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Lactones. Part 15: Synthesis of chiral spirolactones with a carane system—insect feeding deterrents†

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Abstract—Starting from (+)-3-carene **1** several spirolactones with carane backbone were synthesized. δ-Hydroxy-γ-lactone **5** was obtained by acidic lactonization of a γ,δ-epoxy ester. Iodolactone **8** and bromolactone **9** were products of iodolactonization of γ,δ-unsaturated acid **7** and bromolactonization of γ,δ-unsaturated ester **3** respectively. The halo lactones were subjected to reductive dehalogenation with tributyltin hydride and dehydrohalogenation with DBU. The structures of the lactones obtained were confirmed by X-ray analysis and spectral data.

1. Introduction

The innovative idea of the broad application of natural antifeedants for insect pest population control has faced some difficulties. The low contents of these compounds in plants, and hence the high cost of their isolation is the main limitation to their common practical use. Being convinced that if antifeedants find practical application they will be probably synthetic ones, we have started the synthesis of terpenoid lactones as potential insect feeding deterrents. The choice of this group of compounds as a subject of our research was inspired by studies concerning the natural antifeedants. Many papers reported that natural isoprenoid lactones like cinnamolide,[2] bakkenolid A,[3] helenalin[4] and others[5] exhibited high antifeeding activity. In the syntheses carried out in our laboratories the natural terpenes were used as starting materials. Such raw materials allow us to obtain the final products as pure enantiomers. We have already synthesized enantiomeric pairs of lactones with limonene[6] and pinane[7] systems. The biological tests carried out on storage pests indicated that some of our lactones were as active the most potent natural antifeedant—azadirachtin.[8,9] Herein, we present the synthesis of further terpenoid lactones with the carane system.

2. Results and discussion

The key compound in the synthesis of the final lactones (Scheme 1), ester **3**, was obtained via the alcohol **2** from one of the main components of polish turpentine—(+)-3-carane **1** according to procedure described recently.[10] Hydroxy lactone **5** was obtained by acidic ($HClO_4$) lactonization of the epoxy ester **4**, which was formed by oxidation of ester **3** with *m*-chloroperbenzoic acid. The *trans* orientation of the oxirane ring to the cyclopropane ring was confirmed by ^1H NMR analysis. The large difference in chemical shifts of the methyl groups ($\Delta\delta = 0.28$) is similar to the difference seen in the spectrum of *trans*-3,4-epoxycarane.[11] The shape of the 5-H signal (narrow multiplet like triplet) indicates the flattened boat conformation of the cyclohexane ring with the C-2 and C-6 as stem and stern atoms. The *trans* orientation of the oxirane ring to the cyclopropane ring was also confirmed by the structure of the hydroxy lactone **5** (Fig. 1), which was obtained as the product from acidic ($HClO_4$, pH 1.0) lactonization of the epoxy ester **4**. Hydroxy lactone **5** can be formed only from the *trans*-epoxide via the diol ester with *trans*-diequatorial hydroxy groups. This diol is a result of nucleophile attack (H_2O) on C-3 from the opposite side of the oxonium ion, which is formed after H^+

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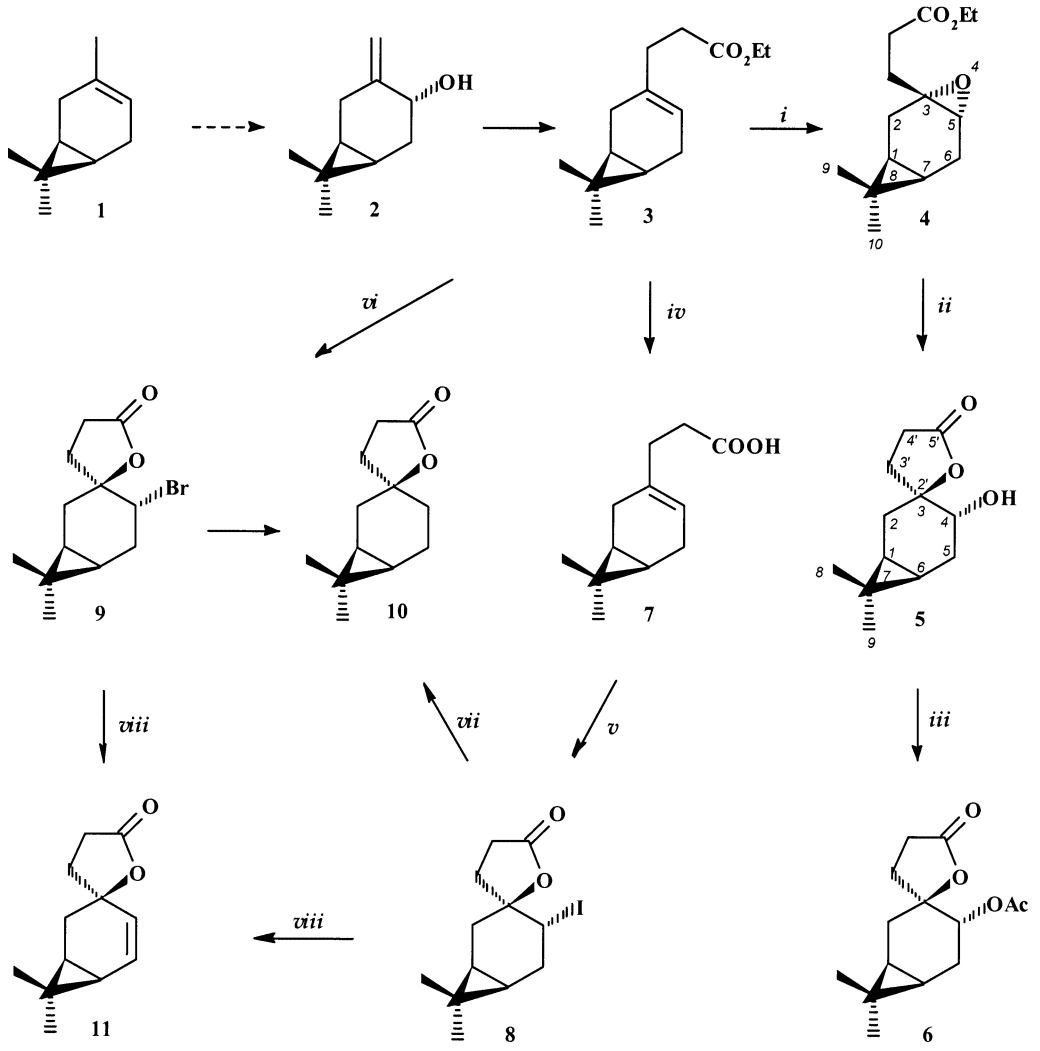

Scheme 1. *Reagents*: (i) MCPBA, CH_2Cl_2; (ii) H^+, H_2O–THF or $BF_3{\cdot}Et_2O$, toluene; (iii) AcCl, Py; (iv) KOH, EtOH; (v) I_2–KI, $NaHCO_3$, Et_2O; (vi) NBS, THF–H_2O; (vii) $(n\text{Bu})_3SnH$, toluene; (viii) DBU, toluene, reflux.

addition to the oxirane oxygen. However, we did not observe the formation of any diol ester in the course of this reaction or during purification, which suggests that the mechanism of this reaction is similar to that proposed for the lactonization of acyclic epoxy esters.[12] According to that mechanism the oxygen of the carbonyl group behaves as a nucleophile in the lactonization process.

This mechanism is also indicated by the result of lactonization of epoxy ester **4** with $BF_3{\cdot}Et_2O$ in toluene. The hydroxy lactone **5** was obtained as the only product. The X-ray structure (Fig. 1) shows that carbon atoms C-1, C-2, C-4, C-5 and C-6 are situated almost in one plane. The coupling constants of 4-H with the protons of the 5-CH_2 group are consistent with the torsional angles between coupled protons. The X-ray analysis indicates the presence of two symmetrically independent molecules in the crystals.

The biological tests carried out earlier[13] showed that in general the acetoxy lactones were more biologically active than their hydroxy lactone precursors. So, hydroxy lactone **5** was also transformed into acetoxy lactone **6** in the reaction with acetyl chloride in the presence of pyridine.

δ-Iodo-γ-lactone **8** was obtained by iodolactonization of acid **7**, which was a product of alkaline hydrolysis of ester **3**. The lactonization was carried out with aqueous I_2–KI solution in diethyl ether under basic conditions.[14] Iodolactone **8** was isolated as the only product of this reaction.[15] Its spiro structure as well as the *trans* orientation of iodine to the C–O bond and the cyclopropane ring was confirmed by X-ray crystallographic analysis (Fig. 2).

The crystals of this compound consist of four symmetrically independent molecules. The flatness of the cyclohexane ring (atoms C-1, C-2, C-4, C-5 and C-6) and the pseudoequatorial orientation of the iodine atom was also confirmed by the shape (dd) and coupling constants ($J = 10.9$ and 7.1 Hz) of the pseudoaxial 4-H with protons of the 5-CH_2-group.

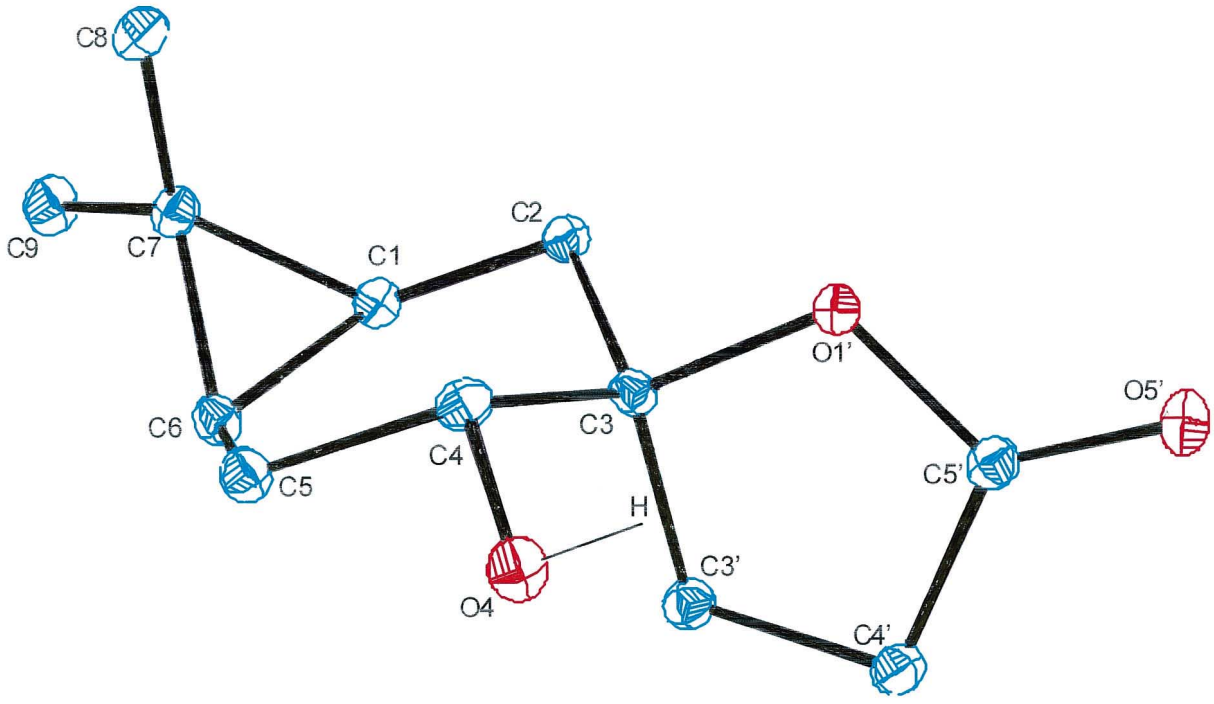

Figure 1.

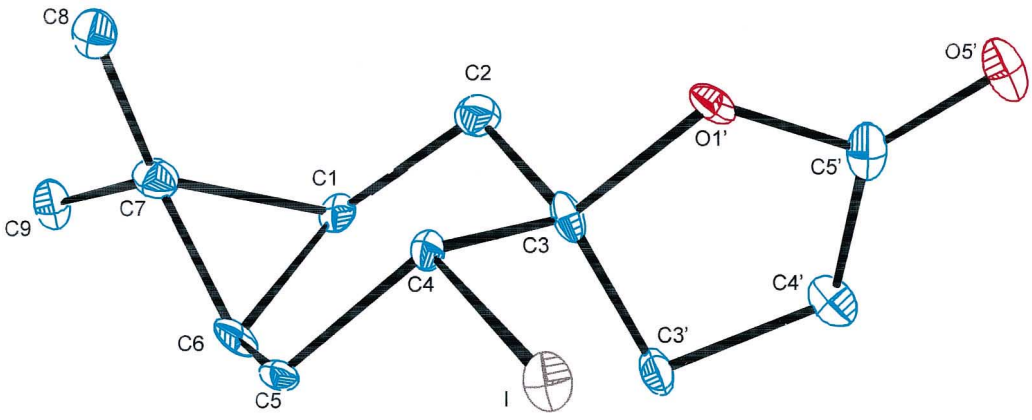

Figure 2.

The next halo lactone, bromolactone **9**, was formed by reaction of ester **3** with *N*-bromosuccinimide in water/tetrahydrofuran solution.[16] The similarity of its ^{1}H NMR spectrum to that of compound **8**, especially the 4-H signal (doublet, $J=10.2$ Hz of doublet 7.3 Hz), indicates the same orientation of halogen atoms in both molecules. The X-ray structure of **9** (Fig. 3) confirmed the suggested similarity of molecules of both halo lactones. The X-ray analysis indicates that three symmetrically independent molecules, slightly differentiated in the shape of the cyclohexane ring, are present in the crystal of this compound. On examining the course of this reaction we did not detect any formation of bromohydrin. Taking this fact into consideration, we suggest the mechanism in which the oxygen of the carboethoxy group acts as a nucleophile and attacks the C-3 carbon atom of the bromonium ion formed in the reaction of the double bond with *N*-bromosuccinimide.

Reductive dehalogenation of both iodo- and bromolactones **8** and **9** led to spirolactone **10** in good yields (71%). The lactones **8** and **9** were also subjected to dehydrohalogenation with 1,8-diazabicyclo[5.4.1]undec-7-ene (DBU) to give the unsaturated lactone **11** in 73% yield. The structure of lactone **11** was confirmed by spectral data. The presence of the γ-lactone ring is confirmed by the presence of an absorption band at 1763 cm^{-1} in the IR spectrum. The two multiplets of olefin protons: doublet ($J=9.8$ Hz) of multiplets (like triplets, $J=1.5$ Hz) at $\delta=5.67$ of 5-H and doublet ($J=9.8$ Hz) at $\delta=5.79$ of 4-H confirmed the C-4–C-5 double bond. Both the ^{1}H NMR and ^{13}C NMR spectra confirm the survival of the cyclopropane ring in the course of this reaction. The presence of signals for carbon atoms C-6, C-7 and C-1 at 19.54, 22.36 and 26.68 in the ^{13}C NMR spectrum indicate unequivocally that the cyclopropane ring was not affected with DBU under the conditions of the reaction.

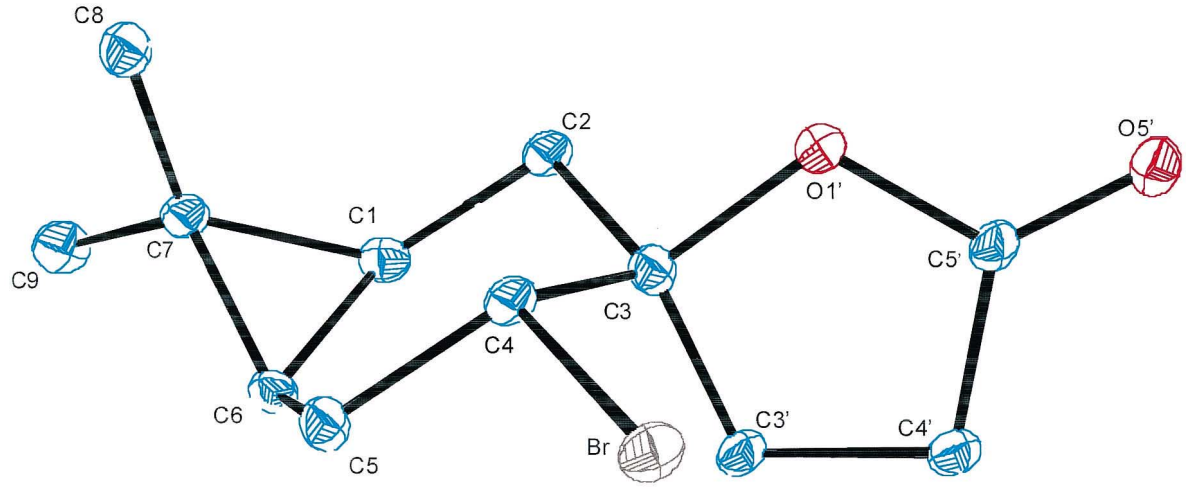

Figure 3.

Till now the lactones **5**, **6** and **8** were tested for feeding deterrent activity against three storage pest insects: the granary weevil beetle (*Sitophilus granarius* L., adults), the confused flour beetle (*Tribolium confusum* Duv., larvae) and the khapra beetle (*Trogoderma granarium* Ev., larvae and adults). All of the compounds tested exhibited good activity (total coefficients of deterrence 100–150) towards *T. granarium*. Acetoxy lactone **6** was also active against larvae of *T. confusum*. The full results of tests of all lactones described in this paper will be presented in a separate publication soon. It is noteworthy that unsaturated lactone **11** possesses an interesting and valuable odour, which was described as fresh, rhubarb with cream–coconut note.[17]

3. Experimental

The course of all reactions, composition of products, and their purity were checked by means of thin-layer chromatography (TLC) and gas chromatography (GC). TLC was carried out on silica gel G (Merck). Chromatograms were developed with a mixture of hexane, diethyl ether and acetone applied in various ratios and detected with 20% ethanolic H_2SO_4 with 0.1% of anisaldehyde. Preparative column chromatography was carried out on silica gel (60–120 mesh, Merck) with mixture of hexane, ethyl ether, ethyl acetate acetone and isopropanol (various ratio) as an eluent. GC analyses were performed on a Hewlett Packard 5890 (seria II) instrument using capillary columns: HP-l, length 25 m, temperature 120–280°C. Melting points (uncorrected) were determined on a Boetius apparatus. IR spectra were taken for liquid films or in KBr on a Perkin–Elmer 621 spectrophotometer. ^{1}H NMR spectra and ^{13}C NMR were recorded for $CDCl_3$ solution on a Bruker Avance DRX 300 apparatus with TMS as the internal standard.. All measurements of crystal were performed on a Kuma KM4CCD κ-axis diffractometer with graphite-monochromated Mo Kα radiation. The crystal was positioned at 65 mm from the KM4CCD camera. 612 Frames were measured at 0.75° intervals with a counting time of 30 s. The data were corrected for Lorentz and polarization effects. No absorption correction was applied. Data reduction and analysis were carried out with the Kuma Diffraction (Wrocław) programs. The structure was solved by direct methods (program SHELXS-97[18] and refined by the full-matrix least-squares method on all F^2 data using the SHELXL-97[19] programs. Non-hydrogen atoms were refined with anisotropic thermal parameters; hydrogen atoms were included from the $\Delta\rho$ maps and refined with isotropic thermal parameters. Crystallographic data for structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre.

3.1. Substrates

(+)-3-Carene **1** (Industrial Chemistry Research Institute, Warsaw) bp 79°C/28 mmHg, $n_D^{20}=1.4732$, $\alpha_D^{20}=+14.7$ (neat) was transformed via crystalline (−)-3(10)-caren-*trans*-4-ol **2** (mp 49–51°C; $[\alpha]_D^{20}=-116.0$ (*c* 5.1, $CHCl_3$) to (+)-ethyl 3-[(1*S*,6*R*)-7,7-dimethylbicyclo[4.1.0]hept-3-en-3-yl]propanoate, **3** (bp 90–92°C/3 mmHg, $n_D^{20}=1.4739$, $[\alpha]_D^{20}=+17.1$ (*c* 2.0, $CHCl_3$)) according to our procedure.[10]

3.2. (+)-Ethyl 3-[(1*S*,3*S*,5*R*,7*R*)-8,8-dimethyl-4-oxatricyclo[5.1.0.0^{3,5}]oct-3-yl]propanoate, 4

A solution of *m*-chloroperbenzoic acid (70%, 1.50 g, 6.1 mmol) in methylene chloride (25 mL) was added to a solution of ester **3** (1.20 g, 5.38 mmol) in methylene chloride (25 mL). When the reaction was complete (TLC, 10 h) the reaction mixture was diluted with diethyl ether and the ethereal solution was washed successively with 10% aqueous sodium sulfite solution, sodium bicarbonate, water and dried ($MgSO_4$). The crude product was purified by column chromatography (silica gel, hexane/acetone, 19:1) to give the epoxy ester

4 (1.10 g, 85%) as an oil: $[\alpha]_D^{26}=+15.9$ (*c* 8.2, $CHCl_3$); IR (film, cm^{-1}): 2921 (s), 1736 (s), 1446 (w), 1376 (w), 181 (s); ^1H NMR ($CDCl_3$): δ 0.43 and 0.47 (two td, $J=8.8$ and 2.2 Hz, 2H, 1-H and 7-H), 0.70 and 0.98 (two s, 6H, 9- and 10-CH_3), 1.22 (t, $J=7.1$ Hz, 3H, -OCH_2CH_3), 1.50 (dd, $J=16.0$ and 2.2 Hz, 1H, 2-H pseudoaxial), 1.59 (td, $J=16.5$ and 2.2 Hz, 1H, 6-H pseudoaxial), 1.80 and 1.87 (two dd, $J=15.6$ and 7.8 Hz, 2H, -$CH_2CH_2CO_2$-), 2.11 (ddd, $J=16.0$, 8.8 and 1.7, 1H, 2-H pseudoequatorial), 2.27 (ddd, $J=16.5$, 8.8 and 1.7 Hz, 1H, 6-H pseudoequatorial), 2.33 (m, like t, $J=7.8$ Hz, 2H, -CH_2CO_2-), 2.82 (m, 1H, 5-H), 4.10 (q, $J=7.1$ Hz, -OCH_2CH_3); ^{13}C NMR: δ 13.84 (q, C-10), 14.04 (q, C-7), 14.47 (d, C-1), 15.56 (s, C-8), 15.97 (d, C-9), 18.94 (t, C-2), 21.33 (t, C-6), 27.62 (q, -OCH_2CH_3), 29.39 (t, -$CH_2CH_2CO_2$-), 31.59 (t, -CH_2CO_2-), 56.94 (s, C-3), 57.41 (d, C-4), 60.35 (t, -OCH_2CH_3), 173.02 (s, -CH_2CO_2-). Anal. calcd for $C_{14}H_{22}O_3$ (238.33): C, 70.59; H, 9.31. Found: C, 70.64; H, 9.26%.

3.3. (+)-(1*S*,3*R*,4*R*,6*R*)-4-Hydroxy-7,7-dimethyldihydro-5′*H*-spiro[bicyclo[4.1.0]heptane-3,2′-furan]-5′-one, 5

The epoxy ester **4** (0.50 g, 2.1 mmol) was added to a mixture of tetrahydrofuran (10 mL), water (5 mL) and perchloric acid (5 drops), the pH of this mixture was 1.0. The reaction mixture was stirred at room temperature for 7 h until the epoxy ester was reacted completely (TLC). Then the mixture was poured into water and the product was extracted with diethyl ether. Ethereal solution was washed with saturated $MaHCO_3$, brine, dried ($MgSO_4$) and solvent was evaporated. The crude product was purified by column chromatography (silica gel, eluent: hexane:isopropanol:acetone:ethyl acetate 60:3:1:1). After crystallization from hexane pure hydroxy lactone **5** was obtained (0.41 g, 92%): mp 113–115°C; $[\alpha]_D^{26}=+16.6$ (*c* 10.6, $CHCl_3$); IR (KBr, cm^{-1}): 3401 (s), 2937 (s), 1756 (s), 1451 (w), 1417 (w), 1217 (w); ^1H NMR: δ 0.70–0.74 (two m, 2H, 1- and 6-H), 0.98 and 0.99 (two s, 6H, 8- and 9-CH_3), 1.47 (dd, $J=14.2$ and 3.7 Hz, 1H, 2-H_A), 1.61 (s, 1H, -OH), 1.74 (m, 1H, 5-H_B), 1.96–2.19 (m, 3H, 3′-CH_2, 2-H_B), 2.40 (ddd, $J=12.7$, 10.0 and 9.0 Hz, 1H, 5-H_A), 2.62 (m, 2H, 4′-CH_2), 3.69 (dd, $J=10.0$ and 7.5 Hz, 1H, 4-H); ^{13}C NMR: δ 15.52 (q, C-9), 17.69 (s, C-7), 18.51 (d, C-1), 20.42 (d, C-6), 23.91 (t, C-2), 26.83 (t, C-5), 28.39 (q, C-8), 28.93 (t, C-3′), 30.22 (t, C-4′), 70.93 (d, C-4), 89.04 (s, C-3), 177 (s, C-5′). Anal. calcd for $C_{12}H_{18}O_3$ (210.27): C, 68.55; H, 8.63. Found: C, 68.31; H, 8.76%. Crystal data: $C_{12}H_{18}O_3$, $M_w=210.27$, $T=100$ K, Cu Kα radiation, orthorhombic, space group $P2_12_12_1$, $a=6.4559(4)$, $b=11.1394(7)$, $c=30.505(2)$ Å, $V=2193.8(2)$ $Å^3$, $Z=4$, $D_{calcd}=1.273\,Mg/m^3$, $\mu=0.090\,mm^{-1}$, $F(000)=912$, crystal size 0.25×0.15×0.15, diffractometer Kuma KM4CCD, $3.65\leq\theta\leq28.81$, 15877 reflections collected, 5353 independent reflections with $I>2\sigma(I)$, 415 parameters.

3.4. (+)-(1*S*,3*R*,4*R*,6*R*)-7,7-Dimethyl-5′-oxodihydro-3′*H*-spiro[bicyclo[4.1.0]heptane-3,2′-furan]-4-yl acetate, 6

The hydroxy lactone **5** (0.13 g, 0.62 mmol) was added to the stirred solution of acetyl chloride (70 μL, 0.9 mmol) and pyridine (0.075 mL, 0.93 mmol). When the reaction was complete (TLC) diethyl ether was added and mixture was washed with 10% HCl solution. The ethereal layer was separated and aqueous layer was additionally extracted with diethyl ether. The combined ethereal extract was washed with 2% H_2SO_4 solution, saturated $NaHCO_3$ solution, brine and dried ($MgSO_4$). After evaporation of solvent the crude product was crystallized from hexane giving pure acetoxy lactone **6** (0.15 g, 94%): mp 80–81°C; $[\alpha]_D^{26}=+14.8$ (*c* 3.7, $CHCl_3$); IR (KBr, cm^{-1}): 2943 (s), 1772 (vs), 1730 (vs), 1456 (w), 1380 (w), 1245 (s), 1178 (s); ^1H NMR ($CDCl_3$): δ 0.73 (m, 2H, 1- and 6-H), 1.00 and 1.03 (two s, 6H, 8- and 9-CH_3), 1.64 (dd, $J=14.7$ and 4.6 Hz, 1H, 2-H_A), 1.80 (ddd, $J=14.6$, 9.6 and 8.4 Hz, 1H, 5-H_B), 2.01 (s, 3H, -C(O)CH_3), 2.11 (m, 2H, 3′-CH_2), 2.33 (dd, $J=14.7$ and 7.9 Hz, 2-H_B), 2.45 (ddd, $J=16.3$, 10.0 and 6.3 Hz, 1H, one of 4′-CH_2), 2.59–2.72 (two m, 2H, 5-H_B and one of 4′-CH_2), 4.78 (dd, $J=9.6$ and 7.5 Hz, 1H, 4-H); ^{13}C NMR: δ 15.57 (q, C-9), 17.74 (s, C-7), 18.06 (d, C-1), 19.98 (d, C-6), 20.95 (q, C-11), 25.24 (t, C-2), 25.88 (t, C-5), 28.08 (q, C-8), 28.82 (t, C-3′), 31.18 (t, C-4′), 74.01 (d, C-4), 85.71 (s, C-3), 169.73 (s, C-10), 176.34 (s, C-5′). Anal. calcd for $C_{14}H_{20}O_4$ (252.31): C, 66.66; H, 7.99. Found: C, 66.52; H, 8.07%.

3.5. (+)-3-[(1*S*,6*R*)-7,7-Dimethylbicyclo[4.1.0]hept-3-en-3-yl]propanoic acid, 7

Ester **3** (2.22 g, 10.0 mmol) was dissolved in solution of KOH (0.79 g, 14.0 mmol) in ethanol (60 mL) and the reaction mixture was heated under reflux for 3 h. The mixture was concentrated in vacuo and the residue was diluted with water. Organic impurities were extracted with diethyl ether. The aqueous solution was acidified with 0.01 M HCl and the product was extracted with diethyl ether. The extract was washed with brine, dried ($MgSO_4$) and evaporated in vacuo to give acid **7** (1.65 g, 85%) as an oil: $[\alpha]_D^{26}=+23.6$ (*c* 3.4, $CHCl_3$); IR (film, cm^{-1}): 2999 (s, br), 1711 (s), 1431 (s), 1375 (w); ^1H NMR ($CDCl_3$): δ 0.55 and 0.63 (two m, 2H, 1-H and 6-H), 0.70 and 0.98 (two s, 6H, 8- and 9-CH_3), 1.83–2.40 (m, 8H, 2-,5-,10-,11-CH_2), 5.24 (m, 1H, 4-CH), 10.0 (s, 1H, -COOH); ^{13}C NMR: δ 13.17 (q, C-9), 16.81 (d, C-1), 16.82 (s, C-7), 18.18 (d, C-6), 20.72 (t, C-2), 23.01 (t, C-5), 28.27 (q, C-8), 32.29 (t, C-10), 32.69 (t, C-11), 120.37 (d, C-4), 133.25 (s, C-3), 180.05 (s, C-12). Anal. calcd for $C_{12}H_{18}O_2$ (194.27): C, 74.19; H, 9.34. Found: C, 74.04; H, 9.42%.

3.6. (–)-(1*S*,3*R*,4*R*,6*R*)-4-Iodo-7,7-dimethyldihydro-5′*H*-spiro[bicyclo[4.1.0]heptane-3,2′-furan]-5′-one, 8

Aqueous $NaHCO_3$ solution (25 mL, 0.5 M) was added to acid **7** (1.25 g, 6.4 mmol) dissolved in diethyl ether (25 mL). The mixture was stirred at room temperature for 30 min and then a solution of KI (5.12 g) and I_2 (2.56 g.) in water (30 mL) was gradually added. The mixture was stirred overnight, then diluted with diethyl ether and washed with $Na_2S_2O_3$ solution. The organic layer was washed with saturated solution of $NaHCO_3$, brine and dried ($MgSO_4$). A solvent was evaporated in vacuo to give crude iodolactone (2.0 g). Crystallization from hexane gave pure product **8** (1.35 g, 65%): mp 86–88°C; $[\alpha]_D^{26}=-76.5$ (*c* 2.9, $CHCl_3$); IR (KBr, cm^{-1}): 2935 (w), 1772 (s),

1456 (w), 1189 (s); ^{1}H NMR ($CDCl_3$): δ 0.62 (ddd, $J=9.9$, 9.2 and 1.7 Hz, 1H, 6-H), 0.87 (td, $J=9.6$ and 4.2 Hz, 1H, 1-H), 1.00 and 1.01 (two s, 6H, 9- and 8-CH_3), 1.71 (dd, $J=14.8$ and 4.2 Hz, 1H, 2-H_A), 2.17–2.75 (m, 7H, 5-CH_2, 4′-CH_2, 3′-CH_2 and 2-H_B), 4.29 (dd, $J=10.9$ and 7.1 Hz, 1H, 4-H); ^{13}C NMR: δ 15.17 (q, C-9), 18.05 (s, C-7), 18.93 (d, C-1), 21.90 (t, C-6), 28.50 (q, C-8), 28.64 (t, C-2), 29.10 (t, C-5), 30.03 (t, C-3′), 32.94 (t, C-4′), 38.23 (d, C-4), 85.19 (s, C-3), 175.53 (s, C-5′). Anal. calcd for $C_{12}H_{17}IO_2$ (320.16): C, 45.02; H, 5.35; I, 39.64. Found: C, 44.96; H, 5.49; I, 39.57%. Crystal data: $C_{12}H_{17}IO_2$, $M_w=320.16$, $T=100$ K, Cu Kα radiation, monoclinic, space group $P2_1$, $a=6.7021(6)$, $b=12.2150(9)$, $c=30.297(3)$ Å, $\alpha=90$, $\beta=93.904(8)$, $\gamma=90°$, $V=2474.5(4)$ Å^3, $Z=8$, $D_{calcd}=1.719$ Mg/m^3, $\mu=2.568$ mm^{-1}, $F(000)=1264$, crystal size 0.15×0.15×0.07, diffractometer Kuma KM4CCD, $3.05\leq\theta\leq28.66$, 17903 reflections collected, 11371 independent reflections $I>2\sigma(I)$, 550 parameters.

3.7. (−)-(1*S*,3*R*,4*R*,6*R*)-4-Bromo-7,7-dimethyldihydro-5′*H*-spiro[bicyclo[4.1.0]heptane-3,2′-furan]-5′-one, 9

To a solution of the ester (1.30 g, 5.9 mmol) in mixture of tetrahydrofuran (21 mL) and water (9 mL) *N*-bromosuccinimide (1.50 g, 8.4 mmol) was added. The mixture was stirred overnight at room temperature. The reaction was diluted with diethyl ether and washed with aqueous solution $NaHCO_3$ and water. Crude product was purified by column chromatography (silica gel, hexane/isopropanol/acetone/ethyl acetate, 60:3:1:1 to give, after crystallization from hexane, pure bromolactone **9** (1.36 g, 71%): mp 81–82°C; $[\alpha]_D^{26}=-32.1$ (*c* 3.2, $CHCl_3$); IR (film, cm^{-1}): 3007 (w), 2946 (s), 1777 (s), 1449 (s), 1194 (s); ^{1}H NMR ($CDCl_3$): δ 0.70 (ddd, $J=9.3$, 7.3 and 2.1 Hz, 1H, 6-H), 0.82 (td, $J=9.3$ and 4.5 Hz, 1H, 1-H), 0.99 and 1.01 (two s, 6H, 9- and 8-CH_3), 1.64 (dd, $J=14.8$ and 4.5 Hz, 1H, 2-H_B), 2.14–2.76 (m, 7H, 3′-CH_2, 4′-CH_2, 5-CH_2 and 2-H_A), 4.12 (dd, $J=10.2$ and 7.3 Hz, 1H, 4-H); ^{13}C NMR: δ 14.33 (q, C-9), 16.92 (s, C-7), 17.52 (d, C-1), 20.22 (d, C-6), 25.92 (t, C-2), 27.34 (q, C-8), 27.34 (t, C-5), 29.82 (t, C-3′), 30.58 (t, C-4′), 56.12 (d, C-4), 84.52 (s, C-3), 174.76 (s, C-5′). Anal. calcd for $C_{12}H_{17}BrO_2$ (273.17): C, 52.76; H, 6.27; Br, 29.25. Found: C, 52.61; H, 6.34; Br, 29.20%. Crystal data: $C_{12}H_{17}BrO_2$, $M_w=273.17$, $T=100$ K, Cu Kα radiation, monoclinic, space group $P2_1$, $a=14.868(3)$, $b=6.4360(10)$, $c=19.309(4)$ Å, $\beta=104.94(3)°$, $V=1785.2(6)$ Å^3, $Z=2$, $D_{calcd}=1.525$ Mg/m^3, $\mu=3.433$ mm^{-1}, $F(000)=840$, crystal size 0.20×0.20×0.15, diffractometer Kuma KM4CCD, $3.53\leq\theta\leq28.71$, 12368 reflections collected, 8060 independent reflections $I>2\sigma(I)$, 412 parameters.

3.8. (+)-(1*S*,3*R*,6*R*)-7,7-Dimethyldihydro-5′*H*-spiro[bicyclo[4.1.0]heptane-3,2′-furan]-5′-one, 10

Tributyltin hydride (0.93 g, 0.86 mL, 3.2 mmol) was added to a solution of bromolactone **9** (0.32 g, 1.2 mmol) in dry toluene. The mixture was stirred for 72 h at room temperature until the bromolactone was reacted completely. Then solvent was removed and residue was purified by column chromatography (silica gel, hexane/acetone/isopropanol, 90:9:1) giving crystalline (from hexane) lactone **10** (0.16 g, 71%): mp 54–55°C; $[\alpha]_D^{26}=+18.9$ (*c* 1.3, $CHCl_3$); IR (KBr, cm^{-1}): 2946 (w), 1777 (s), 1449 (w), 1194 (s); ^{1}H NMR ($CDCl_3$): δ 0.51 (ddd, $J=9.3$, 7.5 and 1.8 Hz, 1H, 6-H), 0.72 (td, $J=9.3$ and 4.4 Hz, 1H, 1-H), 0.98 and 0.99 (two s, 6H, 9- and 8-CH_3), 1.41–2.20 (m, 8H, 2-CH_2, 4-CH_2, 5-CH_2, 3′-CH_2), 2.55 (m, 2H, 4′-CH_2); ^{13}C NMR: δ 14.84 (q, C-9), 17.60 (t, C-5), 17.64 (s, C-7), 17.77 (d, C-6), 19.06 (d, C-1), 28.46 (t, C-2), 28.83 (q, C-8), 29.79 (t, C-4), 30.99 (t, C-3′), 32.78 (t, C-4′), 86.38 (s, C-3), 176.67 (s, C-5′). Anal. calcd for $C_{12}H_{18}O_2$ (194.27): C, 74.19; H, 9.34. Found: C, 74.34; H, 9.25%.

In the same manner lactone **10** was obtained from iodolactone **8** in 70% yield.

3.9. (−)-(1*S*,3*R*,6*R*)-7,7-Dimethyldihydro-5′*H*-spiro[bicyclo[4.1.0]hept-4-ene-3,2′-furan]-5′-one, 11

DBU (0.46 g, 0.45 mL, 3.0 mmol) was added to the bromolactone **9** (0.48 g, 1.8 mmol) in 10 mL of dry toluene and the mixture was heated under reflux for 18 h. When the reaction was complete (TLC) the precipitate formed was filtered off. The filtrate was diluted with diethyl ether, washed (NH_4Cl, brine), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/isopropanol/acetone/ethyl acetate 60:30:1:1) to give unsaturated lactone **11** (0.25 g, 73%) as an oil, which crystallized after standing in a refrigerator: mp 51–56°C; $[\alpha]_D^{26}=-200.4$ (*c* 1.3, $CHCl_3$); IR (film, cm^{-1}): 3030 (w), 2940 (s), 1763 (s), 1461 (w), 1183 (s), 909 (m); ^{1}H NMR ($CDCl_3$): δ 0.95 (two m, 1H, 1- and 6-H), 0.96 and 1.05 (two s, 6H, 8- and 9-CH_3), 1.70 (dd, $J=11.0$ and 4.8 Hz, 1H, 2-H_A), 1.92–2.08 (two m, 2H, 2-H_B and one of 3′-CH_2), 2.24 (ddd, $J=13.0$, 8.6 and 4.8 Hz, one of 3′-CH_2), 2.52 (m, 2H, 4′-CH_2), 5.67 (dm, $J=9.8$ Hz), 1H, 5-H), 5.79 (d, $J=9.8$ Hz, 1H, 4-H); ^{13}C NMR: δ 14.96 (q, C-9), 19.54 (d, C-1), 22.36 (d, C-6), 26.68 (s, C-7), 27.59 (q, C-8), 28.65 (t, C-2), 31.24 (t, C-3′), 34.44 (t, C-4′), 84.86 (s, C-3), 127.61 (d, C-5), 133.80 (d, C-4), 176.92 (s, C-5′). Anal. calcd for $C_{12}H_{16}O_2$ (192.26): C, 74.97; H, 8.39. Found: C, 74.85; H, 8.47%.

This lactone was also obtained from iodolactone **8** in 67% yield in the same way.

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