Phytochemistry, Vol. 21, No. 5, pp. 1045–1048, 1982.
Printed in Great Britain.

0031-9422/82/051045–04$03.00/0

GERMACRANOLIDES FROM *STILPNOPAPPUS* SPECIES*

FERDINAND BOHLMANN, CHRISTA ZDERO, ROBERT M. KING† and HAROLD ROBINSON†

Institute for Organic Chemistry, Technical University of Berlin, D-1000 Berlin 12, West Germany; †Smithsonian Institution, Department of Botany, Stop No. 166, Washington, DC 20560, U.S.A.

(*Received* 24 *July* 1981)

Key Word Index—*Stilpnopappus tomentosus*; *S. glomeratus*; *S. pickelii*; *S. trichospiroides*; Compositae; Vernonieae; sesquiterpene lactones; germacranolides.

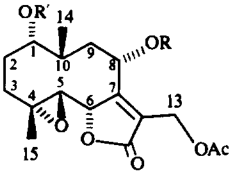
Abstract—The investigation of four *Stilpnopappus* species afforded in addition to known compounds seven new germacranolides, all related to glaucolides. The structures were elucidated by spectroscopic methods. The chemotaxonomy of the genus is discussed briefly.

INTRODUCTION

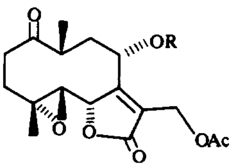
The South American genus *Stilpnopappus* (Compositae, Vernonieae), with *ca* 20 species so far has not been investigated chemically, although we have now studied the constituents of four species. In addition to known compounds several new sesquiterpene lactones were isolated, all related to the glaucolide marginatin or the corresponding methacrylate derivative.

RESULTS AND DISCUSSION

The aerial parts of *Stilpnopappus tomentosus* afforded germacrene D, bicyclogermacrene, caryophyllene, stigmasterol, linolenic acid and glyceride as well as a complex mixture of eight sesquiterpene lactones, which were separated by repeated TLC and HPLC. Their structures were deduced from ^{1}H NMR spectra. The major compounds were the glaucolide derivatives **5** and **6**. The ^{1}H NMR spectral data (Table 1) showed that these lactones only differed in the nature of the ester group, one being a methacrylate and the other a tiglate. The presence of epoxides was indicated by the doublets at δ 2.57 and 2.58 respectively. Spin decoupling showed that these signals were coupled with a multiplet at δ 4.9, which in the case of the tiglate **6** was an overlapping two-proton singlet. Further spin decoupling studies showed that the methyl doublet, obviously that of H-14, was coupled with a downfield shifted double doublet quartet, indicating that a keto group may be present at C-1 or C-9. However, since irradiation of the multiplet at δ 4.9 caused a change of the signals at δ 2.55 and 2.21, which were also coupled with H-10, the keto group had to be placed at C-1. The ^{1}H NMR spectrum of **5** in deuterobenzene allowed a clear assignment of the signals of H-5 through H-10, establishing the proposed positions of the oxygen functions. The couplings observed indicated a 5β-epoxide, an 8α-acyloxy group and a 10β-methyl group, if models were inspected. Though the flexibility of the ten-membered ring was a problem, the most likely conformation agreed well with the observed couplings, particularly if the chemical shifts of H-10 and H-14 were considered, which require a conformation where the methyl group is not deshielded by the keto group, while H-10 should be in plane with the latter. We have given the name stilpnotomentolide to the free 8-hydroxylactone.

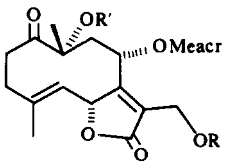


	1	2	3	4
R	Meacr	Meacr	Tigl	Tigl
R′	H	Ac	H	Ac

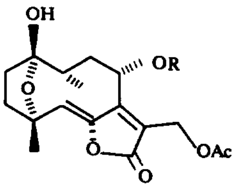


5 R = Meacr

6 R = Tigl

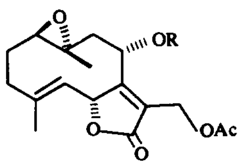


	7	8	9
R	Ac	H	Ac
R′	Ac	H	H



10 R = Meacr

11 R = Tigl



12

---

*Part 404 in the series "Naturally Occurring Terpene Derivatives". For Part 403 see Rustaiyan, A., Niknejad, A., Nazarians, L., Jakupovic, J. and Bohlmann, F. (1982) *Phytochemistry* **21** (in press).

Table 1. ^{1}H NMR spectral data of compounds **5**, **6**, **8** and **9** (400 MHz, CDCl$_3$, TMS as int. standard)

	5	C_6D_6	**6**	C_6D_6	**8**	**9**
H-2	2.70 *ddd* 2.64 *ddd*	1.90 *m*	2.70 *ddd* 2.64 *ddd*	1.90 *m*	3.72 *ddd* 2.58 *m*	3.70 *ddd* 2.58 *m*
H-3	2.30 *ddd* 1.73 *ddd*	1.41 *m*	2.30 *ddd* 1.73 *ddd*	1.41 *m*	2.2–2.0 *m*	2.35 *m*
H-5	2.57 *d*	2.36 *d*	2.58 *d*	2.36 *d*	5.42 *ddq*	5.48 *ddq*
H-6	4.90*m*	4.74 *d*	4.90 *m*	4.79 *d*	5.89 *br d*	5.84 *br d*
H-8		4.84 *dd*		4.88 *dd*	4.81 *dd*	4.80 *dd*
H-9	2.55 *ddd*	2.04 *ddd*	2.68 *m*	2.14 *m*	2.75 *dd*	2.65 *dd*
H-9′	2.21 *ddd*	1.81 *ddd*	2.21 *ddd*	1.81 *ddd*	2.32 *dd*	2.52 *dd*
H-10	2.96 *ddq*	2.39 *ddq*	2.80 *ddq*	2.39 *ddq*	—	—
H-13	4.90 *m*	4.98 *d*	4.86 *s*	4.99 *d*	4.45 *br s*	5.08 *d*
H-13′		4.88 *d*		4.92 *d*		4.62 *dd*
H-14	1.15 *d*	0.64 *d*	1.14 *d*	0.66 *d*	1.27 *s*	1.30 *s*
H-15	1.62 *s*	1.34 *s*	1.62 *s*	1.36 *s*	1.92 *br s*	1.92 *br s*
OCOR	6.12 *br s*	6.08 *br s*	6.87 *br q*	6.84 *br q*	6.10 *br s*	6.10 *br s*
	5.68 *dq*	5.21 *dq*	1.82 *br d*	1.74 *br d*	5.62 *dq*	5.63 *dq*
	1.92 *dd*	1.76 *dd*	1.81 *br s*	1.71 *brs*	1.91 *dd*	1.91 *dd*
OAc	2.07 *s*	1.68 *s*	2.06 *s*	1.66 *s*	—	2.13 *s*

J(Hz): Compounds **5** and **6**: 2, 2′ = 15; 2, 3 = 5; 2, 3′ = 9; 2′, 3 = 6; 2′, 3′ = 5; 3, 3′ = 13; 5, 6 = 9; 8, 9 = 4; 9, 10 = 11; 9′, 10 = 2.5; 9, 9′ = 16; 10, 14 = 7; 13, 13′ = 12.5; compounds **8** and **9**: 2, 2′ = 18; 2, 3 = 7; 3, 5 = 1; 5, 6 = 10;, 5, 15 = 1; 6, 13 = 6, 15 = 1; 8, 9 = 5; 8, 9′ = 9; 9, 9′ = 14; 13, 13′ = 13; OMeacr: 3′, 3′ = 3′, 4′ = 1; OTigl: 3′, 4 = 7.

The minor compounds were the known hirsutinolides **10**[1] and **11**[2] as well as the epoxides **1**–**4**. Their ^{1}H NMR spectra (Table 2) showed that these lactones were closely related to confertolide[3]. Again the typical signals of the methacrylate and tiglate residues showed that **1** and **3** only differed in the nature of the ester groups, which had to be placed at C–8, since the chemical shift of H–13 was the same as in confertolide. The free hydroxyl at C–1 clearly followed from the chemical shift of the corresponding proton, which only showed a broadened singlet, indicating a stereochemistry and a conformation, where the vicinal couplings were all small. Since the H–8 signal was at lower field, as found in **5**, a deshielding

Table 2. ^{1}H NMR spectral data of compounds **1**–**4** (400 MHz, CDCl$_3$, TMS as int. standard)

	1	**2**	**3**	**4**
H-1	4.11 *br s*	5.26 *br s*	4.11 *br s*	5.26 *br s*
H-2	2.22 *m*	2.24 *dddd*	2.22 *m*	2.24 *m*
H-5	2.85 *d*	2.83 *d*	2.85 *d*	2.83 *d*
H-6	4.92 *d*	4.98 *d*	4.92 *d*	4.98 *d*
H-8	5.36 *br d*	5.34 *br d*	5.35 *br d*	5.33 *br d*
H-9	2.16 *m**	2.1 *m**	2.16 *m**	2.2 *m**
H-9′	1.70 *m*†	1.7 *m*†	1.70 *m*†	1.7 *m*†
H-10	2.00 *m*	2.1 *m*	2.00 *m*	2.1 *m*
H-13	4.86 *d*	4.83 *br s*	4.86 *d*	4.82 *br s*
H-13′	4.82		4.82 d	
H-14	1.73 *s*	1.83 *s*	1.73 *s*	1.82 *s*
H-15	0.97 *d*	0.96 *d*	0.96*d*	0.95 *d*
OCOR	6.18 *br s*	6.17 *br s*	6.94 *br q*	6.93 *br q*
	5.71 *dq*	5.70 *dq*	1.85 *br d*	1.83 *br s*
	1.96 *dd*	1.95 *dd*	1.84 *br s*	
OAc	2.04	2.09 *s* 2.04 *s*	2.02 *s*	

*Overlapping with H–2′:
†Overlapping with H–3.
J(Hz): 5, 6 = 9; 8, 9 = 8.5; 10, 14 = 6.5; 13, 13′ = 12; OMeacr: 3′, 3′ = 3′, 4 = 1; OTigl: 3′, 4′ = 7.

effect of the hydroxy group had to be assumed and consequently a C–1α-hydroxyl group was present. This also had a deshielding effect on H–15, which allowed a decision concerning the preferred conformation with H–15 and the C–1 hydroxyl above the plane. The observed couplings of H–8 supported this assumption, $J_{8,9\alpha}$ being large and $J_{8,9\beta}$ very small, as the angle is nearly 90°. Consequently **1** was 1,8-*O*-bis-desacetyl confertolide-8-*O*-methacrylate. The ^{1}H NMR spectral data of **2** and **4** (Table 2) showed that in these lactones the C–1 hydroxyl group was acetylated, as the H–1 signal was drastically shifted downfield. The roots gave lupeyl acetate, germacrene D, and also **1**, **5** and **6**. The aerial parts of *Stilpnopappus pickelii* Mattf. afforded germacrene D, bicyclogermacrene, fatty acid glycerides and again the lactones **5** and **6**. The aerial parts of *Stilpnopappus glomeratus* gave germacrene D, bicyclogermacrene, α-humulene, squalene and the lactones **7** and **8**. The ^{1}H NMR spectral data of **7** were identical with those of glaucolide A[4], while those of **8** were typically different (Table 1), though the splitting of the signals was similar to those of **7**. The molecular formula, as well as the ^{1}H NMR spectrum, indicated that only one ester group was present, which again was methacrylate as indicated by the typical ^{1}H NMR signals. The presence of a free hydroxyl at C–13 was indicated by the chemical shift of H–13 and confirmed by partial acetylation, which led to **9**. The ^{1}H NMR spectral data of the latter (Table 1) further supported the proposed structure of **8**. The free hydroxyl group at C–10 was indicated by the downfield shift of H–2. Consequently **8** was 10,13-bis-desacetylglaucolide A.

The roots afforded traces of tridecapentaynene, trideca-1,11-diene-3,5,7,9-tetrayne, lupeol and lupeyl acetate.

The aerial parts of *Stilpnopappus trichospiroides* gave germacrene D, bicyclogermacrene, α-humelene, lupeyl acetate, fatty acid glycerides and **2**. The chemistry of the genus *Stilpnopappus* so far looks very uniform, all sesquiterpene lactones being closely related. As pointed out earlier[1], marginatin (**12**)[5] and the corresponding methacrylate are the most likely common precusors of all lactones isolated. A close relationship of the genus *Stilpnopappus* to *Vernonia* therefore seems very likely and this genus should be placed in the subtribe Vernoniinae as also follows from taxonomic considerations.

EXPERIMENTAL

Air dried plant material, collected in north-eastern Brazil was extracted with Et_2O–petrol (1:2) and the resulting extracts were separated by CC (Si gel) and further by repeated TLC (Si gel). Known compounds were identified comparing the ^{1}H NMR spectra with those of authentic material. Vouchers are deposited in the U.S. National Herbarium, Washington.

Stilpnopappus tomentosus *Mart. in DC* (*voucher RMK* 8642). The aerial parts (100 g) afforded 5 mg germacrene D, 3 mg bicyclogermacrene, 8 mg caryophyllene, 5 mg stigmasterol, 30 mg linolenic acid, 10 mg fatty acid glycerides, 7 mg **1**, 5 mg **2**, 2 mg **3**, 1 mg **4**, 8 mg **5**, 10 mg **6**, 1 mg **10** and 1 mg **11** (lactones were separated by repeated TLC, Et_2O–petrol, 3:1, and reversed phase HPLC, MeOH–H_2O, 3:2), The roots (20 g) gave 15 mg lupeyl acetate, 2 mg germacrene D, 2 mg **1**, 1 mg **5** and 2 mg **6**.

Stilpnopappus pickelii *Mattf.* (*voucher RMK* 8785). The aerial parts (80 g) gave 5 mg germacrene D, 5 mg bicyclogermacrene, 30 mg fatty acid glycerides, 3 mg **5** and 0.8 mg **6**.

Stilpnopappus glomeratus *Gardn.* (*voucher RMK* 8876). The aerial parts (350 g) afforded 5 mg squalene, 10 mg germacrene D, 10 mg bicyclogermacrene, 10 mg α-humulene, 100 mg **7** and 3 mg **8** (Et_2O–petrol, 3:1, several developments), while the roots (40 g) gave traces of tridecapentaynene, 1 mg trideca-1,11-diene-3,5,7,9-tetrayne, 100 mg lupeyl acetate and 20 mg lupeol.

Stilpnopappus trichospiroides *Mart.* (*voucher RMK* 8791). The aerial parts (300 g) afforded 5 mg germacrene D, 10 mg bicyclogermacrene, 2 mg α-humulene, 30 mg lupeyl acetate and 20 mg **2**.

1,8-O-*Bisdesacetyl confertolide*-8-O-*methacrylate* (**1**). Colourless gum, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 1765 (lactone), 1735, 1230 (OAc), 1710, 1640 (C=CCO_2R); MS *m/z* (rel. int.): 408.178 $[M]^+$(1)($C_{21}H_{28}O_8$), 390 $[M-H_2O]^+$ (3), 378 $[M-CH_2O]^+$(1), 293 $[378-OCOR]^+$ (2), 251 $[293-\text{ketene}]^+$(72), 233 $[293-HOAc]^+$(6), 215 $[233-H_2O]^+$(5), 69 $[C_3H_5CO]^+$ (100).

$$[\alpha]_{24^\circ}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{-35 \quad -38 \quad -43 \quad -61} \quad (\text{CHCl}_3;\, c0.3).$$

8-O-*Desacetyl confertolide*-8-O-*methacrylate* (**2**. Colourless gum, IR$\nu_{max}^{CCl_4}$ cm^{-1}: 1790 (lactone), 1740, 1259 (OAc), 1720(C = CCO_2R); MS *m/z* (rel. int.): 390.168 $[M-HOAc]^+$ (2)($C_{21}H_{26}O_7$), 330$[390-HOAc]^+$(1), 244 $[330-HO_2CR]^+$ (16), 69 $[C_4H_7CO]^+$ (100).

1, 8-O-*Bis-desacetyl confertolide*-8-O-*tiglate* (**3**). Colourless gum, IR$\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 1765 (lactone), 1740 (OAc), 1715 (C=CCO_2R); MS *m/z* (rel. int.): 422.194 $[M]^+$ (1)($C_{22}H_{30}O_8$), 404 $[M-H_2O]^+$ (2), 83 $[C_4H_7CO]^+$ (100).

8-O-*Desacetyl confertolide*-8-O-*tiglate* (**4**). Colourless gum, IR$\nu_{max}^{CCl_4}$ cm^{-1}: 1720 (lactone), 1740 (OAc), 1720 (C=CCO_2R); MS *m/z* (rel. int.): 464 $[M]^+$ (0.1), 404.184 $[M-HOAc]^+$ (1)($C_{22}H_{28}O_7$), 344 $[404-HOAc]^+$ (1), 244 $[344-HO_2CR]^+$ (8), 83 $[C_4H_7CO]^+$ (100).

Stilpnotomentolide-8-O-*methacrylate* (**5**). Colourless gum, IR$\nu_{max}^{CCl_4}$ cm^{-1}: 1790 (lactone), 1760 (OAc), 1730, 1650 (C=CCO_2R); MS *m/z* (rel. int.): 406.163 $[M]^+$ (1)($C_{21}H_{26}O_8$), 346 $[M-HOAc]^+$ (1), 260 $[346-HO_2CR]^+$ (14), 69 $[C_3H_5CO]^+$ (100).

$$[\alpha]_{24^\circ}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{-16 \quad -17 \quad -20 \quad -28} \quad (\text{CHCl}_3;\, c0.27).$$

Stilpnotomentolide-8-O-*tiglate* (**6**). Colourless gum, IR$\nu_{max}^{CHCl_3}$ cm^{-1}: 1770 (lactone), 1735, 1235 (OAc), 1710, 1645 (C=CCO_2R); MS *m/z* (rel. int.): 420.178 $[M]^+$ (1.5)($C_{22}H_{28}O_8$), 360$[M-HOAc]^+$ (1), 260 $(360-HO_2CR]^+$ (6), 83 $[C_4H_7CO]^+$ (100), 55 $[83-CO]^+$ (61).

10,13-O-*Bis-acetyl glaucolide A* (**8**). Colourless gum, IR$\nu_{max}^{CCl_4}$ cm^{-1}: 3420 (OH), 1760 (lactone), 1740 (C=O), 1720 (C=CCO_2R); MS *m/z* (rel. int.): 364.152 $[M]^+$ (0.5)($C_{19}H_{24}O_7$), 346 $[364-H_2O]^+$ (4), 318 $[346-CO]^+$ (11), 260 $[348-HO_2CR]^+$ (28), 232 $[260-CO]^+$ (48), 69 $[C_3H_5CO]^+$ (100).

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

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

REFERENCES

1. Bohlmann, F., Brindöpke, G. and Rastogi, R. C. (1978) *Phytochemistry* **17**, 475.
2. Cowell, P. L., Cassady, J. M., Chang, Ch. and Kozlowski, J. F. (1981) *J. Org. Chem.* **46**, 1108.
3. Toubiana, R., Toubiana, M. J., Tori, K. and Kuriyama, K. (1974) *Tetrahedron Letters* 1753.
4. Padolina, W. G., Yoshioka, H., Nakatani, N., Mabry, T. J., Monti, S. A., Davis, R. E., Cox, G. A., Sim, A., Watson, W. H. and Beth, W. I. (1974) *Tetrahedron* **30**, 1161.
5. Padolina W. G., Nakatani, N., Yoshioka, H., Mabry T. J. and Monti, S. A. (1974) *Phytochemistry* **13**, 2225.