated), mg/m <sup>3</sup>	1.595	1.453	1.369
Absorption coefficient, mm <sup>–1</sup>	0.421	0.113	0.102
Diffractometer/Scan	Bruker SMART CCD/ $\omega$	Bruker SMART CCD/ $\omega$	Bruker SMART CCD/ $\omega$
$\theta$ range, deg	1.58 to 25.01	1.40 to 25.05	1.40 to 25.05
Reflections measured	11015	4402	7588
Independent reflections ( <i>R</i> <sub>int</sub> )	3632 (0.0528)	2755 (0.0284)	2467 (0.0608)
Observed reflections	2378	2107	1431
Data/restraints/parameters	36320/291	2755/0/229	2467/0/198
Extinction coefficient	0.000(2)	0.004(2)	0.009(3)
Goodness of fit on <i>F</i> <sup>2</sup>	0.972	1.036	1.066
Final <i>R</i> indices [ <i>I</i> > 4 $\sigma$ ( <i>I</i> )]	0.0414	0.0378	0.0774
<i>R</i> indices (all data)	0.0741	0.0508	0.1245

Table 2. Fractional Atomic Coordinates and Equivalent Isotropic Displacement Parameters ( $\text{\AA}^2$ ) of Complex of  $\text{K}(\mathbf{1}) \cdot \text{CH}_3\text{OH}$ 

	$x/a$	$y/b$	$z/c$	$U$ (eq)
K	0.8188(1)	0.1455(1)	0.7618(1)	0.045(1)
S	0.5969(1)	0.1643(1)	0.7251(1)	0.035(1)
O1	0.5554(1)	0.2480(3)	0.4729(1)	0.030(1)
O2	0.7722(2)	0.1519(3)	0.3259(1)	0.052(1)
O3	0.8972(2)	0.2621(3)	0.4306(1)	0.051(1)
O4	0.8580(1)	0.3707(3)	0.5594(1)	0.046(1)
O5	0.7395(1)	0.3804(3)	0.6438(1)	0.039(1)
O6	0.5716(1)	0.3303(3)	0.6636(1)	0.031(1)
O7	0.6465(1)	0.0250(3)	0.6933(1)	0.040(1)
O8	0.6479(2)	0.2689(3)	0.7825(1)	0.050(1)
O9	0.5137(2)	0.1018(4)	0.7390(1)	0.059(1)
O10	0.1681(2)	0.2024(3)	0.5229(1)	0.053(1)
O11	0.9761(2)	0.2058(5)	0.7252(2)	0.103(1)
C2	0.5308(2)	0.2708(4)	0.5386(1)	0.027(1)
C3	0.5939(2)	0.3057(4)	0.5964(1)	0.028(1)
C4	0.6833(2)	0.3348(4)	0.5903(2)	0.031(1)
C5	0.7926(2)	0.3176(4)	0.5075(2)	0.034(1)
C6	0.8117(2)	0.2669(4)	0.4412(2)	0.037(1)
C7	0.7444(2)	0.2070(4)	0.3871(2)	0.038(1)
C8	0.6587(2)	0.2049(4)	0.3975(2)	0.034(1)
C9	0.6410(2)	0.2539(4)	0.4644(1)	0.028(1)
C10	0.7059(2)	0.3060(4)	0.5206(1)	0.029(1)
C11	0.7097(3)	0.0733(6)	0.2709(2)	0.060(1)
C12	0.9266(2)	0.4268(6)	0.3999(2)	0.066(1)
C13	1.0252(3)	0.0953(7)	0.6850(3)	0.099(2)
C1'	0.4366(2)	0.2541(4)	0.5342(1)	0.029(1)
C2'	0.3852(2)	0.1937(4)	0.4703(2)	0.033(1)
C3'	0.2958(2)	0.1763(4)	0.4639(2)	0.036(1)
C4'	0.2550(2)	0.2179(4)	0.5215(2)	0.037(1)
C5'	0.3047(2)	0.2830(4)	0.5846(2)	0.039(1)
C6'	0.3930(2)	0.3002(4)	0.5916(2)	0.035(1)
C7'	0.1125(2)	0.1398(5)	0.4600(2)	0.058(1)

$\text{K}(\mathbf{1}) \cdot \text{CH}_3\text{OH}$  revealed two ways in which co-planarity could be increased, *i.e.* (a) the sulfate group is fixed by the potassium chain and bends away from the 2-phenyl moiety, and thus decrease of steric hindrance results in a smaller dihedral angle compared with **2**; (b) flavones can be expected to be planar in any situation where there are forces that can stabilize the partial negative charge on the exocyclic carbonyl oxygen atom.<sup>14</sup> Besides the hydrogen-bonding interaction with the adjacent hydroxyl group, O5 is coordinated with the potassium ion, and thus the partial negative charge can be effectively stabilized.

## Experimental

The aerial parts of *Mikania micrantha* were collected in Hong Kong in June, 2000 and botanically identified at the Department of Biology, The Chinese University of Hong Kong, where a voucher specimen (no. chan 2000-1) is kept.

Isolation and crystallization of compounds **1**, **2** and **3** are shown in Chart 2.

The X-ray diffraction data were collected at room temperature on a Bruker Smart1000 CCD diffractometer with  $\text{MoK}\alpha$  radiation ( $\lambda=0.71073$  Å). The crystal structure was resolved by direct methods using SHELXS-97 and refined by full-matrix least-squares on  $F^2$ . Non-hydrogen atoms were refined with anisotropic temperature factors. Hydrogen atoms of the hydroxyl groups were located from a difference Fourier map while hydrogen atoms bonded to carbons were placed at their geometrically calculated positions, and included in the calculation of structure factors with isotropic temperature factors. A summary of crystallographic data and structure refinement parameters of compounds **1**–**3** are given in Table 1. Final atomic coordinates of  $\text{K}(\mathbf{1}) \cdot \text{CH}_3\text{OH}$  are listed in Table 2.

**Acknowledgements** Partial support was received from Hong Kong Research Grant Council Earmarked Grant CUHK 4206/99P and CUHK 4171/99M, and Industrial Support Fund AF/281/97.

**Supporting Information Available** Complete lists of refined atomic coordinates and relevant information in standard CIF format for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary materials. The CCDC numbers are shown in Table 1. These materials are available free of charge *via* application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (+44) 1223-336033; e-mail: deposit@ccdc.cam.ac.uk].

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