Chemistry of Natural Compounds, Vol. 46, No. 2, 2010

SYNTHESIS AND MOLECULAR STRUCTURE OF HALOHYDRINS OF THE GUAIANOLIDE LUDARTIN

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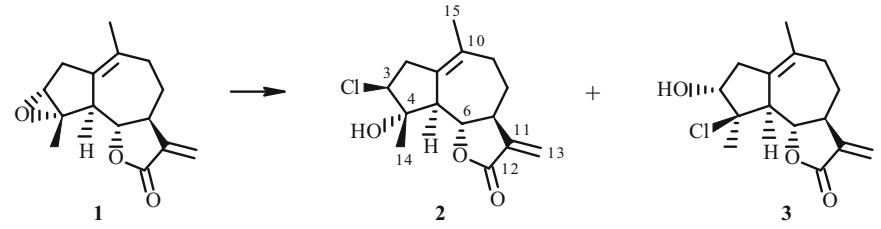
UDC 547:314

Chloro- and bromhydrin derivatives of the sesquiterpene lactone ludartin were synthesized for the first time. Their structures were established by spectral data and an x-ray structure analysis.

Keywords: sesquiterpene lactone, ludartin, halohydrins, x-ray structure analysis, NMR.

Compounds containing a halohydrin moiety were observed in natural biologically active compounds including sesquiterpene lactones [1–3]. Halogenated compounds, many of which exhibit antitumor, cytotoxic, and antifungal activity, are of special interest among the numerous synthetic derivatives of sesquiterpene lactones [4–7].

The goal of our work was to synthesize halohydrin derivatives of the guaianolide ludartin (**1**).



Reaction of **1** with LiCl in the presence of CH_3CO_2H formed a mixture of products. Separation by column chromatography over silica gel isolated two crystalline compounds **2** and **3** with mp 148 (dec.) and 188–190°C, respectively.

The IR spectra of **2** and **3** exhibited absorption bands characteristic of hydroxyls. The PMR spectrum of **2** gave a resonance at δ_H 1.30 ppm as a singlet that was characteristic of a methyl on C-4 and a resonance as a doublet of doublets at δ_H 4.15 ppm with SSCC 8.0 and 11.0 Hz that was assigned to a geminal proton on C-3 (Table 1). The resonance for the C-4 methyl in derivative **3** was shifted strongly to weak field compared with that of **2**. Such a shift of the resonance (by ~0.57 ppm) confirmed that a Cl atom was in a position geminal to the methyl. The resonance for the C-3 proton was present as a doublet at δ_H 4.12 ppm with SSCC 4.0 Hz. The resonance for C-4 in the ^{13}C NMR spectrum of **2** was shifted strongly to weak field by 14 ppm and appeared as a singlet at δ_C 80.56 ppm because of the influence of the hydroxyl. The resonance of this C atom in the other derivative **3** appeared also in this same region at δ_C 80.48 ppm whereas the resonance for C-3 was shifted strongly to weak field by ~27 ppm and appeared as a doublet with δ_C 79.85 ppm. These spectral data confirmed that the epoxide ring opened in **1** from two sides. The location and configuration of the hydroxyl and Cl atom in **2** and **3** were confirmed by an x-ray structure analysis (XSA). Figure 1 shows the molecular structures of **2** and **3**. The bond lengths in the molecules were normal. The conformations of corresponding rings in **2** and **3** were the same. The five-membered rings had the twist conformation with atoms C3 and C4 deviating by –0.335 and 0.379 in **2** and –0.374 and 0.228 Å in **3**. Atoms C6 and C7 also deviated (0.177 and –0.240 in **2**; 0.205 and –0.354 Å in **3**) from the planes of the remaining atoms. The seven-membered ring had the usual chair conformation. These same ring conformations were observed in the crystal structure of the related compound micheliolide (**4**) [8].

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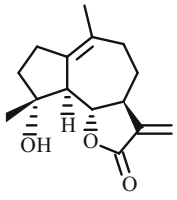
 0009-3130/10/4602-0222

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 **3**

C atom	**2**		**3**	
	δ_H	δ_C	δ_H	δ_C
1	–	132.90 s	–	132.55 s
2a	2.86 (dd, $J_{2a/3}$ = 8.0, $J_{2a/2b}$ = 15.0)	39.45 t	3.0 m	39.77 t
2b	2.35 m		3.0 m	
3	4.15 (dd, $J_{3/2a}$ = 8.0, J = 11.0)	63.77 d	4.12 (d, J = 4.0)	79.85 d
4	–	80.56 s	–	80.48 s
5	2.74 (br.d, $J_{5/6}$ = 10.0)	56.90 d	2.70 (d, J = 10.0)	49.82 d
6	3.83 (t, J = 10.0)	83.53 d	4.08 (t, J = 10.0)	83.55 d
7	2.64 m	49.56 d	2.35 (br.d, J = 16.0)	55.34 d
8a	2.08 m	25.52 t	2.06 m	25.57 t
8b	1.31 m		1.37 m	
9a	2.25 m	34.88 t	2.25 m	34.88 t
9b	2.25 m		2.25 m	
10	–	125.67 s	–	131.02 s
11	–	138.23 s	–	139.09 s
12	–	169.24 s	–	169.90 s
13a	6.21 (d, J = 3.0)	119.78 t	6.16 (d, J = 3.0)	118.84 t
13b	5.50 (d, J = 3.0)		5.44 (d, J = 3.0)	
14-CH_3	1.67 s	23.90 q	1.72 s	25.11 q
15-CH_3	1.30 s	17.38 q	1.87 s	24.79 q
OH	2.64 m overl. w H-7		2.35 (br.d, J = 16.0) overl.w H-7	



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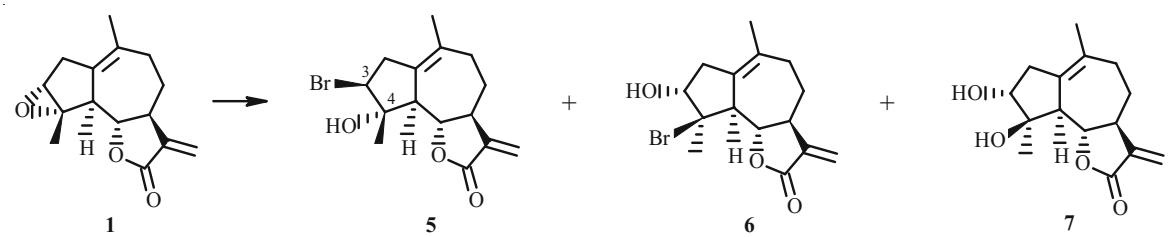
The molecules in **2** and **3** are connected by H-bonds O1–H...O3 (H...O2 2.02 and 2.09 Å; O–H...O 165 and 156° in **2** and **3**) into zig-zag chains along the *b* and *c* axis in **2** and **3**, respectively. In contrast with this, **4** in the crystal uses O–H...O bonds to form dimers. The interactions between chains are different in **2** and **3**. Thus, **2** in the crystal exhibits C7–H...O1 interactions (H...O 2.43 Å, C–H...O 172°) that form layers parallel to the *ab* plane whereas **3** in the crystal has C5–H...Cl1 (H...Cl 2.83 Å, C–H...Cl 162°) interactions between chains that form a three-dimensional architecture. It is interesting to note that the Cl atom in **2** did not have shortened contacts.

Thus, spectral data and XSA established that **2** and **3** had the structures 3β-chloro-4α-hydroxy-5,7α,6β(H)-guaia-1(10),11(13)-dien-12,6-olide and 3α-hydroxy-4β-chloro-5,7α,6β(H)-guaia-1(10),11(13)-dien-12,6-olide, respectively.

We prepared the bromhydrin analogs by reacting **1** with HBr in alcohol. This formed a mixture of three compounds **5–7**. The R_f values of **5** and **6** were very similar whereas that of the third compound **7** was much different, i.e., it was more polar.



1 **5** **6** **7**

TABLE 2. PMR (500 MHz, $CDCl_3$, δ, ppm, J/Hz) and ^{13}C NMR (125.76 MHz, $CDCl_3$, δ, ppm) Spectra of **5**–**7**

C atom	**5**		**6**	**7**
	δ_H	δ_C	δ_H	δ_H
1	–	132.62 s	–	–
2		40.11 t		
2a	2.90 (dd, J = 8.0, 15.0)		3.13 (br.d, J = 15.0)	2.77 m
2b	2.48 m		2.73 m	2.77 m
3	4.19 (dd, J = 8.0, 11.0)	55.82 d	4.33 (br.t, J = 4.0)	3.84 (br.d, J = 4.0)
4	–	80.27 s	–	–
5	2.77 (br.d, J = 10.0)	56.27 d	2.85 (br.d, J = 10.0)	2.81 (br.d, J = 10.0)
6	3.83 (t, J = 10.0)	83.60 d	4.11 (t, J = 10.0)	3.93 (t, J = 10.0)
7	2.63 (br.t, J = 10.0)	49.45 d	2.40 (br.d, J = 16.0)	2.35 (br.d, J = 16.0)
8		25.46 t		
8a	2.09 m		2.09 m	1.96 m
8b	1.33 m		1.40 m	1.32 m
9		34.79 t		
9a	2.25 m		2.27 m	2.17 m
9b	2.25 m		2.13 m	2.06 m
10	–	126.73 s	–	–
11	–	138.15 s	–	–
12	–	169.12 s	–	–
13	–	119.74 t	–	–
13a	6.21 (d, J = 3.0)		6.18 (d, J = 3.0)	6.15 (d, J = 3.0)
13b	5.50 (d, J = 3.0)		5.45 (d, J = 3.0)	5.43 (d, J = 3.0)
14-CH_3	1.67 s	23.79 q	1.73 s	1.73 s
15-CH_3	1.37 s	19.09 q	2.06 s	1.58 s
OH	2.63 (br.t, J = 10.0) overl. w H-7		2.32 br.s	2.26 (br.d, J = 13.0) (3-OH) 2.13 (br.s, 4-OH)

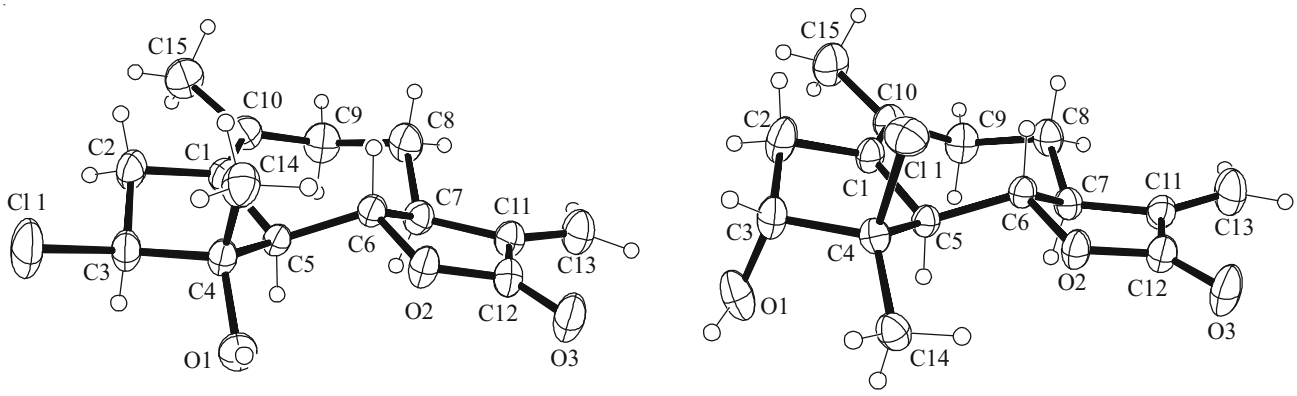


Fig. 1. Molecular structures of **2** and **3**.

The IR spectra of **5** and **6** showed absorption bands characteristic of hydroxyls at 3420 and 3479 cm^{-1}, respectively. In contrast with these derivatives, **7** had two absorption bands for hydroxyls. The resonance of the C-4 methyl shifted to strong field in PMR spectra of **5** and **7** whereas it shifted to weak field by 0.45 ppm in that of **6** because of the influence of the Br atom. The resonance of the C-3 geminal proton in **5–7** shifted to weak field compared with the starting lactone and appeared at δ_H 4.19, 4.33, and 3.84 ppm. Resonances for C-3 and C-4 in the ^{13}C NMR spectrum of **5** were found at δ_C 55.81 and 80.27 ppm, respectively. Two-dimensional ^1H–^1H (COSY) and ^{13}C–^1H (COSY and COLOC) spectra were used to interpret the PMR and ^{13}C NMR spectra of **5**. The proposed configurations in **5–7** were established by comparison with spectral data of **2** and **3**, the structures of which were determined by XSA.

Thus, the results indicated that **5** and **6** were regioisomers and that **7** had the proposed structure 3α,4β-dihydroxy-5,7α,6β(H)-guaia-1(10),11(13)-dien-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 and 125.76 MHz for ^{13}C, δ-scale) using two-dimensional COSY and COLOC (7 Hz) spectra and standard Bruker programs. Elemental analysis was performed on a Eurovector 3000 A (C,H) analyzer. The course of reactions was monitored by TLC using Sorbfil plates and spraying with aqueous $KMnO_4$ solution (2%). Column chromatography used Armsorb silica gel. Starting lactone **1**, mp 100–102°C, was isolated from the aerial part of *Artemisia filatovae* Kupr. [9]. Elemental analysis of **1** agreed with that calculated.

Preparation of 2 and 3. Ludartin (**1**, 200 mg, 0.8 mmol) was dissolved in THF (3 mL), treated with HOAc (0.08 mL), stirred, treated with LiCl (200 mg, 4.8 mmol), and stirred at room temperature (21°C) for 15 h. The products were extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and filtered. Solvent was distilled in a rotary evaporator. The solid (0.3 g) was chromatographed over a column of silica gel (8 g) with elution by petroleum ether:EtOAc (80:20) to isolate the two isomeric chlorohydrins **2** and **3**.

3β-Chloro-4α-hydroxy-5,7α,6β(H)-guaia-1(10),11(13)-dien-12,6-olide (2). Colorless crystals, mp 148°C (dec.) (EtOAc:petroleum ether), $C_{15}H_{19}O_3Cl$, R_f 0.50 (EtOAc:petroleum ether, 2:4), yield 79 mg (35%). Table 1 lists the PMR and ^{13}C NMR spectra. IR spectrum (KBr, ν, cm^{-1}): 3518 (OH), 1718 (γ-lactone C=O), 1669 (C=C).

3α-Hydroxy-4β-chloro-5,7α,6β(H)-guaia-1(10),11(13)-dien-12,6-olide (3). Colorless crystals, mp 188–190°C (EtOAc:petroleum ether), $C_{15}H_{19}O_3Cl$, R_f 0.43 (EtOAc:petroleum ether 2:4), yield 66 mg (29%). Table 1 lists the PMR and ^{13}C NMR spectra. IR spectrum (KBr, ν, cm^{-1}): 3477 (OH), 1752 (γ-lactone C=O), 1662 (C=C).

X-ray structure analysis was performed on a Bruker P4 diffractometer (graphite monochromator, λ Mo-K_α 0.71073 Å, 297 K, θ/2θ-scanning).

Crystallographic data and principal refinement parameters for **2**: $C_{15}H_{19}ClO_3$, MW 282.75, monoclinic system, space group $P2_1$, $a = 7.1727(8)$, $b = 10.033(1)$, $c = 10.159(1)$ Å, $\beta = 99.68(1)°$, $V = 720.7$ Å^3, $Z = 2$, $d_{calcd} = 1.303$ g/cm^3, $\mu = 0.266$ cm^{-1}, scan range $2\theta < 56°$, number of measured reflections 1828, number of reflections with $I \geq 2\sigma(I)$ 1624, number of refined parameters 173, R_1 [$I \geq 2\sigma(I)$] = 0.0452, wR_2 = 0.1287 (all reflections), GOF = 1.033, absolute structure factor (Flack) 0.03(12). Absorption corrections were applied using azimuthal scans (T_{min}/T_{max} = 0.758/0.970).

Crystallographic data and principal refinement parameters for **3**: $C_{15}H_{19}ClO_3$, MW 282.75, orthorhombic system, space group $P2_12_12_1$, $a = 9.0067(9)$, $b = 10.5303(8)$, $c = 15.283(1)$ Å, $V = 1449.5(2)$ Å^3, $Z = 4$, $d_{calcd} = 1.296$ g/cm^3, $\mu = 0.265$ cm^{-1}, scan range $2\sigma < 56°$, number of measured reflections 2011, number of reflections with $I \geq 2\sigma(I)$ 1534, number of refined parameters 172, R_1 [$I \geq 2\sigma(I)$] = 0.0412, wR_2 = 0.1175 (all reflections), GOF = 1.024, absolute structure factor (Flack) 0.05(12). Absorption corrections were applied using azimuthal scans (T_{min}/T_{max} = 0.904/0.954).

The structures were solved by direct methods. Positions and temperature factors of nonhydrogen atoms were refined by anisotropic full-matrix least-squares methods. Hydrogen atoms were located geometrically and included in the refinement using a "rider" model. All calculations were performed using the SHELX-97 programs. Geometric data were analyzed using the PLATON program. Results were deposited in the Cambridge Crystallographic Data Centre (CCDC 716760 and CCDC 716761).

Preparation of 5-7. Ludartin (**1**, 200 mg, 0.8 mmol) was dissolved in EtOH (3 mL), treated dropwise with HBr (0.02 mL), and stirred at room temperature (17°C) for 7 h. Alcohol was distilled in a rotary evaporator. The products were extracted by $CHCl_3$. The organic layer was dried over $MgSO_4$ and filtered. Solvent was evaporated. The solid (0.36 g) was chromatographed over a column with elution by petroleum ether:EtOAc (80:20 and 60:40) to isolate **5-7**.

3β-Bromo-4α-hydroxy-5,7α,6β(H)-guaia-1(10),11(13)-dien-12,6-olide (5). Colorless crystals, mp 125°C (dec.) (EtOAc:petroleum ether), $C_{15}H_{19}O_3Br$, R_f 0.63 (EtOAc:petroleum ether 2:4), yield 50 mg (19%). Table 2 lists the PMR and ^{13}C NMR spectra. IR spectrum (KBr, ν, cm^{-1}): 3420 (OH), 1748 (γ-lactone C=O), 1660 (C=C).

3α-Hydroxy-4β-bromo-5,7α,6β(H)-guaia-1(10),11(13)-dien-12,6-olide (6). Colorless crystals, mp 103°C (dec.) (EtOAc:petroleum ether), $C_{15}H_{19}O_3Br$, R_f 0.58 (EtOAc:petroleum ether 2:4), yield 30 mg (12%). Table 2 lists the PMR spectrum. IR spectrum (KBr, ν, cm^{-1}): 3479 (OH), 1753 (γ-lactone C=O), 1660 (C=C).

3α,4β-Dihydroxy-5,7α,6β(H)-guaia-1(10),11(13)-dien-12,6-olide (7). Colorless crystals, mp 137–140°C (EtOAc:petroleum ether), $C_{15}H_{20}O_4$, R_f 0.21 (EtOAc:petroleum ether 2:4), yield 15 mg (7%). Table 2 lists the PMR spectrum. IR spectrum (KBr, ν, cm^{-1}): 3511 (OH), 3361 (OH), 1749 (γ-lactone C=O), 1662 (C=C).

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