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Stereochemistry of terpene derivatives. Part 5: Synthesis of chiral lactones fused to a carane system—insect feeding deterrents☆

Bożena Frąckowiak,[a] Katarzyna Ochalik,[a] Agata Białońska,[b] Zbigniew Ciunik,[b] Czesław Wawrzeńczyk[c] and Stanisław Lochyński[a,*]

[a]*Department of Bioorganic Chemistry, Faculty of Chemistry, Wrocław University of Technology, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, Poland*
[b]*Faculty of Chemistry, University of Wrocław, F. Joliot-Curie 14, 50-383 Wrocław, Poland*
[c]*Department of Chemistry, Agricultural University, Norwida 25, 50-375 Wrocław, Poland*

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Dedicated to Professor Prezemysław Mastalerz on his 80th birthday

Abstract—Chiral iodo- **9**, bromo- **10** and hydroxylactones **12** condensed with the carane system were obtained. In each case, the synthetic pathway led to an enantiomerically pure diastereoisomer to generate two stereogenic centers. Iodo- **9** and bromolactone **10** possess a γ-lactone group while the hydroxylactone **12** possesses a δ-lactone moiety situated trans to the *gem*-dimethylcyclopropyl ring. The structures of the products were confirmed by X-ray crystallography. These lactones were tested for antifeedant activity against storage pest insects.

1. Introduction

(+)-3-Carene **1**, which belongs to the 'chiral pool', is a valuable substrate in the syntheses of optically active compounds. Easily obtained derivatives of this monoterpene have been used as chiral auxiliaries in enantioselective transformations.[2a] Organoborane reagents obtained from (+)-3-carene were used in the enantioselective allylboration of aldehydes.[2b] The enantioselective addition of diethylzinc to aldehydes was catalyzed by an amino alcohol derivative of carane.[2c] The same chiral auxiliary was used in the addition of lithium cyclopropylacetylide to ketimine to give the chiral HIV-1 non-nucleoside reverse transcriptase inhibitor DPC963.[2d] (+)-3-Carene was also used as a starting material in the synthesis of natural products, for example, artemisin[3a] or pyrethroic acids.[3b] This monoterpene was also a substrate in the synthesis of chiral, biologically active products in which the carane moiety is preserved, such as β-amino acids[4a] and sulfides.[4b]

We were interested in an investigation of the structure–activity correlation for sesquiterpenoid lactones with antifeedant activity. Many such derivatives have already been synthesized using monoterpenes as starting materials.[5] We have used (+)-3-carene as a substrate for optically active lactones. The presence of a double bond and the easy introduction of a hydroxy group into the molecule of this monoterpene make it a convenient starting material for the synthesis of lactones. Previously, we obtained a series of spirolactones from (+)-3-carene.[6] Herein, we report the synthesis of chiral lactones fused to a carane system.

2. Results and discussion

The key compound in the synthesis of lactones is allylic alcohol **5**, which was obtained in a four-step procedure from (+)-3-carene (Scheme 1).[7a] In a reaction of this compound with *m*-chloroperbenzoic acid, *trans*-3,4-epoxycarane **2** was obtained. Next, the ring opening of epoxide **2** with diethylaluminum tetramethylpiperidine provided allylic alcohol **3** as the only product. The synthesis of compound **3** was broadly investigated earlier.[7a–d] We chose the most efficient strategy (above

☆ See Ref. 1.
* Corresponding author. Tel.: +48 71 320 2400; fax: +48 71 347 7175; e-mail: stanislaw.lochynski@pwr.wroc.pl

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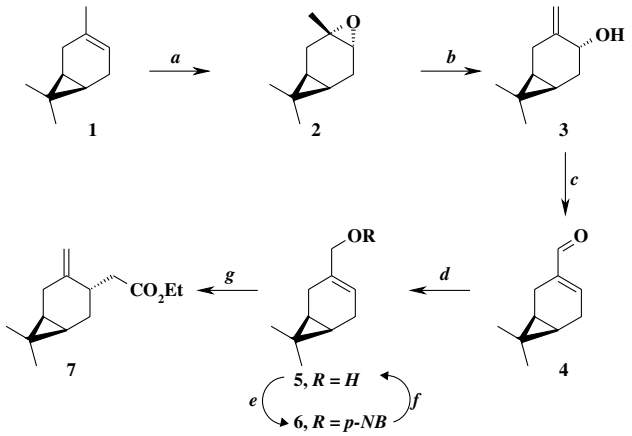


Scheme 1. Reagents: (a) *m*-CPBA, CH_2Cl_2; (b)  , benzene; (c) $Na_2Cr_2O_7$, H_2SO_4; (d) $NaBH_4$; (e) *p*-$NO_2PhCOCl$, Py; (f) KOH, MeOH; (g) $CH_3C(OC_2H_5)_3$, C_2H_5COOH.

90% yield from **1**).[7a] Other methods, such as the isomerization of **2** with aluminum isopropoxide give a mixture of products containing predominantly **3**.[7d]

Compound **3** was converted into aldehyde **4** with chromic acid, as reported by Gollnick and Schade[7b] and by Paquette et al.[7a] This reaction afforded product **4** in good yield only, when substrate **3** was pure (above 99%). The specific rotation of our sample of **4** (−47.6) was different from those reported in the literature (−25.8)[7b] and (−131).[7a] The ^1H NMR spectrum of aldehyde **4** obtained was identical to that previously reported.[7a]

The reduction of aldehyde **4** with sodium borohydride gave allylic alcohol **5** (yield 72% from (+)-3-carene). This alcohol was converted into *p*-nitrobenzoate **6**, which was purified by column chromatography and then hydrolyzed back to **5**. Next, γ,δ-unsaturated ester **7** was obtained from **5** in the Claisen rearrangement (Johnson modification)[8] (Scheme 1). Due to the steric hindrance created by the *gem*-dimethylcyclopropyl group in alcohol **5** only one diastereoisomer of ester **7** was formed in this reaction. In the crystal of **8**, the configuration of the stereogenic center at the C-4 carbon atom was assigned on the basis of the known configuration at the C-1 and C-6 atoms of this unsaturated carboxylic acid (Fig. 1), obtained after hydrolysis of ester **7** (Scheme 2).

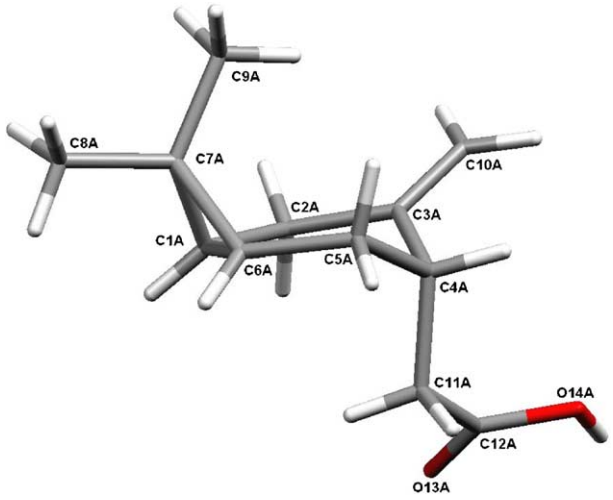
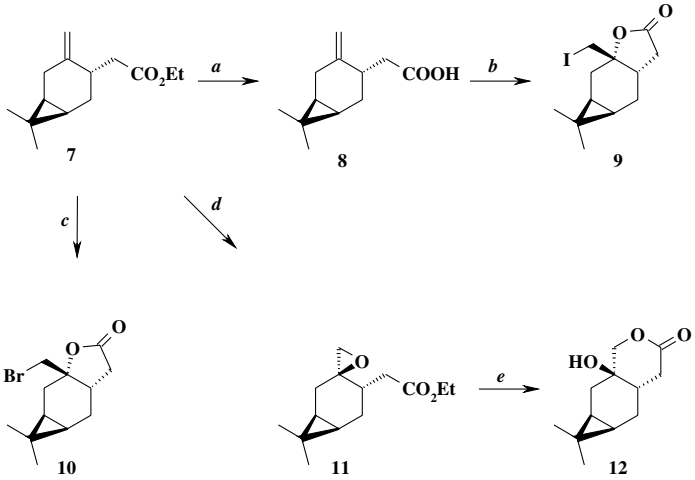


Figure 1. Molecular structure of **8**.

Iodolactonization[9] of the γ,δ-unsaturated acid **8** afforded the tricyclic product **9**, in which the lactone ring is condensed with the carane skeleton. The other halolactone–bromolactone **10** was formed in a reaction of ester **7** with *N*-bromosuccinimide in a water/tetrahydrofuran solution. In all these reactions, γ-lactones **9** and **10** were obtained as single diastereoisomers. The lactone moiety in both compounds **9** and **10** is situated in the trans position to the *gem*-dimethylcyclopropyl group. The trans orientation of the lactone ring in these molecules was confirmed by X-ray crystallographic analysis (Figs. 2 and 3).

Epoxy ester **11** was obtained by oxidation of the γ,δ-unsaturated ester **7** with *m*-chloroperbenzoic acid



Scheme 2. Reagents: (a) KOH, EtOH; (b) I_2, KI, $NaHCO_3$; (c) NBS, THF; (d) *m*-CPBA; (e) $HClO_4$, H_2O–THF.

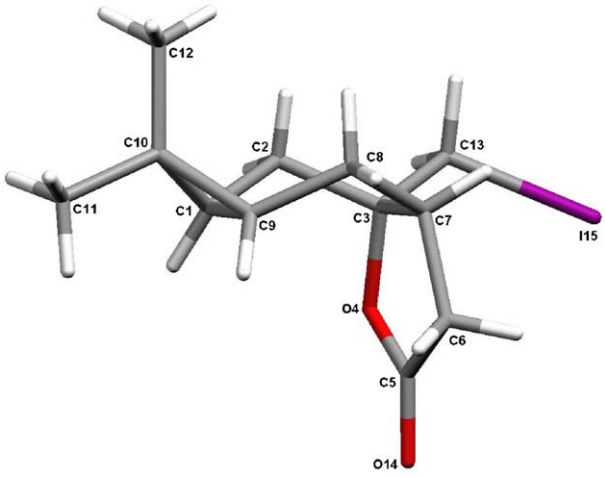


Figure 2. Molecular structure of **9**.

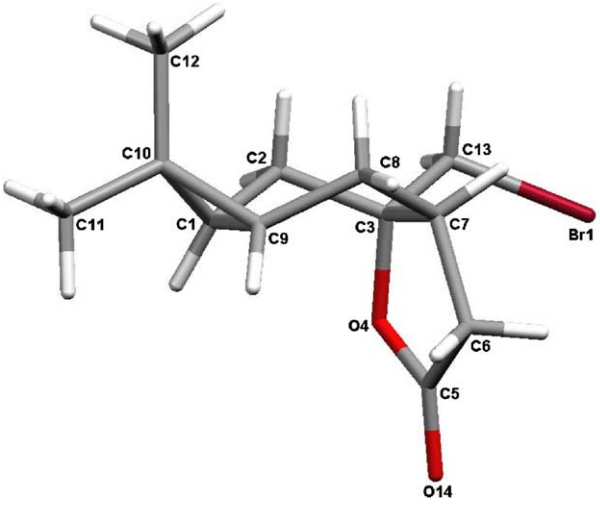


Figure 3. Molecular structure of **10**.

(Scheme 2). Next, hydroxylactone **12** was synthesized by the acidic lactonization of **11**. The IR spectrum of **12** (1740 cm^{-1}) confirmed that the δ-lactone ring was formed. The structure of this compound was determined by X-ray analysis (Fig. 4) served us as a basis for the assignment of the configuration of **11**. According to the mechanism of the hydroxylactonization,[10a,b] the *cis*-hydroxy- *trans*-δ-lactone **12** can only be obtained from **11**, in which the oxirane ring is in the cis position to the *gem*-dimethylcyclopropane ring.

Lactones **9**, **10** and **12** were tested for feeding deterrent activity against three storage pest insects: the grain weevil (*Sitophilus granaries*, adults), the confused flour beetle (*Trogoderma granarium*, larvae) and the khapra beetle (*Tribolium confusum*, larvae and adults). All compounds tested exhibited low or moderate activity towards these pests. The total coefficients of deterrence (T) determined by means as described earlier[5] reach values that fall between 7.5 and 120.9. For comparison, the coefficient for the most potent antifidant, azadirachtin determined in the same manner reaches a value of

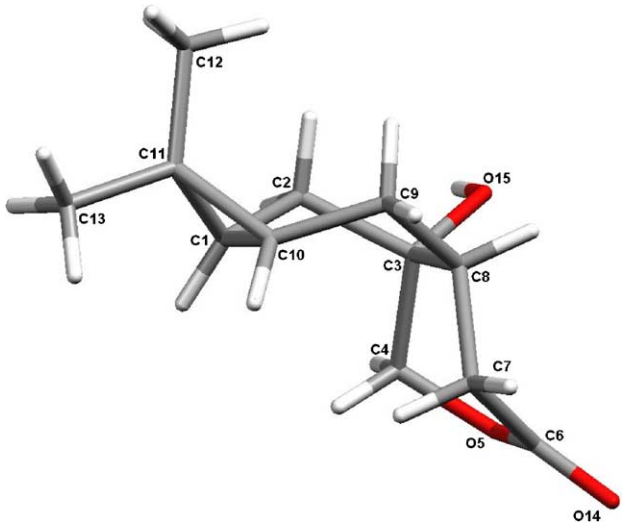


Figure 4. Molecular structure of **12**.

almost 200.[5] These tests demonstrated the influence of the additional groups on the biological activity. Bromolactone **10** was the most active compound against all three species, displaying the highest deterrence for *Trogoderma granarium* ($T = 120.9$). Replacement of the bromine atom with iodine (compound **9**) lowered the activity ($T = 7.5$).

3. Experimental

(+)-3-Carene was purchased from Sigma–Aldrich. The course of all the reactions, composition of products, and their purities were checked by thin-layer chromatography (TLC) and gas chromatography (GC). TLC was carried out on silica gel DC-Alufolien Kieselgel 60 (Merck). Plates were developed in a mixture of hexane, diethyl ether and acetone in various ratios and visualized with 20% ethanolic H_2SO_4, containing 0.1% of anisaldehyde. Preparative column chromatography was carried out on silica gel (230–400 mesh, Merck) with a mixture of hexane, diethyl ether, ethyl acetate and acetone (various ratios) as eluent. Analytical GC was performed on a Hewlett Packard 5890 (seria II) instrument using the capillary column HP-5 (length 25 m, temperature 120–180 °C). Melting points (uncorrected) were determined on a Boetius apparatus. IR spectra were taken from liquid films or in KBr on a Perkin–Elmer 621 spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as an internal standard on a Bruker Avance™ DRX 300 instrument. Chemical shifts (δ) are reported in ppm and coupling constants (J) are given in Hz. ^{13}C–H substitution was determined with a DEPT-135 experiments. Optical rotation measurements were obtained on an Autopol IV automatic polarimeter (Rudolph). X-ray data were collected at 100 K using an Oxford Cryosystem device on a Kuma KM4CCD κ-axis diffractometer with graphite-monochromated MoKα radiation. The data were corrected for Lorentz and polarization effects. Absorption correction was applied for the data of **9** and **10**. Data reduc-

tion and analysis were carried out with the Oxford Diffraction (Wrocław) programs.[11] The structures were solved by direct methods and refined by the full-matrix least-squares method on all F^2 data using programs.[12] Non-hydrogen atoms were refined with anisotropic thermal parameters; all H atoms were found in $\Delta\rho$ maps or placed in calculated positions. Before the last cycle of refinement all H atoms were fixed and were allowed to ride on their parent atoms. Crystallographic data for structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as a supplementary publication numbers.

3.1. Synthesis of (+)-3-caren-10-al 4

Aldehyde **4** was synthesized according to a known procedure.[7a] The crude product was purified by column chromatography (silica gel, hexane–ethyl acetate 30:1) to give **4** as an oil: $[\alpha]_D^{20} = -27.6$ (*c* 1.2, $CHCl_3$); $[\alpha]_D^{20} = -47.6$ (*c* 0.61, benzene); Lit.[7a]: $[\alpha]_D^{20} = -131.0$ (*c* 2.1, benzene); Lit.[7b]: $[\alpha]_D^{20} = -25.8$ (*c* 2.3, benzene); IR (film, cm^{-1}): 2941(vs), 2732(m), 2708(m), 1683(vs), 1420(s), 1170(vs), 744(m); ^1H NMR ($CDCl_3$): 0.69 and 1.07 (2 s, 6H: 3H at C-8 and 3H at C-9); 0.76–0.87 (m, 2H: 1H at C-6 and 1H at C-1); 2.12–2.36 (m, 2H: 1H at C-5 and 1H at C-2); 2.44–2.54 (m, 1H at C-2); 2.65–2.76 (m, 1H at C-5); 6.67–6.72 (m, 1H at C-4); 9.40 (s, 1H at C-10).

3.2. Synthesis of (+)-3-caren-10-ol 5

Sodium borohydride (0.43 g, 11.37 mmol) in ethyl alcohol (22.00 ml) was added in portions to a solution of aldehyde **4** (4.31 g, 28.73 mmol) in ethyl alcohol (65 ml). The mixture was stirred until TLC monitoring showed the absence of substrate **4** (about 1 h). Then, saturated $NaHCO_3$ solution was added and ethyl alcohol removed on a rotary evaporator. The water layer was extracted three times with diethyl ether. The combined organic layers were dried over $MgSO_4$ and the crude product converted to *p*-nitrobenzoate **6**. After purification (the procedure and spectroscopic data described below), the pure product **6** (5.71 g, 18.96 mmol) was diluted in methanol (45 ml) and potassium hydroxide (22.75 mmol) added. The reaction mixture was stirred overnight and after TLC analysis did not show the presence of *p*-nitrobenzoate **6**, the solvent was removed. Next, water was added and the aqueous phase extracted three times with diethyl ether and the organic phase dried over $MgSO_4$. After removing the solvent, alcohol **5** was obtained (2.84 g, 18.67 mmol, 65% yield) as an oil 95% purity (GC). $[\alpha]_D^{20} = +7.1$ (*c* 1.1, $CHCl_3$); IR (film, cm^{-1}): 3330(bs), 2866(s), 1681(w), 1430(s), 1034(m), 1000(s); ^1H NMR ($CDCl_3$): 0.67 (t, $J = 8.3$ Hz, 1H at C-6); 0.72–0.80 (m, 1H at C-1); 0.76 (s, 3H at C-8 or C-9); 1.04 (s, 3H at C-8 or C-9); 1.56 (s, 1H at –OH); 1.90–2.03 (m, 2H at C-2); 2.27–2.50 (m, 2H at C-5); 3.96 (s, 2H at C-10); 5.46–5.67 (m, 1H at C-4); ^{13}C NMR ($CDCl_3$): 13.33 (C-8 or C-9), 16.97 (C-7), 17.10 (C-6), 17.86 (C-1), 20.51 (C-5), 20.54 (C-2), 28.33 (C-8 or C-9), 67.85 (C-10), 121.83 (C-4), 135.36 (C-3). Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.96; H, 10.50.

3.3. Synthesis of (−)-3-carene-10-yl *p*-nitrobenzoate 6

Alcohol **5** (3.06 g, 20.11 mmol) was dissolved in anhydrous pyridine (12.2 ml). *p*-Nitrobenzoic chloride 4.27 g (22.85 mmol) was added to the solution in portions and the mixture stirred overnight. Next, the reaction was warmed up to 60 °C and stirred for 2 more hours. After this time, the mixture was diluted with water (60 ml), saturated $NaHCO_3$ solution (21 ml) was added and the product was extracted with diethyl ether. The combined organic layers were washed with a 5% H_2SO_4 solution, then with water and dried over $MgSO_4$. Crude product **6** was purified by column chromatography (eluent: hexane–ethyl acetate 30:1) to give pure compound **6** (5.71 g, 18.96 mmol) $[\alpha]_D^{20} = -2.9$ (*c* 1.2, $CHCl_3$); IR (film, cm^{-1}): 3112(w), 2900(s), 1725(vs), 1607(s), 1529(vs), 1346(vs), 1271(v), 873(s), 719(vs); ^1H NMR ($CDCl_3$): 0.70 (t, $J = 8.3$ Hz, 1H at C-6); 0.75–0.90 (m, 1H at C-1); 0.79 (s, 3H at C-8 or C-9); 1.05 (s, 3H at C-8 or C-9); 1.93–2.17 (m, 2H at C-2); 2.27–2.51 (m, 2H at C-5); 4.72 (s, 2H at C-10); 5.71–5.80 (m, 1H at C-4); 8.24 (m, 4H at C-13, C-14, C-16 and C-17); ^{13}C NMR ($CDCl_3$): 13.27 (C-8 or C-9), 16.91 (C-6), 17.14 (C-7), 17.78 (C-1), 20.78 (C-5), 21.09 (C-2), 28.29 (C-8 or C-9), 70.39 (C-10), 123.56 (C-4), 126.23 (C-14 and C-16), 130.23 (C-12), 130.70 (C-13 and C-17), 135.86 (C-3), 150.56 (C-15), 164.57 (C-11). Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.83; H, 6.32; N, 4.61.

3.4. Synthesis of ethyl [(−)-3(10)-carene-*trans*-4-yl]-acetate 7

A mixture of alcohol **5** (2.5 g, 16.44 mmol), triethyl orthoacetate (15 ml, 82.20 mmol) and propionic acid (one drop) was heated at 138 °C until TLC analysis did not show the presence of substrate **5**. The unreacted orthoacetate was then distilled off and the crude product **7** purified by column chromatography (eluent: hexane–diethyl ether from 100:1 to 50:1) to give pure product **7** (3.21 g, 14.47 mmol, 88% yield): $[\alpha]_D^{20} = -54.2$ (*c* 1.2, $CHCl_3$); $n_D^{20} = 1.4701$; IR (film, cm^{-1}): 3040(m) 2934(m), 1737(vs), 1252(m), 1156(m), 887(m); ^1H NMR ($CDCl_3$): 0.64 (td, $J = 9.2$, 4.4 Hz, 1H at C-6); 0.74 (t, $J = 8.2$ Hz, 1H at C-1); 0.90 and 0.99 (2 s, 6H: 3H at C-8 and 3H at C-9); 1.25 (t, $J = 7.1$ Hz, 3H at C-14); 1.52 (dt, $J = 14.6$, 4.5 Hz, 1H at C-5); 1.94 (ddd, $J = 14.6$, 9.5, 2.4 Hz, 1H at C-5); 2.24 (d, $J = 16.8$ Hz, 1H at C-2); 2.43–2.52 (m, 2H at C-11); 2.53–2.66 (m, 2H: 1H at C-2 and 1H at C-4); 4.12 (q, $J = 7.1$ Hz, 2H at C-13); 4.63–4.70 (m, 2H at C-10); ^{13}C NMR ($CDCl_3$): 14.29 (C-8 or C-9), 14.57 (C-14), 16.26 (C-6), 18.21 (C-7), 20.64 (C-1), 25.42 (C-5), 25.96 (C-2), 28.68 (C-8 or C-9), 38.13 (C-11), 38.58 (C-4), 60.12 (C-13), 108.39 (C-10), 149.54 (C-3), 172.79 (C-12). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.76; H, 9.84.

3.5. Synthesis of [(−)-3(10)-Caren-*trans*-4-yl]acetic acid 8

Ester **7** (0.60 g, 2.7 mmol) was diluted in ethyl alcohol (20 ml) after which potassium hydroxide (0.22 g, 3.8 mmol) was added. Next, the reaction was warmed

up to 70 °C and stirred until TLC analysis did not show the presence of substrate **7** (3 h) and the solvent removed. Water was then added and the organic impurities extracted with diethyl ether. The aqueous solution was acidified to pH about 4–5 by the addition of 0.01 M HCl and extracted three times with diethyl ether. The organic phase was washed with brine and dried over $MgSO_4$. After removing of the solvent, the crude product **8** was obtained (0.37 g, 1.9 mmol, 72% yield): mp = 57–59 °C; $[\alpha]_D^{20} = -55.4$ (*c* 2.0, $CHCl_3$); IR (KBr, cm^{-1}): 3080(w), 2960(m), 1696(s), 1431(m), 1260(s), 801(m); ^1H NMR ($CDCl_3$): 0.65 (td, $J = 9.2$, 4.4 Hz, 1H at C-6); 0.76 (t, $J = 8.4$ Hz, 1H at C-1); 0.91 and 1.00 (2 s, 6H: 3H at C-8 and 3H at C-9); 1.26 (s, 1H from –OH); 1.54 (dt, $J = 4.7$, 4.3 Hz, 1H at C-5); 1.99 (dd, $J = 9.4$, 1.8 Hz, 1H at C-5); 2.26 (d, $J = 16.6$ Hz, 1H at C-2); 2.47–2.67 (m, 4H: 2H at C-11, 1H at C-2 and 1H at C-4); 4.86–4.76 (m, 2H at C-10); ^{13}C NMR ($CDCl_3$): 14.49 (C-8 or C-9), 16.22 (C-6), 18.27 (C-7), 20.60 (C-1), 25.42 (C-5), 25.94 (C-2), 28.68 (C-8 or C-9), 37.82 (C-11), 38.30 (C-4), 108.72 (C-10), 149.19 (C-3), 178.78 (C-12). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.05; H, 9.41. Crystal data: $C_{12}H_{18}O_2$, $M_w = 194.26$, $T = 100$ (2) K, Mo-K_α radiation, monoclinic, space group $P2_1$, $a = 13.518(3)$ Å, $b = 5.9290(12)$ Å, $c = 13.755(3)$ Å, $\beta = 91.50(3)°$, $V = 1102.1(4)$ Å^3, $Z = 4$, $D_c = 1.171$ Mg m^{-3}, $R = 0.066$, $wR = 0.110$ (1943 reflections, all data) for 253 parameters. CCDC 285888.

3.6. Synthesis of (1*S*,3*S*,7*S*,9*R*)-(+)-10,10-Dimethyl-3-iodomethyl-4-oxatricyclo[7.1.0.^{1,9}0^{3,7}]decan-5-one 9

The mixture of acid **8** (0.28 g, 1.4 mmol) in diethyl ether (6 ml) and 0.5 M solution of $NaHCO_3$ was stirred at room temperature for 30 min. Next, a solution of I_2 (0.58 g, 2.3 mmol) and KI (1.15 g, 6.9 mmol) in water (7 ml) was dropped. The mixture was stirred until TLC monitoring showed the absence of substrate **8** and diluted with diethyl ether. The organic phase was washed with $Na_2S_2O_3$ solution and saturated $NaHCO_3$ solution, brine and dried over $MgSO_4$. The crude product **9** was purified by column chromatography (eluent: hexane–acetone 5:1) to give iodolactone **9** as a white solid (0.36 g, 1.1 mmol, yield 78%); mp = 84–86 °C; $[\alpha]_D^{20} = +48.6$ (*c* 2.3, $CHCl_3$); IR (KBr, cm^{-1}): 2926(s), 1770(vs), 1410(m), 1167(s), 1410(w), 1168(m); ^1H NMR ($CDCl_3$): 0.65–0.80 (m, 1H at C-9); 0.95–1.30 (m, 3H: 2H at C-8 and 1H at C-1); 1.01 and 1.06 (2 s, 6H: 3H at C-11 and 3H at C-12); 1.82 (dd, $J = 14.5$, 6.0 Hz, 1H at C-2); 2.16 (dd, $J = 15.2$, 7.1 Hz, 1H at C-2); 2.45 (dd, $J = 18.4$, 4.7 Hz, 1H at C-6); 2.51–2.60 (m, 1H at C-7); 2.98 (dd, $J = 18.4$, 11.0 Hz, 1H at C-6); 3.27 and 3.43 (2 d, $J = 10.6$ Hz, 2H at C-13); ^{13}C NMR ($CDCl_3$): 14.68 (C-11 or C-12), 16.21 (C-8), 16.94 (C-9), 18.13 (C-1), 19.50 (C-10), 23.46 (C-2), 28.24 (C-11 or C-12), 28.61 (C-6), 35.97 (C-8), 37.02 (C-7), 85.65 (C-3). Anal. Calcd for $C_{12}H_{17}IO_2$: C, 45.02; H, 5.35; I, 39.64. Found: C, 44.95; H, 5.48; I, 39.57. Crystal data: $C_{12}H_{17}IO_2$, $M_w = 320.16$, $T = 100(2)$ K, Mo-K_α radiation, orthorhombic, space group $P2_12_12_1$, $a = 7.8214(2)$ Å, $b = 10.0159(3)$ Å, $c = 15.8284(5)$ Å, $V = 1239.97(6)$ Å^3, $Z = 4$, $D_c = 1.715$ Mg m^{-3}, $\mu = 2.563$ mm^{-1}, $R = 0.022$, $wR = 0.048$ (6240 reflections, all data) for 136 parameters. CCDC 285889.

3.7. Synthesis of (1*S*,3*S*,7*S*,9*R*)-(+)-3-bromomethyl-10,10-dimethyl-4-oxatricyclo[7.1.0.^{1,9}0^{3,7}]decan-5-one 10

Ester **7** (0.20 g, 0.9 mmol) was diluted in THF (14 ml) and water (6 ml) and *N*-bromosuccinimide (0.97 g, 5.43 mmol) then added. The mixture was stirred at the room temperature until TLC analysis did not show the presence of substrate **7**. The reaction mixture was then diluted with diethyl ether and washed with saturated $NaHCO_3$ solution, water and dried over $MgSO_4$. Crude product **10** was purified by column chromatography (eluent: hexane–acetone 5:1) to give bromolactone **10** as a white solid (0.21 g, 0.77 mmol, yield 85%): mp = 86–88 °C; $[\alpha]_D^{20} = +28.7$ (*c* 2.4, $CHCl_3$); IR (KBr, cm^{-1}): 2951(s), 1765(vs), 1411(m), 1164(s); ^1H NMR ($CDCl_3$): 0.66–0.81 (m, 1H at C-9); 0.95–1.15 (m, 3H: 2H at C-8 and 1H przy C-1); 1.01 and 1.06 (2 s, 6H: 3H at C-11 and 3H at C-12); 1.82 (dd, $J = 14.9$, 6.5 Hz, 1H at C-2); 2.13 (dd, $J = 15.2$, 7.0 Hz, 1H at C-2); 2.46 (dd, $J = 18.5$, 4.6 Hz, 1H at C-6); 2.62–2.70 (m, 1H at C-7); 2.98 (dd, $J = 18.5$, 11.2 Hz, 1H at C-6); 3.39 and 3.56 (2 d, $J = 10.8$ Hz, 2H at C-13); ^{13}C NMR ($CDCl_3$): 14.66 (C-11 or C-12), 16.80 (C-9), 17.47 (C-1), 19.19 (C-10), 23.23 (C-8), 27.62 (C-2), 28.20 (C-11 or C-12), 35.40 (C-7), 35.89 (C-13), 40.66 (C-6), 86.14 (C-3), 175.95 (C-5). Anal. Calcd for $C_{12}H_{17}BrO_2$: C, 52.76; H, 6.27; Br, 29.25. Found: C, 52.61; H, 6.34; Br, 29.20. Crystal data: $C_{12}H_{17}BrO_2$, $M_w = 273.17$, $T = 100(2)$ K, Mo-K_α radiation, orthorhombic, space group $P2_12_12_1$, $a = 7.1367(4)$ Å, $b = 9.8459(5)$ Å, $c = 17.2841(8)$ Å, $V = 1214.51(11)$ Å^3, $Z = 4$, $D_c = 1.494$ Mg m^{-3}, $\mu = 3.364$ mm^{-1}, $R = 0.038$, $wR = 0.070$ (3429 reflections, all data) for 136 parameters. CCDC 285890.

3.8. Synthesis of ethyl [(−)-*cis*-3,10-epoxy-*trans*-caran-*trans*-4-yl]acetate 11

m-Chloroperbenzoic acid (70%, 0.81 g, 3.6 mmol) in dry methylene chloride (17 ml) was dropped to the solution of ester **7** (0.80 g, 3.6 mmol) in dry methylene chloride (17 ml). When the reaction was complete (TLC, 1 h), the mixture was diluted with diethyl ether and the organic phase washed with 10% aqueous $Na_2S_2O_3$ solution, saturated $NaHCO_3$ solution, water and dried over $MgSO_4$. Crude product **10** was purified by column chromatography (eluent: hexane–ethyl acetate 15:1) to give epoxyester **11** (0.42 g, 1.8 mmol, yield 49%); $[\alpha]_D^{20} = -27.2$ (*c* 1.1, $CHCl_3$); IR (film, cm^{-1}): 2988(m), 2936(s), 1735(vs), 1259(m), 1160(s); ^1H NMR ($CDCl_3$): 0.66 (td, $J = 9.3$, 4.3 Hz, 1H at C-6); 0.89 (td, $J = 8.8$, 1.1 Hz, 1H at C-1); 0.95 and 1.01 (2 s, 6H: 3H at C-8 and 3H at C-9); 1.26 (t, $J = 7.1$ Hz, 3H at C-14); 1.37 (dd, $J = 15.2$, 0.7 Hz, 1H at C-2); 1.54–1.64 (m, 2H: 1H at C-2 and 1H at C-4); 2.04 (dd, $J = 11.8$, 9.5 Hz, 1H at C-5); 2.15 (ddd, $J = 15.1$, 8.5, 1.1 Hz, 1H at C-5); 2.48–2.53 (m, 3H: 2H at C-10 and 1H at C-11); 2.63 (dd, $J = 5.0$, 1.2 Hz, 1H at C-11); 4.13 (dd, $J = 14.3$, 7.1 Hz, 2H at C-13); ^{13}C NMR ($CDCl_3$):

14.23 (C-8 or C-9), 15.47 (C-14), 16.23 (C-6), 17.76 (C-7), 21.50 (C-1), 23.79 (C-5), 24.74 (C-2), 28.48 (C-8 or C-9), 34.45 (C-11), 36.09 (C-4), 57.39 (C-10), 60.32 (C-13), 172.84 (C-12), 204.50 (C-3). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.63; H, 9.25.

3.9. Synthesis of (1*S*,3*S*,8*S*,10*R*)-(+)-11,11-dimethyl-3-hydroxy-5-oxatricyclo[8.1.0.$^{1.10}$0$^{3.8}$]undecan-6-one 12

Epoxy ester **11** (0.40 g, 1.7 mmol) in THF (4 ml) was dropped into a mixture of tetrahydrofuran (4 ml), water (4 ml) and perchloric acid (four drops), pH of this mixture was 1.0. The reaction mixture was stirred at room temperature for 72 h. Product **12** was extracted with diethyl ether. After solvent evaporation the crude product **12** was chromatographed (eluent: hexane–acetone 4:1). Pure hydroxy lactone **12** was obtained (0.19 g, 54%): mp = 99–100 °C; $[\alpha]_D^{20} = +19.2$ (*c* 3.3, $CHCl_3$); IR (KBr, cm^{-1}): 3396(bw), 2932(w), 1740(m) 1459(w), 1051(m); ^{1}H NMR ($CDCl_3$): 0.53–0.66 (m, 1H at C-10); 1.04 (s, 6H: 3H at C-12 and 3H at C-13); 1.53–1.75 (m, 3H: 1H at C-9 and 2H at C-2); 1.82–2.10 (m, 3H: 1H at C-9, 1H at C-8 and 1H from –OH); 2.36 (dd, $J = 16.0$, 8.9 Hz, 1H at C-7); 2.64 (dd, $J = 16.0$, 5.7 Hz, 1H at C-7); 4.07(dd, $J = 12.1$, 1.1 Hz, 1H at C-4); 4.34 (d, $J = 12.1$ Hz, 1H at C-4); ^{13}C NMR ($CDCl_3$): 14.67 (C-12 or C-13), 18.02 (C-10), 19.40 (C-1), 23.96 (C-9), 28.48 (C-12 or C-13), 29.35 (C-2), 34.31 (C-7), 38.14 (C-8), 70.33 (C-3), 75.47 (C-4), 172.43 (C-6). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.32; H, 8.73. Crystal data: $C_{12}H_{18}O_3$, $M_w = 210.26$, $T = 100(2)$ K, Mo-K_α radiation, triclinic, space group *P*1, $a = 6.3234(19)$ Å, $b = 7.0852(14)$ Å, $c = 12.403(3)$ Å, $\alpha = 86.821(18)°$, $\beta = 85.69(2)°$, $\gamma = 84.77(2)°$, $V = 551.1(2)$ Å^3, $Z = 2$, $D_c = 1.267$ Mg m^{-3}, $R = 0.117$, $wR = 0.164$ (2107 reflections, all data) for 271 parameters. CCDC 285891.

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References

1. For part 4, see: Frąckowiak, B.; Olejniczak, T.; Latajka, R.; Białońska, A.; Ciunik, Z.; Lochyński, S. *Tetrahedron: Asymmetry*, in press.
2. (a) Blaser, H. U. *Chem. Rev.* **1992**, *92*, 935–952; (b) Brown, H. C.; Randad, R. S.; Bhat, K. S.; Zaidlewicz, M.; Racherla, U. S. *J. Am. Chem. Soc.* **1990**, *112*, 2389–2392; (c) Joshi, S. N.; Malhotra, S. V. *Tetrahedron: Asymmetry* **2003**, *14*, 1763–1766; (d) Kauffman, G. S.; Harris, G. D.; Dorow, R. L.; Stone, B. R. P.; Parsons, R. L.; Pesti, J. A.; Magnus, N. A.; Fortunak, J. M.; Confalone, P. N.; Nugent, W. A. *Org. Lett.* **2000**, *2*, 3119–3121.
3. (a) Yadav, J. S.; Satheesh Babu, R.; Sabitha, G. *Tetrahedron Lett.* **2003**, *44*, 387–389; (b) Krief, A. *Pestic. Sci.* **1994**, *41*, 237–257.
4. (a) Gyonfalvi, S.; Szakonyi, Z.; Fulop, F. *Tetrahedron: Asymmetry* **2003**, *14*, 3965–3972; (b) Startseva, V. A.; Nikitina, L. E.; Artemova, N. P.; Dieva, S. A.; Plemenkov, V. V. *Chem. Nat. Compd. (Engl.Transl.)* **2000**, *36*, 468–469.
5. Wawrzeńczyk, C.; Dams, I.; Szumny, A.; Szczepanik, M.; Nawrot, J.; Prądzyńska, A.; Gabryś, B.; Dancewicz, K.; Magnucka, E.; Gawdzik, B.; Obara, R.; Wzorek, A. *Pol. J. Environ. Stud. (Supl. III)* **2005**, *14*, 69–84, and references cited therein.
6. Lochyński, S.; Frąckowiak, B.; Olejniczak, T.; Ciunik, Z.; Wawrzeńczyk, C. *Tetrahedron: Asymmetry* **2002**, *13*, 1761–1767.
7. (a) Paquette, L. A.; Ross, R. J.; Shi, Y.-J. *J. Org. Chem.* **1990**, *55*, 1589–1598; (b) Gollnick, K.; Schroeter, S.; Ohloff, G.; Schade, G.; Schenck, G. O. *Chem. Ber.* **1965**, *687*, 14; (c) Lochyński, S.; Kowalska, K.; Wawrzeńczyk, C. *Flavour Frag. J.* **2002**, *27*, 181–186; (d) Lajunen, M.; Kujala, J. *Acta Chem. Scand.* **1989**, *43*, 813–815.
8. Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T. T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741–743.
9. Mori, K.; Nakazono, Y. *Tetrahedron* **1986**, *42*, 283–290.
10. (a) Bardili, B.; Marschall-Weyerstahl, H.; Weyerstahl, P. *Liebigs Ann. Chem.* **1985**, *275–300*; (b) Olejniczak, T.; Nawrot, J.; Ciunik, Z.; Wawrzeńczyk, C. *Pol. J. Chem.* **2000**, *74*, 673–680.
11. Oxford Diffraction, Poland Sp. z o.o., CrysAlis CCD and CrysAlis Red, V166, 2001.
12. Bruker AXS, SHELXTL V5.1, 1999.