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DITERPENES FROM *HOFFMANNIA STRIGILLOSA*

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Key Word Index—*Hoffmannia strigillosa*; Rubiaceae; diterpenes; clerodanes; hoffmanniaketones; monoterpenes.

Abstract—The aerial parts of *Hoffmannia strigillosa* afforded, in addition to known compounds, seven new diterpenes, five clerodanes, two *ent*-phyllocladanes (8,13-bis-*epi*-*ent*-kauranes) and two new monoterpenes. The structures were elucidated by high field NMR spectroscopy.

INTRODUCTION

Hoffmannia strigillosa is used in folk medicine for the treatment of stomach illness and is called tepecajeta. Nothing is known about the chemistry of this species. We have investigated a species collected in Mexico.

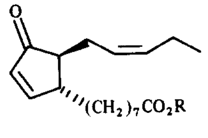
RESULTS AND DISCUSSION

The extract of the aerial parts of *H. strigillosa* Hemsl. gave in addition to some widespread compounds (Experimental) the prostaglandine-like acid **1** and its methylester **2** [1], dimethyl kolavate **3** [2, 3] and further diterpenes **4**–**11** as well as two new monoterpenes **14** and **15**.

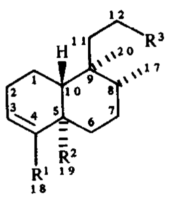
The ^{1}H NMR spectra of compounds **4**–**9** displayed signals typical for clerodane derivatives with the side chain at different oxidation levels. An additional functional group had to be placed at C-19 or C-20. This took the form of a carboxylic group except in the case of the compound **4** where a hydroxymethyl group was present. A few of the acids could be purified only as their methylesters obtained after addition of diazomethane. The relative position of these functional groups at C-19 followed from the downfield shift of neighbouring protons, particularly of H-6. The presence of dimethyl kolavate supported the *trans* AB-ring fusion of all the clerodanes and was proved by NOE experiments (below). The α-substituted butenolide in the side chain of **4** was indicated by the chemical shift of H-14 (Table 1). The splitting of H-10 and the long range coupling (*W*) between H-19′ and H-10 confirmed the *trans* fusion of the AB-rings. The stereochemistry at all chiral centres was deduced from the results of the NOE experiments. Clear effects were observed between H-17 and both H-7, between H-20, H-19, H-11 and H-1α as well as between H-19′, H-18 and H-6α. These results also secured the relative position of the hydroxymethyl group.

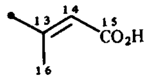
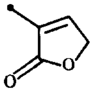
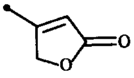
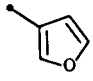
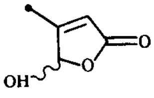
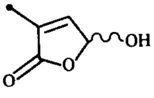
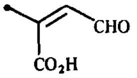
The isomeric nature of the butenolide in the side chain of the acid **5** followed from the upfield chemical shift of H-14 (Table 1). The placement of the carboxylic group at C-5 caused the downfield shift of H-1α, H-7α and H-6α (Table 1) when compared with the chemical shift of the corresponding protons in **4**. The changed situation in the side chain of **6** was concluded from the typical signals of a β-substituted furan and was further supported by the ^{13}C NMR spectrum (Table 2).

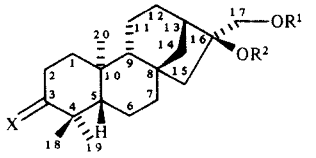
The ^{1}H NMR spectra of the derived methyl esters **7a** and **8a** present in the plant as the acids **7** and **8** differed from that of **5** only in the signals of the butenolide part. The doubling of some signals indicated that epimers were



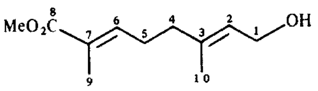
	1	**2**
R	H	OMe



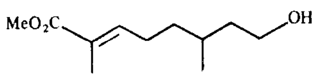
	3	**4**	**5**	**6**	**7**	**8**	**9**
R¹	CO₂H	Me	Me	Me	Me	Me	Me
R²	Me	CH₂OH	CO₂H	CO₂H	CO₂H	CO₂H	CO₂H
R³							



	10	**11**	**12**	**13**
R^1	H	Ac	Ac	Ac
R^2	H	H	Ac	Ac
X	O	O	O	α-OAc,H



14



15

present at C-15 and C-16, respectively. In the case of **7a** the observed NOEs between the methoxy group and H-20 and between H-20, H-1, H-7α, H-11, H-12 and the methoxy group confirmed the complete stereochemistry. In addition to **8a**, a small amount of **9** was isolated. The corresponding compound derived from **7** could not be

Table 2. ^{13}C NMR spectral data of **6**, **10** and **11** ($CDCl_3$)

C	**6***	**10†**	**11**
1	17.5 *t*	38.1 *t*	38.1 *t*
2	33.8 *t*	34.0 *t*	33.9 *t*
3	126.0 *d*	217.7 *s*	214.7 *s*
4	136.2 *s*	47.4 *s*	47.2 *s*
5	48.9 *s*	55.3 *d*	55.2 *d*
6	29.7 *t*	21.6 *t*	21.4 *t*
7	26. 2 *t*	40.6 *t*	40.7 *t*
8	36.5 *d*	43.8 *s*	43.7 *s*
9	39.0 *s*	55.7 *d*	55.7 *d*
10	48.2 *d*	37.1 *s*	37.0 *s*
11	37.8 *t*	19.6 *t*	19.7 *t*
12	28.4 *t*	26.7 *t*	27.0 *t*
13	125.5 *s*	44.0 *d*	44.9 *d*
14	111.0 *d*	48.1 *t*	48.2 *t*
15	138.4 *d*	44.6 *t*	44.7 *t*
16	142.7 *d*	84.3 *s*	82.5 *s*
17	18.6 *q*	65.6 *t*	67.8 *t*
18	15.8 *q*	26.8 *q*	26.9 *q*
19	181.4 *s*	21.6 *q*	21.7 *q*
20	16.4 *q*	14.7 *q*	14.5 *q*
OR	—	—	170.4 *s*
			20.4 *q*

*Some signals may be interchangeable.

†Assigned by hetero COSY.

Table 1. ^{1}H NMR spectral data of **4**–**6** and **7a**–**9a** (400 MHz, $CDCl_3$, δ-values)

H	**4**	**5**	**6**	**7a***	**8a***	**9a**
1α	1.99 *m*	2.37 *m*	2.33 *m*	2.32 *m*	2.30 *m*	2.35 *m*
2α	2.10 *m*	2.24 *m*	2.22 *m*	2.21 *m*	2.21 *m*	2.15–2.30 *m*
2β		2.08 *m*	2.09 *m*	2.08 *m*	2.08 *m*	
3	5.64 *br s*	5.54 *br s*	5.55 *br s*	5.50 *br s*	5.50 *br s*	5.51 *br s*
6α	1.79 *ddd*	2.50 *ddd*	2.49 *ddd*	2.52 *ddd*	2.51 *ddd*	2.51 *ddd*
6β	1.24 *ddd*	1.05 *ddd*	1.07 *ddd*	1.03 *ddd*	1.04 *ddd*	1.04 *ddd*
7α	1.33 *dddd*	1.75 *dddd*	1.75 *dddd*	1.50–1.70 *m*	1.68 *dddd*	1.69 *dddd*
7β	1.43 *dddd*	1.50–1.60 *m*	1.57–1.67 *m*		1.50–1.65 *m*	1.50–1.60 *m*
8	1.55 *m*					
10						
11	1.68 *ddd*	1.69 *m*				
11′	1.55 *m*	1.59 *m*				
12	2.19 *br dd*	2.32 *m*	2.33 *m*	2.41 *m*	2.23 *m*	2.15–2.30 *m*
12′	2.03 *m*	2.13 *m*	2.16 *m*	2.12 *m*	2.04 *m*	
14	7.08 *ddt*	5.85 *ddt*	6.36 *br s*	5.86 *br s*	6.84 *ddd*	6.12 *br d*
15	4.77 *ddd*	—	7.21 *br s*	—	6.09 *br s*	10.04 *d*
16	—	4.74 *d*	7.35 *dd*	6.00 (6.01) *br s*	—	—
17	0.83 *d*	0.81 *d*	0.82 *d*	0.80 (0.79) *d*	0.80 (0.79) *d*	0.78 *d*
18	1.65 *ddd*	1.62 *ddd*	1.62 *br s*	1.56 *ddd*	1.56 *ddd*	1.56 *br s*
	4.04 *d*					
20	3.51 *br d*	0.74 *s*	0.70 *s*	0.63 *s*	0.60 *s*	0.58 *s*
OMe	—	—	—	3.65 *s*	3.64 *s*	3.87 *s*
						3.64 *s*

*The values in parentheses are of the epimer.

J [Hz]: 2,18 = 2′,18 = 3,18 = 1.5; 6α,6β = 6β,7α = 13; 6α,7α = 6α,7β = 3; 6β,7β = 4; 7α,7β = 13.5; 7α,8 = 11; 7β,8 = 4.5; 8,17 = 6.5; compound **4**; 11,11′ = 11,12 = 12,12′ = 14; 11,12′ = 5; 12,14 = 12′,14 = 12,15 = 12′,15 = 14,15 = 1.5; 20,20′ = 11.5; compound **5**: 12,14 = 12′,14 = 14,16 = 1.5; compound **6**: 14,16 = 15,16 = 1.5; compound **8a**: 12,14 = 12′,14 = 14,15 = 1.5; compound **9a**: 14,15 = 7.5.

isolated. We have named compound **4** strigillanol and compounds **5**–**8** strigillanoic acids A–D, respectively.

From the most polar fraction, two further diterpenes (**10** and **11**) were obtained. The ^{13}C NMR spectrum of **10** (Table 2) indicated the presence of a keto group (δ214.4 *s*) and two additional oxygen-bearing carbons (δ84.3 *s* and 65.6 *t*). Acetylation gave a diacetate (Experimental), thus demonstrating that both oxygen atoms were present in hydroxy groups. The general appearance of the ^{1}H NMR spectrum resembled that of the known *ent*-3-oxo-16,17-dihydroxykaurane [4–6]. However, the chemical shifts of most of the signals showed significant differences. Thus **10** was either the 1-oxo-isomer or a stereoisomer. Reduction with $NaBH_4$ gave only one product which was further transformed to the triacetate **13** with equatorial acetoxy group as followed from the couplings of the corresponding signal. A NOE experiment secured the relative position of this group at C-3 (enhancement of H-3 signal by irradiation of H-18). Consequently, a stereoisomer has to be assumed. Extensive decoupling experiments, 2D homo- and hetero correlated spectra as well as additional NOE experiments with the triacetate led finally to the proposed structure. In Table 3 several signals were designated as multiplets; their unequivocal assignment was based on the above experiments, in particular on the results of NOE measurements. Further dipolar interactions were observed between H-18, H-5, H-6β and 3-OAc, between H-19, H-20, H-6α and 3-OAc, between H-20, H-2α, H-15α, H-11α and H-19 as well as between H-17 and H-11. The stereochemistry at C-14 was further supported by differences of chemical shifts of H-15β in natural compounds **10** and **11** and their acetylation products (**12** and **13**) (Table 3). The structure of **11** was easily deduced from the ^{1}H NMR spectrum (Table 3). An additional acetate signal and the downfield shift of H-17 showed that the 17-O-acetate of **10** was present. The ^{13}C NMR spectrum (Table 2) supported the structure. Furthermore, acetylation of **10** and **11** gave the same diacetate (**12**) (Experimental). The absolute configuration followed from the observed positive Cotton-effect of compound **10** [5].

The structure of compound **14**, molecular formula $C_{11}H_{16}O_3$, followed from the ^{1}H NMR spectrum (Table 4) which indicated the presence of a derivative of geraniol with a carbomethoxy group (3.73 *s*). The relative position was deduced from the chemical shift of H-6 and further established by NOE between H-9 and H-5. In the case of compound **15**, the olefinic signal for H-2 was

Table 3. ^{1}H NMR spectral data of compounds **10**–**13** (400 MHz, $CDCl_3$, δ-values)

H	**10**	**11**	**12**	**13**	**13** (C_6D_6)
1α	1.87 *ddd*	1.87 *ddd*	1.87 *ddd*	*	1.35 *m*
1β	1.40 *m*	1.38 *ddd*	1.37 *m*	1.00 *m*	0.72 *m*
2α	2.51 *ddd*	2.52 *ddd*	2.53 *ddd*	*	1.56 *m*
2β	2.38 *ddd*	2.37 *ddd*	2.36 *ddd*	*	1.74 *m*
3	—	—	—	4.45 *dd*	4.69 *dd*
5	1.38 *m*	1.38 *m*	†	0.86 *br d*	0.64 *dd*
6α	1.38 *m*	1.38 *m*	†	1.21 *m*	1.08 *m*
6β	1.49 *m*	1.49 *m*	†	*	1.35 *m*
7α	1.71 *m*	1.72 *m*	†	*	1.52 *m*
7β	1.53 *m*	1.54 *m*	†	*	1.35 *m*
9	1.15 *dd*	1.14 *dd*	1.16 *dd*	1.06 *dd*	0.77 *dd*
11α	1.30 *dddd*	1.29 *dddd*	†	1.26 *m*	1.25 *m*
11β	1.57 *m*	1.58 *m*	†	*	1.06 *m*
12α	1.69 *m*	1.62 *m*	†	*	1.70 *m*
12β	1.46 *m*	1.45 *m*	†	*	1.35 *m*
13	1.93 *br ddd*	1.94 *br ddd*	2.36 *m*	2.32 *br ddd*	2.58 *br ddd*
14α	2.09 *ddd*	2.14 *ddd*	1.91 *ddd*	1.88 *ddd*	2.01 *ddd*
14β	1.11 *dd*	1.09 *dd*	1.13 *dd*	1.10 *br d*	1.03 *br d*
15α	2.07 *dd*	2.09 *dd*	2.20 *dd*	2.19 *dd*	2.25 *dd*
15β	1.26 *br d*	1.30 *br d*	1.80 *br d*	1.74 *br d*	1.95 *br d*
17	3.78 *br d*	4.25 *d*	4.92 *d*	4.91 *d*	5.35 *d*
17′	3.64 *br d*	4.18 *d*	4.42 *d*	4.38 *d*	4.63 *d*
18	1.08 *s*	1.08 *s*	1.08 *s*	0.84 *s*	0.91 *s*
19	1.02 *s*	1.02 *s*	1.02 *s*	0.83 *s*	0.89 *s*
20	0.99 *br s*	0.99 *s*	1.00 *s*	0.88 *s*	0.76 *s*
OAc	—	2.11 *s*	2.07 *s*	2.06 *s*	1.82 *s*
			2.00 *s*	2.04 *s*	1.80 *s*
				1.98 *s*	1.76 *s*

*1.4–1.7 *m*.

†1.25–1.75 *m*.

J [Hz]: 9,11β = 4.5; 9,11α = 11α,11β = 11α,12β = 12; 11α,12α = 6; 12α,13 = 12β,13 = 13,14α ~ 4; 12α,14α = 2.5; 14α,14β = 11; 14β,15α = 1.5; 15α,15β = 15; compounds **10**–**12**: 1α,1β = 13.5; 1α,2α = 1β,2β = 7; 1α,2β = 4; 1β,2α = 11; 2α,2β = 16; 17,17′ = 11.5; compound **13**: 2α,3 = 12; 2β,3 = 4.5; 5,6α = 12; 5,6β = 2; 17,17′ = 12.5.

Table 4. ^{1}H NMR spectral data of compounds **14** and **15** (400 MHz, $CDCl_3$, δ-values)

H	**14**	**15**
1	4.17 *br d*	3.79 *m*
2	5.44 *qt*	1.70–1.25 *m*
3	—	
4	2.15 *br t*	
5	2.30 *td*	2.19 *m*
6	6.73 *qt*	6.75 *qt*
9	1.84 *d*	1.84 *br s*
10	1.69 *s*	0.94 *d*
CO_2Me	3.73 *s*	3.75 *s*

J [Hz]: Compound **14**: 1,2 = 4,5 = 5,6 = 7; 2,10 = 6,9 = 1; compound **15**: 3,10 = 6.5; 5,6 = 7.5; 6,9 = 1.

missing and H-10 methyl appeared as a doublet at δ0.94. Thus **15** was the 2,3-dihydro derivative of **14**. The stereochemistry at C-3 was not established.

EXPERIMENTAL

The air-dried aerial parts (400 g, voucher No. 8129, collected in Cuesta Carvajal N.L. Mexico) were extracted with petrol–Et_2O–MeOH (1:1:1) and the extract (22 g) obtained separated by CC and further by MPC, TLC and/or HPLC (always RP 8, MeOH–H_2O in different ratios: HP1 8:2; HP2 7:3). Known compounds were identified by comparing the ^{1}H NMR spectra with those of authentic material. Conditions of final purification of new compounds are given in parentheses. The known compounds isolated were: 150 mg **1**, 12 mg **2**, 8 mg **3**, 17 mg ursolic acid, 5 mg betulinic acid, 15 mg oleanolic acid, 19 mg phytol, 15 mg spathulenol, 12 mg 5-hydroxy-7,4′-dimethoxy-flavone as well as 50 mg of a mixture of benzaldehyde, benzoic acid, vanillic acid, eudesmicacid, *cis*-and *trans*-coumaric acid and *cis*- and *trans*-ferulic acid. The following new compounds were obtained: 20 mg **4** (MPC, petrol–Et_2O, 9:1), 3 mg **5** (HP2, R_t 11.4 min), 8 mg **6** (TLC, CH_2Cl_2–Et_2O, 19:1, R_f 0.8), 8 mg **7** (TLC as **6**, R_f 0.9), 8 mg **8** (HP2, R_t 16.5 min), 270 mg **10** (HP2, R_t 11.9 min) and 50 mg **11** (HP1, R_t 5.0 min), 2 mg **14** (HP2, R_t 6.3 min) and 2 mg **15** (HP2, R_t 7.9 min). Some of the compounds were purified as their methylesters after addition of CH_2N_2.

Strigillanol (**4**). Oil: IR $\nu_{\max}^{\mathrm{CHCl}_3}\,\mathrm{cm}^{-1}$: 3500 (OH), 1755 ($\gamma$-lactone); MS *m/z* (rel. int.): 318.219 $[M]^+$ (1) (calc. for $C_{20}H_{30}O_3$: 318.219), 287 $[M-CH_2OH]^+$ (90), 205 (34), 139 (36), 121 (58), 57 (100).

Strigillanoic acid A (**5**). Oil: IR $\nu_{\max}^{\mathrm{CHCl}_3}\,\mathrm{cm}^{-1}$: 3500–2700, 1755 ($CO_2H$), 1790 ($\gamma$-lactone); MS *m/z* (rel. int.): 332.199 $[M]^+$ (3) (calc. for $C_{20}H_{28}O_4$: 332.199), 287 $[M-CO_2H]^+$ (8), 221 $[M-\mathrm{sidechain}]^+$ (10), 177 $[221-CO_2]^+$ (24), 121 (44), 111 $[C_6H_7O_2]^+$ (74), 95 (75), 55 (100).

Strigillanoic acid B (**6**). Oil; MS *m/z* (rel. int.): 316.204 $[M]^+$ (16) (calc. for $C_{20}H_{28}O_2$: 316.204), 271 $[M-CO_2H]^+$ (29), 221 $[M-\mathrm{sidechain}]^+$ (26), 175 $[221-HCO_2H]^+$ (51), 121 (65), 107 (78), 95 $[C_6H_7O]^+$ (64), 81 $[C_5H_5O]^+$ (100).

Strigillanoic acid C (**7**). Isolated as its methylester **7a**; IR $\nu_{\max}^{\mathrm{CHCl}_3}\,\mathrm{cm}^{-1}$: 3350 (OH), 1770 ($\gamma$-lactone), 1720 ($CO_2R$); MS *m/z* (rel. int.): 362.209 $[M]^+$ (2) (calc. for $C_{21}H_{30}O_5$: 362.209), 303 $[M-CO_2Me]^+$ (10), 285 $[303-H_2O]^+$ (16), 121 (37), 107 (48), 57 (100).

Strigillanoic acid D (**8**). Isolated as its methylester **8a**: IR $\nu_{\max}^{\mathrm{CHCl}_3}\,\mathrm{cm}^{-1}$: 3380 (OH), 1765 ($\gamma$-lactone), 1715 ($CO_2R$); MS *m/z* (rel. int): 362.209 $[M]^+$ (0.5) (calc. for $C_{21}H_{30}O_5$: 362.209), 303 $[M-CO_2Me]^+$ (4), 285 $[303-H_2O]^+$ (54), 149 (44), 135 (25), 69 (100).

Additionally obtained was 1 mg **9**. Oil; MS *m/z* (rel. int.): 376.226 $[M]^+$ (2) (calc. for $C_{22}H_{32}O_5$: 376.226), 344 $[M-MeOH]^+$ (3.5), 317 $[M-CO_2Me]^+$ (18), 285 $[317-MeOH]^+$ (36), 175 (56), 149 (67), 119 (81), 107 (82), 105 (98), 57 (100).

Hoffmanniaketone (**10**). Crystals, mp 161°; IR $\nu_{\max}^{\mathrm{CHCl}_3}\,\mathrm{cm}^{-1}$: 3540, 3370 (OH), 1695 (C=O); MS *m/z* (rel. int.): 320.235 $[M]^+$ (2.5) (calc. for $C_{20}H_{32}O_3$: 320.235), 289 $[M-CH_2OH]^+$ (100), 271 $[289-H_2O]^+$ (12), 61 (100); CD: $\Delta\varepsilon_{288}+0.2$. 20 mg **10** were heated on a water bath with Ac_2O for 2 hr. After work-up and TLC 5 mg **11** (identical with natural compound, see below) and 10 mg **12** (^{1}H NMR, Table 3) were obtained. To 20 mg **10** in 2 ml MeOH 5 mg $NaBH_4$ were added. After completion of the reaction and usual work-up, the product was acetylated with Ac_2O affording 20 mg **13**; oil: IR $\nu_{\max}^{\mathrm{CHCl}_3}\,\mathrm{cm}^{-1}$: 1730, 1250 (OAc); MS *m/z* (rel. int.): 388.261 $[M-HOAc]^+$ (35) (calc. for $C_{24}H_{36}O_4$: 388.261), 346 $[388-\mathrm{ketene}]^+$ (40), 328 $[388-HOAc]^+$ (64), 268 $[328-HOAc]^+$ (23), 253 $[268-Me]^+$ (25), 135 (56), 121 (64), 112 (73), 95 (87), 69 (100).

Hoffmanniaketone-17-O-*acetate* (**11**). Crystals, mp 142°; IR $\nu_{\max}^{\mathrm{CHCl}_3}\,\mathrm{cm}^{-1}$: 3400 (OH), 1735 ($CO_2R$), 1705 (C=O); MS *m/z* (rel. int.): 362.246 $[M]^+$ (2) (calc. for $C_{22}H_{34}O_4$: 362.246), 289 $[M-CH_2OAc]^+$ (22), 271 $[289-H_2O]^+$ (3), 61 (100). Acetylation of 10 mg of **11** as described above also gave **12**.

Methyl geraniol-8-oate (**14**). Oil; IR $\nu_{\max}^{\mathrm{CHCl}_3}\,\mathrm{cm}^{-1}$: 3500 (OH), 1715 (C=C–COOR); MS *m/z* (rel. int.): 198.126 $[M]^+$ (1) (calc. for $C_{11}H_{18}O_3$: 198.126), 180 $[M-H_2O]^+$ (16), 148 $[180-MeOH]^+$ (14), 121 $[180-CO_2Me]^+$ (90), 114 (100).

Methyl-2,3-dihydrogeraniol-8-oate (**15**). Oil; IR $\nu_{\max}^{\mathrm{CHCl}_3}\,\mathrm{cm}^{-1}$: 3600 (OH), 1715 (C=COOR); MS *m/z* (rel. int.): 200.141 $[M]^+$ (1.5) (calc. for $C_{11}H_{20}O_3$: 200.141), 168 $[M-MeOH]^+$ (42), 127 (48), 101 (55), 95 (100).

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