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EPOXIDATION OF SESQUITERPENE LACTONES TOURNEFORIN AND LUDARTIN

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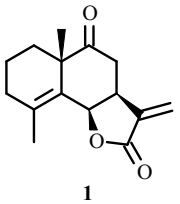
Epoxy derivatives of the sesquiterpene lactones ludartin and tourneforin were synthesized. Their structures were elucidated using spectral data and x-ray structure analysis.

Key words: sesquiterpene lactone, guaianolide, eudesmanolide, epoxy derivative, x-ray structure analysis, NMR spectroscopy.

Sesquiterpene lactones contain various pharmacophore groups, one of which is an epoxide ring. Introduction into sesquiterpene lactones of an epoxide ring is known to increase substantially the biological activity [1, 2]. Therefore, we performed epoxidation of eudesmane- and guaiane-type sesquiterpene lactones containing unsaturated double bonds. We used for the epoxidation peracetic acid that was prepared by the literature method [3]. Reaction of tourneforin (**1**) at room temperature with peracetic acid in $CHCl_3$ produced crystalline compound **2**, mp 195–198°C, in 43% yield.



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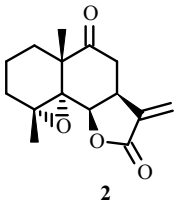

2

Elemental analysis indicated that **2** contained four O atoms. Resonances of protons on C-6, C-3, CH_3-14, and CH_3-15 were shifted in the PMR spectrum of **2** (Table 1). The resonance of lactone proton H-6 (δ_H 4.71) was shifted to strong field by 1.04 ppm (δ_H 5.75 in the starting lactone) due to the formation of the epoxide ring. Resonances of the C-4 methyl and C-10 angular methyl were shifted to strong field by 0.07 and 0.38 ppm, respectively. Furthermore, resonances for protons on C-2 and C-3 shifted by 0.2–0.3 ppm. The presence in the PMR spectrum of two symmetric doublets at δ_H 5.71 (J = 3.0 Hz) and δ_H 6.38 (J = 3.0 Hz) belonging to the exomethylene double bond proved that the reaction was regioselective, i.e., only the C4—C5 double bond was involved in the reaction.

Resonances of C-4 and C-5 in the ^{13}C NMR spectrum (Table 1) were shifted to strong field and appeared as two singlets at δ_C 63.43 and δ_C 65.00 (δ_C 139.75 and 128.19 in the starting molecule). Resonances of C-1, C-3, and C-15 were also shifted by about 4 ppm.

An x-ray structure analysis was consistent with the α-orientation of the epoxide ring. Figure 1 shows the molecular structure of **2**.

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TABLE 1. PMR (500 MHz, $CDCl_3$, δ, ppm, J/Hz) and ^{13}C NMR (125.76 MHz, $CDCl_3$, δ, ppm) Spectra of **2** and **4**

C atom	**2**		**4**	
	δ_H	δ_C	δ_H	δ_C
1			–	59.46 s
1a	1.70 m	29.33 t		
1b	1.35 m			
2a	1.53 m	14.82 t	2.32 br.d (J = 14.0)	35.10 t
2b	1.44 m		1.83 br.d (J = 14.0)	
3			3.39 s	60.81 d
3a	1.93 m	27.37 t		
3b	1.82 m			
4	–	63.43 s	–	65.19 s
5	–	65.00 s	2.36 br.d ($J_{5/6}$ = 10.0)	53.89 d
6	4.71 d (J = 10.0)	76.98 d	3.72 dd ($J_{6/7}$ = 11.0, $J_{6/5}$=10.0)	80.64 d
7	3.76 m	34.91 d	2.60 m	52.42 d
8a	3.00 dd (J = 6.0, 15.0)	39.73 t	2.10 m	23.47 t
8b	2.60 dd (J = 2.0, 15.0)		1.41 m	
9	–	211.28 s		
9a			2.25 q (J = 6.0)	36.98 t
9b			1.41 m	
10	–	45.59 s	–	68.79 s
11	–	136.67 s	–	138.39 s
12	–	169.00 s	–	168.90 s
13a	5.71 d (J = 3.0)	124.61 t	6.14 d (J = 3.0)	118.93 t
13b	6.38 d (J = 3.0)		5.43 d (J = 3.0)	
14	1.10 s (3H)	20.13 q	1.25 s (3H)	20.35 q
15	1.48 s (3H)	20.11 q	1.67 s (3H)	18.39 q

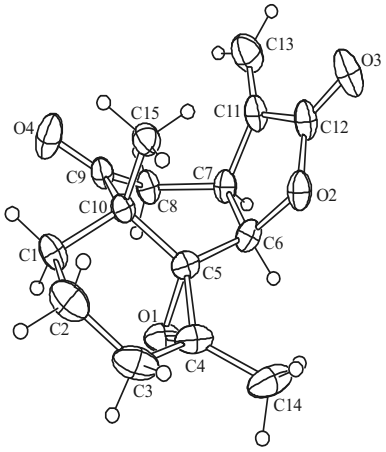
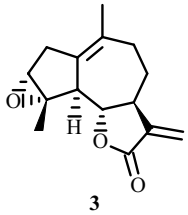


Fig. 1. Molecular structure of **2**.

Bond lengths agreed within uncertainty limits with the statistical average values [4]. Six-membered ring A (C1-C5, C10) had a distorted envelope conformation with C1 deviating by 0.675(3) Å from the plane of the remaining atoms. Six-membered ring B (C5-C10) had a distorted boat conformation with C5 and C8 deviating by 0.526(4) and 0.517(5) Å. The lactone ring was planar within ±0.055 Å. The same conformation of all rings was found in the crystal of starting tourneforin [5]. Ring B in the analogous compound 4α,5α-epoxy-7α-hydroxyeudesmanolide [6] (with a *cis*-fused lactone ring) had the chair conformation, in contrast with **2** and tourneforin. Gas-phase quantum-chemical calculations performed by us for **2** showed that the envelope (C1)—boat conformer (rings A and B) was the most stable whereas the envelope(C1)—chair, envelope(C2)—boat, and envelope(C2)—chair were less stable by 0.8, 2.0, and 3.1 kcal/mol, respectively. Weak H-bonds C–H...O: C7–H7A...O3 [H...O 2.52 Å, C...O 3.157(4) Å, C–H...O 123°] and C13–H13B...O4 [H...O 2.52 Å, C...O 3.157(4) Å, C–H...O 171°] formed a 3D architecture in the crystal. Quantum-chemical calculations were performed using the Priroda program [7] and the density functional method, PBE functional, and 3z basis.



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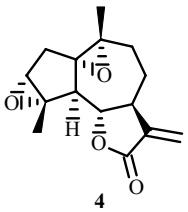

4

Thus, the structure 9-oxo-4(5)α-epoxy-6,7α(H)-eudesm-12,6-olide was proposed for **2** based on the results.

Reaction of the guaianolide ludartin (**3**) with peracetic acid gave **4**.

The PMR spectrum of **4** (Table 1) showed significant shifts for the resonances of C-1, C-2, C-5, C-10, and C-14, which confirmed that the epoxide ring had formed at C1-C10.

The PMR spectra showed the resonance for H-6 as a doublet of doublets and as a triplet in starting **3**, i.e., additional coupling of H-6 to the C-10 methyl protons caused splitting of the resonance. Additional coupling of the lactone proton to methyl protons was also observed in the 2D ^{1}H–^{1}H COSY spectrum. Such coupling of a lactone proton was noted in the cyclopropane derivative of ludartin, the structure of which was established by an x-ray structure analysis [8]. This leads to the conclusion that the methyl had the β-orientation; the epoxide ring, the α-orientation.

Thus, spectral data (PMR, ^{13}C NMR, ^{1}H–^{1}H and ^{13}C–^{1}H COSY, ^{1}H–^{1}H NOESY) of **4** suggested the structure 3(4)α,1(10)α-diepoxy-5,7α,6β(H)-guai-12,6-olide.

EXPERIMENTAL

IR spectra were obtained in KBr on a Vector 22 instrument. NMR spectra were recorded on a Bruker DRX-500 spectrometer (operating frequency 500.13 MHz for ^{1}H; 125.76 MHz, ^{13}C; δ-scale) using standard Bruker programs to record 2D ^{1}H–^{1}H and ^{13}C–^{1}H COSY spectra. Elemental analysis was performed on a Eurovector 3000 A (C, H) analyzer. TLC used Sorbfil plates; column chromatography, silica gel (Armsorb) with detection by spraying with aqueous (2%) $KMnO_4$. Peracetic acid was prepared by the literature method [3]. The course of reactions was monitored by TLC.

Tourneforin (**1**) and ludartin (**3**) were isolated from the aerial part of *Artemisia tournefortiana* Rchb. and *A. filatovae* Kupr., respectively [5, 9].

9-Oxo-4(5)α-epoxy-6,7α(H)-eudesm-12,6-olide (2). Tourneforin (**1**, 200 mg, 0.8 mmol) was dissolved in $CHCl_3$ (2 mL), stirred, treated with peracetic acid (3 mL), and left for 3 d. The mixture was worked up after the reaction was finished. The organic layer was dried, filtered, and evaporated in a rotary evaporator. The solid (0.37 g) was chromatographed over a column of silica gel (8 g) with elution by petroleum ether:EtOAc (80:20) to isolate **2**, mp 195-198°C (EtOAc:petroleum ether), $C_{15}H_{18}O_4$, R_f 0.71 (EtOAc:petroleum ether, 4:2), yield 91 mg (43%).

Table 1 gives the PMR and ^{13}C NMR spectra.

IR spectrum (KBr, ν, cm^{-1}): 1755 (γ-lactone C=O), 1715 (C=O), 1660 (C=C).

X-ray structure analysis was carried out on a Bruker P4 diffractometer [graphite monochromator, λ(Mo-Kα) = 0.71073 Å, 297 K, θ/2θ-scanning]. The crystallographic data and principal refinement parameters for **2** were $C_{15}H_{18}O_4$, MW = 262.29, orthorhombic system, space group $P2_12_12_1$, a = 7.0603(4), b = 8.6073(8), c = 21.830(1) Å, V = 1326.6(2) Å^3, Z = 4, d_{calc} = 1.313 g/cm^3, μ = 0.095 cm^{-1}, scan range 2θ < 55°, number of measured reflections 1780, number of reflections with $I \geq 2\sigma(I)$ 1466, number of refined parameters 173, R_1 [$I \geq 2\sigma(I)$] = 0.0473, wR_2 = 0.1331 (all reflections), GOF = 1.068. Absorption corrections were made using azimuthal scanning (T_{min}/T_{max} = 0.908/0.968). The structure was solved by direct methods. Positions and temperature factors of nonhydrogen atoms were refined isotropically and then anisotropically using full-matrix least-squares methods. H atoms were located geometrically and refined using the rider model. All calculations were performed using the SHELX-97 programs. The results were deposited in the Cambridge Crystallographic Data Centre (CCDC 710101) and can be obtained free at http://www.ccdc.cam.ac.uk/cgi-bin/catreq.cgi.

3(4)α,1(10)α-Diepoxy-5,7α,6β(H)-guai-12,6-olide (4). A solution of **3** (200 mg, 0.8 mmol) in $CHCl_3$ (2 mL) was stirred, treated with peracetic acid (3 mL), and stirred at room temperature for 16 h. After the reaction was finished the mixture

was worked up, dried, and filtered. The solid (0.32 g) was chromatographed over a column of silica gel (8 g) to isolate **4**, mp 178-180°C (EtOAc:petroleum ether), $C_{15}H_{18}O_4$, R_f 0.25 (EtOAc:petroleum ether, 2:4). Yield 106 mg (51%).

Table 1 gives the PMR and ^{13}C NMR spectra.

IR spectrum (KBr, ν, cm^{-1}): 1761 (γ-lactone C=O), 1669 (C=C).

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