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Lactones 23: Synthesis of *cis*-fused bicyclic hydroxy lactones with a *p*-menthane system☆

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Received 13 March 2005; accepted 21 April 2005

Abstract—Enantiomeric pairs of *cis*-fused bicyclic hydroxy lactones with a *p*-menthane system were obtained in a several step synthesis from enantiomerically pure isomers of (+)-(*R*)- and (−)-(*S*)-pulegone. One-pot allyl-Claisen rearrangement of *cis*-pulegols, epoxidation of γ,δ-unsaturated *p*-nitrophenyl esters and acidic lactonization of epoxy esters are key synthetic steps. The structures of the compounds were confirmed by both spectroscopic and crystallographic methods.

1. Introduction

The *p*-menthane lactones family is a valuable class of monoterpenoid compounds mainly for their interesting odoriferous properties.[1–7] Previously we reported the synthesis of several enantiomeric pairs of bicyclic γ-spirolactones **1**–**6** and optically inactive γ-spirolactone **7**, which can be considered as derivatives of three of the best known *p*-menthanolides; (−)-mintlactone **8**, (+)-isomintlactone **9** and wine lactone **10** (Fig. 1).[8a,9] The evaluation of their odoriferous properties showed that, in agreement with our expectations, they exhibit interesting fragrances and can be of considerable interest in the food or cosmetics industry.[8]

However, our interest in the synthesis of monoterpenoid lactones with the *p*-menthane system was focused mainly on searching for new synthetic antifeedants of

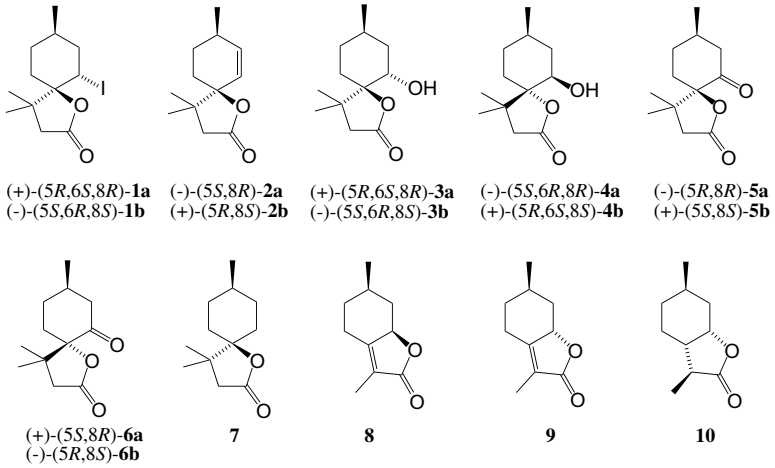

Figure 1. Lactones with the *p*-menthane system.

☆See Ref. 9.

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doi:10.1016/j.tetasy.2005.04.020

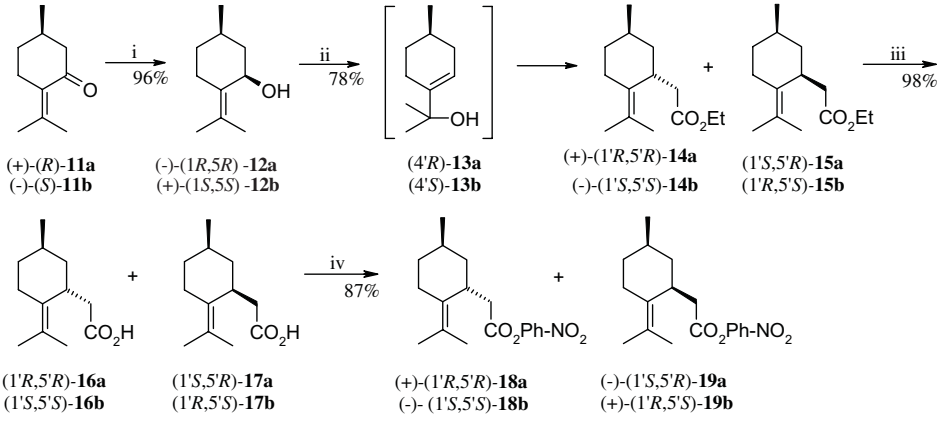
simple structure and availability. The structures of the natural deterrents found in plants, such as the most potent azadirachtin (*Azadirachta indica*, Meliaceae)[10] and ajugarin (*Ajuga remota*, Labiatae),[11] are in most cases too complicated to be synthesized on a large scale. The agricultural application of natural antifeedants is also considerably limited by their low concentration in plants and too expensive isolation to be of much practical value for plant protection. As many natural deterrents incorporate the lactone moiety,[11,12] synthetic monoterpenoid lactones[13] of simple structure can be an alternative option for practical application. Encouraged by the high feeding deterrent activity of δ-hydroxy-γ-spirolactones **3** and **4** and δ-keto-γ-spirolactones **5** and **6** towards the Colorado potato beetle (*Leptinotarsa decemlineata* Say), the lesser mealworm *Alphitobius diaperinus* Panzer and the peach potato aphid (*Myzus Persicae* Sulz.),[14] we synthesized the enantiomeric pairs of *cis*-fused bicyclic hydroxy lactones **22**, **25**, **30** and **31** (Schemes 2 and 5) to investigate the structure–biological activity relationship for these compounds. As the configuration of the stereogenic centres is an extremely important factor for determining biological activity of chiral pheromones,[15] odorants[7,16] and drugs,[17] hydroxy lactones **22**, **25**, **30** and **31** were obtained from enantiomerically pure isomers of (+)-(*R*)- and (−)-(*S*)-pulegone **11a** and **11b** via a one-pot allyl-Claisen rearrangement of (−)-(1*R*,5*R*)- and (+)-(1*S*,5*S*)-pulegol, **12a** and **12b**, respectively. Herein we report the first use of a one-pot combination of allylic and Claisen rearrangements of allylic alcohols in the synthesis of γ,δ-unsaturated esters.

2. Results and discussion

Four enantiomeric pairs of *cis*-fused bicyclic hydroxy lactones with the *p*-menthane system **22a**,**b**, **25a**,**b**, **30a**,**b** and **31a**,**b** (Schemes 2 and 5) were obtained in a several step synthesis from (+)-(*R*)- and (−)-(*S*)-pulegone, **11a** and **11b**, respectively. The first step of the synthesis was the reduction of pulegones with $NaBH_4$ in a mixture of MeOH/H_2O according to the procedure described by us (Scheme 1).[8a,9] A one-pot allyl-Claisen rearrangement of *cis*-pulegols (−)-(1*R*,5*R*)-**12a** or (+)-(1*S*,5*S*)-**12b** in the presence of catalytic amounts of water afforded mixtures of γ,δ-unsaturated ethyl esters (+)-(1′*R*,5′*R*)-**14a** and (1′*S*,5′*R*)-**15a** or (−)-(1′*S*,5′*S*)-**14b** and (1′*R*,5′*S*)-**15b** in a ratio of 80:20. Such a course of the reaction was caused by the allylic rearrangement of *cis*-pulegols to more stable tertiary alcohols (4′*R*)-**13a** or (4′*S*)-**13b**, which were then used as substrates for the Claisen rearrangement.

The orthoacetate modification of the Claisen rearrangement is known to be highly stereoselective; however, in the case of these tertiary allylic alcohols it led to the diastereoisomeric mixture of ethyl esters **14a** and **15a** or **14b** and **15b**. Apart from the main product—ester **14a** or **14b** (80%) with *trans*-situated methyl and ethoxycarbonylmethyl groups—20% of *cis*-ester **15a** or **15b** was also obtained. Although the presence of two ethyl esters was clearly seen by gas chromatography, they were inseparable by means of column and HPLC chromatography. As phenyl esters possess higher UV activity, and therefore can be better detected by HPLC, the *cis*- and *trans*-ethyl esters **14a** and **15a**, or **14b** and **15b** were transformed into the corresponding *p*-nitrophenyl esters (+)-(1′*R*,5′*R*)-**18a** and (−)-(1′*S*,5′*R*)-**19a** or (−)-(1′*S*,5′*S*)-**18b** and (+)-(1′*R*,5′*S*)-**19b**. In order to do this, the mixtures of ethyl esters **14a** and **15a**, or **14b** and **15b**, were hydrolyzed in KOH/EtOH solution to the corresponding acids (1′*R*,5′*R*)-**16a** and (1′*S*,5′*R*)-**17a**, or (1′*S*,5′*S*)-**16b** and (1′*R*,5′*S*)-**17b**, which were subjected to reaction with PCl_5 in anhydrous CCl_4 and then esterification of acid chlorides with sodium *p*-nitrophenolate (Scheme 1).[18] The mixtures of *p*-nitrophenyl esters **18a** and **19a** or **18b** and **19b** (80:20) were separated by preparative HPLC chromatography using a mixture of THF and hexane (99.5:0.5) as eluent. The *cis*-*p*-nitrophenyl ester **19a** or **19b** was eluted first after 21.25 min, whereas the *trans*-isomer **18a** or **18b** had a retention time of 25.27 min. Their enantiomeric purity was confirmed by GC chromatography on a chiral column (cyclodextrin-β-2,3,6-*m*-19).

The assignment of the structures **18a** and **19a** or **18b** and **19b** for the *p*-nitrophenyl ester isomers was based on the



Scheme 1. Reagents and conditions: (i) $NaBH_4$, EtOH, MeOH/H_2O, 0 °C to rt, 2 h; (ii) $CH_3C(OEt)_3$, C_2H_5COOH, H_2O, 3 h at 138 °C, **14a**:**15a** = 80:20; (iii) (a) KOH, EtOH, reflux, 3 h; (b) 0.1 M HCl, **16a**:**17a** = 80:20; (iv) (a) PCl_5, CCl_4, 12 h at 45 °C; (b) NaO–C_6H_4–NO_2-*p*, CH_2Cl_2, 10 h at rt, **18a**:**19a** = 80:20; (c) HPLC, hexane/THF (99.5:0.5).

careful examination of their 300 MHz ^{1}H NMR spectra and confirmed by the X-ray structures of γ-hydroxy-δ-lactone (+)-(1*S*,6*R*,8*R*)-**22a** (Fig. 2) and δ-hydroxy-γ-lactone (−)-(1*R*,4*R*,6*R*)-**25a** (Fig. 3). The H-1′ proton of the *trans*-*p*-nitrophenyl ester **18a** or **18b** can be seen as a multiplet at a lower field ($\delta = 3.47$) compared with the same proton of the *cis*-isomer **19a** or **19b** ($\delta = 3.23$). According to the analysis with a Driding model, this is only possible in the chair-like conformation of cyclohexane ring with the aryloxycarbonylmethyl group at the axial position. In such a conformation the double bond of isopropylidene group and the equatorial H-1′ proton are situated in the same plane, therefore the H-1′ proton of the *trans*-ester **18a** or **18b** is more effectively deshielded by the double bond. The crystal structures of hydroxy lactones **22a** (Fig. 2) and **25a** (Fig. 3) undoubtedly confirmed the trans relationship between the CH_3-8 or CH_3-4 methyl group of the cyclohexane ring and the C5–C6 or C6–C7 bond of the lactone ring.

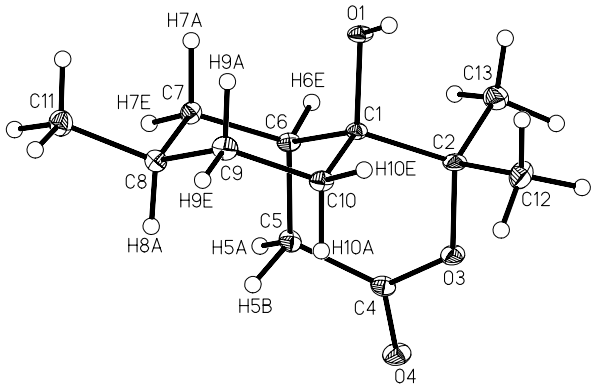


Figure 2. The molecular structure of γ-hydroxy-δ-lactone (+)-(1*S*,6*R*,8*R*)-**22a** with crystallographic numbering.

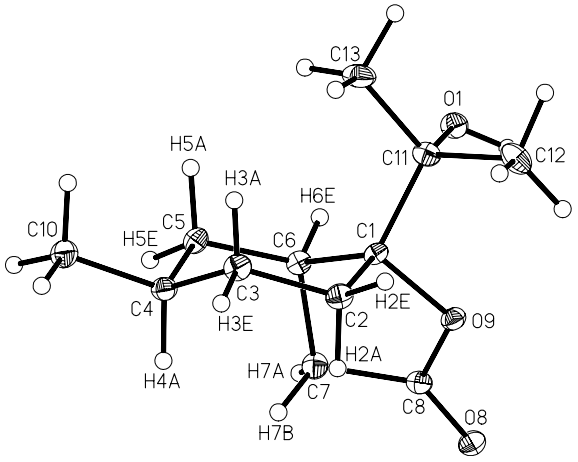


Figure 3. The molecular structure of δ-hydroxy-γ-lactone (−)-(1*R*,4*R*,6*R*)-**25a** with crystallographic numbering.

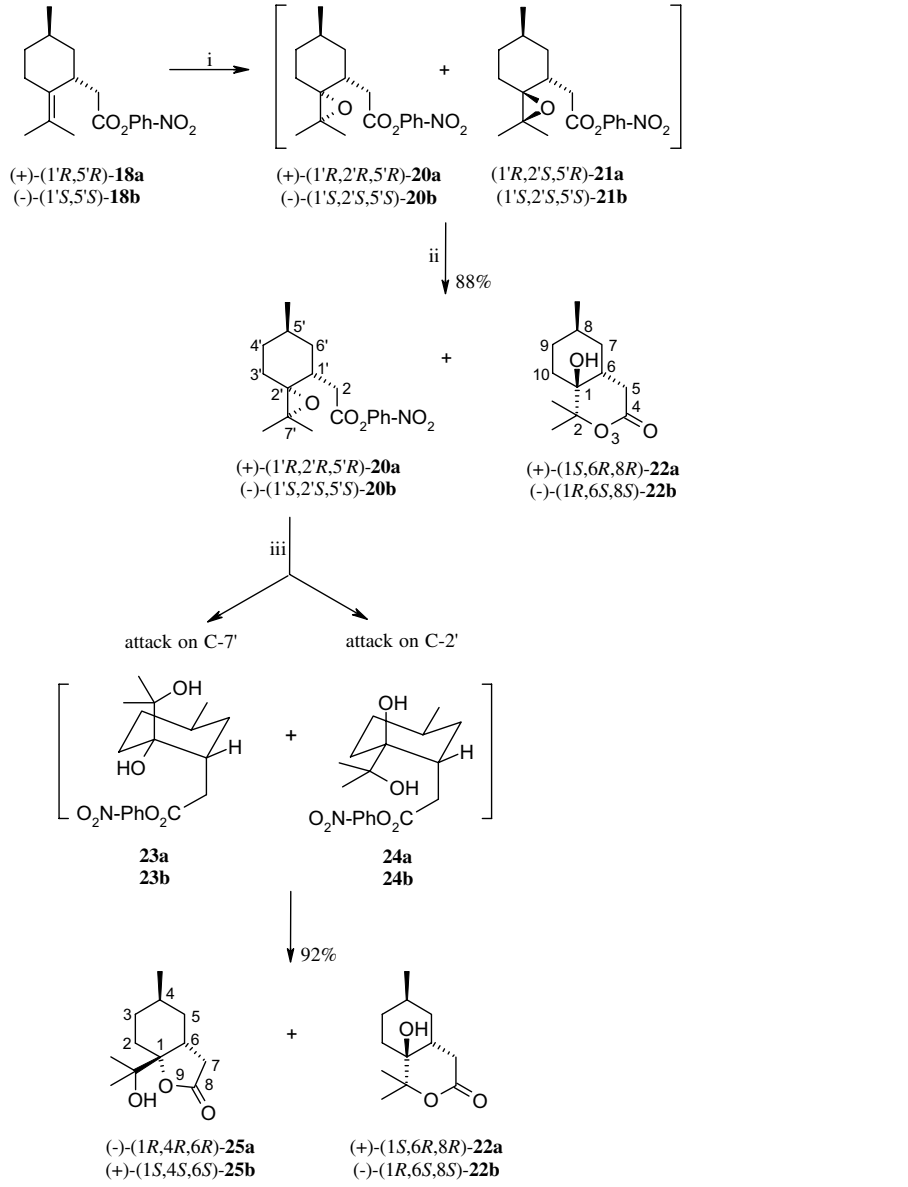
The epoxidation of pure *trans*-*p*-nitrophenyl esters **18a** or **18b** with *m*-chloroperbenzoic acid (*m*-CPBA) afforded the diastereoisomeric mixture of epoxy esters (+)-(1′*R*,2′*R*,5′*R*)-**20a** and (1′*R*,2′*S*,5′*R*)-**21a** or (−)-(1′*S*,2′*S*,5′*S*)-**20b** and (1′*S*,2′*R*,5′*S*)-**21b** (Scheme 2). Unfortunately, these mixtures were inseparable by GC and TLC.

The presence of both diastereoisomers could be only proven by ^{1}H NMR spectrum. The multiplet at $\delta = 2.41$ was ascribed to the H-1′ proton of the isomer **20a** or **20b** with *cis*-situated epoxide ring and aryloxycarbonylmethyl group, while the multiplet at $\delta = 2.22$ to this proton in the *trans*-isomer **21a** or **21b**. From the integration of these signals, it could be seen that the mixture contained 40% of the *cis*-epoxy ester **20a** or **20b** and 60% of the *trans*-isomer **21a** or **21b**. In the case of *trans*-epoxy ester **21a** or **21b**, the proton H-1′ is seen as a multiplet at a higher field $\delta = 2.22$, which indicates a stronger shielding effect of the oxirane ring on this proton. This also suggests the equatorial position of the H-1′ proton and confirms the trans relationship between the epoxide ring and the aryloxycarbonylmethyl substituent. In spite of many attempts, preparative column chromatography afforded only the pure *cis*-isomer **20a** or **20b**. In addition to this epoxy ester, γ-hydroxy-δ-lactone **22a** or **22b** was eluted from the column as the result of the lactonization of the *trans*-epoxy ester **21a** or **21b** on silica gel. The presence of the δ-lactone ring was confirmed by the IR spectrum (1704 cm^{-1}).

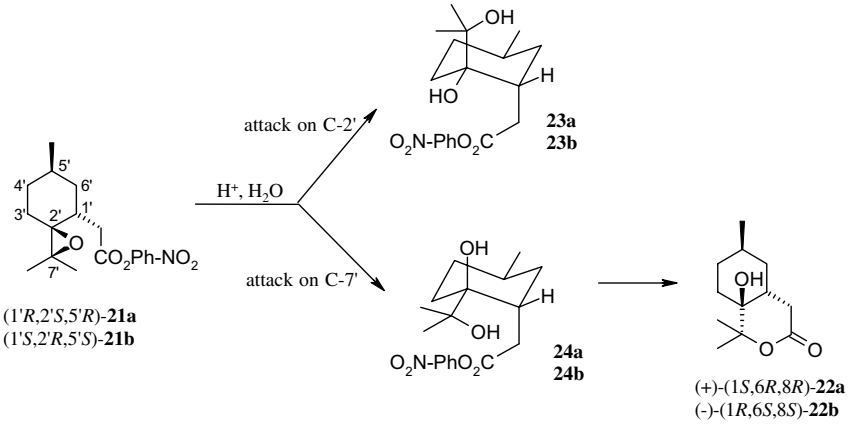
Structures **20a** and **20b** were assigned to the *cis*-epoxy ester isomers on the basis of their 300 MHz ^{1}H NMR spectra. According to the analysis with a Driding model, the oxirane oxygen situated *cis* with respect to the methylene group CH_2-2 shows stronger deshielding effect towards these protons compared with the *trans*-isomer **21a** or **21b**. Both protons of the CH_2-2 group are seen as an AB system (dd, $J = 14.9$ and 7.8 Hz at $\delta = 2.77$ and dd, $J = 14.9$ and 7.4 Hz at $\delta = 2.87$) at a lower field compared with the same protons of the *trans*-isomer (dd, $J = 15.2$ and 11.1 Hz at $\delta = 2.82$ and ddd $J = 15.2$, 4.1 and 0.9 Hz at $\delta = 2.57$).

The established mechanism of acidic lactonization of epoxy esters, induced by H^+ ions, states that the reaction proceeds through diols **23a** and **24a** or **23b** and **24b** (Schemes 2 and 3).[19] Thus, a nucleophile should attack the C-2′ or C-7′ atom from the opposite side of the oxonium ion that is formed after H^+ addition to the oxirane oxygen. In the case of *trans*-epoxy esters **21a** and **21b** with *p*-nitrophenyl group at the axial position, this mode of action only leads to diols **24a** and **24b** with *trans*-diaxial situated hydroxyl and aryloxycarbonylmethyl groups (Scheme 3). This was confirmed by the X-ray structure of the γ-hydroxy-δ-lactone **22a** (Fig. 2). The crystal structure of **22a** undoubtedly confirms the *trans*-diaxial orientation of the hydroxy group at the C-1 atom and the bond C6–C5 of the lactone ring.

The pure *cis*-epoxy esters **20a** and **20b** were subjected to acidic lactonization catalyzed by $HClO_4$ in THF/H_2O solution (Scheme 2). The reaction mixture after 24 h (when the epoxy ester was no longer detected by TLC analysis) contained two isomeric hydroxy lactones **22a** and **25a** or **22b** and **25b** (2.5:97.5), which were then separated by column chromatography. The first fraction



Scheme 2. Reagents and conditions: (i) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 24 h; (ii) silica gel; (iii) THF, $HClO_4$, H_2O, 24 h at rt, **22a**:**25a** = 2.5%:97.5%.



Scheme 3. Acidic lactonization of *trans*-epoxy esters (1′*R*,2′*S*,5′*R*)-**21a** and (1′*S*,2′*R*,5′*S*)-**21b**.

eluted with hexane/ethyl acetate (3:1) afforded the pure δ-hydroxy-γ-lactone **22a** or **22b** ($R_f = 0.21$), whereas the second one afforded a small amount of a mixture of hydroxy lactones **22a** and **25a** or **22b** and **25b**. The

structure of δ-hydroxy-γ-lactones **25a** and **25b** was established on the basis of spectroscopic and crystallographic methods. The presence of the γ-lactone ring was confirmed by the IR spectrum (1764 cm^{-1}). The ratio of lactones obtained **22a** and **25a** (2.5:97.5) indicates that in the case of *cis*-epoxy ester **20a** or **20b** with *p*-nitrophenyl group in the axial position the attack of a nucleophile on the C-7′ atom, leading to the diols **23a** or **23b** with *trans*-diaxial situated hydroxyisoporopyl and aryloxycarbonylmethyl groups, is favourable (Scheme 2). The X-ray structure of the δ-hydroxy-γ-lactone **25a** undoubtedly confirmed the axial position of the hydroxyisopropyl group at the C-1 atom and the axial orientation of the C6–C7 bond (Fig. 3).

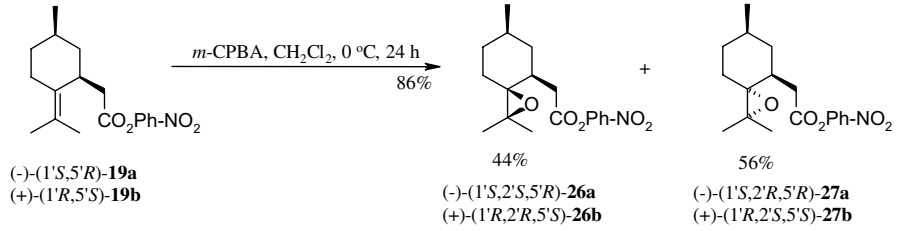
Two other enantiomeric pairs of *cis*-fused bicyclic γ-hydroxy-δ-lactones **30a** and **30b** and δ-hydroxy-γ-lactones **31a** and **31b** were obtained from the pure *p*-nitrophenyl esters **19a** and **19b** with *cis*-situated methyl and aryloxycarbonylmethyl groups (Scheme 4). The epoxidation of *cis*-ester **19a** or **19b** with *m*-CPBA afforded a diastereoisomeric mixture of *cis*- and *trans*-epoxy esters (−)-(1′*S*,2′*S*,5′*R*)-**26a** and (−)-(1′*S*,2′*R*,5′*R*)-**27a** or (+)-(1′*R*,2′*R*,5′*S*)-**26b** and (+)-(1′*R*,2′*S*,5′*S*)-**27b** in the ratio of 44:56.

Fortunately, these epoxy esters were easily separable by column chromatography. The first fraction eluted with hexane/acetone (10:1, $R_f = 0.43$) gave the pure epoxy ester **26a** or **26b** with a *cis*-situated epoxide ring and aryloxycarbonylmethyl group, whereas the second fraction gave *trans*-isomer **27a** or **27b** ($R_f = 0.39$). The structures of epoxy esters **26** and **27** were established on the basis of spectroscopic methods. Similar to the ^1H NMR spectra of epoxy esters **20** and **21** with the axial aryloxycarbonylmethyl group, the oxirane oxygen situated cis with respect to the equatorial methyl group CH_2-2 in epoxy esters **26a** and **26b** shows a stronger deshielding effect towards these protons (dd, $J = 15.1$ and 6.7 Hz at $\delta = 2.63$ and dd, $J = 15.1$ and 8.2 Hz at $\delta = 2.91$) compared with the same protons of *trans*-isomer **27a** or **27b** (d, $J = 10.4$ Hz at $\delta = 2.74$ and t, $J = 10.4$ Hz at $\delta = 2.53$). One proton of the CH_2-2 group in the ^1H NMR spectrum of *trans*-epoxy esters **27a** or **27b** should be seen as a multiplet dd, but similar coupling constants mean that it gives the triplet at a higher field $\delta = 2.53$ ($J = 10.4$ Hz) covering with the multiplet from the proton H-1′.

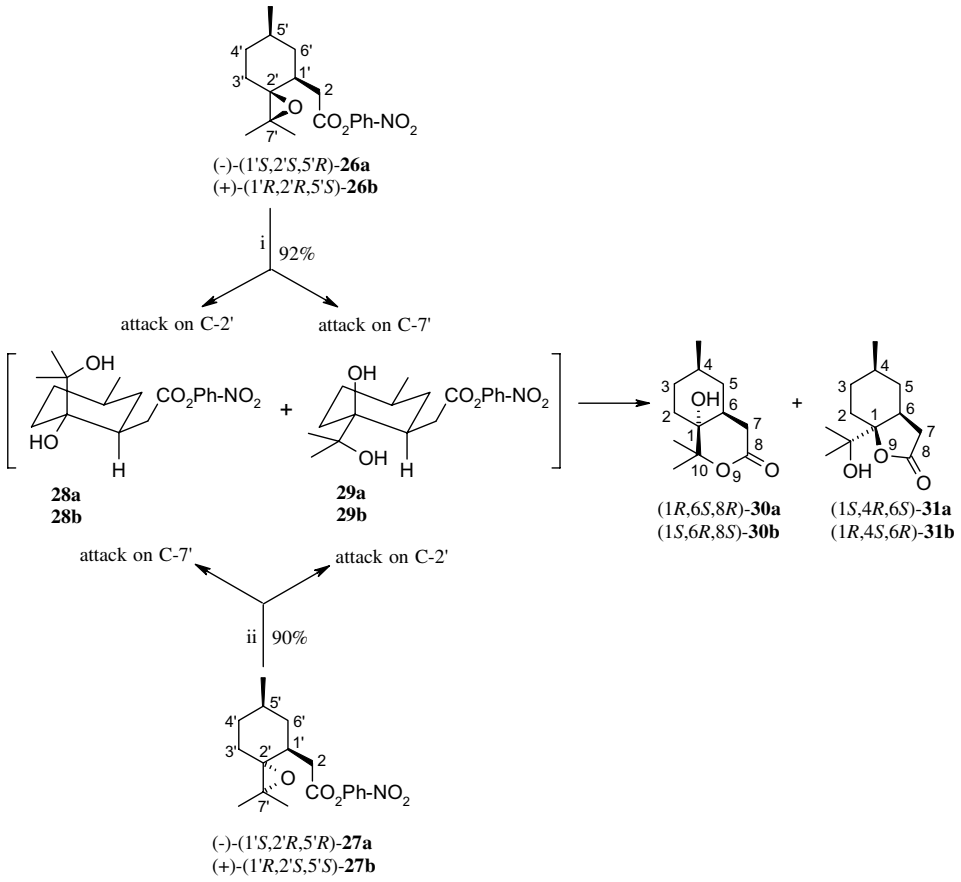
The pure *cis*-epoxy esters **26a** and **26b** were subjected to the acidic lactonization catalyzed with $HClO_4$ in a mixture of THF/H_2O (Scheme 5). After 24 h, the product mixture contained two isomeric hydroxy lactones (1*R*,6*S*,8*R*)-**30a** and (1*S*,4*R*,6*S*)-**31a** or (1*S*,6*R*,8*S*)-**30b** and (1*R* 4*S*,6*R*)-**31b** in a ratio of 24:76.

Similar results were obtained from the pure *trans*-epoxy ester **27a** or **27b**—23% of γ-hydroxy-δ-lactone **30a** or **30b** and 77% of δ-hydroxy-γ-lactone **31a** or **31b**. Although the presence of both hydroxy lactone isomers **30a** and **31a** or **30b** and **31b** was very clearly seen by GC, they were inseparable by means of preparative column and HPLC chromatography. However, the ratio of hydroxy lactones obtained, indicates that in the case of *cis*-epoxy ester **26a** or **26b** with the equatorial aryloxycarbonylmethyl group, the attack of a nucleophile on the C-2′ or C-7′ atom leads to diols **28a** and **29a** or **28b** and **29b**, respectively. As the same was observed for the pure *trans*-epoxy ester **27a** or **27b**, it can be supposed that the equatorial orientation of aryloxycarbonylmethyl group allows it to form diols **29** with the hydroxyisopropyl group at the equatorial position as the main intermediates of the acidic lactonization of epoxy esters **26** and **27**.

Pure *cis*-fused bicyclic γ-hydroxy-δ-lactones **22a** and **22b** and δ-hydroxy-γ-lactones **25a** and **25b** were tested for antifeedant activity against selected storage pest insects (*Sitophilus granarius* L., *Trogoderma granarium* Ev., *Tribolium confusum Duv*.), the lesser mealworm (*Alphitobius diaperinus* Panzer), the Colorado potato beetle (*Leptinotarsa decemlineata* Say) and the peach potato aphid (*Myzus persicae* Sulz). Biological tests were carried out according to the procedures described by Paruch et al.[13c] Szczepanik et al.[13a] and Gabryś et al.,[13d] respectively. The lactones synthesized showed moderate activity against all mentioned storage pest insects (total coefficients of deterrence[13c] −44 to 171).[14d] A strong relationship between biological activity and the configuration of the stereogenic centres was seen for *cis*-fused bicyclic δ-hydroxy-γ-lactones **25a** and **25b**. Lactone **25a** with a (1*R*,4*R*,6*R*)-configuration was a quite good antifeedant against *Tribolium confusum* beetles (total coefficient of deterrence 114), whereas its enantiomer (1*S*,4*S*,6*S*)-**25b** slightly stimulated feeding in these insects (total coefficient of deterrence −44). Hydroxy lactones **22a** and **22b** and **25a** and **25b** appeared to be more effective antifeedants against the Colorado potato beetle, *Leptinotarsa decemlineata* Say, (total coefficients of deterrence 116–175) and the lesser mealworm *Alphitobius diaperinus* Panzer (total coefficients of deterrence 123–184).[14a,d,20] Only γ-hydroxy-δ-lactone **22a** with a (1*S*,6*R*,8*R*)-configuration was active against *M. persicae*. Sulz.[14d] The details of these studies will be the subject of separate publications.



Scheme 4. Epoxidation of *p*-nitrophenyl esters (−)-(1′*S*,5′*R*)-**19a** and (+)-(1′*S*,5′*R*)-**19b**.



Scheme 5. Reagents and conditions: (i) THF, H_2O, $HClO_4$, 24 h at rt, **30a**:**31a** = 24%:76%; (ii) THF, H_2O, $HClO_4$, 24 h at rt, **30a**:**31a** = 23%:77%.

3. Conclusion

Enantiomeric pairs of *cis*-fused bicyclic γ-hydroxy-δ-lactones **22a** and **22b**, **30a** and **30b** as well as δ-hydroxy-γ-lactones **25a** and **25b**, **31a** and **31b** with the *p*-menthane system were obtained in a few step synthesis from enantiomerically pure isomers of (+)-(*R*)- and (−)-(*S*)-pulegone. The synthetic methodology involved a one-pot combination of allylic and Claisen rearrangements of *cis*-pulegols, transesterification of ethyl esters to *p*-nitrophenyl esters through acid chlorides, epoxidation of γ,δ-unsaturated *p*-nitrophenyl esters and acidic lactonization of epoxy esters to the corresponding hydroxy lactones. The structures of compounds were established on the basis of spectroscopic and crystallographic methods. Hydroxy lactones **22a** and **22b** and **25a** and **25b** proved to be very active antifeedants against the Colorado potato beetle (*Leptinotarsa decemlineata* Say) and the lesser mealworm *Alphitobius diaperinus* Panzer. Biological tests for antifeedant activity indicated the strong relationship between biological activity and the configuration of stereogenic centres.

4. Experimental

4.1. General methods

Reagents: (+)-(*R*)-pulegone, (−)-(*S*)-pulegone, triethyl orthoacetate, *m*-chloroperbenzoic acid (77%) and sodium *p*-nitrophenolate (70–80%) were purchased from Aldrich or Fluka (Poland). *^{1}H NMR spectra*: Bruker Avance DRX 300 (300 MHz) spectrometer, TMS as internal standard, for $CDCl_3$ or CD_2Cl_2 solutions. *IR spectra*: Specord M 80 spectrophotometer (Carl Zeiss Jena). *Melting points*: Boetius apparatus (uncorrected). *Optical rotations*: Autopol IV automatic polarimeter (Rudolph), in acetone or ethanol solutions, concentrations denoted in g/100 ml. *GC analyses*: Varian CP-3380 instrument (FID, carrier gas H_2), using the following capillary columns: HP-5 (crosslinked 5% phenyl methyl siloxane) 25 m × 0.32 mm × 0.52 μm and CP-Cyclodextrin-β-2,3,6-*m*-19, 25 m × 0.25 mm × 0.25 μm. *HPLC analyses*: Waters 2690 Separations Module Alliance and Waters 600 Controller instruments, Waters 996 Detector (Photodiode Array Detector UV), using the following columns: Waters Spherisorb® 5 μm silica analytical column (4.6 mm × 250 mm) and Nova-Pack® silica 6 μm preparative column (19 mm × 300 mm), with a mixture of THF and hexane (99.5%:0.5%) as eluent. *Analytical TLC*: Silicagel DC-Alufolien Kieselgel 60 F_{254} (Merck), hexane, acetone and diethyl ether in various ratios as developing systems, 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. *Column chromatography*: silica gel (Kieselgel 60, 40–63 μm, 230–400 mesh, Merck), hexane, acetone and diethyl ether in varying ratios as eluents. *X-ray structural analyses*: 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 ($\lambda = 0.71073$ 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 15–20 s. Accurate cell parameters were determined and refined by a least-squares fit of 1800–2000 of the strongest reflections. The data were corrected for Lorentz and polarization effects. No absorption correction was applied. Data reduction and analysis were carried out with the CrysAlice 'RED' program.[21] Space groups were determined using the XPREP program. The structures were solved by direct methods using the XS program and refined on all F^2 data with the XL program.[22] Non-hydrogen atoms were refined with anisotropic displacement parameters; hydrogen atoms were included from geometry of molecules and $\Delta\rho$ maps. These were refined with isotropic displacement parameters. Crystallographic data for the structures 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 or http://www.ccdc.cam.ac.uk).

4.2. Preparation of ethyl esters (+)-(1′*R*,5′*R*)-14a and (1′*S*,5′*R*)-15a

A mixture of the crude *cis*-pulegol (−)-(1*R*,5*R*)-**12a** (0.97 g, 6.29 mmol), triethyl orthoacetate (9.5 ml, 50.32 mmol), propionic acid (two drops) and a catalytic amount of water was heated at 138 °C for 3 h under the conditions for the distillative removal of ethanol. When the reaction was completed (GC, TLC), the mixture was concentrated in vacuo to remove unreacted orthoacetate. The residue was chromatographed on silica gel. The first fraction, eluted with hexane/diethyl ether (80:1), gave a small amount of ester (+)-(1′*R*,5′*R*)-**14a** (7.4 mg). The second fraction afforded an inseparable mixture of esters (+)-(1′*R*,5′*R*)-**14a** and (1′*S*,5′*R*)-**15a** (according to the GC analysis 80%:20%, 1.1 g, 78% yield).

4.2.1. Ethyl (+)-(1′*R*,5′*R*)-(2′-isoporopyliden-5′-methylcyclohex-1′-yl)acetate: 14a. $[\alpha]_D^{25} = +30.5$ (*c* 3.16, acetone); $n_D^{20} = 1.4781$; IR (film): $\nu = 1748$ cm^{-1} (s, C=O), 1376 (m, $(CH_3)_2C<$), 1264 (m, C–O–C); ^{1}H NMR ($CDCl_3$, 25 °C): $\delta = 0.82$ (d, $J = 6.1$ Hz, 3H, CH_3-5′), 1.11 (m, 1H, one of the CH_2-6′ group), 1.20 (t, $J = 7.1$ Hz, 3H, –OCH_2CH_3), 1.56–1.71 (m, 4H, CH_2-4′, one of the CH_2-6′ group and H-5′), 1.61 (d, $J = 1.2$, 3 Hz, =C–CH_3), 1.66 (d, $J = 2.0$ Hz, 3H, =C–CH_3), 1.83 (m, 1H, one of the CH_2-3′ group), 2.39 (m, 2H, CH_2-2), 2.50 (m, 1H, one of the CH_2-3′ group), 3.31 (m, 1H, H-1′), 4.06 (m, 2H, –OCH_2CH_3).

4.2.2. Ethyl (1′*S*,5′*R*)-(2′-isopropyliden-5′-methylcyclohex-1′-yl)acetate: 15a. Spectral data for the ethyl ester (1′*S*,5′*R*)-**15a** were found from the ^{1}H NMR spectrum ($CDCl_3$, 25 °C) of the mixture of **14a** and **15a**: $\delta = 0.9$ (d, $J = 6.7$ Hz, 3H, CH_3-5′), 3.04 (m, 1H, H-1′), 4.06 (m, 2H, –OCH_2CH_3).

4.3. Preparation of ethyl esters (−)-(1′*S*,5′*S*)-14b and (1′*R*,5′*S*)-15b

According to the procedure described for the preparation of (+)-(1′*R*,5′*R*)-**14a** and (1′*S*,5′*R*)-**15a**, the crude *cis*-pulegol (+)-(1*S*,5*S*)-**12b** (0.90 g, 5.83 mmol) yielded a mixture of unsaturated esters (−)-(1′*S*,5′*S*)-**14b** and (1′*R*,5′*S*)-**15b** (according to the GC analysis 80:20, 1.03 g, 79% yield). Their IR and NMR spectra were identical with those of (+)-(1′*R*,5′*R*)-**14a** and (1′*S*,5′*R*)-**15a**.

4.4. Preparation of acids (1′*R*,5′*R*)-16a and (1′*S*,5′*R*)-17a

A mixture of unsaturated esters (+)-(1′*R*,5′*R*)-**14a** and (1′*S*,5′*R*)-**15a** (80:20, 0.80 g, 3.57 mmol) was refluxed for 3 h in 2.5% KOH/EtOH solution (14 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 products extracted with diethyl ether. The combined ethereal solution was washed with brine, dried over $MgSO_4$ and evaporated in vacuo to give the crude mixture of acids (1′*R*,5′*R*)-**16a** and (1′*S*,5′*R*)-**17a** (according to the GC analysis 80%:20%, 0.69 g, 98% yield).

4.4.1. (1′*R*,5′*R*)-(2′-Isoporopyliden-5′-methylcyclohex-1′-yl)acetic acid 16a and (1′*S*,5′*R*)-(2′-isopropyliden-5′-methylcyclohex-1′-yl)acetic acid 17a. IR (film): $\nu = 3000$ cm^{-1} (m, br, OH), 1724 (s, C=O), 1364 and 1380 (s, $(CH_3)_3C<$). The spectral data for the acids (1′*R*,5′*R*)-**16a** and (1′*S*,5′*R*)-**17a** were found from the ^{1}H NMR spectrum ($CDCl_3$, 25 °C) of the mixture of **16a** and **17a**: (1′*R*,5′*R*)-**16a**: $\delta = 0.83$ (d, $J = 6.1$ Hz, 3H, CH_3-5′), 1.62 (s, 3H, =C–CH_3), 1.65 (d, $J = 1.8$ Hz, 3H, =C–CH_3), 3.33 (m, 1H, H-1′), 11.0 (br s, 1H, –COOH). (1′*S*,5′*R*)-**17a**: $\delta = 0.91$ (d, $J = 6.7$ Hz, 3H, CH_3-5′), 1.64 and 1.65 (two s, 6H, =$C(CH_3)_2$), 3.08 (m, 1H, H-1′), 11.0 (br s, 1H, –COOH).

4.5. Preparation of acids (1′*S*,5′*S*)-16b and (1′*R*,5′*S*)-17b

Treatment of the mixture of ethyl esters (−)-(1′*S*,5′*S*)-**14b** and (1′*R*,5′*S*)-**15b** (80:20, 0.90 g, 4.01 mmol) similar to the hydrolysis of (+)-(1′*R*,5′*R*)-**14a** and (1′*S*,5′*R*)-**15a** afforded the crude mixture of acids (1′*S*,5′*S*)-**16b** and (1′*R*,5′*S*)-**17b** (according to the GC analysis 80%:20%, 0.77 g, 98% yield). Their IR and NMR spectra were identical with those of (1′*R*,5′*R*)-**16a** and (1′*S*,5′*R*)-**17a**.

4.6. Preparation of *p*-nitrophenyl esters (+)-(1′*R*,5′*R*)-18a and (−)-(1′*S*,5′*R*)-19a

PCl_5 (0.92 g, 4.43 mmol) was added in one portion to a stirred mixture of acids (1′*R*,5′*R*)-**16a** and (1′*S*,5′*R*)-**17a** (80:20, 0.87 g, 4.43 mmol) in dry CCl_4 (10 ml). Stirring was continued for 12 h at 45 °C. The solvent was evaporated and the resulting mixture of chlorides dried in vacuo (1 mmHg, 60 °C) for 45 min. The syrup was then dissolved in dry CH_2Cl_2 (30 ml) and anhydrous sodium *p*-nitrophenolate (0.78 g, 4.87 mmol) added in one portion. The mixture was stirred for a further 10 h at

room temperature. When the reaction was completed (TLC, hexane/Et_2O 30:1), the insoluble salt was filtered and the solvent evaporated in vacuo. The crude mixture of *p*-nitrophenyl esters (+)-(1′*R*,5′*R*)-**18a** and (−)-(1′*S*,5′*R*)-**19a** (according to the GC analysis 80%:20%) was purified and separated by HPLC (Nova-Pack® Silica 6 μm preparative column, 19 mm × 300 mm). The first fraction, eluted with hexane/THF (99.5:0.5), gave the pure *p*-nitrophenyl ester (−)-(1′*S*,5′*R*)-**19a** (retention time 21.25 min, 0.25 g). The second fraction afforded the pure *p*-nitrophenyl ester (+)-(1′*R*,5′*R*)-**18a** (retention time 25.27 min, 0.97 g). Total reaction yield was 87%.

4.6.1. *p*-Nitrophenyl (+)-(1′*R*,5′*R*)-(2′-isoporopyliden-5′-methylcyclohex-1′-yl)acetate 18a. $[\alpha]_D^{25} = +14.3$ (*c* 3.45, acetone); $n_D^{20} = 1.5338$; IR (film): 1772 cm^{-1} (s, C=O), 1532 and 1352 (s, C–NO_2), 1496 and 1108 (s, C–C of the *p*-nitrophenyl ring), 1208 (s, C–O–C), 876 (m, C–H of the *p*-nitrophenyl ring); ^1H NMR (CD_2Cl_2, 25 °C): $\delta = 0.88$ (d, $J = 6.1$ Hz, 3H, CH_3-5′), 1.22 (m, 1H, one of the CH_2-6′ group), 1.68 (d, $J = 1.4$ Hz, 3H, =C–CH_3), 1.69 (s, 3H, =C–CH_3), 1.68–1.76 (m, 4H, CH_2-4′, one of the CH_2-6′ group and H-5′), 1.96 (m, 1H, one of the CH_2-3′ group), 2.60 (m, 1H, one of the CH_2-3′ group), 2.69 (dd, $J = 14.1$ and 7.3 Hz, 1H, CH_2-2), 2.78 (dd, $J = 14.0$ and 8.7 Hz, 1H, CH_2-2), 3.47 (m, 1H, H-1′), 7.22 and 8.24 (AA′BB′ system, 4H, –C_6H_4–); $C_{18}H_{23}NO_4$ (317.16): calcd C 68.12, H 7.30, N 4.41, O 20.16; found C 68.14, H 7.34, N 4.40, O 20.19.

4.6.2. *p*-Nitrophenyl (−)-(1′*S*,5′*R*)-(2′-isopropyliden-5′-methylcyclohex-1′-yl)acetate 19a. $[\alpha]_D^{25} = -73.9$ (*c* 1.29, acetone); $n_D^{20} = 1.5338$; IR (film): 1776 cm^{-1} (s, C=O), 1536 and 1352 (s, C–NO_2), 1496 and 1164 (s, C–C of the *p*-nitrophenyl ring), 1212 (s, C–O–C), 872 (m, C–H of the *p*-nitrophenyl ring); ^1H NMR (CD_2Cl_2, 25 °C): $\delta = 0.98$ (d, $J = 6.7$ Hz, 3H, CH_3-5′), 1.20–1.31 (m, 2H, CH_2-6′), 1.53–1.83 (m, 3H, CH_2-4′, H-5′), 1.68 (s, 3H, =C–CH_3), 1.70 (d, $J = 1.8$ Hz, 3H, =C–CH_3), 2.04 (m, 1H, one of the CH_2-3′ group), 2.43 (m, 1H, one of the CH_2-3′ group), 2.57 (dd, $J = 14.5$ and 9.3 Hz, 1H, CH_2-2), 2.68 (dd, $J = 14.5$ and 6.0 Hz, 1H, CH_2-2), 3.23 (m, 1H, H-1′), 7.27 and 8.26 (AA′BB′ system, 4H, –C_6H_4–); $C_{18}H_{23}NO_4$ (317.16): calcd C 68.12, H 7.30, N 4.41, O 20.16; found C 68.10, H 7.29, N 4.42, O 20.17.

4.7. Preparation of *p*-nitrophenyl esters (−)-(1′*S*,5′*S*)-18b and (+)-(1′*R*,5′*S*)-19b

In the same manner as described for the preparation of (+)-(1′*R*,5′*R*)-**18a** and (−)-(1′*S*,5′*R*)-**19a**, the mixture of acids (1′*S*,5′*S*)-**16b** and (1′*R*,5′*S*)-**17b** (80%:20%, 0.96 g, 4.89 mmol) yielded the pure *p*-nitrophenyl esters (−)-(1′*S*,5′*S*)-**18b** (1.08 g) and (+)-(1′*R*,5′*S*)-**19b** (0.28 g). Total reaction yield was 88% (according to the GC analysis 80% of **18b** and 20% of **19b**).

4.7.1. *p*-Nitrophenyl (−)-(1′*S*,5′*S*)-(2′-isoporopyliden-5′-methylcyclohex-1′-yl)acetate 18b. $[\alpha]_D^{25} = -15.2$ (*c* 2.62, acetone). The IR and NMR spectra were identical with those of (+)-(1′*R*,5′*R*)-**18a**.

4.7.2. *p*-Nitrophenyl (+)-(1′*R*,5′*S*)-(2′-isopropyliden-5′-methylcyclohex-1′-yl)acetate 19b. $[\alpha]_D^{25} = +74.8$ (*c* 0.96, acetone). The IR and NMR spectra were identical with those of (−)-(1′*S*,5′*R*)-**19a**.

4.8. Epoxidation of *p*-nitrophenyl ester (+)-(1′*R*,5′*R*)-18a

A solution of *m*-chloroperbenzoic acid (0.59 g, 2.65 mmol) in CH_2Cl_2 (15 ml) was added dropwise to an ice-cooled and stirred solution of the *p*-nitrophenyl ester (+)-(1′*R*,5′*R*)-**18a** (0.7 g, 2.21 mmol) in CH_2Cl_2 (20 ml). The reaction temperature was gradually increased to room temperature and the mixture was stirred for a further 24 h. When the reaction was completed (GC, TLC) the excess of *m*-chloroperbenzoic acid was reduced with saturated $Na_2S_2O_3$ solution. The separated organic layer was washed with 10% Na_2CO_3 solution and brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude mixture of the epoxy esters (+)-(1′*R*,2′*R*,5′*R*)-**20a** and (1′*R*,2′*S*,5′*R*)-**21a** was chromatographed on silica gel. During purification and separation by column chromatography, compound (1′*R*,2′*S*,5′*R*)-**21a** underwent lactonization to the γ-hydroxy-δ-lactone (+)-(1*S*,6*R*,8*R*)-**22a** with only the epoxy ester (+)-(1′*R*,2′*R*,5′*R*)-**20a** separated. The first fraction, eluted with hexane/ethyl acetate (10:1), gave the pure epoxy ester (+)-(1′*R*,2′*R*,5′*R*)-**20a** (0.26 g). The second fraction, eluted with hexane/ethyl acetate (3:1), afforded the pure γ-hydroxy-δ-lactone (+)-(1*S*,6*R*,8*R*)-**22a** (0.25 g). Total reaction yield was 88%.

4.8.1. *p*-Nitrophenyl (+)-(1′*R*,2′*R*,5′*R*)-(2′,7′-epoxy-2′-isoporopyl-5′-methylcyclohex-1′-yl)acetate 20a. $[\alpha]_D^{25} = +37.5$ (*c* 3.11, acetone); $n_D^{20} = 1.5149$; IR (film): $\nu = 1764$ cm^{-1} (s, C=O), 1524 and 1347 (s, C–NO_2), 1490 and 1111 (s, C–C of the *p*-nitrophenyl ring), 1212 (s, C–O–C), 869 (m, C–H of the *p*-nitrophenyl ring); ^1H NMR (CD_2Cl_2, 25 °C): $\delta = 0.93$ (d, $J = 6.3$ Hz, 3H, CH_3-5′), 1.03 and 1.30 (two m, 2H, CH_2-6′), 1.36 and 1.39 (two s, 6H, >C(CH_3)$_2$), 1.45 (m, 1H, one of the CH_2-3′), 1.64–1.88 (m, 3H, CH_2-4′ and H-5′), 1.90 (m, 1H, one of the CH_2-3′ group), 2.41 (m, 1H, H-1′), 2.77 (dd, $J = 14.9$ and 7.8 Hz, 1H, one of the CH_2-2 group), 2.87 (dd, $J = 14.9$ and 7.4 Hz, 1H, one of the CH_2-2 group), 7.33 and 8.24 (AA′BB′ system, 4H, –C_6H_4–).

4.8.2. *p*-Nitrophenyl (1′*R*,2′*S*,5′*R*)-(2′,7′-epoxy-2′-isopropyl-5′-methylcyclohex-1′-yl)acetate 21a. Spectral data for the epoxy ester (1′*R*,2′S,5′*R*)-**21a** were found from the ^1H NMR spectrum (CD_2Cl_2, 25 °C) of the crude mixture of **20a** and **21a**: $\delta = 0.94$ (d, $J = 6.0$ Hz, 3H, CH_3-5′), 1.30 and 1.35 (two s, 6H, >C(CH_3)$_2$), 2.22 (m, 1H, H-1′), 2.57 (ddd, $J = 15.2$, 4.1 and 0.9 Hz, 1H, one of the CH_2-2 group), 2.82 (dd, $J = 15.2$ and 11.1 Hz, 1H, one of the CH_2-2 group), 7.31 and 8.25 (AA′BB′ system, 4H, –C_6H_4–).

4.8.3. (+)-(1*S*,6*R*,8*R*)-1-Hydroxy-2,2,8-trimethyl-3-oxabicyclo[4.4.0]decan-4-one: 22a. $[\alpha]_D^{25} = +43.8$ (*c* 1.46, acetone); mp = 147–149 °C; IR (Nujol): 3432 cm^{-1} (s, OH), 1704 (s, C=O), 1380 and 1372 (m, (CH_3)$_2$C<), 1308 (s, C–OH), 1244 (s, C–O–C) 1120 (s, O–H); ^1H

NMR ($CDCl_3$, 25 °C): δ = 0.9 (d, J = 5.7 Hz, 3H, CH_3-8), 1.15–1.34 (m, 2H, CH_2-7), 1.32 and 1.44 (two s, 6H, >C(CH_3)$_2$), 1.43–1.74 (m, 5H, CH_2-9, CH_2-10 and H-8), 2.37 (m, 1H, H-6), 2.57 (dd, J = 19.4 and 9.7 Hz, 1H, one of the CH_2-5 group), 2.68 (dd, 19.4 and 9.3 Hz, 1H, one of the CH_2-5 group); $C_{12}H_{20}O_3$ (212.29): calcd C 67.89, H 9.49; found C 67.91, H 9.52. Crystal data for (1*S*,6*R*,8*R*)-(+)-**22a**: $C_{12}H_{20}O_3$, M = 212.28, colourless block, crystal dimensions 0.35 × 0.35 × 0.35, monoclinic, space group $P2_1$, a = 9.1494(16), b = 7.4407(11), c = 9.5183(13) Å, β = 118.509(16), V = 569.41(15) Å^3, Z = 2, D_c = 1.238 Mg m^{-3}, T = 100 K, R = 0.0406, Rw = 0.0885 (1974 reflections, all data) for 216 variables. CCDC 252296.

4.9. Epoxidation of *p*-nitrophenyl ester (−)-(1′*S*,5′*S*)-18b

According to the procedure described for the preparation of (+)-(1′*R*,2′*R*,5′*R*)-**20a** and (+)-(1*S*,6*R*,8*R*)-**22a**, the *p*-nitrophenyl ester (−)-(1′*S*,5′*S*)-**18b** (0.85 g, 2.68 mmol) yielded the pure epoxy ester (−)-(1′*S*,2′*S*,5′*S*)-**20b** (0.32 g) and γ-hydroxy-δ-lactone (−)-(1*R*,6*S*,8*S*)-**22b** (0.30 g). Total reaction yield was 89%.

4.9.1. *p*-Nitrophenyl (−)-(1′*S*,2′*S*,5′*S*)-(2′,7′-epoxy-2′-isoporopyl-5′-methylcyclohex-1′-yl)acetate 20b. $[\alpha]_D^{25}$ = −38.9 (*c* 2.46, acetone). Its IR and NMR spectra were identical with those of (+)-(1′*R*,2′*R*,5′*R*)-**20a**.

4.9.2. (−)-(1*R*,6*S*,8*S*)-1-Hydroxy-2,2,8-trimethyl-3-oxa-bicyclo[4.4.0]decan-4-one 22b. $[\alpha]_D^{25}$ = −42.1 (*c* 1.3, acetone). Its IR and NMR spectra were identical with those of (+)-(1*S*,6*R*,8*R*)-**22a**.

4.10. Acidic lactonization of epoxy ester (+)-(1′*R*,2′*R*,5′*R*)-20a

Perchloric acid (60%, 0.25 ml) was added to a solution of the epoxy ester (+)-(1′*R*,2′*R*,5′*R*)-**20a** (0.5 g, 1.5 mmol) in THF (12 ml) and water (6 ml). The mixture was stirred for 24 h at room temperature and the products extracted with diethyl ether. The combined ethereal extracts were washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous $MgSO_4$ and the solvents evaporated in vacuo. The crude mixture of hydroxy lactones (−)-(1*R*,4*R*,6*R*)-**25a** and (+)-(1*S*,6*R*,8*R*)-**22a** (according to the GC analysis 97.5:2.5) was chromatographed on silica gel. The first fraction, eluted with hexane/ethyl acetate (3:1) gave pure δ-hydroxy-γ-lactone (−)-(1*R*,4*R*,6*R*)-**25a** (R_f = 0.21, 0.25 g). The second fraction afforded a small amount of inseparable mixture of hydroxy lactones **25a** and **22a** (0.042 g). Total reaction yield was 92%.

4.10.1. (−)-(1*R*,4*R*,6*R*)-1-(1′-Hydroxy-1′-methylethyl)-4-methyl-9-oxabicyclo[4.3.0]nonan-8-one 25a. $[\alpha]_D^{25}$ = −21.0 (*c* 1.52, acetone); mp = 85–86 °C; IR (Nujol): ν = 3508 cm^{-1} (s, OH), 1764 (s, C=O), 1468 and 1380 (m, >C(CH_3)$_2$), 1300 (s, C–OH), 1244 (s, C–O–C), 1140 (s, O–H); ^{1}H NMR ($CDCl_3$, 25 °C): δ = 0.93 (d, J = 6.4 Hz, CH_3-4), 1.08 and 1.29 (two m, 2H, CH_2-5), 1.24 and 1.31 (two s, 6H, >C(CH_3)$_2$), 1.58–1.77 (m, 4H, one of the CH_2-2 group, CH_2-3 and H-4), 1.97 (m, 1H, one of the CH_2-2 group), 2.47 (dd, J = 18.1 and 8.5 Hz, 1H, one of the CH_2-7 group), 2.70 (dd, J = 18.1 and 10.1 Hz, 1H, one of the CH_2-7 group), 2.93 (m, 1H, H-6). $C_{12}H_{20}O_3$ (212.29): calcd C 67.89, H 9.49; found C 67.76, H 9.39.

Crystal data for (−)-(1*R*,4*R*,6*R*)-**25a**: $C_{12}H_{20}O_3$, M = 212.28, colourless block, crystal dimensions 0.30 × 0.30 × 0.30 mm, orthorhombic, space group $P2_12_12_1$, a = 6.2914(7), b = 8.3463(7), c = 21.5950(17) Å, V = 1133.95(18) Å^3, Z = 4, D_c = 1.243 Mg m^{-3}, T = 100 K, R = 0.0453, Rw = 0.0819 (2678 reflections, all data) for 216 variables. CCDC 252295.

4.11. Acidic lactonization of epoxy ester (−)-(1′*S*,2′*S*,5′*S*)-20b

Treatment of the epoxy ester (−)-(1′*S*,2′*S*,5′*S*)-**20b** (0.4 g, 1.2 mmol) similar to the lactonization of (+)-(1′*R*,2′*R*,5′*R*)-**20a** afforded pure δ-hydroxy-γ-lactone (+)-(1*S*,4*S*,6*S*)-**25b** (0.2 g) and an inseparable mixture of hydroxy lactones **25b** and **22b** (0.03 g).

4.11.1. (+)-(1*S*,4*S*,6*S*)-1-(1′-Hydroxy-1′-methylethyl)-4-methyl-9-oxabicyclo[4.3.0]nonan-8-one 25b. $[\alpha]_D^{25}$ = +22.3 (*c* 1.68, acetone). Its IR and NMR spectra were identical with those of (−)-(1*R*,4*R*,6*R*)-**25a**.

4.12. Epoxidation of *p*-nitrophenyl ester (−)-(1′*S*,5′*R*)-19a

As described for the preparation of epoxides **20** and **21**, the *p*-nitrophenyl ester (−)-(1′*S*,5′*R*)-**19a** (0.22 g, 0.69 mmol) was treated with *m*-CPBA (0.2 g, 0.83 mmol) to give a crude mixture of epoxy esters (−)-(1′*S*,2′*S*,5′*R*)-**26a** and (−)-(1′*S*,2′*R*,5′*R*)-**27a** (according to the GC analysis 44:56), which was then chromatographed on silica gel. The first fraction, eluted with hexane/acetone (10:1), gave the pure epoxy ester (−)-(1′*S*,2′*S*,5′*R*)-**26a** (R_f = 0.43, 0.087 g). The second fraction afforded pure epoxy ester (−)-(1′*S*,2′*R*,5′*R*)-**27a** (R_f = 0.39, 0.11 g). Total reaction yield was 86%.

4.12.1. *p*-Nitrophenyl (−)-(1′*S*,2′*S*,5′*R*)-(2′,7′-epoxy-2′-isoporopyl-5′-methylcyclohex-1′-yl)acetate 26a. $[\alpha]_D^{27}$ = −44.1 (*c* 1.42, acetone); n_D^{20} =1.5152; IR (film): ν = 1765 cm^{-1} (s, C=O), 1524 and 1346 (s, C–NO_2), 1490 and 1111 (s, C–C of the *p*-nitrophenyl ring), 1210 (s, C–O–C), 689 (m, C–H of the *p*-nitrophenyl ring); ^{1}H NMR (CD_2Cl_2, 25 °C): δ = 1.05 (d, J = 6.8 Hz, 3H, CH_3-5′); 1.32–1.49 (m, 3H, CH_2-6′ and one of the CH_2-3′ group), 1.35 and 1.36 (two s, 6H, >C(CH_3)$_2$), 1.68–1.90 (m, 3H, CH_2-4′ and H-5), 2.03 (m, 1H, one of the CH_2-3′ group), 2.48 (m, 1H, H-1′), 2.63 (dd, J = 15.1 and 6.7 Hz, 1H, one of the CH_2-2 group), 2.91 (dd, J = 15.1 and 8.2 Hz, 1H, one of the CH_2-2 group), 7.31 and 8.24 (AA′BB′ system, 4H, –C_6H_4–).

4.12.2. *p*-Nitrophenyl (−)-(1′*S*,2′*R*,5′*R*)-(2′,7′-epoxy-2′-isopropyl-5′-methylcyclohex-1′-yl)acetate 27a. $[\alpha]_D^{27}$ = −14.3 (*c* 0.97, acetone), mp = 85–86 °C; IR (Nujol): ν = 1764 cm^{-1} (s, C=O), 1536 and 1356 (s, C–NO_2),

1500 and 1144 (s, C–C of the *p*-nitrophenyl ring), 1216 (s, C–O–C), 860 (m, C–H of the *p*-nitrophenyl ring); ^{1}H NMR (CD_2Cl_2, 25 °C); 1.02 (d, J = 6.6 Hz, 3H, CH_3-5′), 1.18–1.31 (m, 2H, CH_2-6′), 1.34 and 1.42 (two s, 6H, >C(CH_3)$_2$), 1.62 (m, 1H, one of the CH_2-3′ group), 1.74–1.92 (m, 3H, CH_2-4′ and H-5′), 1.98 (m, 1H, one of the CH_2-3′ group), 2.48 (m, 1H, H-1′), 2.53 (t, J = 10.4 Hz, 1H, one of the CH_2-2 group), 2.74 (d, J = 10.4 Hz, 1H, one of the CH_2-2 group), 7.30 and 8.26 (AA′BB′ system, 4H, –C_6H_4–).

4.13. Epoxidation of *p*-nitrophenyl ester (+)-(1′*R*,5′*S*)-19b

In the same manner as described for the preparation of (−)-(1′*S*,2′*S*,5′*R*)-**26a** and (−)-(1′*S*,2′*R*,5′*R*)-**27a**, *p*-nitrophenyl ester (+)-(1′*R*,5′*S*)-**19b** (0.26 g, 0.82 mmol) yielded the pure epoxy esters (+)-(1′*R*,2′*R*,5′*S*)-**26b** (0.106 g) and (+)-(1′*R*,2′*S*,5′*S*)-**27b** (0.135 g). Total reaction yield was 88%.

4.13.1. *p*-Nitrophenyl (+)-(1′*R*,2′*R*,5′*S*)-(2′,7′-epoxy-2′-isoporopyl-5′-methylcyclohex-1′-yl)acetate 26b. $[\alpha]_D^{27}$ = +45.0 (*c* 0.96, acetone). The IR and NMR spectra were identical with those of (−)-(1′*S*,2′S,5′*R*)-**26a**.

4.13.2. *p*-Nitrophenyl (+)-(1′*R*,2′*S*,5′*S*)-(2′,7′-epoxy-2′-isopropyl-5′-methylcyclohex-1′-yl)acetate 27b. $[\alpha]_D^{27}$ = +15.4 (*c* 1.23, acetone). The IR and NMR spectra were identical with those of (−)-(1′*S*,2′R,5′*R*)-**27a**.

4.14. Acidic lactonization of epoxy ester (−)-(1′*S*,2′*S*,5′*R*)-26a

As described for the preparation of hydroxy lactones **22** and **25**, the acidic lactonization of the epoxy ester (−)-(1′*S*,2′*S*,5′*R*)-**26a** (0.08 g, 0.24 mmol) gave the crude mixture of γ-hydroxy-δ-lactone (1*R*,6*S*,8*R*)-**30a** and δ-hydroxy-γ-lactone (1*S*,4*R*,6*S*)-**31a** (according to the GC analysis 24:76), which was then chromatographed on silica gel. In spite of many attempts, elution with various solvent systems (hexane/acetone 5:1 or hexane/ethyl acetate 3:1) gave an inseparable mixture of hydroxy lactones (1*R*,6*S*,8*R*)-**30a** and (1*S*,4*R*,6*S*)-**31a** (0.047 g, 92% total reaction yield).

4.14.1. (1*R*,6*S*,8*R*)-1-Hydroxy-2,2,8-trimethyl-3-oxabicyclo[4.4.0]decan-4-one (30a) and (1*S*,4*R*,6*S*)-1-(1′-hydroxy-1′-methylethyl)-4-methyl-9-oxabicyclo[4.3.0]nonan-8-one 31a. IR (film): ν = 3484 cm^{-1} (m, br, OH), 1764 (s, C=O), 1716 (s, C=O), 1380 (m, (CH_3)$_2$C<), 1296 (s, C–OH), 1224 (s, C–O–C), 1144 (s, O–H). Spectral data for the hydroxy lactones (1*R*,6*S*,8*R*)-**30a** and (1*S*,4*R*,6*S*)-**31a** were found from the ^{1}H NMR spectrum ($CDCl_3$, 25 °C) of the mixture of **30a** and **31a**.

(1*R*,6*S*,8*R*)-**30a**: 0.92 (d, J = 6.4 Hz, CH_3-8), 1.38 and 1.39 (two s, 6H, (CH_3)$_2$C<), 2.09 (m, 1H, H-6), 2.33 (dd, J = 18.3 and 11.3 Hz, 1H, one of the CH_2-5 group), 2.44 (dd, J = 18.3 and 7.0 Hz, 1H, one of the CH_2-5 group).

(1*S*,4*R*,6*S*)-**31a**: 0.89 (d, J = 6.5 Hz, 3H, CH_3-4), 1.26 and 1.28 (two s, 6H, (CH_3)$_2$C<), 1.95 (dd, J = 17.3 and 3.7 Hz, 1H, one of the CH_2-7 group), 2.61 (m, 1H, H-6), 3.20 (dd, J = 17.3 and 8.1 Hz, 1H, one of the CH_2-7 group).

4.15. Acidic lactonization of epoxy ester (+)-(1′*R*,2′*R*,5′*S*)-26b

According to the procedure described for the preparation of (1*R*,6*S*,8*R*)-**30a** and (1*S*,4*R*,6*S*)-**31a**, epoxy ester (+)-(1′*R*,2′*R*,5′*S*)-**26b** (0.095 g, 0.28 mmol) yielded a mixture of γ-hydroxy-δ-lactone (1*S*,6*R*,8*S*)-**30b** and δ-hydroxy-γ-lactone (1*R*,4*S*,6*R*)-**27b** (according to the GC analysis 24:76, 0.054 g, 90% total reaction yield). Their IR and NMR spectra were identical with those of (1*R*,6*S*,8*R*)-**30a** and (1*S*,4*R*,6*S*)-**31a**.

4.16. Acidic lactonization of epoxy ester (−)-(1′*S*,2′*R*,5′*R*)-27a

Treatment of epoxy ester (−)-(1′*S*,2′*R*,5′*R*)-**27a** (0.09 g, 0.27 mmol) similar to the lactonization of (−)-(1′*S*,2′*S*,5′*R*)-**26a** afforded a mixture of γ-hydroxy-δ-lactone (1*R*,6*S*,8*R*)-**30a** and δ-hydroxy-γ-lactone (1*S*,4*R*,6*S*)-**31a** (according to the GC analysis 23:77, 0.051 g, 90% total reaction yield).

4.17. Acidic lactonization of epoxy ester (+)-(1′*R*,2′*S*,5′*S*)-27b

Treatment of epoxy ester (+)-(1′*R*,2′S,5′*S*)-**27b** (0.083 g, 0.25 mmol) similar to the lactonization of (+)-(1′*R*,2′*R*,5′*S*)-**26b** afforded a mixture of γ-hydroxy-δ-lactone (1*S*,6*R*,8*S*)-**30b** and δ-hydroxy-γ-lactone (1*R*,4*S*,6*R*)-**31b** (according to the GC analysis 23:77, 0.047 g, 88% total reaction yield).

Acknowledgements

This work was supported by the State Committee for Scientific Research (KBN), Grant No. PBZ-KBN-060/T09/2001.

References

1. Guth, H. *J. Agric. Food Chem.* **1997**, *45*, 3022–3026.
2. Guth, H. *Helv. Chim. Acta* **1996**, *79*, 1559–1571.
3. Gaudin, J.-M. *Tetrahedron* **2000**, *56*, 4769–4776.
4. Hinterholzer, A.; Schieberle, P. *Flav. Fragr. J.* **1998**, *13*, 49–55.
5. Näf, R.; Velluz, A. *Flav. Fragr. J.* **1998**, *13*, 203–208.
6. Jagella, T.; Grosch, W. *Z. Lebensm.-Unters. Forsch. A* **1999**, *209*, 16–21.
7. Brenna, E.; Fuganti, C.; Serra, S. *Tetrahedron: Asymmetry* **2003**, *14*, 1–42.
8. (a) Dams, I.; Białońska, A.; Ciunik, Z.; Wawrzeńczyk, C. *J. Agric. Food Chem.* **2004**, *52*, 1630–1634; (b) Dams, I.; Wawrzeńczyk, C.; Kula, J., Polish Patent Application PL-362879 *Bull. Polish Patent Office* **2004**, *7*, 26; (c) Dams, I.; Wawrzeńczyk, C.; Gibka, J., Polish Patent Application PL-362878 *Bull. Polish Patent Office* **2004**, *7*, 26.
9. Dams, I.; Białońska, A.; Ciunik, Z.; Wawrzeńczyk, C. *Eur. J. Org. Chem.* **2004**, 2662–2668.

10. (a) Bilton, J. N.; Broughton, H. B.; Jones, P. S.; Ley, S. V.; Lidert, Z.; Morgan, E. D.; Rzepa, H. S.; Sheppard, R. N.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron* **1987**, *43*, 2805–2815; (b) Broughton, H. B.; Ley, S. V.; Slawin, A. M. Z.; Williams, D. J.; Morgan, E. D. *J. Chem. Soc., Chem. Commun.* **1986**, 46–47; (c) Butterworth, J. H.; Morgan, E. D. *Chem. Commun.* **1968**, 23–24; (d) Kraus, W.; Bokel, M.; Klenk, A.; Pohnl, H. *Tetrahedron Lett.* **1985**, *26*, 6435–6438.
11. Kubo, I.; Lee, Y.-W.; Balogh-Nair, V.; Nakanishi, K.; Chapya, A. *J. Chem. Soc., Chem. Commun.* **1976**, 949–950.
12. (a) Nawrot, J.; Drożdż, B.; Holub, M. *Herba Polonica* **1985**, *31*, 209–213; (b) Nawrot, J.; Harmatha, J.; Nowotny, L. *Biochem. Syst. Ecol.* **1984**, *12*, 99–101; (c) Paul, V. J.; Ciminiello, P.; Fenical, W. *Phytochem.* **1988**, *27*, 1011–1014; (d) Munakata, K. *Pure Appl. Chem.* **1975**, *42*, 57–66; (e) Daniewski, W. M.; Gumułka, M.; Przesmycka, D.; Ptaszyńska, K.; Błoszyk, E.; Drożdż, B. *Phytochem.* **1995**, *38*, 1161–1168; (f) Appel, H. H.; Bond, R. P. M.; Overton, K. H. *Tetrahedron* **1963**, *19*, 635–641.
13. (a) Szczepanik, M.; Grabarczyk, M.; Szumny, A.; Wawrzeńczyk, C. *J. Plant Protection Res.* **2003**, *43*, 87–96; (b) Paruch, E.; Ciunik, Z.; Nawrot, J.; Wawrzeńczyk, C. *J. Agric. Food Chem.* **2000**, *48*, 4973–4977; (c) Paruch, E.; Nawrot, J.; Wawrzeńczyk, C. *Pest Manag. Sci.* **2001**, *57*, 776–780; (d) Halarewicz-Pacan, A.; Gabryś, B.; Dancewicz, K.; Wawrzeńczyk, C. *J. Plant Protection Res.* **2003**, *43*, 133–142.
14. (a) Szczepanik, M.; Dams, I; Wawrzeńczyk, C. *Environ. Entomol.*, submitted for publication; (b) Dams, I.; Wawrzeńczyk, C.; Szczepanik, M.; Gabryś, B.; Dancewicz, K. Polish Patent Application PL-366262 *Bull. Polish Patent Office* **2004**, *18*, 74; (c) Dams, I.; Wawrzeńczyk, C.; Szczepanik, M.; Gabryś, B.; Dancewicz, K., Polish Patent Application PL-366261 *Bull. Polish Patent Office* **2004**, *18*, 73; (d) Dams, I. PhD Thesis, Wrocław University of Technology, Poland, **2004**.
15. (a) Silverstein, R. M.; Brownlee, R. G.; Bellas, T. E.; Wood, D. L.; Browne, L. E. *Science* **1968**, *159*, 889–891; (b) Wood, D. L.; Browne, L. E.; Ewing, B.; Lindahl, K.; Bedard, W. D.; Tilden, P. E.; Mori, K.; Pitman, G. B.; Hughes, P. R. *Science* **1976**, *192*, 896–898; (c) Riley, R. G.; Silverstein, R. M.; Moser, J. C. *Science* **1976**, *183*, 760–762; (d) Tumlinson, J. H.; Klein, M. G.; Doolittle, R. E.; Ladd, T. L.; Proveaux, A. T. *Science* **1977**, *197*, 789–792; (e) Kuwahara, Y.; Matsumoto, K.; Wada, Y.; Suzuki, T. *Appl. Entomol. Zool.* **1991**, *26*, 85–89; (f) Kuwahara, Y.; Yen, L. T. M.; Tominaga, Y.; Matsumoto, K.; Wada, Y. *Agric. Biol. Chem.* **1982**, *46*, 2283–2291; (g) Borden, J. H.; Chong, L.; McLean, J. A.; Slessor, K. N.; Mori, K. *Science* **1976**, *192*, 894–896.
16. (a) Mosandl, A.; Gessner, M. *Z. Lebensm.-Unters. Forsch.* **1988**, *187*, 40–44; (b) Leitereg, T. J.; Guadagni, D. G.; Harris, J.; Mon, T. R.; Teranishi, R. *J. Agric. Food Chem.* **1971**, *19*, 785–787; (c) Haring, H. G.; Rijkens, F.; Boelens, H.; Van der Gen, A. *J. Agric. Food Chem.* **1972**, *20*, 1018–1021; (d) Ohloff, G.; Giersch, W.; Schulte-Elte, K. H.; Enggist, P.; Demole, E. *Helv. Chim. Acta* **1980**, *63*, 1582–1588; (e) Ohloff, G.; Maurer, B.; Winter, B.; Giersch, W. *Helv. Chim. Acta* **1983**, *66*, 192–217; (f) Mosandl, A.; Günther, C. *J. Agric. Food Chem.* **1989**, *37*, 413–418.
17. (a) Beck, G. *Synlett* **2002**, *6*, 837–850; (b) Zaks, A.; Dodds, D. R. *Drug Discovery Today* **1997**, *2*, 513–531; (c) Kenyon, B. M.; Browne, F.; D'Amato, R. J. *Exp. Eye Res.* **1997**, *64*, 971–978; (d) Stephens, T. D.; Bunde, C. J. W.; Fillmore, B. *J. Biochem. Pharmacol.* **2000**, *59*, 1489–1499; (e) Brittain, R. T.; Drew, G. M.; Levy, G. P. *Br. J. Pharmacol.* **1982**, *77*, 105–114; (f) Gold, E. H.; Chang, W.; Cohen, M.; Baum, T.; Ehrreich, S.; Johnson, G.; Prioli, N.; Sybertz, E. J. *J. Med. Chem.* **1982**, *25*, 1363–1370.
18. Tawfik, D. S.; Eshhar, Z.; Bentolia, A.; Green, B. S. *Synthesis* **1993**, 968–972.
19. (a) Olejniczak, T.; Grabarczyk, M.; Wawrzeńczyk, C. *J. Molecular Catal. B: Enzy.* **2001**, *11*, 243–247; (b) Paruch, E.; Ciunik, Z.; Wawrzeńczyk, C. *Eur. J. Org. Chem.* **1998**, 2667–2682.
20. (a) Dams, I.; Szczepanik, M.; Wawrzeńczyk, C. Polish Patent Application PL-370963, *Bull. Polish Patent Office*, in press; (b) Dams, I.; Szczepanik, M.; Wawrzeńczyk, C. Polish Patent Application PL-370964, *Bull. Polish Patent Office*, in press.
21. Oxford Diffraction, Poland Sp. z o.o., CrysAlis CCD and CrysAlis Red, V166, 2001.
22. Bruker AXS, SHELXTL V5.1, 1999.