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A DAUCANOLIDE AND FURTHER FARNESENE DERIVATIVES FROM *AGERATUM FASTIGIATUM**

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Key Word Index—*Ageratum fastigiatum*; Compositae; sesquiterpenes; farnesene derivatives; sesquiterpene lactone; daucane derivative; *ent*-labdane derivative.

Abstract—A reinvestigation of *Ageratum fastigiatum* afforded, in addition to known compounds, several new farnesene derivatives including some tetrahydropyrane derivatives. Furthermore a sesquiterpene lactone derived from daucane and a minor derivative of the *ent*-labdanes isolated previously were isolated. The structures were elucidated by spectroscopic methods.

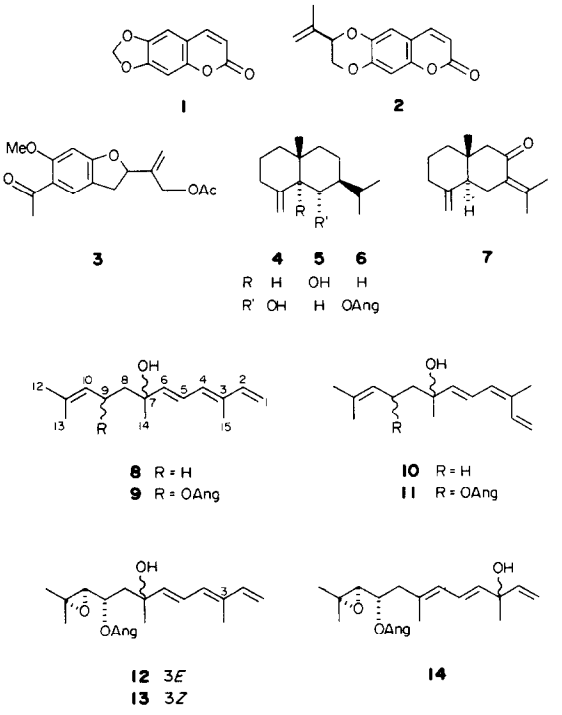
INTRODUCTION

So far out of the large genus *Ageratum* (tribe Eupatorieae subtribe (Ageratinae) only a few species have been studied chemically [1–5]. While three species [1–4] afforded widespread compounds and several chromenes, such as ageratochromene, which have anti-juvenile hormone-like effects [5], *A. fastigiatum* gave some more characteristic constituents, especially nerolidol and eudesmane derivatives as well as some diterpenes [6]. We now have investigated more material of this species. The results will be discussed in this paper.

RESULTS AND DISCUSSION

The roots of *A. fastigiatum* (Gardn.) K. et R. afforded germacrene D, 9-acetoxygeranyl acetate, the coumarins **1** and **2** [7], the euparin derivative **3** [8], the eudesmane derivatives **4** and **7**, the seco-kaurane **21** [9], the dehydronerolidol derivatives **8** [10], **10** [10] and **14** [11] as well as **9, 11, 12, 13** and **15–18**. The *E/Z* isomers of **15** and **17**, however, could not be separated. Furthermore, the lactone **19** was obtained. The structures of **9** and **11** were deduced from the ^{1}H NMR spectra (Table 1) which were close to those of **8** and **10** as well as to those of the known 7-*O*-methyl derivatives [12]. As usual in the *Z*-isomer (**11**) the H-2 signal was shifted much more downfield.

The ^{1}H NMR spectra of **12** and **13** (Table 1) indicated that again a mixture of the Δ^3 *E* and *Z* isomers were present, though a separation was not possible. While most signals were close to those of **9** and **11**, the missing 10,11-double bond caused a large upfield shift of the methyl signals and a replacement of the olefinic signal (H-10) by that of an epoxide (δ 2.89 *d*). The mass spectra of **15–18** showed that the molecular formula ($C_{20}H_{30}O_4$) was the same as that of **12** indicating that isomeric angelates might be present. The ^{1}H NMR spectra (Table 1) indicated that we were dealing with two pairs of Δ^3 *E/Z* isomers. The signals of **15/16** and **17/18** showed only small differences, but the chemical shifts of H-15, H-9 and H-8 differed typically. Spin decoupling allowed the assignment of nearly all signals. The similarity of the chemical shifts of H-1–H-6 and H-15 indicated that this part was the same as in **9** and



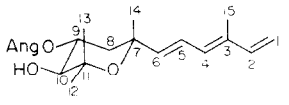
*Part 470 in the series "Naturally Occurring Terpene Derivatives. For Part 469 see Bohlmann, F., Zdero, C., King, R. M. and Robinson, H. (1983) *Phytochemistry* **22**, 1035.

Table 1. ^{1}H NMR spectral data of **9**, **11**, **12** and **15–18** (400 MHz, $CDCl_3$, TMS as int. standard)

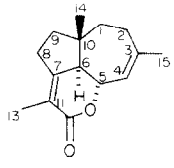
H	9	11	12*	15	16	17	18
1*c*	5.02 *br d*	5.12 *br d*	5.05 *br d*	5.05 *br d*	5.20 *br d*	5.02 *br d*	5.14 *br d*
1*t*	5.20 *br d*	5.23 *br d*	5.23 *br d*	5.24 *br d*	5.28 *br d*	5.20 *br d*	5.24 *br d*
2	6.38 *dd*	6.95 *dd*	6.38 *dd*	6.41 *dd*	7.14 *dd*	6.38 *dd*	6.93 *dd*
4	6.04 *br d*	5.94 *br d*	6.00 *br d*	6.05 *br d*	5.96 *br d*	6.00 *br d*	5.92 *br d*
5	6.60 *dd*	6.72 *dd*	6.63 *dd*	6.69 *dd*	6.83 *dd*	6.54 *dd*	6.67 *dd*
6	5.75 *br d*	5.67 *br d*	5.74 *br d*	5.80 *br d*	5.72 *br d*	5.74 *br d*	5.66 *br d*
8	2.07 *dd*	2.05 *m*	2.0 *m*	2.65 *dd*	2.64 *dd*	2.20 *dd*	2.19 *dd*
8′	1.80 *dd*	1.80 *m*	1.8 *m*	1.64 *dd*	1.59 *dd*	1.78 *dd*	1.77 *dd*
9	5.65 *ddd*	5.65 *ddd*	5.05 *m*	5.06 *m*	5.06 *m*	5.19 *m*	5.19 *m*
10	5.15 *br d*	5.15 *br d*	2.89 *d*	3.50 *br d*	3.50 *br d*	3.56 *br d*	3.55 *br d*
12	1.68 *d*	1.70 *d*	1.35 *s*	1.30 *s*	1.30 *s*	1.37 *s*	1.37 *s*
13	1.70 *d*	1.72 *d*	1.31 *s*	1.24 *s*	1.24 *s*	1.35 *s*	1.34 *s*
14	1.29 *s*	1.30 *s*	1.35 *s*	1.20 *s*	1.20 *s*	1.44 *s*	1.43 *s*
15	1.84 *s*	1.87 *s*	1.88 *s*	1.95 *s*	1.90 *s*	1.85 *s*	1.87 *s*
OAng	6.01 *qq*	6.01 *qq*	6.08 *qq*	6.10 *qq*	6.10 *qq*	6.12 *qq*	6.12 *qq*
	1.93 *dq*	1.95 *dq*	2.00 *dq*	2.01 *dq*	2.01 *dq*	2.00 *dq*	2.00 *dq*
	1.84 *dq*	1.86 *dq*	1.89 *dq*	1.92 *dq*	1.92 *dq*	1.89 *dq*	1.89 *dq*

*13ZH, H-2, 6.97, *dd*, H-5, 6.75, *dd*.

J(Hz): 1*c*, 2 = 10.5; 1*t*, 2 = 17; 4, 5 = 11; 5, 6 = 15.5; 8, 8′ = 15; 8, 9 = 8; 8, 9′ = 5; 9, 10 = 9.5; 10, 12 = 1; 10, 13 = 1.5. Compound **12**: 9, 10 = 9; compounds **15–18**: 8, 8′ = 13; 8, 9 = 4; 8′, 9 = 14; OAng: 3′, 4′ = 7; 3′, 5′ = 4′, 5′ = 1.5



15 3*E*
16 3*Z*
17 3*E*, 7-*epi*
18 3*Z*, 7-*epi*



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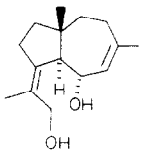

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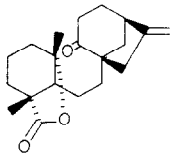

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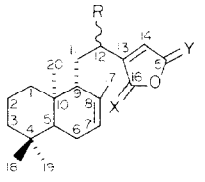
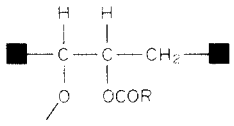


	22	**23**	**24**
R	H	OH	H
X	H,OH	H,OH	=O
Y	=O	=O	H_2

11, respectively. Identical substitution at C-9 and C-10 in all compounds followed from the corresponding signals and from the results of spin decoupling indicating the sequence **A**.



A

The couplings of H-8–H-10 showed the presence of a six-membered ring, most likely a tetrahydropyrane, with equatorial oxygen functions at C-9 and C-10. In agreement with this proposal, in the mass spectrum after elimination of angelic acid the loss of acetone (*m/z* 176) was observed. The differences in the ^{1}H NMR spectra of **15**/**16** and **17**/**18** indicated that in the former pair the 7-methyl group was most likely axial whereas in the latter it was equatorial. Compound **15**, without oxygen functions at C-9 and C-10, we have named agerafastin. The absolute configuration of **15–18** was not determined. Obviously the *E*/*Z* isomeric epoxides **12** and **14** were the common precursors of **15–18**. Protonation of the 7- or 3-hydroxy group, would lead to an ion which could be transformed to **15–18**. This pathway would explain the formation of isomers at C-7. As **12–14** were minor products, it was unlikely that **15–18** were artefacts, especially as **14** was not transformed to **15–18** by treatment with Si gel.

The structure of the lactone **19**, also present in the aerial parts, followed from the spectroscopic data and those of the diol **20** obtained by alanate reduction (Table 2). The molecular formula of the natural compound was $C_{15}H_{20}O_2$ while that of the expected reduction product was $C_{15}H_{24}O_2$ though, in the mass spectrum, only a peak at *m/z* 218 ($C_{15}H_{22}O$) was observed. However, it seemed most likely that the product was a diol which had four additional hydrogens. Accordingly, the presence of a lactone was assumed, which was supported by an IR band at 1720 cm^{-1}. This frequency, however, excluded the

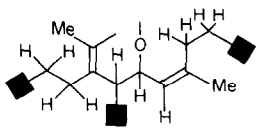
Table 2. ^{1}H NMR spectral data of **19** and **20** (400 MHz, $CDCl_3$, TMS as int. standard)

H	**19**	**20**		**19** (^{13}C, $CDCl_3$)
1	1.77 *ddd*	1.68 *ddd*	C-1	38.6 *t**
1′	1.53 *ddd*	1.56 *ddd*	C-2	30.2 *t*†
2	2.31 *m*	2.19 *m*	C-3	136.9 *s*
2′	2.04 *ddd*		C-4	126.2 *d*
4	5.62 *br s*	5.47 *br s*	C-5	77.6 *d*
5	4.65 *br d*	4.06 *br d*	C-6	53.5 *d*
6	2.35 *br d*	2.57 *br d*	C-7	160.6 *s*
8	2.48 *m*	2.34 *m*	C-8	27.2 *t*†
9	1.70 *ddd*	1.44 *ddd*	C-9	40.1 *t**
9′	1.58 *ddd*	1.29 *ddd*	C-10	43.1 *s*
12	—	4.19 *d*	C-11	119.6 *s*
12′	—	3.90 *br d*	C-12	166.8 *s*
13	1.82 *ddd*	1.77 *br s*	C-13	12.6 *q*
14	0.83 *br s*	0.92 *br s*	C-14	16.7 *q*
15	1.77 *ddd*	1.75 *br s*	C-15	28.6 *q*

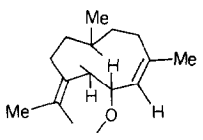
*, † Values with the same sign may be interchangeable.

J(Hz): Compound **19**: 1, 1′ = 13; 1, 2 = 4; 1, 2′ = 12; 1′, 2 = 1′,2′ = 4; 1′, 14 ~ 1; 2, 2′ = 13.5; 4, 5 = 5, 15 = 2; 4, 15 ~ 1.5; 5, 6 = 12; 6, 13 = 2; 8, 9 = 8; 8, 9′ = 11; 8′, 9 = 2; 8′, 9′ = 10; 9, 9′ = 13; 9′, 14 ~ 1; compound **20**: 1, 1′ = 15; 1, 2 = 5; 1, 2′ = 6; 1′, 2 = 4; 1′, 2′ = 10; 1′, 14 ~ 1; 4, 5 = 4.15 = 5, 15 = 6, 13 ~ 1.5; 5, 6 = 11; 8, 9 = 6.5; 8, 9′ = 12; 8′, 9 = 1.5; 8′, 9′ = 8; 9, 9′ = 12.5; 9′, 14 ~ 1;

presence of a γ-lactone. The ^{1}H NMR spectrum showed two olefinic methyl signals indicating two double bonds. The molecular formula, therefore, led to the proposal that a tricyclic lactone was present in agreement with the ^{13}C NMR spectrum which displayed four signals of olefinic carbons. One of these signals (δ 160.6) was obviously that of the β-carbon of a conjugated carbonyl group. The ^{1}H NMR spectrum of **19** displayed only two low field signals. Careful spin decoupling allowed the assignment of all signals. Irradiation at δ 4.65 sharpened the singlet at 5.62 and collapsed the broadened doublet at 2.35 to a broad singlet which itself showed an allylic coupling with an olefinic methyl (1.82 *ddd*). This methyl was also coupled with the signal of an allylic multiplet at δ 2.48 which itself was coupled with a pair of three-fold doublets at 1.70 and 1.58. Further decouplings led to the sequence **B** which could be cyclisized to **C** as the broadened singlet at δ 0.83 showed *W*-couplings with the three-fold doublets at 1.53 and 1.58.



B



C

The addition of the missing carbonyl group and the connection of the open linkages led to structure **19** as the other possibilities would not agree with the spectroscopic data. The stereochemistry was deduced from the observed coupling of $J_{5,6}$. The ^{1}H NMR spectrum of **20** also agreed well with the corresponding structure. Thus, the new lactone was derived from daucane. We have named **19** fastigiolide.

The aerial parts afforded germacrene D, α-humulene, 4-hydroxygermacra-1(10),5-diene, spathulenol, taraxasterol and its acetate, lupeol and its Δ^{12} isomer, glutin-5(6)-en-3β-ol, **1**, **4** [13], **5** [14], **6** [6], **7** [15], **14**, **17–19**, **21–23** [16] and 15-hydroxy-*ent*-labda-7,13-dien-16-oic lactone (**24**). The structure of the latter was deduced from the molecular formula and the ^{1}H NMR spectrum (Experimental). While most signals were nearly identical with those of other labdane derivatives with no substituents at C-1–C-12 and C-17–C-20, the low field narrowly split triplet of triplets at δ 7.11, which was coupled with a two proton double triplet at 4.77 and an allylic multiplet at 2.51 and 2.25, showed that a 15,16-lactone with a 13,14-double bond was present. The absolute configuration was not established.

The chemistry of this *Ageratum* species shows some resemblance to part of the genus *Acritopappus* which is placed in the same subtribe. The chemotaxonomic situation needs clarification by the investigation of more species from the other genera.

EXPERIMENTAL

The air-dried plant material, collected in the province of Goias, Brazil, in Jan. 1981 (voucher RMK 8960, deposited in the U.S. National Herbarium, Washington) was extracted with Et_2O–petrol (1:2) and the resulting extracts were separated by CC (Si gel) and further by TLC (Si gel). Known compounds were identified by comparing the 400 MHz ^{1}H NMR spectra with those of authentic material. The roots (215 g) afforded 150 mg germacrene D, 5 mg 9-acetoxygeranyl acetate, 8 mg **1**, 4 mg **2**, 8 mg **3**, 30 mg **4**, 140 mg **7**, 2 mg **8**, 6 mg **10**, 1 mg **9** and 1 mg **11** (Et_2O–petrol, 1:9, × 13), 2 mg **12** and **13** (Et_2O–petrol, 1:4, × 4), 86 mg **14**, 24 mg **15** and **16** (Et_2O–petrol, 1:5, × 4), 37 mg **17** and

18 (Et_2O–petrol, 1:5, × 4), 8 mg **19** (Et_2O–petrol, 1:10, × 13) and 8 mg **21**. The aerial parts (930 g) gave 800 mg germacrene D, 100 mg α-humulene, 30 mg 4-hydroxygermacra-1 (10), 5-diene, 5 mg spathulenol, 60 mg taraxasterol and 230 mg of its acetate, 15 mg lupeol and its Δ^{12}-isomer, 200 mg glutin-5(6)-en-3β-ol, 180 mg **1**, 70 mg **4**, 4 mg **5**, 400 mg **6**, 50 mg **7**, 235 mg **14**, 20 mg **17** and **18**, 115 mg **19**, 150 mg **21**, 610 mg **22**, 3.6 g **23** and 15 mg **24** (C_6H_6–Et_2O, 99:1).

9-*Angeloyloxy*-7-*hydroxy*-5, 6-*dehydro*-6, 7-*dihydro*-3E-α-*farnesene* (**9**). Colourless gum, UV $\lambda_{max}^{Et_2O}$ nm: 280, 270, 259; MS *m/z* (rel int): 218 $[M-AngOH]^+$ (1), 200 $[218-H_2O]^+$ (2), 185 $[200-Me]^+$ (3), 83 $[C_4H_7CO]^+$ (64), 55 $[83-CO]^+$ (100).

9-*Angeloyloxy*-7-*hydroxy*-5, 6-*dehydro*-6, 7-*dihydro*-3Z-α-*farnesene* (**11**). UV $\lambda_{max}^{Et_2O}$ nm: 280, 270, 259; MS *m/z* 218 $[318-AngOH]^+$ (1), 83 $[C_4H_7CO]^+$ (60), 55 $[83-CO]^+$ (100).

9-*Angeloyloxy*-7-*hydroxy*-10,11-*epoxy*-5, 6-*dehydro*-6,7,10,11-*tetrahydro*-3E- *and* 3Z-α-*farnesene* (**12/13**). Not separated. Colourless gum, UV $\lambda_{max}^{Et_2O}$ nm: 280, 270, 260; MS *m/z* (rel int): 334.214 $[M]^+$ (1) ($C_{20}H_{30}O_4$), 234 $[M-AngOH]^+$ (1), 219 $[234-Me]^+$ (2), 83 $[C_4H_7CO]^+$ (91), 55 $[83-CO]^+$ (100).

9α-*Angeloyloxy*-10β-*hydroxy*-3E- *and* 3Z-*agerafastin* (**15** *and* **16**). Not separated. Colourless gum, UV $\lambda_{max}^{Et_2O}$ nm: 281, 270, 260; MS *m/z* (rel int): 334.214 $[M]^+$ (3) ($C_{20}H_{30}O_4$), 234 $[M-AngOH]^+$ (21), 219 $[234-Me]^+$ (9), 138 $[234-C_3H_6O]^+$ (5), 83 $[C_4H_7CO]^+$ (77), 55 $[83-CO]^+$ (100).

9α-*Angeloyloxy*-10β-*hydroxy*-7-*epi*-3E- *and* 3Z-*agerafastin* (**17** *and* **18**). Not separated. Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1715, 1650 (C=CCOR); UV $\lambda_{max}^{Et_2O}$ nm: 280, 270, 260; MS *m/z* (rel int): 334.214 $[M]^+$ (1) ($C_{20}H_{30}O_4$), 234 $[M-AngOH]^+$ (3), 219 $[234-Me]^+$ (4), 176 $[234-C_3H_6O]^+$ (18), 83 $[C_4H_7CO]^+$ (100), 55 $[83-CO]^+$ (98).

Fastigiolide (19). Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1720 (γ-lactone); MS *m/z* (rel int); 232.146 $[M]^+$ (22) ($C_{15}H_{20}O_2$), 217 $[M-Me]^+$ (100), 203 $[M-CHO]^+$ (11), 189 $[217-CO]^+$ (16);

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\ nm}{-31 \quad -32 \quad -39 \quad -88} (CHCl_3;\ c\ 0.1).$$

To 10 mg **19** in 2 ml Et_2O, 10 mg $LiAlH_4$ was added. Usual work-up and TLC (Et_2O) afforded 6 mg **20**, colourless gum, MS *m/z* (rel int): 218 $[M-H_2O]^+$ (26), 203 $[218-Me]^+$ (28), 189 $[218-CHO]^+$ (9), 121 $[C_9H_{13}]^+$ (100).

15-*Hydroxy*-ent-*labda*-7,13-*dien*-16-*oic-acid lactone* (**24**). Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1760 (γ-lactone); MS *m/z* (rel int): 302.225 $[M]^+$ (9) ($C_{20}H_{30}O_2$), 287 $[M-Me]^+$ (30), 178 $[C_{11}H_{14}O_2, RDA]^+$ (66), 109 $[178-isoprene]^+$ (100); ^1H NMR (400 MHz, $CDCl_3$): δ 1.98 (*br d*, H-6, *J* = 16 Hz), 1.85 (*br dd*, H-6', *J* = 16, 11 Hz), 5.42 (*br s*, H-7), 2.51 (*m*) and 2.25 (*m*, H-12), 7.11 (*tt*, H-14, *J* = 2, 2 Hz), 4.77 (*dt*, H-15, *J* = 2, 2 Hz), 1.71 (*br s*, H-17), 0.85 (*s*, H-18), 0.83 (H-19), 0.73 (*s*, H-20);

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\ nm}{+10 \quad +12 \quad +12 \quad +19} (CHCl_3;\ c = 0.27).$$

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