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FURTHER SESQUITERPENE LACTONES FROM *CALEA* AND *VIGUIERA* SPECIES

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Key Word Index—*Calea clematidea*; *Viguiera linearis*; *V. procumbens*; Compositae; sesquiterpene lactones; germacranolides; heliangolides.

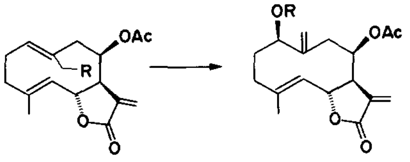
Abstract—The aerial parts of *Calea clematidea* gave three new germacranolides, those of *Viguiera procumbens* two orizabin derivatives and those of *V. linearis* dihydrobudlein A. In addition to these lactones, several known ones were isolated.

INTRODUCTION

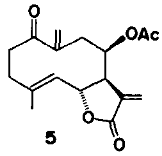
The large genera *Calea* and *Viguiera* (Compositae, tribe Heliantheae) are placed in neighbouring subtribes by Robinson [1] but in very different ones by Stuessy [2]. The chemistry of these two genera is in part very similar. Furoheliangolides are especially present in both genera while *ent*-kaurene derivatives and similar diterpenes, widespread in *Viguiera*, are only reported from *Calea orizabaensis* which, however, is now placed in the separate genus *Tetrachyron* [3]. We now have reinvestigated two *Viguiera* species and *Calea clematidea* Baker. The results will be discussed in this paper.

RESULTS AND DISCUSSION

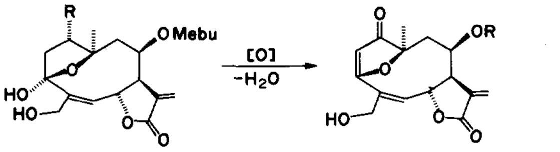
The aerial parts of *Calea clematidea* afforded zingiberene, germacrene D, curcumene, thymol methyl ether, thymohydroquinone dimethyl ether, the acetate of eupatolide (**1**) [4], the acetate of ovatifolin (**2**) which already has been prepared from ovatifolin [5] and three further sesquiterpene lactones, the germacra-4,10(14)-dien-6,12-olides **3**–**5**. The ^{1}H NMR spectra of these lactones were extremely broadened at room temperature and even at 75° many signals were still not clearly resolved. However, spin decoupling provided an assignment for all signals (Table 1). At $-30°$ in the spectrum of **3** the signals of two conformations were visible. NOE difference spectroscopy allowed us to recognize the differences between these conformers. In the main conformer C-14 was below and C-15 above the plane as followed from clear effects between H-14, H-7, H-8 and H-14′, between H-5 and H-7, between H-14′ and H-1, between H-15 and H-6, between H-7, H-5 and H-8 and between H-1 and H-14. As the conformers were in equilibrium, NOEs were also observed between signals which were not irradiated directly. However, from the intensities of the signals clear conclusions were possible which indicated that in the minor conformer C-14 and C-15 were above the plane. The same conclusion also followed from the ^{13}C NMR data of the conformers (see Experimental). The ^{1}H NMR spectrum of **4** was very similar to that of **3** but differed in the chemical shifts, especially of H-1 and H-14, which already indicated a changed oxygen function at C-1. The presence of a peroxy group in **3** was deduced from the low field signals at δ7.85 and 7.92 respectively. Furthermore triphenyl phosphine reduction of **3** afforded **4**. The molecular formula and the ^{1}H NMR spectrum (Table 1) of **5** showed that we were dealing with the corresponding ketone. Though even at +77° some signals were broadened, clear assignments of all signals were possible by spin decoupling. All lactones were closely related to **1**. Lactone **4** is the 8-*O*-acetate of ridentin [6] and **5** is the 8β-acetoxy derivative of anhydroverlotorin [7].



1 R=H **2** R=OAc **3** R=OOH **4** R=H



5



6 R=H **7** R=OH **8** R=Mebu **9** R=Ang; 4β,5-H

From the aerial parts of *Viguiera linearis* (Cav.) Sch. Bip. so far only viguilenin was reported [8]. A reinvestigation gave spathulenol, *ent*-kaurenic acid, 9,11-dihydehydro-*ent*-kaurenic acid and its 12-hydroxy derivative and the sesquiterpene lactones atripliciolide angelate [9], eupatolide [4], isoatripliciolide angelate [10], ivalin [11], budlein A [12], 15-hydroxyatripliciolide

Table 1. ^1H NMR spectral data of **3**–**5** (400 MHz, $CDCl_3$, TMS as internal standard)

	3				**4**	**5**†
	($CDCl_3$)	(C_6D_6, 75°)	($CDCl_3$, −30°)	3′	(C_6D_6, 75°)	(C_6D_6, 77°)
H-1	*	4.09 *br d*	4.40 *dd*	4.09 *br d*	3.79 *m*	—
H-5	*	4.98 *br d*	5.23 *br d*	5.27 *br d*	4.98 *br d*	4.89 *br d*
H-6	*	4.80 *t*	4.94 *t*	4.86 *t*	4.80 *t*	4.64 *t*
H-7	*	2.86 *m*	3.47 *br d*	2.89 *br d*	2.85 *m*	2.41 *m*
H-8	*	5.71 *m*	5.83 *m*	5.58 *br d*	5.73 *m*	5.39 *dd*
H-9	*	2.30 *m*	2.50 *br dd*	3.17 *br dd*	2.35 *br d*	2.83 *dd*
H-9′	*	1.84 *m*	1.85 *dd*	*		2.44 *dd*
H-13	6.23 *d*	6.23 *d*	6.23 *d*	6.26 *d*	6.21 *d*	6.17 *d*
H-13′	5.43 *m*	5.25 *d*	5.39 *d*	5.53 *d*	5.22 *d*	5.17 *d*
H-14	5.29 *m*	4.95 *br s*	5.35 *br s*	5.20 *br s*	4.77 *br s*	5.33 *br s*
H-14′	4.90 *br s*	4.69 *br s*	5.03 *br s*	4.93 *br s*	4.49 *br s*	5.03 *br s*
H-15	*	1.49 *br s*	1.87 *br s*	1.59 *br s*	1.52 *br s*	1.38 *d*
OAc	2.03 *s*	1.65 *s*	2.03 *s*	2.07 *s*	1.63 *s*	1.59 *s*
OOH	*	*	7.85	7.92	—	

*Not identified obscured multiplets.

†H-2 = 2.62 *ddd* and 2.08 *ddd*, H-3 = 2.31 *ddd* and 1.84 *ddd*.

J (Hz): Compound **3**: 1, 2 = 10; 1.2′ = 4; 5, 6 = 6, 7 = 10; 7, 13 = 3; 7, 13′ = 2; 8, 9 = 3.5; 8, 9′ = 11; 9, 9′ = 16; compound **4**: 5, 6 = 6, 7 = 10; 7, 13 = 3.5; 7, 13′ = 3; 9, 9′ = 16; compound **5**: 2, 2′ = 2, 3 = 3, 3′ = 12; 2, 3′ = 2′, 3 = 2′, 3′ ~ 5; 5, 6 = 6, 7 = 10; 7, 13 = 3.5; 7, 13′ = 3; 8, 9 = 3; 8, 9′ = 8; 9, 9′ = 15.

methacrylate [13], 15-hydroxyatripliciolide tiglate [14], leptocarpin acetate [15], desacetylovatifolin [16] and 4,5-dihydrobudlein A (**9**), its structure following from the ^1H NMR spectrum (Table 2). While some signals were close to those of budlein A the absence of the Δ^4-double bond was obvious. Spin decoupling showed that the broadened threefold doublet at $\delta 3.07$ was the signal of H-4. Inspection of a model showed that the couplings of $J_{4,5'}$ and $J_{5',6}$ should be very small as the corresponding angles were around 90°.

The aerial parts of *Viguiera procumbens* (Pers.) Blake, collected in Bolivia, gave two viguestenin derivatives [17]. A reinvestigation of a sample from Peru now gave desacetylovatifolin [16], 17,18-dihydrobudlein A [18] and two further heliangolides, the methyl butyrates **6** and **7**. The ^1H NMR spectrum of **7** was close to that of the corresponding angelate [19]. All signals could be assigned by spin decoupling. NOE difference spectroscopy established the 1α-orientation of the hydroxy group. Thus clear NOEs were observed between H-1 and H-9β, between H-14, H-2α and H-8 as well as between H-6, H-2β and H-9β. The ^1H NMR spectrum of **6** (Table 2) was in part very close to that of **7**. However, as already followed from the molecular formula, the 1-hydroxy group was absent. Again all signals were assigned by spin decoupling. Thus **7** was desacyl orizabin-8-*O*-[2-methylbutyrate] and **6** the corresponding 1-desoxy derivative. The viguilenin dihydro derivative of **7** has already been reported from *Viguiera linearis* [8]. These lactones are probably precursors of the furoheliangolides which are widespread in the genera of the subtribes Helianthinae and Neurolinae. The formulae of **6**–**9** are presented following the rule of Rogers *et al.* [20].

The present investigation again showed that the chemistry of *Calea* and *Viguiera* have some similarities though

Table 2. ^1H NMR spectral data of **6**, **7** and **9** (400 MHz, $CDCl_3$, TMS as internal standard)

	6	**7**	**9**
H-1	2.34 *ddd* 2.23 *ddd*	4.01 *d*	—
H-2α	2.15 *ddd*	2.40 *d*	5.67 *s*
H-2β	1.99 *ddd*	2.55 *dd*	
H-5	5.83 *d*	5.87 *d*	2.48 *ddd* 2.32 *br d*
H-6	5.46 *dd*	5.31 *dd*	4.65 *br dd*
H-7	4.11 *dddd*	4.17 *dddd*	3.24 *br ddd*
H-8	5.51 *ddd*	5.60 *ddd*	5.17 *br dd*
H-9α	1.93 *dd*	1.89 *dd*	2.72 *dd*
H-9β	2.05 *dd*	1.78 *dd*	2.25 *dd*
H-13	6.27 *d*	6.27 *d*	6.34 *d*
H-13′	5.62 *d*	5.62 *d*	5.71 *d*
H-14	1.50 *s*	1.54 *s*	1.39 *s*
H-15	4.24 *br d*	4.21 *br d*	4.05 *dd*
H-15′	4.14 *br d*	4.11 *br d*	3.97 *dd*
OCOR	2.24 *tq*	2.21 *tq*	6.06 *qq*
	1.57 *ddq*	1.55 *ddq*	1.93 *dq*
	1.36 *ddq*	1.36 *ddq*	1.78 *dq*
	0.81 *t*	0.80 *t*	
	1.01 *d*	0.99 *d*	

H-4 = 3.07 *br ddd*.

J (Hz): 5, 6 = 6, 7 ~ 4; 7, 13 = 2.5; 7, 13′ = 2; 15, 15′ = 12.5; OCOR: 2, 3 = 2, 5 = 3, 4 = 7; $3_1, 3_2$ = 14; compound **6**: 1α, 1β = 2α, 2β = 13; 1α, 2β = 2; 1α, 2α = 1β, 2β ~ 7; 1β, 2α = 12; 8, 9α = 4.5; 8, 9β = 10; 9α, 9β = 15; compound **7**: 1, 2β = 4.5; 2α, 2β = 14.5; 8, 9α = 5; 8, 9β = 12; 9α, 9β = 15; compound **9**: 4, 5 = 4, 15 ~ 7; 5, 5′ = 14; 5, 6 = 8.5; 6, 7 = 5; 7, 13 = 3; 7, 13′ = 9.5; 8, 9 = 5; 8, 9′ = 2.5; 9, 9′ = 15.

Calea clematidea did not contain furoheliangolides which are present in many *Calea* but are more widespread in *Viguiera* species. However, ovatifolin derivatives were isolated from both the *Calea* species and from one of the *Viguiera* species. The furoheliangolides and related lactones appear thus to be characteristic for a large part of the Heliantheae and may well indicate that these paleoceous genera are also chemically related.

EXPERIMENTAL

The air dried plant material was extracted with MeOH–Et_2O–petrol (1:1:1), and the resulting extracts were treated with MeOH to remove long chain saturated hydrocarbons. Separation was achieved as reported previously [21]. The extract of the aerial parts (2.7 kg) of *Calea clematidea* (voucher 1531 collected by E. Bordas in Paraguay) gave three CC fractions (SiO_2): 1 (petrol) 2 (Et_2O) and 3 (Et_2O–MeOH, 9:1). TLC (SiO_2, PF 254) of fraction 1 (petrol) gave 10 mg zingiberene (R_f 0.85), 5 mg curcumene (R_f 0.8), 3 mg germacrene D (R_f 0.78), 3 mg thymol methyl ether (R_f 0.35) and 2 mg thymohydroquinone dimethyl ether (R_f 0.20). TLC of fraction 2 (Et_2O–petrol, 1:1) afforded two bands (R_f 0.5 and R_f 0.35). The first band gave by repeated TLC ($CHCl_3$–C_6H_6–Et_2O, 5:5:1) 1 mg **1** (R_f 0.62) while the second gave by TLC (Et_2O–petrol, 3:1, two developments) 5 mg **3** and 5 mg **2** (R_f 0.4). TLC of fraction 3 (Et_2O–petrol, 3:1) gave three bands (3/1–3/3). 3/1 (R_f 0.60) afforded 20 mg of crystals of **3**, 3/2 (R_f 0.45) by repeated TLC ($CHCl_3$–C_6H_6–Et_2O, 2:2:1) gave 5 mg **3** (R_f 0.40), 15 mg **4** (R_f 0.28) and 6 mg **5** (R_f 0.52). TLC of 3/3 (Et_2O) gave 4 mg **5** (R_f 0.68) and 5 mg **4** (R_f 0.45).

The extract of the aerial parts (500 g) of *Viguiera linearis* (collected by B. L. Turner near Xalapa, Mexico) gave three CC fractions: 1 (Et_2O–petrol, 1:9), 2 (Et_2O) and 3 (Et_2O–MeOH, 4:1). TLC of fraction 1 (Et_2O–petrol, 1:4) gave 5 mg spathulenol (R_f 0.73), 10 mg *ent*-kaurenic acid (R_f 0.45) and 8 mg 9,11-dehydro-*ent*-kaurenic acid (R_f 0.43). TLC of fraction 2 (Et_2O–petrol, 3:1, several developments) gave 6 mg 12-hydroxy-9,11-dehydro-*ent*-kaurenic acid (R_f 0.70*), 4 mg atripliciolide angelate (R_f 0.67*) and 3.5 mg eupatolide (R_f 0.70*). TLC of fraction 3 (Et_2O–petrol, 3:1, several developments, then CH_2Cl_2–C_6H_6–Et_2O, 1:1:1, several developments) gave 5 mg leptocarpin acetate (R_f 0.65*), 4 mg isoatripliciolide angelate (R_f 0.63*), 3 mg ivalin (R_f 0.64*), 3 mg budlein A (R_f 0.64*), 3.5 mg 15-hydroxyatripliciolide methacrylate (R_f 0.62*), 2.5 mg of the corresponding tiglate (R_f 0.62*), 2 mg **9** (R_f 0.60*) and 3 mg desacetyl ovatifolin (R_f 0.60*).

The aerial parts of *Viguiera procumbens* (150 g, voucher RMK 9112, collected in Peru) gave a polar CC fraction with Et_2O–MeOH (9:1), which by TLC (Et_2O–petrol, 3:1) gave a polar band (R_f 0.15). Repeated TLC ($CHCl_3$–C_6H_6–Et_2O, 1:1:1, three developments) afforded 15 mg 17,18-dihydrobudlein A (R_f 0.50) and a mixture (R_f 0.35). This mixture was separated by HPLC (RP 8, MeOH–H_2O, 3:2) affording a fraction (R_t 2.3 min) which by TLC ($CHCl_3$–C_6H_6–Et_2O–MeOH, 30:30:30:1, two developments) gave 5 mg desacetyl ovatifolin (R_f 0.38) and 8 mg **7** (R_f 0.30) and 10 mg **6** (R_t 4.5 min).

8β-Acetoxy-1β-peroxycostunolide (**3**). Colourless crystals, mp 145°; IR $\nu^{\mathrm{CHCl_3}}_{\mathrm{max}}$ cm^{-1}: 3520 (OOH), 1765 (γ-lactone), 1740 (OAc); MS *m/z* (rel. int.): 304.131 $[M-H_2O]^+$ (4) (calc. for $C_{17}H_{20}O_5$: 304.131), 288 $[M-H_2O_2]^+$ (5), 262 $[M-HOAc]^+$ (16), 244 $[262-H_2O]^+$ (24), 228 $[262-H_2O_2]^+$ (44), 91 (100); ^{13}C NMR ($CDCl_3$, C-1–C-15): main conformer: 91.2 *d*, 26.0 *t*, 29.8 *t*, 134.9 *s*, 124.7 *d*, 75.2 *d*, 52.5 *d*, 66.7 *d*, 34.2 *t*, 142.0 *s*, 142.7 *s*, 169.9 *s*, 119.6 *t*, 120.4 *t*, 17.6 *q* (OAc: 170.8 *s*, 21.0 *q*); minor conformer: 90.5 *d*, 26.2 *t*, 37.3 *t*, 135.8 *s*, 121.7 *d*, 75.0 *d*, 45.9 *d*, 66.9 *d*, 67.8 *t*, 147.4 *s*, 138.3 *s*, 169.9 *s*, 121.1 *t*, 118.0 *t*, 17.7 *q*, (OAc: 170.2 s, 21.0 *q*).

$$[\alpha]^{\lambda}_{22^\circ} = \frac{589 \quad 578 \quad 546 \quad 436\,\mathrm{nm}}{+122.4 \quad +128.1 \quad +147.2 \quad +261.7}\ (\mathrm{CHCl_3};\ c\ 0.58).$$

Ridentin-8-O-*acetate* (**4**). Colourless oil; IR $\nu^{\mathrm{CHCl_3}}_{\mathrm{max}}$ cm^{-1}: 3600 (OH), 1760 (γ-lactone), 1725 (OAc); MS *m/z* (rel. int.): 306.147 $[M]^+$ (0.5) (calc. for $C_{17}H_{22}O_5$: 306.147), 288 $[M-H_2O]^+$ (3.5), 246 $[M-HOAc]^+$ (24), 328 $[246-H_2O]^+$ (52), 95 (96), 69 (100).

$$[\alpha]^{\lambda}_{22^\circ} = \frac{589 \quad 578 \quad 546 \quad 436\,\mathrm{nm}}{+82 \quad +86 \quad +99 \quad +178}\ (\mathrm{CHCl_3};\ c\ 1.35).$$

8β-Acetoxyanhydroverlotorin (**5**). Colourless oil; IR $\nu^{\mathrm{CCl_4}}_{\mathrm{max}}$ cm^{-1}: 1780 (γ-lactone), 1750, 1250 (OAc), 1680 (C=CCO); MS *m/z* (rel. int.): 304.131 $[M]^+$ (1) (calc. for $C_{17}H_{20}O_5$ 304.131), 262 $[M-\mathrm{ketene}]^+$ (26), 244 $[M-HOAc]^+$ (56), 216 $[244-CO]^+$ (28), 97 (96), 91 (100), 80 (97).

$$[\alpha]^{\lambda}_{24^\circ} = \frac{589 \quad 578 \quad 546 \quad 436\,\mathrm{nm}}{+112 \quad +118 \quad +135 \quad +246}\ (\mathrm{CHCl_3};\ c\ 0.78).$$

Desacyl-1-*desoxyorizabin*-8-O-[2-*methyl butyrate*] (**6**). Colourless oil; IR $\nu^{\mathrm{CHCl_3}}_{\mathrm{max}}$ cm^{-1}: 3600 (OH), 1760 (γ-lactone), 1725 (CO_2R); MS *m/z* (rel. int.): 380 $[M]^+$ (0.1), 362.173 $[M-H_2O]^+$ (3) (calc. for $C_{20}H_{26}O_6$: 362.173), 344 $[362-H_2O]^+$ (1.5), 278 $[M-RCO_2H]^+$ (5), 260 $[278-H_2O]^+$ (12), 242 $[260-H_2O]^+$ (8), 85 $[C_4H_9CO]^+$ (26), 57 $[85-CO]^+$ (100).

$$[\alpha]^{\lambda}_{22^\circ} = \frac{589 \quad 578 \quad 546 \quad 436\,\mathrm{nm}}{-87 \quad -108 \quad -125 \quad -222}\ (\mathrm{CHCl_3};\ c\ 0.49).$$

Desacyl-orizabin-8-O-[2-*methyl butyrate*] (**7**). Colourless oil; IR $\nu^{\mathrm{CHCl_3}}_{\mathrm{max}}$ cm^{-1}: 3600 (OH), 1760 (γ-lactone), 1725 (CO_2R); MS *m/z* (rel. int.): 378.168 $[M-H_2O]^+$ (0.7) (calc. for $C_{20}H_{26}O_7$: 378.168), 294 $[M-RCO_2H]^+$ (0.5), 276 $[294-H_2O]^+$ (3), 232 $[276-CH_2CHOH]^+$ (3), 85 $[C_4H_9CO]^+$ (38), 57 $[85-CO]^+$ (100). $[\alpha]^{22}_{D} = -125$ ($CHCl_3$; *c* 0.1).

4β,5-Dihydrobudlein A (**9**). Colourless oil; IR $\nu^{\mathrm{CHCl_3}}_{\mathrm{max}}$ cm^{-1}: 3600 (OH), 1765 (γ-lactone), 1710 (C=CC=O, C=CCO_2R), 1600 (C=C–O); MS *m/z* (rel. int.): 392.147 $[M]^+$ (0.3) (calc. for $C_{20}H_{24}O_8$: 392.147), 83 $[C_4H_7CO]^+$ (100), 55 $[83-CO]^+$ (84).

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*R_f values in Et_2O–MeOH, 9:1.

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