Lactones, 3[◇]

Synthesis of Spirolactones from the Limonene System

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Four enantiomeric pairs of spirolactones were obtained in a four step synthesis from (+) and (–) limonene. The Claisen rearrangement and iodolactonization were the key steps of the syntheses presented. The structures of products were confirmed by X-ray crystallography of **11**, **18b**, and **19**.

Biological tests for the feeding deterrency of terpenoid lactones obtained earlier[1] showed that, in agreement with our expectation, they exhibit quite good activity towards selected insect storage pests (*Sitophilus granarius*, *Tribolium confusum*, and *Trogoderma granarium*)[2]. Total coefficients of deterrence against the species mentioned above, determined in tests according to a method described by Nawrot et al.,[3] reach values that fall between 140 and 150. In comparison, the coefficients for the most potent antifeedant, azadirachtin, determined in the same manner, range from 174 to 194.

Encouraged by these results, we have synthesized three enantiomeric pairs of γ-spirolactones with the *p*-menthene system starting from (*R*)- or (*S*)-limonene. In our previous syntheses of odoriferous or biologically active compounds, for example cyclic analogues of the juvenile hormones,[4][5][6] we have also usually used monoterpene derivatives as starting materials. There are at least three reasons for such a choice. The first arises from the fact that terpene systems are very common in many useful, biologically active natural products. Another reason is the ease of biodegradation of synthetic isoprenoid compounds by natural environment. Finally, in addition to being readily avaiable and cheap, terpenes contain one or two chiral centres with modest functionalization, which make them especially convenient as building blocks for chiral synthesis.

Results and Discussion

The first pair of enantiomeric unsaturated spirolactones **12a** and **12b** was synthesized from isomeric *R*-(**1a**) and *S*-(**1b**) limonenes (Scheme 1).

The oxidation of limonenes with *m*-chloroperbenzoic acid led to diastereoisomeric mixtures of known *cis*- and *trans*-epoxides (**2a**, **3a**) and (**2b**, **3b**),[7][8] which, without separation and purification, were isomerized with lithium diisopropyl amide[9] to mixtures of diastereoisomers, the *cis*- and *trans*-isocarveols **4a**, **5a** and **4b**, **5b**, respectively.[9][10] These mixtures were subjected to the orthoacetate[11] modification of the Claisen rearrangement. Enantiomerically pure (*R*)- (**6a**) or (*S*)-isomers (**6b**) of ethyl 3-(4-isopropenyl-1-cyclohexen-1-yl)propionoate were the products of these reactions. Their enantiomeric purity was confirmed by GC on a chiral column (cyclodextrin-B-2,3,6-M-19). Esters **6a** and **6b** were transformed into the corresponding acids **7a** and **7b** in good yield (90%) by hydrolysis with ethanolic KOH solution. The key step of the synthesis was the iodolactonization of the acids obtained according to the procedure described by Mori.[12] The δ-iodo-γ-lactones **8a** and **8b** were isolated as the only products of this reaction. The presence of the γ-lactone ring was confirmed by the IR spectrum ($\tilde{\nu}$ = 1796 cm^{-1}). The established mechanism of iodolactonization states that the iodonium ion and the carboxylic anion approach the double bond from opposite sides.[13][14][15][16] 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.[17] Thus, assuming the equatorial position of the isopropenyl group, we expected an axial position of the iodine substituent and an axial orientation of the alkoxy C−O bond. These expectations were confirmed by the ^{1}H-NMR spectrum and X-ray structure of 3,5-dinitrobenzoate **11**. The axial position of iodine was proved by the triplet structure of the H-6 multiplet (J = 2.0 Hz), indicating the equatorial position of this proton. The next piece of information from the ^{1}H-NMR spectrum concerns

[◇] Part 2: Ref.[1].

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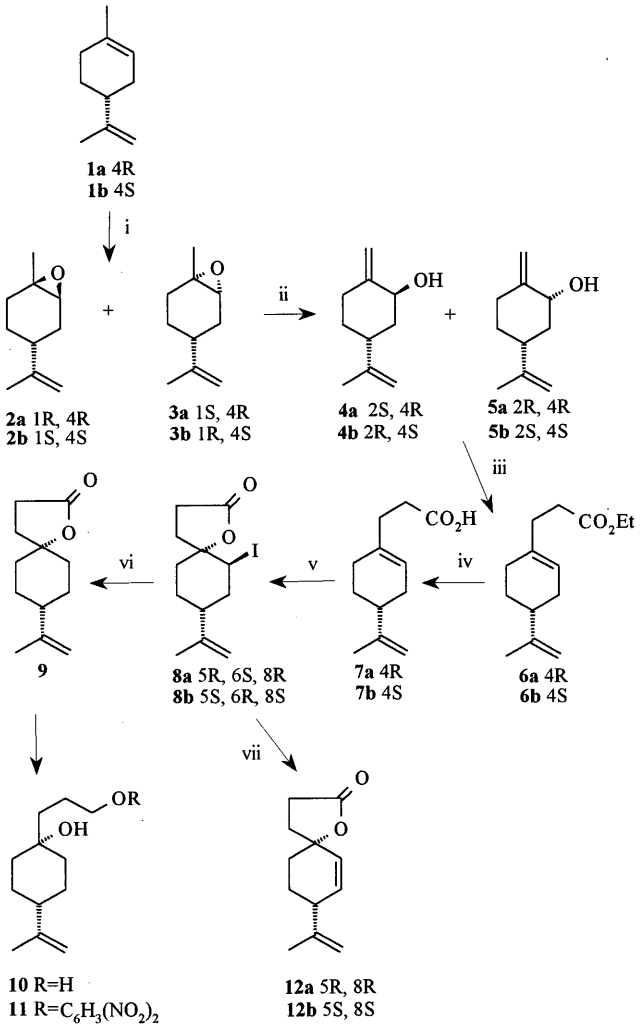
Scheme 1



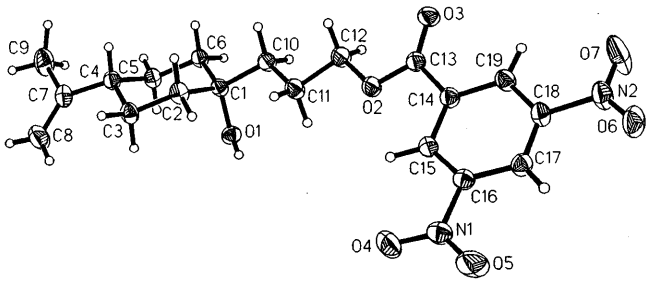
Reagents: (i) MCPBA, CH_2Cl_2, 0°, (ii) LDA, Et_2O, hexane, (iii) $CH_3C(OC_2H_5)_3$, C_2H_5COOH, 138°, (iv) KOH, EtOH, reflux, (v) I_2, KI, $NaHCO_3$, Et_2O, (vi) $(n\text{-}Bu)_3SnH$, C_6H_6, (vii) DBU, benzene, reflux.

the conformation of the lactone ring. The shape of the signal of the C-3 methylene protons [a doublet (J = 8.2 Hz) of a doublet (J = 8.0 Hz)] suggests a slightly twisted conformation of the lactone ring, with the C-3 atom out of the plane.

The axial orientation of the alkoxy C−O bond was confirmed by the X-ray structure of the 3,5-dinitrobenzoate of the diol **10**. This diol was the product of $LiAlH_4$ reduction of lactone **9**, which was obtained by the reduction of both **8a** and **8b** with tributyltin hydride.[18] The X-ray structure (Figure1) undoubtedly confirms the axial position of hydroxyl group at C-1 and indirectly, as suggested earlier, the axial position of iodine atom in the iodolactones **8a** and **8b**.

The iodolactones **8a** and **8b** were subjected to dehydrohalogenation with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[19] to give the lactones **12a** and **12b** respectively in good yields (about 90%). The small coupling constants, $J_{7\text{-H,8-H}}$ = 2.6 Hz and $J_{6\text{-H,8-H}}$ = 0.9 Hz, indicate an almost

Figure 1. Molecular structure of **11** with crystallographic numbering

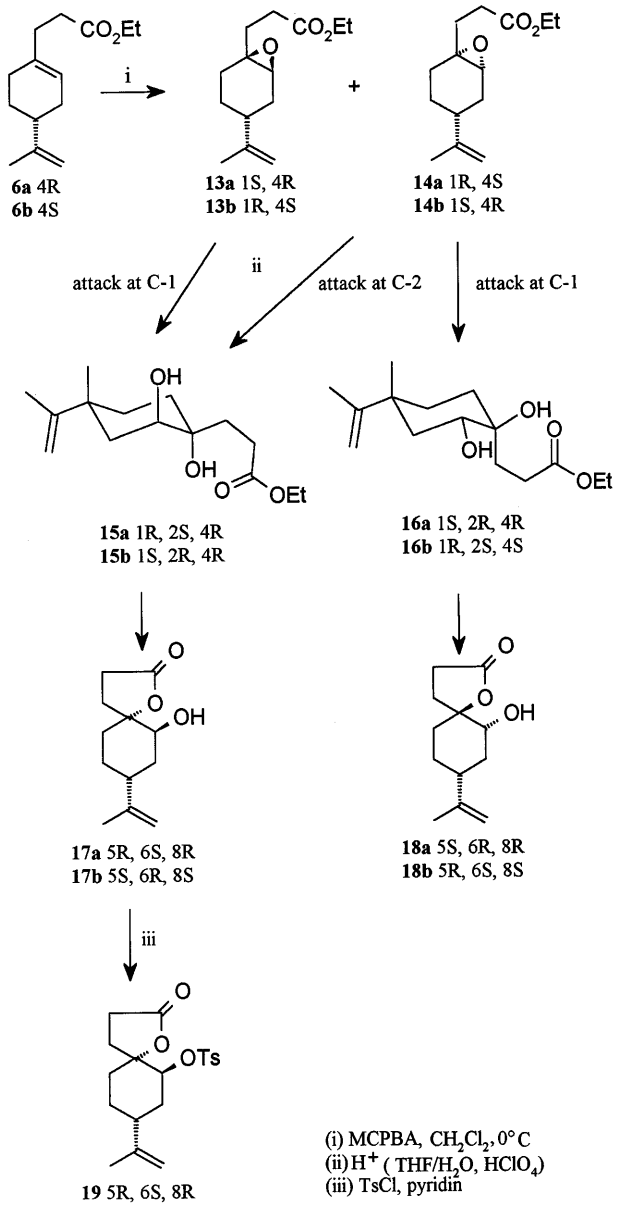


perpendicular position of 8-H with respect to the C-6−C-7 double bond, and the half-chair conformation of the cyclohexene ring.

Two enantiomeric pairs of δ-hydroxy-γ-spirolactones **17a**, **17b** and **18a**, **18b** were also synthesized from the esters **6a** and **6b** (Scheme 2). The epoxidation of esters **6a** or **6b** with *m*-chloroperbenzoic acid afforded diastereoisomeric mixture of **13a** and **14a** or **13b** and **14b** respectively. Unfortunately, these mixtures were inseparable by GC and TLC. The presence of both diastereoisomers could be only shown by the ^{1}H-NMR spectrum. According to the model analysis, the doublet (J = 6.7 Hz) at δ = 3.06 is ascribed to H-2 of the *cis*-isomer (**14a** and **14b**) and the triplet (J = 5.7 Hz) at δ = 3.01 to this proton in the *trans*-isomer (**13a** and **13b**). From integration of these signals it follows that the mixture contains 55% of the *trans*- and 45% of the *cis*-isomer. In spite of many attempts, preparative column chromatography afforded only the pure *cis*-isomer (**14a** or **14b**). In addition to this epoxy ester, we also eluted from the column the lactone **17a** or **17b**, the result of the lactonization of epoxy ester **13a** or **13b**, respectively. The ease of lactonization of this epoxy ester was confirmed by its reaction under acidic conditions. The reaction of a mixture of **13a** (55%) and **14a** (45%) catalysed by $HClO_4$ in THF/H_2O solution (pH = 1.5) after 20 h (when the epoxy ester was no longer detected by TLC analysis) gave the mixture of lactones **17a** (73%) and **18a** (27%). Similar results were obtained from an experiment where an aqueous solution of potassium tartrate (pH = 3.56) was applied. But in this case the reaction was completed after 7 d. The pure oxide **14a** was also subjected to reaction with aqueous potassium tartrate. When the reaction was interrupted at an early stage (2 d), the diolester **15a** was isolated in addition to the lactones **17a** and **18a**. The axial orientation of hydroxyl group at C-2 in this diolester was confirmed by the shape of the signal of H-2 (the pseudo-triplet).

Fortunately, the mixture of lactones was easily separable by column chromatography. The first eluted lactone was **18a** (R_f = 0.53, eluent hexane/ethyl acetate, 1:1) and the second lactone **17a** (R_f = 0.42). The structure of **17a** was again determined on the basis of its spectroscopic data and from the X-ray structure of its tosylate (**19**). The γ-lactone moiety was confirmed by the absorption band at 1792 cm^{-1}. A triplet (J = 3.5 Hz) at δ = 3.82 in the spectrum of **17a** and a triplet (J = 3.0 Hz) at δ = 4.55 in the spectrum

Scheme 2



of the tosylate **19,** both of 6-H, suggest, at the same time, the equatorial position of this proton and the axial position of hydroxyl group. The full confirmation of the structure of tosylate **19** and, indirectly, of the lactone **17a** was provided by the X-ray structural analysis of **19** (Figure 2).

In addition to the chair conformation of the cyclohexane ring and the axial orientation of the tosyloxy group, selected torsion angles between atoms in the lactone ring indicate that the 3-CH_2 group is out of the plane of this ring.

In the case of the lactones **18a** or **18b** the equatorial orientation of the hydroxyl group is confirmed by the shape of the multiplet for 6-H. The doublet (J = 11.9 Hz) of the doublet (J = 4.3 Hz) splitting of this proton unequivocally indicates its axial position. The X-ray structure of **18b** (Figure 3) confirmed the assignation presented above.

Selected torsion angles between the 6-H and 7-H axial and equatorial protons are consistent with the vicinal coupling constants between them. As in the case of the lactones **17a** and **17b** the 3-CH_2 group is out of the plane of the lactone ring.

Figure 2. Molecular structure of **19** with crystallographic numbering

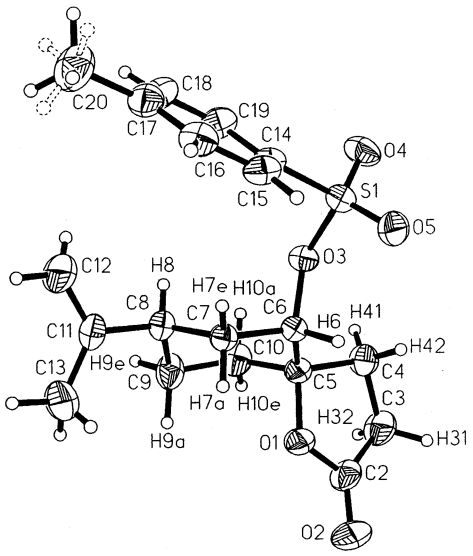
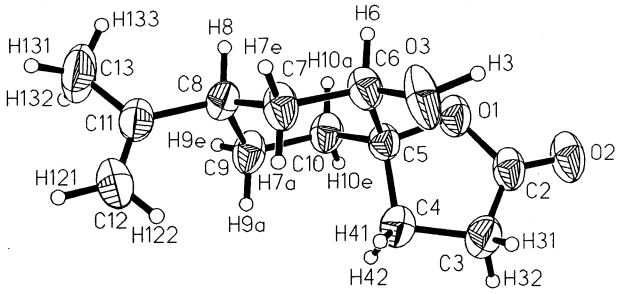


Figure 3. Molecular structure of **18b** with crystallographic numbering



Returning to the lactonization process, some explanatory remarks are necessary. Firstly, the lactonization of epoxy esters, induced by H^+ ions, proceeds through the diols **15a** and **16a** or **15b** and **16b**. According to earlier observations concerning the cleavage of an oxirane ring in the limonene 1, 2-oxides,[7] the nucleophile should attack the C-1 atom from the opposite side of the oxonium ion, which is formed after H^+ addition to the oxirane oxygen. In the case of the *trans*-epoxides **13a** and **13b** this mode of action leads to the *trans*-diaxial diols **15a** and **15b** with the alkylcarbethoxy group in the equatorial position. In the case of the *cis*-epoxides **14a** and **14b** attack at C-1 leads to *trans*-diequatorial diols **16a** and **16b** with the alkylcarbethoxy group in the axial position. As this conformation is energetically unfavourable, the attack of a nucleophile at C-2 in the epoxides **14a** and **14b**, leading to the diols **15a** and **15b**, is reasonable, too. From the *cis*-epoxides, **14a** or **14b**, both diols, **15a** and **16a** or **15b** and **16b,** are therefore formed. Such a pattern of diol (**15a**, **15b** and **16a**, **16b**) formation explains the ratio of lactones, **17a** or **17b** (75%) and **18a** or **18b** (25%), in the products of the lactonization of mixture

of the epoxy esters **13a** and **14a** or **13b** and **14b**, as well as 30% of **17a** and 70% of **18a** in the lactonization of the pure epoxy ester **14a**.

The lactones synthesized were tested for deterrent activity against three storage pest insects: the grain weevil (*Sitophilus granarius*, adults), the confused flour beetle (*Tribolium confusum*, adults and larvae) and the khapre beetle (*Trogoderma granarium*, larvae). Compounds tested showed moderate activity towards adults *T. confusum* and *S. granarius* (total coefficients of deterrence 80−100) and high activity against larvae of *T. Confusum* (total coefficients of deterrence 152−187).[20] The results indicate also that the deterrent activity depends considerably on the configurations of the chiral centres. The isomers **12a**, **17a**, and **18a** were more active than their enantiomers **12b**, **17b**, and **18b**. The details of these biological studies will be the subject of a separate publication.

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Experimental Section

(+)-(*R*)-Limonene, (−)-(*S*)-limonene, triethyl orthoacetate, tributyltin hydride, 1,8-diazabicyclo[5.4.0]undec-7-ene, diisopropyl amine, and *m*-chloroperbenzoic acid were purchased from Fluka. − ^{1}H NMR: Bruker Avance DRX 300, 300 MHz, TMS as internal standard, for solutions ($CDCl_3$). IR: Specord M 80 spectrophotometer (Carl Zeiss Jena). − Melting points: Boetius apparatus. − Optical rotation: Autopol IV automatic polarimeter (Rudolph), in acetone, concentrations denoted in g/100 ml. − GC analyses: Hewlet Packard 5890 (series II), using capillary columns: HP-1 (Crosslinked Methyl Silicone Gum) 25 m × 0.32 mm × 0.52 μm, HP-5 (Crosslinked 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: Silicagel DC-Alufolien Kieselgel 60 F_{254} (Merck), hexane/ethyl acetate in varying ratios, compounds 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: Silica gel (kieselgel 60, 40−63 μm, 230−400 mesh, Merck) hexane/ethyl acetate in varying ratios as eluents.

(1R,2S,4R)-1-Methyl-4-(1-methylethenyl)-1-cyclohexene 1,2-Epoxide (**2a**) *and (1S,2R,4R)-1-Methyl-4-(1-methylethenyl)-1-cyclohexene 1,2-Epoxide* (**3a**): The compounds were prepared by the reaction of (+)-(*R*)-limonene (3 g, 22.1 mmol) with MCPBA in CH_2Cl_2 by a standard method. The products were purified by column chromatography (silica gel, hexane/ethyl acetate, 18:1) and a mixture of (**2a**) and (**3a**) was obtained, (2.46 g, 73.4%).

cis (**2b**) and *trans* (4*S*)-1,2-epoxylimonene (**3b**): Obtained (2.58 g, 66%) by the same procedure from (*S*)-limonene (3.5 g, 25.7 mmol).

(2S,4R)-2-Methylene-5-(1-methylethenyl)cyclohexanol (**4a**) *and (2R,4R)-2-Methylene-5-(1-methylethenyl)cyclohexanol* (**5a**): The mixture of epoxides **2a** and **3a** in 85 ml of dry hexane was added dropwise to 9.17 g (85.6 mmol) of LDA in 100 ml of diethyl ether 5.2 g (34.2 mmol). The mixture was stirred under nitrogen at room temp. for 24 h. Then 100 ml of water was added, the organic phase was separated and washed (1 M HCl, sat. $NaHCO_3$, water) and concentrated in vacuo. The crude oil was purified by column chromatography (silica gel, hexane/ethyl acetate, 5:1) to give 3.1 g of a mixture of *cis* and *trans* (4*R*)-isocarveols (60%).

cis (**4b**) and *trans* (4*S*)-isocarveol (**5b**): Obtained (3.08 g, 56%), by the same procedure, from (**2b**) and (**3b**) (5.5 g, 40.4 mmol).

Ethyl [(4R)-(+)-[4-(1-Methylethenyl)cyclohex-1-en-1-yl]propionate (**6a**): A mixture of (4*R*)-isocarveols **4a** and **5a** (3.1 g, 20.4 mmol), triethyl orthoacetate (18.6 ml, 102 mmol), and propionic acid (1 drop) as a catalyst was heated at 138° for 10 h while EtOH was constantly removed from the reaction mixture. Then triethyl orthoacetate was evaporated off and the crude product chromatographed (silica gel, hexane/EtOAc, 18:0.5). The pure ester **6a** (3.9 g, 86%) was obtained: $[\alpha]_D^{25} = +65.5$ (*c* = 5.8, acetone); $n_D^{20} = 1.4754$. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 1.73 (s, 3 H, 9-CH_3), 2.28 (m, 2 H, 3-CH_2), 2.41 (m, 2 H, 11-CH_2), 4.13 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 4.62 (m, 2 H, 8-CH_2), 5.44 (m, 1 H, 2-H). − IR (film): $\tilde{\nu}$ = 3100 cm^{-1} (w, >C=CH_2), 1748 (s, C=O), 1652 (m, >C=CH_2), 896 (s, >C=CH_2). − $C_{14}H_{22}O_2$ (222.3): calcd. C 75.63, H 9.97; found C 75.41, H 10.05.

Ethyl [(4S)-(−)-4-(1-Methylethenyl)cyclohex-1-en-1-yl]propionate (**6b**): (3.72 g, 88%) Obtained by the same procedure from the mixture of **4b** and **5b** (2.9 g, 19.1 mmol); $[\alpha]_D^{25} = -60.1$ (*c* = 4.5, acetone).

[(4R)-(+)-4-(1-Methylethenyl)cyclohex-1-en-1-yl]propionic Acid (**7a**): Ester **6a** (1.68 g, 7.6 mmol) was dissolved in 25 ml of KOH/EtOH soln. (0.6 g of KOH) and the mixture refluxed for 2 h. The mixture 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 neutralized by the addition of 0.01 M HCl and extracted with diethyl ether. The ethereal extract was washed with brine, dried with $MgSO_4$, and evaporated in vacuo to give acid **7a** (1.44 g, 98%); $[\alpha]_D^{27} = +60.5$ (*c* = 6.3, acetone); m.p. 67−68°C. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.73 (s, 3 H, 9-CH_3), 2.28 (m, 2 H, 10-CH_2), 2.47 (m, 2 H, 11-CH_2), 4.70 (m, 2 H, =CH_2), 5.46 (m, 1 H, 2-H), 10.00 (br. s, 1 H, COOH). − IR (CCl_4): $\tilde{\nu}$ = 3000 cm^{-1} (s, br., OH), 1720 (s, C=O), 1652 (m, >C=CH_2), 900 (s, >C=CH_2). − $C_{12}H_{18}O_2$ (194.3): calcd. C 74.19, H 9.34; found C 74.08, H 9.42.

[(4S-(−)-4-(1-methylethenyl)-1-cyclohexen-1-yl]propionic Acid (**7b**): Obtained (1.28 g, 96%) by the same procedure from **6b** (1.52 g, 6.8 mmol); $[\alpha]_D^{27} = -61.8$ (*c* = 1.4, acetone).

(5R,6S,8R)-(+)-6-Iodo-8-(1-methylethenyl)-1-oxaspiro[4.5]decan-2-one (**8a**): A 0.5 M $NaHCO_3$ solution (25 ml) was added to a solution of **7a** (1.36 g, 7 mmol) in diethyl ether (25 ml). The mixture was stirred at room temp. for 30 min and then refluxed. To the refluxing mixture a soln. of KI (7.0 g) and I_2 (3.6 g) in water (30 ml) was gradually added. The mixture was stirred under reflux for 5 h. After cooling, it was diluted with ether, washed with $Na_2S_2O_3$ soln., and the ethereal layer was separated. It was next washed with sat. $NaHCO_3$ soln., brine, dried with $MgSO_4$, and concentrated in vacuo to give 2.25 g of crude iodolactone. Recrystallization from *n*-hexane afforded 1.82 g (81%) of **8a**; m.p. 78.5−81°C; $[\alpha]_D^{26} = +125.6$ (*c* = 6.3, acetone). $^{-1}$H NMR (300 MHz, toluene): δ = 1.60 (s, 3 H, 13-CH_3), 2.48 (dd, J_1 = 8.2 Hz, J_2 = 8.0 Hz, 2 H, 3-CH_2), 3.88 (t, $J_{6,7}$ = 2 Hz, 1 H, 6-H), 4.82 (m, 2 H, =CH_2). − IR (CCl_4): $\tilde{\nu}$ = 3100 cm^{-1} (w, >C=CH_2), 1796 (s, C=O), 1652 (w, >C=CH_2), 904 (m, >C=CH_2).− $C_{12}H_{17}IO_2$ (320.2): calcd. C 45.02, H 5.35; found C 45.09, H 5.41.

(5S,6R,8S)-(−)-6-Iodo-8-(1-methylethenyl)-1-oxaspiro[4.5]decan-2-one (**8b**): Obtained (1.48 g, 75%) by the same procedure from **7b** (1.2 g, 6.2 mmol); m.p. 79−81°C; $[\alpha]_D^{26} = -131.1$ (*c* = 6.4, acetone).

8-(1-Methylethenyl)-1-oxaspiro[4.5]decan-2-one (**9**): Tributyltin hydride (1.5 g, 5.2 mmol) was added to a solution of iodolactone

8a (0.82 g, 2.6 mmol) in dry benzene (3 ml) under N_2. The mixture was stirred for 3 d at room temp. and then it was chromatographed (silica gel, hexane/EtOAc, 9:1) to give 0.47 g (95%) of **9**; m.p. 32−33°C. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.73 (s, 3 H, 13-CH_3), 2.00 (t, $J_{4,3}$ = 8.4 Hz, 2 H, 4-CH_2), 2.60 (t, $J_{3,4}$ = 8.4 Hz, 2 H, 3-H), 4.71 (m, 2 H, =CH_2). − IR (film): $\tilde{\nu}$ = 3100 cm^{-1} (w, >C=CH_2), 1780 (s, C=O), 1652 (m, >C=CH_2), 896 (s, >C=CH_2). − $C_{12}H_{18}O_2$ (194.3): calcd. C 74.19, H 9.34; found C 74.31, H 9.25.

1-Hydroxy-1-(3-hydroxypropyl)-4-(1-methylethenyl)cyclohexane (**10**): Diol **10** (0.09 g, 87%) was obtained by $LiAlH_4$ reduction of **9** (0.1 g, 0.52 mmol) using a standard method (yield 87%); m.p. 58−60°C. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.73 (s, 3 H, 9-CH_3), 2.12 (s, br., 2 H, OH), 3.67 (t, $J_{12,11}$ = 6.0 Hz, 2 H, CH_2OH), 4.7 (m, 2 H, =CH_2). − IR (CCl_4): $\tilde{\nu}$ = 3624 cm^{-1} (w, OH), 3317 (s, br., OH), 1644 (m, >C=CH_2), 890 (s, >C=CH_2). − $C_{12}H_{22}O_2$ (198.3): calcd. C 72.68, H 11.18; found C 73.02, H 11.03.

{3-[1-Hydroxy-4-(1-methylethenyl)cyclohex-1-yl]propyl}-3,5-dinitrobenzoate (**11**): 0.07 g (0.36 mmol) of diol **10** was treated with 0.083 g (0.36 mmol) of 3,5-dinitrobenzoyl chloride using a standard method. 0.11 g (80%) of ester **11** was obtained; m.p. 82−84°C. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (br. s, 1 H, OH), 1.74 (s, 3 H, 12-CH_3), 4.49 (t, $J_{9,8}$ = 6.8 Hz, 2 H, 9-CH_2), 4.71 (m, 2 H, =CH_2), 9.15 (d, J = 2.1 Hz, 2 H, −C_6H_3, 2, 6-H), 9.2 (t, J = 2.2 Hz, 1 H, C_6H_3, 4-H). − IR (CCl_4): $\tilde{\nu}$ = 3300 cm^{-1} (m, br., OH), 3120 (m, >C=CH_2), 1740 (s, C=O), 1636 (m, Ar), 1625 (m, >C=CH_2), 1556 (s, NO_2), 1352 (s, NO_2), 1288 (s, C−O−C). − $C_{19}H_{24}N_2O_7$ (392.4): calcd. C 58.16, H 6.16, N 7.14; found C 58.03, H 6.25, N 7.21.

Crystal Data for **11**: $C_{19}H_{24}N_2O_7$, M_W = 392.40, T = 293K, Cu-K_α radiation, triclinic, space group $P\bar{1}$, a = 7.048(2) Å, b = 9.656(2), c = 14.923(3), α = 76.95(2), β = 81.34(2), γ = 88.74(2)°, V = 978.0(4) Å^3, Z = 2, D_c = 1.333 Mg·m^{-3}, μ = 0.858 mm^{-1}, F(000) = 416, crystal size 0.30 × 0.25 × 0.17 mm, diffractometer Kuma KM4, 2 ≤ θ ≤ 81°, 3999 collected and independent refl. with I > 2σ(I), 350 parameters. The structure was solved using the SHELXS-97 program and refined (including H-atoms) using SHELXL-97 to $R_1(F)$ = 0.0509, $wR_2(F^2)$ = 0.1514 and S = 1.125. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101192. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (internat.) + 44(1223)336-033, e-mail: deposit@ccdc.cam.ac.uk].

(5R,8R)-(+)-8-(1-Methylethenyl)-1-oxaspiro[4.5]dec-6-en-2-one (**12a**): 0.35 g (1.1 mmol) of iodolactone **8a** was dissolved in 25 ml of dry benzene and 0.3 g (2.2 mmol) of DBU was added. The reaction mixture was refluxed under nitrogen for 12 h. The precipitate 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/EtOAc, 5:1) to give 0.19 g (92%) of lactone **12a**; $[\alpha]_D^{24}$ = +24 (c = 1.2, acetone); n_D^{20} = 1.5051. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.74 (s, 3 H, 13-CH_3), 2.63 (m, 2 H, 3-CH_2), 2.73 (m, 1 H, 8-H), 4.79 (m, 2 H, =CH_2), 5.70 (dd, $J_{6,7}$ = 10.2 Hz, $J_{6,8}$ = 0.9 Hz, 1 H, 6-H), 5.87 (dd, $J_{7,6}$ = 10.2 Hz, $J_{7,8}$ = 2.6 Hz, 1 H, 7-H). − IR (film): $\tilde{\nu}$ = 3100 cm^{-1} (w, >C=CH_2), 1780 (s, C=O), 1652 (m, >C=CH_2). − $C_{12}H_{16}O_2$ (192.3): calcd. C 74.97, H 8.39; found C 74.56, H 8.50.

(5S,8S)-(−)-8-(1-Methylethenyl)-1-oxaspiro[4.5]dec-6-en-2-one (**12b**): Obtained (0.27 g, 91%) by the same procedure, from **8b** (0.5 g, 1.56 mmol); $[\alpha]_D^{24}$ = −19.5 (c = 1.1, acetone).

Ethyl [(1R,2S,4R)-1,2-Epoxy-4-(1-methylethenyl)cyclohexan-1-yl]propionate (**13a**) *and Ethyl [(+)-(1S,2R,4R)-1,2-Epoxy-4-(1-methylethenyl)cyclohexan-1-yl]propionate* (**14a**): A solution of MCPBA (55%, 0.88 g, 2.8 mmol) in dry methylene chloride (15 ml) was added dropwise to a stirred cold (0−5°C) solution of ester **6a** (0.62 g, 2.8 mmol) in methylene chloride (20 ml). The mixture was stirred for 24 h at 0°C and then was washed ($Na_2S_2O_3$, Na_2CO_3, water) and dried ($MgSO_4$). The solvent was evaporated off and 0.53 g of products was obtained (80%). The crude mixture of epoxy esters **13a** and **14a** was used to the next reaction without purification. When purified by column chromatography the compound **13a** underwent lactonization to **17a** and only the epoxy ester **14a** is separated. **14a**; $[\alpha]_D^{24}$ = +97.6 (c = 2.1, acetone). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.67 (s, 3 H, 9-CH_3), 2.38 (t, J = 7.7 Hz, 2 H, 11-CH_2), 3.01 (d, $J_{2,3}$ = 6.7 Hz, 1 H, 2-H), 4.1 (q, J = 7.1 Hz, 2 H, OCH_2CH$_3$), 4.67 (m, 2 H, =CH_2). − IR (film): $\tilde{\nu}$ = 3096 cm^{-1} (w, >C=CH_2), 1748 (s, C=O), 1652 (m, >C=CH_2), 896 (s, >C=CH_2).

Ethyl [(1S,2R,4S)- (**13b**) *and (1R,2S,4S)-(−)-1,2-Epoxy-6-hydroxy-4-(1-methylethenyl)cyclohexan-1-yl]propionate* (**14b**): A mixture of **13b** and **14b** (0.49 g, 81%) were obtained by the same procedure from **6b** (0.56 g, 2.5 mmol). **14b**: $[\alpha]_D^{24}$ = −105.4 (c = 0.44, acetone); n_D^{20} = 1.6825.

(5R,6S,8R)-(+)-6-Hydroxy-8-(1-methylethenyl-1-)oxaspiro-[4.5]decan-2-one (**17a**) *and (5S,6R,8R)-(+)-6-Hydroxy-8-(1-methylethenyl)-1-oxaspiro[4.5]decan-2-one* (**18a**): The crude mixture of epoxy esters **13a** and **14a** (0.53 g, 2.2 mmol) in THF (10 ml) was added to a 5 ml of H_2O with 7 drops of $HClO_4$. The reaction mixture was stirred for 24 h and extracted with diethyl ether. The ethereal extract was washed with saturated $NaHCO_3$, brine and dried with $MgSO_4$. After solvent evaporation, the product mixture was separated by column chromatography (silica gel, hexane/ethyl acetate, 1:1) to give the lactones **17a** (0.3 g, 72%) and **18a** (0.12 g, 28%). Total yield 88%.

17a (oily liquid): $[\alpha]_D^{26}$ = +44.2 (c = 8.5, acetone). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.73 (s, 3 H, 13-CH_3), 2.6 (t, $J_{3,4}$ = 8.4 Hz, 2 H, 3-CH_2), 3.82 (t, $J_{6,7}$ = 3.5 Hz, 1 H, 6-H), 4.75 (m, 2 H, =CH_2). − IR (CCl_4): $\tilde{\nu}$ = 3492 cm^{-1} (m, br., OH), 1792 (s, C=O), 1652 (w, >C=CH_2), 900 (m, >C=CH_2). − $C_{12}H_{18}O_3$ (210.3): calcd. C 68.55, H 8.63; found C 68.33, H 8.38.

18a: $[\alpha]_D^{26}$ = −0.4 (c = 2.1, acetone); m.p. 105−106°C. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.73 (s, 3 H, 13- CH_3), 3.9 (dd, $J_{6,7a}$ = 11.9 Hz, $J_{6,7e}$ = 4.3 Hz 2 H, 3-CH_2), 4.73 (m, 2 H, =CH_2). − IR (CCl_4): $\tilde{\nu}$ = 3452 cm^{-1} (m, br., OH), 1788 (s, C=O), 1656 (w, >C=CH_2), 904 (m, >C=CH_2). − $C_{12}H_{18}O_3$ (210.3): calcd. C 68.55, H 8.63; found C 68.45, H 8.62.

The hydroxy lactones **17b** (0.29 g, 73%) and **18b** (0.11 g, 27%) were obtained by the same procedure, from the mixture of epoxy esters (**13b**) and (**14b**) (0.49 g, 2.1 mmol). Total yield 86%. **17b**: $[\alpha]_D^{26}$ = −37.1 (c = 6.4, acetone). **18b**: $[\alpha]_D^{26}$ = +0.3 (c = 4.5, acetone); m.p. 105−106°C.

Crystal Data for **18b**: $C_{12}H_{18}O_3$, M_W = 210.26, T = 293K, Cu-K_α radiation, monoclinic, space group $P2_1$, a = 9.168(2) Å, b = 6.585(1), c = 10.105(2), β = 108.86(3)°, V = 577.3(2) Å^3, Z = 2, D_c = 1.210 Mg × m^{-3}, μ = 0.694 mm^{-1}, F(000) = 228, crystal size 0.25 × 0.18 × 0.15 mm, diffractometer Kuma KM4, 2 ≤ θ ≤ 88°, 2347 collected refl., 2291 independent refl. with I > 2σ(I), 137 parameters (H-atom parameters were fixed). During the measure-

Table 1. Selected torsion angles [°] for **19**

O1−C5−C6−O3	171.8	C2−C3−C4−C5	−23.0
C4−C5−C−H6	−57	H31−C3−C4−H41	95
H7a−C7−C6−H6	−53	H31−C3−C4−H42	−38
H7e−C7−C6−H6	59	H32−C3−C4−H41	−28
C5−O1−C2−C3	2.8	H32−C3−C4−H42	−160
O1−C2−C3−C4	13.5		

Table 2. Selected torsion angles [°] for **18b**

O1−C5−C6−O3	−67.4	C3−C4−C5−O1	11.9
H6−C6−C7−H7e	−59	H1−C3−C4−H41	−14
H6−C6−C7−H7a	−176	H32−C3−C4−H41	106
C5−O1−C2−C3	−4.0	H31−C3−C4−H42	−135
O1−C2−C3−C4	12	H32−C3−C4−H42	−14
C2−C3−C4−C5	−14.2		

ment of the crystal a significant decay (sublimation) about 25% of three standard reflections was observed. The structure was solved using the SHELXS-97 program and refined (including H-atoms) using SHELXL-97 to $R_1(F) = 0.1054$, $wR_2(F^2) = 0.3047$ and $S = 1.318$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101192. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (internat.) + 44(1223)336-033, e-mail: deposit@ccdc.cam.ac.uk].

Ethyl [(1R,2S,4R)-(+)-1,2-Dihydroxy-4-(1-methylethenyl)-1-cyclohexyl]propionate (**15a**): $[\alpha]_D^{21} = +9.2$ ($c = 2.1$, acetone); $n_D^{20} = 1.6760$. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.73 (s, 3 H, 9-CH_3), 3.62 (m like t, 1 H, 2-H), 4.16 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.72 (m, 2 H, $=CH_2$). − IR (CCl_4): $\tilde{\nu}$ = 3460 cm^{-1} (s, br., OH), 3100 (w, >C=CH_2), 1724 (s, C=O), 1652 (m, >C=CH_2), 900 (s, >C=CH_2). − $C_{14}H_{24}O_4$ (256.3): calcd. C 65.60, H 9.44; found C 65.32, H 9.58.

(5R,6S,8R)-(+)-8-(1-Methylethenyl)-6-tosyloxyoxaspiro-[4.5]decan-2-one (**19**): Tosyloxy lactone **19** was obtained by the reaction of hydroxylactone **17a** (0.09 g, 0.43 mmol) with tosyl chloride (0.12 g, 0.65 mmol) using a standard method. 0.1 g (61.5%) of **19** was obtained: $[\alpha]_D^{23} = +28.7$ ($c = 1.8$, acetone); m.p. 92−93°C. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.57 (s, 3 H, 13-CH_3), 2.46 (s, 3 H, Ar−CH_3), 2.53 (t, $J_{3,4}$ = 8.3 Hz, 2 H, 3-CH_2), 4.55 (t, $J_{6,7}$ = 3.0 Hz, 1 H, 6-H), 4.60 and 4.68 (two m, 2 H, $=CH_2$), 7.37 and 7.8 (AA′BB′ system, 4 H, C_6H_4); IR (CCl_4): $\tilde{\nu}$ = 1784 cm^{-1} (s, C=O), 1652 (w, >C=CH_2), 1608 (m, Ar), 1376 (s, SO_2), 1180 (s, SO_2), 904 (s, >C=CH_2). − $C_{19}H_{24}O_5$ S (364.5): calcd. C 62.62, H 6.64, S 8.80; found C 62.48, H 6.73, S 8.87.

Crystal Data for **19**: $C_{19}H_{24}O_5S$, $M_W = 364.44$, $T = 293$K, Cu-K_α radiation, monoclinic, space group $P2_1$, $a = 8.406(1)$ Å, $b = 5.790(1)$, $c = 19.502(4)$, β = 96.91(3)°, $V = 942.3(3)$ Å^3, $Z = 2$, $D_c = 1.284$ Mg·m^{-3}, μ = 1.743 mm^{-1}, $F(000) = 388$, crystal size 0.20 × 0.20 × 0.10 mm, diffractometer Kuma KM4, $2 \leq \theta \leq 81°$, 2663 collected refl, 2511 independent refl. with $I > 2\sigma(I)$, 312 parameters. The structure was solved using the SHELXS-97 program and refined (H-atoms from one methylene group are disordered with the ocupancy factor equal 0.5 and fixed) using SHELXL-97 to $R_1(F) = 0.0294$, $wR_2(F^2) = 0.0756$ and $S = 1.082$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101192. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (internat.) + 44(1223)336-033, e-mail: deposit@ccdc.cam.ac.uk].

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