New Axane and Oppositane Sesquiterpenes from *Teclea nobilis*

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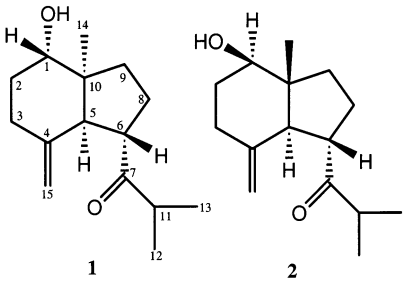
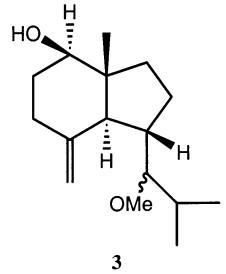
Two new isomeric axane and oppositane sesquiterpene derivatives, named teclenone A (**1**) and teclenone B (**2**), were isolated from the aerial parts of *Teclea nobilis*. Their structures have been established on the basis of ^{1}H and ^{13}C NMR spectral data, notably 2D NMR ^{1}H−^{1}H COSY, ^{1}H−^{13}C HMQC, ^{1}H−^{13}C HMBC, and ^{1}H−^{1}H 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 Aldhureim, 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 $C_{15}H_{24}O_2$. Its octahydro-1*H*-indene carbon skeleton was suggested on the basis of its ^{1}H and ^{13}C 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 ^{1}H 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 ^{13}C 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 ^{1}H 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 ^{1}H−^{1}H COSY, ^{1}H−^{13}C HMQC, and gradient ^{1}H−^{13}C 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 ^3J 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 ^2J and ^3J 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 ^{1}H−^{1}H 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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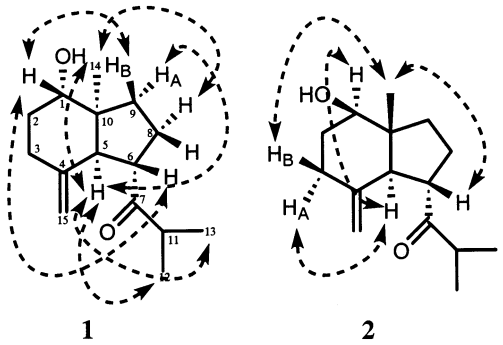
Table 1. ^{1}H and ^{13}C NMR Data for Teclenone A (**1**) and Teclenone B (**2**)

	1			**2**		
H/C	^{1}H	^{13}C	HMBC	^{1}H	^{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
2α	1.49 m	32.1 t	C-1, C-4, C-10	1.48 m	31.8 t	C-1, C-4, C-10
2β	1.81 m			1.79 m		
3α	2.25 m	30.4 t	C-1, C-2, C-4	2.09 m	30.2 t	C-1, C-2, C-4
3β			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	
8α	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
8β	1.96 m			2.09 m		
9α	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
9β	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.



1 **2**

Figure 1. Key 2D NMR ^{1}H−^{1}H 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 ^{1}H and ^{13}C NMR spectral data of **2** ($C_{15}H_{24}O_2$) were in close agreement with those observed for 1β-hydroxy-4(15)-oppositene derivative **3** [1α-(1-methoxy-2-methylpropyl)-3aα-methyl-7-methyleneoctahydroinden-4β-ol],[11] except for the presence of a carbonyl group at C-7 instead of the methoxyl substituent. Furthermore, a close comparison of the ^{1}H and ^{13}C NMR spectra of **2** with **1** and those of other 1β-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 desheiding of C-1 to δ 78.9 and sheiding of C-5, C-14, and C-15 to δ_C 54.0, δ_C 12.4, and δ_C 106.9, respectively (versus δ_{C-1} 71.4, δ_{C-5} 59.9, δ_{C-14} 18.0, and δ_{C-15} 112.7 for **1**), due to the presence of the C-1β-hydroxyl group, and agrees with those previously reported for **3**[11] (δ_{C-1} 79.3, δ_{C-5} 55.5, δ_{C-14} 12.3, and δ_{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 *Pseudomonus 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* (Umberiferae)[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-cycloppositene[13] 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)-cycloaxene[13] 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 (^{1}H) 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 quadruple 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 PF_{254} 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 × 100 mL) presaturated with each other. Flash chromatography of the MeCN residue (22 g) over silica gel (450 g), using EtOAc (1% → 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 [**1α-(1-Oxo-2-methylpropyl)-3aα-methyl-7-methyleneoctahydroinden-4α-ol**] **(1):** gum; $[\alpha]_D$ +28.9° (*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 $[M]^+$ (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 $[M + Na]^+$ (calcd for $C_{15}H_{24}O_2Na$, 259.3396).

Teclenone B [**1α-(1-Oxo-2-methylpropyl)-3a*β*-methyl-7-methyleneoctahydroinden-4*β*-ol**] **(2):** gum; $[\alpha]_D$ +75.8° (*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 $[M]^+$ (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 $[M + Na]^+$ (calcd for C_{15} $H_{24}O_2Na$, 259.3396).

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