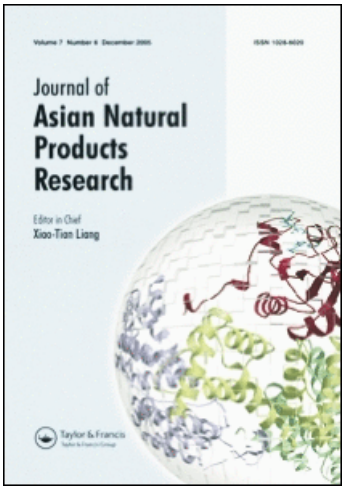

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Chemical constituents of *Nouelia insignis* Franch

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Two new diterpenes and *ent*-15α-hydroxykaur-16-*en*-19-oic acid 11,12-acetonide **(3)**, together with 23 known compounds were isolated from the dried aerial parts of *Nouelia insignis* Franch. The structures of new compounds were determined to be *ent*-14β,15α-dihydroxykaur-16-*en*-19-oic acid **(1)**, *ent*-14β-hydroxy-15-oxokaur-16-*en*-19-oic acid **(2)** on the basis of spectral and chemical evidence. The structure of *ent*-11α,16α-epoxy-15α-hydroxy-16*S*-kaur-19-oic acid **(4)** was confirmed by X-ray crystallographic analysis.

Keywords: *Nouelia insignis*; *Ent*-kaurene; Diterpenic acid; Sesquiterpene lactone; Steroid

1. Introduction

Nouelia insignis Franch, an endemic plant and a monotype species of the genus *Nouelia* Franch, is distributed in Sichuan–Yunnan region, especially in Panzhihua City of China. The genera *Nouelia* and *Leucomeris* (Compositae) are cytologically related. *Nouelia* may be descendant of old plants, which was developed as an ornamental plant in China. The plant of *Leucomeris* Kurz, a sibling genus of *Nouelia* Franch, was used as anti-inflammatory medicinal herb to cure cough and snake bite [1]. The chemical investigation on *N. insignis* has not been reported.

This study on the aqueous ethanolic extract of the aerial parts of *N. insignis* led to the isolation of two new *ent*-kaurene-type diterpenes, *ent*-14β,15α-dihydroxykaur-16-*en*-19-oic acid **(1)** and *ent*-14β-hydroxy-15-oxokaur-16-*en*-19-oic acid **(2)**, *ent*-15α-hydroxykaur-16-*en*-19-oic acid 11,12-acetonide **(3)** (figure 1), and 23 known compounds *ent*-11α,16α-epoxy-15α-hydroxy-16*S*-kaur-19-oic acid **(4)** [2], ent-15α-hydroxykaur-16-*en*-19-oic acid (**5**) [3], *ent*-11α,12α,15α-trihydroxykaur-16-*en*-19-oic acid **(6)** [4], *ent*-12α,15α-dihydroxykaur-16-*en*-19-oic acid **(7)** [2], 8β,9-dihydro-onoseriolide **(8)** [5], taraxerone **(9)** [6], β-taraxerol **(10)** [6], α-taraxerol **(11)** [7], 2,6-dimethoxy 1,4-benzoquinone **(12)** [8], stigmasterol **(13)** [9], 3-*O*-β-D-glucopyranosyl stigmasterol **(14)** [10], β-sitosterol **(15)**, β-daucosterol **(16)**,

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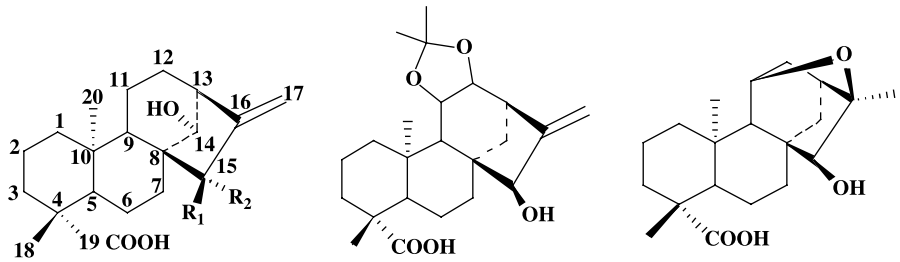

1 R_1=OH, R_2=H
2 R_1R_2=O

3 **4**

Figure 1. The structures of **1**–**4**.

2,3-dihydroxypropyl hexadecoate **(17)** [11], palmitic acid **(18)** [12], tetracosanoic acid **(19)** [13], pentacosan-1-ol **(20)** [14], taraxasteryl acetate **(21)** [15,16], pseudo taraxasteryl acetate **(22)** [17], caffeic acid **(23)** [18], sucrose **(24)** [19], glutinol **(25)** [20], and rutin **(26)**. These compounds were identified prodominantly on the basis of spectral data. The structure of **4** was confirmed by X-ray crystallographic analysis (figure 3).

2. Results and discussion

Compound **1** was obtained as colourless needles. Two tertiary methyls (δ_H 0.80, 3H, *s*; δ_H 1.12, 3H, *s*; δ_C 15.6, 29.0), an *exo*-methylene (δ_H 4.91 *brs*, 4.89 *brs*; δ_C 105.7), and two oxygenated methines (δ_H 3.58 *d*, 3.76 *s*; δ_C 64.9, 81.9) were recognized from the ^{1}H and ^{13}C NMR spectral data (table 1). Twenty carbon signals were observed in the ^{13}C NMR spectrum, which were in accordance with its molecular formula $C_{20}H_{30}O_4$, provided by the quasi-molecular ion peak at *m/z* 357.2043 $[M + Na]^+$ in the HRESIMS. Comparison of the evidence mentioned above and the NMR spectral data in table 1 with those of *ent*-12α,15α-dihydroxykaur-16-*en*-19-oic acid, isolated from *Pteris longipes* [2], suggested that compound **1** should be also an *ent*-kaurane type diterpene. The IR absorption bands at ν_{max} 3430, 3427, 3200–2600, and 1694 cm^{-1} showed the presence of hydroxyl groups and the carboxyl group, therefore according to the molecular formula, two hydroxyl groups and one carboxyl group. The assignment of the ^{1}H and corresponding ^{13}C NMR signals was succeeded on the basis of HMQC and ^{1}H–^{1}HCOSY experiments. Two hydroxyl groups were located at C-14 and C-15 based on the HMBC correlations (figure 2) from H-17 (δ 4.89 and 4.91, each 1H, brs) and H-9 (δ 1.41, 1H, s) to C-15 (δ 81.9), and from H-9 (δ 1.41, 1H, brs) to C-14 (δ 64.9). The HMBC correlations between H-18 (δ 1.12, 3H, s) and C-3 (δ 37.9), C-5 (δ 56.1), and COOH (δ 179.0) suggested that the carboxyl group was located at C-4.

The configuration of OH-14β and OH-15α were determined upon the following NOESY correlations (figure 2) between H-14 and H-13, H-9, OH-15, between H-15 and OH-14, and between H-13 and H-17. The NOESY correlation between H-18 and H-5 indicated that the carboxyl group could be assigned to C-19. Thus, the structure of compound **1** was elucidated as *ent*-14β,15α-dihydroxykaur-16-*en*-19-oic acid.

Compound **2** was obtained as colourless flaky crystal. The quasi-molecular ion peak at *m/z* 355.2043 $[M + Na]^+$ in the HRESIMS revealed the molecular formula $C_{20}H_{28}O_4$. Comparison of the ^{1}H and ^{13}C NMR spectral data of compounds **1** and **2** (table 1) indicated

Table 1. NMR spectral data of compounds **1** and **2** (**1** in DMSO-d_6, **2** in $CDCl_3$)*.

position	***1*** δ_H (mult., *J* in Hz)	δ_C	position	***2*** δ_H (mult., *J* in Hz)	δ_C
1	1.91 (1H, brd, 13.1)	40.4	1	1.94 (1H, brd, 14.2)	39.7
	1.09 (1H, m)			1.08 (1H, m)	
2	1.77 (1H, m)	19.3	2	1.99 (1H, m)	19.9
	1.66 (1H, m)			1.94 (1H, m)	
3	2.01 (1H, brd, 13.1)	37.9	3	2.19 (1H, brd, 13.7)	37.6
	1.02 (1H, m)			1.06 (1H, m)	
4		43.3	4		43.6
5	1.01 (1H, brs)	56.1	5	1.24 (1H, brs)	55.9
6	1.79 (1H, m)	21.7	6	1.83 (1H, m)	18.8
	1.38 (1H, m)			1.49 (1H, m)	
7	1.76 (1H, m)	42.0	7	2.37 (1H, brd, 12.0)	36.6
	1.45 (1H, m)			1.45 (1H, m)	
8		44.8	8		50.5
9	1.41 (1H, brs)	54.8	9	1.40 (1H, brs)	63.1
10		38.0	10		39.0
11	1.36 (1H, m)	39.3	11	1.91 (1H, m)	33.8
	0.82 (1H, m)			1.41 (1H, m)	
12	1.86 (1H, dt, 13.2, 3.5)	36.0	12	2.10 (1H, dt, 13.1, 3.6)	41.1
	0.99 (1H, brd, 13.2)			1.98 (1H, brd, 13.1)	
13	1.51 (1H, m)	39.2	13	2.06 (1H, m)	36.9
14	3.58 (1H, d, 4.7)	64.9	14	4.05 (1H, d, 4.6)	66.3
15	3.76 (1H, s)	81.9	15		209.6
16		158.6	16		150.2
17	4.91 (1H, brs)	105.7	17	5.87 (1H, s)	113.0
	4.89 (1H, brs)			5.27 (1H, s)	
18	1.12 (3H, s)	29.0	18	1.28 (3H, s)	28.9
19	12.03 (1H, s, COOH)	179.0	19		181.9
20	0.80 (3H, s)	15.6	20	0.95 (3H, s)	15.6

* Assignments were succeeded by HSQC, HMBC, and NOESY experiments.

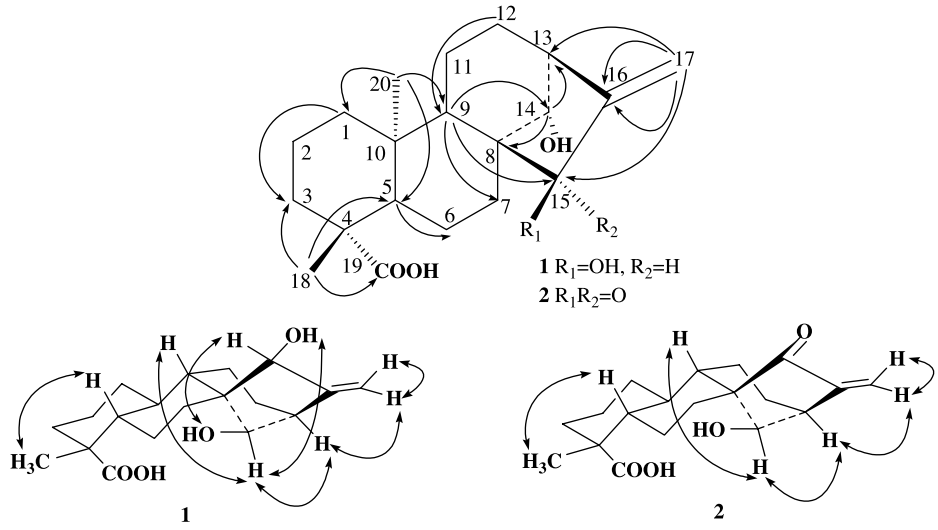

Figure 2. Important HMBC (→) and NOESY (↔) correlations in compounds **1** and **2**.

that the structure of **2** was almost identical to that of **1**, except that the oxymethine (C-15) in **1** was replaced by the carbonyl group in **2**. Compound **1** was converted to **2** by DDQ [21]. Compound **2** was thus determined to be *ent*-14β-hydroxy-15-oxokaur-16-*en*-19-oic acid, which was confirmed by HSQC, HMBC and NOESY experiments (figure 2).

Compound **3** was obtained as colourless needles. The ^{1}H and ^{13}C NMR spectra showed the presence of four tertiary methyls, an *exo*-methylene and three oxygenated methines. The presence of twenty-three signals in ^{13}C NMR spectrum is consistent with the molecular formula $C_{23}H_{34}O_5$, provided by the quasi-molecular ion peak at *m/z* 413.2043 $[M + Na]^+$ in the HRESIMS. An isopropylidene group was recognized from the IR absorption bands at ν_{max}1162 and 1056 cm^{-1}, and the ^{13}C NMR signals at δ 112.4, 25.6, and 26.0. The above evidence indicated that compound **3** should be an acetonide of an *ent*-kaurane-type diterpene.

The comparison of the ^{1}H and ^{13}C NMR data of compound **3** with those of **6** [2] suggested that compound **3** was 11,12-acetonide of **6**. In view of the isolation process, compound **3** may be an artifact of **6**, which was verified by the conversion of **6** in acetone to **3** in the presence of silica gel at room temperature.

3. Experimental

3.1 General experimental procedures

Melting points were measured with an X-6 melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 341 automatic polarimeter. UV and IR spectra were carried out on a Lambda 35 spectrometer and a Perkin–Elmer Spectrum One FT-IR spectrometer (KBr disk), respectively. Mass spectra were obtained on a Finnigan-LCQ^{DECA} mass spectrometer (ESIMS) and a Bruker Daltonics Bio-TOF-Q mass spectrometer (HRESIMS). NMR spectra were recorded on a Bruker Avance 600 spectrometer with TMS as internal standard (^{1}H: 600 MHz, ^{13}C: 150 MHz). Column chromatography (CC) was carried out on silica gel (200–300 mesh, Qingdao Haiyang Chemical Group Co. of China), Silica gel 60 (0.015–0.040 mm, Merck), MCI gel (75–150 μm, Mitsubishi), and RP-C_{18} silica gel (Prepex 40–63 μm, Phenomenex). Precoated plates (silica gel GF_{254}, 0–40 μm) activated at 110°C for 2 h were used for thin-layer chromatography (TLC).

3.2 Plant material

The aerial parts of *N. insignis* were collected in Yanbian County, Panzhihua City of Sichuan Province in May 2004 and identified by Prof. Fading Fu in Chengdu Institute of Biology, the Chinese Academy of Sciences (CAS). A voucher specimen (A-182) is deposited at the Herbarium of Chengdu Institute of Biology, CAS.

3.3 Extraction and isolation

The air-dried and powdered aerial part of *N. insignis* (4.5 kg) was soaked with 95% ethanol (25 L × 3, each 7 d) at room temperature. The solvents were removed under reduced pressure to give 354 g residue, which was suspended in H_2O (1.5 L) and then extracted

successively with petroleum ether (60–90°C, 1.5 L × 4), ethyl acetate (1.5 L × 8) and *n*-butanol (1.5 L × 5) to afford corresponding fractions A (34.3 g), B (56.5 g), and C (114.5 g).

Fraction B (56.5 g) was subjected to CC over silica gel (ϕ 8 × *L* 600 cm, 750 g) eluted with petroleum ether–acetone (50:1, 20:1, 10:1, 5:1, v/v, each 1.5 L) and then eluted with $CHCl_3$—MeOH (10:1, 5:1, 3:1, 1:1, v/v, each 1.5 L) to yield subfractions B_1 (0.7 g), B_2 (0.8 g), B_3 (156 mg), B_4 (0.8 g), B_5 (2.9 g), B_6 (5.0 g), B_7 (25.2 g), and B_8 (14.8 g). Compounds **1** (22 mg), **4** (57 mg) and **9** (20 mg) were precipitated from B_4, B_1 and B_2, respectively. B_3 (156 mg) was separated by silica gel column (ϕ 2 × *L* 25 cm, 20 g) eluted with petroleum ether–acetone (10:1, v/v) to give compounds **13** (15 mg) and **15** (12 mg). Compounds **10** (118 mg), **11** (214 mg) and **25** (23 mg) were obtained from B_2, which was separated by silica gel column (ϕ 2.5 × *L* 30 cm, 40 g) eluted with petroleum ether-EtOAc (20:1, v/v). B_5 was decolored on an MCI gel column (ϕ 3 × *L* 40 cm, 50 g) eluted with MeOH—H_2O (8:1, v/v) to yield subfraction $B_{5(1)}$, compound **12** (13 mg) was obtained by recrystallizing $B_{5(1)}$ from methanol. B_6 was subjected to CC on MCI gel (ϕ 3 × *L* 40 cm, 50 g) eluted with MeOH—H_2O (3:2, v/v) to yield subfractions $B_{6(1)}$ and $B_{6(2)}$. Using $CHCl_3$—CH_3OH (15:1, v/v) as solvent, $B_{6(1)}$ was separated by CC over silica gel (ϕ 3.5 × *L* 50 cm, 80 g) to give compounds **3** (12 mg), **14** (35 mg), **16** (65 mg), and **23** (45 mg). A mixture of compounds **6** and **7** (98 mg) was isolated from $B_{6(2)}$ by silica gel column (ϕ 1.5 × *L* 35 cm, 16 g) eluted with $CHCl_3$—CH_3OH (15:1, v/v).

Fraction A was subjected to CC on MCI gel (ϕ 5 × *L* 60 cm, 50 g) eluted with MeOH—H_2O (3:2, 7:3, 4:1, 9:1, 19:1, 1:0, v/v, each 1.0 L) to yield six subfractions A_1–A_6. A_2 (2.8 g) was separated over silica gel column (ϕ 2 × *L* 45 cm, 80 g) eluted with petroleum ether–acetone (15:1, v/v) to give compounds **17** (12 mg) and **18** (83 mg). Compounds **2** (6 mg), **5** (53 mg), and **8** (5 mg) were obtained from A_1 (1.3 g) separated by CC on silica gel (ϕ 2 × *L* 25 cm, 40 g) eluted with petroleum ether–acetone (10:1, v/v). A_4 (3.2 g) was separated over silica gel column (ϕ 3 × *L* 45 cm, 150 g) eluted with petroleum ether-EtOAc (20:1, v/v) to afford compounds **19** (48 mg) and **20** (8 mg). A mixture of compounds **21** and **22** (188 mg) was obtained by separating A_6 over silica gel column (ϕ 2 × *L* 40 cm, 90 g) eluted with cyclohexane-EtOAc (50:1, v/v).

Fraction C was subjected to macroporous resin column (D_{101}, pore size 13–14 nm, 26–60 mesh) to remove sugar by using CH_3OH—H_2O (0:1, 7:3, 9:1, 1:0) as solvents to give subfractions C_1–C_3. Compound **26** (140 mg) was precipitated from C_3 (20 g) in methanol. Compound **24** (185 mg) was isolated from C_1 (15 g) over a silica gel column (ϕ 5 × *L* 60 cm, 500 g) eluted with $CHCl_3$—CH_3OH (5:1, v/v).

3.4 Conversion of compound 1 to compound 2

To the THF solution (5 mL) of compound **1** (10 mg) was added DDQ (21 mg). The mixture was refluxed at 70°C for 5 h and monitored by TLC. Compound **2** was obtained with 86% yield *via* silica gel CC.

3.5 Conversion of compound 6 to compound 3

To the acetone solution (5 mL) of compound **6** (3 mg) was added a small amount of silica gel (15 mg). The mixture was kept at 30°C for 48 h and monitored by TLC. Compound **3** was obtained with 46% yield *via* silica gel CC.

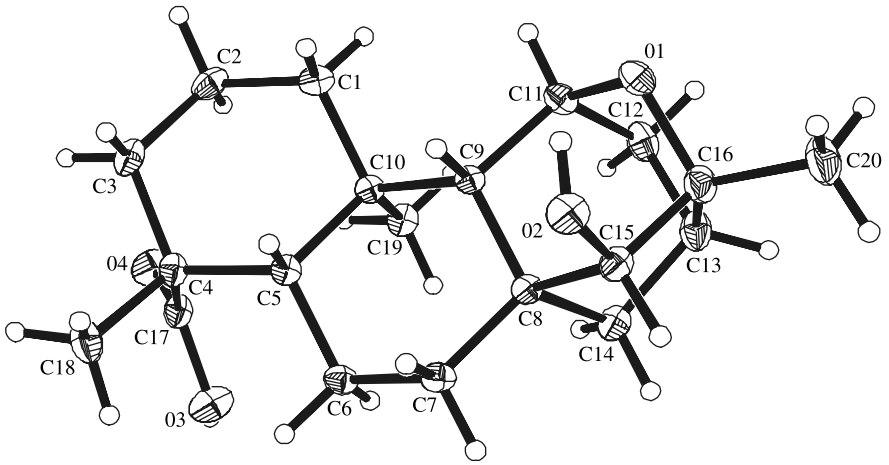

Figure 3. OPTER diagram of compound **4**.

3.6 Identification

Ent-14β,15α-dihydroxykaur-16-*en*-19-oic acid **(1)**: Colourless needles (acetone), m.p. 145–146°C; $[\alpha]_D^{20}$-131 (*c* 0.04, CH_3OH); ESIMS (positive mode) *m/z*: 357 $[M + Na]^+$; HRESIMS (positive ion) *m/z*: 357.2043 $[M + Na]^+$ (calcd for $C_{20}H_{30}NaO_4$, 357.2036); IRν_{max}(KBr)cm^{-1}: 3430 (OH), 2936, 1963 (COOH), 2869, 1468, 1053 (C—O—C), 973 (C═CH_2), 757; ^{1}H and ^{13}C NMR spectral data see table 1.

Ent-14β-hydroxy-15-oxokaur-16-*en*-19-oic acid **(2)**: Colourless flaky crystal (acetone), m.p. 235–236°C; $[\alpha]_D^{20}$-140 (*c* 0.10, CH_3OH); ESIMS (positive mode) *m/z*: 355 $[M + Na]^+$; HRESIMS (positive ion) *m/z*: 355.1882 $[M + Na]^+$ (calcd for $C_{20}H_{28}NaO_4$, 355.1880); IRν_{max}(KBr)cm^{-1}: 3478 (OH), 2927, 2871, 1726 (COOH), 1692 (C═O), 1644, 1276, 1179, 1047 (C—O—C), 935 (C═CH_2), 797; ^{1}H and ^{13}C NMR spectral data see table 1.

Ent-15α-hydroxykaur-16-*en*-19-oic acid 11,12-acetonide **(3)**: Colourless needles (MeOH), m.p. 204–205°C; $[\alpha]_D^{20}$-217 (*c* 0.05, CH_3OH); ESIMS (positive mode) *m/z*: 413 $[M + Na]^+$; HRESIMS (positive ion) *m/z*: 413.2310 $[M + Na]^+$ (calcd for $C_{23}H_{34}NaO_5$, 413.2298); IRν_{max}(KBr)cm^{-1}: 3400 (OH), 2936, 1723 (COOH), 1467, 1380, 1207, 1162, 1056 (C—O—C), 1027, 866 (C═CH_2), 780; ^{1}H NMR ($CDCl_3$): δ 2.18 (1H, d, $J = 13.4$ Hz, H-5), 2.97 (1H, d, $J = 6.1$ Hz, H-9), 4.14 (1H, t, $J = 6.3$ Hz, H-11), 4.11 (1H, t, $J = 6.5$ Hz, H-12), 2.57 (1H, t, $J = 5.1$ Hz, H-13), 3.78 (1H, brd, $J = 10.0$ Hz, H-15), 5.27 and 5.13 (each 1H, brs, H-17), 1.47 (3H, s), 1.31 (3H, s), 1.26 (3H, s), 0.91 (3H,s); ^{13}C NMR ($CDCl_3$): δ 39.8 (C-1), 18.9 (C-2), 37.6 (C-3), 45.1 (C-4), 55.6 (C-5), 21.1 (C-6), 34.1 (C-7), 44.3 (C-8), 49.2 (C-9), 38.1 (C-10), 73.1 (C-11), 78.0 (C-12), 43.7 (C-13), 38.0 (C-14), 82.0 (C-15), 152.4 (C-16), 107.4 (C-17), 28.8 (C-18), 182.3 (C-19), 15.5 (C-20), 112.4 (C-21), 25.9 (C-22), 25.6 (C-23).

Ent-11α,16α-epoxy-15α-hydroxy-16*S*-kaur-19-oic acid **(4)**: Colourless orthorhombic crystal (acetone), m.p. 264–265°C; $[\alpha]_D^{20}$-64 (*c* 0.83, CH_3OH); ESIMS *m/z*: 357 $[M + Na]^+$. The IR and NMR data were identical to those reported [2]. The X-ray crystallographic analysis confirmed the structure (figure 3).

X-ray crystallography of **4**: A colourless crystal was obtained from acetone. Crystal data: $C_{20}H_{30}O_4$; *M*r = 334.44; dimensions 0.56 × 0.36 × 0.16 mm; monoclinic, space group C_2, $a = 9.7738(14)$ Å, $b = 11.5661(13)$ Å, $c = 15.559(2)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 1758.8(4)$ Å^3,

$Z = 4$, $D_{calc} = 1.263\,g/cm^3$, $\lambda = 0.71073\,Å$, $\mu(Mo\ K\alpha) = 0.086\,mm^{-1}$, $F(000) = 728$, $T = 292$ (2) K. Of the 2381 reflections that were collected, 2198 were unique ($R_{int} = 0.0117$); the structure was refined by full-matrix least-squares on F^2. Final refinement: data/restraints/parameters = 2198/0/229; $R_1 = 0.0466$ (all data), $wR_2 = 0.0913$ (all data); Absolute structure parameter = 0(10), and GOF = 1.072. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.176 and $-0.122\,e^-/Å^3$, respectively. CCDC 6116339 contains the crystallographic data for this paper [22].

Compounds **5**–**14** and **17**–**25** were identified by comparing their ^{1}H- and ^{13}C-NMR, MS, and IR spectral data with those reported. Compounds **15**, **16**, and **26** were identified by comparing them with authentic samples on TLC and by co-m.p.

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[22] CCDC 6116639 contains the crystallographic data for this paper. These data can be obtained free of charge via www.cccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK, fax: +44 1223 336033.