Hindawi
Journal of Chemistry
Volume 2018, Article ID 6135281, 8 pages
https://doi.org/10.1155/2018/6135281

Research Article

Enantioselective Lactonization of 3,3,6-Trimethyl-4(E)-heptenoic Acid Esters

Robert Obara,[1] Jacek Łyczko ,[2] and Antoni Szumny[2]

[1]*Institute of Chemistry, Jan Kochanowski University, Świętokrzyska 15G, 25-406 Kielce, Poland*
[2]*Department of Chemistry, Wrocław University of Environmental and Life Sciences, Norwida 25, 50-375 Wrocław, Poland*

Correspondence should be addressed to Jacek Łyczko; jacek.lyczko@upwr.edu.pl

Received 8 July 2018; Accepted 22 October 2018; Published 2 December 2018

Academic Editor: Artur M. S. Silva

Studies on the use of lactonization in the asymmetric synthesis of 6,6-dimethyl-4-isopropyl-3-oxabicyclo[3.1.0]hexan-2-one were described. An asymmetrically induced lactonization reaction was performed on 3,3,6-trimethyl-4(E)-heptenoic acid esters (**1**) and enantiomerically pure alcohols such as (−)-menthol (**a**), (+)-menthol (**b**), (−)-borneol (**c**), (+)-isomenthol (**d**), (−)-isopinocampheol (**e**), and (S)-(−)-1-(2-bornylphenyl)-1-ethanol (**f**). The enantiomerically pure alcohols that were used as ancillary chiral substances were characterized by markedly different values of induction power; menthol (**a**, **b**), borneol (**c**), and phenetyl alcohol (**f**) performed better in asymmetric δ-lactonization, whereas isomenthol (**d**) and isopinocampheol (**e**) tended to favor asymmetric γ-lactonization.

1. Introduction

Both natural and synthetic lactones are a well-known group of compounds due to their interesting and useful properties. Among them, especially terpenoid and sesquiterpenoid lactones are abundant in nature [1–8]. They are discernible in the smell of flowers [2, 9], in the smell and flavor of fruit [10–13], and in plants [14, 15]. Moreover, lactones are present in foodstuffs. They are known as components of the fragrance of alcoholic beverages such as whisky [16, 17], sherry [18], and wine [19–21]. They are present in bakery, diary, and meat-processing products [22–28]. Synthetic compounds having a lactone group are an important category of additives in foodstuffs [26]. Lactones having a *gem*-dimethylcyclopropane system are useful as substrates in the synthesis of *cis*-chrysanthemic acid and pyrethroids. Several gem-dimethylcyclopropane halolactones possess strong antimicrobial activity [29, 30]. Mazur et al. proved antifeedant activity against storage pests, i.e., granary weevil, khapra beetle, and confused flour beetle [31].

They have frequently been reported as synthesis products [32–38], obtained by addition of diazopropane to butenolide [33, 34] or via reductive transformation of imides [35]. Bicyclic lactones having a *gem*-dimethylcyclopropane system have also been obtained as products of cyclization of γ, δ-epoxyamide in the presence of lithium diisopropylamide [36] or 1,3-cyclization of β-chloroisopropyl-γ-lactones with potassium tert-butoxide [37, 38]. Furthermore, bicyclic δ-lactones having a *gem*-dimethylcyclopropane system have been reported as intermediate products of the synthesis of (+)-*trans*-chrysanthemic acid with (+)-3-carene [39, 40]. A review [41] on stereoselective cyclopropanation reactions discussed several new methods for synthesizing bicyclic lactones with a cyclopropane ring. They were obtained by enantioselective cyclopropanation in the presence of rhodium- [41–43] or copper-based [44–46] or chiral catalysts. Bicyclic lactones were also obtained by enzymatic desymmetrization of cyclopropane diesters [47, 48]. A reaction between optically pure epichlorohydrines with sodium malonate also yields bicyclic lactones with a cyclopropane group and is characterized by good enantioselectivity [49, 50]. Last up-to-date review of an asymmetric approach for halolactonization was published by Nolsøe and Hanson in 2014 [30].

This work presents a new method for the asymmetric synthesis of γ-halo-δ-lactones **3**, **5**, **7** substrates for the

synthesis of 6,6-dimethyl-4-isopropyl-3-oxabicyclo[3.1.0] hexan-2-one as a source of enantiomerically pure *cis*-chrysanthemic acid.

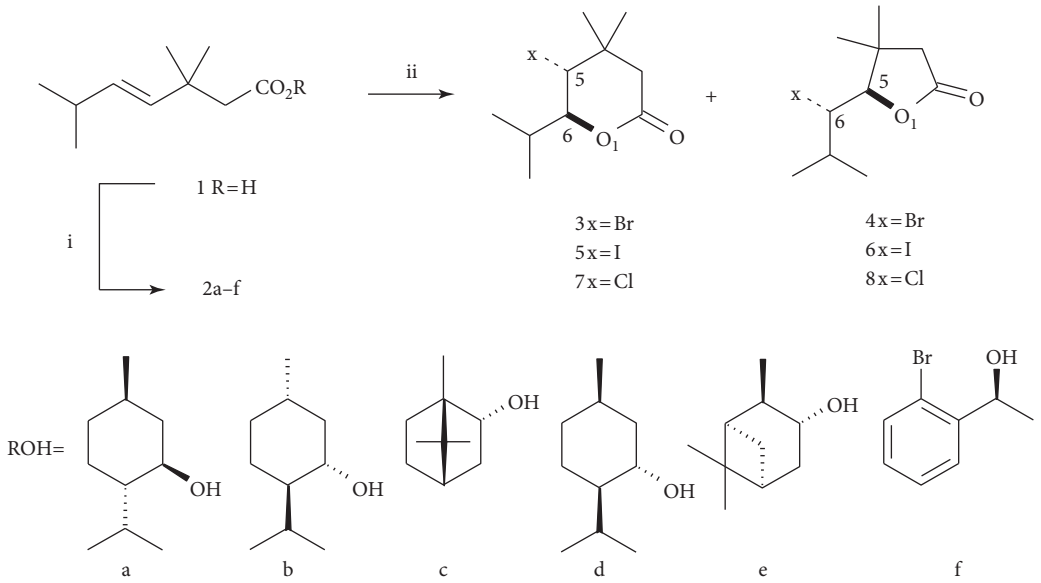
2. Results and Discussion

Studies on enantioselective lactonization were performed for esters **2a**–**f** of 3,3,6-trimethyl-4(E)-heptenoic acid (**1**) and chiral, enantiomerically pure alcohols **a**–**f** (Scheme 1). 3,3,6-Trimethyl-4(E)-heptenoic acid (**1**) is a synthetic terpenoid. Its carbon backbone structure is present in natural terpenes such as artemisia alcohol and Yomogi alcohol. A method for synthesizing 3,3,6-trimethyl-4(E)-heptenoic acid (**1**) was developed and reported previously [43]. The method is based on reaction of isopropylmagnesium chloride with 3-methyl-2-butenal, Claisen rearrangement of the resulting alcohol via orthoacetate modification, and alkaline hydrolysis of the resulting ester. The esters **2a**–**f** were synthesized by reacting 3,3,6-trimethyl-4(E)-heptenoic acid chloride with enantiomerically pure alcohols **a**–**f** in the presence of triethylamine and catalytic amounts of DMAP (4-N,N-dimethylaminopyridine). The enantiomerically pure alcohols used were (−)-menthol (**a**), (+)-menthol (**b**), (−)-borneol (**c**), (+)-isomenthol (**d**), (−)-isopinocampheol (**e**), and (S)-(−)-1-(2-bornylphenyl)-1-ethanol (**f**). The resulting esters were purified chromatographically. The structure of the resulting esters was confirmed by IR and ^{1}H NMR spectra. High values of the chemical shifts of carbinol protons, being in the range from δ = 4.62 ppm for **2a** to δ = 6.13 ppm for **2f**, are typical of esters of secondary alcohols, in which such proton is unshielded by the carboester group orbital π and, in the case of **2f**, additionally, by the adjacent aromatic ring. Interestingly enough, despite the chirality of the carbinol proton in the ester molecule, anisotropy of the methyl groups located on C-3 on the side of the carboxylic acid residue was not observed, with the exception of one compound. The signals from such groups are usually six-proton singlets, except for **2f**, where their signals in the form of two tri-proton singlets are chemically shifted from each other by 0.01 ppm. A more frequently observed phenomenon is diastereotopicity of the hydrogen atoms located on C-2 on the carboxyl side, caused by the chiral alcohol residue. Type AB signal of the protons in the form of two doublets is observed in all menthol esters (**2a**, **2b**, δ = 2.18 and 2.23 ppm, J = 13.3 Hz) as well as 1-(2-bornylphenyl)-ethanol ester (**2f**, δ = 2.27 and 2.33 ppm, J = 13.4 Hz). Absolute optical rotation in chloroform was measured for each ester.

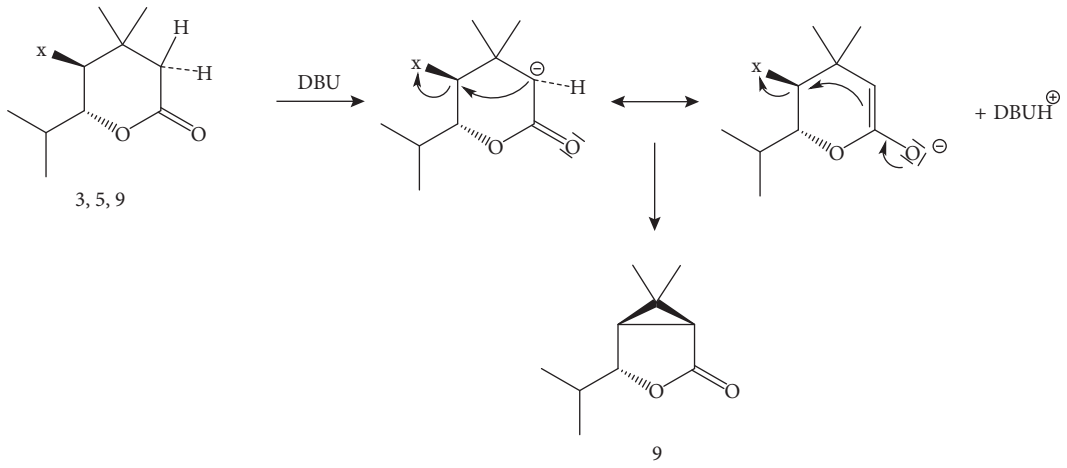
The main objective of the present work was to investigate the usefulness of halolactonization of enantiomerically pure alcohol esters **2a**–**f** for enantioselective synthesis of lactones. N-halosuccinimides were used as the lactonizing substances. When used in the electrophilic cyclization of γ, δ-unsaturated esters having a dimethyl substitute in the C-3 position, the compounds tend to give, as dominant products in a kinetic process, thermodynamically less stable γ-halo-δ-lactones **3**, **5**, **7**, which are easily transformed into a bicyclic lactone **9** (Scheme 2). The product is a useful substrate in the synthesis of chrysanthemic acid. Moreover, NXS-type reactants are more convenient in laboratory conditions, enabling single-phase reactions to be performed. In order to provide a homogeneous reaction mixture, ester lactonization with NXS is carried out with the use of organic solvents that are miscible with water as one of the substrates. In this work, THF containing water in the ratio 20 : 1 was used as a solvent. A typical lactonization procedure consisted in preparing the solution of a suitable ester **2a**–**f** in a THF/H_2O mixture, cooling it down to a suitable temperature, and then adding dropwise the solution of a suitable N-halosuccinimide in THF or, in the case of low reactivity, N-chlorosuccinimide (NCS), gradually adding the solid. After the complete conversion of the ester **2a**–**f**, a small amount of 10% HCl was added to the reaction mixture and the solution was heated at 40°C until the complete decomposition of intermediate compounds. Any excess of haloimide was removed by means of sodium thiosulfate. Isomeric halolactones were purified by column chromatography over silica gel, performed twice.

Halolactonization is an electrophilic *anti*-addition to a C=C double bond; therefore, it is a highly stereoselective reaction. The halolactones **3**–**8** being formed in the process have, at all times, the *trans*-orientation of the substituents introduced and, for a fixed configuration of the C=C double bond, halolactones are formed in a diastereoselective manner. Obviously, when performed on non-chiral and enantiomerically impure (optically inactive) esters, the reaction provides racemic mixtures of the respective stereoisomers. As shown in Scheme 2, 1,3-elimination-cyclization of δ-lactones **3**, **5**, **7** yielding a bicyclic compound **9** is also a diastereoselective synthesis. In addition, the mutual orientation of the isopropyl substituents and the cyclopropane ring in the bicyclic lactone **9** being formed depend stereospecifically on the mutual orientation of the substituents X and R in the tetrahydropyranyl ring. If the C=C double bond in the ester has an E configuration, then the bicyclic product (**9**) of dehydrohalogenation of γ-halo-δ-lactones **3**, **5**, **7** acquires a *trans*-configuration. Possible mechanisms of halolactonization of analogous γ, δ-unsaturated substrates were proposed by Denmark and Burk [51], which were carried out via irreversible cyclization and one in which the nucleophile is deprotonated after cyclization.

The resulting esters of 3,3,6-trimethyl-4(E)-heptenoic acid and enantiomerically pure alcohols **2a**–**f** were subjected initially to bromolactonization under the effect of N-bromosuccinimide. In order to establish optimum reaction conditions providing high product yields in addition to high enantioselectivity, lactonization was carried out at different temperatures. The reactions for (−)-menthol ester (**2a**) were carried out at +20°C, 0°C, −20°C, and −40°C. It was observed that enantioselectivity for the formation of γ-bromo-δ-lactone **3** was low at +20°C, while at −40°C the reaction rate was low and the product yield was reduced. Moreover, the ratio between lactones δ (**3**) and γ (**4**) in the postreaction mixture was observed to decrease with temperature. Therefore, other bromolactonization reactions were investigated at temperatures 0°C and −20°C. Any enantiomeric excess of the resulting lactones was determined by chiral gas chromatography with a capillary column,



Scheme 1: (i) (a) $SOCl_2$, C_6H_6, reflux and (b) ROH, Et_3N, DMAP, Et_2O, rt; (ii) NXS, THF/H_2O.



Scheme 2

packed with enantiomerically pure γ-cyclodextrin. When determining the enantiomeric composition of the resulting compounds, it was observed that δ-halo-γ-lactones **4**, **6**, **8** were divided satisfactorily into enantiomeric fractions at retention times up to 30 minutes. Unfortunately, isomeric γ-halo-δ-lactones **3**, **5**, **7**, the typical principal products of the reaction, were not divided chromatographically into enantiomers, even at retention times of more than 60 minutes. Therefore, the resulting γ-halo-δ-lactones **3**, **5**, **7** were subjected to dehydrohalogenation with the use of DBU which, via 1,3-elimination, underwent cyclization to form bicyclic lactone **9**, which was further effectively divided into enantiomers under the effect of γ-cyclodextrin. In the analysis of the enantiomers of the bicyclic lactone **9**, the retention times recorded were $22.50'$ and $24.24'$, which means the difference between them is more than $1.7'$.

The configuration of chiral centers in the obtained stereoisomers of γ-halo-δ-lactones **3**, **5**, **7** was determined indirectly, taking advantage of the fact that the product of their 1,3-elimination-cyclization **9** is a known compound, obtained in the form of enantiomers, and having an established stereochemical structure. The configurations of the obtained stereoisomers were correlated by measuring the sign of optical rotation and comparison with literature data [28]. Knowing that 1,3-dehydrohalogenation-cyclization is a diastereoselective process, the stereochemical structure of the eliminated, enantiomerically pure halolactones **3**, **5**, **7** was established from the configuration of chiral centers of the resulting bicyclic lactone **9**, according to the mechanism presented in Scheme 2. The enantiomeric composition of the resulting δ-halo-γ-lactones **4**, **6**, **8** was expressed as the ratio between the enantiomers, stated in the increasing order of retention times, recorded in the course of the analysis on chiral GC.

In all the electrophilic cyclizations of esters conducted by the present authors, the resulting γ-bromo-δ-lactone **3**

was always the dominant product, constituting from 54% (**2a**, −40°C) to 77% (**2d**, −20°C) of product weight. The presence of nonracemic reaction products was detected in every bromolactonization reaction. The enantiomerically pure alcohols that were used as ancillary chiral substances were characterized by markedly different values of induction power; menthol (**a**, **b**), borneol (**c**), and phenetyl alcohol (**f**) performed better in asymmetric δ-lactonization, whereas isomenthol (**d**) and isopinocampheol (**e**) tended to favor asymmetric γ-lactonization. It turned out that, among the used chiral ancillary substances, only (−-)-menthol (**a**) induced the formation of γ-bromo-δ-lactone **3** having the configuration (5S, 6R), whereas (−)-borneol (**c**), (+)-isomenthol (**d**) and (S)-1-(2-bornylphenyl)ethanol (**f**) enabled the formation, in excess, of the second enantiomer (5R, 6S). The highest enantioselectivity during δ-lactonization was observed in the case of menthol ester **2a** (enantiomeric excess (ee) 36%) and borneol **2c** ester (24% ee). For benzyl alcohol ester **2f** and isomenthol **2d**, enantiomeric excess was 13%ee and 11%ee, respectively. Isopinocampheol (**e**) proved to be inductively inactive. The highest ratios between the enantiomers of bromolactone **4** obtained in asymmetric γ-lactonization reactions were recorded for the isomenthol **2d** (21%ee) and the lowest for the benzyl alcohol **2f** (2%ee). Reduction of the temperature of the reaction mixture tended to lead to increased enantioselectivity of lactonization. The only exception was the synthesis of δ-bromo-γ-lactone **4** from menthol ester **2a** and **2b**, during which the relationship was inversed: the value of ee increased with temperature from 0%ee at −40°C to 14%ee at +20°C. As mentioned before, reduction of temperature to less than −20°C resulted in much longer duration of the process and markedly lower reaction yields. The recorded value of enantioselectivity of bromolactonization of (+)-menthol ester **2b** (37%ee), although somewhat higher than that for (−)-menthol (**a**), was within the limits of measurement error for the GC apparatus and may be attributable to the higher optical purity of (+)-menthol (**b**) used in the reaction.

The promising results of asymmetric bromolactonization have encouraged the present authors to investigate chiral esters in iodo- and chlorolactonization reactions with the use of N-iodo- and N-chlorosuccinimide (NIS and NCS). The reactions were carried out in a similar manner as the bromolactonization before. In comparison with NBS, both reactions proceeded at a lower rate; therefore, chlorolactonization was affected at a room temperature. Menthol esters **2a** and borneol esters **2c**, both showing the highest abilities to symmetrize δ-lactonization, were tested in the reactions. Moreover, in the reaction with NIS, the authors tested isomenthol ester **2d**, which was characterized by the strongest asymmetric induction in the course of γ-lactonization. The highest enantiomeric excess of product (30%ee) was observed for γ-iodo-δ-lactone **5**, obtained, as before, from menthol ester, at a temperature of −40°C. The highest enantioselectivity of δ-iodo-γ-lactonization (18%ee) was also recorded for menthol ester **2a**. Whereas, for δ-lactones, a decrease in temperature leads to an increase in the values of enantiomeric excess, and in the case of δ-iodo-γ-lactone **6,** a decrease in temperature leads to a decrease in the process enantioselectivity in every iodolactonization test. It is worth noting that iodolactonization under the effect of NIS is definitely more regioselective, compared with bromolactonization under the effect of NBS and the content of γ-iodo-δ-lactone in the lactone mixture was typically higher than 80%, and the highest (85%) for borneol ester **2c**. As in bromolactonization, a decrease in the temperature of iodolactonization resulted in lower regioselectivity of the synthesis of γ-iodo-δ-lactone **5** and for menthol ester **2a**, its percentage dropped from 83% at 0°C to 75% at −40°C. Chlorolactonization reactions were characterized by very low enantioselectivity for the formation of γ-chloro-δ-lactone **7** (8%ee for menthol ester **2a**) or its lack for δ-chloro-γ-lactone **8** (er. 50 : 50). Moreover, the authors observed a considerable decrease in regioselectivity and, in the case of menthol ester **2a**, δ-chloro-γ-lactone **8** was simply the principal product (57%).

The optical rotations determined for the products were as follows:

(5S,6R)-5-Bromo-4,4-dimethyl-6-isopropyltetrahydro-2H-pyran-2-one (3): $[\alpha]_D^{20} = +6.9^\circ$ (c = 1.34, $CHCl_3$) (calculated)

(5S,6R)-4,4-Dimethyl-5-iodo-6-isopropyltetrahydro-2H-pyran-2-one (3): $[\alpha]_D^{20} = +7.8^\circ$ (c = 2.01, $CHCl_3$) (calculated)

(1S,4R,5R)-6,6-Dimethyl-4-isopropyl-3-oxabicyclo [3.1.0]hexan-2-one (9): $[\alpha]_D^{20} = +70.9^\circ$ (c = 2.63, $CHCl_3$) (calculated)

3. Experimental

Chemicals were purchased from Fluka and Sigma-Aldrich (Poznań, Poland). The progress of reactions and purity of compounds synthesized were checked by TLC on silica gel-coated aluminum or plastic plates using a solvent system hexane : ethyl acetate in various ratios. The same eluents and methylene chloride were used in the course of preparative column chromatography on silica gel (Kieselgel 60, 230–400 mesh). GC analyses were performed on a Varian CP3380 instrument, using capillary columns: HP-5 (cross-linked 5% phenyl methyl siloxane), 30 m × 0.53 mm × 0.88 μm and HP-1 (cross-linked methyl siloxane), 25 m × 0.32 mm × 0.52 μm or on a Hewlett Packard HP5890 Series II instrument using a CP-cyclodextrin, 25 m × 0.25 mm × 0.25 μm chiral column. ^{1}H NMR spectra were recorded on a Bruker Avance DRX 300 MHz spectrometer for $CDCl_3$ solutions, with tetramethylsilane (TMS) as an internal standard. The IR spectra were taken for liquid films or KBr pellets on a FTIR Thermo-Mattson IR spectrometer. Melting points (uncorrected) were measured on a Boetius apparatus.

3.1. Synthesis of Esters of Enantiomerically Pure Alcohols: General Procedure. To a solution of 0.004 mole of carboxylic acid **1** in 10 ml of dry benzene, 0.58 ml (0.952 g, 0.008 mol) of thionyl chloride was added, and the mixture was heated under a reflux condenser in the absence of moisture for 2

hours. The postreaction solution was sent to a rotary evaporator to evaporate the benzene and any excess of thionyl chloride. After the complete evaporation of the solvent and thionyl chloride, the residue was dissolved in 20 ml of anhydrous diethyl ether and the resulting solution was added dropwise to the solution of 0.004 mole of enantiomerically pure alcohol in 20 ml of diethyl ether with addition of 1.68 ml (1.22 g; 0.012 mol) of triethylamine and catalytic amounts of DMAP (0.1 g, 4-N,N-dimethylaminopyridine), after cooling the solution to 0°C. Stirring was continued at a room temperature for 12 hours, and the progress of the reaction was controlled by means of TLC. The trimethylammonium chloride sediment was dissolved in 40 ml of water, and the etheric residue was washed twice with 5% HCl and brined before being dried over anhydrous $MgSO_4$. After evaporation of diethyl ether, the resulting crude esters were purified by preparative column chromatography over silica gel (eluent: 30 : 1 hexane : ethyl acetate). Their physical and spectral data are given as follows:

(−)-(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl-3,3,6-trimethyl-4(E)-heptenoate (2a): colorless liquid, n_D^{20} = 1.4609, $[\alpha]_D^{20} = -52^\circ$ (c = 2.54, $CHCl_3$), 1.07 g 86%. IR (cm^{-1}, film): 2872 (s), 1728 (s), 1384 (m), 1368 (m), 976 (m). ^{1}H NMR (δ ppm, $CDCl_3$, TMS): 0.72 (d, 3H; J = 7.0 Hz, -CH_3), 0.85 (d, 3H; J = 7.0 Hz, -CH_3), 0.86 (d, 3H; J = 6.5 Hz, -CH_3), 0.93 (d, 6H; J = 7.0 Hz, -CH_3), 1.08 (s, 6H, -$C(CH_3)_2$-), 0.8–2.0 (m, 9H; menthol), 2.15–2.20 (m, 1H; =CH-C**H**-), 2.18 (d, 1H; J = 13.3 Hz, one of -CO-CH_2-), 2.23 (d, 1H; J = 13.3 Hz, one of -CO-CH_2-), 4.62 (dt; 1H; J = 10.9; 4.7 Hz, -CH-O-), 5.28 (dd; 1H; J = 15.7; 6.3 Hz, =CH-), 5.41 (dd; 1H; J = 15.7; 0.9 Hz, -CH=).

(+)-(1S,2R,5S)-2-Isopropyl-5-methylcyclohexyl-3,3,6-trimethyl-4(E)-heptenoate (2b): colorless liquid, n_D^{20} = 1.4612, $[\alpha]_D^{20} = +53^\circ$ (c = 2.54, $CHCl_3$), 1.012 g 82%. IR (cm^{-1}, film): 2872 (s), 1728 (s), 1384 (m), 1368 (m), 976 (m). ^{1}H NMR (δ ppm, $CDCl_3$, TMS): 0.72 (d, 3H; J = 7.0 Hz, -CH_3), 0.85 (d, 3H; J = 7.0 Hz, -CH_3), 0.86 (d, 3H; J = 6.5 Hz, -CH_3), 0.93 (d, 6H; J = 7.0 Hz, -CH_3), 1.08 (s, 6H, -$C(CH_3)_2$-), 0.8–2.0 (m, 9H; menthol), 2.15–2.20 (m, 1H; =CH-C**H**-), 2.18 (d, 1H; J = 13.3 Hz, one of -CO-CH_2-), 2.23 (d, 1H; J = 13.3 Hz, one of -CO-CH_2-), 4.62 (dt; 1H; J = 10.9; 4.7 Hz, CH-O-), 5.28 (dd; 1H; J = 15.7; 6.3 Hz, =CH-), 5.41 (dd; 1H; J = 15.7; 0.9 Hz, -CH=).

(−)-(1S,2R,4S)-1,7,7-Trimethylbicyclo[2.2.1]hept-2-yl-3,3,6-trimethyl-4(E)-heptenoate (2c): colorless liquid, n_D^{20} = 1.4712, $[\alpha]_D^{20} = -31^\circ$ (c = 2.75, $CHCl_3$), 0.954 g, 78%. IR (cm^{-1}, film): 2872 (s), 1732 (s), 1384 (m), 1232 (m), 1112 (m), 1028 (m), 976 (m). ^{1}H NMR (δ ppm, $CDCl_3$, TMS): 0.80 (s, 3H; -CH_3), 0.84 (s, 3H; -CH_3), 0.87 (s, 3H; -CH_3), 0.93 (d, 6H; J = 6.7 Hz, -CH($C\mathbf{H}_3$)$_2$), 1.08 (s, 6H; -$C(CH_3)_2$-), 0.86–1.94 (m, 7H; bornyl), 2.14–2.22 (m, 1H; =CH-C**H**-), 2.25 (s, 2H; -CO-CH_2-), 4.81 (dd; 1H; J = 9.9; 3.5 Hz, >CH-O-), 5.29 (dd; 1H; J = 15.7; 6.4 Hz, =CH-), 5.42 (dd; 1H; J = 15.7; 0.9 Hz, -CH=).

(+)-(1S,2R,5R)-2-Isopropyl-5-methylcyclohexyl-3,3,6-trimethyl-4(E)-heptenoate (2d): colorless liquid, n_D^{20} = 1.4614, $[\alpha]_D^{20} = +11^\circ$ (c = 2.40, $CHCl_3$), 0.984 g, 80%. IR (cm^{-1}, film): 2872 (s), 1728 (s), 1384 (m), 1132 (m), 972 (m). ^{1}H NMR (δ ppm, $CDCl_3$, TMS): 0.83 (d, 3H; J = 6.7 Hz; -CH_3), 0.90 (d, 3H; J = 6.7 Hz; -CH_3), 0.92 (d, 3H; J = 6.9 Hz; -CH_3), 0.94 (d, 6H; J = 6.7 Hz, -CH_3), 1.09 (s, 6H; -CH_3), 1.10–1.94 (m, 9H; isomenthol), 2.14–2.22 (m, 1H; -CH-), 2.23 (s, 2H; -CO-CH_2-), 4.98–5.04 (m; 1H; -CH-O-), 5.29 (dd; 1H; J = 15.7; 6.3 Hz, =CH-), 5.42 (dd; 1H; J = 15.7; 0.9 Hz, -CH=).

(−)-(1R,2R,3R,5S)-2,6,6-Trimethylbicyclo[3.1.1]hept-3-yl-3,3,6-trimethyl-4(E)-heptenoate (2e): colorless liquid, n_D^{20} = 1.4696, $[\alpha]_D^{20} = -17^\circ$ (c = 1.46, $CHCl_3$), 0.880 g, 72%. IR (cm^{-1}, film): 2860 (s), 1728 (s), 1384 (m), 1152 (m), 976 (m). ^{1}H NMR (δ ppm, $CDCl_3$, TMS): 0.93 (s, 3H; -CH_3), 0.94 (d, 6H; J = 6.9 Hz, -CH($C\mathbf{H}_3$)$_2$), 1.03 (d; 1H; J = 9.9 Hz, -CH-), 1.07 (d, 1H, J = 7.5 Hz, -CH-), 1.10 (s, 6H; -$C(CH_3)_2$-), 1.20 (s, 3H, -CH_3), 1.60–1.67 (m, 1H, -CH-), 1.77–1.81 (m, 1H, -CH-), 2.07–2.11 (m, 1H, -CH-), 2.15–2.23 (m, 1H; -CH-), 2.24 (s, 2H; -CO-CH_2-), 2.30–2.38 (m, 1H, -CH-), 2.50–2.58 (m, 1H, -CH-), 4.97–5,03 (m; 1H; -CH-O-), 5.30 (dd; 1H; J = 15.9; 6.2 Hz, =CH-), 5.42 (dd; 1H; J = 15.9; 0.9 Hz, -CH=).

(−)-(S)-1-(2-Bromophenyl)ethyl-3,3,6-trimethyl-4(E)-heptenoate (2f): pale yellow liquid, n_D^{20} = 1.5012, $[\alpha]_D^{20} = -11^\circ$ (c = 0.90, $CHCl_3$), 1.088 g, 77%. IR (cm^{-1}, film): 2866 (s), 1738 (s), 1392 (s), 1112 (m), 1028 (m), 967 (m). ^{1}H NMR (δ ppm, $CDCl_3$, TMS): 0.91 (d, 3H; J = 6.7 Hz, -CH($C\mathbf{H}_3$)CH_3), 0.93 (d; 3H; J = 6.8 Hz, -CH(CH_3)$C\mathbf{H}_3$), 1.10 (s, 6H; -$C(CH_3)_2$-), 1.47 (d, 3H, J = 6.5 Hz, -CH_3), 2.12–2.23 (m, 1H, =CH-C**H**-), 2.27 (d, 1H; J = 13.4 Hz one of -CO-CH_2-), 2.33 (d, 1H; J = 13.4 Hz one of -CO-CH_2-), 5.30 (dd; 1H; J = 15.7; 3.6 Hz, =CH-), 5.43 (dd; 1H; J = 15.7; 0.9 Hz, -CH=), 6.13 (q; 1H; J = 6.5 Hz; CH-O-), 7.08–7.13 (m, 1H, H-5′) 7.26–7.31 (m, 1H, H-4′), 7.44 (dd; 1H; J = 7.8, 1.8 Hz, H-3′), 7.50 (dd; 1H; J = 8.0, 1.2 Hz, H-6′).

3.2. Halolactonization: General Procedure. An enantiomerically pure alcohol ester (0.002 mole) and 0.5 ml of water were dissolved in 10 ml of THF. The solution was cooled down to a suitable temperature and doses of 0.003 mole of N-bromosuccinimide or N-iodosuccinimide solution in 5 ml of THF or 0.003 mole of N-chlorosuccinimide in solid state were added. The reaction solution was stirred at a suitable temperature for the length of time shown in Table 1. After formation of the initial ester, as shown by TLC, 5 ml of 10% HCl was added to the reaction mixture and heated at 40°C for 1 hour. THF was evaporated in a rotary evaporator, and the residue was extracted twice using 20 ml portions of diethyl ether. The etheric solution was washed twice with a saturated solution of sodium thiosulfate and with brine before being dried over anhydrous $MgSO_4$. Halolactones were separated by preparative

Table 1: Isolated yield*.

Substrate	T (°C)	t (h)	X	Composition of product mixture						Yield* (%)
				δ-Lactones (% GC)		(%ee)	γ-Lactones (% GC)		er.	
2a	20	12	Br	**3**	59	28	(5S,6R)	**4**	41	57 : 43	89
2a	0	24	Br	**3**	59	34	(5S,6R)	**4**	41	52 : 48	76
2a	−20	36	Br	**3**	56	35	(5S,6R)	**4**	44	50 : 50	76
2a	−40	72	Br	**3**	54	36	(5S,6R)	**4**	46	50 : 50	68
2b	−20	36	Br	**3**	57	37	(5R,6S)	**4**	43	52 : 48	76
2c	0	24	Br	**3**	58	10	(5R,6S)	**4**	42	50 : 50	73
2c	−20	36	Br	**3**	57	24	(5R,6S)	**4**	43	44 : 56	69
2d	0	24	Br	**3**	60	0		**4**	40	50 : 50	81
2d	−20	36	Br	**3**	77	11	(5R,6S)	**4**	23	40 : 60	73
2e	0	24	Br	**3**	57	0		**4**	43	45 : 55	81
2e	−20	36	Br	**3**	55	0		**4**	45	44 : 56	78
2f	0	24	Br	**3**	62	5	(5R,6S)	**4**	38	49 : 51	77
2f	−20	36	Br	**3**	66	13	(5R,6S)	**4**	34	49 : 51	80
2a	0	36	I	**5**	83	15	(5S,6R)	**6**	17	59 : 41	72
2a	−20	60	I	**5**	80	28	(5S,6R)	**6**	20	58 : 42	71
2a	−40	100	I	**5**	75	30	(5S,6R)	**6**	25	55 : 45	62
2c	0	36	I	**5**	85	13	(5R,6S)	**6**	15	45 : 55	77
2c	−20	60	I	**5**	83	17	(5R,6S)	**6**	17	48 : 52	68
2d	0	36	I	**5**	84	9	(5R,6S)	**6**	16	44 : 56	73
2d	−20	60	I	**5**	72	12	(5R,6S)	**6**	28	46 : 54	69
2a	20	72	Cl	**7**	43	8	(5S,6R)	**8**	57	50 : 50	76
2c	20	72	Cl	**7**	50	3	(5R,6S)	**8**	50	50 : 50	81

column chromatography on silica gel. δ-Halo-γ-lactone was isolated using an eluent in the form of an 8 : 1 hexane-ethyl acetate mixture, and γ-halo-δ-lactone and enantiomerically pure alcohol were separated using methylene chloride as the eluent. Their physical and spectral data are given as follows:

trans-5-Bromo-4,4-dimethyl-6-isopropyl-tetrahydro-2H-pyran-2-one (3): white crystals, m.p. 80-83°C; IR (cm^{-1}, KBr) 1732 (s), 1192 (s), 1120 (s), 1016 (s), ^{1}H NMR (δ ppm, $CDCl_3$, TMS): 0.90 (d, 3H, J = 6.8 Hz, -CH(C**H**$_3$)CH$_3$), 1.12 (d, 3H, J = 6.8 Hz, -CH(CH$_3$)C**H**$_3$), 1.15 (s, 3H, -C(C**H**$_3$)CH$_3$-), 1.16 (s, 3H, -C(CH$_3$)C**H**$_3$-), 2.36 (d, 1H, J = 17.3 Hz, one of -CH$_2$CO$_2$-), 2.40 (m, 1H, -C**H**(CH$_3$)$_2$-), 2.68 (d, 1H, J = 17.3 Hz, one of -CH$_2$CO$_2$-), 3.92 (d, 1H, J = 10.4 Hz, -CHBr-), 4.40 (dd, 1H, J = 10.7, 1.7 Hz, -CH-O-).

erythro-5-(1-Bromo-2-methylpropyl)-4,4-dimethyldihydrofuran-2(3H)-one (4): white crystals, m.p. 46–49°C, IR (cm^{-1}, KBr): 1780 (s), 1288 (s), 1124 (s), 1024 (s). ^{1}H NMR (δ ppm, $CDCl_3$, TMS): 0.95 (d, 3H, J = 6.6 Hz, -CH(C**H**$_3$)CH$_3$), 1.03 (d, 3H, J = 6.6 Hz, -CH(CH$_3$)C**H**$_3$), 1.18 (s, 3H, -C(C**H**$_3$)CH$_3$-), 1,43 (s, 3H, -C(CH$_3$)C**H**$_3$-), 2.23 (m, 1H, -C**H**(CH$_3$)$_2$-), 2.33 (d, 1H, J = 17.1 Hz, one of -CH$_2$CO$_2$-), 2.53 (d, 1H, J = 17.1 Hz, one of -CH$_2$CO$_2$-), 4.00 (dd, 1H, J = 10.7, 2.2 Hz, -CHBr-), 4.34 (d, 1H, J = 10.7 Hz, -CH-O-).

trans-4,4-Dimethyl-5-iodo-6-isopropyl-tetrahydro-2H-pyran-2-one (5): white crystals, m.p. 96-97°C, IR (cm^{-1}, KBr) 1744 (s), 1240 (s), 1168 (s), 1008 (s). ^{1}H NMR (δ ppm, $CDCl_3$, TMS): 0.84 (d, 3H, J = 6.8 Hz, -CH(C**H**$_3$)CH$_3$), 1.10 (d, 3H, J = 6.8 Hz, -CH(CH$_3$)C**H**$_3$), 1.11 (s, 3H, -C(C**H**$_3$)CH$_3$-), 1.16 (s, 3H, -C(CH$_3$)C**H**$_3$-), 2.37 (d, 1H, J = 17.3 Hz, one of -CH$_2$CO$_2$-), 2.51 (m, 1H, -C**H**(CH$_3$)$_2$-), 2.71 (d, 1H, J = 17.3 Hz, one of -CH$_2$CO$_2$-), 4.05 (d, 1H, J = 10.4 Hz, -CHI-), 4.52 (dd, 1H, J = 11.2, 1.7 Hz, -CH-O-).

erythro-4,4-Dimethyl-5-(1-iodo-2-methylpropyl)-dihydrofuran-2(3H)-one (6): white crystals, m.p. 46–48°C, IR (cm^{-1}, KBr): 1764 (s), 1284 (s), 1224 (s), 1172 (s), 964 (s). ^{1}H NMR (δ ppm, $CDCl_3$, TMS): 0.86 (d, 3H, J = 6.4 Hz, -CH(C**H**$_3$)CH$_3$-), 0.99 (d, 3H, J = 6.4 Hz, -CH(CH$_3$)C**H**$_3$-), 1.15 (s, 3H, -C(C**H**$_3$)CH$_3$-), 1,49 (s, 3H, -C(CH$_3$)C**H**$_3$-), 1.50 (m, 1H, -C**H**(CH$_3$)$_2$-), 2.32 (d, 1H, J = 17.2 Hz, one of -CH$_2$CO$_2$-), 2.51 (d, 1H, J = 17.2 Hz, one of -CH$_2$CO$_2$-), 4.05 (dd, 1H, J = 11.0, 2.5 Hz, -CHI-), 4.48 (d, 1H, J = 11.0 Hz, -CH-O-).

trans-5-Chloro-4,4-dimethyl-6-isopropyl-tetrahydro-2H-pyran-2-one (7): white crystals, m.p. 71–73°C, IR (cm^{-1}, KBr) 1736 (s), 1256 (s), 1228 (s), 1020 (s), 816 (m), 668 (m). ^{1}H NMR (δ ppm, $CDCl_3$, TMS): 0.89 (d, 3H, J = 6.8 Hz, -CH(C**H**$_3$)CH$_3$), 1.08 (d, 3H, J = 6.9 Hz, -CH(CH$_3$)C**H**$_3$), 1.10 (s, 3H, -C(C**H**$_3$)CH$_3$-), 1.11 (s, 3H, -C(CH$_3$)C**H**$_3$-), 2.20–2.28 (m, 1H, -C**H**(CH$_3$)$_2$-), 2.29 (d, 1H, J = 17.3 Hz, one of -CH$_2$CO$_2$-), 2.58 (d, 1H, J = 17.3 Hz, one of -CH$_2$CO$_2$-), 3.75 (d, 1H, J = 10.4 Hz, -CH-Cl), 4.21 (dd, 1H, J = 10.4, 1.9 Hz, -CH-O-).

erythro-5-(1-Chloro-2-methylpropyl)-4,4-dimethyldihydrofuran-2(3H)-one (8): white crystals, m.p. 37–39°C, IR (cm^{-1}, KBr): 1780 (s), 1232 (s), 1200 (s), 1000 (s), 976 (s), 752 (s), 658 (s). ^{1}H NMR (δ ppm, $CDCl_3$, TMS): 0.93 (d, 3H, J = 6.6 Hz, -CH(C**H**$_3$)CH$_3$), 1.02 (d, 3H, J = 6.8 Hz, -CH(CH$_3$)C**H**$_3$), 1.15

(s, 3H, -C(C**H**$_3$)CH$_3$-), 1,35 (s, 3H, -C(CH$_3$)C**H**$_3$-), 2.30 (d, 1H, J = 17.1 Hz, one of -CH$_2$CO$_2$-), 2.31–2.40 (m, 1H, -C**H**(CH$_3$)$_2$-), 2.50 (d, 1H, J = 17.1 Hz, one of -CH$_2$CO$_2$-), 3.88 (dd, 1H, J = 10.5, 2.3 Hz, -CH-Cl) 4.16 (d, 1H, J = 10.5 Hz, -CH-O-).

3.3. Dehydrohalogenation Procedure. To a solution of γ-halo-δ-lactone (**3**, **5**, **7**) (1 mmol) in 5 ml of dichloromethane, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.3 mmol) was added and the mixture was stirred at room temperature for 2–6 h. Then, the reaction mixture was diluted with 10 ml of diethyl ether, washed with water, and brined and dried with MgSO$_4$. The crude product was purified by column chromatography (silica gel, hexane-ethyl acetate, 6 : 1). Physical and spectral data are given below:

trans-6,6-Dimethyl-4-isopropyl-3-oxabicyclo[3.1.0]hexan-2-one (9): colorless liquid, n_D^{20} = 1.4588; IR (cm^{-1}, film): 1756(s), 1184(s), 1028(s); ^{1}H NMR (δ ppm, CDCl$_3$, TMS): 1.00 (d, 6H, J = 5.3 Hz, -CH(C**H**$_3$)$_2$), 1.17 (s, 3H, -C(C**H**$_3$)CH$_3$-), 1.19 (s, 3H, -C(CH$_3$)C**H**$_3$-), 1.82 (d, 1H, J = 6.0 Hz, H-5), 1.90 (m, 1H, -C**H**(CH$_3$)$_2$), 1.94 (d, 1H, J = 6.0 Hz, H-1), 4.04 (d, 1H, J = 4.6 Hz, H-4).

Data Availability

The NMR source data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

The project was supported by the Wroclaw Centre of Biotechnology under the Leading National Research Centre (KNOW) Programme for the years 2014–2018.

References

[1] B. Pisarski and C. Wawrzeńczyk, "Lactones 30. Reaction of halolactones with trialkylphosphites," *Tetrahedron Letters*, vol. 47, no. 38, pp. 6875–6877, 2006.

[2] G. Ohloff, *Scent and Fragrances*, Springler-Verlag, Berlin, Germany, 1992.

[3] T. H. Parliament and R. J. McGorin, *Flavor Chemistry*, S. J. Risch and H. Chi-Tang, Eds., American Chemical Society, Washington, DC, USA, 2000.

[4] K. Takahashi, T. Someya, S. Muraki, and T. Yoshida, "Chemical composition of fragrant materials. IV. A new keto-alcohol, (−)-mintlactone, (+)-isomintlactone and minor components in peppermint oil," *Agricultural and Biological Chemistry*, vol. 44, pp. 1535–1543, 1980.

[5] R. Näf and A. Velluz, "Phenols and lactones in Italo-Mitcham peppermint oilMentha × piperita L," *Flavour and Fragrance Journal*, vol. 13, no. 3, pp. 203–208, 1998.

[6] B. M. Fraga, "Natural sesquiterpenoids," *Natural Product Reports*, vol. 23, pp. 943–972, 2006.

[7] Y. Asakawa, M. Toyota, F. Nagashima, T. Hashimoto, and L. El Hassane, "Sesquiterpene lactones and acetogenin lactones from the hepaticae and chemosystematics of the liverworts frullania, plagiochila and porella," *Heterocycles*, vol. 54, no. 2, pp. 1057–1093, 2001.

[8] M. Durán-Peña, J. Ares, J. Hanson, I. G. Collado, and R. Hernández-Galán, "Biological activity of natural sesquiterpenoids containing a gem-dimethylcyclopropane unit," *Natural Product Reports*, vol. 32, no. 8, pp. 1236–1248, 2015.

[9] O. A. Onayade, A. M. G. Looman, J. J. C. Scheffer, and Z. O. Gbile, "Lavender lactone and other volatile constituents of the oleoresin from seeds of Garcinia kola Heckel," *Flavour and Fragrance Journal*, vol. 13, no. 6, pp. 409–412, 1988.

[10] E. Gomez and C. A. Ledbetter, "Development of volatile compounds during fruit maturation: characterization of apricot and plum × apricot hybrids," *Journal of the Science of Food and Agriculture*, vol. 74, no. 4, pp. 541–546, 1997.

[11] T. Yamamoto, *Current Topics in Flavours and Fragrances: Towards a New Millenium of Discovery*, K. A. D. Swift, Ed., Kluwer Academic, Dordrecht, The Netherlands, 1999.

[12] A. Mosandl, *Flawourings*, H. Ziegler and E. Ziegler, Eds., Wiley-VCH, Weinheim, Germany, 1998.

[13] T. Kitaura, H. Endo, H. Nakamoto, M. Ishihara, T. Kawai, and J. Nokami, "Isolation and synthesis of a new natural lactone in apple juice (Malus × domestica var. orin)," *Flavour and Fragrance Journal*, vol. 19, no. 3, pp. 221–224, 2004.

[14] M. L. Ruiz Del Castillo, M. Herraiz, and G. P. Blanch, "Determination of the enantiomeric composition of γ-lactones in edible oils by on-line coupled high performance liquid chromatography and gas chromatography," *Journal of Agricultural and Food Chemistry*, vol. 48, no. 4, pp. 1186–1190, 2000.

[15] T. Naito, T. Katsuhara, K. Niitsu, Y. Ikeya, M. Okada, and L. H. Mitsuhashi, "Phthalide dimers from ligusticum chuangxiong hort," *Heterocycles*, vol. 32, no. 12, pp. 2433–2442, 1991.

[16] K. L. Wilkinson, G. M. Elsey, R. H. Prager, A. P. Pollnitz, and M. A. Sefton, "Rates of formation of cis-andtrans-oak lactone from 3-methyl-4-hydroxyoctanoic acid," *Journal of Agricultural and Food Chemistry*, vol. 52, no. 13, pp. 4213–4218, 2004.

[17] T. Ebata, K. Matsumoto, H. Yoshikoshi et al., "Synthesis of (+)-trans-whisky lactone, (−)-cis-whisky lactone, (+)-cognac lactone and (+)-eldanolide," *Heterocycles*, vol. 36, no. 5, pp. 1017–1026, 1993.

[18] J. A. Moreno, L. Zea, L. Moyano, and M. Medina, "Aroma compounds as markers of the changes in sherry wines subjected to biological ageing," *Food Control*, vol. 16, no. 4, pp. 333–338, 2005.

[19] H. Guth, "Determination of the configuration of wine lactone," *Helvetica Chimica Acta*, vol. 79, no. 6, pp. 1559–1571, 1996.

[20] H. Guth, "Identification of character impact odorants of different white wine varieties," *Journal of Agricultural and Food Chemistry*, vol. 45, no. 8, pp. 3022–3026, 1997.

[21] S. Pérez-Olivero, M. Pérez-Pont, J. Conde, and J. P. Pérez-Trujillo, "Determination of lactones in wines by headspace solid-phase microextraction and gas chromatography coupled with mass spectrometry," *Journal of Analytical Methods in Chemistry*, vol. 2014, Article ID 863019, 10 pages, 2014.

[22] D. G. Peterson and G. A. Reineccius, "Determination of the aroma impact compounds in heated sweet cream butter," *Flavour and Fragrance Journal*, vol. 18, no. 4, pp. 320–324, 2003.

[23] H. D. Belitz, W. Grosch, and P. Schieberle, "Aroma Substances," in *Food Chemistry*, pp. 362–365, Springer-Verlag, Berlin, Germany, 2004.
[24] M. Alewijn, B. A. Smith, E. L. Sliwinski, and J. T. M. Wouters, "The formation mechanism of lactones in Gouda cheese," *International Dairy Journal*, vol. 17, no. 1, pp. 59–66, 2007.
[25] G. Macleod, *Flavour of Meat, Meat Products and Seafoods*, Blackie Academic and Professional, London, UK, 1998.
[26] N. Pintauro, *Flavour Technology*, Noyes Data Corp. (NDC), Park Ridge, NJ, USA, 1971.
[27] D. S. Mottram, R. A. Edwards, and H. A. Macfie, "A comparison of the flavour volatiles from cooked beef and pork meat systems," *Journal of the Science of Food and Agriculture*, vol. 33, no. 9, pp. 934–944, 1982.
[28] I. Cho and D. Peterson, "Chemistry of bread aroma: a review," *Food Science and Biotechnology*, vol. 19, no. 3, pp. 575–582, 2010.
[29] M. Grabarczyk, K. Wińska, W. Mączka, B. Żarowska, A. Białońska, and M. Anioł, "Hydroxy lactones with the gem-dimethylcyclohexane system—synthesis and antimicrobial activity," *Arabian Journal of Chemistry*, 2015, In press.
[30] J. Nolsøe and T. Hansen, "Asymmetric iodolactonization: an evolutionary account," *European Journal of Organic Chemistry*, vol. 2014, no. 15, pp. 3051–3065, 2014.
[31] M. Mazur, W. Gładkowski, M. Podkowik et al., "Lactones 43. New biologically active lactones: β-cyclocitral derivatives," *Pest Management Science*, vol. 70, no. 2, pp. 286–294, 2014.
[32] D. Arlt, M. Jeutelat, and R. Lantzsch, "Synthesen von pyrethroidsäuren," *Angewandte Chemie*, vol. 93, no. 9, pp. 719–738, 1981.
[33] J. Mann and A. Thomas, "A novel approach to cis-chrysanthemic acids," *Tetrahedron Letters*, vol. 27, no. 30, pp. 3533-3534, 1986.
[34] M. Franck-Neumann, M. Sedrati, J. P. Vigneron, and V. Bloy, "Stereo-und enantioselektive Synthese der beidencis-Chrysanthemumsäure-methylester in hoher optischer Reinheit," *Angewandte Chemie*, vol. 97, no. 11, pp. 995-996, 1985.
[35] T. Mukaiyama, H. Yamashita, and M. Asami, "An asymmetric synthesis of bicyclic lactones and its application to the asymmetric synthesis of (1R, 3S)-cis-chrysanthemic acid," *Chemical Letters*, vol. 12, no. 3, pp. 385–388, 1983.
[36] M. Majewski and V. Snieckus, "Synthesis of pyrethroid amides via epoxy amide cyclization," *Journal of Organic Chemistry*, vol. 49, no. 15, pp. 2682–2687, 1984.
[37] J. Mann and A. Weymouth-Wilson, "A new approach to cis-chrysanthemic acid," *Carbohydrate Research*, vol. 216, pp. 511–515, 1991.
[38] S. Takano, A. Kurotaki, M. Takahashi, and K. Ogasawara, "Chiral route to cis-caronaldehyde from D-mannitol," *Journal of the Chemical Society, Perkin Transactions 1*, vol. 1, pp. 91–97, 1987.
[39] D. Bakshi, V. K. Mahindroo, R. Soman, and S. Dev, "Monoterpenoids—VII," *Tetrahedron*, vol. 45, no. 3, pp. 767–774, 1989.
[40] S. Lochyński, B. Jarosz, M. Walkowicz, and K. Piątkowski, "Modification of synthesis of dihydrochrysanthemolactone from (+)-car-3-ene," *Journal für Praktische Chemie*, vol. 330, no. 2, pp. 284–288, 1988.
[41] H. Lebel, J. F. Marcoux, C. Molinaro, and A. B. Charette, "Stereoselective cyclopropanation reactions," *Chemical Reviews*, vol. 103, no. 4, pp. 977–1050, 2003.
[42] M. P. Doyle, R. J. Pieters, S. F. Martin, R. E. Austin, C. J. Oalmann, and P. Mueller, "High enantioselectivity in the intramolecular cyclopropanation of allyl diazoacetates using a novel rhodium (II) catalyst," *Journal of the American Chemical Society*, vol. 113, no. 4, pp. 1423-1424, 1991.
[43] M. P. Doyle, R. E. Austin, A. S. Bailey et al., "Enantioselective intramolecular cyclopropanations of allylic and homoallylic diazoacetates and diazoacetamides using chiral dirhodium (II) carboxamide catalysts," *Journal of the American Chemical Society*, vol. 117, no. 21, pp. 5763–5775, 1995.
[44] M. P. Doyle, C. S. Peterson, Q.-L. Zhou, and H. Nishiyama, "Comparative evaluation of enantiocontrol for intramolecular cyclopropanation of diazoacetates with chiral CuI, RhII and RuII catalysts," *Chemical Communications*, no. 2, pp. 211-212, 1997.
[45] A. M. P. Koskien and L. Munoz, "Intramolecular cyclopropanation: stereospecific synthesis of (E)- and (Z)-1-aminocyclopropane-1-carboxylic acids," *Journal of Organic Chemistry*, vol. 58, no. 4, pp. 879–886, 1993.
[46] C. Fang, D. Paull, J. Hethcox, C. R. Shugrue, and S. F. Martin, "Enantioselective iodolactonization of disubstituted olefinic acids using a bifunctional catalyst," *Organic Letters*, vol. 14, no. 24, pp. 6290–6293, 2012.
[47] J. D. Moore, K. T. Sprott, A. D. Wróblewski, and P. R. Hanson, "Double diastereoselective intramolecular cyclopropanation top-chiral [3.1.0]-bicyclic phosphonates," *Organic Letters*, vol. 4, no. 14, pp. 2357–2360, 2002.
[48] G. Sabbioni and J. B. Jones, "Enzymes in organic synthesis. 39. Preparations of chiral cyclic acid-esters and bicyclic lactones via stereoselective pig liver esterase catalyzed hydrolyses of cyclic meso diesters," *Journal of Organic Chemistry*, vol. 52, no. 20, pp. 4565–4570, 1987.
[49] P. Walser, P. Renold, V. N'Goka, F. Hosseinzadeh, and C. Tamm, "Stereoselective hydrolysis of substituted cyclopropanedicarboxylates with pig liver esterase," *Helvetica Chimica Acta*, vol. 74, no. 8, pp. 1941–1952, 1991.
[50] R. Obara, A. Szumny, A. Żołnierczyk et al., "Lactones 17. Synthesis of bicyclic lactones with the methyl- or gem-dimethylcyclopropane system," *Polish Journal of Chemistry*, vol. 55, pp. 819–825, 2005.
[51] S. Denmark and M. Burk, "Lewis base catalysis of bromo- and iodolactonization, and cycloetherification," *Proceedings of the National Academy of Sciences*, vol. 107, no. 48, pp. 20655–20660, 2010.