Phytochemistry, 1981, Vol. 20, pp. 267–270. © Pergamon Press Ltd. Printed in England. 0031-9422/81/0201-0267 $02.00/0

SEVEN GERMACRANOLIDES AND FOUR EUDESMANOLIDES FROM *TITHONIA ROTUNDIFOLIA**

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(*Received* 8 *May* 1980)

Key Word Index—*Tithonia rotundifolia*; Compositae; sesquiterpene lactones; germacranolides; eudesmanolides.

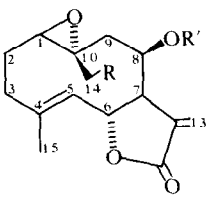
Abstract—The aerial parts of *Tithonia rotundifolia* afforded, in addition to two known sesquiterpene lactones, eleven new ones, seven germacranolides and four eudesmanolides. The structures were determined by ^{1}H NMR spectroscopy.

INTRODUCTION

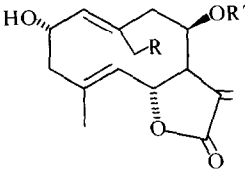
Several species from the genus *Tithonia* (tribe Heliantheae, subtribe Helianthinae) have already been investigated chemically. Most of them afforded germacranolides with a 3,10-oxygen bridge [1–7] and widespread acetylenes [8]. *T. rotundifolia* (Mill.) Blake also has been investigated and the presence of tagitinin D is reported [1, 3]. An investigation of material from Brazil afforded, in addition to 8β-angeloyloxyreynosin (**8**) [9] and leptocarpin (**14**) [10], seven new germacranolides (**1**–**7**) and four eudesmanolides (**9**, **10**, **12** and **13**). Though these lactones are different from those reported before from this genus, they are related to those typical for the subtribe.

RESULTS AND DISCUSSION

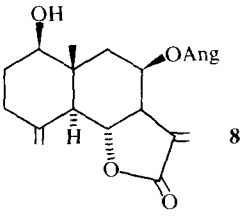
The Et_2O–petrol extract of *T. rotundifolia* afforded germacrene D, caryophyllene, phytol and a complex mixture of sesquiterpene lactones, which could be



	1	2	3	4	5
R	H	H	OH	OAc	OAc
R′	Ang	Epang*	Ang	Ang	Epang



	6	7
R	H	OAc
R′	Ang	Ang



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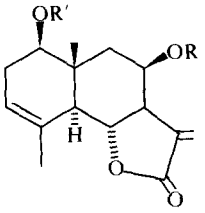
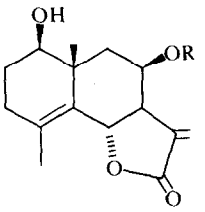
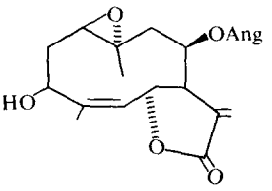


	9	10	11
R	Ang	Epang	Ang
R′	H	H	Ac

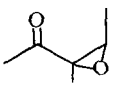


12 R = Ang
13 R = Epang



14

* Epang =



* Part 305 in the series "Naturally Occurring Terpene Derivatives". For Part 304 see: Bohlmann, F., Gupta, R. K., King, R. M. and Robinson, H. (1981) *Phytochemistry* **20**, 331.

Table 1. ^{1}H NMR spectral data of compounds **1**–**7** (270 MHz, TMS as internal standard, $CDCl_3$)

	1	**2**	**3**	**4**	**5**	**6**	**7**
1-H	2.77 *dd*	2.77 *dd*	2.90 *dd*	2.84 *dd*	2.90 *dd*	5.01 *dd*	5.26 *br.d*
2α-H			1.69 *dddd*	1.51 *dddd*			
2β-H	2.14 *dddd*	2.16 *dddd*	2.15 *dddd*	2.23 *dddd*	2.25 *dddd*	4.77 *dddd*	4.85 *ddd*
3α-H	2.45 *ddd*	2.42 *ddd*	2.45 *ddd*	2.49 *ddd*	2.50 *ddd*	2.74 *dd*	2.75 *dd*
3β-H	2.28 *ddd*	2.30 *ddd*	2.29 *ddd*	2.31 *ddd*	2.33 *ddd*	2.13 *dd*	2.18 *dd*
5-H	5.37 *br.d*	5.35 *br.d*	5.38 *br.d*	5.41 *br.d*	5.41 *br.d*	5.01 *br.d*	5.06 *m**
6-H	5.14 *dd*	5.13 *dd*	5.13 *dd*	5.14 *dd*	5.12 *dd*	5.11 *dd*	
7-H	2.94 *dddd*	2.95 *dddd*	2.94 *dddd*	2.96 *dddd*	2.96 *m*	2.97 *dddd*	2.98 *dddd*
8-H	5.76 *br.d*	5.81 *br.d*	5.77 *br.d*	5.74 *br.d*	5.71 *br.d*	5.82 *br.d*	5.82 *br.d*
9α-H	1.33 *br.d*		1.17 *br.d*	1.14 *br.d*	1.22 *br.d*	2.36 *br.dd*	2.22 *br.d*
9β-H	2.87 *dd*	2.83 *dd*	3.22 *dd*	3.26 *dd*	3.21 *dd*	2.89 *dd*	3.28 *dd*
13-H	6.31 *d*	6.31 *d*	6.32 *d*	6.32 *d*	6.32 *d*	6.33 *d*	6.34 *d*
13′-H	5.58 *d*	5.54 *d*	5.59 *d*	5.57 *d*	5.50 *d*	5.62 *d*	5.62 *d*
14-H, 14′-H	1.16 *s*	1.24 *s*	3.78 *dd*, 3.46 *dd*	4.17 *d*, 3.87 *br. d*	4.00 *d*, 4.20 *br. d*	1.55 *br. s*	4.82 *d*, 4.08 *d*
15-H	1.88 *d*	1.92 *br. d*	1.85 *d*	1.89 *d*	1.90 *d*	1.79 *d*	1.74 *br. s*
OCOR	6.15 *qq*	3.05 *q*	6.14 *qq*	6.22 *qq*	3.05 *q*	6.13 *qq*	6.17 *qq*
	2.00 *dq*	1.25 *d*	1.99 *dq*	2.06 *dq*	1.28 *d*	1.99 *dq*	2.01 *dq*
	1.88 *dq*	1.54 *s*	1.90 *dq*	1.82 *dq*	1.46 *s*	1.85 *dq*	1.82 *dq*
OAc				1.96 *s*	2.12 *s*		1.96 *s*

* in C_6D_6: 4.52 (*br. d*, 5-H), 4.99 (*dd*, 6-H).

J = (Hz): **1**–**5**: 1, 2α = 2.5; 1, 2β = 11; 2α, 2β = 14; 2α, 3α = 5; 2α, 3β = 2.5; 2β, 3α = 12; 2β, 3β = 2; 3β, 3β = 13; 5, 6 = 11; 5, 15 = 1.3; 6, 7 = 9; 7, 8 ~ 1; 7, 13 = 3.5; 7, 13′ = 3; 8, 9α ~ 1.5; 8, 9β = 6; 9α, 9β = 15; (**3**–**5**: 14, 14′ = 11.5; 9α, 14′ ~ 1; **3**: 14, OH = 8; 14′, OH = 5); **6**,**7**: 1, 2 = 10; 2, 3α = 10; 2, 3β = 5; 3α, 3β = 11; 5; 6 = 10; 5, 15 = 1.5; 6, 7 = 9; 7, 13 = 3.5; 7, 13′ = 3; 7, 8 ~ 1; 8, 9α ~ 1.5; 8, 9β = 5; 9α, 9β = 14.5 (**7**: 14, 14′ = 12.5); OAng: 3′, 4′ = 7; 3′, 5′ = 4′, 5′ ~ 1.5; Epoxyang. 3′, 4′ = 5.

separated by repeated TLC, in part with silver nitrate coated plates only. Careful ^{1}H NMR investigations, especially spin decoupling, led to the structures **1**–**10** and **12**–**14**, **8** [9] and **14** [10] as described previously. The ^{1}H NMR data of **1**–**5** are very similar (Table 1). The presence of a 6,12-*trans*-lactone was indicated by the broadened doublet around δ 5.4 ppm (J = 10 Hz) and a double doublet at about 5.13 (J = 10, 9 Hz), while the 8β-orientation of the ester residues followed from the couplings of 8-H ($J_{7,8} \sim 1$ Hz). The 1,10-epoxide caused a typical double doublet at 1-H between 2.77 and 2.90 ppm (J = 2 Hz), depending on the substitution at C-14. The nature of the ester parts easily could be deduced from the ^{1}H NMR data. Also the substitution at C-14 clearly followed from the corresponding doublets in the spectra of **3**–**5**. The hydroxy group in **3** caused an additional splitting of these signals. Acetylation afforded **4**. The compound without substitution at C-8 and C-14 we have named tithifolin.

The ^{1}H NMR data of **6** are very similar to those of eupaserrin [11], which differs in the ester part only. The introduction of the 14-acetoxy group (**7**) led again to the appearance of two doublets for 14-H (Table 1), while the other signals were very similar to those of **6**, indicating identical stereochemistry. **6** and **7** are derivatives of eupatolide. The ^{1}H NMR data of **9**, **10** and the acetate **11**, obtained by acetylation of **9**, as well as those of **12** and **13** (Table 2) clearly showed that *trans*-eudesman-6,12-olides are present. In the spectra of **9**–**11** a typical triplet at 4.4 ppm (J = 10 Hz) was visible, while those of **12** and **13** displayed a broadened doublet at 5.12, due to the homoallylic coupling with 3- and 15-H. The 8β-orientation of the ester groups could be deduced again from the observed couplings, which were the same as those in **8** [9] and similar compounds. Also the equatorial orientation of the 1-hydroxy group followed from the observed couplings (J = 11, 5 Hz), while the nature of the ester groups and the position of the double bond could be assigned by the typical signals (Table 2). While **9** and **10** are balchanin derivatives, **12** and **13** are substituted arbusculins B.

If we look at the structures isolated from this species it is probable that **1** is the precursor, of course, of **2**–**5**, but also of **8**–**10**, **12** and **13**. **14** is the only lactone, which is closely related to the lactones isolated before from *Tithonia* species. By a lack of 3-hydroxyl the epoxide ring could be opened to form the typical 3, 10-oxygen bridge. Lactones related to **6** are reported from *Helianthus* [12, 13], which is placed in the same subtribe, as well as from *Tetragonotheca*, which contains melampolides [14]. Surely further species should be studied to see whether the lactones isolated now are more widespread or not.

EXPERIMENTAL

^{1}H NMR: 270 MHz, TMS as int. standard, MS: 70 eV, direct inlet; CI, *isobutane*; optical rotation: $CHCl_3$. The air-dried aerial parts collected in north eastern Brazil (voucher RMK 7996) were extracted with Et_2O–petrol at room temp. and the resulting extract was separated by column chromatography (SiO_2, act. Grade II). With petrol 10 mg caryophyllene and 2 mg germacrene D were eluted and with Et_2O–petrol (1:3), 15 mg phytol. The

Table 2. ^{1}H NMR spectral data of compounds **9**–**13** (270 MHz, TMS as internal standard, $CDCl_3$)

	9	**10**	**11**	**12**	**13**
1-H	3.68 *br. dd*	3.70 *br. dd*	4.90 *dd*	3.56 *br. dd*	3.57 *br. dd*
2-H	2.45 *m*	2.45 *m*	2.5 *m* 2.3 *m*	1.65 *m*	1.65 *m*
3α-H 3β-H	5.37 *br. s*	5.37 *br. s*	5.37 *br. s*	2.16 *m* 2.25 *m*	2.15 *m* 2.25 *m*
5-H	2.3 *m*	2.3 *m*	2.3 *m*	—	—
6-H	4.42 *dd*	4.45 *dd*	4.40 *dd*	5.12 *br. d*	5.11 *br. d*
7-H	2.83 *dddd*	2.82 *m*	2.81 *dddd*	2.95 *dddd*	2.95 *dddd*
8-H	5.83 *dd*	5.93 *m*	5.78 *dd*	5.85 *dd*	5.93 *dd*
9α-H	1.58 *dd*	1.63 *dd*	1.59 *dd*	1.64 *dd*	1.62 *dd*
9β-H	2.38 *dd*	2.32 *dd*	2.14 *dd*	2.42 *dd*	2.34 *dd*
13-H	6.17 *d*	6.16 *d*	6.17 *d*	6.25 *d*	6.24 *d*
13'-H	5.47 *d*	5.45 *d*	5.45 *d*	5.55 *d*	5.52 *d*
14-H	1.08 *s*	1.11 *s*	1.14 *s*	1.25 *s*	1.28 *s*
15-H	1.89 *br. s*	1.89 *br. s*	1.90 *br. s*	1.90 *br. s*	1.89 *br. s*
OCOR	6.11 *qq*	3.04 *q*	6.12 *qq*	6.10 *qq*	3.04 *q*
	1.99 *dq*	1.30 *d*	2.00 *dq*	1.99 *dq*	1.29 *d*
	1.85 *dq*	1.54 *s*	1.85 *dq*	1.86 *dq*	1.55 *s*
OAc	—	—	2.06 *s*	—	—

J (Hz): **9**–**11**: 1, 2α = 6.5; 1, 2β = 9; 5, 6 = 6, 7 = 11; 7, 8 ~ 3; 7, 13 = 3.5; 7, 13' = 3; 8, 9α = 3.5; 8, 9β = 2; **12**–**13**: 1, 2α = 5; 1, 2β = 11; 6, 7 = 11; 7, 8 = 3; 7, 13 = 3.5; 7, 13' = 3; 8, 9β = 2.

polar fractions (Et_2O and Et_2O–MeOH, 10:1) were further separated by TLC (SiO_2, GF 354). The less polar part on repeated TLC ($CHCl_3$–MeOH, 100:1) afforded 2 mg **1**, 1 mg **9**, 1 mg **12** and 4 mg **14**, while the more polar fractions yielded on repeated TLC ($CHCl_3$–MeOH, 30:1) 2 mg **2**, 5 mg **3**, 8 mg **4**, 2 mg **5**, 3 mg **6**, 4 mg **7**, 2 mg **8**, 0.5 mg **10** and 0.5 mg **13**. **10** and **13** could be separated by $AgNO_3$-coated SiO_2 only.

8β-Angeloyloxytithifolin (**1**). Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1780 (γ-lactone), 1725 (C=CCO_2R), MS *m/e* (rel. int.): 346.178 (M^+, 0.3) ($C_{20}H_{26}O_5$), 246 (M − RCO_2H, 9), 83 ($C_4H_7CO^+$, 100), 55 (83 − CO, 83).

$$[\alpha]_{24}^{\circ} = \frac{589}{+35.5}\ \frac{578}{+38.2}\ \frac{546}{+45.5}\ \frac{436\,nm}{+81.8}\quad (c = 0.11).$$

8β-[2,3-Epoxy-2-methylbutyryloxy]-tithifolin (**2**). Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1780 (γ-lactone), 1740 (CO_2R), MS *m/e* (rel. int.): 362.173 ($C_{20}H_{26}O_6$, 3), 246 (M − RCO_2H, 28), 57 (100).

$$[\alpha]_{24}^{\circ} = \frac{589}{+8.0}\ \frac{578}{+15.0}\ \frac{546}{+18.0}\ \frac{436\,nm}{+28.0}\quad (c = 0.1).$$

8β-Angeloyloxy-14-hydroxytithifolin (**3**). Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3620 (OH), 1770 (γ-lactone), 1730 (C=CCO_2R), MS *m/e* (rel. int.): 362.173 ($C_{20}H_{26}O_6$, 0.5), 262 (M − RCO_2H, 1), 244 (262 − H_2O, 3), 83 ($C_4H_7CO^+$, 100), 55 (83 − CO, 52).

$$[\alpha]_{24}^{\circ} = \frac{589}{+10.3}\ \frac{578}{+10.6}\ \frac{546}{+12.9}\ \frac{436\,nm}{+24.6}\quad (c = 0.3).$$

Acetylation (Ac_2O, 4-pyrrolidinopyridine, room temp.) afforded **4**.

8β-Angeloyloxy-14-acetoxytithifolin (**4**). Colourless crystals, mp 192–196 (Et_2O). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1770 (γ-lactone), 1740 (OAc), 1720, 1650 (C=CCO_2R), MS *m/e* (rel. int.): 404.184 (M^+, 0.5) ($C_{22}H_{28}O_7$), 344 (M − HOAc, 0.5), 304 (M − AngOH, 0.5), 244 (304 − HOAc, 6), 83 ($C_4H_7CO^+$, 100), 55 (83 − CO, 98).

$$[\alpha]_{24}^{\circ} = \frac{589}{+29.1}\ \frac{578}{+30.0}\ \frac{546}{+35.6}\ \frac{436\,nm}{+70.0}\quad (c = 0.3).$$

8β-[2,3-Epoxy-2-methylbutyryloxy]-14-acetoxytithifolin (**5**). Colourless crystals, mp 197–202 (Et_2O), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1780 (γ-lactone), 1745 (OAc, CO_2R), MS *m/e* (rel. int.): 420.178 (M^+, 1) ($C_{22}H_{28}O_8$), 320 (M − RCO_2H, 2), 57 (100).

2α-Hydroxyeupatolide 8-O-angelate (**6**). Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3610 (OH), 1780 (γ-lactone), 1725 (C=CCO_2R), MS *m/e* (rel. int.): 346.178 (M^+, 0.5) ($C_{20}H_{26}O_5$), 246 (M − RCO_2H, 10), 228 (246 − H_2O, 5), 83 ($C_4H_7CO^+$, 100), 55 (83 − CO, 57), CI: 347 (M + 1, 11), 247 (M + 1 − RCO_2H, 100), 229 (247 − H_2O, 82).

$$[\alpha]_{24}^{\circ} = \frac{589}{+133.3}\ \frac{578}{+140.0}\ \frac{546}{+160.8}\ \frac{436\,nm}{+299.2}\quad (c = 0.12).$$

2α-Hydroxy-14-acetoxyeupatolide 8-O-angelate (**7**). Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1780 (γ-lactone), 1740 (OAc), 1720 (C=CCO_2R), MS *m/e* (rel. int.): 362.163 ($C_{20}H_{26}O_6$, M − ketene, 3), 344 (M − HOAc, 2), 304 (M − AngOH, 1), 244 (304 − HOAc), 226 (244 − H_2O), 83 ($C_4H_7CO^+$, 100), 55 (83 − CO, 67), CI: (M + 1, 68), 305 (M + 1 − AngOH, 32), 245 (305 − HOAc, 100).

$$[\alpha]_{24}^{\circ} = \frac{589}{+65.4}\ \frac{578}{+67.7}\ \frac{546}{+78.0}\ \frac{436\,nm}{+144.9}\quad (c = 0.3).$$

8β-Angeloyloxybalchanin (**9**). Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3640 (OH), 1790 (γ-lactone), 1730 (C=CCO_2R), MS *m/e* (rel. int.): 346.178 (M^+, 4) ($C_{20}H_{26}O_5$), 246 (M − RCO_2H, 21), 228 (246 − H_2O, 9), 83 ($C_4H_7CO^+$, 100), 55 (83 − CO, 67).

$$[\alpha]_{24}^{\circ} = \frac{589}{+58.0}\ \frac{578}{+62.0}\ \frac{546}{+68.0}\ \frac{436\,nm}{+126.0}\quad (c = 0.05).$$

1 mg **9** were heated for 4 hr at 70° with 0.1 ml Ac_2O. TLC (Et_2O–petrol, 1:1) afforded 1 mg **11**, colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1790 (γ-lactone), 1750 (OAc), 1720 (C=CCO_2R), MS *m/e* (rel. int.): 320 (M − HOAc, 30), 228 (328 − AngOH, 14), 83 ($C_4H_7CO^+$, 100).

8β-[2,3-Epoxy-2-methylbutyryloxy]-balchanin (**10**). Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3620 (OH), 1780 (γ-lactone), MS *m/e* (rel. int.): 362.173 (M^+, 5) ($C_{20}H_{26}O_6$), 55 (100).

8β-Angeloyloxy-1β-hydroxyarbusculin B (**12**). Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3620 (OH), 1780 (γ-lactone), 1720 (C=CCO_2R), MS *m/e* (rel. int.): 346.178 (M^+, 2) ($C_{20}H_{26}O_5$), 246 (M − RCO_2H, 58), 228 (246 − H_2O, 12), 83 ($C_4H_7CO^+$, 74), 55 (83 − CO, 100).

8β-[2,3-Epoxy-2-methylbutyryloxyl-1β-hydroxyarbusculin B (**13**). Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3620 (OH), 1780 (γ-lactone), MS *m/e* (rel. int.): 362.173 (M^+, 7) ($C_{20}H_{26}O_6$), 246 (M − RCO_2H, 100), 228 (246 − H_2O, 30).

Acknowledgements – We thank Drs. Scott A. Mori and P. Alvim, Centro de Pesquisas do Cacau at Itabanu, Bahia, Brazil, for their help during plant collection and the Deutsche Forschungsgemeinschaft for financial support.

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