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GLAUCOLIDES AND GUAIANOLIDES FROM *ARTEMISIA AFRA*

J JAKUPOVIC, H KLEMEYER, F BOHLMANN and E H GRAVEN*

Institute for Organic Chemistry, Technical University of Berlin, D-1000 Berlin 12, F R G, *University of Fort Hare, R S A

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Key Word Index—*Artemisia afra*, Compositae, sesquiterpene lactones, guaianolides, glaucolides, cyperone derivative

Abstract—*Artemisia afra* afforded in addition to several known compounds 10 new guaianolides and five glaucolides as well as 12-hydroxy-α-cyperone The structures were elucidated by high field NMR techniques and some chemical transformations.

INTRODUCTION

Artemisia afra is the only species of this genus which occurs in South Africa As it contains a useful essential oil it is cultivated in the Ciskei. Little is known about the non-volatile compounds The roots contain typical acetylenes present also in other *Artemisia* species [1] The aerial parts gave scopoletin [2] and isofraxidin [1]. A reinvestigation afforded many further constituents which are discussed in this paper.

RESULTS AND DISCUSSION

The aerial parts gave α- and β-thujone, camphor, ascaridol, spathulenol, the known guaianolides **1a** [3], **1b** [4], **2a** [5], **2b** [6], **2c** [6], **2d** [5], **2e** [6], **2f** [6], **3a** [7], **3b** [7], **3c** [7], **4a** [7] and **5a** [8] as well as **3d–3j**, **4b**, **5b** and **5c** Furthermore the glaucolides **6**, **7a**, **7b**, **8** and **9** were isolated The roots afforded in addition to the reported acetylenes [1], β-farnesene, α-humulene, squalene, isofraxidin and its β-D-glucopyranoside [9] as well as 12-hydroxy-α-cyperone [10].

The ^{1}H NMR data of **3d** (Table 1) were close to those of **3a–3c** their configuration being established again by NOE difference spectroscopy. The presence of a hydroperoxide group in **3d** led to the expected small shift differences, especially of H-2, H-3 and H-5 Reduction with triphenylphosphine gave **3a**. The ^{1}H NMR spectrum of **3e** (Table 1) clearly showed that the corresponding desacetyl derivative of **3a** was present. Similarly, the data of **3f** indicated the presence of the corresponding bishydroperoxide

The ^{1}H NMR spectra of **3g** and **3h** (Table 1) differed from those of **3b** and **3c** by the downfield shift of H-6 which is typical for 4-*epi* isomers. The relative position of the hydroxy groups followed from the effects of the hydroperoxy group In the case of **3g**, H-9 is shielded by the latter group while in the case of **3h**, H-5 is deshielded. Both lactones were transformed to **3k** by reduction.

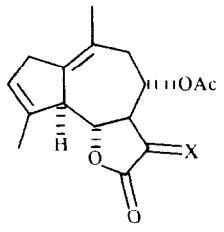
The ^{1}H NMR spectra of **3i** and **3j** (Table 1) indicated the presence of epimeric bishydroperoxides. In the case of **3i**, H-5 is deshielded. Accordingly, this isomer should be the 4α-hydroperoxide.

The ^{1}H NMR spectrum of **4b** (Table 1) was close to that of **4a**. Small shift differences indicated the presence of epimers. This was established by the observed NOEs. While in the case of **4a** a clear effect between H-14 and H-8 was present in **4b** this effect was absent.

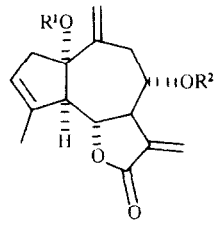
The ^{1}H NMR spectrum of **5b** (Table 1) showed that due to a 10α-hydroperoxide group (δ 8 04 *s*) the signals of H-9α and H-7 were slightly shifted. Reduction of **5b** afforded **5a** The absence of signals for exomethylene protons and a methyl doublet at δ 1 35 indicated that **5c** was the 11β,13-dihydro derivative (Table 1)

The ^{1}H NMR spectrum of **6** (Table 2) indicated the presence of a diacetate of a germacranolide This was supported by spin decoupling which further indicated that one acetoxy group was at C-3 and a second at C-13. No H-7 signal was observed and H-6 displayed a broadened doublet at relatively low field (δ 5 46) A pair of doublets (δ 4 88 and 4 81) indicated that **6** was a glaucolide This was further supported by the presence of homoallylic couplings between H-6 and H-13 Glaucolides so far are only very common in the tribe Vernonieae [10] However, some are reported from a *Cotula* species [11] We have named lactone **6** artemisiaglaucolide. The stereochemistry was established by the observed NOEs between H-14, H-2′ (7%) and H-8′ (5%), between H-15 and H-6 (13%) as well as between H-5 and H-3 (10%). This further indicated that in the preferred conformation the methyls at C-4 and C-10 were above the plane as observed also for costunolide [12].

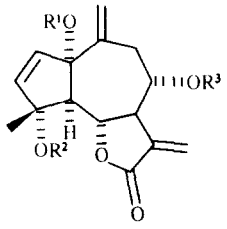
The ^{1}H NMR spectra of **7a**, **7b** and **8** (Table 2) could be interpreted only at elevated temperature This is typical for 10-membered ring compounds Spin decoupling showed that the lactones **7a** and **7b**, which could not be separated, were isomeric germacranolides again with a 7,11-double bond and acetoxy groups at C-3 and C-13. It seemed most likely that they were epimeric at C-1. This was established by manganese dioxide oxidation which led to a single ketone (**7c**) Again the configurations of **7a** and **7b** were determined by the observed NOEs While **7a** gave clear effects between H-15, H-6 (12%) and H-1 (4%) as well as between H-5 and H-3 (15%) the isomer **7b** gave NOEs between H-1, H-3 (7%) and H-14 (5%) as well as between H-15 and H-6 (14%). In the ^{1}H NMR of **8** the signals of the exomethylene protons were replaced by a signal of an olefinic methyl and that of an olefinic proton. Spin decoupling showed that a Δ^9 isomer of **7a** was



	1a	1b
X	CH_2	αMe H

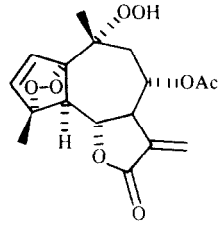


	2a	2b	2c	2d	2e	2f
R^1	H	OH	OH	H	OH	OH
R^2	Ac	Ac	H	Ac	Ac	H
				Δ^9		

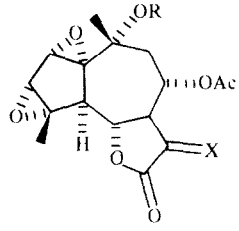


	3a	3b	3c	3d	3e	3f	3g*	3h*	3i*	3j*	3k*
R^1	H	H	OH	OH	H	OH	OH	H	OH	OH	H
R^2	H	OH	H	OH	H	OH	H	OH	OH	OH	H
R^3	Ac	Ac	Ac	Ac	H	H	Ac	Ac	Ac	Ac	Ac
							4 *epi*			4 *epi*	

* **3g**–**3k** Δ^9



4a
4b 10 *epi*



	R	X
5a	H	CH_2
5b	OH	CH_2
5c	OH	αMe,H

present A clear NOE between H-14 and H-9 (10%) required a *Z*-double bond. A NOE between H-15 and H-6 (15%) further required a preferred conformation with the methyl at C-4 above the plane. Accordingly, the couplings of H-1 allowed the determination of the configuration at this centre It is probable that **7a**, **7b** and **8** are formed by enzymatic oxidation of **6** through the corresponding hydroperoxides which could not be detected We have named **7a** and **7b** 1α- and 1β-hydroxyafraglaucolide and **8** 1α-hydroxyisoafraglaucolide

The ^{1}H NMR spectrum of **9** (Table 2) indicated the presence of an eudesmanolide closely related to ridentin B [13] though the H-3 signal was shifted downfield and again signals for H-7 and for exomethylene protons were missing They were replaced by a pair of doublets and the H-6 signal was at lower fields All the data, therefore, agreed with the structure of a further glaucolide The configuration at C-1 and C-3 followed from the corresponding couplings The structure was further supported by the ^{13}C NMR data (Experimental) It is probable that lactone **9** is formed from **7b** (see Scheme) We have named this lactone eudesmaafraglaucolide

The ^{1}H NMR spectrum of **10** (Experimental) was close to that of α-cyperone The presence of a 12-hydroxy group was deduced from the replacement of the olefinic methyl signal by that of a two-proton singlet at δ4 18

Table 1 ^{1}H NMR spectral data of compounds **3d**–**3k**, **4b**, **5b** and **5c** (400 MHz, $CDCl_3$, δ values)

H	3d	3e*	3f	3g	3h	3i	3j	3k	4b	5b	5c	multiplicity
2	6 03	5 54	6 13	6 15	6 18	6 12	6 37	5 92	6 67	3 67	3 58	*d*
3	6 23	5 85	6 19	5 86	6 02	6 19	5 97	5 97	6 34	3 32	3 33	*d*
5	2 98	2 33	2 36	2 52	2 63	3 67	2.71	2 41	2 42	2 72	2 67	*d*
6	4 13	4 06	4.36	4 45	4.45	4 21	4 47	4 45	4.23	4 25	4 23†	*dd*
7	3 49	3 35	3 07	4 08	3.82	3 98	3 77	4 14	3 52	3 56	2 52‡	*dddd*
8	4 84	3 66	3 82	5 16	5.32	5 31	5 30	5 20	5 33	5 24	5 18‡	*ddd*
9	2 87	2 53	2 71	5 58§	5.82§	5 85§	5 78§	5 68§	2 66	2 39	2 27	*dd*
9′	2 75	2 90	2 75						2 15	1 85	1 70	*dd*
13	6 33	6 33¶	6 35	6 30	6.29	6 28	6 28	6 29	6 22	6 24	1 35	*d*
13′	5 87	6 26	6 34	5 74	5.68	5 68	5 68	5 73	5 50	5 62		*d*
14	5 31‖ 5 02‖	5 00‖ 4 77	5 29‖ 5 10‖	1 84¶	1 85¶	1 80‖	1 84	1 85‖	1 54	1 60	1 55	*s*
15	1 34	1 27	1 62	1 56	1 60	1 23	1 59	1 57	1 75	1 18	1 18	*s*
OR	2 16			2 15	2 16	2 16	2 16	2 14	2 20	2 12	2 07	*s*
	8 46			7 44	8 29	9 25	8 14		8 30	8 04	7 92	*br s*
	8 31					8 75	7 41					*br s*

* $CDCl_3/CD_3OD$ 4 1, †11-H 2 52, ‡*m*, §*dq*, ‖*br s*, ¶*dd*

J[Hz] 2, 3 = 5 5, 5, 6 = 11, 6, 7 = 8 5, 7, 8 = 10, 7, 13 = 3, 7, 13′ = 2.5, 8, 9 = 6, 8, 9′ = 10, 9, 9′ = 13

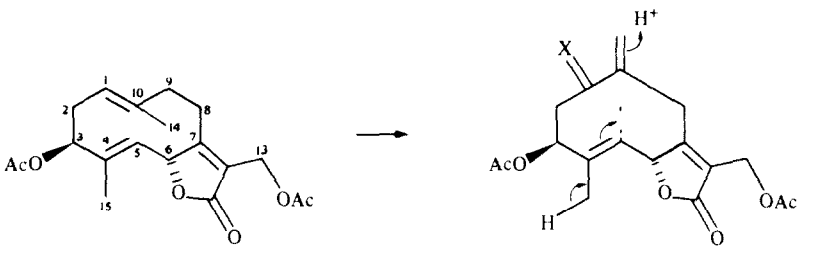
Table 2 ^{1}H NMR spectral data of compounds **6**, **7a**, **7b**, **8** and **9** (400 MHz, $CDCl_3$, δ-values)

H	6	7a (60°)	7b (60°)	7c	8 (60°)†	9
1	4 81 *m*	4 06 *br*	4 19 *br t*	—	4 14 *dd*	3 25 *dd*
2	2.53 *m*	2 40 *m*	2 11 *dd*	3 74 *dd*	2 01 *ddd*	1 96 *ddd*
2′	2 34 *ddd.*	2 20 *m*		2 65 *dd*	1 85 *ddd*	1 46 *ddd*
3	5 18 *br dd*	5 32 *dd*	5 14 *br t*	5 55 *t*	4 80 *dd*	4 92 *br dd*
5	4.50 *br d*	5 00 *br d*	5 10 *br d*	4 87 *br d*	4 83 *dq*	1 58 *br d*
6	5 46 *br d*	5 39 *br d*	5 45 *br d*	5 35 *br d*	5 40 *br d*	4 90 *br d*
8	3 03 *br dd*	3 05 *m**	3 30 *m**	3 11 *br dd*	3 15 *ddq*	2 84 *ddd*
8′	2 27 *m*	2 63 *m**	2 55-	2 86 *br dd*	2 86 *br dd*	2 28 *br ddd*
9	2 53 *m*	2 35 *m**	2 40 *m**	2 33 *m*	4 90 *ddq*	2 10 *ddd*
9′	2 20 *m*			2 10 *m*		1 07 *br ddd*
13	4 88 *br d*	4 90 *br d*	4 86 *br s*	4 88 *br d*	4 74 *br d*	4 61 *br d*
13′	4 81 *br d*	4 84 *br d*		4 81 *br d*	4.66 *br d*	4 56 *br d*
14	1 62 *br s*	5 17 *br s* 4 94 *br s*	5 25 *br s* 4 90 *br s*	5 84 *br s* 5 71 *d*	1 62 *dd*	0 74 *br s*
15	1.75 *br s*	1 87 *br s*	1 86 *d*	1 80 *d*	1 80 *d*	5.01 *dd* 4 89 *dd*
OR	2 11 *s*	2 10 *s*	2 09 *s*	2 12 *s*	1 98 *s*	1 94 *s*
	2 10 *s*	2 08 *s*	2 07 *s*	2 11 *s*	1 94 *s*	1 87 *s*

* Not first order, †$CDCl_3/CD_3OD$ 4 1

J[Hz] Compound **6** 1, 2′ = 2, 2′ = 2′, 3 ~ 12, 2, 3 = 6, 5, 6 = 10, 8, 8′ = 13, 8, 9 = 8, 13, 13′ = 12 5, Compound **7a** 2, 3 = 6, 2′, 3 = 9, 5, 6 = 10, 13, 13′ = 13, compound **7b** 1, 2 = 2,3 = 7, 5, 6 = 10, 5, 15 = 1, compound **8** 1, 2 = 11, 1, 2′ = 5, 2, 2′ = 13, 2, 3 = 7, 2′, 3 = 10, 5, 6 = 10 5, 5, 15 = 8, 14 = 9, 14 ~ 1 5, 8, 9 = 5, 8′, 9 = 11, 9, 9′ = 13, 13, 13′ = 13, compound **9** 1, 2 = 4 5, 1, 2′ = 2, 2′ = 2′, 3 = 12, 2, 3 = 5, 3, 15 = 3, 15′ = 5, 15 = 5, 15′ = 1 5, 5, 6 = 10 5, 8, 8′ = 8′, 9′ = 9, 9′ ~ 14, 8, 9 = 2, 8, 9′ = 4 5, 8′, 9 = 6, 13, 13′ = 13

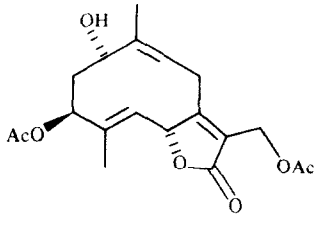
While highly oxygenated guianolides of types **1**–**5** are characteristic for *Artemisia* species the isolation of glaucolides is very unusual It is very interesting that these glaucolides are not derived from the guaianolides present in a large variety in this species This may support the proposal that all sesquiterpene lactones are formed via germacranolides and not by transformation of the corresponding guaianes or eudesmanes Furthermore, it is remarkable that the glaucolides unlike the guaianolides have no oxygen functions at C-8 Recently we have isolated similar glaucolides from *A judaica* [14] As these lactones are also reported from a *Cotula* species [11] and an *Artemisia* species [15] they may be of chemotaxonomic importance



6

7a 7b 7c

X αOH,H βOH,H =O



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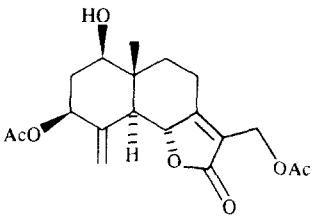
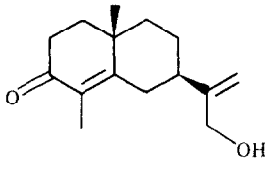


9



10

EXPERIMENTAL

The plant material was grown on the experimental station of the University of Fort Hare (voucher 86/29) The air-dried material was extracted with MeOH–Et_2O–Petrol (1 1 1) and worked-up as reported previously [16] The extract of the roots (230 g) was separated by CC (silica gel) into four fractions which were further separated by TLC (silica gel PF 254) Finally in addition to the acetylenes reported previously [1] 4 mg α-humulene, 10 mg β-farnesene, 10 mg squalene and 10 mg **10** (purified by HPLC (R_t 6 3 min) (MeOH–H_2O, 7 3, always RP 8, *ca* 100 bar)) From the most polar CC fraction 50 mg ferulic acid, 110 mg isofraxidin and 500 mg of its β-D-glucopyranoside were obtained The extract of the aerial parts (160 g) was separated by CC into four fractions Fraction 1 gave by TLC (Et_2O–petrol, 1 9) 80 mg α- and 100 mg β-thujone, 120 mg ascaridol and 100 mg camphor Fraction 2 was separated by flash chromatography (silica gel, ϕ 30–60 μ) (=MPC) into nine fractions (petrol with increasing amounts of Et_2O) (2/1–2/9) TLC of 2/1 gave 5 mg spathulenol HPLC of 2/2 (MeOH–H_2O, 13 7) afforded 5 mg **1a** (R_t 15 0 min) and 1 mg **1b** (R_t 21 0 min) HPLC of 2/3 (same solvent) gave 5 mg **2b** and 4 mg **2e** Fraction 2/4 gave by HPLC (same solvent) 4 mg **2a**, 2 mg **2d** and 3 mg **4a** Fraction 2/5 (MeOH–H_2O 3 2) gave 3 mg **3j** (R_t 4 5 min) and 3 mg **3d** (R_t 5 0 min) HPLC of fraction 2/6 (MeOH–H_2O, 3 2) afforded 3 mg **3g** and 3 mg **3h** (R_t 4 5 min) and 4 mg **3b** (R_t 5 0 min) HPLC of 2/7 (MeOH–H_2O 9 11) gave 4 mg **3c** (R_t 11 0 min) and of fraction 2/8 (MeOH–H_2O, 2 3) 3 mg **3g** (R_t 13 0 min) and 5 mg **3i** (R_t 23 0 min) HPLC of 2/9 (MeOH–H_2O, 1 1) gave 3 mg **3c** (R_t 7 0 min) CC fraction 3 was separated again by MPC into five fractions (3/1–3/5) HPLC of 3/1 (MeOH–H_2O, 1 1) gave 5 mg **4b**, 3 mg **2a**, 4 mg **2d** and 2 mg **6** HPLC of 3/2 (MeOH–H_2O 1 1) afforded 5 mg **3j**, 3 mg **3d**, 2 mg **2c** and 4 mg **2f** HPLC of 3/3 (MeOH–H_2O, 1 1) gave 2 mg **3i** (R_t 4 5 min) and 2 mg **3b** (R_t 5 0 min) HPLC of 3/4 (MeOH–H_2O, 1 1) gave 1 mg **3f** (R_t 4 0 min), 7 mg **3g** (R_t 5 0 min), 4 mg **5b** (R_t 6 5 min), 3 mg **5c** (R_t 7 0 min) and 2 mg **3i** (R_t 8 5 min) HPLC of 3/5 (MeOH H_2O, 1 1) gave 3 mg **5b** and 3 mg **3a** (R_t 7 5 min) MPC of CC 4 gave a polar fraction (MeOH–Et_2O, 1 4) which afforded by HPLC (MeOH–H_2O, 2 3) 4 mg **3e** (R_t 6 5 min), 10 mg **5a** (R_t 7 0 min), 7 5 mg **7a**/**b** (R_t 13 0 min, *ca* 1 1), 5 mg **8** (R_t 14 5 min) and 4 mg **9** (R_t 19 0 min) The less polar fraction gave by TLC 30 mg isoscopoletin, 30 mg acacetin-7-*O*-methyl ether and 30 mg scopoletin Known compounds were identified by comparison of their 400 MHz ^{1}H NMR spectra with those of authentic material The mass spectral data are summarized in Table 3 Some hydroperoxides gave no useful spectra They were transformed by reduction to

Table 3. CIMS data of the guaianolides and their reduction products respectively

	$[M+1]^+$	
3a	321 (4)	279 (40), 261 (9), 243 (100)
3e	(EI) 278 (1) $[M]^+$	263 (8), 82 (65), 55 (100)
3i	—	319 $[M+1-H_2O_2]^+$ (7), 259 [319 $-HOAc]^+$ (10), 61 $[AcOH+1]^+$ (100)
3j	353 (3)	319 (20), 259 (37), 225 $[259-H_2O_2]^+$ (21), 61 (100)
3k	321 (3)	279 [321 − ketene]$^+$ (100)
4b	353 (12)	319 (8), 259 (21), 151 (100)
5c	355 (3)	337 (6), 321 (6), 144 (100)

the corresponding hydroxy derivatives by addition of excess of triphenyl-phosphine in $CHCl_3$ to the hydroperoxides. After 5 min, TLC gave the pure hydroxy compounds in almost quantitative yield.

Artemisia glaucolide (**6**) Colourless oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1} 1765 (γ-lactone), 1735 (OAc), MS *m/z* (rel int) 348 157 $[M]^+$ (2) (calc for $C_{19}H_{24}O_6$ 348 157), 306 $(M-ketene]^+$ (2), 288 [M $-HOAc]^+$ (4), 246 [288 − ketene]$^+$ (68), 228 (288 − HOAc]$^+$ (22), 178 (100), CD (MeCN) $\Delta\varepsilon_{252}+0\,67$

1α- *and* 1β-*Hydroxyafraglaucolide* (**7a/b**) Colourless oil, IR $\nu_{max}^{CHCl_3}$, cm^{-1} 3600 (OH), 1765 (γ-lactone), 1740 (OAc), MS *m/z* (rel. int.). 364.152 [M]$^+$ (0.3) (calc. for $C_{19}H_{24}O_7$: 364.152), 304 [M − HOAc]$^+$ (4 5), 262 [304 − ketene]$^+$ (21), 244 [304 $-HOAc]^+$ (42), 60 (100)

5 mg **7a/b** in 3 ml Et_2O was stirred for 2 hr with 50 mg MnO_2 TLC afforded 3 mg **7c**, MS *m/z* (rel. int.). 362.137 [M]$^+$ (1) (calc. for $C_{19}H_{22}O_7$ 362 137), 302 [M − HOAc]$^+$ (0 5), 60 [HOAc]$^+$ (100), ^{1}H NMR Table 2.

1α-*Hydroxyisoafraglaucolide* (**8**). Colourless oil, IR $\nu_{max}^{CHCl_3}$, cm^{-1} 3600 (OH), 1765 (γ-lactone), 1740 (OAc), MS *m/z* (rel. int): 364.152 $[M]^+$ (0.5) (calc. for $C_{19}H_{24}O_7$. 364.152), 322 [M − ketene]$^+$ (2), 305 [M − OAc]$^+$ (6), 262 [322 − HOAc]$^+$ (12), 244 $[262-H_2O]^+$ (20), 60 (100), CD (MeCN): $\Delta\varepsilon_{239}-1\,1$

Eudesmaafraglaucolide (**9**) Colourless oil; IR $\nu_{max}^{CHCl_3}$, cm^{-1}. 3580 (OH), 1765 (γ-lactone), 1750 (OAc); MS *m/z* (rel. int.) 364 152 $[M]^+$ (5) (calc for $C_{19}H_{24}O_7$ 364.152), 304 [M $-HOAc]^+$ (9), 262 [304 − ketene]$^+$ (36), 244 [304 − HOAc]$^+$ (100), 216 $[244-CO]^+$ (68), 60 (88), ^{13}C NMR ($CDCl_3$, C-1–C-15). δ74.0 *d*, 36.2 *t*, 78.0 *d*, 140.6 *s*, 52.3 *d*, 70.4 *d*, 169.2 *s*, 22.2 *t*, 36 0 *t*, 41 1 *s*, 118.7 *s*, 170 0 *s*, 54 6 *t*, 9.9 *q*, 107.0 *t*, OAc 172 8 *s*, 170.9 *s*, 20.4 *q*, 20.1 *q*, CD (MeCN). $\Delta\varepsilon_{260}-1\,1$

12-*Hydroxy-α-cyperone* (**10**) Colourless oil, IR $\nu_{max}^{CCl_4}$ cm^{-1} 3600 (OH), 1670, 1610 (C=CC=O), MS *m/z* (rel int). 234.162 $[M]^+$ (6) (calc for $C_{15}H_{22}O_2$ 234.162), 216 $[M-H_2O]^+$ (62), 201 $[216-Me]^+$ (88), 91 $[C_7H_7]^+$ (100), ^{1}H NMR ($CDCl_3$) δ1 81 (*br ddd*, H-1, $J=13$, 13, 4 5 Hz), 1.70 (*m*, H-1β), 2 40 (*ddd*, H-2, $J=17$, 4 5, 3 5), 2 52 (*ddd*, H-2β, $J=17$, 13, 6), 2 78 (*m*, H-6), 2 12 (*m*, H-6β), 2.12 (*m*, H-7), 1 7 (*m*, H-8, H-9β), 1 45 (*m*, H-9), 4.18 (*br s*, H-12), 5 13 and 5 00 (*br s*, H-13), 1 23 (*s*, H-14), 1 74 (*d*, H-15, $J=1$)

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