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A NEW CLASS OF MONOCYCLIC DITERPENES FROM EREMOPHILA FOLIOSISSIMA KRAENZLIN. (MYOPORACEAE)+

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Abstract - Three diterpene acids, representing a new class of monocyclic diterpenes, have been isolated from E. foliosissima Kraenzlin. (Myoporaceae). Chemical and spectroscopic evidence is presented for their structure and absolute configuration. These diterpenes can be considered as isoprenologues of the bisabolene sesquiterpenes.

The bicyclic and tricyclic diterpenes produced by species of the Eremophila genus contain C5-extended sesquiterpene skeletons. Five separate classes have been identified so far.[1] In biogenetic terms, all of these can be derived, at least formally, by considering the cyclisation of a C5-extended bisabolonium cation. However, no examples containing the skeleton of this simple putative intermediate had been found in Eremophila species. In continuation of our work aimed at mapping the biosynthetic pathways available to Eremophila, we have investigated the resin of E. foliosissima Kraenzlin. We now report on the structure and absolute configuration of three bisabolene isoprenologues isolated from this species. These compounds occur naturally as carboxylic acids but were separated and purified more conveniently as the corresponding methyl esters (1, 9 and 10).

The most polar metabolite isolated from the methylated fraction was the hydroxy acetate ester (1) (ν_{max} 3470, 1735, 1715 cm^{-1}). The compound was unstable and did not show a molecular ion in the MS. The ^{13}C-NMR spectrum however showed signals for 23 carbon atoms which included those associated with a methyl ester (δ167.8, s; 51.9, q), an acetate (δ170.3, s; 21.2, q) on a secondary carbon (δ68.9, d), a tertiary carbinol (δ67.3, s) and three olefinic groups (δ132.5, 134.3, d; 139.3, d, and 133.8, s; 123.2, d, and 133.8, s). On this basis the compound could be assigned the formula of $C_{23}H_{36}O_5$ and must be monocyclic. The ^{1}H-NMR spectrum substantiated the presence of the functional groups.Extensive decoupling and INDOR experiments yielded the connectivity patterns shown in Fig. 1 and pointed in favour of (1) containing a tertiary allylic hydroxyl group. Confirmation of this came from PCC oxidation[2] of (1) which gave the cyclohexenone (2), $C_{23}H_{34}O_5$ (ν_{max} 1735, 1715, 1670 cm^{-1}; δ_C 200.1,s). Further more, dehydration of (1) with p-toluenesulphonic acid in the presence of oxygen provided the 1,4-disubstituted benzene (3). Evidence for the presence of the terpenoid side chain was obtained by degradation of (3) to 3-(4-methylphenyl)-butanoic acid (7)[3] by standard methods (Scheme 1) in a sequence which provided two compounds (5 and 7) later used to derive the absolute configuration of (1) (see below). The formation of 3-(4-methylphenyl)-butanoic acid (7) and the requirement from spectral analysis for the presence of a conjugated ester and a 4-methylpent-3-enyl moiety leads to structure (1) for the most polar metabolite from E. foliosissima. Transesterification of (1) with sodium methoxide

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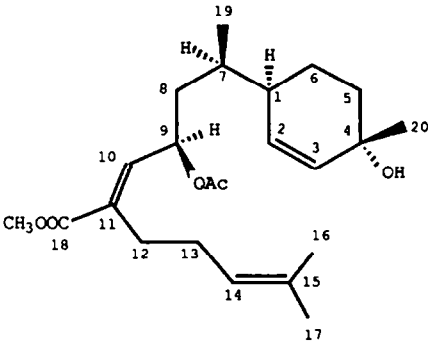
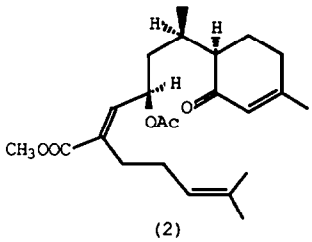


C	δ ^{13}C	δ ^{1}H	Multiplicity ($J_{H,H}$ Hz)
1	41.3	2.02	m
2	132.5	5.58	dd (9.5, 1.4)
3	134.3	5.7	dt (9.5, 1.0, 1.0)
4	67.3		
5	37.2	1.8, 1.52	m
6	21.1	1.6, 1.4	m
7	32.7	1.65	m
8	38.0	1.8, 1.30	m
9	68.9	5.63	ddd (10.0, 9.0, 3.5)
10	139.3	6.52	d (9.0)
11	133.8		
12	27.6	2.40	m
13	27.5	2.10	m
14	123.2	5.12	tq (7.4, 1.3)
15	133.8		
16	17.6	1.62	br s
17	25.7	1.68	br s
18	167.8		
19	16.7	0.96	d (6.7)
20	29.7	1.29	s
OCH_3	51.9	3.75	s
OAc	170.3	2.02	s
	21.2		

Figure 1. NMR data for the hydroxy acetate ester (1). Assignments are based on ^{1}H-^{1}H decoupling and INDOR measurements



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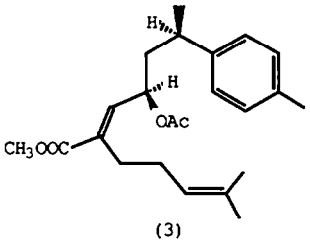

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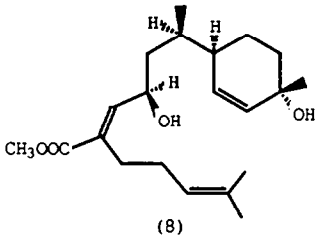

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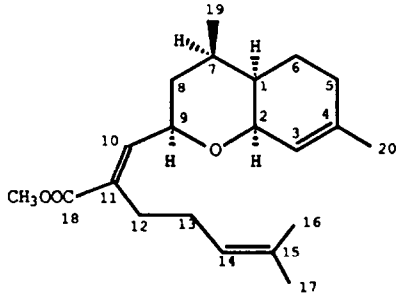
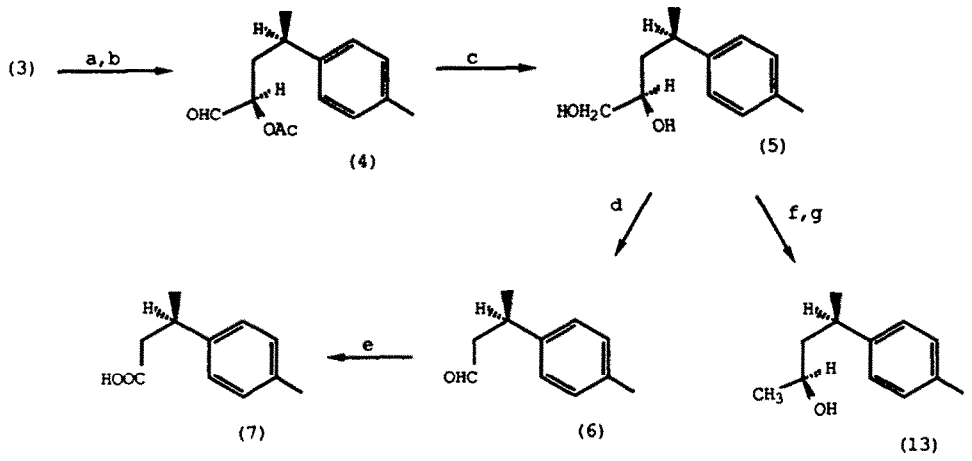


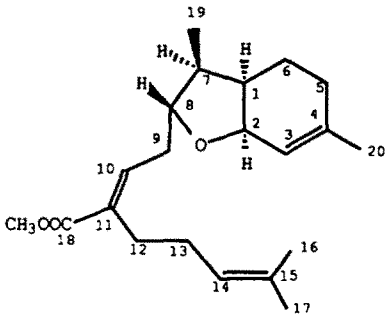
C	δ ^{13}C	δ ^{1}H	Multiplicity ($J_{H,H}$ Hz)
1	38.3	1.51	m
2	74.9	3.79	br d (3.9)
3	121.2	5.55	d (3.9)
4	141.3		
5	31.2	1.8, 2.15	m
6	16.1	1.70	m
7	33.0		
8	34.9	1.31	m
9	73.7	4.20	ddd (8.9)
10	142.0	6.71	d (8.9)
11	132.6		
12	27.9	2.33	m
13	27.9	1.80, 2.15	m
14	123.8	5.14	t (7.0)
15	132.6		
16	17.6	1.60	br s
17	25.7	1.69	br s
18	168.3		
19	18.9	0.95	d (6.9)
20	23.5	1.70	s
OCH_3	51.7	3.70	s

Figure 2. NMR data for the tetrahydropyran (9). Assignments are based on ^{1}H-^{1}H, ^{13}C-^{1}H correlation and ^{1}H decoupling measurements.



Scheme 1. (a) O_3, CH_2Cl_2 (b) Zn (c) $LiAlH_4$, Et_2O (d) $NaIO_4$, H_2O, dioxan (e) Jones reagent, acetone (f) TsCl, C_5H_5N (g) $LiAlH_4$, Et_2O

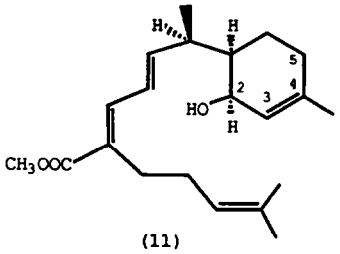
yielded the crystalline diol (8) which was found to be unstable in solutions of $CDCl_3$. In fact, heating a solution of (8) in $CDCl_3$ in an NMR tube at 45° for 20 hr resulted in the conversion of (8) to the tetrahydropyran (9), the structure of which followed from detailed spectral analysis (^1H-^1H- correlation, ^1H-homonuclear decoupling) (Fig. 2). Interestingly, this compound proved to be identical with another metabolite isolated from the methylated acidic fraction of E. foliosissima. A third compound from this fraction, and separable only with difficulty from (9), was assigned structure (10) on the following evidence. The ^{13}C-NMR spectrum of (10) included a subset of signals which were essentially identical with those assigned to C11-C18 in the spectrum of the tetrahydropyran (9). The results from ^1H-^1H decoupling and correlation experiments are shown in Fig. 3. Of particular importance is the observation that the β-proton (δ 6.86) of the α,β-unsaturated ester function appears as a triplet (J 7.3 Hz) and shows coupling to two mutually coupled protons at δ 2.36 and 2.46 (J 14.2 Hz). These in turn show couplings of 6.6 and 4.2 Hz to an oxymethine proton (δ 3.75) which is further coupled to a proton at δ 2.15.



C	δ ^{13}C	δ ^1H	Multiplicity ($J_{H,H}$ Hz)
1	42.8	1.95	m
2	75.1	4.23	dd (4.4, 4.2)
3	120.2	5.58	br s
4	140.5		
5	29.6	1.95	m
6	19.8	1.27, 1.58	m
7	41.5	2.15	m
8	81.8	3.75	m
9	33.4	2.36	ddd (14.2, 7.3, 6.6)
		2.46	ddd (14.2, 7.3, 4.2)
10	139.3	6.86	t (7.3)
11	133.4		
12	27.7	2.28	m
13	27.7	2.00	m
14	123.6	5.11	t (7.0)
15	132.2		
16	17.6	1.56	br s
17	25.7	1.68	br s
18	168.2		
19	11.6	0.97	d (6.9)
20	23.7	1.72	s
OCH_3	51.7	3.69	s

Figure 3. NMR data for the tetrahydrofuran (10). Assignments are based on ^1H-^1H, ^{13}C-^1H correlation and ^1H-decoupling measurements.

The multiplicity of this proton simplified on irradiation of the doublet at δ 0.97 for the secondary methyl group. Evidence for the δ-oxy-conjugated ene system was obtained by treatment of (10) with LDA which yielded the (E,E)- conjugated diene (11) (λ_{max} 269, log ε 4.35). The ^{1}H-NMR spectrum of (11) showed the proton at the terminus of the diene system (H-8, δ 5.96) to be coupled (J 9.4 Hz) to the proton (H-7, δ 2.40) which also showed coupling to the secondary methyl (δ 1.13). The presence and substitution pattern of the cyclohexene ring, already inferred from spectroscopic analysis of (10), was also indicated from the ^{1}H- and ^{13}C-NMR spectra of (11). Furthermore the chemical shifts and multiplicities of the oxymethine proton (δ_2 4.15, Wh/2 6 Hz) and the vinylic proton (δ_3 5.65; dd, J 5.4 and 1.6 Hz) in the ^{1}H-NMR of (11) showed better correlation with those observed for cis-piperitol (12) (δ 4.18, Wh/2 9 Hz; 5.64, br d, J 5 Hz) than those for trans-piperitol (δ 4.06, Wh/2 13 Hz; 5.38, Wh/2 5 Hz)[4]. More strikingly, the chemical shifts assigned to carbons 2 to 5 in (11) (δ 64.4, 123.7, 140.2, 31.3) corresponded closely with those reported[5] for the equivalent carbons in (12) (δ 64.0, 123.7, 139.3, 31.4) but not with those for trans-piperitol (δ 68.8, 125.4, 137.1, 30.0). Supporting evidence for the structure assigned to (10) was obtained by degradation of (10) to the 1-(4-methylcyclohex-3-en-1-yl) ethanol (22) (Scheme 2) a compound which also served in the assignment of the absolute configuration of (10).



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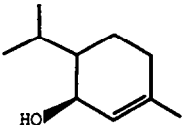


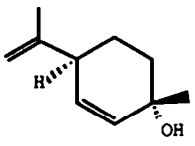
(12)

Absolute Configurations of (1), (9) and (10)

A full description of the structure of each diterpene requires the configuration at five centres to be clarified. In each case the double bond at C10 was shown to have the E-configuration, the chemical shift of the vinylic proton (δ > 6.5) comparing favourably with that calculated[6] for a similarly substituted E-double bond (δ 6.60) but not with that for a Z-double bond (δ 6.03). In all cases NOE's were observed between the vinylic proton and the methoxy-carbonyl protons of the α,β-unsaturated ester group. The monocyclic alcohol (1) and the tetrahydropyran (9) have the same stereochemistry at C6, 7 and 9 since the deacetyl derivative of (1) on cyclization yields (9). The degradation of (1) to 3-(4-methylphenyl)-butanoic acid (7)[3] (Scheme 1) provided the R-enantiomer thus establishing the R-configuration at C7 in (1) and (9). The configuration at C9 was obtained by application of the Horeau method[7] to the compound (13) derived by deoxygenation of the primary alcohol of (5) (Scheme 1). The results indicate that the carbinol carbon in (13) possesses the S-configuration and therefore C9 in (1) and (9) can be assigned the R-configuration.

The conformation of the tetrahydropyran ring in (9) and the relative configuration at C1, 2, 7 and 9 was revealed from application of NOE difference spectral techniques. Significant NOE's were observed between H9 and H2, H9 and H7, placing these three hydrogen in a 1,3-diaxial relationship to each other. Other interactions were observed between the secondary methyl at C7 and H1 and, significantly, between H1 and H2 thus placing H1 in an equatorial position. Supporting evidence for this can be gleaned from the observation that the chemical shift for the secondary methyl at C7 (δ 18.9) is consistent[8] with that expected for an equatorial methyl with a neighbouring axial methylene group. Given that the absolute configurations at C7 and C9 are R- and R-, respectively, this leads to the R-configuration at C1 in both (1) and (9) and the S-configuration at C2 in (9). Thus the absolute stereochemistry of the tetrahydropyran diterpene of E. foliosissima is that shown in (9).

The absolute configuration of (1) is also established with the exception of C1. Ohloff and Giersch[9] have shown that for the menthadien-1-ols (14) and (15) the pseudo-equatorial hydroxyl



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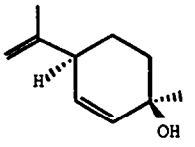
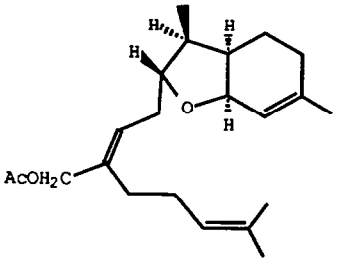


(15)

group in (14) is esterified with phenylbutyric anhydride whereas the pseudo-axial hydroxyl in (15) did not react. The hydroxy ester (1) was found to react with phenylbutyric anhydride under similar conditions thus indicating that the alkyl substituents are in a cis-relationship.

The absolute configuration of the four asymmetric centres of the tetrahydrofuran (10) was established by two independent degradation sequences. The first involved cleavage of the C2 ether bond and application of the method of Horeau[7] for determining the configuration of the secondary hydroxyl group at C8. To this end (10) was converted to the primary allylic acetate (16) which on treatment with Li/NH_3 yielded the secondary alcohol (17), contaminated with 12% of the Δ^2-isomer. A Horeau determination indicated that C8 had the R-configuration, a tentative assignment at this stage since a mixture was used. The configuration at C1 and C7 was determined by degradation of (11) to the 1-(4-methylcyclohex-3-en-1-yl)ethanol (22) which was shown to be enantiomeric to a sample of 1R,1'R-isomer (28) synthesised from (+)-limonene (Scheme 3). The sequence in the degradation of (11) is shown in Scheme 2 and fully described in the experimental.



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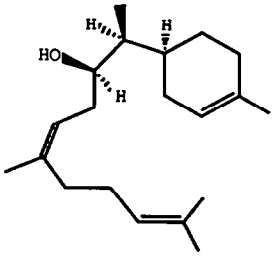

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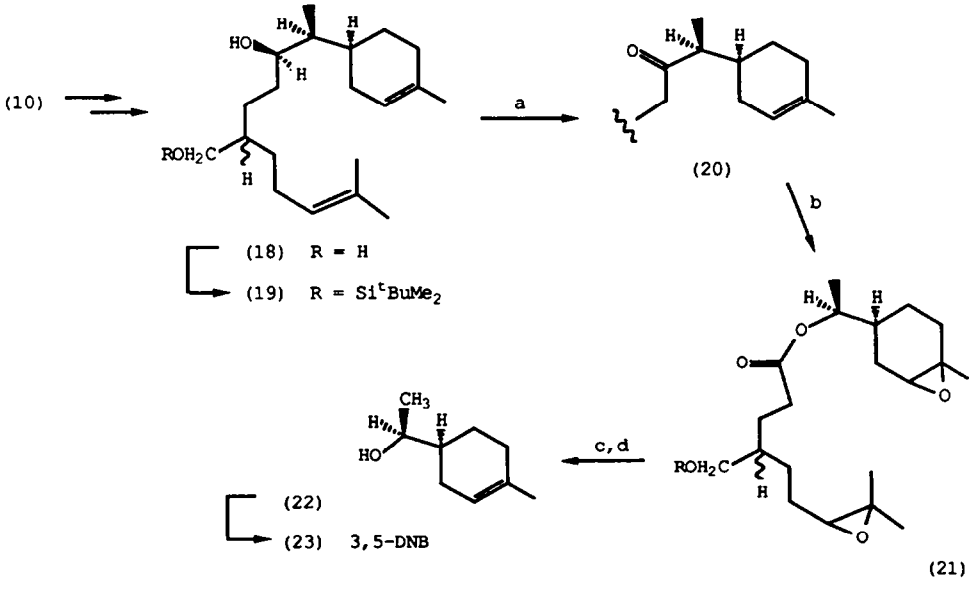
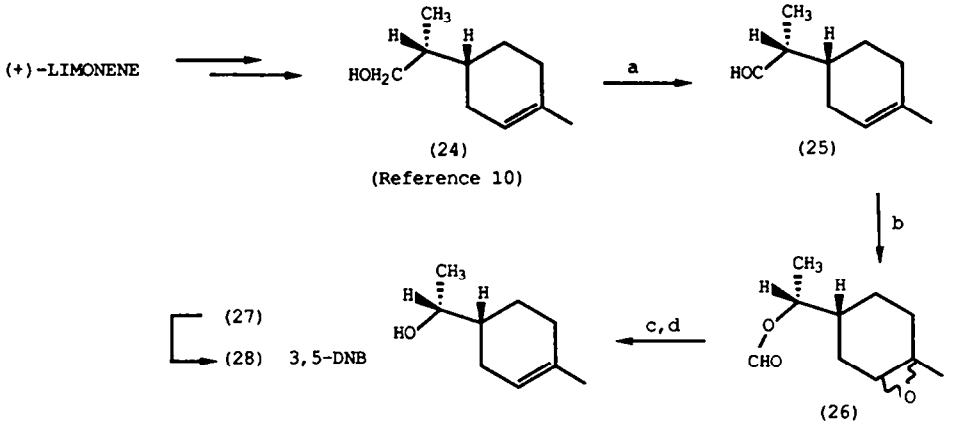


Scheme 2. (a) PDC, CH_2Cl_2, NaOAc (b) m-CPBA, $NaHCO_3$, CH_2Cl_2

(c) Zn, NaI, NaOAc, AcOH (d) KOH, MeOH

The configuration at C2 can be assigned as S since the ^{1}H- and ^{13}C-NMR spectra of the product (11) from the LDA reaction of (10) supported a cis-piperitol part structure. Confirmation of the relative and hence the absolute stereochemistry assigned came from a NOESY spectrum which showed NOE's between the secondary methyl at C7 and H8, H7 and H1, and H1 and H2.



Scheme 3. (a) PDC, CH_2Cl_2 (b) m-CPBA, $NaHCO_3$, CH_2Cl_2

(c) Zn, NaI, NaOAc, AcOH (d) $LiAlH_4$, Et_2O

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

Carbons	2	3	11[b]	16	17	28[c]
1	51.2	143.6	39.2	42.8	34.4	38.7
2	200.1	126.8	64.4	74.9	32.1	27.6
3	127.2	129.4	123.7	120.4	121.0[d]	122.4
4	161.2	138.8	140.2	140.3	134.0	134.5
5	30.9	129.4	31.3	29.8	31.0	29.8
6	23.8	126.8	21.6	19.9	28.1	25.0
7	24.1	42.4	44.4	41.6	43.0	77.7
8	38.2	35.9	148.7	82.5	73.1	
9	68.8	68.7	125.6	33.1	32.4	
10	139.5	139.1	139.5	127.0	121.5[d]	
11	133.8	134.6	129.6	135.6	139.3	
12	27.7	27.7	28.1[d]	28.7[d]	26.9[e]	
13	27.7	27.7	27.2[d]	26.9[d]	26.6[e]	
14	123.6	123.6	123.7	124.1	124.2	
15	132.7	135.8	132.4	132.1	132.0	
16	17.7	17.7	17.6	17.7	17.6	
17	25.7	25.7	25.7	25.7	25.7	
18	168.1	168.1	169.0	68.7	23.5[f]	
19	16.8	22.4	18.3	11.9	10.9	17.4
20	21.1	21.0	23.4	23.8	23.6[f]	23.4
OCH_3	51.9	51.9	51.6			
OAc	170.4	170.4		171.0		
OAc	21.1	21.1		21.0		

a. ($CDCl_3$; 20.1 MHz) Multiplicities of signals were determined by SFORD and GASPE techniques and are consistant with assignments

b. Obtained at 75 MHz, $CDCl_3$

c. The numbering system used for the diterpene has been retained. Values for benzoate group: δ_c 162.6(s), 134.7(s), 129.5(2d), 148.9(2s), 119.5(d).

d-f. Values in any one column may be interchanged.

EXPERIMENTAL

General experimental details have been described.[11] Unless otherwise stated, optical rotations were measured for $CHCl_3$ solutions, IR spectra for CCl_4 solutions, ^1H- and ^{13}C-NMR spectra for $CDCl_3$ solutions. 300 MHz ^1H-NMR and 75 MHz ^{13}C-NMR spectra were recorded on a Brucker AM-300 (Varian XL-300 spectrometer for compound (10)).

Isolation of metabolites from E. foliosissima Kraenzlin. Leaves and outer branches (750 g) of a sample of the plant, collected 32 km north of Mt Magnet, Western Australia, were soaked with acetone (3 l) for 20 hr. The recovered extract was taken up in ether and washed with saturated $NaHCO_3$ solution (2x), and the ether solution was concentrated to give a crude extract (57.5 g). A portion of this extract (23 g) was treated with ethereal diazomethane to give a crude methyl ester fraction which was chromatographed by rapid silicic acid filtration (RSF) to afford two fractions consisting of mainly the methyl ester (1) (6.2 g) and a mixture of the methyl esters (9) and (10) (7.5 g; 2:1). Purification of the first fraction by radial chromatography afforded (1) as an unstable oil. ^1H- and ^{13}C-NMR: see Fig. 1; IR (ν_{max}) 3465, 1733, 1717, 1646 cm^{-1}, MS: m/z 342(M^+-60, 2%), 300 (26), 282 (14), 267 (14), 255 (23), 245 (96), 193 (34), 148 (80), 120 (100). Radial chromatography (EtOAc: light petroleum, 1:9) of portions of the less polar fraction provided pure samples of the tetrahydropyran (9) and the tetrahydrofuran (10), in order of elution. The tetrahydropyran (9) was obtained as an oil, b.p. 220° (bath)/0.3 mm, $[\alpha]_D$ -94.1° (c, 0.5) (Found: C, 76.55; H, 9.88. $C_{21}H_{32}O_3$ requires C, 75.85; H, 9.71%). IR (ν_{max}) 1715, 1670, 1648 cm^{-1}; ^1H- and ^{13}C-NMR: see Fig. 2. MS: m/z 332 (M^+, 1%), 314 (2), 300 (3), 245 (20), 193 (16), 161 (20), 148 (26), 121 (100), 93 (41). The tetrahydrofuran (10) was obtained as an oil, b.p. 175° (bath)/0.25 mm, $[\alpha]_D$ -49.5° (c, 0.6) (Found: C, 75.81; H, 9.65. $C_{21}H_{32}O_3$ requires C, 75.85, H, 9.71%). IR (ν_{max}) 1721, 1655, 1650 cm^{-1}; ^1H- and ^{13}C-NMR: see Fig. 3. MS: m/z 332 (M^+, 2%), 263 (2), 151 (26), 123 (18), 93 (100), 81 (14).

Pyridinium chlorochromate oxidation of the ester (1). The ester (1) (127 mg) in dry CH_2Cl_2 (10 ml) was added to a stirred solution of PCC (280 mg) in dry CH_2Cl_2 (20 ml). The mixture was stirred for 2 hr at room temperature then was diluted with ether (20 ml) and filtered through a plug of silicic acid under reduced pressure. The organic solution was concentrated to give, after radial chromatography (light petroleum/ethyl acetate, 4:1), the enone (2) (100 mg) as an oil, b.p. 180-185° (bath)/0.05 mm, $[\alpha]_D$ -25.0° (c, 0.14) (Found: C, 70.81; H, 8.98; $C_{23}H_{34}O_5$ requires C, 70.72; H, 8.78%). IR (ν_{max}) 1737, 1718, 1669, 1635 cm^{-1}; ^1H-NMR (80 MHz): δ 1.01 (d, J 7.0 Hz, $(H19)_3$); 1.29 (m, H8b); 1.60 (s, $(H16)_3$); 1.68(s, $(H17)_3$); 1.85 (m, H8a); 1.93 (s, $(H20)_3$); 2.08 (s, acetoxy methyl); 3.72 (s, $-OCH_3$); 5.13 (t, J 7.0 Hz, H14); 5.65 (ddd, J 9.0, 8.7, 1.0 H9), 5.84 (br s, $W_{h/2}$ 5Hz, H3), 6.53 (d, J 9.0 Hz, H10); ^{13}C-NMR: see Table 1. MS: m/z 340 (M^+ -60), 298 (14), 261 (38), 229 (36), 193 (14), 188 (29), 137 (80), 135 (28), 110 (100).

Aromatization of (1). The ester (1) (530 mg) in dry toluene (10 ml) was stirred with a solution of TsOH in dry toluene (6.5 ml aliquot of an 8.6 mg/ml solution) for 2 hr with O_2 bubbling through the solution at 60°. The reaction mixture was cooled, poured into 10% $NaHCO_3$ solution and usual workup gave, after radial chromatography (light petroleum-EtOAc, 4:1), the aromatic ester (3) (289 mg) as an oil (Found: M-HOAc 312.208, $C_{21}H_{32}O_4$ requires M-HOAc 312.209). ^1H-NMR (80 MHz): δ 1.24 (d, J 6.9 Hz, $(H19)_3$); 1.55 (br s, $(H16)_3$); 1.67 (br s, $(H17)_3$); 1.93 (s, acetoxy methyl); 2.31 (s, $(H20)_3$); 2.34 (m, H7); 3.73 (s, methyl ester); 5.05 (br t, J 7 Hz, H14); 5.56 (m, H9); 6.49 (d, J 9.2 Hz, H10); 7.08 (s, H2,3,5,6); ^{13}C-NMR: see Table 1. MS: m/z 312 (6), 265 (5), 216 (6), 193 (23), 161 (9), 133 (9), 119 (100), 69 (14).

Conversion of (3) to 3-(4-methylphenyl)butanoic acid (7). The aromatic ester (3) (100 mg) in CH_2Cl_2 (10 ml) was treated with ozonized oxygen at -70° for 10 min. The solution was allowed to reach room temperature then acetic acid (2 ml) and Zn powder (100 mg) were added and the mixture stirred for 15 min. The Zn powder was removed by filtration, the filtrate was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ solution and usual workup with CH_2Cl_2 gave a colourless oil (85 mg), which contained the aldehyde(4). The crude fraction was dissolved in ether (5 ml) and treated with $LiAlH_4$ (200 mg) for 2 hr at room temperature. Recovery of the product gave the diol (5) (24 mg) as an oil (Found: M^+ 194.130. $C_{12}H_{18}O_2$ requires M 194.131). ^1H-NMR (80 MHz): δ1.26 (d, J 6.9 Hz, $(5H)_3$); 1.70 (m, $(H3)_2$); 2.32 (s, aromatic methyl); 2.82 (m, H2), 3.60 (m, $(H1)_2$); 7.11 (s, aromatic protons). MS: m/z 194 (M^+, 2%), 176 (6), 158 (5), 145 (9), 119 (100), 105 (11), 91 (12). The diol (5) (24 mg) was dissolved in dioxan (2 ml), a solution of $NaIO_4$ (50 mg) in H_2O (1 ml) was added and the mixture stirred at room temperature for 18 hr. Usual workup with ether gave a colourless oil (18 mg) which appeared from its ^1H-NMR spectrum to consist of a mixture of the aldehyde (6) and its hydrate (20 mg). The mixture in acetone (2 ml) was treated with Jones reagent (0.5 ml) to give the acid (7) (16 mg) as an oil, $[\alpha]_D$ -44.2° (c, 1.8; C_6H_6). The acid was converted into the S-benzyl-iso-thiouronium salt which was recrystallized from acetone as plates, m.p. 152.5-153° (lit.[3] m.p. 151-152°). The acid obtained on hydrolysis of the salt was an oil, $[\alpha]_D$ -66.4° (c, 0.3 C_6H_6), lit.[3] value for the S-enantiomer $[\alpha]_D$ + 65° (c, 4.6; C_6H_6). ^1H-NMR (80 MHz): δ 1.29 (d, J 6.3 Hz, $(H4)_3$); 2.31 (s, 4' methyl protons); 2.61 (m, $(H2)_2$); 3.51 (m, H3); 7.11 (s, aromatic protons). MS: m/z 178 (M^+, 18%), 119 (100), 91 (18).

Interrelation of (1) and (9). The ester (1) (330 mg) in dry MeOH (10 ml) was stirred with NaOMe (100 mg) at room temperature for 2 hr, then the mixture was poured into ice-cold 10% HCl solution. Usual workup with ether gave, after radial chromatography (light petroleum-EtOAc, 4:1), the diol (8) (192 mg) which was recrystallized from pentane as clusters of microcrystalline needles, m.p. 75-76°, $[\alpha]_D$ + 4.0° (c, 0.7). ^1H-NMR (90 MHz): δ 0.96 (d, J 6.5 Hz, $(H19)_3$); 1.26 (s, $(H20)_3$); 1.58 (br s, $(H16)_3$); 1.68 (br s, $(H17)_3$); 3.73 (s, methyl ester); 4.47 (m, H9); 5.12 (br t, J 7.0 Hz, (H14); 5.65 (br s, H2 and H3); 6.65 (d, J 8.9 Hz, H10). The diol (8) (100 mg) in $CDCl_3$

(2 ml), in a 10 mm NMR tube, was heated at 45° for 20 hr, after which time the ^{1}H-NMR spectrum indicated the presence of the ester (9). The recovered product $[\alpha]_D$-98.6° (c, 0.56) was found to be identical in all respects with the least polar ester (9) isolated from the methylated extract of E. foliosissima.

Preparation and absolute configuration of (13). The diol (5) (130 mg) in pyridine (2 ml) was treated with p-toluenesulphonyl chloride (192 mg) at room temperature for 20 hr. The product recovered was dissolved in ether and stirred with $LiAlH_4$ (250 mg) at room temperature for 18 hr. The product obtained was purified by radial chromatography (light petroleum–EtOAc, 9:1) to give the alcohol (13) (60 mg) as an oil, b.p. 140° (bath)/0.5 mm, $[\alpha]_D$-8.9° (c, 0.6) (Found: C,80.54; H, 10.20. $C_{12}H_{18}O$ requires C, 80.83; H, 10.19%). ^{1}H-NMR (80 MHz): δ 1.16 (d, J 6.4 Hz); 1.24 (d, J 6.5 Hz); 2.31 (s, aromatic methyl); 2.81 (m, benzylic proton); 3.75 (m, oxymethine); 7.11 (s, aromatic protons). MS: m/z 178(M^+; 14%), 160 (12), 145 (92), 119 (100), 105 (32), 91(21). The alcohol (13) (30 mg, 0.168 mmol) in dry pyridine (0.5 ml) was stirred with phenylbutric anhydride (104 mg, 0.337 mmol) for 16 hr at room temperature. The excess anhydride was hydrolysed by stirring with water (0.5 ml) for 45 min and the acids were titrated with 0.101 M NaOH solution in the presence of benzene (0.5 ml). The basic solution was extracted with $CHCl_3$, the aqueous material was acidified with 10% HCl, then extracted with $CHCl_3$ to give a mixture of laevorotatory acids, $[\alpha]_D$-5.9° (benzene). The chemical yield was determined at 100% and the optical yield 18.4%.

Reaction of the ester (10) with lithium diisopropylamide. n-BuLi (1.0 ml, 1.66 mmol) was added to solution of dry diisopropylamine (238 µl, 1.7 mmol) in dry THF (freeze degassed, 4 ml) at -78° under an Ar atmosphere. The solution was stirred for 15 min and a 1.13 ml aliquot (1.5 eq.) was removed by syringe and added to a solution of the ester (10) (104 mg, 0.31 mmol) in dry THF (5 ml) at -78°. The solution was stirred at -78° to -60° for 0.75 hr, then Me_3SiCl (100 µl) was added and the solution allowed to reach room temperature (30 min). The reaction mixture was poured into 10% HCl solution and usual workup with ether gave, after radial chromatography, the diene ester (11) (40 mg) as a colourless oil, b.p. 230° (bath)/0.15 mm, $[\alpha]_D$-129.0° (c, 0.25) (Found: C, 75.91; H, 9.67. $C_{21}H_{32}O_3$ requires C, 75.85; H, 9.71%). UV (λ_{max} MeOH) 269 nm (log ε 4.35); ^{1}H-NMR (300 MHz): δ 1.13 (d, J 6.6 Hz, $(H19)_3$); 1.20 (m, H1); 1.35 (m, $(H6)_2$); 1.59 (s, $(H16)_3$); 1.67 (s, $(H17)_3$); 1.70 (s, $(H20)_3$); 1.97 (m, $(H5)_2$); 2.11 (m, $(H13)_2$); 2.40 (m, H7, $(H12)_2$), 3.75 (s, methyl ester); 4.15 (dd, J 5.4, 2.0 Hz, H2); 5.14 (br t, J 7 Hz,H14); 5.65 (dd, J 5.4,1.6 Hz, H3); 5.96 (dd, J 9.4, 14.9 Hz, H8); 6.34 (dd, J 14.9, 11.3 Hz, H9); 7.19 (d, J 11.3 Hz, H10). ^{13}C-NMR: see Table 1. MS: m/z 332 (M^+, 0.6%) 314 (4) 272 (6) 245 (53) 185 (26) 159 (20) 141 (38) 123 (29) 109 (46) 93 (100) 81 (27) 69 (56).

Preparation of (17) and Horeau determination. The ester (11) (170 mg, 0.51 mmol) in dry ether (10 ml) was stirred with $LiAlH_4$ (120 mg) at 0° for 1 hr. The excess hydride was decomposed with EtOH and the reaction mixture poured into 10% HCl solution. Usual workup with ether gave the corresponding allylic alcohol (151 mg) as an oil, b.p. 160–162° (bath)/0.25 mm, $[\alpha]_D$-67.4° (c, 0.65) (Found: C, 78.15; H, 10.49. $C_{20}H_{32}O_2$ requires C, 78.88; H, 10.60%. ^{1}H-NMR (80MHz): δ 0.99 (d, J 6.9 Hz, $(H19)_3$); 1.60 (br s, $(H16)_3$); 1.68 (br s, $(H17)_3$); 1.73 (br s, $(H20)_3$); 3.66 (m, $W^h/2$ 20 Hz, H8); 4.04 (br s, $(H18)_2$); 4.23 (br d, J 5 Hz, H2); 5.14 (m H14); 5.59 (m, H3 and H10); MS: m/z 304 (M^+, 0.4%) 286 (0.4) 151 (18) 123 (15) 93 (100) 81 (16) 69 (9). The allylic alcohol (150 mg) was stirred with acetic anhydride (1 ml) in dry pyridine (3 ml) for 18 hr at room temperature. The product recovered gave, after radial chromatography, the allylic acetate (16) (132 mg) as an oil, b.p. 160–165° (bath)/0.25 mm, $[\alpha]_D$-45.2° (c, 0.64) (Found: C, 75.99; H, 9.85. $C_{22}H_{34}O_3$ requires, C, 76.24; H, 9.90%). The allylic acetate (120 mg, 0.35 mmol) in dry ether (5 ml) and dry t-BuOH (2 ml) was added to a solution of Li methal (100 mg) in liquid NH_3 (20 ml) at -70°. The reaction mixture was stirred at -75° to -55° for 5.5 hr then NH_4Cl was added portionwise until the blue colour faded (0.5 g). Usual workup with ether gave after radial chromatography (light petroleum–EtOAc, 4:1) then HPLC (C-18, 20% H_2O–MeOH), the alcohol (17) (68 mg) as an oil containing 12% of the Δ^2-isomer (GLC). ^{1}H-NMR (80 MHz): δ 0.82 (d, J 7.0 Hz, $(H19)_3$); 1.62 (br s, $(H16)_3$, $(H18)_3$); 1.67 (br s, $(H17)_3$); 1.80 (br s, $(H20)_3$); 2.05 (m, allylic methylenes); 3.54 (m, H8); 5.20 (m, vinyl protons); ^{13}C-NMR: see Table 1. MS: m/z 290 (M^+, 1%) 153 (12) 138 (5) 135 (8) 123 (26) 107 (20) 95 (100) 94 (58) 93 (35) 81 (17) 69 (77). IR (ν_{max}) 3622, 3570 cm^{-1}. The alcohol (17) (12 mg, 0.04 mmol) in dry pyridine (0.1 ml) was stirred with phenylbutyric anhydride (25.7 mg, 0.083 mmol) for 20 hr at room temperature. The excess anhydride was hydrolysed by stirring with water (2 drops) for 40 min, then the acids were titrated with 0.01 M NaOH solution. The basic solution was extracted with $CHCl_3$, the aqueous material was acidified with 10% HCl solution then extracted with $CHCl_3$ to give a mixture of dextrorotatory acids, $[\alpha]_D$+4.0° (benzene). The chemical yield was determined at 100% and the optical yield 12.5%.

Degradation of (11) to (22) (Scheme 2). The ester (11) (2.0 g, 6.02 mmol) in dry ether (20 ml) and dry t-BuOH (4 ml) was added to a solution of Li metal (420 mg, 60.2 mmol) in liquid NH_3 (100 ml) at -70°. The reaction mixture was stirred at -75° to -50° for 4.5 hr then NH_4Cl was added portionwise until the blue colour faded (1 g). Usual workup with ether gave a viscous green oil (1.92 g) which was subjected to RSF, then radial chromatography (light petroleum–EtOAc, 4:1), to afford the diols (18) (597 mg) (4:1 ratio), one spot by TLC. The crude mixture of the diols (515 mg, 1.67 mmol) in dry CH_2Cl_2(10 ml) was stirred with t-butyldimethylsilyl chloride (256 mg, 1.7 mmol) and diisopropylethylamine (569 µl, 430 mg, 3.40 mmol) under N_2 for 21 hr. RSF of the reaction mixture gave the silyl ethers (19) (444 mg, 63%), one spot by TLC, which was used without further purification. The mixture of silyl ethers (19) (440 mg, 1.04 mmol) in dry CH_2Cl_2(10 ml) was stirred with pyridinium dichromate (1.96 g, 5.20 mmol) and anhydrous NaOAc (82 mg) for 2.5 hr under N_2. RSF of the reaction mixture gave the mixture of keto silyl ethers (20) (390 mg). IR (film, ν_{max}) 1706 cm^{-1}. To the mixture of keto silyl ethers (20) (390 mg, 0.93 mmol) in dry CH_2Cl_2(10 ml) was added powdered $NaHCO_3$ (390 mg, 4.64 mmol) and m-chloroperbenzoic acid (700 mg, 3.25 mmol of peracid). The mixture was stirred under N_2 at room temperature for 22 hr, when TLC

analysis indicated no starting material was present. The reaction mixture was filtered, the filtrate taken up into ether and washed with saturated $NaHCO_3$ solution (3x), then usual workup with ether gave a colourless oil (493 mg). ^{1}H-NMR analysis showed that complete epoxidation of the double bonds had occurred, but only partial oxidation of the keto group had occurred (13%) to give the ester (21). The product was taken up into CH_2Cl_2 and treated with the peracid (215mg) and $NaHCO_3$(234 mg) as before. ^{1}H-NMR analysis of the recovered product indicated 43% oxidation of the keto group had occurred as well as the formation of a significant amount of chlorobenzoate esters. The crude product from the peracid oxidation (400 mg) was taken up in dry CH_2Cl_2 (10 ml) and stirred with NaOAc (400 mg), AcOH (2 ml), NaI (1.2 g) and powdered Zn (800 mg) for 3 hr at room temperature under N_2. The mixture was filtered, diluted with ether and washed with 10% HCl solution and saturated $NaHCO_3$ solution. Usual workup with ether gave a colourless oil (300 mg). ^{1}H-NMR analysis indicated the presence of the ester (21) (20% of the material). The mixture containing the ester (21) (300 mg) in MeOH (2 ml) was stirred with 10% KOH solution (2 ml) at 50° for 1 hr. Usual workup with ether gave a yellow oil (190 mg), which was shown to contain the secondary alcohol (22) by TLC and GC analyses (co-injection with a sample of the authentic alcohol). This material (190 mg) in dry pyridine (2 ml) was stirred with 3,5-dinitrobenzoyl chloride (200 mg) at room temperature for 22 hr. Usual workup with ether and radial chromatography (light petroleum-EtOAc, 9:1) of the recovered product, gave a crystalline fraction (21 mg) which was repeatedly recrystallized from n-pentane to give the 3,5-dinitrobenzoate (23) (5 mg), m.p. 105-106°, $[\alpha]_D$ -11.0° (c, 0.22). The ^{1}H-NMR spectrum (80 MHz) and mass spectrum were identical with those obtained for (28) (see below).

Synthesis of (1R,1'R)-1-(4-methylcyclohex-3-enyl)ethanol (27) (Scheme 3). The alcohol (24) and its 3,5-dinitrobenzoate derivative, m.p. 94-95°, $[\alpha]_D$ +35.6° (c, 0.8)(lit.[10] m.p. 94-95°, $[\alpha]_D$ +36.7° (c, 0.77)) were prepared from R(+)limonene as described by Pawson et al.[10]

A solution of (24) (1.85 g) in CH_2Cl_2 (100 ml) was treated with PDC (13.5 g) and the mixture was stirred for 18 hr. The aldehyde (25) (1.7 g) was recovered as an oil; ^{1}H-NMR (80 MHz); δ 1.04 (d, J 6.3Hz); 1.63 (br s); 5.35 (br m); 9.65 (d, J 2.3 Hz), and was characterized as the 2,4-dinitrophenylhydrazone, m.p. 128-129° (Found: C, 57.65; H, 5.95. $C_{16}H_{20}N_4O_4$ requires C, 57.82; H, 6.07%). To the aldehyde (25) (1.58 g, 10.4 mmol) in dry CH_2Cl_2 (50 ml) was added powdered $NaHCO_3$ (2.35 g, 28 mmol) and m-chloroperbenzoic acid (4.64 g, 22.9 mmol of peracid). The mixture was stirred at room temperature under N_2 for 43 hr, then was filtered. The filtrate was diluted with ether (50 ml) and washed with saturated $NaHCO_3$ solution (3x). Usual workup gave the mixture of epoxy formates (26) (1.5 g) which was dissolved in dry CH_2Cl_2 (50 ml) and treated with NaOAc (1.0 g), AcOH (5 ml), NaI (4.5g) and powdered Zn (3 g). The mixture was stirred for 3 hr at room temperature. The product recovered (1.12g) in dry ether (50 ml) was stirred with $LiAlH_4$ (1.0 g) for 30 min at room temperature under N_2. The excess hydride was decomposed with wet ether, then usual workup with ether gave the alcohol (27) (710 mg), as a light yellow oil. ^{1}H-NMR (80 MHz): δ 1.18 (d, J 6.3 Hz); 1.65 (br s); 3.58 (dq, J 6.3, 6.2 Hz); 5.37 (br s). MS: m/z 140 (M^+, 6%) 122 (27) 107 (34) 93 (100) 91 (22) 79 (36) 67 (30). The crude alcohol (27) (300 mg, 2.14 mmol) in dry pyridine (8 ml) was stirred with 3,5-dinitrobenzoyl chloride (1.48 g, 6.42 mmol) for 20 hr at room temperature. The reaction mixture was diluted with H_2O (20 ml) and usual workup with ether gave a brown oil (853 mg). Radial chromatography gave the 3,5-dinitrobenzoate (28) (395 mg) m.p. 106.5-107° (hexane), $[\alpha]_D$ +11.3° (c, 1.0) (Found: C, 57.47; H,5.33. $C_{16}H_{18}N_2O_6$ requires C, 57.46; H 5.43%). ^{1}H-NMR (80 MHz): δ 1.40 (d, J 6.3 Hz); 1.67 (br s); 5.17 (m); 5.39 (br m); 9.17 (m, aromatic H); ^{13}C-NMR: see Table 1. MS: m/z 195 (7) 122 (66) 107 (35) 94 (22) 93 (100) 91 (13) 79 (16).

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