Notes

Antibacterial Diterpenes from *Plectranthus ernstii*

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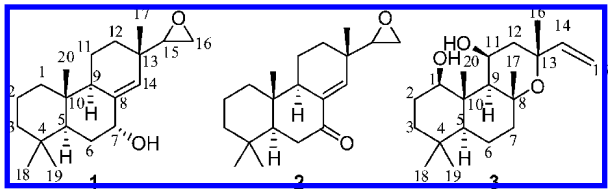
Three new diterpenoids including two pimaranes (**1** and **2**) and a labdane (**3**) were isolated from the whole herb of *Plectranthus ernstii*. The structures of these compounds were determined as *rel*-15(ζ),16-epoxy-7α-hydroxypimar-8,14-ene (**1**) and *rel*-15(ζ),16-epoxy-7-oxopimar-8,14-ene (**2**), and compound **3** was elucidated as 1*R*,11*S*-dihydroxy-8*R*,13*R*-epoxylabd-14-ene on the basis of single-crystal X-ray structural analysis. Compound **1** exhibited moderate antistaphylococcal activity against a range of multidrug-resistant (MDR) and methicillin-resistant (MRSA) strains of *Staphylococcus aureus* with a minimum inhibitory concentration (MIC) of 32 μg/mL. All three diterpenes exhibited antimycobacterial activity against three strains of rapidly growing mycobacteria with MIC values ranging from 8 to 128 μg/mL.

Plectranthus ernstii Codd. belongs to the Lamiaceae family, and the genus has been shown to be a rich source of diterpenes, particularly of the abietane, labdane, and neoclerodane classes,[1−3] and while the phytochemistry of the genus has been reviewed,[4] this particular species does not appear to have been phytochemically studied before. Many *Plectranthus* species are used as ornamentals but also have economic and medicinal value, particularly in infectious disease.[5,6] Medicinal uses include the treatment of a range of ailments, particularly digestive, skin, infective, and respiratory problems.[7] *P. ernstii* is a South African species and exists in several forms including "Oribi",[8] which is cultivated widely in the UK as an attractive house plant with pale blue spur-like flowers and aromatic leaves. The ability of many *Plectranthus* species to produce antibacterial metabolites, particularly of the diterpene class, prompted us to investigate the chemistry and antibacterial activity of extracts from this species. This paper details the characterization of two new pimarane diterpenes (**1** and **2**) and a labdane diterpene (**3**).



All of the isolated compounds were evaluated against a panel of methicillin- and multidrug-resistant (MDR) *Staphylococcus aureus* strains and selected species of rapidly growing mycobacteria (RGM).

The aerial parts of *P. ernstii* were dried and extracted in a Soxhlet apparatus. Compound **1** was isolated as a white, amorphous powder from the *n*-hexane extract. The ^{1}H and ^{13}C NMR spectra (Table 1) provided signals that were characteristic of a pimarane diterpene.[9,10] By inspection of the HMBC and COSY spectra it could be determined that compound **1** had connectivities of a pimarane diterpene. From the HMBC data, a *geminal* pair of methyl groups (H_3-18 and H_3-19) exhibited a ^2J correlation to a quaternary carbon, C-4, as well as ^3J correlations to C-3 (CH_2) and C-5, a methine carbon. COSY correlations between H_2-3 and H_2-2 and also between H_2-2 and H_2-1 were also observed. A methyl singlet (C-20) showed a ^2J correlation to C-10 and ^3J correlations to C-1 (CH_2) and two methine carbons (C-5 and C-9), therefore completing ring A of the pimarane skeleton. The methine hydrogen H-9, located at the ring junction of rings B and C, provided ^2J correlations to a methylene carbon (C-11) and an olefinic quaternary carbon (C-8, $\delta_C = 141.7$) as well as a ^3J correlation to the olefinic partner C-14 ($\delta_C = 130.2$). The olefinic hydrogen of this carbon (H-14, $\delta_H = 5.43$) provided a ^3J correlation to a downfield methine carbon positioned at C-7. Due to the downfield appearance of this carbon, a hydroxy group was placed here. H-7 exhibited a COSY correlation with a methylene group (H_2-6), confirming its assignment, and also a ^3J correlation to C-5, completing ring B of the pimarane. The olefinic hydrogen, H-14, also exhibited a ^2J HMBC correlation to C-13 along with ^3J correlations to C-12 (CH_2) and C-15, an oxymethine carbon. A ^2J HMBC correlation between H_2-12 and C-11 as well as a COSY coupling between these two sets of methylene hydrogens completed ring C. A methyl singlet (C-17) exhibited a ^2J HMBC correlation to C-13 along with ^3J correlations to C-12, C-14, and C-15, fixing this methyl group here in accordance with a pimarane skeleton. The oxymethine resonance H-15 gave a COSY coupling to an oxymethylene pair of hydrogens (H_2-16). The HRESIMS of **1** suggested a pseudomolecular formula of $C_{20}H_{33}O_2$ $[M + H]^+$ (305.2487). In addition to the hydroxy group at C-7, this indicated that C-15 and C-16 were also linked together by an epoxide bridge.

The relative configuration of **1** was determined by inspection of the ^{1}H and NOESY spectra. H-7 appeared as a triplet in the ^{1}H NMR spectrum with a coupling constant of 2.5 Hz, indicating that this hydrogen should be in an equatorial position (β-oriented) and therefore the hydroxy group should be axial (α-oriented). An NOE between the olefinic hydrogen H-14 and the oxymethine proton H-15 implied that this epoxide moiety should be in an equatorial position (α) with the methyl group at position 17 in an axial and β-orientation. A further NOESY correlation between H-14 and H-7 supported the previous assignment of this hydrogen as equatorial

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Table 1. ^{1}H and ^{13}C NMR Data (500 and 125 MHz, $CDCl_3$) for Compounds **1**−**3**[a]

	1		**2**		**3**	
position	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
1	1.08 dt (3.5, 12.5)	39.1	1.11 dt (4.5, 13.0)	38.8	3.48 dd (4.5,11.0)	78.8
	1.71 m		1.79 m			
2	1.45 m	18.9	1.45 m	18.6	1.63 m	28.9
			1.58 m		1.73 m	
3	1.22 m	42.0	1.51 m	41.7	1.26 m	39.5
	1.44 m				1.39 dt (3.5, 13.5)	
4		32.8		33.1		32.8
5	1.57 m	46.9	1.47 m	50.0	0.83 m	55.7
6	1.58 m	29.3	2.28 dd (13.5, 18.5)	37.4	1.47 m	44.0
	1.79 m		2.57 m		1.85 m	
7	4.20 t (2.5)	73.2		200.5	1.49 m	20.2
					1.64 m	
8		141.7		137.3		75.4
9	2.13 m	46.5	2.05 m	51.2	1.54 d (5.5)	55.1
10		38.4		36.0		43.7
11	1.47 m	17.7	1.45 m	18.3	4.37 dt (6.0, 9.0)	65.6
			1.76 m			
12	1.35 dt (3.5, 13.0)	30.9	1.42 m	30.5	2.02 dd (9.0, 14.0)	40.3
	1.43 m		1.57 m		2.27 dd (8.5, 14.0)	
13		34.4		36.0		73.0
14	5.43 bs	130.2	6.61 bs	140.9	5.89 dd (10.5, 17.0)	147.1
15	2.80 dd (2.5, 4.0)	59.8	2.85 dd (2.5, 3.5)	59.0	4.95 dd (1.5, 11.0)	111.2
					5.19 dd (1.5, 17.0)	
16	2.56 dd (2.5, 4.5)	43.9	2.56 m	43.8	1.24 s	32.1
	2.66 t (4.5)		2.66 t (4.0)			
17	1.02 s	22.8	1.06 s	22.7	1.16 s	13.6
18	0.91 s	33.4	0.87 s	32.6	0.85 s	32.8
19	0.86 s	21.9	0.90 s	21.1	0.80 s	21.1
20	0.76 s	14.0	0.83 s	13.9	1.48 s	27.8

[a] Coupling constants (Hz) in parentheses.

(β). Compound **1** is therefore assigned as *rel*-15(ζ),16-epoxy-7α-hydroxypimar-8,14-ene and is reported here for the first time.

Compound **2** was isolated from the *n*-hexane extract and exhibited signals similar to those of compound **1**, indicating the presence of a further pimarane diterpene. The HRESIMS of **2** differed from that of **1** by a loss of two hydrogens with an *m*/*z* 303.2320 $[M + H]^+$, indicating a pseudomolecular formula of $C_{20}H_{31}O_2$. The appearance of a quaternary carbon at $\delta_C = 200.5$ (C-7) provided evidence for the presence of a ketonic carbonyl. The *geminal* pair of methyls (H_3-18 and H_3-19) yielded HMBC signals to a methylene group (CH_2-3), to a quaternary carbon ($\delta_C = 33.1$, C-4) to which they were directly attached, and to a methine carbon (C-5). The methine hydrogen (H-5) associated with this carbon provided correlations to both hydrogens of a downfield methylene ($\delta_H = 2.28$ and 2.56, H_2-6), placing this group here. A ^{2}J HMBC correlation between H_2-6 and C-7 enabled the positioning of the ketonic carbonyl to be assigned at C-7. This was further confirmed by a ^{3}J HMBC correlation between the olefinic proton H-14 ($\delta_H = 6.61$) and C-7. The remaining resonances of compound **2** were highly similar to those of **1** (Table 1), and again NOESY correlations supported the assignment of identical configurations at C-5, C-9, C-10, and C-13. Compound **2** was therefore assigned as *rel*-15(ζ),16-epoxy-7-oxopimar-8,14-ene and is reported here for the first time. Compounds **1** and **2** are structurally related to pimarane diterpenes isolated from *Salvia mellifera* that possess an intact 15−16 double bond.[11]

Compound **3** was isolated as a colorless oil from the *n*-hexane extract and yielded ^{1}H and ^{13}C NMR signals indicative of a labdane diterpene. By inspection of the HMBC and COSY spectra it could be shown that compound **3** had the connectivities typical of a labdane diterpene.[5] By inspection of the HMBC and DEPT-135 data a methyl singlet (CH_3-20) provided a ^{2}J correlation to C-10 and ^{3}J correlations to C-5 and C-9 (both CH) and an oxymethine carbon (C-1). The hydrogen directly attached to this carbon appeared as a double doublet ($J = 4.5$, 11.0 Hz), placing it in an axial orientation. This hydrogen coupled to two hydrogens of a methylene group (C-2), which in turn coupled to a second group of methylene protons (CH_2-3). From the HMBC spectrum, a pair of *geminal* methyl groups exhibited a ^{2}J correlation to C-4 and ^{3}J correlations to C-3 and C-5, therefore completing ring A. The methine signal, H-5, exhibited a COSY correlation to a methylene group (H_2-6), which in turn coupled to a second methylene group (H_2-7). A fourth methyl singlet (C-17) provided a ^{2}J correlation to an oxygen-bearing quaternary carbon (C-8) as well as ^{3}J correlations to C-7 and C-9, thus completing ring B of the labdane diterpene nucleus. A fifth methyl singlet (C-16) exhibited a ^{2}J correlation to a second oxygen-bearing quaternary carbon (C-13) as well as ^{3}J correlations to a methylene group (C-12) and an olefinic carbon (C-14). The olefinic hydrogen associated with this carbon (H-14) provided COSY couplings to both hydrogens of an *exo*-methylene group (H_2-15), completing the olefin moiety. The methine hydrogen at C-9 coupled to a deshielded proton (H-11, $\delta_H = 4.37$) and together with the downfield appearance of C-11 indicated that a hydroxy group should be placed here. The molecular weight determined by HRESIMS (*m*/*z* 323.2597 $[M + H]^+$) meant that ring C of the labdane should be completed by an ether linkage between the two oxygen-bearing quaternary carbons C-8 and C-13. From the coupling constant of H-1 of 11.0 Hz this hydrogen must be axial and α-oriented, placing the hydroxy group in an equatorial position (β). Two 1,3 interactions between H-1 and H-5 and H-5 and H-9 placed these hydrogens in an α-orientation (axial). An NOE between the H_3-18 and both hydrogens of H_2-3 placed this group in an equatorial position (α). A 1,3 interaction between the axial proton of H_2-2 and H_3-19 placed this methyl group in a β-orientation. NOEs between H_3-19 and H_3-20 as well as H_3-20 and H_3-17 placed these methyl groups cofacial in a β-orientation. A 1,3 interaction between H_3-17 and H_3-16 also placed this group on the same face (β), leaving the olefin moiety to be α-oriented (equatorial). A large coupling constant for H-11 (9.0 Hz) would indicate that H-11 should be axial (β), leaving the hydroxy group to be α-oriented (equatorial). However, given the presence of several bulky substituents on ring C, a number of conformations could be adopted. To resolve this issue and assign configuration at C-11 and all of the stereogenic centers, single-crystal X-ray structural analysis

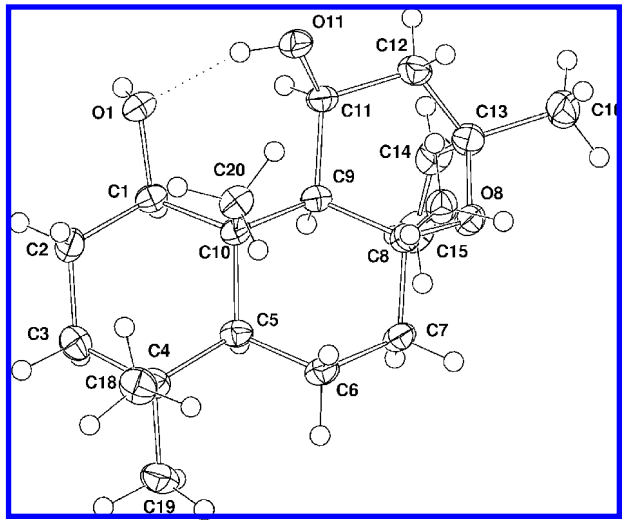

Figure 1. Molecular structure and numbering scheme of **3**. The non-hydrogen atom ellipsoids are shown at the 50% probability level.

Table 2. Minimum Inhibitory Concentrations of Compounds **1**−**3** in μg/mL

strain	**1**	**2**	**3**	Nor[a]	Eryth[b]	Tet[c]	Eth[d]
S. aureus SA-1199B (NorA)	32	[e]	[e]	32			
S. aureus RN4220 (MsrA)	32	[e]	[e]		128		
S. aureus XU-212 (TetK, mecA)	32	[e]	[e]			128	
S. aureus EMRSA-15	32	[e]	[e]	2			
S. aureus ATCC 25923	32	[e]	[e]	0.5			
Mycobacterium fortuitum	16	128	128				4
Mycobacterium phlei	8	64	128				2
Mycobacterium smegmatis	16	128	128				0.5

[a] Norfloxacin. [b] Erythromycin. [c] Tetracycline. [d] Ethambutol. [e] Not active at 128 μg/mL.

was conducted and **3** was crystallized from EtOAc (Figure 1). This indicated that the hydroxy at C-11 is actually β-oriented and that the C ring of **3** is a twist boat conformer. Compound **3** is therefore assigned as 1*R*,11*S*-dihydroxy-8*R*,13*R*-epoxylabd-14-ene and is reported here for the first time. Both the 1*R* and 11*S* hydroxy analogues of compound **3** have been reported from *Rhizophora apiculata*[12] and *Juniperus oxycedrus*,[13] respectively.

Certain diterpenes, such as totarol, have been shown to possess multifaceted activities as potent antibacterials with minimum inhibitory concentration values of 2 μg/mL and at the same time behaving as efflux pump inhibitors.[14] Several pimarane diterpenes have also been reported as bacterial resistance modifying agents.[15] All three compounds were therefore tested for antimycobacterial activity against a panel of fast-growing mycobacteria (Table 2), with **1** showing the greatest activity, ranging from 8 to 16 μg/mL, whereas compounds **2** and **3** demonstrated only weak activity. Compound **1** also exhibited moderate antistaphylococcal activity against multidrug-resistant (MDR) and methicillin-resistant (MRSA) strains of *Staphylococcus aureus* with a minimum inhibitory concentration (MIC) of 32 μg/mL. Surprisingly the simple change from 7-hydroxy (**1**) to 7-oxo (**2**) resulted in a loss of antistaphylococcal activity, presumably as a result of increased lipophilicity and poorer uptake. The activity against effluxing and MRSA strains is noteworthy, and the use of standardized extracts containing these components could find utility as topical antibacterial preparations, particularly given their lipophilicity and the need for replacements for mupirocin and fusidic acid creams, to which resistance is arising.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Bellingham and Stanley ADP 200 polarimeter. IR spectra were recorded on a Nicolet 360 FT-IR spectrophotometer and UV spectra on a Thermo Electron Corporation Helios spectrophotometer. NMR spectra were recorded on a Bruker AVANCE 500 MHz spectrometer. Chemical shift values (δ) were reported in parts per million (ppm) relative to appropriate internal solvent standard, and coupling constants (*J* values) are given in hertz. Mass spectra were recorded on a Finnigan MAT 95 high-resolution, double-focusing, magnetic sector mass spectrometer. Accurate mass measurement was achieved using voltage scanning of the accelerating voltage. This was nominally 5 kV, and an internal reference of heptacosa was used. Resolution was set between 5000 and 10 000.

Plant Material. *Plectranthus ernstii* was purchased from Oakland Nurseries (Burton-on-the-Wolds, Loughborough, UK). The material was identified by A.P., and a voucher specimen (MS/SG/07/2006/PE) is deposited at the Centre for Pharmacognosy and Phytotherapy.

Extraction and Isolation. The whole herb of *P. ernstii* (275 g) was air-dried, coarsely powdered, and sequentially extracted with *n*-hexane (3.5 L), $CHCl_3$ (3.5 L), and MeOH (3.5 L) in a Soxhlet apparatus. The *n*-hexane extract (8.7 g) was adsorbed onto silica gel (13 g) and subjected to vacuum-liquid chromatography (VLC) on silica gel (130 g) eluting with *n*-hexane containing 10% increments of EtOAc to give 12 fractions (200 mL each). VLC fraction 5 (6:4 *n*-hexane−EtOAc) was further fractioned by solid-phase extraction (SPE) on a normal-phase column (silica, 60 g). Fraction 5, eluted with 8:2 hexane−EtOAc (50 mL), was then fractioned by reversed-phase SPE (C_{18}, 60 g) eluting with H_2O containing 10% increments of MeOH (50 mL) to give 11 fractions. Preparative TLC of fraction 10 on a reversed-phase TLC plate using a 9:1 MeCN−H_2O system afforded compound **1** (4.9 mg). Compound **3** was isolated by reversed-phase preparative TLC of SPE fraction 9 using a 95:5 MeCN−H_2O system. This afforded 41.9 mg of **3**. VLC fraction 4 of the *n*-hexane extract was subjected to SPE on a silica normal-phase column (60 g) eluting with 9:1 *n*-hexane−EtOAc (50 mL). Fraction 2 was then further fractioned by SPE in reversed-phase mode (C_{18}, 60 g) eluting with H_2O containing 10% increments of MeOH (50 mL) to give 11 fractions. Preparative TLC of SPE fraction 10 using an 8:2 MeCN−H_2O system yielded compound **2** (6.9 mg).

Antibacterial Assay. *Staphylococcus aureus* ATCC 25923 was the generous gift of E. Udo (Kuwait University, Kuwait). *S. aureus* RN4220 containing plasmid pUL5054, which carries the gene encoding the MsrA macrolide efflux protein, was provided by J. Cove.[16] *S. aureus* XU-212, possessing the TetK tetracycline efflux protein, was provided by E. Udo.[17] SA-1199B, which overexpresses the *norA* gene encoding the NorA MDR efflux protein, was provided by G. Kaatz.[18] *Mycobacterium* species were acquired from the NCTC. All *S. aureus* strains were cultured on nutrient agar and incubated for 24 h at 37 °C prior to minimum inhibitory concentration (MIC) determination. Mycobacterial strains were grown on Columbia Blood agar (Oxoid) supplemented with 7% defibrinated horse blood (Oxoid) and incubated for 72 h at 37 °C. Bacterial inocula equivalent to the 0.5 McFarland turbidity standard were prepared in normal saline and diluted to give a final inoculum density of 5×10^5 cfu/mL. The inoculum (125 μL) was added to all wells, and the microtiter plate was incubated at 37 °C for 18 h. The MIC was recorded as the lowest concentration at which no bacterial growth was observed as previously described.[10]

***rel*-15(ζ),16-Epoxy-7α-hydroxypimar-8,14-ene (1):** white, amorphous powder; $[\alpha]^{16}_D$ −84 (*c* 0.047, $CHCl_3$); UV λ_{max} (log ε) ($CHCl_3$) 241 (2.61); IR (film) ν_{max} 3526 (br), 2924, 2867, 1456, 1387, 1369, 1024, 787 cm^{-1}; HRESIMS *m/z* 305.2487 $[M + H]^+$ (calcd for $C_{20}H_{33}O_2$ *m/z* 305.2475); ^1H and ^{13}C NMR data, Table 1.

***rel*-15(ζ),16-Epoxy-7-oxopimar-8,14-ene (2):** white, amorphous powder; $[\alpha]^{16}_D$ −43 (*c* 0.092, $CHCl_3$); UV λ_{max} (log ε) ($CHCl_3$) 248 (3.97); IR (film) ν_{max} 2961, 2920, 2864, 1684, 1616, 1457, 1388, 1262, 1218 cm^{-1}; HRESIMS *m/z* 303.2320 $[M + H]^+$ (calcd for $C_{20}H_{31}O_2$ *m/z* 303.2318); ^1H and ^{13}C NMR data, Table 1.

1*R*,11*S*-Dihydroxy-8*R*,13*R*-epoxylabd-14-ene (3): colorless oil; $[\alpha]^{16}_D$ +18 (*c* 1.21, $CHCl_3$); UV λ_{max} (log ε) ($CHCl_3$) 242 (2.14); IR (film) ν_{max} 3324 (br), 2938, 2864, 1456, 1369, 1067, 998, 755 cm^{-1}; HRESIMS *m/z* 323.2597 $[M + H]^+$ (calcd for $C_{20}H_{35}O_3$ *m/z* 323.2581); ^1H and ^{13}C NMR data, Table 1.

X-ray Crystallographic Data of 3. **3**·H_2O: $C_{20}H_{34}O_3$, H_2O, M = 340.49, monoclinic, a = 6.8213(1) Å, b = 12.9640(1) Å, c = 11.3897(1) Å, β = 104.690(1)°, V = 974.28(2) Å^3, T = 100(2) K, space group $P2_1$, specimen: 0.23 × 0.20 × 0.06 mm^3, μ = 0.624 mm^{-1}, D_c (Z = 2) = 1.161 g cm^{-3}, λ(Cu Kα) = 1.54178 Å, $T_{min/max}$ = 0.80, $2\theta_{max}$ = 134.4°. A total of 12 963 reflections were collected, of which 3441 were unique (R_{int} = 0.0195); R_1 = 0.030, wR_2 = 0.083, S = 0.94;

$|\Delta\rho_{max}| = 0.20$ e·Å^{-3}. Data collection was by means of an Oxford Diffraction Gemini diffractometer. Following multiscan absorption corrections the structure was determined and refined by full-matrix refinement on F^2 using the SHELXL 97[19] program. Hydroxy and water molecule H atoms were located and refined without restraints. The remaining hydrogen atoms were placed in calculated positions and refined as part of riding models. The absolute configuration was determined by refinement of the Flack absolute structure parameter, $x = 0.09(12)$, and is as shown in Figure 1. (Full X-ray crystallographic data are available as Supporting Information.) Crystallographic data for the structure **3** (CCDC-702204) reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, via the Internet at http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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Supporting Information Available: This material is available free of charge via the Internet at http://pubs.acs.org.

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