Three New Cytotoxic *ent*-Kaurane Diterpenoids from *Isodon weisiensis* C. Y. Wu

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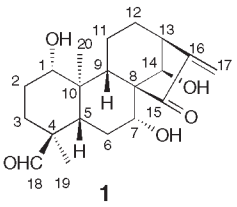
Three new cytotoxic *ent*-kaurane diterpenoids, (1α,7α,14β)-1,7,14-trihydroxy-*ent*-kaur-16-en-15,18-dione (**1**), (1α,7α,14β)-1,7,14,18,20-pentahydroxy-*ent*-kaur-16-en-15-one (**2**), and (3β,7α,14β)-3,7,14-tris(acetyloxy)-*ent*-kaur-16-en-15-one (**3**), were isolated from *Isodon weisiensis* C. Y. Wu. Their structures were elucidated by spectroscopic methods, including 2D-NMR techniques, and the crystal structure of **1** was determined by single-crystal X-ray-diffraction analysis. The chosen crystal of **1** was orthorhombic, space group $P2_12_12_1$, and there were two molecules with little difference in bond length and bond angle in the least-asymmetry unit. Compounds **1**–**3** showed significant cytotoxic activities against human-cancer cell lines Bel-7402 and HO-8910.

Introduction. – More than 30 *Isodon* species are being used in Chinese folk medicines. A number of *ent*-kaurane diterpenoids have been isolated from the genus *Isodon*, which were proved to have varied biological activities, *i.e.*, antibacterial, anti-inflammatory, antitumor, *etc.* [1]. *Isodon weisiensis* C. Y. Wu is wildely distributed in the south of the Gansu Province, and has been used as a local folk medicine in China for treatment of gastric ulcer, enteritis, and hepatitis. In previous phytochemical investigations on *I. weisiensis* C. Y. Wu, only two *ent*-kaurane diterpenoids, weisiensin A and trichorabdal A [2], were isolated from the plant collected in Yunnan Province. Our investigation of *I. weisiensis* C. Y. Wu distributed in Gansu Province led to the isolation of three new cytotoxic diterpenoids **1**–**3**. Their spectral data, coupled with a consideration of the structures of diterpenes isolated so far from the genus *Isodon* [1], suggested that compounds **1**–**3** have the basic skeleton of *ent*-kaur-16-en-15-one (C(20) not functionalized). Our pharmacological research indicated that compounds of this type show the most significant cytotoxicity activities among the four major structural types present in *Isodon* species, namely 20-nonoxygenated *ent*-kauranes, 20-oxygenated *ent*-kauranes, 8,9-seco-*ent*-kauranes, and 6,7-seco-*ent*-kauranes.

The biological activity of the compounds depends on certain key structural and conformational features. It is highly important in pharmacology to establish the accurate molecular configuration by single-crystal X-ray diffraction. Although more than 160 20-nonoxygenated *ent*-kauronoids have been isolated from the genus *Isodon*, the structures of only four compounds, mebadonin, xindongnin B, leucophyllin F, and leucophyllin C, have been determined by X-ray diffraction [1]. We report herein the isolation and structural elucidation of three new *ent*-kauranoids, the relative config-

uration of **1** as determined by single-crystal X-ray-diffraction analysis, and the biological evaluation of **1**–**3**.



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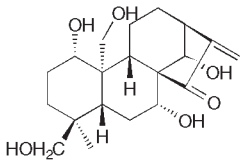

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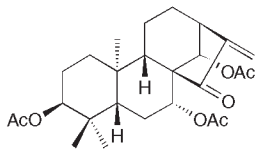

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Results and Discussion. – The FAB-MS spectrum of **1** showed the quasimolecular ion at *m/z* 349 ($[M+H]^+$) consistent with the molecular formula $C_{20}H_{28}O_5$. The structure fo **1**, deduced by a detailed analysis of the spectroscopic data (*Tables 1* and *2*), was confirmed by an X-ray-diffraction analysis (see below). Furthermore, the X-ray crystal structure established that the OH groups at C(1) and C(7) were α-orientated and OH–C(14) was β-orientated. Thus, the structure of **1** was elucidated as (1α,7α,14β)-1,7,14-trihydroxy-*ent*-kaur-16-en-15,18-dione.

The IR spectrum of **1** (1726 and 1651 cm^{-1}) and the NMR data (δ(H) 6.28 and 5.30 (each 1 H, *s*); δ(C) 205.7, 150.2, and 115.8) were consistent with an *exocyclic* CH_2=C group conjugated with a C=O group at a five-membered ring [3]. The 20 C-atoms found in the ^{13}C- and DEPT-NMR spectra arose from 2 Me, 5 CH_2, and 6 CH groups including three oxygenated ones, three quaternary C-atoms, two olefinic C-atoms, the C=O group mentioned above, and an aldehyde C=O group, which obviously suggested a diterpene skeleton. The spectral data of **1** was similar to, previously reported data of *ent*-kaur-16-en-15-one [4–6]. The typical ^{1}H- and ^{13}C-NMR signals of **1** at δ(H) 3.51 (*dd*, 1 H), δ(H) 4.83 (*dd*, 1 H), 5.23 (br *s*, 1 H), and 9.26 (*s*, 1 H), and at δ(C) 79.1 (*d*), 73.5 (*d*), δ_C 75.8 (*d*), and 205.7 (*d*) established the presence of 3 OH groups and an aldehyde group. The cross-peaks observed in the HMBC plot disclosed that three OH groups and the aldehyde group were located at C(1), C(7), C(14), and C(4), respectively (*Table 2*).

The single-crystal X-ray-diffraction analysis of **1** revealed that the chosen crystal is a natural equimolar mixture of two molecules with small differences in the bond-length and bond-angle data in the least-asymmetry unit, and that their three six-membered rings are in a chair-like conformation. The five-membered rings adopt a twist-envelope-like conformation, as shown in *Fig. 1*. The molecules form an extensive network *via* the intramolecular H-bonds O(10)–H···O(8) (2.586(1)Å) and O(3)–H···O(5) (2.597(1)Å) and the intermolecular H-bonds O(2)–H···O(4) (2.874(1)Å); O(5)–H ···O(7) (2.742(1)Å), O(8)–H···O(3) (2.736(1)Å), and O(7)–H···O(10) (2.843(1)Å), as shown in *Fig. 2*.

The molecular formula of compound **2** was established as $C_{20}H_{30}O_6$ from its HR-ESI-MS. Analysis of the spectral data (*Tables 1* and *2*) and comparison with those of **1** allowed the elucidation of the structure of **2** as (1α,7α,14β)-1,7,14,18,20-pentahydroxy-*ent*-kaur-16-en-15-one.

The IR spectrum of **2** indicated the presence of OH groups (3445, 3340 cm^{-1}) and an α,β-unsaturated carbonyl group (1728, 1648 cm^{-1}). This was confirmed by the following ^{13}C- and ^{1}H-NMR data: δ(C) 81.3, 74.7, 76.7, 70.7, and 62.5 (OH-substituted C), and δ(C) 209.5, 150.9, 115.2, and δ(H) 6.27 and 5.68 (CH_2=CC=O moiety). The ^{13}C-NMR spectrum showed 20 C-signals, attributed to 1 Me, 8 CH_2 including an exocyclic one, 2 OCH_2, 6 CH including 3 OCH, and 5 quaternary C-atoms. The ^{1}H-NMR spectrum exhibited 2 *s* at δ 6.27 (^{1}H) and 5.68 (^{1}H), attributable to the excocylic CH_2 protons next to a C=O group, 4 *d* at δ 4.77 (J = 12.0, 1 H), 4.45

Table 1. *^{1}H- and ^{13}C-NMR Data* (400 and 100 MHz, resp.) *of Compounds* **1**–**3**. δ in ppm, J in Hz.

	1[a])		**2**[a])		**3**[b])	
	δ(H)	δ(C)[c])	δ(H)	δ(C)[c])	δ(H)	δ(C)[c])
H–C(1) or CH_2(1)	3.51 (*dd*, *J* = 10.0, 6.8)	79.1 (*d*)	3.68 (*dd*, *J* = 11.2, 4.0)	81.3 (*d*)	1.57–1.60 (*m*), 1.45–1.48 (*m*)	33.1 (*t*)
CH_2(2)	1.15–1.17 (*m*), 1.50 (*ddd*, 13.6, 13.6, 4.0)	30.2 (*t*)	2.08–2.11 (*m*), 2.93–2.96 (*m*)	30.4 (*t*)	1.67–1.70 (*m*), 1.64–1.67 (*m*)	22.5 (*t*)
CH_2(3) or H–C(3)	1.68 (*t*, *J* = 4.0), 1.68 (*t*, *J* = 4.0)	32.1 (*t*)	1.41–1.44 (*m*), 2.67–2.70 (*m*)	33.1 (*t*)	4.66 (*t*, *J* = 5.6)	77.1 (*d*)
C(4)	–	49.7 (*s*)	–	37.4 (*s*)	–	36.6 (*s*)
H–C(5)	1.60–162 (*m*)	44.7 (*d*)	1.88 (*dd*, *J* = 11.8, 1.6)	45.3 (*d*)	1.65 (*d*, *J* = 11.6)	47.3 (*d*)
CH_2(6)	1.92–1.94 (*m*), 1.83 (*ddd*, *J* = 6.8, 6.4, 2.0)	28.0 (*t*)	2.17 (*ddd*, *J* = 12.4, 12.4, 12.4), 2.36 (*ddd*, *J* = 12.0, 8.0, 1.4)	29.9 (*t*)	1.95 (*d*, *J* = 12.0), 1.60–1.62 (*m*)	23.8 (*t*)
H–C(7)	4.83 (*dd*, *J* = 12.0, 3.6)	73.5 (*d*)	5.06 (*dd*, *J* = 12.0, 4.0)	74.7 (*d*)	5.45 (*dd*, *J* = 11.2, 4.8)	75.8 (*d*)
C(8)	–	62.6 (*s*)	–	62.1 (*s*)	–	61.9 (*s*)
H–C(9)	1.96 (*s*)	56.0 (*d*)	2.06 (*d*, *J* = 8.8)	56.9 (*d*)	1.51–1.53 (*m*)	55.7 (*d*)
C(10)	–	44.6 (*s*)	–	48.1 (*s*)	–	39.8 (*s*)
CH_2(11)	1.64–1.65 (*m*), 3.59 (*dd*, *J* = 13.6, 4.4)	20.3 (*t*)	1.73–1.74 (*m*), 3.31–3.34 (*m*)	21.6 (*t*)	1.74 (*dd*, *J* = 4.8, 2.2), 1.62 (*t*, *J* = 3.0)	17.2 (*t*)
CH_2(12)	2.21–1.24 (*m*), 2.13 (*ddd*, *J* = 7.2, 5.6, 2.0)	31.6 (*t*)	1.69–1.72 (*m*), 1.96–1.99 (*m*)	31.5 (*t*)	1.81 (*t*, *J* = 10.8), 1.76 (*ddd*, *J* = 6.4, 4.2, 2.2)	32.2 (*t*)
H–C(13)	3.23 (br. *s*)	47.2 (*d*)	3.30 (br. *s*)	47.6 (*d*)	3.02 (br. *s*)	44.1 (*d*)
H–C(14)	5.23 (br. *s*)	75.8 (*d*)	5.34 (*s*)	76.7 (*d*)	6.02 (*s*)	75.0 (*d*)
C(15)	–	208.1 (*s*)	–	209.5 (*s*)	–	204.0 (*s*)
C(16)	–	150.2 (*s*)	–	150.9 (*s*)	–	145.6 (*s*)
CH_2(17)	6.28 (*s*), 5.30 (*s*)	115.8 (*t*)	6.27(*s*), 5.68 (*s*)	115.2 (*t*)	6.09 (*s*), 5.50 (*s*)	118.2 (*t*)
CH(18), CH_2(18), or Me(18)	9.26 (*s*) (CHO)	205.7 (*d*)	3.61, 3.26 (*AB d*, *J* = 11.2)	70.7 (*t*)	0.89 (*s*, Me)	27.6 (*q*)
Me(19)	1.14 (*s*, Me)	14.1 (*q*)	0.93 (*s*)	18.6 (*q*)	0.91 (*s*, Me)	21.0 (*q*)
Me(20) or CH_2(20)	1.42 (*s*, Me)	15.1 (*q*)	4.77, 4.45 (*AB d*, *J* = 12.0)	62.5 (*t*)	1.09 (*s*, Me)	17.9 (*q*)
3 AcO	–	–	–	–	2.03 (*s*), 2.08 (*s*), 2.04 (*s*)	168.0 (*s*), 170.6 (*s*), 170.9 (*s*) 20.9 (*q*), 21.4 (*q*), 21.7 (*q*)

[a]) In C_5D_5N. [b]) In $CDCl_3$. [c]) Multiplicities determined by a DEPT experiment.

(*J* = 12.0, 1 H), 3.61 (*J* = 11.2, 1 H), and 3.26 (*J* = 11.2, 1 H) assignable to the OCH_2 protons, and 1 *s* at δ 0.93 (3 H) due to 1 Me group attached to a quaternary C-atom. The above data indicated that the basic skeleton of compound **2** was similar to that of **1**. The cross-peaks observed in the HMBC revealed that the 5 OH groups are located at C(1), C(7), C(14), C(18), and C(20) (*Table 2*). The NOESY plots exhibited the correlations H_β–C(1)/H_β–C(5) and H_β–C(9), H_β–C(7)/H_β–C(5) and H_β–(9), and H_α–C(14)/H_α–C(12) and CH_2(20).

Table 2. *$^{13}C,^{1}H$ Long-Range HMBC Correlations for Compounds* **1**–**3**

	1	**2**	**3**
C(1)	H_β–C(2), CH_2(3), CH_3(20)	CH_2(2), H_α–C(3)	CH_2(2), H_α–C(3)
C(2)	–	H_α–C(3)	–
C(3)	H_β–C(2), CH_3(19)	CH_2(2), CH_2(18), CH_3(19)	CH_2(2), CH_3(18), CH_3(19)
C(4)	H_β–C(2), CH_2(3), H_β–C(5) H–C(18), CH_3(19)	CH_2(2), H_α–C(3), H_β–C(5), CH_2(18), CH_3(19)	CH_2(2), H_α–C(3), H_β–C(5), CH_3(18), CH_3(19)
C(5)	CH_2(6), H_β–C(9), CH_3(19)	H_β–C(1), H_α–C(3), H_β–C(9), CH_2(18), CH_3(19), CH_2(20)	H_β–C(1), H_α–C(3), H_β–C(9), CH_3(18), CH_3(19), CH_3(20)
C(6)	–	H_β–C(5), H_β–C(7),	H_β–C(5)
C(7)	H_β–C(5), H_α–C(6)	H_β–C(5), H_α–C(6)	H_β–C(5), H_α–C(6)
C(8)	H_α–C(6), H_β–C(7), H_β–C(9), H_β–C(11), H_α–C(12), H_α–C(14)	H_β–C(6), H_β–C(7), H_β–C(9), H_β–C(11), H_α–C(14)	H_α–C(6), H_β–C(7), H_β–C(9), H_β–C(11), H_α–C(12), H_α–C(14)
C(9)	H_β–C(1), H_β–C(5), H_β–C(7), H_α–C(11), CH_3(20)	H_β–C(1), H_β–C(5), H_α–C(11), CH_2(20)	H_β–C(5), H_α–C(11), CH_3(20)
C(10)	H_β–C(5), H_β–C(9), H_β–C(11), H_α–C(12), CH_3(20)	H_β–C(1), H_α–C(12), H_β–C(9), CH_2(20)	H_β–C(1), H_α–C(12), H_β–C(9), CH_3(20)
C(11)	H_β–C(9), H_β–C(12)	H_β–C(9)	H_β–C(9)
C(12)	H_β–C(9), H_β–C(11), H_α–C(13)	H_β–C(9), H_β–C(11), H_α–C(14), CH_2(17)	H_β–C(9), H_β–C(11), H_α–C(14), CH_2(17)
C(13)	H_β–C(11), H_β–C(12)	H_β–C(11), CH_2(12)	CH_2(12)
C(14)	H_β–C(7), H_β–C(9), H_β–C(12), H_α–C(13)	H_β–C(7), H_β–C(12)	H_β–C(7)
C(15)	H_α–C(13), H_α–C(14)	H_α–C(14), CH_2(17)	H_α–C(14), CH_2(17)
C(16)	H_β–C(12), H_α–C(14)	H_β–C(12), H_α–C(14), CH_2(17)	H_α–C(14), CH_2(17)
C(17)	H_α–C(14)	–	–
C(18)	H_β–C(2), CH_2(3), CH_3(19)	H_β–C(5), CH_3(19)	H_β–C(5), CH_3(19)
C(19)	H_β–C(2), CH_2(3), H–C(18)	H_β–C(5)	H_β–C(5), CH_3(18)
C(20)	H_β–C(1), H_β–C(9)	H_β–C(1)	CH_2(1), H_β–C(5)
3 AcO	–	–	H_α–C(3), H_β–(7), H_α–(14), resp.

Compound **3** gave rise to a molecular-ion peak at *m/z* 461($[M+1]^+$) in the FAB-MS, consistent with the molecular formula $C_{26}H_{36}O_7$, which was confirmed by its ^{13}C-NMR and DEPT spectra. Comparison of the ^{1}H-NMR and ^{13}C-NMR data of **3** with those of leukamenin E [7] established that the two compounds have the same structure, except that, in the latter, two OH groups are at C(7) and C(14), whereas, in the former, these are replaced by two AcO groups. The structure of compound **3** was determined as (3β,7α,14β)-3,7,14-tris(acetyloxy)-*ent*-kaur-16-en-15-one.

The IR spectrum of **3** showed characteristic absorption bands for the carbonyl groups and double bonds at 1719 and 1654 cm^{-1}. These assignments were confirmed by the following ^{1}H-NMR and ^{13}C-NMR data: δ(H) 6.09 and 5.50 (CH_2=C); δ(C) 204.0, 170.9, 170.6, and 168.0 (C=O), and δ(C) 145.6 and 118.2 (CH_2=C). The ^{13}C- and DEPT-NMR spectra of **3** showed 26 C-signals. The positions of the AcO groups were indicated by the downfield shift of H–C(7) and H–C(14) in **3** as compared to leukanenin E [7]. Furthermore, the cross-peaks in the HMBC plot confirmed the presence of AcO groups at C(3), C(7) and C(14).

Compounds **1**–**3** were examined for their cytotoxicity against two kinds of human-tumor cell lines, Bel-7402 and HO-8910, and found to be significantly cytotoxic, with

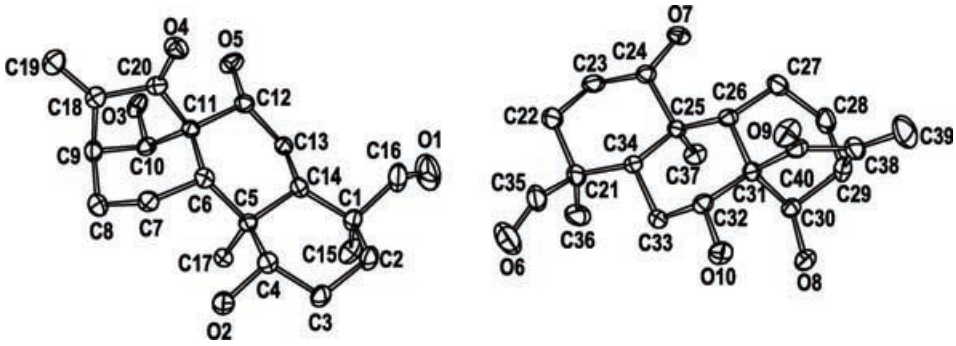

Fig. 1. *Molecular structure of compound* **1** *at 30% ellipsoid probability*

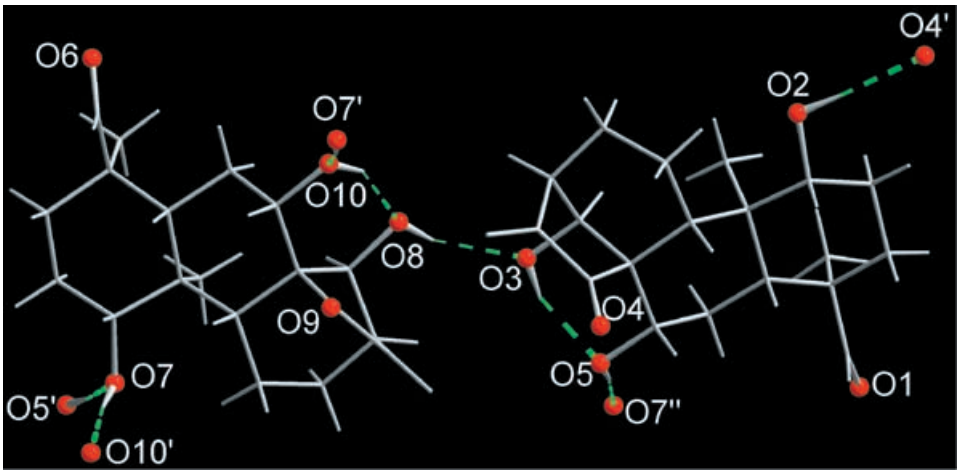

Fig. 2. *Crystal structure of* **1**. H-Bonds are represented as dashed lines.

IC_{50} values of 15.42 ± 2.06, 68.6 ± 2.17, and 1.09 ± 0.38 μM, and 21.60 ± 2.60, 58.5 ± 2.55, and 2.65 ± 0.76 μM, respectively.

This work was supported by the foundation of the *Innovation Project Council of Northwest Normal University* (NWNUKJCXGC) and the *National Natural Science Foundation of China* (No-20274034).

Experimental Part

General. CC = Column chromatography. M.p.: *Kofler* microscope *(Reichert)* apparatus, uncorrected. Optical rotation: *Perkin-Elmer 241* polarimeter. IR Spectra: *IFS 120 H* IR spectrometer; $\tilde{\nu}$ in cm^{-1}. ^1H-, ^{13}C-, and 2D-NMR Spectra *Varian INOVA-400* spectrometer; $SiMe_4$ as internal standard; δ in ppm, J in Hz. HR-ESI-MS and FAB-MS: *Bruker APEX II FT-MS* and an *ZAB-HS* mass spectrometers, respectively; in m/z.

Plant Material. The leaves of *Isodon weisiensis* C. Y. Wu were collected in Li County of Gansu Province, China, in August 2003, and identified by Prof. *Kun Sun.* A voucher specimen (XCC03-8-16) was deposited in the College of Life Sciences, Northwest Normal University.

Extraction and Isolation. The dried and powdered leaves (7.5 kg) of *I. weisiensis* C. Y. Wu were extracted three times with 60% Me_2CO at r.t. and filtered. The filtrate was concentrated and then partitioned with

petroleum ether and AcOEt. The petroleum ether extract was subjected to CC (SiO_2) (1.0 kg, 200–300 mesh), petroleum ether/acetone 60:1, 50:1, 40:1, 30:1, 25:1, 20:1, 15:1, 10:1, 8:1, 5:1, 3:1, and 1:1 (TLC monitoring): crude *Fractions 1–8*. *Fr. 2* (2.5 g) was resubjected to CC (SiO_2 (50 g SiO_2, 200–300 mesh), petroleum ether/acetone 60:1, 50:1, 40:1, 30:1, 25:1, 20:1, 15:1, 10:1): **2** (16 mg) and **3** (20 mg). *Fr. 6* (4.0 g) was also resubjected to CC SiO_2 (80 g, 200–300 mesh), petroleum ether/acetone 20:1, 15:1, 10:1, 8:1, 5:1, 3:1 and 1:1): **1** (65 mg).

(1α,7α,14β)-1,7,14-Trihydroxy-ent-*kaur-16-en-15,18-dione* (**1**): Colorless crystals. M.p. 208–210°. $[\alpha]_D^{20} = -68$ ($c = 0.2$, C_5H_5N). IR (KBr): 3466, 3278, 2933, 2873, 1726, 1651, 1471, 1073, 1030, 963. ^{1}H- and ^{13}C-NMR: *Table 1*. FAB-MS: 371 ($[M+Na]^+$), 349 ($[M+H]^+$), 331 ($[M+H-H_2O]^+$), 313 ($[M+H-2\times H_2O]^+$), 285, 176, 89, 57.

(1α,7α,14β)-1,7,14,18,20-Pentahydroxy-*ent*-kaur-16-en-15-one (**2**): Colorless needles. M.p. 236–238°. $[\alpha]_D^{20} = -96$ ($c = 0.15$, MeOH). IR (KBr): 3445, 3340, 2935, 2883, 1728, 1648, 1442, 1261, 1058, 937. ^{1}H and ^{13}C-NMR: *Table 1*. HR-ESI-MS 384.2381 ($[M+NH_4]^+$) $C_{20}H_{34}NMO_6$; calc. 384.2386).

(3β,7α,14β)-3,7,14-Tris(acetyloxy)-ent-*kaur-16-en-15-one* (**3**): Colorless needles. M.p. 106–108°. IR (KBr): 2943, 1719, 1654, 1249, 1043. ^{1}H and ^{13}C-NMR: *Table 1*. FAB-MS: 483 ($[M+Na]^+$), 461 ($[M+H]^+$), 401 ($[M-H_2O-OAc]^+$), 359 ($[M-H_2O-2\times OAc]^+$), 316, 229, 121, 67, 55.

X-Ray-Crystallographic Analysis of **1**[1]). A crystal of the dimension 1.30 × 0.85 × 0.20 mm was mounted on a glass fiber. X-Ray diffraction intensity data were collected with a *Siemens-P4* diffractometer equipped with a graphite-monochromated Mo*Kα* radiation λ 0.71073 Å) by an ω scan mode at 293 K. A total of 22902 reflections were measured within $2.91° \le \theta \le 25.03°$, yielding 6331 unique reflections ($R_{int} = 0.0503$). The compound crystallizes in an orthorhombic space group $P2_12_12_1$ with $a = 13.072$ (5), $b = 13.982$ (5), $c = 19.604$ (7) Å; $V = 3585$ (2) Å^3, $Z = 2$, $d_{calc.}$ 1.292 Mg/m^3, $F(000) = 1504$, $\mu = 0.092$ mm^{-1}. The crystal structure was solved by direct methods with *Siemens* SHELXTL™, version 5 package of crystallographic software [8], and refined by full-matrix least-square refinement on F^2. All non-H-atoms were refined anisotropically. The final refinement converged at $R = 0.0608$, $wR = 0.1527$ ($w = 1/(s^2(F_0^2) + (0.0854\,P)^2 + 0.8904\,P)$, where $P = (F_0^2 + 2F_c^2)/3$), $(\Delta/\sigma)_{max} = 0.001$. The largest peak and deepest hole on the final difference *Fourier* map were 0.255 and −0.164 e/Å^3, respectively.

Cytotoxicity against Human-Tumor Cell Lines Bel-7402 and HO-8910. Compounds **1**–**3** were evaluated for cytotoxic potential against human-cancer cell lines Bel-7402 and HO-8910 as previously described [9].

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Received March 9, 2005

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[1]) CCDC-263630 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre* via www.ccdc.cam.ac.uk/data_request/cif.