New Eudesmane Sesquiterpenes from *Plectranthus cylindraceus*

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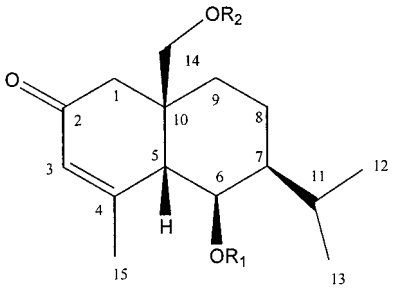
Three new eudesmane sesquiterpenes, plectranthone (**1**), desacetylplectranthone (**2**), isodeacetylplectranthone (**3**), and the three known flavonols pachypodol, casticin, and chrysosplenol D were isolated for the first time from the aerial parts of *Plectranthus cylindraceus*. Their structures have been established on the basis of spectral data. The structures and relative stereochemistries of **1** and **2** were confirmed by single-crystal X-ray analysis.

As part of an ongoing research program at the Department of Pharmacognosy, College of Pharmacy, King Saud University, aimed at the discovery of antimicrobials from higher plants, it was decided to screen *Plectranthus cylindraceus* for activity. *P. cylindraceus* Hochst. ex Benth (family Lamiaceae [Labiatae]), is a folk medicine widely used in the southern and western regions of Saudi Arabia both as a disinfectant and as a deodorant.[1] It is known locally as Al-Shar and is characterized by being a perennial, succulent, aromatic herb that grows wild on the rocky hills in the southwestern regions of Saudi Arabia.[2] As far as the original objectives were concerned, the study unfortunately culminated in the isolation of thymol as the sole product responsible for the antimicrobial action of this plant. Thymol is also responsible for the culinary uses of the fresh plant, especially in the southern region of Arabia.[2] On the other hand, the investigation did lead to the isolation of three new eudesmane sesquiterpenes, whose isolation and structure elucidation are the subject of this manuscript.



1: R_1= $^{18}COCH_3$, R_2= $^{19}COCH_3$

2: R_1= $^{18}COCH_3$, R_2= H

3: R_1= H , R_2= $^{19}COCH_3$

Results and Discussion

The dried, powdered aerial parts of *P. cylindraceus* were percolated with 95% EtOH at room temperature. The extract was active against *Mycobacteria* and Gram-positive bacteria in the agar dilution assay.[3] Flash chromatography over Si gel, using *n*-hexane with increasing concentrations of EtOAc as eluent, yielded three new *cis*-eudesmane sesquiterpenes (**1**−**3**) and the three known flavonols, pachypodol,[4] casticin,[5] and chrysosplenol D.[5] Thymol was also isolated and found to be the sole agent responsible for the antimicrobial effect, as confirmed by bioautography.[6]

Plectranthone (**1**) was isolated as colorless prisms. Its molecular formula was determined as $C_{19}H_{28}O_5$ on the basis of the ion peak at *m*/*z* 276 [M − CH_3COOH]$^+$ and NMR data. Its IR spectrum showed absorption bands for two different carbonyl functions, an α,*β*-unsaturated ketone (1670 cm^{-1}) and a double-intensity ester band (1725 cm^{-1}). The ^{13}C NMR spectrum showed 19 carbon resonances, including five quartets, four triplets, five doublets, and five singlets. The presence of an isopropyl group was indicated by the fact that two of the methyl carbons resonated at δ_C 21.1 and 21.2 and correlated with two doublets, each of which integrated for three protons and resonated at δ_H 0.88 (J = 6.7 Hz) and 0.86 (J = 6.7 Hz). Two of the remaining methyl carbons resonated at δ_C 21.5 and correlated with two singlets resonating at δ_H 2.03 and 2.04, suggesting that **1** contained two acetate groups; two ester carbonyl signals at δ_C 170.8 and 171.2 supported these assignments. The fifth methyl group resonated at δ_H 1.99 as a singlet, correlating with δ_C 23.2. Furthermore, the two olefinic carbons of the α,*β*-unsaturated ketone resonated as a singlet (δ_C 158.0, C-4) and a doublet (δ_C 128.7, C-3), with the carbonyl carbon absorbing at δ_C 198.4.

Interestingly, the ^1H NMR spectrum of **1** exhibited two AB coupling systems. One of these was due to the protons of the isolated methylene group at C-1 (δ_C 47.8, δ_H 2.06, J = 15.8 Hz, and δ_H 2.55, J = 15.8 Hz). The other AB system (δ_C 69.7, δ_H 3.86, J = 11.0 Hz and δ_H 4.40, J = 11.0 Hz) was ascribed to the pair of protons at C-14. The only oxygenated methine carbon signal (δ_C 71.6, C-6) in the spectrum correlated with the proton resonating at δ_H 5.56 (br s). From the COSY spectrum, this proton was found to couple with two other protons resonating at δ_H 3.01 as a broad singlet (H-5) and δ_H 0.90 as a multiplet (H-7). The coupling patterns of H-5 with H-6 and of H-6 with H-5 and H-7 pointed to dihedral angles between H_6/H_5 and H_6/H_7 approaching 90°, which could only be accommodated by a cis ring junction as depicted in structure **1**.

Desacetylplectranthone (**2**) was isolated as colorless needles. The ion peak at *m*/*z* 234 [M − CH_3COOH]$^+$ and

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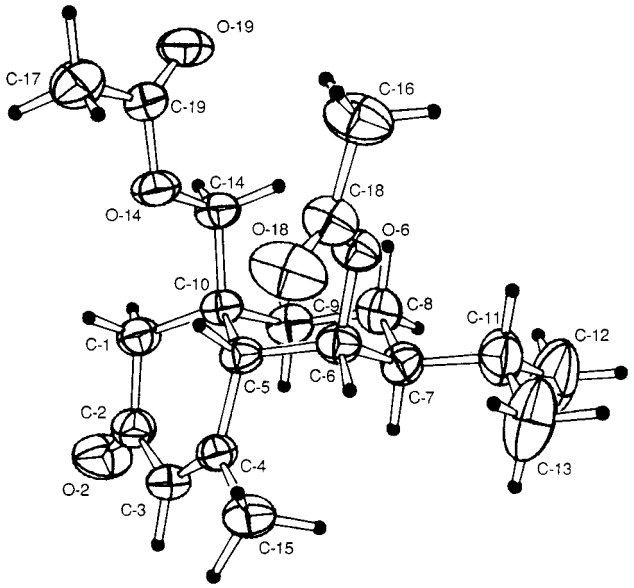

Figure 1. ORTEP diagram (40% probability ellipsoids) showing the crystallographic atom numbering scheme and solid-state conformation of plectranthone (**1**); small filled circles represent hydrogen atoms.

NMR data revealed that the molecular formula was $C_{17}H_{26}O_4$. The IR and NMR spectral data showed that **2** was very closely related to **1**. However, the IR spectrum of **2** contained an absorption band at 3460 cm^{-1}, indicative of a hydroxyl function, in addition to bands for an α,β-unsaturated ketone (1650 cm^{-1}) and an ester (1720 cm^{-1}) carbonyl group. From the NMR data it was deduced that **2** was a desacetyl derivative of **1** into which it was readily converted by acetylation using acetic anhydride in pyridine. The collective aforementioned spectral data suggested that **1** and **2** were eudesmane sesquiterpenes with a cis ring junction.

Single-crystal X-ray analyses performed on both **1** and **2** confirmed the proposed structures and yielded the relative stereochemistries. Both crystal structures were solved by direct methods (see Experimental Section). A view of the solid-state conformation of **1**, with the crystallographic atom numbering scheme, is presented in Figure 1; the fused ring system in **2** has, as would be expected, a very similar conformation to that in **1**. Corresponding bond lengths in **1** and **2** agree well and lie close to accepted values.[7] Endocyclic torsion angles ω_{ij} (σ 0.2−0.3°) about the bonds between atoms *i* and *j* in the cyclohexane ring of **1** are $\omega_{5,6}$ −51.4, $\omega_{6,7}$ 54.9, $\omega_{7,8}$ −56.3, $\omega_{8,9}$ 55.5, $\omega_{9,10}$ −50.3, $\omega_{10,5}$ 47.5°, and thus this ring has a chair form, which is slightly flattened to minimize 1,3-diaxial repulsions between substituents at C-6 and C-10. A like situation exists in **2**, where the corresponding torsion angles are −53.5, 54.4, −54.1, 54.0, −50.5, and 49.6°. The effects of the ring flattening are transmitted into the cyclohexane ring where they result in nonplanarity of the C−C(=O)−C=C−C moiety. Endocyclic torsion angles for this ring in **1** (σ 0.3−0.4°), with corresponding values for **2** (σ 0.3−0.6°) in parentheses, $\omega_{1,2}$ 39.9 (37.5), $\omega_{2,3}$ −10.5 (−7.5), $\omega_{3,4}$ −2.5 (−3.0), $\omega_{4,5}$ −14.2 (−16.4), $\omega_{5,10}$ 41.6 (43.9), $\omega_{10,1}$ −54.9 (−54.8°), indicate that it approximates a half-chair form in both compounds rather than an envelope form with C-10 as the out-of-plane atom. In crystals of **2**, an O−H...O hydrogen bond [O-14...O-2 = 2.809(3) Å] associates molecules related by the crystallographic 2_1 screw axis along the *a*-direction.

Isodesacetylplectranthone (**3**) was shown to have molecular formula $C_{17}H_{26}O_4$ from the presence of an ion peak at *m/z* 234 $[M - CH_3COOH]^+$ and NMR data. The NMR data showed that **3** was also a desacetyl derivative of **1**. As **2** was shown to be the 14-desacetyl derivative of **1**, it was concluded that **3** must be the 6-desacetyl derivative and a positional isomer of **2**. Acetylation of **3** yielded, as expected, compound **1**.

Upon subjecting the ethanol extract of *P. cylindraceus* to bioautography[6] on Si gel plates and using *Bacillus subtilis* as the test organism, none of the isolated compounds demonstrated any activity. The active zone corresponded to the phenol thymol, which is known to occur in numerous *Plectranthus* species.[8,9] In fact, further antimicrobial evaluation of the isolated pure compounds (**1**− **3**, and pachypodol, casticin, and chrysosplenol D) revealed no activity against the test microorganisms at a concentration of 100 μg/mL of the test compound. Compounds **1** and **2** were submitted to the National Cancer Institute (NCI) to evaluate their in vitro anticancer activity against MCF7 (breast), NCI−H460 (lung), and SF-268 (CNS) cancer cell lines, and they were found to be inactive in this regard, also.

Recently, several new bioactive compounds were isolated from *Plectranthus* species.[1,10−12] Although the genus *Plectranthus* (*Rabdosia*) is noted for its diterpene constituents,[13] the occurrence of sesquiterpenes in this genus is quite rare. Apart from 1(10)-aristolen-13-al,[14] no other sesquiterpenes have been reported from Plectranthus.

Experimental Section

General Experimental Procedures. Melting points were determined in open capillary tubes using a Mettler 9100 electrothermal melting point apparatus and were uncorrected. IR spectra were recorded in KBr disks using either a PYE UNICAM infrared spectrophotometer or an ATI Mattson Genesis Series FTIR spectrophotometer. UV spectra were measured in MeOH using a UV-160 IPC UV-vis dual-beam spectrophotometer. Optical rotations were obtained with a Perkin-Elmer 241 MC polarimeter. The ^1H and ^{13}C NMR spectra were obtained on a Bruker DRX-500 spectrometer operating at 500 and 125 MHz, respectively. Both ^1H and ^{13}C NMR spectra were recorded in either $CDCl_3$ or DMSO-d_6, and the chemical shift values were expressed in δ (ppm) relative to the internal standard TMS. For the ^{13}C NMR spectra, spectral editing was determined by DEPT. 2D NMR data were obtained using the standard pulse sequence of the Bruker DRX-500 for COSY, HETCOR, HMQC, HMBC, and NOESY. LR EIMS were obtained using a Shimadzu QP5000 gas chromatography/mass spectrometer.

Plant Material. The aerial parts of *P. cylindraceus* were collected in August 1997, at Wadi Al Uss, near Abha, Saudi Arabia. A voucher specimen was deposited at the herbarium of Medicinal, Aromatic and Poisonous Plants Research Center, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia.

Extraction and Isolation. The dried, ground aerial parts (1.34 kg) were percolated at room temperature with 95% EtOH (4 L × 3), and the extract was evaporated in vacuo to leave 43 g of residue. Part of this crude extract (20 g) was chromatographed over Si gel (500 g, 4 × 130 cm), using increasing concentrations of EtOAc in *n*-hexane as eluent, to yield the three new eudesmane sesquiterpenes, **1** (1.265 g), **2** (285 mg), and **3** (44 mg), and pachypodol[4] (37 mg), casticin[5] (582 mg), and chrysosplenol D[5] (113 mg).

Plectranthone (1): colorless prisms (EtOAc−petroleum ether); mp 134−135 °C; $[\alpha]^{25}_D$−36.9° (*c* 0.03, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 237 (3.13) nm; IR (KBr) ν_{max} 2900, 1725, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz), see Table 1; ^{13}C NMR ($CDCl_3$, 125 MHz), see Table 1; EIMS (70 eV) *m/z* 276 $[M-CH_3COOH]^+$ (15), 216 $[M-2CH_3COOH]^+$ (4).

Desacetylplectranthone (2): colorless needles ($CHCl_3$−ether); mp 213−214 °C $[\alpha]^{25}_D$−35.2° (*c* 0.03, $CHCl_3$); UV

Table 1. ^{1}H and ^{13}C NMR Assignments for Compounds **1**−**3**

	1[a]		**2**[b]		**3**[b]	
position	δ_C[c]	δ_H (m, *J* Hz)	δ_C[c]	δ_H (m, *J* Hz)	δ_C[c]	δ_H (m, *J* Hz)
1	47.8, t	2.06 (d, 15.8) 2.55 (d, 15.8)	47.3, t	1.85 (d, 15.9) 2.56 (d, 15.9)	46.9, t	2.41 (d, 15.9) 2.06 (d, 15.9)
2	198.4, s		198.9, s		197.9, s	
3	128.7, d	5.90 (br s)	127.7, d	5.85(br s)	127.4, d	5.82 (s)
4	158.0, s		159.0, s		160.0, s	
5	44.0, d	3.01 (br s)	42.6, d	3.00 (s)	48.1, d	2.70 (s)
6	71.6, d	5.56 (br s)	71.0, d	5.44 (s)	67.4, d	4.30 (br s)
7	43.2, d	0.90 (m)	42.5, d	0.93 (m)	44.5, d	0.70 (ddd, 7.5, 7.5, 7.5)
8	20.9, t	1.38 (m) 1.60 (m)	20.7, t	1.37 (m) 1.54 (m)	20.0, t	1.40 (m) 1.40 (m)
9	28.8, t	1.48 (m) 1.48 (m)	28.3, t	1.29 (m) 1.29 (m)	28.3, t	1.31 (m) 1.37 (m)
10	38.6, s		40.3, s		38.7, s	
11	29.1, d	1.48 (m)	28.5, d	1.44 (m)	28.3, d	1.61(m)
12	21.1, q[d]	0.88 (d, 6.7)[d]	20.6, q[d]	0.85 (d, 6.8)[d]	20.0, q[d]	0.85 (d, 6.6)[d]
13	21.2, q[d]	0.86 (d, 6.7)[d]	20.9, q[d]	0.87 (d, 6.8)[d]	21.0, q[d]	0.92 (d, 6.6)[d]
14	69.7, t	3.86 (d, 11.0) 4.40 (d, 11.0)	66.2, t	3.14 (d, 9.7) 3.74 (d, 9.7)	69.2, t	4.23 (d, 10.9) 4.37 (d, 10.9)
15	23.2, q	1.99 (s)	22.8, q	1.99(s)	23.2, q	1.93 (s)
16	21.5, q	2.03 (s)[e]	21.5, q	2.04 (s)		
17	21.5, q	2.04 (s)[e]			21.1, q	2.02 (s)
18	170.8, s[f]		170.5, s			
19	171.2, s[f]				170.7, s	
OH				4.73 (br s)		4.90 (d, 4.3)

[a] Spectra recorded in $CDCl_3$. [b] Spectra recorded in DMSO-d_6. [c] Multiplicities were determined by DEPT 135. [d−f] Assignments may be interchanged within the same column.

(MeOH) λ_{max} (log ϵ) 239 (3.98) nm; IR (KBr) ν_{max} 3460, 2800, 1720, 1650 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz), see Table 1; ^{13}C NMR (DMSO-d_6, 125 MHz), see Table 1; EIMS (70 eV) *m*/*z* 234 [M−CH_3COOH]$^+$ (15).

Isodesacetylplectranthone (3): colorless viscous liquid; $[\alpha]^{25}_D$−5.2° (*c* 0.06, $CHCl_3$); IR (KBr) ν_{max} 3455, 2954, 1741, 1664 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz), see Table 1;^{13}C NMR (DMSO-d_6, 125 MHz), see Table 1; EIMS (70 eV) *m*/*z* 234 [M−CH_3COOH]$^+$ (1).

Pachypodol: yellow needles (EtOAc−hexane); mp 171−172 °C ([lit.[15]] 168−170 °C); spectral data indistinguishable from those previously reported.[4,16]

Casticin: yellow needles (EtOAc−petroleum ether); mp 188−189 °C ([lit[5]] 185−187 °C); spectral data indistinguishable from those previously reported.[5,17]

Chrysosplenol D: yellow needles ($CHCl_3$−hexane); mp 248−250 °C ([lit.[5]] 238−240 °C); spectral data indistinguishable from those previously reported.[5]

Acetylation of 2 and 3. Compounds **2** and **3** were acetylated separately using the same procedure. A solution of **2** or **3** (5 mg) in Ac_2O−pyridine (1:1) was stirred at room temperature for 2 h. The mixture was evaporated under a N_2 stream. The residue was identified as **1** on the basis of co-chromatography and superimposable IR spectra.

X-ray Crystal Structure Analyses of Plectranthone (1) and Desacetylplectranthone (2). Crystal data for **1**: $C_{19}H_{28}O_5$, MW 336.43, trigonal, space group $P3_1$ (C_3^2), no. 144, $a = b =$ 12.990(1) Å, $c = 9.702(1)$ Å, $\alpha = \beta = 90.0(-)°$, $\gamma = 120.0(-)°$, $V = 1417.8(4)$ Å^3, $Z = 3$, $D_c = 1.182$ g·cm^{-3}, μ (Cu Kα radiation, $\lambda = 1.5418$ Å) = 6.5 cm^{-1}; crystal dimensions: 0.30 × 0.30 × 0.40 mm. Crystal data for **2**: $C_{17}H_{26}O_4$, MW 294.39, orthorhombic, space group $P2_12_12_1$(D_2^4), no.19, $a = 9.622(1)$ Å, $b =$ 21.943(2) Å, $c = 7.728(1)$ Å, $V = 1631.7(5)$ Å, $Z = 4$, $D_c = 1.198$ g cm^{-3}, μ(Cu Kα radiation) = 6.4 cm^{-1}; crystal dimensions: 0.10 × 0.16 × 0.40 mm.

All measurements were made at 298 K on an Enraf-Nonius CAD-4 diffractometer (Cu Kα radiation, graphite monochromator). The space group was determined in each case from the Laue symmetry and systematic absences (00*l* when $l \neq 3n$ for **1**; *h*00 when $\neq 2n$, 0*k*0 when $k \neq 2n$, 00*l* when $l \neq 2n$ for **2**). Refined unit-cell parameters were calculated from the diffractometer setting angles for 25 reflections ($36° < \theta < 40°$) widely separated in reciprocal space. Intensity data (1946 $+h,+k,\pm l$ reflections for **1**, 1947 $+h,+k,+l$ reflections for **2**), recorded by means of $\theta-2\theta$ scans [scanwidth (0.80 + 0.14 tan θ)°; $\theta_{max} = 75°$], yielded 1588 and 1218 reflections with $I > 2.0\sigma(I)$ for **1** and **2**, respectively, for use in the structure analyses and parameter refinements. The intensities of four reference reflections, monitored every 2 h during data collection, showed no significant variation (<2% overall). The data were corrected for the usual Lorentz and polarization effects, and empirical absorption corrections [T_{max}:T_{min} (relative) = 1.00:0.93 for **1**, = 1.00:0.94 for **2**] were also applied.

Both crystal structures were solved by direct methods. Approximate coordinates for all non-hydrogen atoms were obtained from *E*-maps. For both compounds, the enantiomer was chosen to yield a β-isopropyl configuration at C-7. Positional and temperature factor parameters (first isotropic and then anisotropic) were adjusted by means of several rounds of full-matrix least-squares calculations during which $\sum w\Delta^2$ [$w = 1/\sigma^2|F_o|$, $\Delta = (|F_o| - |F_c|)$] was minimized. Hydrogen atoms were incorporated at their calculated positions, and an extinction correction (*g*) was included as a variable during the later iterations. The parameter refinements converged (max.shift: esd = 0.03) at $R = \sum||F_o| - |F_c||/|F_o| = 0.037$, $R_w = [\Sigma w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2} = 0.050$, GOF = $[\sum w\Delta^2/(N_{observns} - N_{param})]^{1/2}$ = 1.07, $g = 5.22(5) \times 10^{-5}$] for **1** and $R = 0.040$, $R_w = 0.051$, GOF = 1.22, $g = 3.4(3) \times 10^{-6}$ for **2**. No unusual features were present in final difference Fourier syntheses [$\Delta\rho$(e/Å^3; max: min) = 0.13:−0.13 for **1**, 0.15:−0.13 for **2**].

Crystallographic calculations were performed by use of the Enraf-Nonius Structure Determination Package (SDP 3.0). For all structure−factor calculations, neutral atom- scattering factors and their anomalous scattering corrections were taken from International Tables.[18]

Biological Assays. Preliminary antimicrobial screening showed that the ethanol extract possesses activity against Gram-positive bacteria and *Mycobacteria*, while it was inactive against Gram-negative bacteria and fungi. Hence, the EtOH extract was subjected to bioautography[6] on Si gel plates (5 × 10 cm; solvent EtOAc−*n*-hexane 1:3) using *B. subtilis* ATCC 6633 as the test organism. The zone of inhibition observed after 24 h of incubation, R_f 0.85−0.57, corresponded to thymol.

In vitro quantitative antimicrobial activity evaluation of the pure compounds (**1**−**3**, and pachypodol, casticin, and chrysosplenol D) was performed using the agar dilution assay.[3]

Test organisms were *B. subtilis* ATCC 6633, *Candida albicans* ATCC 10231, *Escherichia coli* ATCC 25922, *Mycobacterium smegmatis* ATCC 35797, *Pseudomonas aeruginosa* ATCC 15442, and *Staphylococcus aureus* ATCC 29213. Chloramphenicol was used as a positive control for Gram-positive and Gram-negative bacteria, nystatin for *C. albicans*, and isoniazide for *M. smegmatis*.

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Supporting Information Available: Tables of fractional atomic coordinates and temperature factor parameters, bond lengths, bond angles, and torsion angles for **1** and **2**.[19] This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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