Oxidation Products of Zeylanidine

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The oxidation of zeylanidine (**1**) afforded two new sesquiterpene dilactones, **4** and **5**, besides two known compounds, neoliacine (**2**) and zeylanidinone (**3**). The structures of the novel oxidized products were elucidated on the basis of spectroscopic techniques, and the structure of compound **5** was further confirmed by X-ray crystallographic analysis. The mechanism for the oxidation of **1** to **4** and **5** has been postulated.

The furan rings of furanogermacranolide sesquiterpenes are very susceptible to oxidation if dissolved in solvents such as chloroform and then exposed to air.[1−3] Previously, Wang et al. studied the oxidation of zeylanidine (**1**), a furanogermacranolide isolated from *Neolitsea zeylanica*,[4,5] and reported the formation of three sesquiterpene dilactones.[1] From a chloroform-soluble extract of the stems of *Neolitsea parvigemma* Kan. & Sas. (Lauraceae), **1** was isolated along with seven other related compounds.[6] To examine the oxidation products of **1** with different oxidizing agents, **1** was dissolved in $CHCl_3$ and *m*-chloroperbenzoic acid (*m*-CPBA)−$CHCl_3$, respectively. We chose *m*-CPBA as an oxidizing agent because of the ease of use, the stability of this reagent, and the usually good product yields.[7] In this paper we wish to report the oxidation products using different oxidizing agents and the mechanism of formation of these oxidation products.

Zeylanidine (**1**) on treatment with $CHCl_3$ (see Experimental Section) afforded two known dilactones, neoliacine (**2**)[1] and zeylanidinone (**3**),[1] and a new dilactone **4**. Treatment of **1** with *m*-CPBA−$CHCl_3$ afforded **4** and a second new compound, **5**.

Compound **4** was obtained as white needles. Its molecular formula was established as $C_{17}H_{18}O_8$ by HRMS (found *m*/*z* 350.1019, calcd 350.1015). The UV spectrum showed a maximum at 227 nm, characteristic for an unsaturated lactone.[8] The IR spectrum showed the presence of saturated lactone (1775 cm^{-1}), unsaturated lactone (1750 cm^{-1}), and acetate (1740 cm^{-1}) groups. Two lactone functionalities were supported by signals at δ 169.1 and 170.4 in the ^{13}C NMR spectrum (Table 1). Because this compound is an autoxidation product, the additional lactone function must have resulted from oxidation of the furan moiety. The fact that the signal at δ 7.26 for H-12 in **1**[1] was absent and replaced by a new singlet at δ 5.13 for H-9 in **4** strongly indicated oxidation of the furan moiety. The chemical shifts of **4** were compared with those of the starting material **1**. The two protons of H-2 (δ 3.42) and H-10 (δ 5.62) in **4** were shifted further upfield relative to the analogous signals (δ 3.67 and 6.00, respectively) in **1**.[1] Accordingly, it was inferred that the furan moiety was oxidized to form an α,β-unsaturated γ-lactone ring. Based on the X-ray crystallographic analysis of **1**[9] and the proposed mechanism (Scheme 1), the stereochemistry of H-2 has been assigned as being β oriented, with H-6, H-7, and H-10 in the α-orientation. The H-9 proton of **4** was assigned an α-orientation because of its small coupling constant (0.8 Hz) with H-10. The remaining signals in the ^1H NMR spectrum, δ 1.15 for H-14, δ 2.06 for H-13, δ 3.98 for H-6, and δ 5.63 for H-7, were close to those of **1** (Table 2).[1] The above observations and the analysis of its COSY and HETCOR spectra led to the establishment of the structure of this compound as 1β(2α),5α(6β)-diepoxy-1α,11-dimethyl-7β(15),9β(12)-diether-10β-acetyl-tricyclo⟨10,2,1,0⟩pentadeca-8(11)-ene-12,15-dione.

Table 1. ^{13}C NMR Chemical Shifts of Compounds **1**−**5**[a]

	compound				
carbon	**1**	**2**	**3**	**4**	**5**
C-1	60.83 s	147.24 s	61.09 s	59.31 s	57.04 s
C-2	56.73 d	88.14 d	61.75 d	56.82 d	54.65 d
C-3	20.96 t	27.19 t	20.31 t	21.13 t	19.97 t
C-4	21.27 t	18.43 t	22.62 t	21.37 t	21.81 t
C-5	61.43 s	55.51 s	55.76 s	58.92 s	59.86 s
C-6	60.39 d	60.29 d	62.17 d	59.56 d	60.58 d
C-7	72.57 d	71.12 d	71.61 d	74.40 d	72.57 d
C-8	116.37 s	147.86 s	140.38 s	152.77 s	147.44 s
C-9	150.58 s	115.07 s	146.07 s	82.08 d	107.19 s
C-10	68.33 d	122.91 d	115.22 d	70.46 d	73.54 d
C-11	121.46 s	132.93 s	137.94 s	130.92 s	140.20 s
C-12	138.95 d	169.32 s	167.24 s	169.07 s	169.19 s
C-13	8.37 q	8.91 q	10.00 q	10.00 q	9.80 q
C-14	16.43 q	12.28 q	19.17 q	15.30 q	16.85 q
C-15	171.82 s	172.06 s	169.42 s	170.44 s	170.39 s
Ac	169.48 s			169.83 s	169.56 s
Ac	20.60 q			20.39 q	20.34 q

[a] Measured at 50 MHz, in $CDCl_3$, with TMS as internal standard. Chemical shifts are in δ values.

Compound **5** was obtained as white needles. Its molecular formula was established as $C_{17}H_{18}O_9$ by HRMS (found *m*/*z* 366.0952, calcd 366.0950). The UV spectrum showed a maximum at 226 nm, characteristic for an unsaturated lactone.[8] The IR spectrum showed the presence of saturated lactone (1780 cm^{-1}), unsaturated lactone (1760 cm^{-1}), acetate (1745 cm^{-1}), and hydroxyl (3400 cm^{-1}) groups. In the ^1H NMR spectrum, except for the absence of the H-9 proton signal, the general features of the ^1H NMR spectrum of **5** paralleled those observed for **4**. Two three-proton singlets (3H for each) were present at δ 1.93 and 1.63, assignable for an acetoxyl methyl and the C-14 methyl groups, in addition to a methyl group present at δ 2.04, which was assigned to C-11. Three singlets, δ 4.69 for H-6, δ 5.46 for H-7, and δ 5.53 for H-10, were close to analogous data recorded for **4**. Two singlets at δ 169.2 and 170.4 in the ^{13}C NMR spectrum of **5** indicated that two lactone

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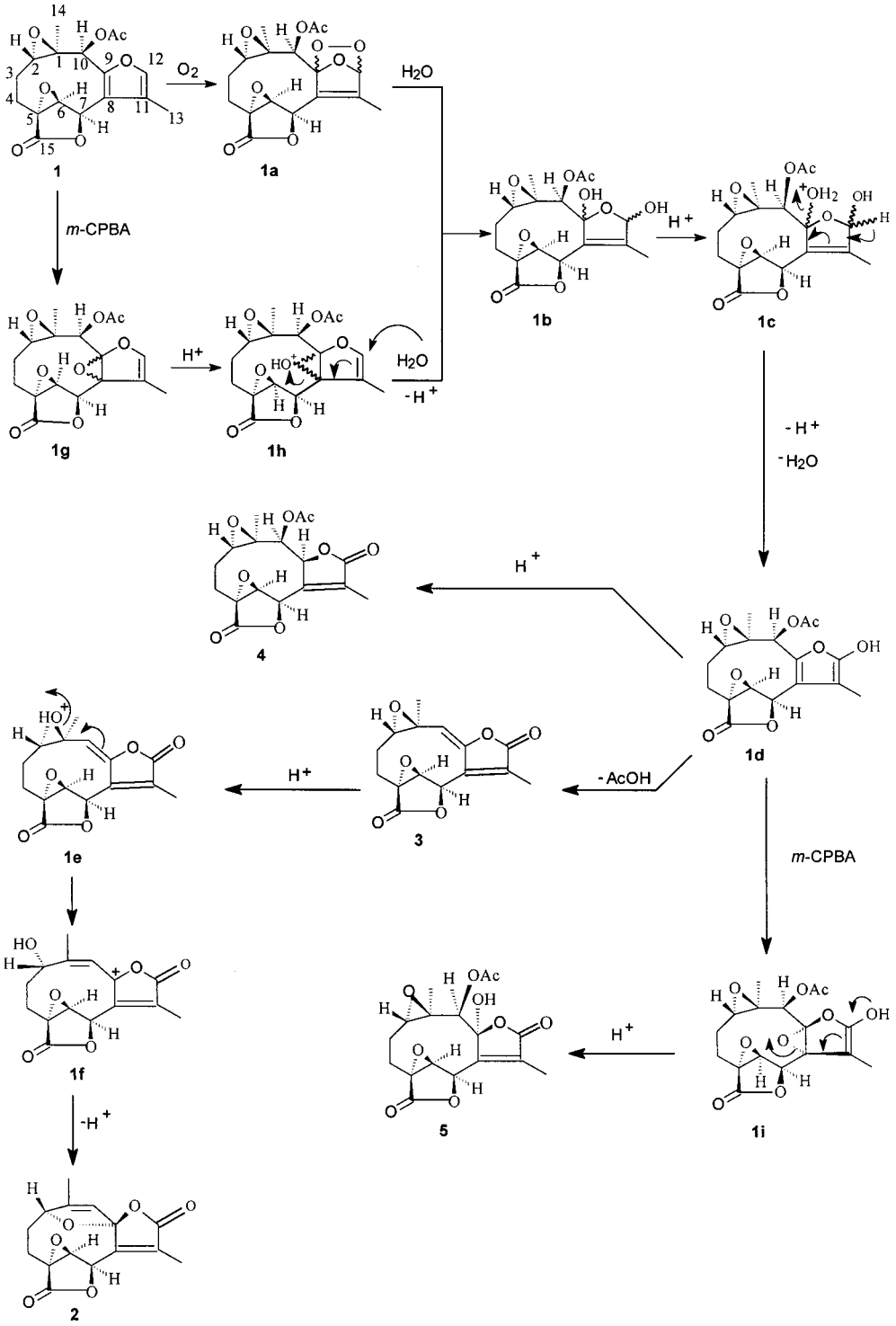
Scheme 1. Postulated Mechanism for the Oxidation of **1** To Give **2**−**5**



functionalities were present. Comparison of the spectral data of **4** and **5** clearly indicated that **5** possessed a hydroxyl group at C-9 instead of a proton, as in **4**. A singlet at δ 107.2, indicating the existence of a hemiketal, was observed in the ^{13}C NMR spectrum, strongly supporting this assignment. Based on the above information, the structure of **5** was established as 1β(2α),5α(6β)-diepoxy-1α,11-dimethyl-7β(15),9β(12)-diether-9α-hydroxy-10β-acetyl-tricyclo⟨10,2,1,0⟩pentadec-8(11)-ene-12,15-dione. The structure of **5** was determined unambiguously by X-ray crystallographic analysis (Figure 1), which confirmed its relative configuration.

The proposed mechanism for the oxidation of **1** and the formation of **2**−**5** from **1** in this investigation is summarized in Scheme 1. The reaction of **1** with oxygen gives peroxide **1a**,[10,11] which was hydrolyzed to **1b** by the treatment of water. Protonation of **1b** and subsequent loss of water and proton led to the stable aromatic moiety **1d**, which could then tautomerize to the more stable **4** or undergo elimination of acetic acid to form **3**. Again, protonation of **3** and subsequent ring opening would form carbocation **1f**. Finally, **2** was generated by elimination of a proton from **1f**. Epoxidation of **1** with *m*-CPBA gives **1g**. Protonation of **1g**, followed by ring opening with water would lead to **1b**. Again, protonation of **1b** and subsequent loss of water and proton would give **1d**, which could

Table 2. ^{1}H NMR Chemical Shifts of Compounds **1**−**5**

	compound				
position	**1**[a]	**2**[b]	**3**[b]	**4**[b]	5[b]
H-2	3.67 dd (10.0; 1.0)	5.20 br s	3.16 dd (9.6; 5.4)	3.42 d (10.8)	3.20−3.30 m
H-3	1.50−1.65 m	2.03−2.10 m	1.65−1.71 m	1.44−1.52 m	1.66−1.75 m
H-3	2.20−2.32 m	2.17−2.23 m	2.64−2.72 m	2.16−2.21 m	2.64−2.73 m
H-4	1.83 ddd (14.8; 8.5; 1.0)	1.83−1.92 m	1.65−1.71 m	1.75−1.82 m	1.54−1.63 m
H-4	3.03 ddd (15.6; 9.3; 9.0)	2.59 ddd (15.4; 11.3; 6.4)	2.64−2.72 m	2.89−2.97 m	2.55−2.67 m
H-6	3.96 s	4.33 s	4.15 d (0.4)	3.98 s	4.69 s
H-7	5.38 s	5.43 s	5.56 d (0.8)	5.63 s	5.46 br s
H-9				5.13 br s	
H-10	6.00 s	5.36 q (1.3)	6.15 d (0.4)	5.62 d (0.8)	5.53 s
H-12	7.26 s				
H-13	2.07 s	2.05 s	2.16 d (0.8)	2.06 s	2.04 d (0.8)
H-14	1.15 s	1.88−1.96 m	1.54 s	1.15 s	1.63 s
OAc	2.05 s			2.12 q (0.8)	1.93 s

[a] Measured at 200 MHz, in $CDCl_3$, with TMS as internal standard. Coupling constants (J in Hz) are in parentheses. Chemical shifts are in δ values. [b] Measured at 400 MHz.

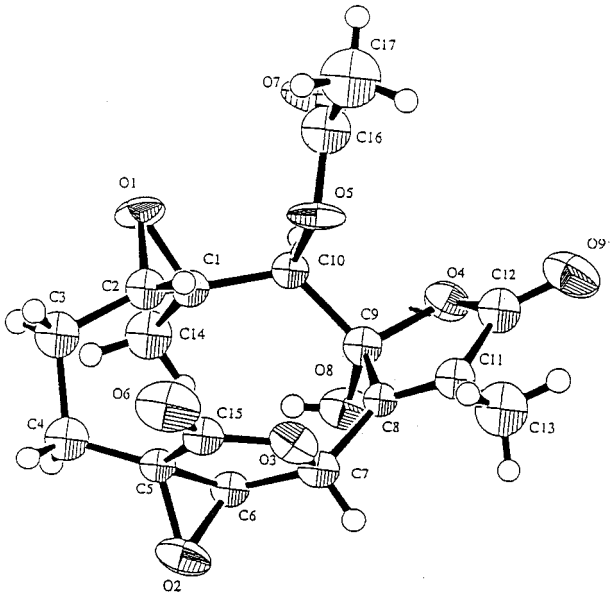


Figure 1. ORTEP diagram for **5**.

tautomerize to **4** or react with *m*-CPBA to form **1i**. Finally, the epoxide would undergo ring opening reaction to form **5**. Based on the results of X-ray crystallographic analysis of **5**, the OH-9 proton was assigned as in an α-orientation. The treatment of **1d** with *m*-CPBA would be expected to lead to the α-epoxide compound **1i**.

Experimental Section

General Experimental Procedures. Melting points were determined using a Yanagimoto micro-melting point apparatus and are uncorrected. The UV spectra were obtained on a Hitachi 200−20 spectrophotometer, and the IR spectra were measured on a Hitachi 260−30 spectrophotometer. ^{1}H NMR spectra were recorded with a Varian Gemini NMR spectrometer at 400 and 200 MHz, and ^{13}C NMR spectra were recorded with a Varian Gemini NMR spectrometer at 50 MHz, in $CDCl_3$ using TMS as internal standard. MS were obtained with a JEOL JMS−HX110 mass spectrometer at 70 eV. *m*-CPBA was purchased from Wako Pure Chemical Industries, Ltd. Co., Japan. Si gel 60 (Merck, 230−400 mesh) was used for column chromatography, precoated Si gel plates (Merck, Kieselgel 60 F_{254}, 0.20 mm) were used for analytical TLC, and precoated Si gel plates (Merck, Kieselgel 60 F_{254}, 0.50 mm) were used for preparative TLC.

Oxidation of Zeylanidine (1). The oxidation followed the procedure described by Ulubelen et al.[12] A $CHCl_3$ solution (70 mL) of **1** (9.0 g) was exposed to air at room temperature for 14 days, by which time all of the starting material had disappeared. Removal of $CHCl_3$ in vacuo left a light brown viscous residue (9.1 g) that was chromatographed over Si gel (370 g) and eluted with mixtures of *n*-hexane−$CHCl_3$−Me_2-CO of increasing polarity to yield 30 fractions (120 mL each). The combined and dried fractions (1.21 g) eluted from *n*-hexane−$CHCl_3$ (1:10) were further purified by Si gel column chromatography with *n*-hexane−$CHCl_3$ (1:5) to give **2** (453 mg). The fraction (896 mg) eluted with $CHCl_3$ was further separated and purified by Si gel column chromatography with $CHCl_3$−Me_2CO (40:1) to give **3** (236 mg) and **4** (132 mg). A solution of *m*-CPBA (2 g) in $CHCl_3$ (30 mL) was added gradually to a solution of **1** (3.0 g) in $CHCl_3$ (25 mL) with stirring at room temperature. The stirring was continued for 1 h and then the solution was left at room temperature for 14 days, by which time all **1** had disappeared. Removal of $CHCl_3$ in vacuo left a light brown, viscous residue (3.02 g) that was chromatographed over Si gel (120 g) and eluted with increasing polarities of *n*-hexane−$CHCl_3$−Me_2CO mixtures to yield 12 fractions (120 mL each). A fraction (342 mg) eluted with $CHCl_3$ was further separated and purified by Si gel column chromatography with $CHCl_3$−Me_2CO (35:1) to give **4** (120 mg). A fraction (264 mg) eluted with $CHCl_3$−Me_2CO (12:1) was further separated and purified by Si gel column chromatography with $CHCl_3$−Me_2CO (10:1) to yield **5** (105 mg).

Compound 4: white prisms from MeOH; mp 232−234 °C; $[\alpha]^{24}_D$ +15.6° (*c* 2.0, $CHCl_3$), UV (EtOH) λ_{max} (log ϵ) 227 (3.96) nm; IR (KBr) ν_{max} 3080, 1775, 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.63 (1H, s, H-7), 5.62 (1H, d, J = 0.8 Hz, H-10), 5.13 (1H, br s, H-9), 3.98 (1H, s, H-6), 3.42 (1H, d, J = 10.8 Hz, H-2), 2.89−2.97 (1H, m, H-4), 2.16−2.21 (1H, m, H-3), 2.12 (3H, q, J = 0.8 Hz, OAc), 2.06 (3H, s, H-13), 1.75−1.82 (1H, m, H-4), 1.44−1.52 (1H, m, H-3), 1.15 (3H, s, H-14); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.4 (s, C-15), 169.8 (s, O*C*OCH$_3$), 169.1 (s, C-12), 152.8 (s, C-8), 130.9 (s, C-11), 82.1 (d, C-9), 74.4 (d, C-7), 70.5 (d, C-10), 59.6 (d, C-6), 59.3 (s, C-1), 58.9 (s, C-5), 56.8 (d, C-2), 21.4 (t, C-4), 21.1 (t, C-3), 20.4 (q, OCO*C*H$_3$), 15.3 (q, C-14), 10.0 (q, C-13); EIMS *m*/*z* 350 [M$^+$] (6), 307 (13), 291 (15), 154 (92), 137 (100), 120 (17); HREIMS *m*/*z* 350.1019 (calcd for $C_{17}H_{18}O_8$, 350.1015).

Compound 5: white prisms from MeOH; mp 242−244 °C; $[\alpha]^{24}_D$ +38.1° (*c* 2.0, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 226 (3.87) nm; IR (KBr) ν_{max} 3400, 1780, 1760 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.53 (1H, s, H-10), 5.46 (1H, br s, H-7), 4.69 (1H, s, H-6), 3.20−3.30 (1H, m, H-2), 2.64−2.73 (1H, m, H-3), 2.55−2.67 (1H, m, H-4), 2.04 (3H, d, J = 0.8 Hz, H-13), 1.93 (3H, s, OAc), 1.66−1.75 (1H, m, H-3), 1.63 (3H, s, H-14), 1.54−1.63 (1H, m, H-4); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.4 (s, C-15), 169.6 (s, O*C*OCH$_3$), 169.2 (s, C-12), 147.4 (s, C-8), 140.2 (s, C-11), 107.2 (s, C-9), 73.5 (d, C-10), 72.6 (d, C-7), 60.6 (d, C-6), 59.9 (s, C-5), 57.0 (s, C-1), 54.7 (d, C-2), 21.8 (t, C-4), 20.3 (q, OCO*C*H$_3$), 20.0 (t, C-3), 16.9 (q, C-14), 9.8 (q, C-13); EIMS *m*/*z* 366 [M$^+$] (7), 348 (10), 306 (43), 177 (21), 137 (100); HREIMS *m*/*z* 366.0952 (calcd for $C_{17}H_{18}O_9$, 366.0950).

Single-Crystal X-ray Analysis of 5. Crystal data: $C_{17}H_{18}O_9$, *Mr* 366.32; orthorhombic, space group $P2_12_12_1$; $a = 10.846$ (2), $b = 15.634$ (4), $c = 10.519$ (3) Å, V = 1783.6 (7) Å^3, $Z = 4$, $D_{calc} = 1.364$ g/cm^3, μ(Mo Kα radiation $\lambda = 0.71069$ Å). A colorless crystal with dimensions of 0.33 × 0.33 × 0.50 mm was mounted on a glass fiber and analyzed using a Rigaku AFC6S diffractometer. Friedel pairs of ($+h$, $+k$, $+l$) were collected with $\omega-2\theta$ mode scanning up to 2θ max of 50.1°. After data averaging, 908 reflections with $I > 3.00\sigma(I)$ were retained for the structure analysis, and the usual Lorentz and polarization corrections were applied. Refined unit-cell parameters were calculated from the diffractometer, setting angles for 20 reflections ($8.72 < \theta < 13.6°$). The crystal structure was solved by the direct method. Hydrogen atoms were placed at idealized position ($d_{C-H} = 0.95$ Å). The refinement converged at $R = 0.065$ ($Rw = 0.048$). Attempts to determine the chirality implied by the space group were not successful. Full crystallographic data are deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

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