Phytochemistry, Vol. 24, No. 3, pp. 505–509, 1985.
Printed in Great Britain.

0031–9422/85 $3.00 + 0.00

CUAUTHEMONE SESQUITERPENOIDS FROM *BLUMEA ALATA*

FERDINAND BOHLMANN, MICHAEL WALLMEYER, JASMIN JAKUPOVIC, THOMAS GERKE, 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, Washington, DC 20560, U.S.A.

(*Received* 11 *April* 1984)

Key Word Index—*Blumea* spp.; *Pterocaulon virgatum*; Compositae; Inuleae; sesquiterpenes; cuauthemone derivatives; thymol derivatives; himachalane derivatives; eremophilane derivative.

Abstract—The investigation of five *Blumea* species afforded, in addition to known compounds, several cuauthemone derivatives, most of them being 7,11-epoxides, some thymol derivatives, an eremophilane epoxide and a himachalane diol. From *Pterocaulon virgatum* a further himachalane derivative was isolated. The structures were elucidated by spectroscopic methods and in part by partial synthesis.

INTRODUCTION

The large genus *Blumea* (Compositae, tribe Inuleae) is placed in the *Pluchea* group [1]. So far, only limited results on the chemistry are available. In addition to tridecapentaynene and the corresponding thiophenes [2], mainly monoterpenes [3–6], some flavones [7] and coniferyl diangelate [8] have been isolated. We have now studied five species as well as one *Pterocaulon* species. The results are discussed in this paper.

RESULTS AND DISCUSSION

The aerial parts of *Blumea alata* (D. Don.) DC. afforded, in addition to α-humulene, caryophyllene and squalene, minute amounts of the cuauthemone derivatives **1–4**, **6**, **7** and **9**. The ^{1}H NMR spectrum (Table 1) of **9** was close to that of **8** [9–11]. However, the nature of the ester residue was different as followed from the ^{1}H NMR signals. The changed signals (5.09 *q*, 1.30 *d*, 1.34 *s*, 1.98 *s*) indicated the presence of an ester residue,

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

	1	2	3	4	4 (C_6D_6)	5	6	7	9
H-1α	1.63 *ddd*	1.67 *ddd*	1.66 *ddd*	1.58 *ddd*	1.42 *ddd*	1.55 *ddd*	*	1.63 *ddd*	
H-1β	1.39 *ddd*	1.43 *ddd*	1.40 *ddd*	1.39 *ddd*	0.82 *ddd*	1.39 *ddd*	1.26 *m*	1.32 *ddd*	
H-2α	2.0 *m*	2.0 *m*	1.97 *m*	2.02 *dddd*	1.84 *dddd*	2.01 *dddd*	*	2.07 *dddd*	
H-2β	1.89 *dddd*	1.82 *dddd*	1.90 *dddd*	1.82 *dddd*	1.29 *dddd*	1.79 *dddd*	1.80 *dddd*	1.88 *dddd*	
H-3β	4.96 *dd*	5.89 *dd*	4.96 *dd*	5.90 *dd*	6.01 *dd*	5.88 *dd*	5.83 *dd*	5.90 *dd*	5.87 *dd*
H-5α	2.0 *m*	2.40 *dd*	2.12 *dd*†	2.33 *m*	1.95 *dd*	2.49 *dd*	2.89 *dd*	3.07 *d*	
H-6α	2.20 *dd*	2.35 *m*	2.19 *dd*†	2.11 *m*	2.28 *dd*	2.08 *dd*	2.21 *dd*	7.17 *d*	2.89 *br d*
H-6β	2.0 *m*	2.0 *m*	2.14 *dd*†		1.87 *dd*	2.15 *dd*	*		2.1 *m*
H-9α	2.08 *d*	1.82 *d*	2.16 *d*	2.17 *br d*	1.90 *br d*	2.09 *d*	2.84 *d*	2.31 *s*	2.18 *d*
H-9β	2.36 *d*	2.36 *d*	2.37 *d*	2.35 *d*	2.15 *d*	2.16 *d*	*		2.24 *d*
H-12	1.20 *s*	1.23 *s*	1.25 *s*	1.24 *s*	1.09 *s*	1.35 *s*	1.90 *br s*	1.48 *s*	1.85 *s*
H-13	1.44 *s*	1.47 *s*	1.45 *s*	1.48 *s*	1.24 *s*	1.44 *s*	5.19 *br s* 5.18 *br s*	1.53 *s*	2.06 *s*
H-14	1.03 *s*	1.09 *s*	1.03 *s*	1.06 *br s*	0.57 *br s*	1.09 *s*	0.97 *s*	1.01 *s*	0.97 *s*
H-15	1.24 *s*	1.57 *s*	1.22 *s*	1.57 *s*	1.16 *s*	1.59 *s*	1.53 *s*	1.61 *s*	1.58 *s*
OAc	—	1.92 *s*	—	1.96 *s*	1.62 *s*	1.96 *s*	1.93 *s*	1.98 *s*	1.96, 1.98 *s*
OCOR	6.15 *qq*	6.13 *qq*	3.11 *qq*	3.09 *q*	2.55 *q*	3.07 *q*	6.12 *qq*	6.08 *qq*	5.09 *q*
	2.04 *dq*	2.04 *dq*	1.33 *d*	1.34 *d*	1.18 *d*	1.31 *d*	2.05 *dq*	2.01 *dq*	1.30 *d*
	1.96 *dq*	1.92 *dq*	1.63 *s*	1.54 *s*	1.38 *s*	1.56 *s*	1.95 *dq*	1.91 *dq*	1.34 *s*
OOH	—	—	—	—	—	—	8.05 *s*	7.79 *s*	

*Overlapped multiplets.

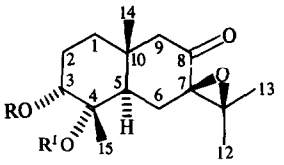
†Not first order.

J (Hz): 1α, 2α = 3; 1α, 2β = 14; 1β, 2α = 3; 1β, 2β = 3; 2α, 2β = 16; 2α, 3β = 3.5; 2β, 3β = 2; 5α, 6α = 3; 5α, 6β = 13; 6α, 6β = 14; 9α, 9β = 13.5; 9α, 14 ~ 1; compound **5**: 5α, 6α = 5; 6α, 6β = 12; compound **7**: 5α, 6 = 2; compound **9**: 2α, 3 = 3.5; 2β, 3 = 3; 6, 6′ = 13; 9, 9′ = 15; 3′, 4′ = 6; OAng: 3′, 4′ = 7; 3′, 5′ = 4′, 5′ = 1.5; OEpang: 3′, 4′ = 5.5.

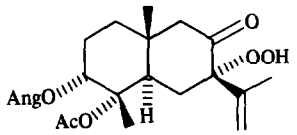
where the epoxyangelate was opened by acetic acid. The mass spectrum only showed a fragment at *m/z* 392 ($C_{22}H_{32}O_6$) which was formed by loss of acetic acid. However, by chemical ionization a weak $[M+1]^+$ peak (*m/z* 453) was observed.

The ^{1}H NMR spectrum of **4** (Table 1), molecular formula $C_{22}H_{32}O_7$, clearly showed that an acetate and an epoxyangelate residue were present. Many signals were again similar to those of **8**. However, the signals of the olefinic methyls were replaced by two singlets at δ 1.24 and 1.48. As followed from the molecular formula, **4** had one more oxygen, compared with **8**. Thus the presence of a 7,11-epoxide was very likely. All data including ^{13}C NMR (see Experimental) agreed with this assumption. To establish the structure and to determine the stereochemistry at C-7, we transformed **8** to **4** by reaction with hydrogen peroxide in the presence of sodium hydroxide. In addition to **4**, the epimeric epoxide **5** was obtained. When the ^{1}H NMR spectra (Table 1) of **4** and **5** were compared, the shift differences for H-5 and H-12 indicated the proposed assignment of the configurations at C-7 and C-11. While in $CDCl_3$ some signals were not first order, in deuteriobenzene all the signals of **4** could be assigned. Clear NOEs between H-14 and H-15 also allowed us to differentiate between the methyl singlets since H-15 also showed a NOE with H-3β. The fact that **5** was the main product supported the proposed configuration since the β-methyl groups surely favour attack from the α-side.

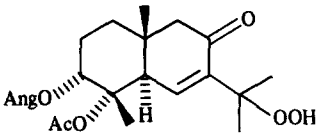
The ^{1}H NMR spectrum of **3** (Table 1) showed that it



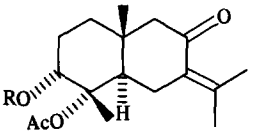
	1	2	3	4	5
R	Ang		Epang		Epang
R^1	H	Ac	H	Ac	Ac (α-epoxide)



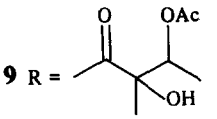
6



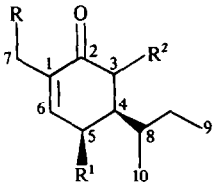
7



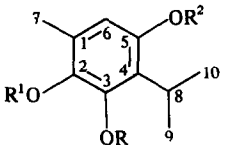
8 R = Epang



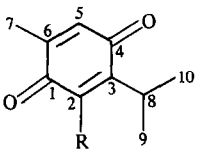
9 R =



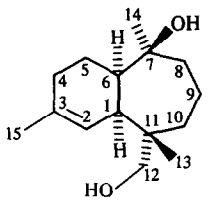
10 R = OAng, R^1 = OH, R^2 = H
11 R = R^1 = H, R^2 = OAng



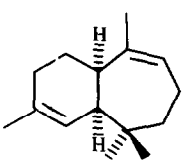
	12	13	14	15	16
R	H	H	Ac	Ac	Ac
R^1	H	Ac	H	Ac	Ac
R^2	Ac	H	Ac	H	Ac



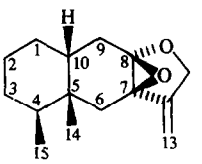
17 R = H
18 R = OAc



19



20



21

was the desacetyl derivative of **4**. Accordingly, the H-15 signal was shifted upfield. The ^{1}H NMR spectra of **1** and **2** (Table 1) clearly showed that we were dealing with the corresponding angelates. The spectra therefore only differed from those of **3** and **4** by the signals of the ester residue.

The ^{1}H NMR spectra of **6** and **7** (Table 1) indicated the presence of hydroperoxides by the low-field singlets (δ7.79 and 8.05, respectively). While **6** had an isopropenyl side chain, **7** was a conjugated ketone with a low-field doublet at δ7.17 for H-6, as followed from spin decoupling. From the chemical shift of two methyl singlets, the position of the hydroperoxide group was deduced. As in both cases most of the other signals were close to those of **8**, the structures of these ketones were established. The low-field shift of H-5 in the spectrum of **6** further showed that the 7α-hydroperoxide was present. Most likely **6** and **7** were formed by reaction of **8** with oxygen, though **8** itself was not isolated from this species. The roots gave tridecapentaynene, α-humulene, thymohydroquinone dimethyl ether and **11** [12].

The aerial parts of *B. mollis* (D. Don.) Merrill gave limonene, α- and β-farnesene, eugenol and **10**, the ^{1}H NMR spectrum of which (see Experimental) was in part similar to that of **11**. However, the olefinic methyl signal was replaced by a pair of signals at δ4.92 and 4.86 and H-5 was a broad double-doublet at δ4.55 indicating a free hydroxyl at C-5. Thus the angelate was at C-7. The $J_{4,5}$ coupling showed that these hydrogens were *cis* to each other. The roots of *B. viscosa* (H.B.K.) Badillo gave α-humulene, thymohydroquinone dimethyl ether and coniferyl diangelate [8].

The aerial parts of *B. gariepina* DC. afforded isocomene [13], β-isocomene [14], silphinene [14], modhephene [14], thymol, its acetate, large amounts of thymoquinone (**17**), the corresponding acetoxy derivative **18** as well as the phenolic compounds **12**–**14** and the diol **19**. The structure of **18** was established by synthesis. Fries reaction of **17** gave in addition to the isomeric 2,5,6-triacetate the desired triacetate **16**, which was transformed by hydrolysis, air oxidation and acetylation to **18**. The relative positions of the oxygen functions in **12**–**14** were deduced by spin decoupling, which showed the presence of a coupling between H-6 and H-7.

The relative position of the acetoxy group in **12** could also be confirmed by NOE difference spectroscopy. Clear NOEs were obtained between H-7 and H-6, between the acetate methyl and H-6 and H-8, as well as between the hydroxyl and H-8. As hydrogenation of **18** afforded a diol which was different from **13**, the structure of this acetate was also established. Again the NOEs agreed with this structure.

For comparison, **16** was transformed by partial saponification to **15**, where the relative position of the oxygen functions again was established by the NOEs. When the ^{1}H NMR signals of **14** were compared with those of **15**, the shift difference of H-7 indicated a free hydroxyl group at C-2, and that of H-6 an acetate group at C-5.

The structure of **19** was deduced from the ^{1}H NMR spectrum (see Experimental) which was close to that of himachalol, the 12-desoxy derivative of **19**. Most signals could be assigned by spin decoupling. The presence of an 11α-methylol group was deduced from the downfield shift of H-6 on comparison with that of himachalol [15, 16], and the *cis*-anellation followed from the small $J_{1,6}$ coupling as well as from the W-coupling of H-1 with H-5 and from the missing coupling of H-5 with H-6 since only in a *cis*-anellated compound is the angle between these protons nearly 90°.

We isolated a closely related sesquiterpene from the roots of *Pterocaulon virgatum* (L.) DC., also belonging to the tribe Inuleae and to the same subtribe as *Blumea* [1], together with thiophene acetylenes. Careful ^{1}H NMR investigations led to structure **20**, which we have named γ-himachalene as only the position of the Δ^7-double bond differed from the known α- and β-isomer [15, 16]. Spin decoupling allowed us to assign the complete sequence and therefore the seven-membered ring could be closed by the quaternary carbon (C-11). *cis*-Anellation again followed from the $J_{1,6}$ coupling.

From the aerial parts of a further *Blumea* species, which was collected in Transvaal, but so far has not been named, the eremophilane derivative **21** was isolated in addition to germacrene D. High-resolution mass spectroscopy gave the molecular formula $C_{15}H_{22}O_2$ while the ^{1}H NMR spectrum (see Experimental) showed the presence of two methyl groups, one tertiary (0.98 *s*) and one secondary (0.78 *d*), two exomethylene protons and a methylene attached to oxygen, as followed from the chemical shifts. Spin decoupling indicated that the latter showed allylic couplings with the olefinic protons. Furthermore, a pair of doublets at δ2.07 and 1.83 (in deuteriobenzene, in $CDCl_3$ 1.97 *s*) required an isolated methylene group while a pair of double-doublets had to be assigned to H-9, from the results of spin decoupling. Thus the only possible structure was **21**. The configurations at C-4 and C-10 were deduced from the couplings while the presence of a β-epoxide followed from the downfield shift of H-10 (δ2.27 *dddd*), which would not agree with an α-epoxide. The fragmentation pattern in the mass spectrum also supported the proposed structure of **21**. The base peak was *m/z* 124 (C_9H_{16}) obviously formed by the splitting of the 5, 6 and the 8, 9 bonds while *m/z* 111 ($C_6H_7O_2$) was the counterpart.

The chemistry of the genus *Blumea* shows some relationship to *Pluchea* in the co-occurrence of the acetylenic compounds, the cuauthemone and thymol derivatives as well as **10** [12], though the results obtained so far do not show a very uniform picture. Obviously more species have to be studied.

EXPERIMENTAL

The air-dried plant material was worked-up in the usual way [17]. The aerial parts (20 g) of *Blumea alata* (voucher 81/25, collected in Transvaal; all vouchers have been deposited at the Herbarium of the Botanic Research Institute, Pretoria) gave CC (SiO_2) fractions as follows: 1 (petrol), 2 (Et_2O) and 3 (Et_2O–MeOH, 9:1). TLC (SiO_2 PF 254) of fraction 1 (petrol) gave 8 mg α-humulene and 5 mg caryophyllene. TLC of fraction 2 (Et_2O–petrol; 1:1, 2 developments) gave 8 mg **2** (R_f 0.42) and 12 mg **4** (R_f 0.36). TLC of fraction 3 (Et_2O–petrol, 9:1) gave a mixture, which was further separated by HPLC (RP 8, MeOH–H_2O, 7:3, *ca* 100 bar and flow rate, 3 min) affording 3 mg **1** (R_t 9 min), 2 mg **3** (R_t 7.5 min), 1 mg **9** (R_t 4.8 min) and a mixture of **6** and **7** (R_t 3.5 min) which was separated by TLC (Et_2O) giving 1 mg **6** (R_f 0.35) and 2 mg **7** (R_f 0.30)

The roots (20 g) gave, on TLC (Et_2O–petrol, 1:9), 15 mg α-humulene, 3 mg trideca-3,5,7,9-pentayn-1-ene, 15 mg thymohydroquinone dimethyl ether and 2 mg **11**.

The aerial parts (40 g) of *Blumea mollis* (collected in Transvaal, voucher 81/278) gave CC fractions as follows: 1 (petrol), 2

(Et_2O–petrol, 1:9) and 3 (Et_2O). TLC of fraction 1 (petrol) gave 12 mg α- and 5 mg β-farnesene and 10 mg limonene. TLC of fraction 2 (Et_2O–petrol, 1:9) afforded 5 mg eugenol and TLC of fraction 3 (Et_2O) gave 2 mg **10** (R_f 0.57).

The roots (13 g) of *Blumea viscosa* (collected in Guatemala, voucher RMK 7364, deposited at the U.S. National Herbarium, Washington) gave, on TLC (Et_2O–petrol, 1:10), 7 mg α-humulene, 25 mg thymohydroquinone dimethyl ether and 2 mg coniferyl diangelate.

The aerial parts (320 g) of *Blumea gariepina* (collected in Transvaal, vouchers 81/71 and 81/214) gave CC fractions as follows: 1 (petrol), 2 (Et_2O–petrol, 1:9), 3 (Et_2O–petrol, 1:1) and 4 (Et_2O and Et_2O–MeOH, 9:1). TLC of fraction 1 (petrol) and GC/MS gave 20 mg caryophyllene, *ca* 10 mg isocomene, 10 mg β-isocomene, 10 mg silphinene and 10 mg modhephene (calc. from the ^1H NMR spectrum of the mixture). TLC of fraction 2 (Et_2O–petrol, 1:3) gave 5 mg thymol acetate, 5 mg thymol and 300 mg thymoquinone. TLC of fraction 3 (Et_2O–petrol, 2:3) gave 3 mg **18** (R_f 0.48) and TLC of fraction 4 (Et_2O–petrol, 7:3) afforded 1 mg **14** (R_f 0.55), 2 mg **12** (R_f 0.45), 2 mg **13** (R_f 0.42) and 1 mg **19** (R_f 0.25).

The roots (20 g) of *Pterocaulon virgatum* (collected in Brazil, province Bahia, voucher RMK 8961, deposited at the U.S. National Herbarium, Washington) gave, on TLC (Et_2O–petrol, 1:20), 3 mg 2-pentadiinyl-5-[but-3-in-1-en-4-yl]thiophene, 10 mg 2-propinyl-5-[hexa-3,5-diin-1-en-6-yl]thiophene, 18 mg thymohydroquinone dimethyl ether and a mixture of hydrocarbons, which were separated by TLC ($AgNO_3$-coated SiO_2, Et_2O–petrol, 1:30) affording 2 mg γ-humulene, 1 mg β-bisabolene and 9 mg **20** (R_f 0.42).

The aerial parts (15 g) of a *Blumea* species (collected in Transvaal, voucher 81/253) gave, on TLC (Et_2O–petrol, 3:7), 1 mg germacrene D and 1 mg **21** (R_f 0.34). From the extract of 2 g roots, also 1 mg **21** was obtained.

Known compounds were identified by comparison of the 400 MHz ^1H NMR spectra with those of authentic compounds and by co-TLC.

7β,11-Epoxycuauthemone 3-O-*angelate* (**1**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3580 (OH), 1720 (C=O, C=CCO_2R); MS *m/z* (rel. int.): 350.209 $[M]^+$ (38) (calc. for $C_{20}H_{30}O_5$: 350.209), 335 $[M-Me]^+$ (17), 250 $[M-RCO_2H]^+$ (5), 232 $[250-H_2O]^+$ (38), 83 $[C_4H_7CO]^+$ (100), 55 $[83-CO]^+$ (94).

4-O-*Acetyl-7β,11-epoxycuauthemone* 3-O-*angelate* (**2**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1745, 1245 (OAc), 1720 (C=O, C=CCO_2R); MS *m/z* (rel. int.): 392.220 $[M]^+$ (3) (calc. for $C_{22}H_{32}O_6$: 392.220), 332 $[M-HOAc]^+$ (1.5), 317 $[332-Me]^+$ (1), 232 $[332-RCO_2H]^+$ (100), 83 $[C_4H_7CO]^+$ (61), 55 $[83-CO]^+$ (75).

7β,11-Epoxycuauthemone 3-O-*epoxyangelate* (**3**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3580 (OH), 1730 (C=O, C=CCO_2R); MS *m/z* (rel. int.): 366.204 $[M]^+$ (88) (calc. for $C_{20}H_{30}O_6$: 366.204), 351 $[M-Me]^+$ (52), 250 $[M-RCO_2H]^+$ (10), 232 $[250-H_2O]^+$ (100).

4-O-*Acetyl-7β,11-epoxycuauthemone* 3-O-*epoxyangelate* (**4**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1745, 1245 (OAc), 1730 (C=O, CO_2R); MS *m/z* (rel. int.): 308.215 $[M]^+$ (4) (calc. for $C_{22}H_{32}O_7$: 408.215), 348 $[M-HOAc]^+$ (1), 232 $[348-RCO_2H]^+$ (100), 217 $[232-Me]^+$ (6); ^{13}C NMR ($CDCl_3$, C-1–C-15): 33.4 *t*, 26.8 *t*, 71.6 *d*, 82.7 *s*, 46.8 *d*, 23.1 *t*, 70.2 *s*, 204.8 *s*, 60.1 *t*, 38.3 *s*, 63.1 *s*, 19.7 *q*, 19.0 *q*, 19.1 *q*, 17.7 *q*, 168.9 *s* and 21.8 *q* (OAc); 165.9 *s*, 127.9 *s*, 138.0 *d*, 20.6 *q* and 15.7 *q* (OCOR) (quartets assigned by selective decoupling).

To 10 mg **8** in 2 ml MeOH, 1 ml H_2O_2 containing 20 mg NaOH was added at room temp. After 3 hr, TLC (Et_2O–petrol, 3:1) afforded 3 mg **4**, identical with the natural compound (^1H NMR and co-TLC) and 5 mg **5**, colourless gum; ^1H NMR: see Table 1.

4-O-Acetyl-7α-hydroperoxy-11,13-dehydro-7,11-dihydrocuauthemone 3-O-*angelate* (**6**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3500 (OH), 1750 (OAc), 1730 (C=O, CO_2R); MS (CI, *i*-butane) *m/z* (rel. int.): 349 $[M+1-HOAc]^+$ (6), 315 $[349-H_2O_2]^+$ (54), 215 $[315-RCO_2H]^+$ (100).

4-O-Acetyl-11-hydroperoxy-6,7-dehydro-7,11-dihydrocuauthemone 3-O-*angelate* (**7**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3450 (OH), 1750 (OAc), 1730 (CO_2R), 1675 (C=CC=O); MS (CI, *i*-butane) *m/z* (rel. int.): 349 $[M+1-HOAc]^+$ (6), 315 $[349-H_2O_2]^+$ (55), 215 $[315-RCO_2H]^+$ (100).

4-O-Acetyl cuauthemone 3-O-[*2-methyl-2-hydroxy-3-acetoxybutyrate*] (**9**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1740 (CO_2R, OAc), 1690 (C=CC=O); MS *m/z* (rel. int.): 392.220 $[M-HOAc]^+$ (16) (calc. for $C_{22}H_{32}O_6$: 392.220), 216 $[392-RCO_2H]^+$ (100), 201 $[216-Me]^+$ (12); CI (*i*-butane): 453 $[M+1]^+$ (0.5), 393 $[453-HOAc]^+$ (10), 333 $[393-HOAc]^+$ (100).

7-Angeloyloxy-5β-hydroxycarvotacetone (**10**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1720 (C=CCO_2R), 1680 (C=CC=O); MS *m/z* (rel. int.): 248.141 $[M-H_2O]^+$ (7) (calc. for $C_{15}H_{20}O_3$: 248.141), 167 $[M-OCOR]^+$ (5), 166 $[M-RCO_2H]^+$ (15), 149 $[167-H_2O]^+$ (7), 83 $[C_4H_7CO]^+$ (100), 55 $[83-CO]^+$ (97); ^1H NMR ($CDCl_3$): δ2.50 *dd* (H-3), 2.59 *dd* (H-3'), 1.7 *m* (H-4), 4.55 *br dd* (H-5), 6.94 *dt* (H-6), 4.92 *br d* (H-7), 4.86 *dd* (H-7'), 1.83 *m* (H-8), 1.08 *d* (H-9), 1.01 *d* (H-10), 6.12 *qq*, 2.00 *dq* and 1.93 *dq* (OAng) [*J* (Hz): 3, 3' = 16; 3, 4 = 12; 3', 4 = 4.5; 4, 5 = 3; 5, 6 = 5.5; 5, 7 = 6, 7 = 1.5; 7, 7' = 14; 8, 9 = 8, 10 = 6.5].

5-Acetoxy-2-hydroxythymol (**12**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3520 (OH), 1765 (OAc); MS *m/z* (rel. int.): 224.105 $[M]^+$ (18) (calc. for $C_{12}H_{16}O_4$: 224.105), 182 $[M-ketene]^+$ (100); ^1H NMR ($CDCl_3$): 6.33 *s* (H-6), 2.18 *s* (H-7), 3.12 *qq* (H-8), 1.31 *d* (H-9, H-10, *J* = 7 Hz), 2.30 *s* (OAc).

2-Acetoxy-5-hydroxythymol (**13**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3520 (OH), 1765 (OAc); MS *m/z* (rel. int.): 224.105 $[M]^+$ (20) (calc. for $C_{12}H_{16}O_4$: 224.105), 182 $[M-ketene]^+$ (100), 167 $[182-Me]^+$ (74), ^1H NMR ($CDCl_3$): δ6.28 *s* (H-6), 2.11 *s* (H-7), 3.11 *qq* (H-8), 1.29 *d* (H-9, H-10, *J* = 7 Hz), 2.30 (OAc).

5-Acetoxy-2-hydroxythymol acetate (**14**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}. 3500 (OH), 1765 (OAc); MS *m/z* (rel. int.): 266.116 $[M]^+$ (6), (calc. for $C_{14}H_{18}O_5$: 266.115), 224 $[M-ketene]^+$ (25), 187 $[224-ketene]^+$ (100), 167 $[182-Me]^+$ (70); ^1H NMR ($CDCl_3$): 6.45 *s* (H-6), 2.19 *s* (H-7), 3.17 *qq* (H-8), 1.30 *d* (H-9, H-10, *J* = 7 Hz), 5.31 (OH), 2.31 and 2.38 *s* (OAc).

2-Acetoxythymoquinone (**18**). Yellow crystals, mp 30° (Et_2O–petrol); IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1770 (OAc), 1670 (C=CC=O); MS *m/z* (rel. int.): 222.089 $[M]^+$ (5) (calc. for $C_{12}H_{14}O_4$: 222.089), 180 $[M-ketene]^+$ (100), 152 $[180-CO]^+$ (12), 137 $[152-Me]^+$ (9); ^1H NMR ($CDCl_3$): 6.56 *q* (H-5), 2.04 *d* (H-7), 3.12 *qq* (H-8), 1.19 *d* (H-9, H-10), 2.34 *s* (OAc) [*J* (Hz): 6, 7 = 1.5; 8, 9 = 8, 10 = 7]; ^{13}C NMR ($CDCl_3$, C-1–C-10): 186.7 *s*, 148.9 *s*, 140.6 *s*, 180.8 *s*, 134.1 *d*, 143.7 *s*, 15.1 *q*, 25.2 *d*, 20.2 *q*, 20.2 *q*, (20.3 *q*, 168.0 *s*, OAc).

Synthesis of **18**. To 2 g thymoquinone suspended in 5 ml Ac_2O, 0.5 ml $BF_3 \cdot Et_2O$ was added. After stirring for 2 hr, the mixture was heated for 3 hr at 70°. After cooling, 2.7 g **16** and 2,6-diacetoxythymol acetate were obtained. To 1 g of the mixture in 5 ml MeOH, 0.2 ml 1 M NaOH was added. After 3 hr at 20°, usual work-up and TLC (CH_2Cl_2–petrol, 7:3) gave in addition to products of partial hydrolysis 170 mg 3-hydroxythymoquinone, which was heated 2 hr with Ac_2O at 70°, yellow crystals from Et_2O–petrol, mp 30° (**18**). All spectral data were identical to those of the natural product. Among the products of hydrolysis, also 30 mg of **16** were obtained; ^1H NMR ($CDCl_3$): δ6.82 *s* (H-6), 2.14 *s* (H-7), 3.02 *qq* (H-8), 1.21 *d* (H-9, H-10), 2.29 *s*, 2.31 *s* and 2.32 *s* (OAc).

Partial saponification of **16** afforded **15**; ^{1}H NMR ($CDCl_3$): δ6.40 *s* (H-6), 2.05 *s* (H-7), 3.12 *qq* (H-8), 1.25 *d* (H-9, H-10), 2.27 *s* and 2.31 *s* (OAc). Hydrogenation of **18** (Et_2O–Pd–$BaSO_4$) afforded 2,5-dihydroxythymol acetate; ^{1}H NMR ($CDCl_3$): δ6.17 *s* (H-6), 2.04 *s* (H-7), 3.15 *qq* (H-8), 1.32 *d* (H-9, H-10), 2.35 *q* (OAc).

7β,12-Dihydroxyhimachal-2-ene (**19**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3400 (OH); MS (CI, *i*-butane) *m/z* (rel. int.): 221 $[M+1-H_2O]^+$ (100), 203 $[221-H_2O]^+$ (16), 191 $[221-CH_2O]^+$ (29); ^{1}H NMR ($CDCl_3$): 2.56 *br s* (H-1), 5.50 *dtq* (H-2), 2.03 *m* (H-4), 1.96 *ddd* (H-5, H-6), 2.03 *m*, 1.81 *m*, 1.53–1.40 *m* (H-8–H-10), 3.30 *d* (H-12), 3.54 *d* (H-12'), 0.79 *s* (H-13), 1.63 *br s* (H-14), 1.27 *s* (H-15) [*J* (Hz): 1, 2 = 6; 1, 5 = 2.5; 1, 6 ~ 5; 2, 15 = 2, 4 ~ 1.3; 4, 5 = 9; 5, 5' = 14; 12, 12' = 10.5].

γ-Himachalene (**20**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3050, 885 (C=CH_2); MS *m/z* (rel. int.): 204.188 $[M]^+$ (59) (calc. for $C_{15}H_{24}$: 204.188), 189 $[M-Me]^+$ (24), 161 (31), 133 (77), 119 (84), 105 (78), 93 (100), 91 (78); $[\alpha]_D$ −9° ($CHCl_3$; *c* 0.9); ^{1}H NMR ($CDCl_3$): δ2.15 *br s* (H-1), 5.55 *ddq* (H-2), 1.95 *m* (H-4), 1.68 *m* (H-4'), 1.95 *m* (H-5), 1.68 *m* (H-5'), 2.33 *m* (H-6), 5.47 *dtq* (H-8), 2.24 *m* (H-9), 1.88 *m* (H-9'), 1.59 *ddd* (H-10), 1.38 *ddd* (H-10'), 1.05 *s* and 1.00 *s* (H-12, H-13), 1.71 *br s* (H-14), 1.70 *br s* (H-15) [*J* (Hz): 1, 2 = 3.5; 1, 6 ~ 5; 2, 4 = 2, 15 = 6, 8 = 8, 12 = 1.5; 8, 9 = 5; 8, 9' = 6.5; 9, 10 = 4.5; 9', 10 = 7; 9, 10' = 10; 9', 10' = 4; 10, 10' = 13.5].

7β,8β-Epoxy-8α,12-oxido-10βH-eremophil-11(13)-ene (**21**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3050, 890 (C=CH_2); MS *m/z* (rel. int.): 234.162 $[M]^+$ (11) (calc. for $C_{15}H_{22}O_2$: 234.162), 219 $[M-Me]^+$ (5), 124 $[C_9H_{16}]^+$ (100), 111 $[C_6H_7O_2^+]^+$ (58), 109 $[124-Me]^+$ (92); ^{1}H NMR ($CDCl_3$): δ1.59 *m* (H-4), 1.97 *s* (H-6) [C_6D_6 1 83 *d* and 2.07 *d* (*J* = 13.5 Hz)], 2.09 *dd* (H-9), 1.98 *dd* (H-9'), 2.27 *dddd* (H-10), 4.81 *dt* (H-12), 4.75 *dt* (H-12'), 5.11 *t* (H-13), 5.04 *t* (H-13'), 0.82 *s* (H-14), 0.68 *d* (H-15) [*J* (Hz): 1, 10 = 2; 1', 10 = 8; 4, 15 = 7; 9, 9' = 13; 9, 10 = 12; 9', 10 = 5.5; 12, 12' = 12; 12, 13 = 2].

Acknowledgements—We thank Dr. B de Winter and Miss M. Welman, Botanic Research Institute, Pretoria, for their help during plant collection and the Deutsche Forschungsgemeinschaft for financial support.

REFERENCES

1. Merxmüller, H., Leins, P. and Roessler, H. (1977) in *The Biology and Chemistry of the Compositae* (Heywood, V. H., Harborne, J. B. and Turner, B. L., eds.), p. 579. Academic Press, London.
2. Bohlmann, F., Burkhardt, T. and Zdero, C. (1973) *Naturally Occurring Acetylenes*, p. 351. Academic Press, London.
3. Karrer, W. (1958) *Konstitution und Vorkommen der Organischen Pflanzenstoffe*. Birkhäuser, Basel.
4. Trujii, H., Tani, Y. and Ueda, H. (1977) *Nippon Nogei Kagaku Kaishi* 609.
5. Bokadia, K. P., Joshi, S. K. and Bokadia, M. M. (1976) *Acta Cienc. India* **2**, 239.
6. Bohlmann, F., Zdero, C. and Nair, A. G. R. (1979) *Phytochemistry* **18**, 1062.
7. Rao, C., Rao, T. and Muralikrishna, B. (1977) *Planta Med.* 235.
8. Bohlmann, F. and Zdero, C. (1969) *Tetrahedron Letters* 69.
9. Nakanishi, K., Crouch, R., Miura, R., Dominguez, X. A., Zanudio, A. and Villarreal, R. (1974) *J. Am. Chem. Soc.* **96**, 609.
10. Bohlmann, F. and Mahanta, P. K. (1978) *Phytochemistry* **17**, 1189.
11. Dominguez, X. A., Franco, R., Cano, G., Villarreal, R., Bapuji, M. and Bohlmann, F. (1981) *Phytochemistry* **20**, 2297.
12. Bohlmann, F. and Zdero, C. (1976) *Chem. Ber.* **109**, 2653.
13. Zalkow, L. H., Harris, R. N., III, Van Derveer, D. and Bertrand, J. A. (1977) *J. Chem. Soc. Chem. Commun.* 456.
14. Bohlmann, F. and Jakupovic, J. (1980) *Phytochemistry* **19**, 259.
15. Joseph, T. C. and Dev, S. (1968) *Tetrahedron* **24**, 3809.
16. Bisarya, S. C. and Dev, S. (1968) *Tetrahedron* **24**, 3861.
17. Bohlmann, F., Zdero, C., King, R. M. and Robinson, H. (1984) *Phytochemistry* **23**, 1979.