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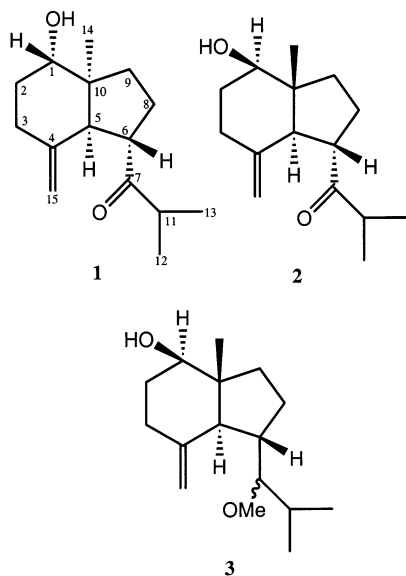
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Received December 28, 2001

Two new isomeric axane and oppositane sesquiterpene derivatives, named teclenone A (**1**) and teclenone B (**2**), were isolated from the aerial parts of *Teclea nobilis*. Their structures have been established on the basis of ¹H and ¹³C NMR spectral data, notably 2D NMR ¹H–¹H COSY, ¹H–¹³C HMQC, ¹H–¹³C HMBC, and ¹H–¹H NOESY experiments. This appears to be the first report of the rare axane and oppositane sesquiterpenes from the plant family Rutaceae.

Teclea nobilis Delile (Rutaceae), locally known as Al-dhureim, is a shrub used in folk medicine as an analgesic and antipyretic and also in the treatment of gonorrhea.¹ Earlier phytochemical studies on this species^{2–4} revealed the presence of quinoline and furoquinoline alkaloids, while limonoids, tetranortriterpenes, triterpenes, alkaloids, and flavonoid glucosides were isolated from *T. ouabanguiensis*, *T. grandifolia*, *T. verdoorniana*, and *T. sudanica*, respectively.^{5–9} In addition, the ethanol extract of *T. nobilis* was reported to have antipyretic and analgesic activities.¹⁰ The present investigation reports the isolation and structure elucidation of two isomeric axane and oppositane sesquiterpene ketones, teclenone A (**1**) and teclenone B (**2**), from the aerial parts of *T. nobilis* collected in the Southern regions of Saudi Arabia.



The MeCN fraction of the *n*-hexane extract was subjected to flash chromatography, followed by centrifugal preparative thin-layer chromatography (see Experimental Section), to afford compounds **1** and **2** in yields of 0.003% and 0.0029%, respectively. Both of the compounds were obtained as gums and found to be homogeneous on TLC.

Compound **1** was analyzed by HRMS for the molecular formula C₁₅H₂₄O₂. Its octahydro-1*H*-indene carbon skeleton was suggested on the basis of its ¹H and ¹³C NMR spectral data^{11–13} (Table 1). Teclenone A (**1**) demonstrated the presence of a carbonyl (ν_{\max} 1710 cm^{−1}; δ_{C-7} 217.3), a hydroxyl (ν_{\max} 3470 cm^{−1}; δ_{C-1} 71.4), and an exocyclic methylene (ν_{\max} 1660 cm^{−1}; δ_{C-4} 145.3, δ_{C-15} 112.7) groups. The ¹H NMR spectrum of **1** exhibited signals for a tertiary methyl (δ 0.90, s, H-14), an oxymethine (δ 3.64, dd, J = 11.8, 4.2 Hz, H-1), and an exocyclic methylene (δ 4.73, 4.64, each s, H-15), while the ¹³C NMR revealed two singlets (δ_C 145.3, 49.9), three doublets (δ_C 71.4, 59.9, 51.9), and four triplets (δ_C 32.1, 30.4, 27.3, 36.9), consistent with a 1-hydroxy-4(15)-methyleneoctahydroindene base skeleton.^{11–13} In addition, the ¹H NMR spectrum exhibited two secondary methyls (δ 1.02, 0.97, each d, J = 6.9 Hz) and a methine (δ 2.50, 1H, m), attributable to H-11–H-13, respectively. The assignments of spectral data and stereochemistry for **1** were established by extensive 2D NMR experiments involving the analysis of its ¹H–¹H COSY, ¹H–¹³C HMQC, and gradient ¹H–¹³C HMBC spectra.

The HMBC experiment established the placement of the hydroxyl, carbonyl, and methyl groups at the C-1, C-7, and C-14 positions, respectively, by ³ J correlations between the signals at δ 3.64 (H-1), δ_{C-9} 36.9, and δ_{C-14} 18.0; δ 2.53 (H-5), δ_{C-1} 71.4, δ_{C-3} 30.4, δ_{C-7} 217.3, δ_{C-14} 18.0, and δ_{C-15} 112.7. In addition, the HMBC established the assignments of the C-4 and C-6 carbons by ² J and ³ J correlations between δ 3.25 (H-6), δ_{C-4} 145.3, and δ_{C-7} 217.3, as well as correlations between H-15 (δ 4.73 and 4.64), δ_{C-3} 30.4, and δ_{C-5} 59.9. Finally, placement of the C-6 isobutanone substituent was established by cross-peaks between δ 2.50 (H-11), δ_{C-12} 18.4, δ_{C-13} 17.7, and C-7; the latter was correlated to C-6. On the basis of the foregoing data the gross structure was established as shown (**1**).

The relative stereochemical assignments of carbons C-1, C-5, C-6, and C-10 were resolved using the ¹H–¹H NOESY experiments (Figure 1). These showed correlations between δ 3.64 (H-1), 3.25 (H-6), and 2.03 (H-9B), indicating that the protons are *cis* to each other and β -oriented. On the other hand, H-5 showed cross-peaks with H-12 (δ 1.02), H-13 (δ 0.97), and H-9A (δ 1.42), suggesting that the protons are *cis* to each other and placed at the opposite side (α -oriented) of the molecule. In addition, H-5 (δ 2.53) showed correlations with H-14 (δ 0.90), thereby confirming that compound **1** has a *cis*-fused octahydro-1*H*-indene (axane) ring junction. Thus, the hydroxyl at C-1, H-5, and C-10 methyl groups were placed at the α -face of the

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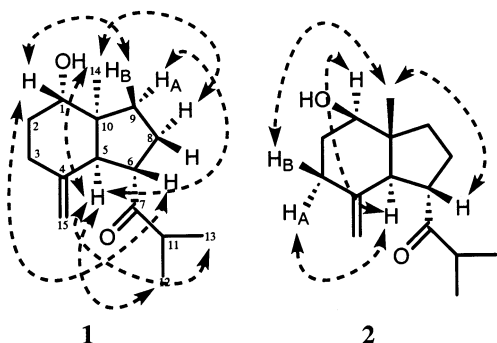
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Table 1. ^1H and ^{13}C NMR Data for Teclenone A (**1**) and Teclenone B (**2**)

H/C	1			2		
	^1H	^{13}C	HMBC	^1H	^{13}C	HMBC
1	3.64 dd (11.8, 4.2) ^a	71.4 d ^b	C-2, C-9, C-10, C-14	3.62 dd (11.3, 4.6)	78.9 d	C-2, C-5, C-9, C-10, C-14
2 α	1.49 m	32.1 t	C-1, C-4, C-10	1.48 m	31.8 t	C-1, C-4, C-10
2 β	1.81 m			1.79 m		
3 α	2.25 m	30.4 t	C-1, C-2, C-4	2.09 m	30.2 t	C-1, C-2, C-4
3 β			C-15	2.26 m		C-5, C-15
4		145.3			146.1	
5	2.53 d (10.9)	59.9 d	C-1, C-3, C-4, C-6, C-7, C-10, C-14, C-15	2.57 d (11.1)	54.0 d	C-1, C-4, C-6, C-7, C-10, C-14, C-15
6	3.25 ddd (10.3, 10.9, 6.8)	51.9 d	C-4, C-5, C-7, C-8	3.17 ddd (10.1, 11.1, 6.6)	47.8 d	C-4, C-5, C-7, C-8
7		217.3 s			217.1 s	
8 α	1.81 m	27.3 t	C-5, C-7, C-9, C-10	1.59 m	27.2 t	C-6, C-7, C-9, C-10
8 β	1.96 m			2.09 m		
9 α	1.42 m	36.9 t	C-1, C-5, C-6, C-8, C-10, C-14	1.48 m	37.8 t	C-1
9 β	2.03 m			1.79 m		
10		49.9 s			48.7 s	
11	2.50 m	41.7 d	C-7, C-12, C-13	2.72 q	41.1 d	C-7, C-12, C-13
12	1.02 d (6.9) ^c	18.4 q ^c	C-7, C-11, C-13	1.10 d (6.8) ^c	18.6 q ^c	C-11, C-13
13	0.97 d (6.9) ^c	17.7 q ^c	C-7, C-11, C-12	1.08 d (6.8) ^c	18.6 q ^c	C-11, C-12
14	0.90 s	18.0 q	C-1, C-5, C-9	0.67 s	12.4 q	C-1, C-5, C-9, C-10
15	4.73 s, 4.64 s	112.7 s	C-4, C-5	4.76 s, 4.38 s	106.9 s	C-4, C-5

^a Coupling constants (J values in Hz) are in parentheses. ^b Multiplicities of carbon signals were determined by DEPT (135°) experiments.

^c Interchangeable signals.

**Figure 1.** Key 2D NMR ^1H – ^1H HOESY correlations (dashed lines) for compounds **1** and **2**.

molecule, opposite the β -oriented methine protons H-1 and H-6. On the basis of the foregoing data, the relative stereochemistry was assigned as shown in Figure 1.

The ^1H and ^{13}C NMR spectral data of **2** ($\text{C}_{15}\text{H}_{24}\text{O}_2$) were in close agreement with those observed for 1 β -hydroxy-4(15)-oppositene derivative **3** [1 α -(1-methoxy-2-methylpropyl)-3 $\alpha\alpha$ -methyl-7-methyleneoctahydroinden-4 β -ol],¹¹ except for the presence of a carbonyl group at C-7 instead of the methoxyl substituent. Furthermore, a close comparison of the ^1H and ^{13}C NMR spectra of **2** with **1** and those of other 1 β -hydroxy-4(15)-oppositene derivatives^{11,12} (Table 1) led to the conclusion that, indeed, **2** was a 7-oxo derivative of **3**. Thus, the structure and stereochemistry of **2** were unambiguously established by detailed 2D NMR studies, including COSY, HMQC, HMBC, and NOESY experiments. The ^{13}C NMR spectrum revealed the anticipated deshielding of C-1 to δ 78.9 and shielding of C-5, C-14, and C-15 to δ 54.0, δ 12.4, and δ 106.9, respectively (versus $\delta_{\text{C-1}}$ 71.4, $\delta_{\text{C-5}}$ 59.9, $\delta_{\text{C-14}}$ 18.0, and $\delta_{\text{C-15}}$ 112.7 for **1**), due to the presence of the C-1 β -hydroxyl group, and agrees with those previously reported for **3**¹¹ ($\delta_{\text{C-1}}$ 79.3, $\delta_{\text{C-5}}$ 55.5, $\delta_{\text{C-14}}$ 12.3, and $\delta_{\text{C-15}}$ 107.2) and related oppositane derivatives. Two significant differences were noted from the NOESY spectrum of **2**, when compared with **1** (Figure 1). The NOESY of **2** showed correlations between δ 3.62 (H-1), δ 2.09 (H-3A), and δ 2.57 (H-5), indicating that the protons are *cis* to each other and α -oriented. On the other hand, H-6 (δ 3.17) showed a cross-peak with H-14 (δ 0.67); the latter

correlated with H-3B (δ 2.26), indicating that they are *cis* to each other and β -oriented. As a result, the hydroxyl group at C-1 was placed at the β -face of the molecule and opposite the α -oriented methine protons H-1 and H-5. Furthermore, the NOESY showed no correlation between H-5 and H-14, thereby suggesting that **2** has a *trans* ring junction. Finally, compounds **1** and **2** were evaluated for in vitro antibacterial (*Staphylococcus aureus*, methicillin-resistant *S. aureus*, and *Pseudomonas aeruginosa*), antifungal (*Candida albicans* and *Cryptococcus neoformans*), and antimalarial (*Plasmodium falciparum* D6 and W2 clones) activities and found to be inactive in these assays.

This appears to be the first report of teclenone A (**1**) and teclenone B (**2**) from a natural source, as well as the first report of the rare axane and oppositane sesquiterpenes from the plant family Rutaceae. Oppositane sesquiterpenes had previously been reported from *Torillus japonica* (Umbeliferae)⁵ and the liverwort *Chiloscyphus pallescens* (Hepaticae),¹⁴ and axane sesquiterpenes from the sponge *Axinella cannabina*.¹⁵ Axanes and oppositanes are formed by rearrangement of germacrane D, and their biogenetic pathway has recently been suggested by Bülow and König (2000).¹³ Thus, 4-cycloaxene and 4-cyclooppositene¹³ appear to be the biogenetic precursors of axane and oppositol type compounds **1** and **2**, respectively. It is intriguing to note that teclenone A (**1**) has the same stereochemistry as 4(15)-cycloaxene¹³ at the chiral centers C-5 and C-10, the latter carrying an α (relative stereochemistry) methyl group, while the oppositane derivatives from higher plants, including *Torillus japonica*^{11–13} and *Dysoxylum variable*,¹⁶ are epimeric at C-10.

Experimental Section

General Experimental Procedures. UV spectra were recorded in MeOH, using a Shimadzu UV-1601PC spectrophotometer, and IR spectra were obtained in a thin film on a Perkin-Elmer 5808 spectrophotometer. The NMR spectra were recorded on a Bruker Avance DRX 500 instrument at 500 MHz (^1H) and at 125 MHz (^{13}C) in CDCl_3 , using TMS as internal standard. Multiplicity determinations (DEPT) and 2D NMR spectra (gradient DQF-COSY, HMQC, gradient HMBC, and NOESY) were run using the standard Bruker pulse program. HRMS were obtained by direct injection using Bruker Bioapex-

FTMS with electro-spray ionization (ESI). EIMS were measured using an E.I. Finnigan model 4600 quadrupole system or a Shimadzu QP500 GC/mass spectrometer. Optical rotations were recorded in CHCl_3 at ambient temperature, using a Perkin-Elmer 241 MC polarimeter. TLC analyses were carried out on silica gel G 254 plates, with the solvent system *n*-hexane–EtOAc (1:1). For flash column chromatography, silica gel 60 (40 μm) was used with *n*-hexane–EtOAc mixtures as solvent system. Centrifugal preparative TLC (CPTLC) was performed using a Chromatotron (Harrison Research Inc. model 7924) on 1 or 2 mm silica gel PF₂₅₄ disks, with a N_2 flow rate of 2–4 mL min^{-1} . The isolated compounds were visualized by spraying with 5% anisaldehyde– H_2SO_4 and heating the plates to 100 °C.

Plant Material. The aerial parts of *T. nobilis* were collected in March 1999, from Al-Namas, Saudi Arabia. A voucher specimen (#14050) was deposited at the Herbarium of the Medicinal, Aromatic and Poisonous Plants Research Center, King Saud University, Riyadh, Saudi Arabia.

Extraction and Isolation. The ground aerial parts of *T. nobilis* (1.15 kg) were successively extracted with *n*-hexane, followed by EtOH, in a Soxhlet for 72 h (yields 46 and 85 g, respectively). The gummy residue of the *n*-hexane extract, obtained after evaporation in vacuo, was partitioned between *n*-hexane (300 mL) and MeCN (4 \times 100 mL) presaturated with each other. Flash chromatography of the MeCN residue (22 g) over silica gel (450 g), using EtOAc (1% \rightarrow 10%) in *n*-hexane as solvent, yielded 200 fractions (each 150 mL), which were pooled into 25 fractions according to their TLC patterns. Fraction 10 (1.27 g) was subjected to CPTLC (Chromatotron, 2 mm silica gel disk), using CHCl_3 as solvent, which afforded three fractions (A–C). Fraction B (70 mg) was purified by a silica gel column, with *n*-hexane–EtOAc (9.5:0.5) as solvent, to yield **1** (34.5 mg), while fraction C (213 mg) was subjected to CPTLC (Chromatotron, 1 mm silica gel disk), using CHCl_3 as solvent, which afforded **2** (31.4 mg).

Teclenone A [1 α -(1-Oxo-2-methylpropyl)-3 α -methyl-7-methyleneoctahydroinden-4 α -ol] (1): gum; $[\alpha]_{\text{D}}^{25} +28.9^\circ$ (*c* 1.5, CHCl_3); UV (MeOH) λ_{max} (log ϵ) 229 (3.16) 285 (2.40) nm; IR (CHCl_3) ν_{max} 3470, 3090, 2980, 2960, 2890, 1710, 1660, 1485, 1070, 920 cm^{-1} ; ^1H and ^{13}C NMR, see Table 1; EIMS m/z 236 $[\text{M}]^+$ (0.2), 193 (1), 165 (8), 147 (52), 121 (12), 105 (19),

91 (17), 83 (57), 79 (12), 71 (12), 43 (100); HRMS m/z 259.3359 $[\text{M} + \text{Na}]^+$ (calcd for $\text{C}_{15}\text{H}_{24}\text{O}_2\text{Na}$, 259.3396).

Teclenone B [1 α -(1-Oxo-2-methylpropyl)-3 α -methyl-7-methyleneoctahydroinden-4 β -ol] (2): gum; $[\alpha]_{\text{D}}^{25} +75.8^\circ$ (*c* 1.8, CHCl_3); UV (MeOH) λ_{max} (log ϵ) 231 (2.60), 279 (2.10), 280 (sh) (2.10); IR (CHCl_3) ν_{max} 3450, 3090, 2990, 2950, 2900, 1710, 1660, 1475, 1065, 895 cm^{-1} ; ^1H and ^{13}C NMR, see Table 1; EIMS m/z 236 $[\text{M}]^+$ (0.2), 193 (2), 165 (13), 147 (88), 121 (20), 105 (29), 91 (22), 83 (14), 79 (15), 71 (17), 43 (100); HRMS m/z 259.3373 $[\text{M} + \text{Na}]^+$ (calcd for $\text{C}_{15}\text{H}_{24}\text{O}_2\text{Na}$, 259.3396).

Acknowledgment. The authors thank Dr. S. Abidin, College of Pharmacy, King Saud University, for identification of the plant material, Ms. Sharon Sanders, Mr. Charlie Dawson, Ms. Miranda Logan, and Mr. John Trott, NCNPR, University of Mississippi, for technical assistance, and Mr. Frank M. Wiggers, for recording NMR spectra, and Dr. D. Chuck Dunbar, for HRMS.

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NP0106485