Lactones. 9.[†] Synthesis of Terpenoid Lactones—Active Insect Antifeedants

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Starting from (+)- and (−)-perillyl alcohols, via Claisen rearrangement and iodolactonization, four enantiomeric pairs of γ-lactones were obtained. The structures of compounds were established by both spectroscopic and crystallographic methods. The lactones were tested for antifeeding activity toward grain storage pests—the granary weevil beetle (*Sitophilus granarius* L.), the khapra beetle (*Trogoderma granarium* Ev.), and the confused flour beetle (*Tribolium confusum* Duv.). The results of the tests proved that two compounds, (1*R*,4*R*,6*R*)-(−)-4-(1-methylethenyl)-9-oxabicyclo[4.3.0]nonan-8-one (**8a**) and its enantiomer (**8b**), are very active antifeedants against all of the above tested species. The lactone **8b** is also active against the peach-potato aphid (*Myzus persicae* Sulz.). The activity depends on the absolute configurations of compound chiral centers. Additionally, the lactones **8a** and **8b** are characterized by interesting fragrances.

Keywords: *Terpenoid lactones; antifeedant; odorous compounds; iodolactonization; Claisen rearrangement; limonene*

INTRODUCTION

Terpenoid lactones are widely spread in nature. Many of them, such as two menthane derivatives, (−)-mintlactone and (+)-isomintlactone, are the components of essential oils used for flavoring and aromatic substances (Chavan et al., 1993). Being common secondary metabolites of plants, lactones were found to be a part of a plant's protective system against its predators. Many compounds with the lactone ring, mainly mono- and sesquiterpenoids, were proved to be active antifeedants toward insects, such as various aphid species and grain storage pests (Asakawa et al., 1988; Streibl et al., 1983; Harmatha and Nawrot, 1984; Daniewski et al., 1993, 1995). The grain pests are especially persistent and difficult to control in central Europe.

In the search for new, active pest control chemicals, we have synthesized many mono-, bi-, and tricyclic terpenoid lactones. Monocyclic lactones were obtained in both racemic and pure enantiomeric forms (Olejniczak, 1998). The bi- and tricyclic ones were synthesized from natural chiral compounds, limonene and pinene, so they were obtained as pure enantiomers (Paruch et al., 1997, 1998). Many of them exhibited quite good deterrent activity against insects that feed on stored grain (Wawrzeńczyk et al., 1998).

Here we present the synthesis of four enantiomeric pairs of iodolactones and lactones—the limonene derivatives. The compounds obtained were tested for inhibition of feeding of the storage pests *Sitophilus granarius* (beetles), *Tribolium confusum* (beetles and larvae), and *Trogoderma granarium* (larvae).

MATERIALS AND METHODS

Reagents. (*R*)-(+)-Perillyl alcohol (>99%), (*S*)-(−)-perillyl alcohol (99%), triethyl orthoacetate, and tributyltin hydride were purchased from Fluka.

Bioassays. Biological tests were conducted as described by Nawrot et al. (1986). The insects used for the tests (*S. granarius* L. beetles, *Tri. confusum* Duv. beetles, *Tro. granarium* Ev. larvae, and *Tri. confusum* Duv. larvae) were reared in the laboratory at 26 ± 1 °C and 60 ± 5% relative humidity on a wheat grain or whole wheat meal diet. Wheat wafer disks (1 cm in diameter) were used as the test food. The disks were immersed in 1% acetone solutions of the tested compounds and, after evaporation of the solvent, offered to 3 adult *S. granarius*, 20 adults and 10 larvae of *T. confusum*, and 10 larvae of *T. granarium*. The wafer disks were weighed before the experiments and 5 days after the pests had been feeding on them. In each of five replications, the insects were offered two wafer disks immersed in acetone or two disks saturated with lactone solution ("no-choice test"), or they had a choice between a disk with acetone and the one with lactone ("choice test"). The weight of food consumed was the basis for calculation of the three coefficients of deterrence: (a) the absolute coefficient of deterrence $A = (CC − TT/CC + TT) \times 100$; (b) the relative coefficient of deterrence $R = (C − T/C + T) \times 100$; and (c) the total coefficient of deterrence as a sum of the absolute and the relative coefficients $T = A + R$. In the above equations CC is an average weight of food consumed from the control wafer disk and TT an average weight of food consumed from a test disk in the no-choice test, whereas C and T mean the same, respectively, in the choice test. The total coefficient of deterrence served as the index of activity.

The test on aphids *Myzus persicae* was carried out according to the procedure described by Polonsky et al. (1989). The aphids were maintained on Chinese cabbage using a 16:8 light/dark photoperiod. The tested compounds as 0.1% ethanolic solutions were applied on one side of the upper side of Chinese

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cabbage leaves (at ~0.01 mL/cm²). The other side of the midrib was treated with solvent to act as a control. The aphids were confined on the leaf surface under Petri plate lids placed centrally, so that the insects had a choice between equal areas of treated and control surfaces. There were 20 aphids in each Petri plate and 10 replicated treatments per test. The numbers of aphids found on treated or control areas were counted after 24 h. Results were analyzed by analysis of variance at $p = 0.05$. The compounds active as 0.1% solutions were also tested at a concentration of 0.01%.

General Procedures. *¹H NMR spectra* were measured for solutions (CDCl₃) with a Bruker Avance DRX 300, 300 MHz, with TMS as internal standard.

IR spectra were recorded with a Specord M 80 spectrophotometer (Carl Zeiss Jena).

Melting points were determined using a Boetius apparatus.

Optical rotation was measured with an Autopol IV automatic polarimeter (Rudolph) in acetone as the solvent with the concentrations denoted in grams per 100 cm³.

GC analyses were performed with a Hewlett-Packard 5890 (series II), using capillary columns: HP-1 (cross-linked methyl silicone gum) 25 m × 0.32 mm × 0.52 μm; HP-5 (cross-linked 5% Ph Me silicone) 30 m × 0.32 mm × 0.5 μm; cyclodextrin-B-2,3,6-M-19, 25 m × 0.25 mm × 0.25 μm.

Analytical TLC was carried out employing silica gel DC−Alufolien Kieselgel 60 F₂₅₄ (Merck) with hexane/ethyl acetate in different ratios as developing systems. Compounds were detected by spraying the plates with 1% Ce(SO₄)₂/2% H₃-[P(Mo₃O₁₀)₄] in 10% H₂SO₄, followed by heating to 120 °C.

Column chromatography was performed with silica gel (Kieselgel 60, 40−63 μm, 230−400 mesh, Merck) with hexane−ethyl acetate in different ratios as eluents.

Ethyl [(2S,4R)-1-Methylene-4-(1-methylethenyl)cyclohex-2-yl]-acetate (2a) and Ethyl [(2R,4R)-1-Methylene-4-(1-methylethenyl)cyclohex-2-yl]acetate (3a). The mixture of (4R)-(+)-perillyl alcohol (1a) (1.155 g, 7.6 mmol), triethyl orthoacetate (10 mL, 55 mmol), and propionic acid (1 drop) as a catalyst was heated at 138 °C for 9 h (EtOH was constantly removed from the reaction mixture). The triethyl orthoacetate was then evaporated off, and the crude products were chromatographed (silica gel, hexane/EtOAc 18:0.5). An inseparable mixture of esters **2a** (88%) and **3a** (12%) was obtained (1.44 g, total yield = 85%). Physical and spectral data of this mixture: [α]$_D^{20}$ = +23.35° (*c* 1.2, acetone); ¹H NMR (CDCl₃) δ 1.22 (t, *J* = 7.1 Hz, 3 H, OCH₂CH₃), 1.68 (s, 3 H, 10−CH₃), 2.10−2.25 (m, 3 H, 6−CH₂, 4−H), 2.43 (dd, *J* = 14.4 and 7.7 Hz, 1H, part of AB system of 11−CH₂), 2.49 (dd, *J* = 14.4 and 8.1 Hz, 1H, part of AB system of 11−CH₂), 2.92 (m, 1 H, 2−H), 4.09 (q, *J* = 7.1 Hz, 2 H, OCH₂-CH₃), 4.65 and 4.68 (2 m, 2 H, 7=CH₂), 4.68 (m, 2 H, 9=CH₂); IR (film) ν 3088 (w, >C=CH₂), 1748 (s, C=O), 1656 (m, >C=CH₂), 1164 (m, C−O−C) cm⁻¹.

Ethyl [(2R,4S)-1-Methylene-4-(1-methylethenyl)cyclohex-2-yl]-acetate (2b) and Ethyl [(2S,4S)-1-Methylene-4-(1-methylethenyl)cyclohex-2-yl]acetate (3b). By the same procedure, from (4S)-(−)-perillyl alcohol **1b** (1.273 g, 8.4 mmol) was obtained a mixture of esters **2b** (87%) and **3b** (13%) (1.506 g, total yield 81%). Specific rotation of this mixture: [α]$_D^{20}$ = −20.76° (*c* 1.7, acetone).

[(2S,4R)-1-Methylene-4-(1-methylethenyl)cyclohex-2-yl]acetic Acid (4a) and [(2R,4R)-1-Methylene-4-(1-methylethenyl)-cyclohex-2-yl]acetic Acid (5a). A mixture of esters **2a** and **3a** (1.4 g, 6.3 mmol) was dissolved in 20 mL of KOH/EtOH solution (0.3 g of KOH) and refluxed for 2 h. Then it was concentrated in vacuo to remove EtOH. The residue was diluted with water, and organic impurities were extracted with diethyl ether. The aqueous solution was then neutralized by the addition of 0.1 M HCl and extracted with diethyl ether. The ethereal extract was washed with brine, dried over MgSO₄, and evaporated in vacuo to give a mixture of acids **4a** and **5a** (1.1 g, yield = 90%). Physical and spectral data of this mixture: [α]$_D^{25}$ = +18.2° (*c* 1.2, acetone); ¹H NMR (CDCl₃) δ 1.64 (s, 3 H, 10−CH₃), 2.45 (dd, *J* = 14.8 and 7.7 Hz, 1H, part of AB system of 11−CH₂), 2.50 (dd, *J* = 14.8 and 7.8 Hz, 1H,

part of AB system of 11−CH₂), 2.89 (m, 1 H, 2−H), 4.61−4.67 (m, 4 H, 7=CH₂ and 9=CH₂), 9.5 (br s, 1 H, COOH); IR (film) ν = 3074 (s, OH), 1709 (s, C=O), 1646 (m, >C=CH₂), 893 (m, >C=CH₂) cm⁻¹ .

[(2R,4S)-1-Methylene-4-(1-methylethenyl)cyclohex-2-yl]acetic Acid (4b) and [(2S,4S)-1-Methylene-4-(1-methylethenyl)-cyclohex-2-yl]acetic Acid (5b). By the same procedure, from 1.5 g of esters **2b** and **3b** was obtained a mixture of acids **4b** and **5b** (1.19 g, total yield = 91%). Specific rotation of this mixture: [α]$_D^{25}$ = −19.4° (*c* 1.0, acetone).

(1R,4R,6R)-(−)-1-Iodomethyl-4-(1-methylethenyl)-9-oxabicyclo-[4.3.0]nonan-8-one (6a) and (1S,4S,6R)-(+)-1-Iodomethyl-4-(1-mehtylethenyl)-9-oxabicyclo[4.3.0]nonan-8-one (7a). A 0.5 M NaHCO₃ solution (18 mL) was added to a solution of acids **4a** and **5a** (1.23 g, 5.8 mmol) in diethyl eter (20 mL). The mixture was stirred at room temperature for 30 min and then refluxed. To the refluxing mixture was gradually added a solution of KI (5.8 g) and I₂ (2.95 g) in water (23 mL). The mixture was stirred under reflux for 8 h. After cooling, it was diluted with diethyl ether (50 mL) and washed with Na₂S₂O₃ solution, and the ethereal layer was separated. It was next washed with saturated NaHCO₃ solution and then brine, dried over MgSO₄, and concentrated in vacuo to give 1.61 g of a mixture of crude iodolactones **6a** and **7a** (yield = 87%). Separation by column chromatography (silica gel hexane/EtOAc 9:1), followed by recrystallization from *n*-hexane/EtOAc (4.5:1), afforded pure products: **6a** (1.252 g) and **7a** (0.094 g).

6a: [α]$_D^{22}$ = −47.5° (*c* 1.26, acetone); mp 79−80 °C; ¹H NMR (CDCl₃) δ 1.73 (s, 3 H, 12−CH₃), 2.36 (dt, *J*$_{gem}$ = 13.9 Hz, *J*$_{2e,3}$ = 3.5 Hz, 1 H, 2−He), 2.6 and 2.66 (AB system, *J*$_{gem}$ = 17.2 Hz, *J*$_{7a,6}$ = 10.7 Hz, *J*$_{7b,6}$ = 9.9 Hz, 2 H, 7−CH₂), 2.80 (m, 1 H, 6−H), 3.54 and 3.59 (AB system, *J* = 18.1 Hz, 2 H, CH₂I), 4.75 (m, 2 H, =CH₂); IR (CCl₄) ν = 3100 (w, >C=CH₂), 1804 (s, C=O), 1656 (w, >C=CH₂), 1152 (m, C−O−C) cm⁻¹.

7a: [α]$_D^{20}$ = +9.23° (*c* 0.9, acetone); mp 79−82 °C; ¹H NMR (CDCl₃) δ 1.72 (s, 3 H, 12−CH₃), 2.16 (d, *J*$_{gem}$ = 17.4 Hz, 1 H, 7−Hb), 2.22 (dt, *J*$_{gem}$ = 15.0 Hz, *J*$_{2e,3}$ = 3.5 Hz, 1 H, 2-He), 2.67 (dt, *J*$_{6,7a}$ = 6.6 Hz, *J*$_{6,5e}$ = 6.6 Hz, *J*$_{6,5a}$ = 11.6 Hz, 1 H, 6−H), 2.85 (dd, *J*$_{gem}$ = 17.5 Hz, *J*$_{7a,6}$ = 6.6 Hz, 1 H, 7−Ha), 3.29, 3.32 (AB system, *J* = 17.0 Hz, 2H, 13−CH₂), 4.71 (m, 2 H, 11−CH₂); IR (KBr) ν = 3072 (w, >C=CH₂), 1776 (s, C=O), 1643 (w, >C=CH₂), 1172 (m, C−O−C), 531 and 520 (w, C−I) cm⁻¹.

(1S,4S,6S)-(+)-1-Iodomethyl-4-(1-methylethenyl)-9-oxabicyclo-[4.3.0]nonan-8-one (6b) and (1R,4R,6S)-(−)-1-Iodomethyl-4-(1-methylethenyl)-9-oxabicyclo[4.3.0]nonan-8-one (7b). By the same procedure a mixture of iodolactones **6b** and **7b** (1.12 g, 70%) was obtained from acids **4b** and **5b** (0.97 g). After separation, pure **6b** (0.50 g) and **7b** (0.072 g) were obtained.
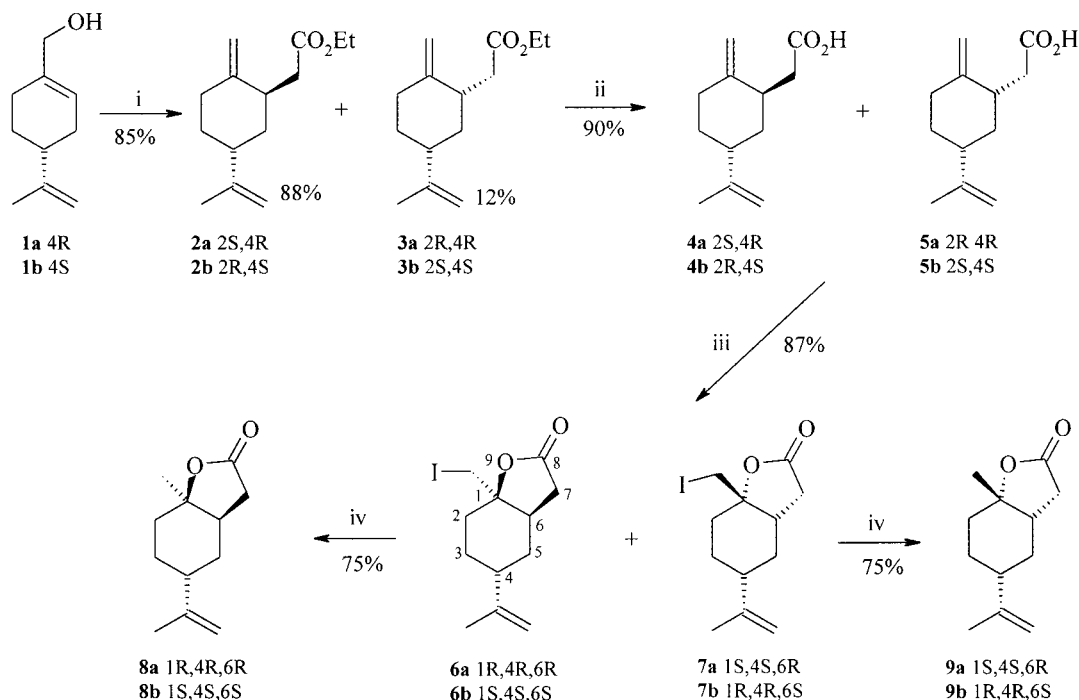
6b: [α]$_D^{23}$ = +44.4° (*c* 1, acetone); mp 76−78 °C.

Crystal data for 6b: C₁₂H₁₇O₂I, M$_w$ = 320.16, *T* = 293 K, Mo Kα radiation, monoclinic, space group C2, *a* = 23.817 (5) Å, *b* = 6.808 (10), *c* = 8.451 (2), *V* = 1281.1(4) Å³, *Z* = 4, *D*$_c$ = 1.66 Mg·m⁻³, μ = 2.480 mm⁻¹, *F*(000) = 632, crystal size 0.20 × 0.20 × 0.15 mm, diffractometer Kuma KM4, 5.16 ≤ 2θ ≤ 52°, 2357 collected reflections, 2300 independent reflections with *I* > 2σ(*I*), 193 parameters. The structure was solved using the SHELXS-86 program and refined (including H-atoms) using SHELXS-93 to *R*₁(*F*) = 0.0280, *wR*₂(*F*²) = 0.0736, and *S* = 1.087.

7b: [α]$_D^{25}$ = −24.2° (*c* 0.94, acetone); mp 78−80 °C.

(1R,4R,6R)-(−)-4-(1-Methylethenyl)-9-oxabicyclo[4.3.0]nonan-8-one (8a). Tributyltin hydride (0.55 g, 1.9 mmol) was added to a solution of iodolactone **6a** (0.17 g, 0.5 mmol), in dry benzene (2 mL) under N₂. The mixture was stirred for 7 days at room temperature, and then it was chromatographed (silica gel, hexane/EtOAc 9:1). The lactone **8a** was obtained (0.06 g, yield = 60%): [α]$_D^{26}$ = −32.8° (*c* 0.84, acetone); mp 62−64 °C {Rico et al. (1998): [α]$_D$ = −25.6° (*c* 0.99, acetone); mp = 53−55 °C}; ¹H NMR (CDCl₃) δ 1.49 (s, 3 H, 13−CH₃), 1.76 (s, 3 H, 12−CH₃), 2.47 (m, 1 H, 6−H), 2.50 and 2.67 (AB system, *J*$_{gem}$ = 18.6 Hz, *J*$_{7a,6}$ = 14.7 Hz, *J*$_{7b,6}$ = 7.6 Hz, 2 H, 7−CH₂), 4.75 (m, 2 H, 11=CH₂); IR (KBr) ν = 3087 (w, >C=CH₂), 1787 (s, C=O), 1645 (m, >C=CH₂), 1213 (s, C−O−C) cm⁻¹.

Synthesis of Terpenoid Lactones

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Scheme 1

i) $CH_3C(OEt)_3$, C_2H_5COOH, 138°C; ii) KOH/EtOH; iii)I_2, KI, $NaHCO_3$, Et_2O/H_2O; iv)(n-Bu)$_3$SnH, benzene

*(1S,4S,6S)-(+)-4-(1-Methylethenyl)-9-oxabicyclo[4.3.0]nonan-8-one (**8b**).* Obtained according to the same procedure (0.05 g, 76.5%) from **6b** (0.11 g): $[\alpha]_D^{26} = +38.0°$ (*c* 1.08, acetone); mp 64−65 °C.

*(1S,4S,6R)-(−)-4-(1-Methylethenyl)-9-oxabicyclo[4.3.0]nonan-8-one (**9a**).* Obtained according to the same procedure as **8a** (0.028 g, 74.5%) from **7a** (0.062 g) (oil): $[\alpha]_D^{25} = -3.6°$ (*c* 1.2, acetone); ^{1}H NMR (CDCl$_3$) δ 1.36 (s, 3 H, 13−CH$_3$), 1.71 (s, 3 H, 12−CH$_3$), 2.15 (d, 3 H, J_{gem} = 17.2 Hz, 1 H, 7−He), 2.22 (m, 1 H, 6−H), 2.92, (dd, J_{gem} = 17.2 Hz, $J_{7a,6}$ = 6.6 Hz, 1 H, 7−Ha), 4.69 (m, 2 H, 11=CH$_2$); IR (film) ν = 3084 (w, >C=CH$_2$), 1769 (s, C=O), 1645 (w, >C=CH$_2$), 1125 (s, C−O−C) cm^{-1}.

*(1R,4R,6S)-(+)-4-(1-Methylethenyl)-9-oxabicyclo[4.3.0]nonan-8-one (**9b**).* Obtained according to the same procedure as **9a** (0.031 g, yield 62.4%) from **7b** (0.082 g) (oil): $[\alpha]_D^{27} = +7.5°$ (*c* 0.5, acetone).

RESULTS AND DISCUSSION

Syntheses. Enantiomeric pairs of lactones **8a,8b** and **9a,9b** were obtained in a four-step synthesis from (4*R*)-(+)- and (4*S*)-(−)-perillyl alcohols (**1a** and **1b**) (Scheme 1). The alcohols were subjected to the orthoacetate modification of the Claisen rearrangement (Johnson et al., 1970). This reaction is known to be highly stereo-selective; however, in this case it led to a diastereoiso-meric mixture of products. Apart from the main product—ester **2a** (or **2b**) with *trans* situated isopropenyl and carbethoxymethyl groups—12% of *cis* ester **3a** (or 13% of ester **3b**, respectively) was also obtained. Although the presence of two esters was clearly seen by gas chromatography, they were inseparable by means of column chromatography. The mixture of *cis* and *trans* esters **2a,3a** (or **2b,3b**) was transformed into an insepa-rable mixture of corresponding acids **4a** and **5a** (or **4b,5b**) by hydrolysis with ethanolic KOH solution.

The lactone ring was closed by the iodolactonization of the acids carried out under kinetic conditions accord-ing to the procedure described by Mori and Nakazono

(1986). Diastereoisomeric lactones **6a** and **7a** (or **6b** and **7b**) were separated by crystallization from hexane/ethyl acetate (ratio 9:1, isomers **6a** and **6b** crystallize first), followed by column chromatography of the mixture obtained from the crystallization filtrate.

The presence of γ-lactone rings was confirmed by the IR spectrum (1780 cm^{-1} for **6a,b** and 1788 cm^{-1} for **7a,b**). Halolactonization generally proceeds to prefer-entially afford *cis*-fused lactones (Dowle and Davies, 1979; House et al., 1963), even though other modes of reaction do not appear to be prohibited on steric grounds. It also conforms to the general *trans* diaxial pattern observed for other ionic additions to flexible cyclohexene systems (Dowle and Davies, 1979; Ireland et al., 1991). Application of the rules mentioned above to a chair conformation of cyclohexane ring with pre-ferred, equatorial orientation of isopropenyl group and, assumed, 2*S* configuration in **4a** (and respectively 2*R* in **4b**) led us to the prediction that the iodomethyl group, as well as the C−O bond, must be axial. These expecta-tions were confirmed by ^{1}H NMR spectrum and the X-ray structure of **6b** (Figure 1).

The values of the torsion angles (Table 1) indicate that the cyclohexane ring is slightly flattened on C$_1$−C$_6$−C$_5$. The coupling constants in ^{1}H NMR are consistent with the values of the torsion angles between protons.

The structures of the minority iodolactones **7a** and **7b** were confirmed by the ^{1}H NMR spectrum. The iodomethyl group is equatorial in this case, which diminishes the deshielding effect of the oxygen atom of the lactone ring on −CH$_2$I protons, observed for **6a,b**. Another consequence of such a configuration is that one of the 7-H protons is close to the iodomethyl group (δ 2.85). The second 7-H atom is apart from it and does not undergo the deshielding effect. Consequently, its chemical shift is only 2.16 ppm. Moreover, there is no coupling between this proton and the 6-H proton, which
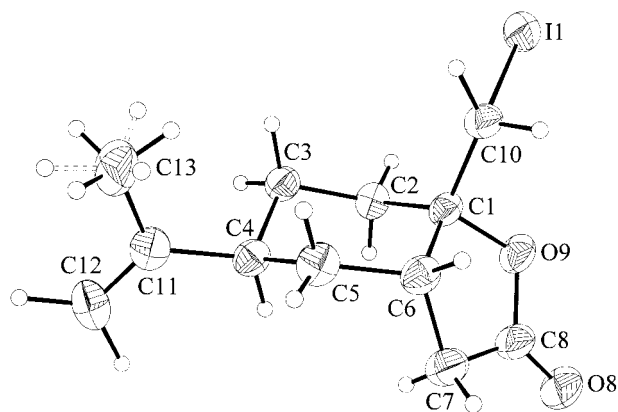
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Figure 1. Crystal structure of **6b**.

Table 1. Selected Torsion Angles (Degrees) for 6b

H2e−C2−C3−H3a	−49	H6−C6−C7−H7β	27
H2e−C2−C3−H3e	64	C4−C5−C6−C7	−71.9
H2a−C2−C3−H3a	−166	O9−C1−C2−C3	161.2
H2a−C2−C3−H3e	−53	C10−C1−C2−C3	−78.6
H3a−C3−C4−H4	179	C11−C4−C5−C6	179.1
H3e−C3−C4−H4	73	O9−C1−C6−C7	−29.5
H4−C4−C5−H5e	−86	C10−C1−C6−C7	−144.0
H4−C4−C5−H5a	−172	C10−C1−C6−C5	89.2
H5e−C5−C6−H6	−62	C2−C1−C6−C5	−40.7
H5a−C5−C6−H6	32	C2−C3−C4−C11	−173.0
H6−C6−C7−H7α	163		

indicates a slight distortion of the lactone ring, with the C-6 atom out of the plane.

Treatment of iodolactones **6a**, **6b**, **7a**, and **7b** with tributyltin hydride afforded corresponding lactones **8a**, **8b**, **9a**, and **9b** in good yields (60, 76, 75, and 62%, respectively).

Biological Activities. The main products of the reactions—iodolactones **6a** and **6b** and the lactones **8a** and **8b** obtained from them—were tested for feeding deterrent activity toward the storage pests: adults of the granary weevil beetle (*S. granarius*), adults and larvae of the confused flour beetle (*Tri. confusum*), and larvae of the khapra beetle (*Tro. granarium*). These pests are very difficult to control as they feed on products used almost directly for consumption. Especially troublesome is the granary weevil, which reproduces very quickly. In good conditions its population may increase severalfold during a few months. Moreover, it is very resistant to low temperatures and even at −10 °C manages to survive for several weeks. Fumigation with methyl bromide, used so far for grain protection, poses food safety concerns, whereas another fumigant—phosphine—is less effective because the insects gradually adapt to it. Accordingly, there is a strong need for a new method of grain protection against these pests.

The results of the tests of the lactones are presented in Table 2 as the total coefficients of deterrence. For compounds with no activity the value oscillates around 0, whereas for very good deterrents it ranges from 150 to 200 (Nawrot et al., 1986).

The best antifeedant properties were observed for lactone **8a** (Table 2). The activity of this compound toward all tested pests is comparable to that of the most active of known feeding deterrents—azadirachtin and bisabolangelone (Nawrot et al., 1984, 1987). Its enantiomer (**8b**) is also very active toward beetles (*Tri. confusum, S. granarius*) but slightly less active against

Table 2. Feeding Deterrent Activity of Lactones 6a,b and 8a,b

No	Structure	Total coefficients of deterrence[a]			
		Trogoderma granarium (larvae)	*Tribolium confusum* (larvae)	*Tribolium confusum* (adults)	*Sitophilus granarius* (adults)
6a		38.6	62.2	94.0	161.0[b]
6b		25.7	17.4	136.5	139.4
8a		200.0[b]	200.0[b]	197.2[b]	198.3[b]
8b		130.4	153.0[b]	173.4[b]	195.0[b]
Azadirachtin		194.2	188.4	185.0	174.3
Bisabolange-lone		200.0	200.0	195.0	139.0

[a] Deterrence: inhibition of feeding; total coefficient of deterrence: $T = A + R$ (*A*, absolute coefficient of deterrence, measured in no-choice tests; *R*, relative coefficient of deterrence, measured in choice tests). [b] Very high antifeeding activity.

larvae (*Tri. confusum, Tro. granarium*). Iodolactone **6a** is a strong deterrent against *S. granarius*, whereas **6b** possesses relatively high activity against beetles of *S. granarius* and *Tri. confusum*.

The synthesized compounds were also tested against the peach-potato aphid (*M. persicae*). The lactone **8b** was active toward this species at both applied concentrations (0.1 and 0.01%).

Obtained in small quantities, iodolactones **7a** and **7b** and the products of their reduction—lactones **9a** and **9b**—were not promising from the synthetic point of view, so their antifeeding activity was not evaluated.

The results presented confirm the importance of the chiral center configuration of a compound in expression of its biological activity. The sensitivity of insects to antifeedants depends on their developmental stage.

Odor Properties. It is not surprising that lactones **8a** and **8b**, containing the limonene system, possess interesting odors. The fragrance of **8a** is a moderately intense, agreeable, herbaceous odor with lupine flower and parsley root notes, whereas that of the **8b** isomer is faint, mushroomy, and moldy with a floral note.

Synthesis of Terpenoid Lactones

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