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A NEW STEREOCHEMICAL CLASS OF BICYCLIC SESQUITERPENES FROM *EREMOPHILA VIRGATA* W.V. FITZG. (MYOPORACEAE)†

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Abstract - Three sesquiterpene acids, representing a new stereochemical class of bicyclic sesquiterpenes, have been isolated from *Eremophila virgata* W.V. Fitzg. (Myoporaceae). Chemical and spectroscopic evidence is presented for their structure and relative stereochemistry. The absolute configuration was determined by single-crystal X-ray diffraction analysis of a derivative of the major metabolite (**1**). A fourth acid is shown to be a diastereoisomer of **1**.

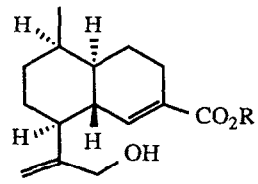
Many *Eremophila* species (Myoporaceae) that have adapted to arid region environments produce significant quantities of resin which accumulates on the leaf surfaces and terminal branches. Our studies have shown[1] that these resins contain largely oxygenated diterpenes and various amounts of flavones. Mono- and sesquiterpenes are almost always present in the essential oil fraction albeit in small amounts. Investigation of the resin of *Eremophila virgata* W.V. Fitzg. revealed that it is a complex mixture of sesquiterpene acids. These have been separated and their structures and relative stereochemistries have been assigned on the basis of chemical and spectroscopic evidence. Of the four acids (**1**-**4**) identified, three, (**1**, **3**, **4**), have been chemically interrelated and shown to share a common stereochemistry. A single crystal X-ray diffraction analysis of a derivative of **1** establishes the absolute stereochemistry of this set. The fourth acid, (**2**), for which only the relative stereochemistry was determined, is shown to be a diastereoisomer of **1**.

The ether extract of *E. virgata* (11.3% dry wt) was fractionated into acidic and neutral components. A portion of the acidic fraction was methylated with diazomethane. Gc analysis indicated the presence of four compounds: the methyl esters of **1** (52%), **2** (31%), **3** (8%) and **4** (9%). Although **1** and **2** could be separated with difficulty from **3** and **4** they could not be separated from each other cleanly as acids, methyl ester or acetate derivatives either by radial plate or hpl chromatography. The two compounds could be distinguished by ^{1}H- and ^{13}C nmr spectroscopy which also indicated that they were diastereomeric sesquiterpenes containing an α,β-unsaturated carboxylic acid, an allylic primary alcohol and a 1,1-disubstituted double bond. Chemical evidence for this came from formation of the monomethyl esters (**5** and **6**) and monoacetates which could be hydrogenolysed to a mixture of acids **7** and **8**.

Considering the spectroscopic data obtained on **1** and **2** and their derivatives and application of the isoprene rule led us to assume the cadinane structure as a working hypothesis.

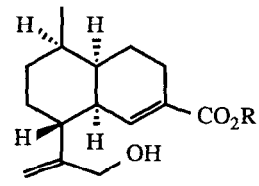
† The Chemistry of Eremophila spp XXXII. Part XXXI. Phytochemistry, 1989 (in press).

In the event treatment of a mixture of the methyl esters (**5** and **6**) with sodium methoxide in methanol[2] gave two distinct products which could be separated by radial plate chromatography (RPC) into **9** and **10** (Fig. 1). The minor compound (**10**), $C_{16}H_{24}O_3$, lacked absorption for a hydroxyl group in the ir spectrum



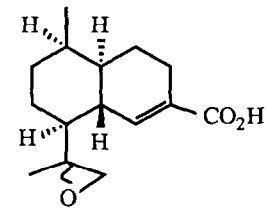
1 R=H

5 R=Me



2* R=H

6* R=Me



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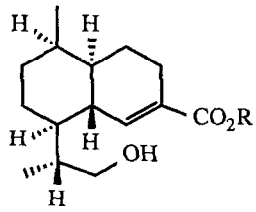
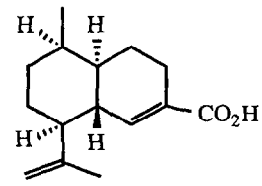


4 R=H

13 R=Me



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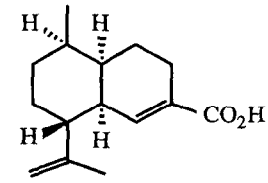

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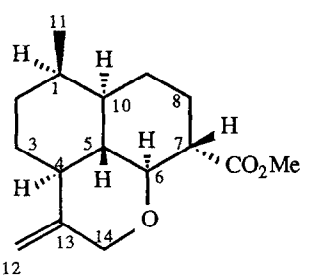
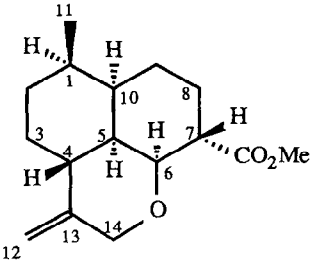
*Relative stereochemistry only

and the ^{13}C nmr spectrum included signals for two carbons linked to oxygen (δ_C 66.9, t; 76.4, d), a methyl ester (δ_C 175.1, s; 51.7, q), a 1,1-disubstituted olefin (δ_C 148.0, s; 106.6, t), five carbons carrying a single hydrogen (δ_C 33.6, 35.2, 40.9, 41.1, 64.4, all d) and a methyl group (δ_C 19.5, q). The ^1H nmr spectrum showed the methyl group to be secondary (δ_H 0.89, J 6.6 Hz). An oxymethine proton (δ_H 3.99) was shown to have coupling (J 11.4 Hz) to a proton (δ_H 3.25), assigned α- to a carbomethoxy group, which in turn is coupled to a methylene group (δ_H 2.04, 1.52). The other coupling (5.1 Hz) to the oxymethine proton arises from a proton resonating at δ_H 1.83 which is also coupled to two individual protons at δ_H 2.25 (J 10 Hz) and δ_H 1.65. This establishes the connectivity C4-C5-(C10)-C6-C7. Further decoupling, ^1H-^{13}C, and ^1H-^1H correlation experiments revealed the connectivity C7-C8-C9-C10-C1-C11 and by deduction, C4 must be separated from C1 by two methylene groups. Similar analysis of the major product (**9**) was fully consistent with the structure proposed (Fig. 1).



9



10

C	$\delta^{13}C$	$\delta^{1}H^{a}$	$\delta^{13}C$	$\delta^{1}H^{a}$
1	31.4	1.91 m	40.9	1.65 m
2	32.4		28.6	
3	21.5	1.45 eq, m	28.3	1.25 ax, m
		1.61 ax, m		1.89 eq, m
4	44.3	1.80 m	33.6	2.25 m
5.	45.3	1.08 m	46.4	1.83 m
6	81.5	3.44 dd (10.4, 9.7)	76.4	3.99 dd (11.4, 5.1)
7	49.2	2.38 ddd (12.4, 10.4, 3.8)	41.1	3.25 ddd (11.7, 11.4, 3.7)
8	27.8	1.55 ax, m	27.9	1.52 ax, m
		1.92 eq, m		2.04 eq, m
9	28.9		18.5	1.23 ax, m; 1.50 eq, m
10	41.9	1.40 m	35.2	
11	13.1	0.86 d (7.2)	19.5	0.89 d (6.6)
12	106.5	4.70 a, m $Wh_{/2}$ 4.5	106.7	4.70 m, $Wh_{/2}$ 4.5
		4.80 b, m $Wh_{/2}$ 4.0		4.84 m, $Wh_{/2}$ 4.0
13	147.4	-	148.0	
14	73.4	4.01 ax, d (12.2)	66.9	4.27 ax, d (12.8)
		4.18 eq, d (12.2)		3.93 eq. d (12.8)
15	175.3	-	175.1	-
16	51.7	3.70 s	51.7	3.70 s

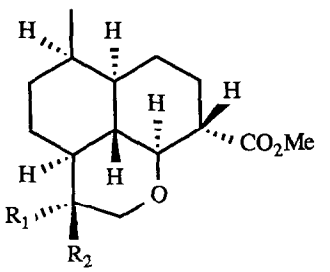
a Multiplicity and ($J_{H,H}$ Hz).

Figure 1. NMR data for the ethers (**7**) and (**8**).
Assignments are based on ^{1}H-^{1}H, ^{1}H-^{13}C correlation and ^{1}H-decoupling measurements.

To establish that the two ethers (**9** and **10**) came from the respective alcohols (**5** and **6**) each was separately treated with LDA at -78°.[2] In each case a single hydroxy ester was obtained which had identical gc retention time with the major and minor hydroxy ester respectively. Furthermore all the signals in the ^{13}C nmr spectrum of the mixture of **5** and **6** could be shown to correspond to those present in the spectra of the pure hydroxy esters produced from the ethers (**9** and **10**). Formation of **9** and **10** provided a method for the separation of the two main metabolites of *E. virgata* and, as explained below, these two tricyclic compounds provided nmr spectra the analyses of which allowed their relative stereochemistries to be deduced.

Of the two minor metabolites the epoxide (**3**) was the easier to obtain pure. The ^1H nmr spectrum included an ABq at δ 2.79 and 2.64 (J 4.8 Hz) for the oxirane methylene and a singlet at δ 1.30 for the oxirane methyl group which had replaced the allylic primary hydroxy functionality present in **1** and **2**. Treatment of **4** with zinc-sodium iodide-sodium acetate-acetic acid-1,2-dichloroethane gave the deoxygenation product (**7**) and the acid (**1**) whose ^1H- and ^{13}C nmr spectra had signals which corresponded to those attributed to the major component in the mixture of **1** and **2** and whose methyl ester derivative was identical with **5**.

The fourth metabolite (**4**) could only be isolated with difficulty as the ether (**11**) and more conveniently after ozonolysis of a mixture of **9** and **10** (see below). The ^{13}C nmr spectrum of **11** was almost identical with that of **9** with the exception that the olefinic carbons had been replaced by a secondary methyl group. The ^1H nmr spectrum included signals for the oxymethylene group at δ 3.80 (J 11.3, 4.5 Hz) and 3.08 (J 11.3, 11.2 Hz). The large vicinal coupling of the latter proton indicates a *trans*-diaxial relationship and thus the secondary methyl group is equatorial. Hydrogenation of **9** provided a mixture of epimers (35:65; **11** and **12**) the minor component of which had an identical ^{13}C nmr spectrum with that of the dihydroether (**11**). This result when



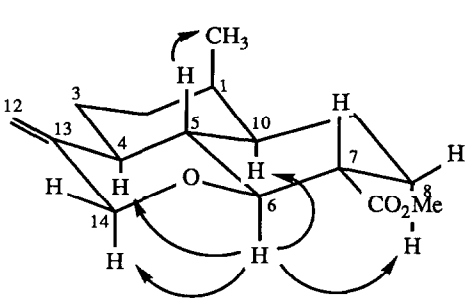
	R_1	R_2
11	Me	H
12	H	Me

taken in conjunction with the derived stereochemistry of **9** and the fact that hydrogenation occurs preferentially from the less hindered side of the molecule provides supporting evidence for the configuration at C13 in the dihydroether (**11**). Treatment of **11** with LDA yielded the dihydro hydroxy ester (**13**) which represents a derivative of the natural metabolite (**4**).

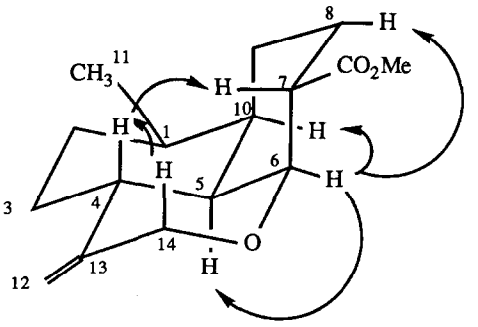
The interrelationships established between **3** and **4** and **1** show that these three metabolites share the same stereochemistry. On the other hand a comparison of the ^{13}C nmr spectra of **5** and **6** reveals their diastereomeric relationship.

Relative Stereochemistry of the *E. virgata* metabolites

The assignment of the relative stereochemistry to **9** was achieved by analysis of the ^1H- and ^{13}C nmr spectra with ^1H-^1H, ^1H-^{13}C correlation and NOE difference experiments. The more decisive results are summarised below. The oxymethine proton, H6, showed large coupling (J 10.4 Hz) to the carboxymethine proton (H7) and to H5 (J 9.7 Hz) placing these in a *trans*-diaxial relationship. Furthermore H5 showed large couplings to H10 (J 11.1 Hz) and to H4 (J 11.1 Hz). This condition can be met only with the all *trans*-arrangement shown in B. The secondary methyl group resonates at δ_C 13.1 indicating[3] its axial arrangement adjacent to an equatorial C-C bond (C9-C10).



A



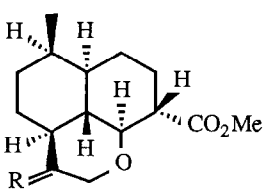
B

A series of NOE difference spectra were recorded and showed interactions between H6 and the set H4, H8 ax, H10 and H14 ax supporting the all-chair arrangement. An NOE between H5 and H11 indicates the axial nature of the methyl at C1 (see A).

Similar analysis of the ether (**10**) gave the following results. The oxymethine proton, H6, is *trans*-diaxially arranged with H7 (J 11.3 Hz) with an axial-equatorial coupling to H5 (J 5.1 Hz). In turn H5 and H4 show a *trans*-diaxial arrangement (J 10 Hz) thus the C4-C5 ring junction in *trans*- and the remaining ring junction C5-C10 is *cis*- (see B). The carbon chemical shift of the secondary methyl at C1 (δ_C 19.5) is that expected[3] for an equatorial methyl with a vicinal axial C-C bond. From NOE difference spectra H4 interacted with H7 and H14 ax and H6 with H5, H10 and H8 ax. Significant NOE effects were also observed between H14 eq and H12a and between H12b and H_2-3 (see B).

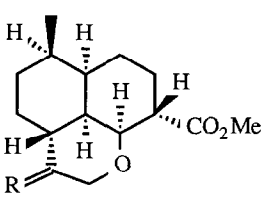
Absolute Stereochemistry of **1**

To determine the absolute configuration of the major metabolites of *E. virgata*, X-ray crystallographic analyses of heavy atom derivatives was considered more convenient. To this end each of the ethers (**9** and **10**) was converted to the *nor*-ketones (**14** and **15**) by ozonolysis and their respective crystalline *p*-bromo-benzenesulphonyl hydrazones (**16** and **17**) were prepared. In the event only **16** could be obtained in a form suitable for single-crystal X-ray diffraction. The result described below indicate the absolute configuration of **16**, and hence of **1**, **3** and **4**, to be as shown. Despite repeated attempts the hydrazone (**17**) could not be obtained in a suitable crystalline form and tended to decompose on recrystallization from alcoholic solvents.



14 R = O

16 R = $NNHSO_2PhBr$

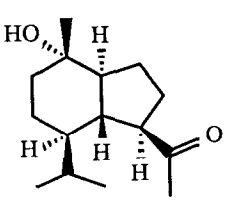


15* R = O

17* R = $NNHSO_2PhBr$

*Relative stereochemistry only

A number of sesquiterpenes have been isolated from *Eremophila* species. On the one hand there is a group of furanosesquiterpenes[4-7] and on the other a carbocyclic group containing examples of calamenene,[8] eremophilane,[9,10] eudesmane,[11] aromadendrane,[12] oplopanone[13] and zizaene[14] types. The metabolites from *E. virgata* represent a new class of bicyclic sesquiterpenes for *Eremophila*. In this context it is interesting to note that (+)-oplopanone (**18**), isolated from *E. miniata*,[13] and the metabolites **1**, **3** and **4** belong to the same stereochemical set, suggesting that these may arise from a common precursor. Furthermore **1**, **3** and **4** represent a new stereochemical class of the "cadinene" group. In this group four classes have been identified previously based on the nature of the ring fusion and the orientation of the 3 carbon chain at C4, but ignoring the orientation of the secondary methyl at C1. If the orientation at this centre is fixed then there are eight diastereomeric classes possible. Of these, four have been named cadinane, muurolane, bulgarane, and amorphane.[15] The fungal sesquiterpene, panal (**19**)[16], and the diketone (**20**) from *Eupatorium trapezoideum*,[17] represent two others (type 5 and 6 respectively), and the metabolites **1**, **3** and **4** are members of a seventh stereochemical class. The remaining metabolite, **2**, could have either a muurolane or *ent*-type 5 stereochemistry.



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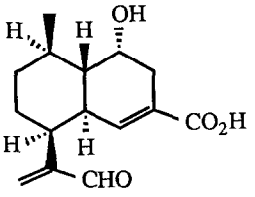

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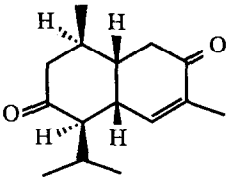

20

Table 1. ^{13}C nmr spectra of selected compounds. Chemical shifts (δ) in ppm relative to TMS[a]

Carbons	3	5	6	9	11	13[d]	14	15
1	32.2	32.3	42.8[b]	32.4	31.5	31.7	30.9	41.6
2	32.5	33.2	34.5	33.0	32.9	33.1	31.8	27.9
3	22.6[b]	25.4	25.4	25.1[b]	23.2	23.6	18.1	24.6
4	37.4	37.9[b]	39.0[b]	36.9[c]	43.3[b]	37.6[b]	52.5[b]	42.1[b]
5	49.3	46.6[b]	42.2[b]	50.8[c]	49.4[b]	43.1[b]	43.8[b]	42.4[b]
6	142.6	142.0	142.7	144.8	81.6	82.7	79.9	75.0
7	130.4	130.1	129.9	129.5	46.8	48.9	48.7	43.7
8	25.0[b]	27.3	29.3	27.4[b]	27.9	28.0	27.8	27.5
9	27.1[b]	28.7	16.4	27.0[b]	29.1	29.1	28.4	18.1
10	41.7	41.9	34.8	41.6	41.3	41.6	42.7	34.7
11	12.5	12.4	19.4	12.5	13.2	13.2	12.8	19.3
12	56.5	110.1	109.4	112.3	13.9	12.6	-	-
13	57.7	151.2	151.8	147.1	36.4	33.6	206.6	208.9
14	16.5	65.1	65.7	19.4	74.4	74.9	74.5	68.9
15	172.6	168.2	168.2	173.1	175.4	176.0	174.7	174.6
16	-	51.5	51.5	-	51.6	51.7	51.8	52.0

a ($CDCl_3$; 75.5 MHz) Multiplicities of signals were determined by SFORD and GASPE techniques and are consistent with assignments.

b-c Values in any one column may be interchanged.

d Obtained by subtracting signals for **11** from spectrum of a mixture of **11** and **12**.

Crystallography

Crystal data:- $C_{21}H_{27}BrN_2O_4S$, M = 483.4, Monoclinic, space group $P2_1$ (C_2^2, No. 4), a = 9.064(5), b = 7.813(4), c = 15.799(10) Å, β = 100.74(5)°, U = 1099(1) Å^3, $D_c(Z = 2)$ = 1.46 g.cm^{-3}. $F(000)$ = 500. Monochromatic Mo $K\alpha$ radiation, λ = 0.71069 Å, μ_{Mo} = 19.6 cm^{-1}; specimen: 0.22 x 0.46 x 0.16 mm. $A^*_{min,max}$ (Gaussian correction) 1.37, 1.54. T~295 K.

Structure determination:- A unique data set was measured to $2\theta_{max}$ = 45°, using a Syntex $P2_1$ four-circle diffractometer in conventional $2\theta/\theta$ scan mode; 1345 independent reflections were obtained, 1176 with $I > 2\sigma(I)$ being considered 'observed' and used in the full-matrix least squares refinement. Anisotropic thermal parameters were refined for the non-hydrogen atoms; $(x, y, z, U_{iso})_H$ were included constrained at estimated values. (N.B. H_N(122) was definitively located from a difference map).

Residuals on $|F|$, R, R' at convergence were 0.035, 0.028 for the given chirality; for the opposite hand 0.045, 0.037. Statistical weights derived from $\sigma^2(I) = \sigma^2(I_{diff}) + 0.00007\ \sigma^4\ (I)_{diff}$ were used. Neutral atom complex scattering factors were employed;[19] computation used the XTAL 83 program system[20] implemented by S.R. Hall on a Perkin-Elmer 3240 computer. Pertinent results are given in Figure 2 and Table 2; material deposited comprises molecular geometry, structure factor amplitudes, and thermal and hydrogen atom parameters.†

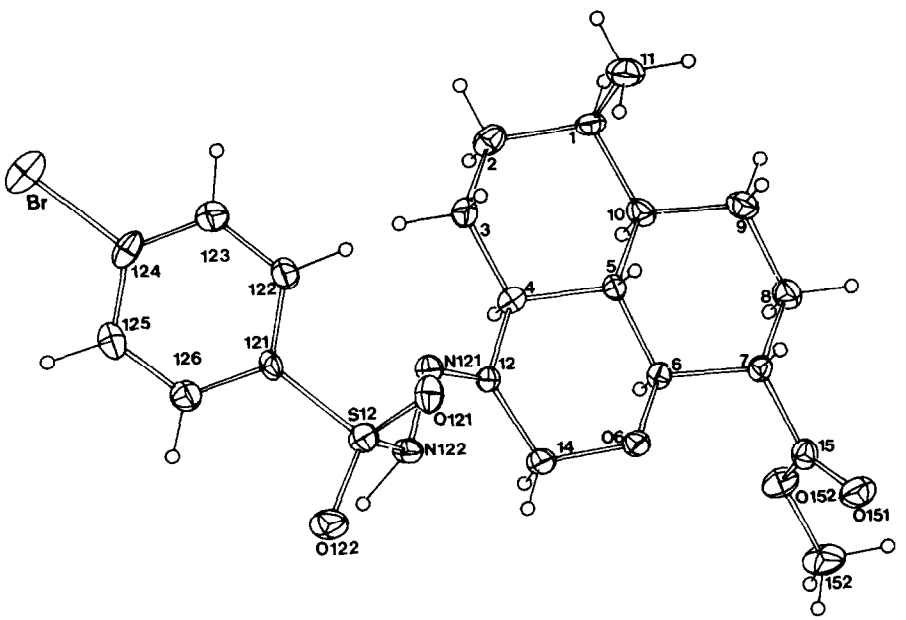

Figure 2. Projection of the single molecule of (**16**). 20% probability thermal ellipsoids are shown for the non-hydrogen atoms together with skeletal numbering. Hydrogen atoms have an arbitrary radius of 0.1Å

† Copies available on application to the Editorial Office

Table 2. Non-hydrogen atom coordinates.

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
Br	0.1637(1)	0*	0.06501(7)	C(15)	0.7280(10)	1.4581(11)	0.4211(6)
C(1)	0.7300(10)	1.0743(11)	0.1024(5)	O(151)	0.6494(7)	1.5572(8)	0.4513(3)
C(11)	0.5916(10)	1.1450(14)	0.0404(4)	O(152)	0.8622(6)	1.4102(8)	0.4618(3)
C(2)	0.7185(10)	0.8812(12)	0.1124(6)	C(152)	0.9216(9)	1.4880(17)	0.5428(5)
C(3)	0.6017(8)	0.8280(10)	0.1666(5)	N(121)	0.4404(7)	0.7492(9)	0.2954(4)
C(4)	0.6414(9)	0.9110(10)	0.2554(5)	N(122)	0.3665(6)	0.7027(8)	0.3639(3)
C(5)	0.6470(9)	1.1062(10)	0.2475(5)	S(12)	0.1999(3)	0.6195(4)	0.3322(1)
C(6)	0.6858(8)	1.1855(9)	0.3366(5)	O(121)	0.1082(6)	0.7474(8)	0.2838(4)
O(6)	0.5783(6)	1.1370(7)	0.3884(3)	O(122)	0.1619(5)	0.5478(8)	0.4091(3)
C(7)	0.6882(8)	1.3795(10)	0.3336(5)	C(121)	0.2085(9)	0.4491(10)	0.2607(5)
C(8)	0.7998(9)	1.4360(10)	0.2773(5)	C(122)	0.1823(9)	0.4833(13)	0.1723(6)
C(9)	0.7631(9)	1.3581(12)	0.1877(5)	C(123)	0.1726(10)	0.3491(14)	0.1147(6)
C(10)	0.7590(9)	1.1635(12)	0.1902(5)	C(124)	0.1872(9)	0.1877(13)	0.1438(6)
C(12)	0.5414(9)	0.8603(10)	0.3180(5)	C(125)	0.2152(10)	0.1513(12)	0.2323(6)
C(14)	0.5786(10)	0.9557(11)	0.4020(5)	C(126)	0.2272(10)	0.2865(13)	0.2883(6)

* Defines origin

EXPERIMENTAL

General experimental details have been reported.[18] Unless otherwise stated Gc analyses were carried out with an HP 5790A instrument using an HP Ultra-1 column (cross-linked methyl silicon gum phase, 50 m, 0.02 mm, film thickness o.1 μm) and the conditions were as follows: T_1 70°C (0.5 min) T_2 250°C (5.0 min), rate 20°/min.

Isolation of metabolites of *E. virgata*. Leaves and terminal branches of the plant (700 g), collected 60 km south of Coolgardie, Western Australia in October 1980, were extracted with ether. The extract (79 g, 11.3% dry wt of plant) was partitioned between 8% aq. $NaHCO_3$ and 10% aq. NaOH. The caustic fraction (9.04 g) and the neutral fraction (9.50 g) contained little terpenoid material and were not investigated further. A sample of the $NaHCO_3$ soluble fraction was treated with ethereal CH_2N_2 and the product obtained was analysed by gc and gcms: **5** (52%), R_t 10.93 min, M^+ 264; **6** (31%), R_t 10.83, M^+ 264; **13** (9%), R_t 11.19, M^+ 266; methyl ester of **3** (8%), R_t 10.23, M^+ 264. A portion (7.48 g) of the $NaHCO_3$ souble fraction (45.2 g) was filtered through charcoal and the oil obtained (6.74 g) was chromatographed by rapid silicic acid filtration (RSF) using mixtures of solvents (light petroleum-CH_2Cl_2-ETOAc) of increasing polarity to give (a) fractions containing the epoxide (**4**) (700 mg) contaminated with conjugated aldehyde corresponding to **1** and (b) a mixture of the hydroxy acids (**1**, **2** and **3**) (3.93 g). Gc analysis of the corresponding methyl esters: **5** (58%), **6** (35%), **13** (7%).

Derivatives of **1**, **2** and **4**. (a) A mixture of the acids (3.75 g) in pyridine (50 ml) was treated with Ac_2O (7 ml). The product recovered with ether was an oil (3.74 g). The ^1H nmr spectrum of the mixture showed the integral for the acetoxy protons (δ 2.0) to be three times that for H-6 (δ 6.8-7.1). MS *m/z* 272 (M-18) (26%), 232 (22). (b) The mixture of acetates (1.01 g) in dry MeOH (20 ml) was stirred with Pd/C (120 mg) under H_2 at rt. The white solid obtained (0.75 g) was dissolved in CH_2Cl_2 and chromatographed by radial plate chromatography (RPC) to give (i) the mixture of acids (**7** and **8**) (0.22 g) as a white solid (Found: C, 77.0; H, 9.4; M^+ 234.1581. $C_{15}H_{22}O_2$ requires: C, 76.9; H, 9.5%; M^+ 234.1620). ν_{max} 3550, 1680 cm^{-1}; MS *m/z* 234 (M^+) (30%), 149 (100); (ii) the acetate of **4** (15 mg); MS m/z 276 (M^+-18) (19%), 234 (15), 175 (100). The corresponding methyl ester showed a single peak at R_t 11.56 min.

Cyclization of **5**, **6** and **13**. A mixture of the hydroxy esters (2.52 g) in dry MeOH (20 ml) was added slowly to a stirred solution of NaOMe (4 g) in MeOH (100 ml) at O° under argon. The mixture was heated at 65° for 3 hr then acidified with 10% HCl and extracted with ether. A portion (1.33 g) of the product recovered (2.07 g) was chromatographed by RPC (10% EtOAc-light petroleum) to give (a) a mixture of the cyclic ethers (**9**) and (**11**) as a semi-crystalline oil (0.69 g). Gc analysis showed two peaks: **9**, R_t 10.09 min (86%) and **11**, R_t 9.93 min (14%). Repeated fractional crystallization from MeOH gave the *ether* (**9**) as needles, mp 85-86°, $[\alpha]_D$ +20.8° (*c*, 1.7; $CHCl_3$) (Found: C, 72.5; H, 9.1; M^+ 264.1775. $C_{16}H_{24}O_3$ requires C, 72.7; H, 9.2; M^+ 264.1725). ν_{max} 1741 cm^{-1}, ^1H- and ^{13}C nmr: see Fig. 1. MS *m/z* 264 (M^+) (71%), 249 (39), 233 (13), 231 (30), 204 (46), 187 (65), 147 (100), 107 (81); and (b) the *ether* (**10**) (0.3 g), mp 69-71°, $[\alpha]_D$ +170° (*c*, 0.6; $CHCl_3$) (Found: C, 72.2; H, 9.0. $C_{16}H_{24}O_3$ requires C, 72.7; H, 9.2%. Found M^+-32: 232.1440. M^+-32 requires 232.1463). ν_{max} 1731 cm^{-1}; ^1H- and ^{13}C nmr: see Fig. 1. MS *m/z* 232 (M^+-32) (64), 204 (32), 187 (100), 147 (55), 107 (50), 95 (39), 81 (67), 77 (31). Gc analysis showed a single peak at R_t 10.43 min;

Ring opening of ethers (**9**), (**10**) and (**11**) (a) The cyclic ether (**9**) (45 mg, 0.17 mmol) in freeze degassed THF (1 ml) at -78° was treated with LDA (0.38 ml, 0.34 mmol) under argon. The reaction mixture was allowed to come to room temperature and was left for 2 hr. Recovery of the product with ether gave the *hydroxy ester* (5) (43 mg) as an oil, R_t 10.93 min (Found: M^+-32, 232.1423, $C_{15}H_{20}O_2$ requires 232.1463). ν_{max} 3620, 3600-3400, 1720, 1650 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 6.85, br s, $Wh_{/2}$ 4.0 Hz, H6; 5.23, m, $Wh_{/2}$ 4.0 Hz and 4.95, br s, $Wh_{/2}$ 3.0 Hz, H12a and H12b; 4.12, br s, $Wh_{/2}$ 3.5 Hz, H_2-14; 3.70, s, OCH_3, 0.91, d, J 7.2 Hz, H_3-11; ^{13}C nmr: see Table 1. MS *m/z* 264 (M^+) (7%), 246 (10), 232 (78), 187 (48), 176 (49), 105 (100). (b) The cyclic ether (**10**) (115 mg, 0.44 mmol) was treated as above with LDA (4.84 ml, 4.4 mmol), left at rt for 25 hr and then heated at 50° for 30 min. The product recovered with ether was purified by RPC (15% EtOAc-light petroleum) to give the *hydroxy ester* (**6**) (5 mg) as an oil (Found: M^+ 264.1787. $C_{16}H_{24}O_3$ requires M^+ 264.1725). ν_{max} 3620, 3600-3400, 1720, 1650 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 6.93, m, $Wh_{/2}$ 10 Hz, H6; 5.17, m, $Wh_{/2}$ 3.5 Hz and 5.03, br s, $Wh_{/2}$ 3 Hz, H12a and H12b; 4.07, br s, $Wh_{/2}$ 3.5 Hz, H_2-14; 3.71, s, OCH_3; 0.96, d, J 6.7 Hz, H_3-11, ^{13}C nmr: see Table 1. MS *m/z* 264 (M^+) (2%), 246 (10), 232 (22), 187 (82), 145 (82), 137 (74), 105 (100). (c) The dihydro ether (**11**) (81 mg, 0.31 mmol) was treated as above with LDA (0.67 ml, 0.61 mmol) and the mixture was allowed to come to 25° over 1 hr. The product recovered (74 mg) was purified by RPC as above to give the *dihydro hydroxy*

ester (**13**) (12 mg) as crystals, mp 69-70°, $[\alpha]_D$-20° (c, 0.3; $CHCl_3$). ν_{max} 3620, 3650-3420, 1720, 1650 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ 7.09, br s, $Wh_{/2}$ 6 Hz, H6, 3.73, s, OCH_3, 3.55, m, $Wh_{/2}$ 3 Hz and 3.53, m, $Wh_{/2}$ 3 Hz, H_2-14; 0.87, d, J 6.9 Hz and 0.86, d, J 7.0 Hz, H_3-11 and H_3-12; ^{13}C nmr: see Table 1. MS *m/z* 266 (M^+) (4%), 234 (52), 207 (45), 175 (100).

Purification of epoxide (**3**). A portion of the crude epoxide (460 mg) in MeOH (20 ml) at 0° was stirred with $NaBH_4$ (173 mg) overnight. The product recovered (453 mg) was purified by RSF. Gradient elution with light petroleum and EtOAc gave the *epoxide* (**3**) (300 mg) which crystallised from ether as needles, mp 180-181°, $[\alpha]_D$ +117°: (*c*, 0.9; $CHCl_3$) (Found: C, 71.7; H, 8.8; M^+ 250.1547. $C_{15}H_{22}O_3$ requires C, 72.0; H, 8.9; M^+ 250.1569). ν_{max} 1695, 1645 cm^{-1}; ^1H nmr δ: 7.14, br s, H6; 2.79, d, and 2.64, d, J_{gem} 4.8 Hz, H12a and H12b; 2.40, m, H8 eq; 2.12, m, H8 ax; 2.07, m, H5; 1.91, m, $Wh_{/2}$ 19 Hz, H1; 1.30, s, H_3-13, 0.90, d, J 7.2 Hz, H_3-11; ^{13}C nmr: see Table 1. MS *m/z* 250 (M^+) (2%), 232 (27), 193 (57), 192 (87), 189 (33), 147 (98), 131 (52), 123 (35), 119 (47), 105 (93), 91 (100).

Deoxygenation of epoxide (**3**). The epoxide (**3**) (147 mg) in 1,2-dichloroethane (15 ml) was stirred with NaI (880 mg), NaOAc (100 mg), AcOH (1 ml) and Zn (1.2 g) and the mixture heated under reflux for 3 hr. The product recovered (125 mg) was separated by RPC (4% MeOH:CH_2Cl_2) to give (a) the *acid* (**7**) (40 mg) which crystallised from ether as needles, mp 158°-162°, $[\alpha]_D$ -144° (*c*, 0.5, $CHCl_3$) (Found: C, 76.3; H, 9.3; M^+ 234.1596. $C_{15}H_{22}O_2$ requires C, 76.9; H, 9.5; M^+ 234.1620). ν_{max} 3550, 1700 cm^{-1}; ^1H nmr δ:6.98, br s, $Wh_{/2}$ 5 Hz, H6; 4.86, m, $Wh_{/2}$ 4.5 Hz and 4.76, m, $Wh_{/2}$ 4.5 Hz, H12a and H12b; 2.42, m, H4; 1.71, br s, H_3-14; 0.91, d, J 7.2 Hz, H_3-11; ^{13}C nmr: see Table 1. MS *m/z* 234 (M^+) (37%), 219 (20), 193 (20), 192 (17), 189 (26), 188 (25), 149 (100). The Gc retention time of the derived methyl ester, R_t 9.72 min, corresponded to that observed for the major component in the methylated mixture obtained by hydrogenolysis of the allylic acetates derived from **1** and **2**; and (b) the *hydroxy acid* (**1**) (19 mg) which crystallised from ether in white clusters, mp 132°, $[\alpha]_D$ -19° (*c*, 0.8; $CHCl_3$) (Found: C, 71.5; H, 8.8; M^+ -18, 232.1434. $C_{15}H_{22}O_3$ requires C, 71.8; H, 8.9%; M^+-18, 232.1463). ν_{max} 3620, 3600-3000, 1710, 1650 cm^{-1}; ^1H nmr δ: 6.95, br s, $Wh_{/2}$ 4.5 Hz, H6; 5.22, br s, $Wh_{/2}$ 4.0 Hz, and 4.95, br s, $Wh_{/2}$ 3.0 Hz, H12a and H12b; 4.11, br s, $Wh_{/2}$ 3.5 Hz, H_2-14; 0.91, d, J 7.2 Hz, H_3-11. MS *m/z* 250 (M^+) (2%), 232 (68), 217 (16), 187 (43), 162 (51), 147 (55), 145 (57), 131 (73), 107 (68), 105 (96), 79 (100). The gc retention time of the derived methyl ester (R_t 10.93 min) was identical with that of **5**.

Ozonolysis of **9** and **10**. (a) A mixture of the cyclic ether (**9** and **11**) (513 mg) in a 7.3 ratio, was dissolved in CH_2Cl_2 (15 ml) and pyridine (0.5 ml) and treated with ozonised O_2 at -78°. The reaction mixture was stirred with Zn (1.8 g) and AcOH (1 ml) for 1 hr. The product recovered (495 mg) was chromatographed by RPC (10% EtOAc:light petroleum) to give (i) *dihydro ether* (**13**) (144 mg) as a clear oil, $[\alpha]_D$ +30.8° (*c*, 1.0, $CHCl_3$) (Found: M^+ 266.1866. $C_{16}H_{26}O_3$ requires 266.1882). Gc, R_t 9.93 min; ν_{max} 1745 cm^{-1}; ^1H nmr: δ 3.80, dd, J_{gem} 11.3 Hz, $J_{13,14\ eq}$ 4.5 Hz, H14 eq; 3.70, s, OCH_3; 3.25, dd, $J_{5,6}$ 9.9 Hz, $J_{6,7}$ 10.4 Hz, H6, 3.08, dd, J_{gem} 11.3 Hz, $J_{13,14\ ax}$ 11.2 Hz, $H_{14\ ax}$; 2.36, ddd, $J_{7,8eq}$ 3.7 Hz, $J_{6,7}$ 10.4 Hz, $J_{7,8ax}$ 12.3 Hz, H7; 1.91, m, H8 eq; 1.45, m, H8 ax; 1.02, m, H5, 0.86, d, J 6.7 Hz, H_3-11; 0.74, d, J 6.6 Hz, H_3-12; ^{13}C nmr: see Table 1. MS *m/z* 266 (M^+) (13%), 248 (11), 235 (8), 207 (37), 206 (100), 165 (73), 147 (30); and

(ii) the *nor*-ketone (**14**) (134 mg) as crystals, mp 114°, $[\alpha]_D$ + 114.4° (*c*, 0.1, $CHCl_3$) (Found: C, 67.7; H, 8.4; M^+ 266.1497. $C_{15}H_{22}O_4$ requires C, 67.7; H, 8.3%; M^+ 266.1518). Gc, R_t 10.5 min; ν_{max} 1740 cm^{-1}; ^1H nmr δ: 4.09, d, J_{gem} 14.9 Hz, and 4.02, dd, J_{gem} 14.9 Hz, and 4.02, dd, J_{gem} 14.9 Hz, $J_{7,14b}$ 0.7 Hz, H14a and H14b; 3.74, m, H6; 3.72, s, OCH_3; 2.40, ddd, $J_{7,8\ eq}$ 3.8 Hz, $J_{6,7}$ 10.2 Hz, $J_{7,8ax}$ 12.3 Hz, H7; 2.14, m, H4; 2.02, m, H8 eq; 1.89, m, H1; 1.87, m, H3 eq; 1.60, m, H8 ax; 1.52, m, H5; 1.45, m, H3 ax; 0.86, d, J 7.2 Hz, H_3-11; ^{13}C nmr: see Table 1. MS *m/z* 266 (M^+) (20%), 238 (10), 235 (9), 223 (46), 191 (36), 155 (72), 148 (100). (b) The cyclic ether (**10**) (200 mg) was treated as in (a) to give the *nor*-ketone (**15**) (141 mg) as an oil, $[\alpha]_D$ +45° (*c*, 5.1; $CHCl_3$) (Found: M^+ 266.1494. $C_{15}H_{22}O_4$ requires 266.1518). Gc: single peak at R_t 10.89 min; ν_{max} 1725 cm^{-1}; ^1H nmr δ: 4.12, dd, $J_{5,6}$ 5.4 Hz, $J_{6,7}$ 11.3 Hz, H6; 4.11, d and 3.96, d, J_{gem} 15.9 Hz, H14a and H14b; 3.74, s, OCH_3; 3.07, ddd, $J_{7,8\ eq}$ 3.9 Hz, $J_{6,7}$ 11.3 Hz, $J_{7,8\ ax}$ 12.0 Hz, H7; 2.46, m, H4; 0.91, d, J 6.8 Hz, H_3-11. MS *m/s* 266 (M^+) (27%), 235 (18), 223 (78), 207 (18), 206 (19), 191 (100), 148 (68).

p-Bromobenzenesulphonylhydrazone derivatives of (**14**) and **15**). (a) The *nor*-ketone (**14**) (70 mg) in MeOH was treated with a solution of *p*-bromobenzenesulphonyl hydrazine (70 mg) in MeOH (3 ml) and the mixture was stirred for 6 hr. The product was recovered by filtration and crystallised from EtOAc-MeOH to give the hydrazone (**16**) (105 mg) as plates, mp 161-163°. (b) Similar treatment of **15** (93 mg) gave the crystalline hydrazone (**17**) (165 mg), mp 141-142° (dec).

Hydrogenation of the cyclic ether (**9**). The ether (**9**) (326 mg) in MeOH was stirred with 10% Pd/C (33 mg) under hydrogen for 18 hr. The product recovered (214 mg) on gc analysis showed the presence of **11** (35%), R_t 11.98 min, and **12** (65%), R_t 11.78 min. (Conditions: T_1 100°C (0.5 min), T_2 250°C (5 min), rate 7.5°C/min). The ^{13}C nmr spectrum of the mixture contained signals corresponding to those observed in the spectrum of pure **11**. The remaining signals were consistent with structure **12**.

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