

NOVEL S-CONTAINING LACTONES FROM MONOTERPENE OXIDES

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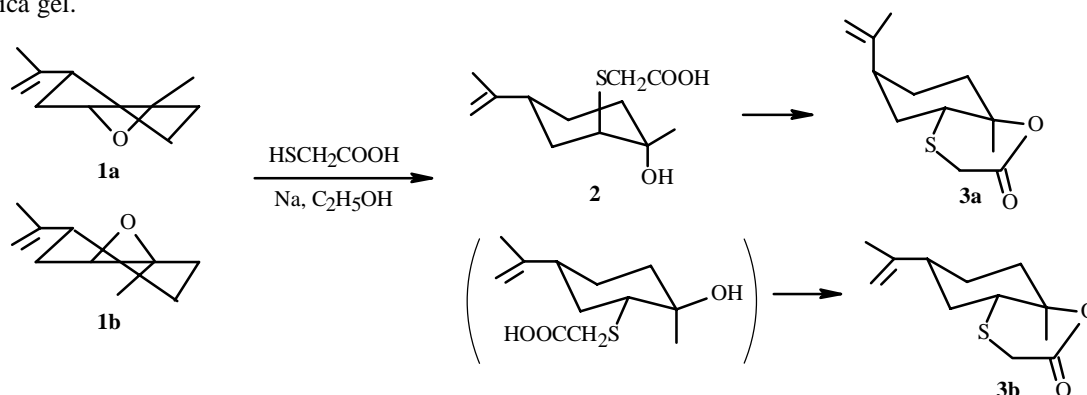
A new type of S-containing terpene lactones was produced by the reactions of limonene-1,2-oxide and β -pinene- α -oxide with mercaptoacetic acid.

Key words: limonene-1,2-oxide, β -pinene- α -oxide, mercaptoacetic acid, S-containing lactones.

It is well known from the literature that compounds with a lactone ring have a broad spectrum of biological activity [1-3]. Therefore, natural terpenes are being extensively studied in the search for new ecologically safe biologically active compounds. In order to develop a synthetic approach to novel potentially biologically terpenoids, we propose a method for synthesizing S-containing lactones via the reaction of monoterpene oxides with mercaptoacetic acid.

We have previously demonstrated that 3-carene oxide and limonene-8,9-oxide react with mercaptoacetic acid to form both the addition product and the corresponding S-containing lactones [4, 5]. The lactone forms as a result of elimination of water from the corresponding adduct. The reaction can proceed spontaneously under the reaction conditions. Thus, the reaction mixture contains the addition product together with a certain amount of the lactone. In some instances, the lactone is the only product; in others, the lactone forms during isolation of the product by column chromatography (CC) over silica gel. Additional heating of the isolated product is sometimes required to close the lactone ring [6].

The reaction of limonene-1,2-oxide (**1**), which was an equimolar mixture of the *cis*- (**1a**) and *trans*-isomers (**1b**), with mercaptoacetic acid in the presence of sodium ethoxide gave two products **2** and **3** in a 2.5:1 ratio (**2:3**) that were isolated by CC over silica gel.



The IR spectrum of **2** had bands characteristic of hydroxyl and carboxyl (1710, 3500 cm⁻¹) whereas that of **3** showed bands typical of ester vibrations (1230-1250, 1720 cm⁻¹) and lacked bands characteristic of hydroxyl. The IR spectra of **2** and **3** contained vibrational bands characteristic of an exocyclic multiple bond (890, 1650 cm⁻¹) and a C–O bond (1115 cm⁻¹), the position of which was characteristic of compounds with a tertiary hydroxyl.

GC—MS of **2** were consistent with the formation of the pure addition product of one molecule of mercaptoacetic acid to one molecule of the oxide (*m/z* 244). Two closely spaced peaks with *m/z* 226 in the GC—MS of **3** indicated that it existed as two structurally similar compounds containing a lactone.

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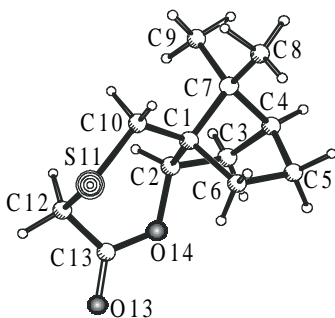


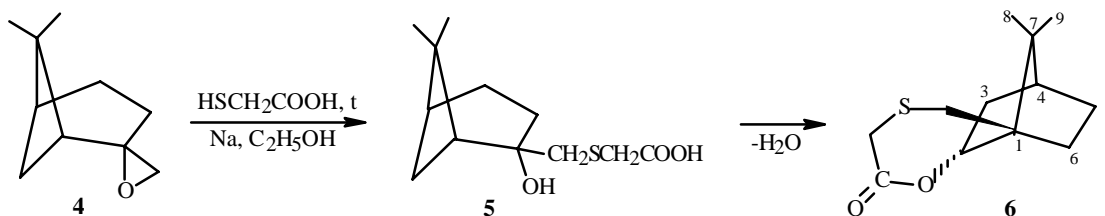
Fig. 1. Molecular structure of **6** from an XSA.

The PMR spectrum of **2** had a doublet of doublets at 3.05 ppm that corresponded to the C-2 methine proton with SSCC 3.8 (ee) and 5.0 Hz (ae), which indicated that the functional groups were axial. The signal of the C-2 methine proton in the PMR spectrum of the mixture of **3a** and **3b** appeared as two poorly resolved triplets at 2.62 and 2.68 ppm; of the C-4 methine proton, a multiplet at 2.0-2.2 ppm.

Product **3** is with a high degree of probability a mixture of the S-containing lactones with equatorial (**3b**) and axial (**3a**) isopropenyl groups. Apparently the adduct that formed initially from *cis*-epoxide **1b** had diequatorial substituents, in which both functional groups were situated favorably for dehydration. This was completely converted to the corresponding lactone **3b** whereas adduct **2** from the *trans*-oxide underwent only partial dehydration to form **3a** from the inverted chair conformation in which the isopropenyl group became axial.

This was confirmed by the fact that **3a** can be prepared as the pure compound by heating **2** in a small quantity of toluene with simultaneous removal of the azeotropic mixture. The PMR spectrum of **3a** showed the signal for the C-4 methine proton as a triplet of doublets at 2.10 ppm with SSCC 3.6 (ee) and 6.0 Hz (ae). This was consistent with an equatorial proton and an axial isopropenyl.

The reaction of β -pinene- α -oxide (**4**) with mercaptoacetic acid under the same conditions produced exclusively **5**. The IR spectrum of **5** contained characteristic vibrational bands for OH (3550 cm^{-1}), carboxyl ($1710, 2600\text{-}2700$), and a tertiary C–O (1115). During isolation of **5** by CC over silica gel, part of it converted to the corresponding lactone **6** as it passed through the column. This was demonstrated using TLC. The IR spectrum of the lactone contained characteristic vibrational bands for ester ($1235\text{-}1255\text{ cm}^{-1}$) and carbonyl (1720).



An x-ray structure analysis (XSA) showed that **6** contained a bornane system fused at the 1- and 2-positions to a seven-membered lactone ring (Fig. 1).

A search of the Cambridge Crystallographic Database (2001 version) indicated that such tricyclic systems are common. A total of 91 compounds containing the bornane system and an additional ring fused to it at the 1- and 2-positions is known. However, it is interesting that the additional ring in all known structures is closed in the *exo*-position of the bornane C-2 whereas the lactone ring in **6** is closed in the *endo*-position of C-2.

Apparently there are no substantial steric hindrances in **6**. The norbornane framework is practically undistorted (Table 1). The six-membered ring has the boat conformation. The angle between the planar fragments C1-C2-C3-C4 and C1-C6-C5-C4 is $112.02(7)^\circ$. The seven-membered lactone ring has the chair conformation, the C1-C2-C12-S11 base of which is slightly twisted with C1 and C12 deviating to one side of the average plane of C1-C2-C12-S11 by $0.038(1)\text{ \AA}$ and C2 and S11, to the other side by the same distance. The four-atom plane C12-C13-O14-C2 forms a smaller dihedral angle with the base of the chair than the three-atom plane C1-C10-S11, $117.0(1)$ and $121.6(1)^\circ$, respectively. The intermolecular distances in **6** have normal van-der-Waals contacts.

TABLE 1. Principal Geometric Parameters of **6** from XSA

Bond length	Å	Bond length	Å
S11-C10	1.809 (2)	C2-C3	1.544 (2)
S11-C12	1.804 (2)	C3-C4	1.537 (3)
O13-C13	1.206 (2)	C4-C5	1.529 (3)
O14-C2	1.458 (2)	C4-C7	1.546 (2)
O14-C13	1.339 (2)	C5-C6	1.547 (3)
C1-C2	1.546 (2)	C7-C8	1.532 (3)
C1-C6	1.542 (2)	C7-C9	1.526 (3)
C1-C7	1.570 (2)	C12-C13	1.502 (2)
C1-C10	1.512 (2)		
Bond angle	ω , deg.	Bond angle	ω , deg.
C10-S11-C12	99.82 (9)	S11-C10-C1	115.1 (1)
C2-O14-C13	121.5 (1)	C3-C4-H4	114 (2)
C2-C1-C6	107.2 (1)	C5-C4-C7	102.7 (2)
C2-C1-C7	100.4 (1)	C4-C5-C6	103.3 (1)
C2-C1-C10	114.8 (1)	C1-C7-C4	93.1 (1)
C6-C1-C7	101.9 (1)	C1-C7-C8	113.2 (2)
C6-C1-C10	116.4 (1)	C1-C7-C9	115.0 (1)
C7-C1-C10	114.1 (1)	C4-C7-C8	114.4 (1)
O14-C2-C1	114.4 (1)	C4-C7-C9	114.0 (2)
O14-C2-C3	107.3 (1)	C8-C7-C9	107.0 (1)
C1-C2-C3	103.8 (1)	O13-C13-O14	118.1 (2)
C2-C3-C4	103.1 (1)	O13-C13-C12	122.0 (2)
C3-C4-C5	107.7 (2)	O14-C13-C12	119.8 (2)
C3-C4-C7	102.1 (1)		
Torsion angle	τ , deg.	Torsion angle	τ , deg.
C12-S11-C10-C1	-61.8 (1)	C10-C1-C7-C4	-179.5 (1)
C10-S11-C12-C13	84.0 (2)	C10-C1-C7-C8	62.2 (2)
C13-O14-C2-C1	74.9 (2)	C10-C1-C7-C9	-61.1 (2)
C13-O14-C2-C3	-170.5 (2)	C2-C1-C10-S11	63.9 (2)
C2-O14-C13-O13	178.3 (2)	C6-C1-C10-S11	-62.6 (2)
C2-O14-C13-C12	-3.2 (3)	C7-C1-C10-S11	179.1 (1)
C6-C1-C2-O14	47.0 (2)	O14-C2-C3-C4	-122.6 (1)
C6-C1-C2-C3	-69.6 (2)	C1-C2-C3-C4	-1.1 (2)
C7-C1-C2-O14	153.1 (1)	C2-C3-C4-C5	72.2 (2)
C7-C1-C2-C3	36.5 (1)	C2-C3-C4-C7	-35.5 (2)
C10-C1-C2-O14	-84.1 (2)	C7-C4-C5-C6	36.4 (2)
C10-C1-C2-C3	159.3 (1)	C3-C4-C7-C1	56.3 (2)
C2-C1-C6-C5	71.0 (1)	C3-C4-C7-C8	173.5 (2)
C7-C1-C6-C5	-34.1 (2)	C3-C4-C7-C9	-62.9 (2)
C10-C1-C6-C5	-158.9 (1)	C5-C4-C7-C1	-55.3 (1)
C2-C1-C7-C4	-56.2 (1)	C5-C4-C7-C8	61.9 (2)
C2-C1-C7-C8	-174.4 (1)	C5-C4-C7-C9	-174.4 (1)
C2-C1-C7-C9	62.2 (2)	C4-C5-C6-C1	-0.9 (2)
C6-C1-C7-C4	54.1 (2)	S11-C12-C13-O13	104.7 (2)
C6-C1-C7-C8	-64.1 (2)	S11-C12-C13-O14	-73.7 (2)
C6-C1-C7-C9	172.5 (2)		

Apparently a high degree of strain in the hypothetical pinane molecule in which the ring containing the lactone would be *spiro*-fused to the bicyclic framework of the terpene is the driving force for isomerization of the pinane structure during dehydration.

Furthermore, the acidity of the silica gel also enhances the isomerization. Therefore, it is completely reasonable that the strongly basic reaction mixture not contained even a trace of the lactone.

Thus, the reaction of monoterpene oxides with mercaptoacetic acid in basic medium is a convenient method for preparing S-containing lactones, which are formed by dehydration of the corresponding adducts. The structure of the resulting lactone depends to a large extent on steric factors, the lability of the terpenoid system, and its tendency to undergo various types of isomerization.

EXPERIMENTAL

PMR spectra in CDCl_3 were obtained on a Varian UNITY-300 instrument (300 MHz); IR spectra, in mineral oil on a 75-IR spectrometer; mass spectra, in a Turbo Mass Gold (Perkin—Elmer) mass spectrometer using a capillary column (30 m \times 320 μm , $v_{\text{He}} = 1.2$ mL/min), 70 eV ionization energy, 250°C injector, and 150°C ion-source.

X-ray structure analysis of crystals was performed on an Enraf-Nonius CAD-4 automated four-circle diffractometer in K-geometry. The data set for **6** was collected at +20°C. Crystals of **6** ($\text{C}_{12}\text{H}_{18}\text{SO}_4$) were monoclinic, space group $P2_1$, $a = 7.220(4)$, $b = 6.729(2)$, $c = 12.216(9)$ Å, $\beta = 96.38(5)^\circ$, $V = 589.8(6)$ Å³, $Z = 2$, $\text{MW} = 226.34$, $d_{\text{calc}} = 1.27$ g/cm³, $\mu(\text{Mo}) = 22.16$ cm⁻¹, $F(000) = 244.0$. Intensities of 1369 reflections were measured ($\lambda\text{Cu K}\alpha$ -radiation, $\omega/2\theta$ -scanning, $2\theta_{\text{max}} < 74.2^\circ$), 1348 with $I > 3\sigma$. Absorption correction was applied empirically ($\mu_{\text{Cu}} 22.2$ cm⁻¹). The structure was solved by direct methods using the SIR program [7] and was refined first isotropically and then anisotropically. H atoms were found in difference electron-density syntheses and refined isotropically in the final refinement stage. All calculations were performed using the MOLEN programs [8] on an AlphaStation 200 computer. The absolute structure and, consequently, the absolute configuration (*X*) was established by refining the direct and inverted structures. The R factor for the direct structure was 0.048, $R_w = 0.082$; for the inverted structure, 0.052 and 0.086, respectively. According to the Hamilton test [9], the direct structure corresponded to the absolute one with 95% probability. The final R factors were $R = 0.028$ and $R_w = 0.039$ for 1286 independent reflections with $F^2 \geq 3\sigma$.

Reaction of Monoterpene Oxides with Mercaptoacetic Acid. A solution of sodium ethoxide (1.5 g Na, 0.065 mol) in absolute ethanol (50 mL) was treated with mercaptoacetic acid (0.021 mol) and oxide (2 g, 0.013 mol). The reaction mixture was heated (80°C), stirred for 3-5 h, diluted with water, washed with HCl solution (3%) until the pH was 3, extracted with ether, and dried over MgSO_4 . Solvent was distilled off. The products were isolated by CC over silica gel (hexane:ether, 2:1) as light-yellow oily liquids. Compound **3** was a thick resinous liquid with amorphous crystals; **6**, white crystals, mp 92-93°C; n_d^{20} (**2**) 1.5336; n_d^{20} (**3**) 1.4971; n_d^{20} (**5**) 1.5349. Overall yield of **2** and **3**, 74%; **5**, 65%.

[trans-1-Hydroxy-4-(methylethenyl)cyclohexyl-2-ylthio]ethanoic Acid (2). IR spectrum (ν , cm⁻¹): 3500 (OH), 1710 (COOH). PMR spectrum (δ , ppm, J/Hz): 1.42 (3H, s, H-7), 1.77 (6H, s, H-10), 2.18 (1H, td, $J = 3.3, 7.5, 12.0$, H-4), 3.05 (1H, dd, $J = 3.8, 5.0$, H-2), 3.28 (2H, s, SCH_2), 4.78 (2H, s, H-9), 6.22 (1H, s, COOH). Mass spectrum (m/z , I_{rel} , %): 244 (7) $[\text{M}]^+$, 226 (60), 183 (12), 139 (100), 135 (47), 119 (30), 93 (87), 91 (72), 83 (42), 43 (41).

Lactone of [trans-1-Hydroxy-4-(methylethenyl)cyclohexyl-2-ylthio]ethanoic Acid (3). IR spectrum (ν , cm⁻¹): 1230-1250, 1720 (COOR). PMR spectrum (δ , ppm, J/Hz): 1.20 (3H, s, H-7), 1.61 (6H, s, H-10), 2.15 (1H, td, $J = 2.2, 4.0, 12.0$, H-4), 2.82 (1H, dd, $J = 3.8, 5.0$, H-2), 2.93 (2H, s, SCH_2), 4.62 (2H, s, H-9). Mass spectrum (m/z , I_{rel} , %): 226 (8) $[\text{M}]^+$, 28 (100), 183 (24), 158 (5), 144 (19), 43 (34).

(1-Hydroxy-7,7-dimethylbicyclo[3.1.1]heptyl-10-methylthio)ethanoic Acid (5). PMR spectrum (δ , ppm, J/Hz): 0.94, 1.21 (6H, 2s, H-8,9), 2.95, 3.10 (2H, AB-centers, $J = 11.7$, H-10), 3.28 (2H, s, SCH_2), 3.15 (s, OH), 6.12 (1H, s, COOH). Mass spectrum (m/z , I_{rel} , %): 244 (5) $[\text{M}]^+$, 226 (66), 183 (12), 167 (19), 139 (100), 136 (21), 135 (58), 134 (75), 119 (29), 93 (87), 91 (72), 83 (44), 43 (44).

Lactone of (1-Hydroxy-7,7-dimethylbicyclo[3.1.1]heptyl-10-methylthio)ethanoic Acid (6). IR spectrum (ν , cm⁻¹): 1235-1255, 1720 (COOR). Mass spectrum (m/z , I_{rel} , %): 226 (6) $[\text{M}]^+$, 183 (22), 136 (24), 135 (58), 93 (82), 83 (52), 43 (48).

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