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Lactones. 21.† Synthesis and Odoriferous Properties of Lactones with the *p*-Menthane System

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Starting from (*R*)-(+)- and (*S*)-(−)-pulegone, enantiomeric pairs of esters and lactones with the *p*-menthane system were obtained. The Claisen rearrangement of allylic alcohols and iodolactonization of γ,δ-unsaturated acids were the key steps of syntheses presented. The structures of compounds were determined by both spectroscopic and crystallographic methods. Some of the synthesized compounds are characterized by interesting odoriferous properties.

KEYWORDS: Terpenoid lactones; *p*-menthanolides; pulegone; odorous compounds; Claisen rearrangement; iodolactonization; dehalogenation

INTRODUCTION

Lactones with the *p*-menthane system are a very interesting and valuable group of terpenoid compounds. They are widely spread in nature as minor components of essential oils, which are used for flavoring, cosmetics production, and medicinal purposes.

Two of the most known *p*-menthane derivatives, (−)-mintlactone (**1a**) and (+)-isomintlactone (**2a**) (**Figure 1**), were identified in the essential oils of several *Mentha* species (*1*−*4*). *M. piperita* L., cultivated in Italy, is also the natural source of lactones **3** and **4** (*4*). In 1997, Iwabuchi reported the isolation of enantiomeric (+)-mintlactone (**1b**) from the oils of the woods *Bursera graveolens* (*5*). Although *p*-menthanolides **1** and **2** are present in small quantities in the mint oils, they seem to be important compounds from biosynthetic and phylogenetic points of view (*6*−*7*).

Lactone **5**, called "wine lactone", was detected in several white wines by Guth (*8*−*9*). It was also identified by Southwell in the excreted urine of koala animals fed with *Eucalyptus punctata* (*10*). This trace component in wine, showing coconut sweet odor and particularly low threshold (10^{-5} ng/L of air), appears to be an important flavor compound. Guth synthesized all eight possible stereoisomers of lactone **5** to determine their threshold values and to assign the configuration of natural wine lactone (*8*). The large differences of the odor threshold values observed for the two enantiomers of each pair showed that 3*S* configuration is correlated with a lower threshold. *p*-Menthanolide **6** was also isolated from the metabolized essential oil of *Eucalyptus punctata* but without assignment of the absolute configuration of the chiral centers (*10*).

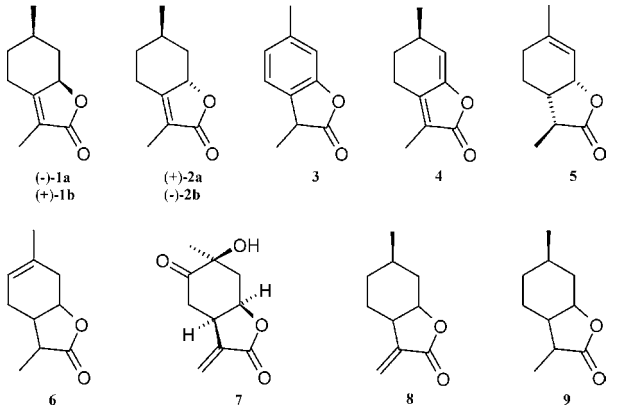

Figure 1. Lactones with the *p*-menthane system.

The isolation of many naturally occurring biologically active mono- and sesquiterpenoid α-methylene-γ-butyrolactones, such as isolated from paeony root (*Paeonia albiflora* PALLAS *trichocarpa* BUNGE) paeonilactone-B (**7**) (*11*), has resulted in the synthesis of *p*-menthanolides **8** (*12*−*14*).

All the possible saturated analogues of α-methylene-γ-butyrolactones **8** were synthesized by Gaudin (*15*). *p*-Menthanolides **9** possess very interesting olfactory properties. In general, their odors are more coumarinlike and less lactonic than the odor of mintlactone (**1**). They are of considerable interest to the perfume industry, due to their exceptional intensity and typical hay character of coumarin.

Our interests in synthesis of monoterpenoid lactones with the *p*-menthane system are caused by their high biological activity and interesting odoriferous properties. Biological tests for the

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feeding deterency of *p*-menthanolides, synthesized by us earlier from optically pure isomers of perillyl alcohol and limonene (*16*), showed their quite good activity toward selected insect storage pests (*Sitophilus granarius* L., *Tribolium confusum* Duv., and *Trogoderma granarium* Ev.) (*17*). Some of them possess interesting fragrances (*18*). Their odoriferous properties and biological activity are influenced by the configuration of the chiral centers.

In search for new, biologically active monoterpenoid compounds, we have synthesized enantiomeric pairs of esters and lactones from (*R*)-(+)- and (*S*)-(−)-pulegone (**10a** and **10b**). Here we present the synthesis of enantiomeric pairs of new compounds with the *p*-menthane system possessing interesting odoriferous properties. The chemical synthesis of optically pure compounds plays an important role in the development of new drugs, agrochemicals, food additives, flavors and fragrances. It is well established that chiral discrimination is of primary importance in odor perception and drug disposition (*19*−*22*).

EXPERIMENTAL SECTION

Reagents. (*R*)-(+)-pulegone, (*S*)-(−)-pulegone, triethyl orthoacetate, tributyltin hydride, 1,8-diazabicyclo[5.4.0]undec-7-ene were purchased from Aldrich and Fluka.

General Procedures. *Analytical TLC.* Analytical TLC was performed on silica gel (Kieselgel 60 F_{254}, Merck) with mixtures of hexane, acetone, and diethyl ether in various ratios as developing systems. Compounds were detected by spraying the plates with 1% $Ce(SO_4)_2$/2% $H_3(P(Mo_3O_{10})_4)$ in 10% H_2SO_4, followed by heating to 120 °C.

Column Chromatography. Column chromatography was carried out on silica gel (Kieselgel 60, 40−63 μm, 230−400 mesh, Merck) with mixtures of hexane, acetone, and diethyl ether in various ratios as eluents.

GC Analyses. GC Analyses were performed with a Varian CP-3380 instrument, using the following capillary columns: HP-1 (cross-linked methyl siloxane), 25-m × 0.32-mm × 0.52-μm; HP-5 (cross-linked 5% phenyl methyl siloxane), 25-m × 0.32-mm × 0.52-μm (injector temp 250 °C, detector temp 300 °C (FID), carrier gas H_2); and CP-Cyclodextrin-β-2,3,6-m-19, 25-m × 0.25-mm × 0.25-μm (injector temp 150 °C, detector temp 200 °C (FID), carrier gas H_2).

Temperature Programs. **11a** and **11b**: 5 min at 180 °C, raised to 300 °C at 30 °C/min and held 1 min; retention times, 4.069 for **11a** and 4.084 for **11b** (HP-5). **12a** and **b** and **13a** and **b**: 5 min at 120 °C, raised to 300 °C at 30 °C/min and held 1 min; retention times, 5.128 for **12a**, 5.130 for **12b**, 4.805 for **13a,** and 4.812 for **13b** (HP-1). **14a** and **b**, **15a** and **b** and **16**: 5 min at 280 °C, raised to 300 °C at 30 °C/min and held 1 min; retention times, 4.404 for **14a**, 4.398 for **14b**, 2.939 for **15a**, 2.921 for **15b,** and 2.614 for **16** (HP-5).

^{1}H NMR Spectra. ^{1}H NMR Spectra were recorded in $CDCl_3$ or acetone-d_6 solutions on a Bruker Avance DRX 300 (300 MHz) spectrometer with TMS as internal standard.

IR Spectra. IR spectra were taken for liquid films on a Specord M80 infrared spectrophotometer (Carl Zeiss Jena).

Melting Points. Melting points (uncorrected) were determined using a Boetius apparatus.

Optical Rotations. Optical rotations were measured with an Autopol IV automatic polarimeter (Rudolph) in acetone or ethyl alcohol as the solvent with the concentrations denoted in grams per 100 mL.

X-ray Crystal Analysis. X-ray data were collected at low temperature using an Oxford Cryosystem device on a Kuma KM4CCD κ-axis diffractometer with graphite-monochromated MoKα radiation (λ = 0.71073 Å). The crystal was positioned at 65 mm from the CCD camera. Frames (n = 612) were measured at 0.75° intervals with a counting time of 20 s. The data were corrected for Lorentz and polarization effects. No absorption correction was applied. Data reduction and analysis were carried out with the Oxford Diffraction programs. The structure was solved by direct methods (program SHELXS-97) and refined by the full-matrix least-squares method on all F^2 data using the SHELXL-97 programs. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were included from geometry of molecules and $\Delta\rho$ maps. They were refined with isotropic displacement parameters. Crystallographic data for the structure reported in this paper (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre. Copies of this information may be obtained free of charge from the Director, CCDC, 12 UNION Road, Cambridge 1EZ. UK (fax, +44−1223−336033; e-mail, deposit@ccdc.cam.ac.uk).

Odor Evaluation. Odoriferous characteristic was done by a group of perfumers from Technical University of Łódź under the direction of Prof. J. Góra. The odor evaluation was performed for ethanolic solutions of samples (10%) with the use of a strip blotter.

Synthesis and Separation of Compounds. *cis-(1R, 5R)-(−)-Pulegol* (***11a***). A suspension of $NaBH_4$ (0.4 g, 10.57 mmol) in EtOH (21 mL) was added dropwise to an ice-cooled solution of pulegone (*R*)-(+)-**10a** (1.5 g, 9.85 mmol) in MeOH (18 mL) and water (3.6 mL). Stirring was continued for 2 h at room temperature. When the reaction was completed (TLC, hexane/acetone 20:1), the mixture was poured into brine, and the product was extracted with hexane. The combined extracts were washed with water and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo, and the crude product (1*R*, 5*R*)-(−)-**11a** (1.51 g; according to the GC analysis, 96% purity) was used for the next step without further purification: $[\alpha]_D^{25} = -105.2°$ (c = 1.9, EtOH); mp = 30−31 °C (lit. (*23*): $[\alpha]_D = -104°$, EtOH:H_2O 95:5; mp = 29−30 °C). ^{1}H NMR (acetone-d_6): 1.07 (d, J = 6.8 Hz, 3H, CH_3-5), 1.33−1.42 (m, 1H, H-5), 1.49−1.58 (m, 2H, CH_2-group), 1.62 and 1.74 (two s, 6H, $(CH_3)_2C$=), 1.66−1.72 (m, 2H, CH_2-group), 2.11 and 2.34 (two m, 2H, CH_2-group), 3.25 (br. s, 1H, −OH), 4.58 (m, 1H, H − 1). IR (nujol): 3300 (br. s, OH), 1340 and 1272 (s, C−OH), 1116 (s, OH).

cis-(1S,5S)-(+)-Pulegol (***11b***). In the same manner as described for the preparation of (1*R*, 5*R*)-(−)-**11a**, pulegone (*S*)-(−)-**10b** (1 g, 6.57 mmol) yielded the crude *cis*-pulegol (1*S*, 5*S*)-(+)-**11b** (0.95 g; according to the GC analysis, 97% purity): $[\alpha]_D^{25} = +103.8°$ (c = 1.6, EtOH). Its IR and ^{1}H NMR spectra were identical to those of (1*R*, 5*R*)-(−)-**11a**.

Ethyl (4R)-(+)-3-Methyl-3-(4-methyl-1-cyclohexen-1-yl)butanoate (**12a**). A mixture of the crude *cis*-pulegol (1*R*, 5*R*)-(−)-**11a** (1.51 g, 9.79 mmol), triethyl orthoacetate (15 mL, 80 mmol) and catalytic amount of propionic acid (1 drop) was heated at 138 °C for 8 h under the conditions for distillative removal of ethyl alcohol. When the reaction was completed (GC, TLC), the mixture was concentrated in vacuo to remove unreacted orthoacetate. The residue was chromatographed on silica gel. Elution with hexane/diethyl ether (80:1) gave the pure ester (4*R*)-(+)-**12a** (1.89 g, 86% yield): $[\alpha]_D^{25} = +44.1°$ (c = 5.63, acetone); n_D^{20}= 1.4630. ^{1}H NMR ($CDCl_3$): 0.91 (d, J = 6.1 Hz, 3H, CH_3-4), 1.10 and 1.13 (two s, 6H, $(CH_3)_2C<$), 1.20 (t, J = 7.1 Hz, 3H, $-OCH_2CH_3$), 1.44−1.66 (m, 4H, CH_2-groups), 1.96−2.10 (m, 3H, CH_2-group and H − 4), 2.29 and 2.32 (AB system, J = 13.2 Hz, 2H, CH_2 − 2), 4.04 (q, J = 7.1 Hz, 2H, $-OCH_2CH_3$), 5.41 (m, 1H, H-2). IR (film): 1748 (s, C=O), 1392 and 1372 (s, $(CH_3)_2C<$), 1232 and 1120 (s, C−O−C).

Ethyl (4S)-(−)-3-Methyl-3-(4-methyl-1-cyclohexen-1-yl)butanoate (**12b**). According to the procedure described for the preparation of (4*R*)-(+)-**12a**, the crude *cis*-pulegol (1*S*, 5*S*)-(+)-**11b** (1.6 g, 10.37 mmol) yielded the unsaturated ester (4*S*)-(−)-**12b** (1.95 g, 84%): $[\alpha]_D^{25} = -44.4°$ (c = 3.87, acetone). Its IR and NMR spectra were identical to those of (4*R*)-(+)-**12a**.

(4R)-(+)-3-Methyl-3-(4-methyl-1-cyclohexen-1-yl)butanoic Acid (**13a**). The unsaturated ester (4*R*)-(+)-**12a** (0.95 g, 4.23 mmol) was refluxed for 3 h in 2.5% KOH/EtOH solution (13 mL). After cooling and evaporating the solvent, the residual solid was dissolved in water and washed with diethyl ether to remove organic impurities. The water layer was acidified with 0.1 M HCl solution, and the product was extracted with diethyl ether. The combined ethereal solution was washed with brine, dried ($MgSO_4$), and evaporated in vacuo to give the crude acid (4*R*)-(+)-**13a** (0.81 g, 98% yield): $[\alpha]_D^{27} = +47.8°$ (c = 5.9, acetone); n_D^{20} = 1.4710. ^{1}H NMR ($CDCl_3$): 0.91 (d, J = 6.2 Hz, 3H, CH_3-4), 1.13 and 1.15 (two s, 6H, $(CH_3)_2C<$), 1.53−1.72 (m, 4H, CH_2-groups), 2.00−2.15 (m, 3H, CH_2-group and H-4), 2.33 and 2.35 (AB system, J

= 13.3 Hz, 2H, CH_2 − 2), 5.46 (m, 1H, H − 2), 10.00 (br. s, 1H, −COOH). IR (film): 3000 (m, br., OH), 1716 (s, C=O).

(*4S*)-(−)-*3-Methyl-3-(4-methyl-1-cyclohexen-1-yl)butanoic Acid* (**13b**). Treatment of the ester (4*S*)-(−)-**12b** (0.82 g, 3.66 mmol) similar to the hydrolysis of (4*R*)-(+)-**12a** afforded the crude acid (4*S*)-(−)-**13b** (0.70 g, 97% yield): $[\alpha]_D^{27} = -48.9°$ (c = 3.6, acetone). Its IR and NMR spectra were identical to those of (4*R*)-(+)-**13a**.

(*5R,6S,8R*)-(+)-*6-Iodo-4,4,8-trimethyl-1-oxaspiro[4.5]decan-2-one* (**14a**). A 0.5 M $NaHCO_3$ solution (10 mL) was added to a solution of the unsaturated acid (4*R*)-(+)-**13a** (0.63 g, 3.2 mmol) in diethyl ether (15 mL). The mixture was stirred at room temperature for 30 min and then refluxed. To the refluxing mixture was gradually added a solution of I_2 (1.62 g, 6.4 mmol) and KI (3.19 g, 19.2 mmol) in water (12 mL). The mixture was stirred for 3 h under reflux. After cooling, the reaction mixture was diluted with diethyl ether (50 mL) and washed with saturated $Na_2S_2O_3$ solution to reduce the excess of iodine. The separated ethereal layer was washed with saturated $NaHCO_3$ solution and brine and dried over $MgSO_4$. Filtration and evaporation of the solvent under reduced pressure gave the crude iodolactone (5*R*,6*S*,8*R*)-(+)-**14a** as a pale yellow thick oil. The crude product was chromatographed on silica gel with hexane/acetone (20:1) to afford the pure iodolactone (5*R*,6*S*,8*R*)-(+)-**14a** (0.96 g, 93% yield) as a colorless oil: $[\alpha]_D^{24} = +118.0°$ (c = 4.8, acetone); $n_D^{20} = 1.5460$. ^{1}H NMR ($CDCl_3$): 0.94 (d, J = 5.9 Hz, 3H, CH_3-8), 1.23 and 1.32 (two s, 6H, $(CH_3)_2C<$), 1.40−1.74 (three m, 3H, CH_2-9 and one of the CH_2-7 group), 1.88−2.00 (m, 3H, CH_2-10 and H-8), 2.27 (td, J = 14.0 and 4.3 Hz, 1H, one of the CH_2-7 group), 2.20 and 2.60 (AB system, J = 17.2 Hz, 2H, CH_2-3), 4.36 (m, 1H, H-6). IR (film): 1792 (s, C=O), 1240 (s, C−O−C).

(*5S,6R,8S*)-(−)-*6-Iodo-4,4,8-trimethyl-1-oxaspiro[4.5]decan-2-one* (**14b**). By use of the procedure described for the preparation of (5*R*, 6*S*, 8*R*)-(+)-**14a**, the unsaturated acid (4*S*)-(−)-**13b** (0.53 g, 2.7 mmol) yielded the iodolactone (5*S*,6*R*,8*S*)-(−)-**14b** (0.83 g, 95%): $[\alpha]_D^{24} = -116.5°$ (c = 4.22, acetone). Its IR and NMR spectra were identical to those of (5*R*,6*S*,8*R*)-(+)-**14a**.

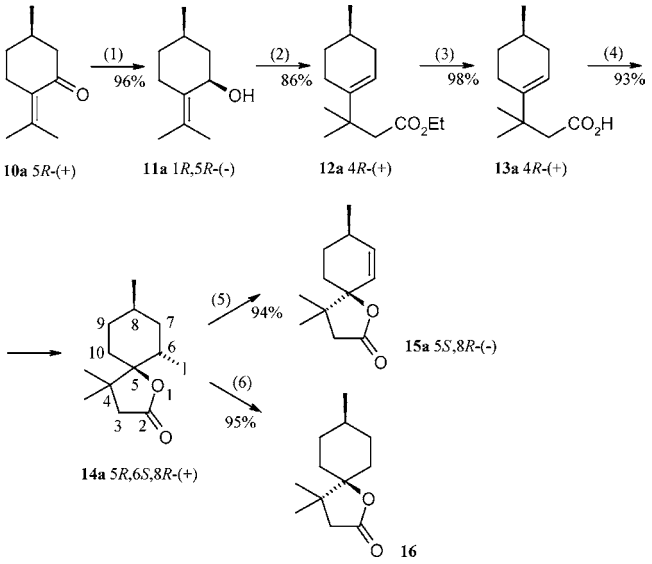
(*5S,8R*)-(−)-*4,4,8-Trimethyl-1-oxaspiro[4.5]dec-6-en-2-one* (**15a**). 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.82 g, 5.4 mmol) was added to a solution of the iodolactone (5*R*,6*S*,8*R*)-(+)-**14a** (0.87, 2.7 mmol) in dry benzene (30 mL). The mixture was refluxed under N_2 for 24 h. After cooling, the precipitate was filtered off, and the filtrate was concentrated in vacuo. The residue was diluted with diethyl ether (50 mL). The ethereal solution was washed with saturated NH_4Cl solution and brine, dried ($MgSO_4$), and evaporated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/acetone (20:1) gave the crystalline lactone (5*S*,8*R*)-(−)-**15a** (0.49 g, 94% yield): $[\alpha]_D^{26} = -61.7°$ (c = 2.3, acetone); mp = 72−73 °C. ^{1}H NMR ($CDCl_3$): 1.00 (d, J = 7.2 Hz, 3H, CH_3-8), 1.03 and 1.06 (two s, 6H, $(CH_3)_2C<$), 1.33−1.94 (four m, 4H, CH_2-9 and CH_2-10), 2.06 (m, 1H, H-8), 2.28 and 2.60 (AB system, J = 17.0 Hz, 2H, CH_2-3), 5.62 (dm, $J_{H-6,\ H-7}$ = 10.2 Hz, 1H, H-7), 5.85 (d, J = 10.2 Hz, 1H, H-6). IR ($CHCl_3$): 3072 (w, HC=CH), 1768 (s, C=O), 1656 (w, HC=CH), 1268 (s, C−O−C).

(*5S,8R*)−(−)-***15a***. $C_{12}H_{18}O_2$, M = 194.26, monoclinic, space group $P2_1$, a = 6.4890(10) Å, b = 9.070(2) Å, c = 9.441(2) Å, β = 100.35-(3)°, V = 546.61(19) Å^3, Z = 2, D_c = 1.180 Mg m^{-3}, T = 100 K, R = 0.0300, Rw = 0.0727 (2454 reflections for I > 2σI) for 199 variables. CCDC no. 226232.

(*5R,8S*)−(+)-*4,4,8-Trimethyl-1-oxaspiro[4.5]dec-6-en-2-one* (**15b**). In the same manner as described for the preparation of (5*S*,8*R*)-(−)-**15a**, the iodolactone (5*S*,6*R*,8*S*)-(−)-**14b** (0.83 g, 2.58 mmol) yielded the unsaturated lactone (5*R*,8*S*)-(+)-**15b** (0.5 g, 96%): $[\alpha]_D^{26} = +61.89°$ (c = 2.6, acetone). Its IR and NMR spectra were identical with those of (5*S*,8*R*)-(−)-**15a**.

4,4,8-Trimethyl-1-oxaspiro[4.5]decan-2-one (**16**). Tributyltin hydride (1.73 g, 5.96 mmol) was added dropwise to a solution of the iodolactone (5*R*,6*S*, 8*R*)-(+)-**14a** (0.96 g, 2.98 mmol) in dry benzene under N_2. The mixture was stirred for 48 h at room temperature and then chromatographed on silica gel. Elution with hexane/acetone (20:1) gave the lactone **16** (0.58 g, 95% yield): $n_D^{20} = 1.4725$. ^{1}H NMR ($CDCl_3$): 0.86 (d, J = 5.3 Hz, 3H, CH_3-8), 1.03 (s, 6H, $(CH_3)_2C<$), 1.28−1.44 (m, 5H, CH_2-groups and H-8), 1.58−1.60 (m, 2H, CH_2-group), 1.76−1.80 (m, 2H, CH_2-group), 2.38 (s, 2H, CH_2-3). IR (film): 1784 (s, C=O), 1236 (s, C−O−C).

Scheme 1. (1) $NaBH_4$, EtOH, $MeOH/H_2O$, 0 °C, 2 h; (2) $CH_3C(OEt)_3$, C_2H_5COOH, 138 °C, 8 h; (3) KOH/EtOH, reflux 3 h, then 0.1 M HCl; (4) I_2, KI, $NaHCO_3$, Et_2O/H_2O, reflux 3 h; (5) DBU, benzene, reflux 24 h; (6) $(n\text{-}Bu)_3SnH$, benzene, 48 h



Treatment of the iodolactone (5*S*,6*R*,8*S*)-(−)-**14b** (0.71 g, 2.2 mmol) similar to the reduction of (5*R*,6*S*,8*R*)-(+)-**14a** afforded the saturated lactone **16** (0.40 g, 93% yield).

RESULTS AND DISCUSSION

Enantiomeric pair of lactones **15a**, **15b**, and optically inactive γ-spirolactone **16** were obtained in a five step synthesis from (*R*)-(+)- and (*S*)-(−)-pulegone (**10a** and **10b**) (**Scheme 1**). The first step of the synthesis was the reduction of pulegones with sodium borohydride according to the standard procedure (*24*). A mixture of methyl alcohol/water (5:1) as a solvent and a small excess of $NaBH_4$ were used to shorten the time of the reaction. The choice of sodium borohydride as a hydride reducing agent was motivated by its high stereoselectivity in reducing of α,β-unsaturated ketones. The use of $CeCl_3$ to prevent the formation of saturated alcohols was not necessary. The course of the reactions and the purity of the products were controlled by GC on a capillary column (HP-5). Allylic alcohols *cis*-(1*R*,5*R*)-(−)- and *cis*-(1*S*,5*S*)-(+)-pulegol (**11a** and **11b**) were the main products of the reductions. The stereochemical assignment of *cis*-pulegols was based on the value of optical rotation (*23*). Their structure was also confirmed by ^{1}H NMR and IR spectra (*25*, *26*).

The crude pulegols, without further purification (according to the GC analysis, 96 and 97% purity, respectively), were subjected to the orthoacetate modification of Claisen rearrangement (*27*). Enantiomerically pure (4*R*)-(+)-**12a** and (4*S*)-(−)-**12b** isomers of ethyl 3-methyl-3-(4-methyl-1-cyclohexen-1-yl)butanoate were obtained in good yields (86 and 84%) as the products of these reactions. Their enantiomeric purity (e.e., 99%) was confirmed by GC on a chiral column (cyclodextrin-β-2,3,6-m-19). The γ,δ-unsaturated esters **12a** and **12b** were transformed into the corresponding acids (4*R*)-(+)-**13a** and (4*S*)-(−)-**13b** by their hydrolysis with ethanolic KOH solution.

The key step of the synthesis was the iodolactonization of enantiomeric γ,δ-unsaturated acids **13a** and **13b** carried out according to the procedure described by Mori and Nakazano (*28*). δ-Iodo-γ-lactones (5*R*,6*S*,8*R*)-(+)-**14a** and (5*S*,6*R*,8*S*)-

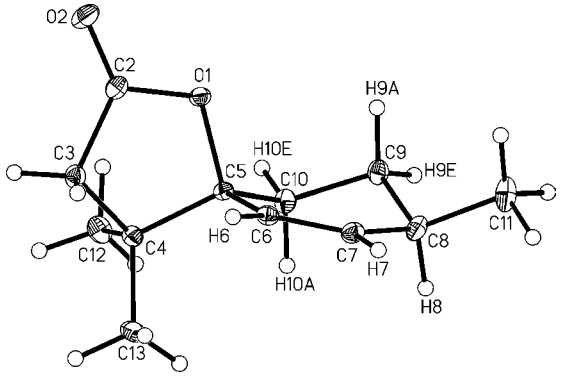
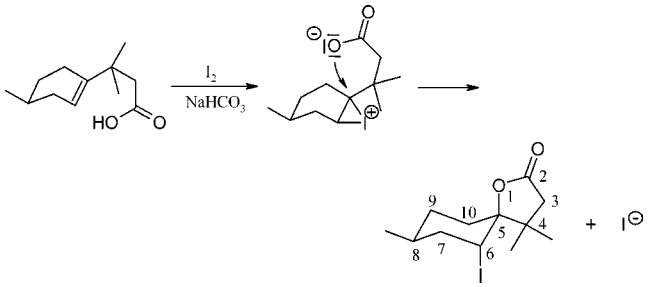


Figure 2. Molecular structure of (5*S*,8*R*)-(−)-**15a** with crystallographic numbering

Scheme 2. Iodolactonization of the Acids **13a** and **13b**



(−)-**14b** were isolated as the only products of these reactions. The presence of the γ-lactone ring was confirmed by the IR spectrum (1792 cm^{-1}). The established mechanism of iodolactonization states that the carboxylic anion approaches the iodonium ion from the opposite side (*29*−*32*). General stereochemical rules concerning ionic additions to the flexible cyclohexene system imply that the attached groups should be in trans-diaxial positions in relation to each other (*31*, *33*). Thus, assuming the equatorial position of the methyl group, we expected an axial position of the iodine substituent and an axial orientation of the alkoxy C−O bond (**Scheme 2**).

These expectations were confirmed by the ^{1}H NMR spectra of iodolactones **14a** and **14b**. The axial position of iodine is suggested by the shape of H-6 multiplet that looks like a narrow quartet as a result of coupling with CH_2-7 and long-distance coupling with equatorial H-10 proton.

The iodolactones **14a** and **14b** were subjected to the dehydrohalogenation with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (*34*) to give unsaturated lactones (5*S*,8*R*)-(−)-**15a** and (5*R*,8*S*)-(+)-**15b** in good yields (about 90%). The X-ray structure of the lactone **15a** (**Figure 2**) undoubtedly confirms the axial orientation of the alkoxy C−O bond and indirectly, as suggested earlier, the axial position of iodine atom in the iodolactones **14a** and **14b**. The lack of coupling constant $J_{H-7,\ H-8}$ in the ^{1}H NMR spectrum of **14a** or **14b** is a result of dihedral angle between C7−H7 and C8−H8. X-ray analysis showed the value 83° for this angle.

Reductive dehalogenation of iodolactones **14a** and **14b** with tributyltin hydride (*35*) caused the loss of chirality and resulted in formation of only one optically inactive γ-spirolactone **16**. The measurements of optical rotation confirmed the lack of chiral centers in the molecules of **16**. The structure of optically inactive γ-spirolactone **16** was established on the basis of ^{1}H NMR and IR spectra.

According to our expectations, synthesized esters and lactones, containing the *p*-menthane system, possess interesting fragrances (**Table 1**). The odoriferous properties of corresponding enantiomers are slightly influenced by the absolute configuration of the chiral centers present in the molecules of the odorant. The fragrance of ester (4*R*)-(+)-**12a** is fruity with a ripe pear note, whereas its enantiomer (4*S*)-(−)-**12b** has fruity−pear odor with a woody note. A relationship between odoriferous properties and configuration of the chiral centers is further seen for unsaturated γ-lactones (5*S*,8*R*)-(−)-**15a** and (5*R*,8*S*)−(+)-**15b**. The lactone **15a** possesses coconut odor, while the fragrance of **15b** is floral with a fresh and sweet fruit of coconut tree note. Comparison of the fragrances of enantiomeric esters and lactones confirmed the well-known dependence of osmotic properties of the compound on the steric shape of its molecule, in this case on the absolute configuration of the chiral centers (*22*). Optically inactive γ-spirolactone **16** possesses a penetrating, refreshening, and cooling odor with a mentholic−menthonic note.

Table 1. Odoriferous Characteristic of Esters **12** and Lactones **15**–**16**

compound	odor description
(4*R*)-(+)-**12a**	fruity with a ripe pear note
(4*S*)-(−)-**12b**	fruity-pear with a woody note
(5*S*,8*R*)-(−)-**15a**	coconut
(5*R*,8*S*)-(+)-**15b**	floral with a fresh and sweet fruit of coconut tree
16	penetrating, refreshening, cooling with a mentholic–menthonic note

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