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LABDANE AND DEHYDRONEROLIDOL DERIVATIVES FROM *BRICKELLIA DIFFUSA**

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Key Word Index—*Brickellia diffusa*; Compositae; sesquiterpenes; dehydronerolidol derivatives; diterpenes; labdane derivatives.

Abstract—An investigation of *Brickellia diffusa* afforded three new dehydronerolidol derivatives and five new labdane derivatives, all highly oxygenated. The structures were elucidated by spectroscopic methods and a few chemical transformations. The compounds isolated showed close relationships to those isolated from *Brickellia* sp.

In a continuation of our chemical investigations of members of the tribe Eupatorieae we have now studied the constituents of *Brickellia diffusa* A. Gray. The roots afforded germacrene D, phytol and five dehydronerolidol derivatives, the known angelates **1** [1] and **2** [2] as well as the diangelate **3**, the mixed diester **4** and the ditiglate **5**. The structures of **3–5** followed from the ^{1}H NMR spectral data (Table 1). While the relative configurations at C-3 and C-9 could not be determined, those at C-9 and C-10 followed from the couplings observed. Obviously in all three compounds a hydrogen bond is present leading to a fixed conformation. As the coupling $J_{9,10}$ was only 1.7 Hz the proposed stereochemistry was possible. The relative position of the ester groups in **4** could not be established with certainty. The shift differences of the olefinic signal of the angelate residues may support the proposed structure, as the downfield shift can be explained for an ester group between two oxygen functions. The absolute configuration of these esters is not known.

The aerial parts afforded in addition to germacrene D and phytol, five diterpenes, the labdane derivatives **6**, **8** and **10–12**. The ^{1}H NMR spectral data of **7** (Table 2), obtained by reaction of **6** with diazomethane, showed the presence of a diangelate with an aldehyde group (δ 9.32*s*). Furthermore, signals for two olefinic protons and an olefinic methyl group could be recognized, while the three methyl singlets and the similarity of the ^{1}H NMR data with those of related labdane derivatives [2] supported the proposed carbon skeleton. A very similar acid with ester groups at C-2 and C-3 was isolated from *Brickellia squarrosa* [2]. Consequently the signals of H-2 and H-3 were nearly identical. The couplings clearly indicate the α-orientation of both oxygen functions. The position of the aldehyde group followed from the chemical shift of H-7, while the presence of a 12-keto group could be deduced from the downfield shifted H-11 double doublets. Spin decoupling further allowed the assignment of the H-9 signal, its irradiation collapsed the H-11 signals to doublets and sharpened the H-7 signal. Further irradiations allowed the assignment of the H-6 signals, while those of H-1 and H-5 were

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

	3	**4**	**5**
H-1*c*	5.05 *dd*	5.02 *dd*	5.02 *dd*
H-1*t*	5.22 *dd*	5.22 *dd*	5.22 *dd*
H-2	5.95 *dd*	5.95 *dd*	5.95 *dd*
H-4	5.65 *d*	5.65 *d*	5.65 *d*
H-5	6.38 *dd*	6.38 *dd*	6.38 *dd*
H-6	5.79 *br d*	5.79 *br d*	5.79 *br d*
H-8	2.30 *m*	2.29 *m*	2.30 *m*
H-9	5.56 *ddd*	5.53 *ddd*	5.53 *ddd*
H-10	4.98 *d*	4.92 *d*	4.92 *d*
H-12	1.23 *s*	1.22 *s*	1.21 *s*
H-13	1.21 *s*	1.21 *s*	1.19 *s*
H-14	1.81 *br s*	1.80 *br s*	1.79 *br s*
H-15	1.37 *s*	1.37 *s*	1.36 *s*
OCOR	6.19 *qq*	6.08 *qq*	6.98 *br q*
	6.07 *qq*	1.98 *dq*	6.85 *br q*
	2.02 *dq*	1.85 *dq*	1.84 *br d*
	1.98 *dq*	6.98 *br q*	1.79 *br d*
	1.96 *dq*	183 *br d*	1.89 *br s*
	1.84 *dq*	1.89 *br s*	1.79 *br s*

J (Hz): 1*c*,1*t* = 0.7; 1*c*,2 = 10; 1*t*,2 = 17.5; 4,5 = 15; 5,6 = 11; 8,9 = 6; 8′,9 = 8; 9,10 = 1.7; OAng: 3′,4′ = 7; 3′,5′ = 4′,5′ = 1.3.

*Part 389 in the series "Naturally Occurring Terpene Derivatives". For Part 388 see Bohlmann, F., Singh, P., Jakupovic, J., King, R. M. and Robinson, H. (1982) *Phytochemistry* **21**, 371.

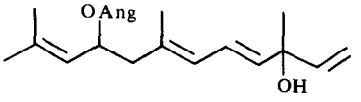
Table 2. ^{1}H NMR spectral data of compounds **7–13** (400 MHz, $CDCl_3$, TMS as internal standard)

	7*	**8**	**9†**	**10**	**11**	**12**	**13**	C_6D_6–$CDCl_3$,(1:1)‡
H-1α H-1β	2.0–1.7 *m*	2.0–1.7 *m*	2.0–1.7 *m*	2.0–1.7 *m*	2.0–1.7 *m*		1.85 *m*	1.63 *m*
H-2	5.36 *ddd*	4.23 *ddd*	5.27 *ddd*	5.31 *ddd*	5.31 *ddd*		5.35 *ddd*	5.30 *ddd*
H-3	5.20 *d*	5.04 *d*	5.17 *d*	5.21 *d*	5.21 *d*		5.25 *d*	5.25 *d*
H-6	2.43 *m*	2.00 *m*	2.00 *m*	2.00 *m*	2.10–1.9 *m*		2.43 *dddd*	1.91 *br d*
H-6′	2.32 *m*						2.19 *dddd*	1.71 *dddd*
H-7	6.85 *m*	5.54 *br*	5.51 *br*	5.65 *br*	5.64 *br*		7.47 *ddd*	7.23 *ddd*
H-9	3.18 *br*	2.00 *m*	2.00 *m*	2.61 *br d*	2.78 *br d*	2.63 *br d*	2.91 *br d*	2.75 *br d*
H-11	2.97 *dd*	1.85–1.7 *m*	1.62 *dd*	1.75 *dd*	1.8–1.6 *m*		1.72 *dd*	1.50 *dd*
H-11′	2.78 *dd*		1.76 *dd*	1.62 *dd*			1.8 *m*	1.42 *dd*
H-14	5.70 *br s*	5.74 *q*	5.74 *q*	5.80 *q*	5.84 *q*	5.80 *q*	5.91 *q*	5.41 *q*
H-16	2.18 *br s*	2.06 *d*	2.08 *d*		2.05 *d*	2.03 *d*	2.12 *d*	1.57 *d*
H-17	9.32 *s*	4.52 *br d* 4.28 *br d*	4.53 *br d* 4.28 *br d*	4.54 *br d* 4.16 *br d*	5.90 *br*	6.09 *br*	—	—
H-18	1.19 *s*	1.07 *s*	1.12 *s*	1.17 *s*	1.15 *s*		1.18 *s*	0.85 *s*
H-19	0.98 *s*	0.92 *s*	0.93 *s*	1.02 *s*	0.99 *s*	0.98 *s*	0.97 *s*	0.73 *s*
H-20	0.96 *s*	0.87 *s*	0.91 *s*	0.93 *s*	0.92 *s*	0.91 *s*	0.94 *s*	0.65 *s*
OCOR	6.09 *br q*	6.14 *qq*	6.08 *qq*	6.08 *br q*	6.07 *br q*		6.09 *qq*	5.87 *qq*
	6.05 *br q*	2.02 *dq*	2.00 *dq*	6.06 *br q*	7.04 *br q*		6.07 *qq*	5.85 *qq*
	2.01 *br q*	1.92 *dq*	1.93 *dq*	1.99 *dq*	1.97 *br d*		1.98 *dq*	
	1.95 *br q*			1.93 *dq*	1.91 *br d*		1.94 *br*(6 H)	1.94 *dq*
	1.95 *br q*			1.95 *dq*	1.93 *br s*		1.79 *dq*	1.86 *dq*
	1.78 *br s*			1.78 *dq*	1.77 *br s*			1.80 *dq*

*OMe 3.61 *s*.
†OAc 1.98 s.
‡H-5 1.57 *dd*.
J(Hz): 1α,2α = 4,5; 1α,2β = 12; 2β,3β = 2.5; 5α,6α = 4.5; 5α,6β = 12; 6α,6β = 20; 6α,7 ~ 4; 6β,7 = 3.5; 6α,9α = 6β,9α = 7,9α = 7,17 ~ 1.5; 9,11 = 12; 9.11′ = 5; 11,11′ = 13; 14,16 = 1; OAng: 3′,4′ = 7; 3′,5′ = 4′,5′ = 1.5.

overlapped multiplets partly hidden by the angelate methyl signals. The stereochemistry of the 13,14-double bond followed from the chemical shift of H-14. We have named compound **6** without an oxygen function at C-2 brickellidiffusic acid.

The ^{1}H NMR spectral data of **8** and **10** and those of **9** obtained by acetylation of **8** (Table 2) again indicated that 2α, 3α-orientated oxygen functions were present. The chemical shift of H-2 in the spectrum of **8** further showed that the hydroxyl group was at C-2. Again the ^{1}H NMR data were in part similar to those of related labdanes. The nature of the side chain was deduced from the molecular formulae, the IR spectrum and the ^{1}H NMR data. Two broadened doublets were coupled with the olefinic signal, which could only be that of H-7. Furthermore, an olefinic narrowly split quartet was coupled with an olefinic methyl signal. The chemical shifts required a conjugation of this double bond with a carbonyl group, which could only be that of a γ-lactone, as the IR spectrum clearly indicated the presence of this group. Consequently the only possible structures were those of spiroketals. As in the ^{1}H NMR spectra of **9** and **10** some clear differences could be observed and the stereochemistry at C-13 was obviously different. In the spectrum of the diangelate **10** the H-9 signal was deshielded. This can be explained only if the oxygen of C-15 is α-orientated at C-13. Consequently in **8** and **9** this stereochemistry was reversed. The assignment of the signals was again established by spin decoupling, though a few signals were overlapping multiplets. The ^{1}H NMR spectral data of **11** and **12**, which could not be separated, showed that epimeric hemiacetals were most probably present. Both compounds were transformed by oxidation to the bis lactone **13**, its ^{1}H NMR spectral data (Table 2) in C_6D_6–$CDCl_3$ (1:1) could be fully interpreted. The presence of a 2α, 3α-diangelate was deduced from the similarity of the corresponding signals, if compared with those of **7** and **10**. Irradiation of the H-2 signal allowed the



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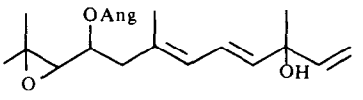

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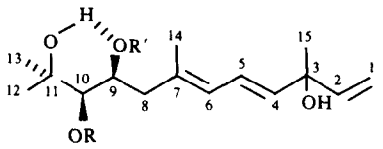
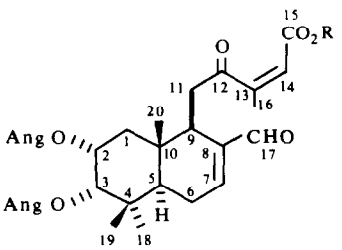
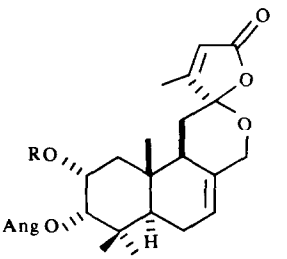


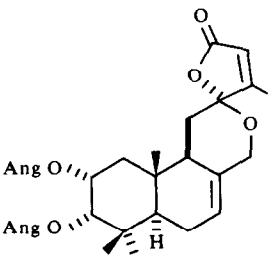
	3	**4**	**5**
R	Ang	Tigl	Tigl
R'	Ang	Ang	Tigl



6 R=H
7 R=Me



8 R=H
9 R=Ac



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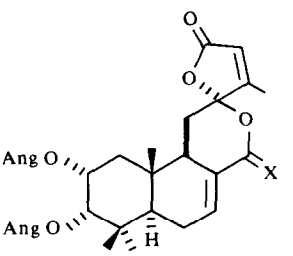

11 X=αOH,H
12 X=βOH,H
13 X=O

assignment of the H-1 signals. The downfield olefinic signal obviously was that of H-7 as it was at much higher field in the spectra of **11** and **12**. Its irradiation allowed the assignment of the H-6 and H-9 signals, as the latter showed allylic coupling. Irradiation of the H-9 signal collapsed the double doublet at δ 1.50 and 1.42 to doublets and sharpened the signals of H-6 and H-7, which were broadened by allylic and homoallylic couplings. Finally, the H-5 signal was assigned by irradiation of the H-6β signal. Its couplings established the presence of a *trans*-decalin derivative. The downfield shift of the H-9 signal again required an α-orientation of the γ-lactone oxygen at C-13. Accordingly the optical rotation of **13** was laevorotatory as was that of **10**, while **8** with the proposed opposite stereochemistry also showed opposite rotation. Obviously **11** and **12** were formed from **6** by hemiacylal formation of the acid with the keto group followed by hemiketal formation with the aldehyde group at C-7. While the first step was stereospecific, the second gave both epimers in equal amounts. Also **8** and **10** are closely related to **6**. However, in this case the C-7 aldehyde group was reduced first. Surprisingly, the stereochemistry of the acylal formation is influenced by the nature of the oxygen function at C-2. Inspection of a model showed that perhaps in the free acid a hydrogen bridge of the carboxylic OH with the 2-hydroxyl group may influence the direction of the hemiketal formation. The absolute configuration of the new diterpene has not been determined. However, since the closely related angelates from other *Brickellia* sp. [2] belong to the labdane series, the same configuration for **6**, **8**, **10** and **13** was very likely. Highly oxygenated dehydronerolidol and labdane derivatives seem to be characteristic at least for a group of *Brickellia* sp. [2–5]. So far only two species of this large genus with about 100 species have been reported to contain other diterpenes [2, 3], while several afforded a large variety of flavones [6], most of these species, however, have not been investigated for other compounds. Further investigations may show whether these types of compounds are characteristic for the whole genus or not.

EXPERIMENTAL

The air dried plant material, grown from seeds (voucher RMK 8549) was extracted with Et_2O–petrol (1:2) and the resulting extracts were separated first by CC (Si gel) and further by TLC (Si gel). The roots (20 g) afforded 5 mg germacrene D, 5 mg phytol and a mixture of **1**–**5**, which could be separated by repeated TLC using C_6H_6–CH_2Cl_2–Et_2O (1:1:1). Finally 10 mg **1**, 12 mg **2**, 10 mg **3**, 8 mg **4** and 5 mg **5** were obtained. The aerial parts (80 g) afforded 25 mg germacrene D, 5 mg phytol and a polar fraction, which on repeated TLC gave 10 mg **10** (C_6H_6–CH_2Cl_2–Et_2O, 2:2:1), 5 mg **8** (C_6H_6–CH_2Cl_2–Et_2O, 1:1:1), 10 mg **11** and **12** (*ca* 1:1) (same solvent) and after addition of CH_2N_2 20 mg **7** (same solvent).

9, 10-*Diangeloyloxy*-11-*hydroxy*-10, 11-*dihydrobrickelliol* (**3**). Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1720, 1650 (C=CCO$_2$R); MS *m/z* (rel. int.): 416.256 [M − H_2O]$^+$ (0.4 ($C_{25}H_{36}O_5$), 334 [M − HOAng]$^+$ (0.5), 316 [334 − H_2O]$^+$ (0.6), 258 [316 − O=CMe_2]$^+$ (3), 216 [316 − HOAng]$^+$ (1), 83 [C_4H_7CO]$^+$ (100), 55 [83 − CO]$^+$ (42).

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{-8.2 \quad -8.9 \quad -10.0 \quad -16.5} (CHCl_3;\ c\ 0.38).$$

9-*Angeloyloxy*-10-*tigloyloxy*-11-*hydroxy*-10, 11-*dihydrobrickelliol* (**4**). Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1725, 1650 (C=CCO$_2$R); MS *m/z* (rel. int.): 416.256 [M − H_2O]$^+$ (0.5)($C_{25}H_{36}O_5$), 334 [M − HOAng]$^+$ (0.5), 316 [334 − H_2O]$^+$(0.5), 258 [316 − Me_2CO]$^+$ (2), 216 [316 − HOAng]$^+$ (2), 83 [C_4H_7CO]$^+$ (100), 55 [83 − CO]$^+$ (51).

9, 10-*Ditigloyloxy*-11-*hydroxy*-10, 11-*dihydrobrickelliol* (**5**). Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1710 (C=CCO$_2$R); MS *m/z* (rel. int.): 316 [M − H_2O, HOTigl]$^+$ (0.5), 258 [316 − Me_2CO]$^+$ (1), 83 [C_4H_7CO]$^+$ (100), 55 [83 − CO]$^+$ (64); CI (*iso*-butane): 417 [M + 1 − H_2O]$^+$ (11), 317 [417 − HOTigl]$^+$ (100), 217 [317 − HOTigl]$^+$ (98), 101 [TiglOH + 1]$^+$ (37).

Brickellidiffusic acid angelate (**6**). Isolated as its methyl ester **7**, colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2720, 1690 (C=CCHO), 1720, 1645 (C=CCO$_2$R); MS *m/z* (rel. int.): 542.288 [M]$^+$ (0.5)($C_{31}H_{42}O_8$), 524 [M − H_2O]$^+$ (20), 442 [M − HOAng]$^+$ (2), 83 [C_4H_7CO]$^+$ (100), 55 [83 − CO]$^+$ (62).

2α-*Hydroxy*-17, *O-dihydrobrickellidiffusic acid spiro ketal lactone* (**8**). Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}; 3600 (OH), 1780 (γ-lactone), 1720, 1650 (C=CCO$_2$R); MS *m/z* (rel. int.): 430.236 [M$^+$] (1.5)($C_{25}H_{34}O_6$), 412 [M − H_2O]$^+$ (4), 312 [412 − HOAng]$^+$ (10), 297 [312 − Me]$^+$ (2), 83 [C_4H_7CO]$^+$ (100), 55 [83 − CO]$^+$ (55).

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{+59 \quad +61 \quad +70 \quad +129} (CHCl_3;\ c\ 0.4).$$

Compound **8** (5 mg) was heated for 1 hr with 0.1 ml Ac_2O at 70°. TLC(C_6H_6–CH_2Cl_2–Et_2O, 1:1:1) afforded 3 mg **9**, colourless gum, ^{1}H NMR see Table 2.

2α-*Angeloyloxy*-17, *O-dihydrobrickellidiffusic acid spiro ketal lactone* (**10**). Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1780 (γ-lactone), 1720, 1650 (C=CCO$_2$R); MS *m/z* (rel. int.): 512 [M]$^+$ (0.5), 412.225 [M − HOAng]$^+$ (6)($C_{25}H_{32}O_5$), 313 [412 − OAng]$^+$ (12), 312 [412 − HOAng]$^+$ (6), 83[C_4H_7CO]$^+$ (100), 55[83 − CO]$^+$ (58).

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{-43 \quad -46 \quad -53 \quad -95} (CHCl_3;\ c\ 0.3).$$

Epimeric spiro ketals of **6** (**11** *and* **12**). Colourless gum, ^{1}H NMR see Table 2. 10 mg **11** and **12** in 3 ml Et_2O were stirred for 2 hr with 10 mg MnO_2. TLC (C_6H_6–CH_2Cl_2–Et_2O, 1:1:1) afforded 8 mg **13**, colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1800(γ-lactone), 1755(δ-lactone), 1725, 1650 (C=CCO$_2$R); MS *m/z* (rel. int.): 526.257 [M]$^+$ (0.3)($C_{30}H_{38}O_8$), 426 [M − HOAng]$^+$ (2), 327 [426 − OAng]$^+$ (8), 83 [C_4H_7CO]$^+$ (100), 55 [83 − CO]$^+$ (44).

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{-57 \quad -60 \quad -69 \quad -124} (CHCl_3;\ c\ 0.42).$$

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REFERENCES

1. Bohlmann, F. and Zdero, C. (1971) *Chem. Ber.* **104**, 964.
2. Bohlmann, F. and Zdero, C. (1976) *Chem. Ber.* **109**, 1436.
3. Bohlmann, F., Bapuji, M., Jakupovic, J., King, R. M. and Robinson, H. (1982) *Phytochemistry* **21**, 186.
4. Bohlmann, F. and Zdero, C. (1969) *Tetrahedron Letters* 5109.
5. Bohlmann, F., Suwita, A. and Mabry, T. J. (1978) *Phytochemistry* **17**, 763.
6. Mabry, T. J., Timmermann, B. N., Roberts, M. F., Ulubelen, A. and Mues, K. (1980) *Planta Med.* **39**, 220 (and references therein).