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Convenient Chemoenzymatic Route to Optically Active β-Aryl-δ-iodo-γ-lactones and β-Aryl-γ-iodo-δ-lactones with the Defined Configurations of Stereogenic Centers

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Two δ-iodo-γ-lactones and two γ-iodo-δ-lactones substituted at the β-position with phenyl or 4-methylphenyl ring have been synthesized in both enantiomeric forms. The starting materials were enantiomerically enriched allyl alcohols with an (*E*)-4-phenylbut-3-en-2-ol system (*ee* in the range 88–99 %), which were obtained by lipase-catalyzed transesterification. Alcohols were subjected to orthoacetate modification of the Claisen rearrangement. The high stereoselectivity of this reaction led to retention of (*E*)-configuration of the double bond and complete transfer of chirality from the allyl alcohol to the benzylic position C-3. As a result, chiral γ,δ-unsaturated esters with retained configuration of the stereogenic center were produced. Their hydrolysis and iodolactonization afforded new enantiomers of iodolactones with high or excellent *ee* (97–99 %). Their configuration at C-4 was a direct result of the configuration at C-3 of the acid subjected to iodolactonization, whereas stereocenters at C-5 and C-6 were formed as a consequence of the reaction mechanism. For most of the synthesized isomers, the predicted configurations were established by X-ray analysis. The presented chemoenzymatic pathway represents a useful strategy that can be applied in the asymmetric synthesis of variety of lactones from 4-arylbut-3-en-2-ols.

Introduction

Among the biologically active lactones, numerous biological properties have been determined for those containing an aromatic ring. Reported data concern mostly their anticancer,[1] antimicrobial,[2] antiparasitic,[3] antifeedant (towards insects) and insecticidal,[4] anti-inflammatory,[5] and antiplatelet[6] properties. Most of the compounds have been obtained or isolated in enantiomerically pure forms.

A range of strategies have been applied to the synthesis of chiral lactones. The crucial stereochemical steps may involve chemical methods, for example diastereoselective addition of alkenyl Grignard reagents to chiral amides,[7] diastereoselective alkylation of chiral derivative of succinic acid,[8] Sharpless asymmetric dihydroxylation,[2e] or palladium-catalyzed enantioselective allylic substitution.[9] On the other hand, many biocatalytic reactions are applied as a stereoselective step of lactone synthesis, including oxidation of cyclic ketones by Baeyer–Villiger monooxygenases,[10] enantioselective hydrolysis of 2-aryl-4-pentenenitriles by the nitrile hydratase/amidase-containing *Rhodococcus* sp. AJ270 whole cells,[11] baker's yeast reduction of γ- and δ-ketoacids and esters[12] or baker's yeast simultaneous reduction of the carbonyl group and conjugated double bond in α,β-unsaturated β-formyl esters.[13] One of the most common biocatalytic methods is lipase-catalyzed kinetic resolution of different direct lactone precursors such as γ-hydroxy esters,[14] 1,4- or 1,5-diols,[15] δ-hydroxyamides,[16] or phenylselenoesters.[17]

A convenient synthetic pathway leading to the lactone moiety involves *ortho*-Claisen rearrangement of allyl alcohols followed by hydrolysis of γ,δ-unsaturated esters and lactonization of the resulting acids.[18] By using this methodology, in our previous work, we synthesized some racemic β-aryl-δ-halo-γ-lactones and β-aryl-γ-halo-δ-lactones starting from simple aromatic aldehydes.[19] Some of them showed cytotoxic activity against Jurkat (human leukaemia) and D17 (canine osteosarcoma) cancer lines. Taking into consideration the possible effect of configuration of stereogenic centers on the physicochemical and biochemical properties of drugs, we decided to develop the synthesis of both enantiomers of the lactones of interest. The chemoenzymatic pathway presented herein was based on the lipase-catalyzed resolution of racemic allyl alcohols with the 4-arylbut-3-en-2-ol system. Enantiomerically enriched alcohols were used to synthesize enantiomeric pairs of β-aryl-δ-iodo-γ- and β-aryl-γ-iodo-δ-lactones (Scheme 1).

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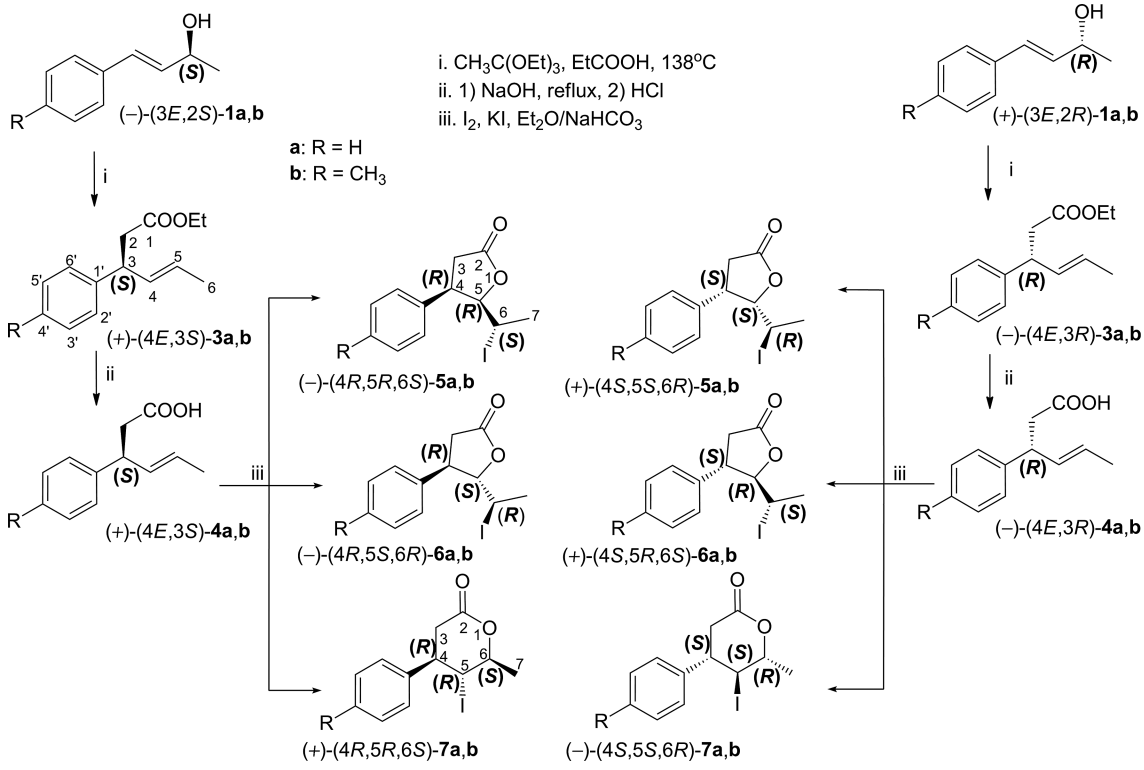


Scheme 1. Synthesis of enantiomeric pairs of iodolactones **5**–**7a**,**b** from both enantiomers of alcohols **1a**,**b**.

Results and Discussion

The starting materials in the chemoenzymatic synthesis of β-aryl-δ-iodo-γ-lactones **5a**,**b** and **6a**,**b**, and β-aryl-γ-iodo-δ-lactones **7a**,**b** (Scheme 1) were two racemic allyl alcohols with 4-phenylbut-3-en-2-ol system **1a**,**b**, which were previously synthesized in a two-step synthesis from benzaldehyde and *p*-methylbenzaldehyde.[19]

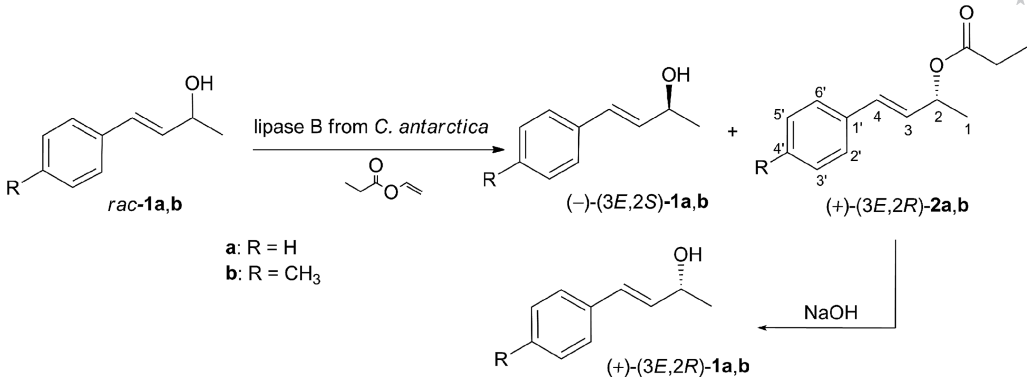
Being interested in both enantiomers of the starting alcohols, we took into consideration the earlier studies on the kinetic resolution of racemic alcohol **1a** by lipase-catalyzed transesterification. Resolution of alcohol **1a** in toluene on a preparative scale was carried out by using lipase from *Pseudomonas cepacia* immobilized on diatomaceous earth and isopropenyl acetate as the acyl donor.[20] After 4 h of the process they obtained (–)-alcohol **1a** with 98%*ee* and its (+)-acetate with 87%*ee*. Exchange of the enzyme carrier to ceramic particles resulted in better enantiomeric excess of (+)-ester (98%) but the *ee* of the unreacted (–)-**1a** was lowered to 96%. The reaction was conducted in diisopropyl ether (DIPE) at 40 °C for 9 h.[21] The best results so far have been obtained by Brenna et al.;[22] in this case, (–)-alcohol **1a** and (+)-ester, both with 98%*ee* were obtained after 24 h reaction carried out in *tert*-butyl methyl ether using vinyl acetate and *Burkholderia cepacia* lipase. In our reaction system we decided to apply lipase B from *Candida antarctica* (Novozym 435, CAL-B) and vinyl propionate as the acyl donor. This enzyme was earlier successfully employed in the resolution of a series of secondary aliphatic allyl alcohols[23] and δ-hydroxy esters.[24] Quirin et al.[25] used CAL-B for the transesterification of **1b** with vinyl acetate in a solvent-free system, affording (–)-alcohol **1b** with 99%*ee* after 24 h of process, but no information about the *ee* of ester was given.

Our results, which are summarized in Table 1, showed that, similar to other lipases, CAL-B showed a high preference towards transesterification of (+)-(*R*)-alcohols **1a**,**b**. Applied conditions significantly accelerated the rate of reaction and, after 2 h of preparative-scale process in DIPE at approximately 50% conversion, we obtained (+)-(*R*)-propionates **2a**,**b** and unreacted (–)-(*S*)-alcohols **1a**,**b** in yields of 38–47% (Scheme 2).

Table 1. Results of enzymatic transesterification of racemic alcohols **1a**,**b**.[a]

Entry	Substrate	Conversion [mol-%]	*ee* of (–)-(*S*) alcohol [%]	*ee* of (+)-(*R*)-propionate [%]
1	**1a**	51	>99	99 (**2a**)
2	**1b**	55	95	88 (**2b**)

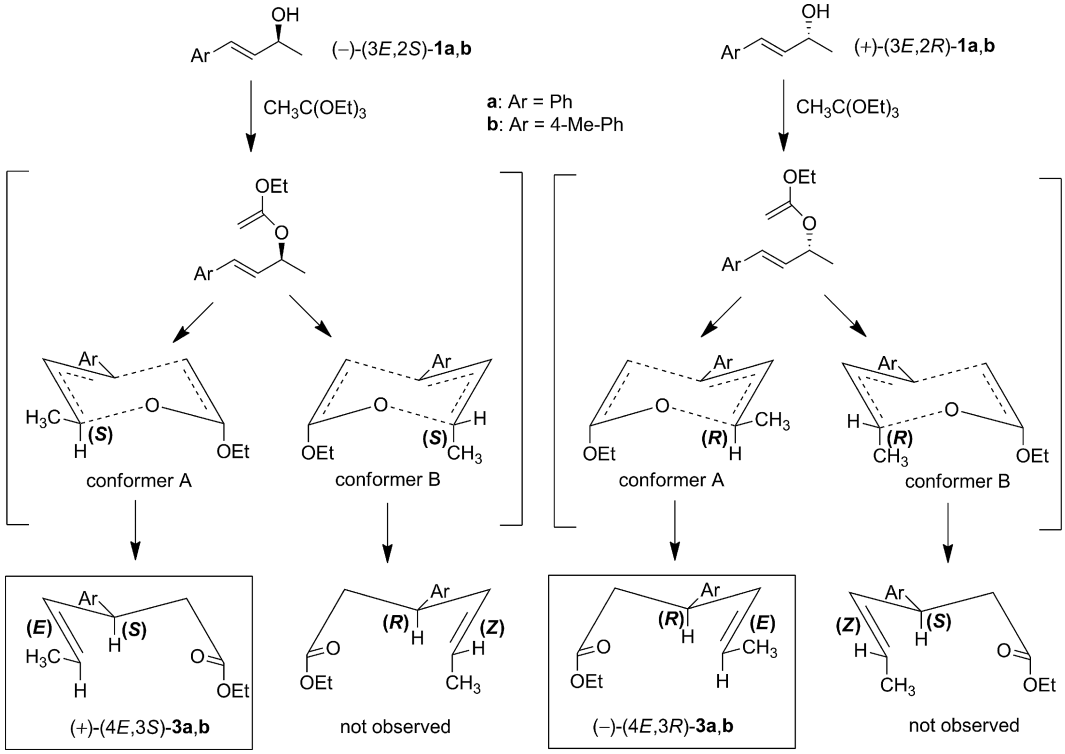
[a] Reaction was carried out at room temperature in DIPE for 2 h using lipase B from *C. antarctica* and vinyl propionate as the acyl donor.



Scheme 2. Synthesis of both enantiomers of alcohols **1a**,**b** using lipase-catalyzed kinetic resolution.

Excellent enantiomeric excesses were obtained for unreacted alcohol (–)-**1a** and propionate (+)-**2a** (> 99% and 99%, respectively, Table 1, entry 1); in the case of the alcohol with a *p*-methylphenyl ring, the optical purity of the products was lower [95%*ee* of alcohol (–)-**1b** and 88%*ee* of propionate (+)-**2b**, entry 2]. Propionate (+)-**2b** was not described previously. Both propionates (+)-**2a**,**b** were hydrolyzed under basic conditions (NaOH) (Scheme 2) to afford (+)-alcohols **1a**,**b** in 91–95% yield and *ee* values identical to those determined for propionates. Configurations of stereogenic centers of (–)- and (+)-alcohols **1a**,**b** and propionate (+)-**2a** were assigned by comparison of their specific rotation values with reported values.[20,25,26] The configuration of propionate (+)-**2b** was assigned based on the configuration of its hydrolysis product, alcohol (–)-**1b**.

(–)-(*S*)-Alcohols **1a**,**b** and (+)-(*R*)-alcohols **1a**,**b** were subjected to the Claisen rearrangement according to the ortho-acetate Johnson modification, which afforded γ,δ-unsaturated esters (+)-(*S*)-**3a**,**b** and (–)-(*R*)-**3a**,**b**, respectively, in 79–87% yields (Scheme 1). During this reaction, allyl alcohol undergoes transvinyl etherification with triethyl orthoacetate, and the forming alkoxy vinyl allyl ether rearranges to γ,δ-unsaturated ester (Scheme 3). The structure of products was confirmed by spectroscopic analysis. In the case of enantiomers of **3a**, strong bands at 1735 and 1159 cm^{-1} in the IR spectrum indicated the presence of an



Scheme 3. Stereochemical course of Johnson–Claisen rearrangement of alcohols with the 4-arylbut-3-en-2-ol system.

ester moiety. Protons of the ethoxy group were represented in the ^{1}H NMR spectrum by a quartet at δ = 4.05 ppm and triplet at δ = 1.15 ppm. Similar data were obtained for both enantiomers of the esters with a 4-methylphenyl ring (**3b**).

Studies on the mechanism of the Johnson–Claisen rearrangement proved that the stereochemical outcome of this reaction depends on the configuration of the double bond of the starting allyl alcohol as well as on the conformation of the six-membered ring formed in the transition state.[27] In the case of *E*-isomers of starting alcohols **1a**,**b**, the esters formed from transition-state A retain the configuration of the double bond as well as the configuration of the stereogenic center, whereas transition-state B gives esters with the opposite configurations of both double bond and the stereogenic center. The possible chair-like conformations, which may be formed in the transition state during formation of esters **3a**,**b**, are presented in Scheme 3. They have significantly different energy states; conformer A is energetically favored because of the lack of 1,3-diaxial interactions between the ethoxy group and the methyl substituent, which occur in conformer B. Therefore, only the formation of the product from conformer A is observed. In this case, apart from retention of the *E* configuration, in both enantiomers of esters **3a** and **3b** the stereochemical consequence of the reaction was a complete transfer of chirality from the C-2 atom of allyl alcohols to the C-3 benzylic atom of the esters. As a result, (*S*,*E*)-esters **3a**,**b** were obtained from (*S*,*E*)-alcohols **1a**,**b**, whereas rearrangement of (*R*,*E*)-alcohols **1a**,**b** afforded esters **3a**,**b** with (*R*,*E*)-configuration. Configuration of the double bond in both enantiomers of esters **3a**,**b** was unequivocally confirmed by the value of the coupling constant between the olefinic protons 4-H and 5-H found in the ^{1}H NMR spectra (J = 15.3 Hz for esters **3a** and 15.0 Hz for esters **3b**). Confirmation of configuration at C-3 was made for (+)-**3a**. In this case, comparison of the specific rotation sign determined for the product of its hydrolysis [acid (+)-(*S*)-**4a**] with reported data for the isomer of **4a** obtained by Ocejo et al.,[28] proved the *S*-configuration of both acid (+)-**4a** and ester (+)-**3a**. Based on these assignments, the absolute configuration of a whole series of esters **3a**,**b** was ascertained by analogy. Enantiomeric pairs of esters **3a**,**b** were analyzed by chiral GC analysis and their enantiomeric excesses remained the same as determined for starting allyl alcohols.

The transfer of chirality in the Johnson–Claisen rearrangement of enzymatically resolved allyl alcohols with the 4-arylbut-3-en-2-ol system have been applied in the synthesis of different chiral chemicals such as (*R*)-baclofen,[29] *cis*-7-methoxy-calamenene,[30] and (*R*)- and (*S*)-3-methyl-2-phenylbutylamine.[22] In our studies, esters **3a**,**b** in both enantiomerical form were used for the synthesis of optically pure iodolactones (Scheme 1). In the first step, esters **3a**,**b** were hydrolyzed in ethanolic NaOH solutions to the corresponding acids **4a**,**b** in 72–91% yields. Their structures were confirmed by characteristic broad absorption bands from the carboxylic group in the range 2700–3550 cm^{-1} in the IR spectra and by the absence of signals from the ethoxy group in the ^{1}H NMR spectra. In all cases, the double bond retained its *E*-configuration, as indicated by the coupling constant (J = 15.0 Hz) between protons 4-H and 5-H. The enantiomeric compositions of synthesized acids **4a**,**b** was not changed in comparison to esters **3a**,**b**, which was proved by chiral GC analysis.

The final step of the synthesis was iodolactonization[31] of both enantiomers of acids **4a**,**b** using iodine and potassium iodide in the biphasic $Et_2O/NaHCO_3$ system. In each case, the composition of the reaction mixtures (Table 2) showed the presence of three products: two γ-lactones and one δ-lactone. The products of 5-*exo*-cyclization (*cis*-γ-lactones **5a**,**b** and *trans*-γ-lactones **6a**,**b**) predominated over the products of 5-*endo*-cyclization (δ-lactones **7a**,**b**). The highest content was observed for *cis*-δ-iodo-γ-lactones, which made up 40–56%, whereas *trans*-δ-iodo-γ-lactones constituted 23–35% of the reaction mixture. These results are consistent with the commonly observed predomination of products formed at higher rate under kinetic reaction conditions.[31] In this case, minimization of electrostatic interactions between the iodonium ion and the aromatic ring in the transition state favors formation of the *cis*-isomers.

Table 2. The composition [%] of the iodolactonization products of acids **4a**,**b** (according to GC analysis).

	Product of iodolactonization		
Acid	*cis*-δ-iodo-γ-lactone	*trans*-δ-iodo-γ-lactone	γ-iodo-δ-lactone
(+)-**4a**	(–)-**5a**	(–)-**6a**	(+)-**7a**
	42.5	33.3	24.2
(–)-**4a**	(+)-**5a**	(+)-**6a**	(–)-**7a**
	40.4	35.3	24.3
(+)-**4b**	(–)-**5b**	(–)-**6b**	(+)-**7b**
	54.7	23.4	21.9
(–)-**4b**	(+)-**5b**	(+)-**6b**	(–)-**7b**
	55.7	26.7	17.6

The products were separated by column chromatography and subjected to crystallization. Their structures were established on the basis of spectroscopic data and, for both enantiomers of lactones **5a**,**b** and **7a**,**b**, also by crystallographic analysis.

X-ray analysis of enantiomeric pairs of γ-lactones **5a**,**b** (Figure 1)[32] revealed the *cis*-orientation of the aromatic ring at C-4 and the iodoethyl substituent at C-5. The spatial structure explains the appearance of the signal from proton 6-H at relatively high field (δ = 3.47 ppm in enantiomers of **5a** and 3.46 ppm in enantiomers of **5b**), which is caused by its location in the shielding cone of the aromatic ring. In contrast, the 6-H proton in the *trans*-γ-lactones **6a**,**b** is situated out of the shielding area of aromatic ring and absorbs the energy at significantly lower field in comparison to the *cis*-isomers: δ = 4.38 ppm in the case of enantiomers of **6a** and δ = 4.37 ppm in the case of enantiomers of **6b**.

Different spatial orientations of the aromatic ring at C-4 and the iodomethyl substituent at C-5 towards the γ-lactone ring also caused noticeable changes in the multiplicities of the signals from 5-H and 6-H. In the spectra of *trans*-γ-lactones **6a**,**b** proton 5-H gives an apparent triplet because of the same value of coupling constant with 4-H and 6-H (J = 5.4 Hz), whereas for *cis*-isomers **5a**,**b**, the signal was

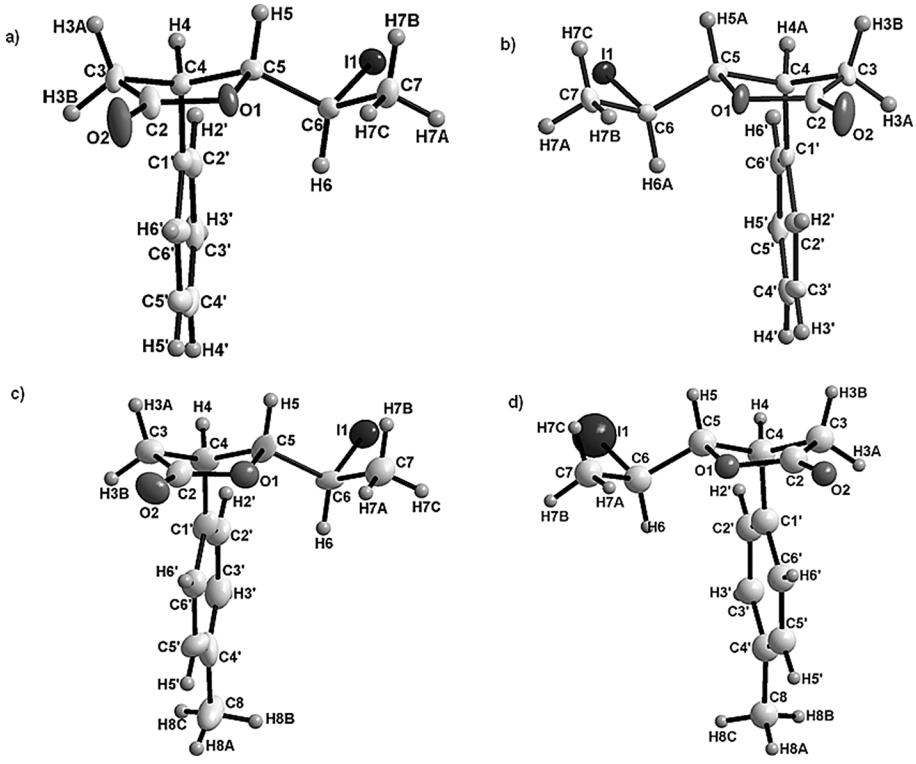


Figure 1. Crystal structures of δ-iodo-γ-lactones: (a) (–)-(4*R*,5*R*,6*S*)-**5a**, (c) (–)-(4*R*,5*R*,6*S*)-**5b**, and their enantiomers: (b) (+)-(4*S*,5*S*,6*R*)-**5a** and (d) (+)-(4*S*,5*S*,6*R*)-**5b**.

observed as doublet of doublets with J = 10.8 and 5.1 Hz. The signal from 6-H, which for *cis*-isomers was observed as a doublet of quartets, in the spectra of *trans*-isomers appears as a quartet of doublets because of the significant lower coupling constant between 6-H and 5-H (J = 5.4 Hz for *trans*-isomers vs. J = 10.8 Hz for *cis*-isomers). According to the Karplus relationship, the vicinal coupling constants are the results of different dihedral angles between corresponding bonds.[33] Analysis of the Dreiding models of obtained lactones and J values found in the ^{1}H NMR spectra clearly confirmed the *trans* orientation of substituents in the enantiomers of lactones **6a**,**b**.

Crystal structure of enantiomeric pairs of lactones **7a**,**b** revealed the half-chair conformation of the six-membered ring and showed the relative orientations of the three substituents (Figure 2).[32] They were located in energetically favorable pseudoequatorial positions, with the iodine atom at C-5 situated *trans* towards both the aryl ring at C-4 and the methyl group at C-6. Coupling constant values between 4-H, 5-H, and 6-H protons (J = 10.2 Hz for lactones **7a** and J = 10.5 for lactones **7b**) were typical for their pseudoaxial orientations. The multiplet from the 6-H proton was shifted to δ = 4.78 ppm (in the case of lactones **7a**) or 4.77 ppm (in the case of lactones **7b**) through the deshielding effect of the oxygen atom in the lactone ring.

The method of crystallographic analysis applied in our studies also allowed the complete assignment of the absolute configuration of the stereogenic centers in the case of enantiomeric pairs of *cis*-γ-lactones **5a** and **5b** (Figure 1) as well as enantiomeric pairs of δ-lactones **7a** and **7b** (Figure 2). This was possible because of sufficient anomal dispersion for the iodine atoms.

The results proved that from (+)-(*S*)-enantiomers of acids **4a**,**b**, we obtained (–)-(4*R*,5*R*,6*S*)-enantiomers of *cis*-γ-lactones (**5a** and **5b**) and (+)-(4*R*,5*R*,6*S*)-enantiomers of δ-lactones (**7a** and **7b**). Their antipodes: (+)-(4*S*,5*S*,6*R*)-enantiomers of *cis*-γ-lactones (**5a** and **5b**) and (–)-(4*S*,5*S*,6*R*)-enantiomers of δ-lactones (**7a** and **7b**) were obtained from (–)-(*R*)-enantiomers of acids **4a**,**b** (Scheme 1).

To determine the absolute configurations for enantiomeric pairs of *trans*-γ-lactones **6a**,**b**, which could not be obtained in crystalline form, the mechanism of iodolactonization was taken into account. This is presented in Scheme 4 for both enantiomers of acids **4a**,**b**. The configuration at C-4 in both *cis*- and *trans*-iodolactones is the result of the configuration of the starting acid. Considering lactonization of (*S*)-acids **4a**,**b**, the change of configuration at C-4 from (*S*) to (*R*) is only the result of different priority of substituents at the stereogenic center after formation of the iodonium ion and subsequent lactone ring closure. The configurations of the new stereogenic centers at C-5 and C-6 results from the reaction mechanism in which the carboxylate ion attacks carbon C-5 from the opposite side of the iodonium ion;[34] the consequence of this is an antiperiplanar orientation of the C–O and C–I bonds (Figure 1). In the case of *cis*-isomers, the result of the aforementioned mechanism is *R*-configuration at C-5 and *S*-configuration at C-6, which was confirmed by crystallographic measurements for (–)-**5a** and (–)-**5b**; in the case of *trans*-isomers, the same mechanism results in the opposite configurations (5*S*

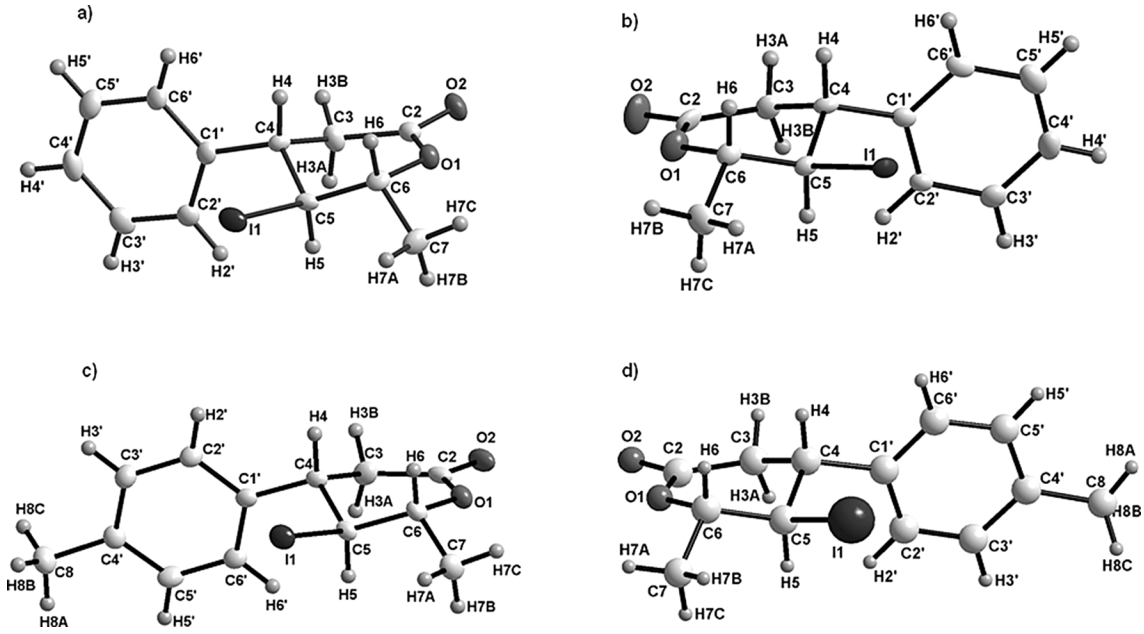
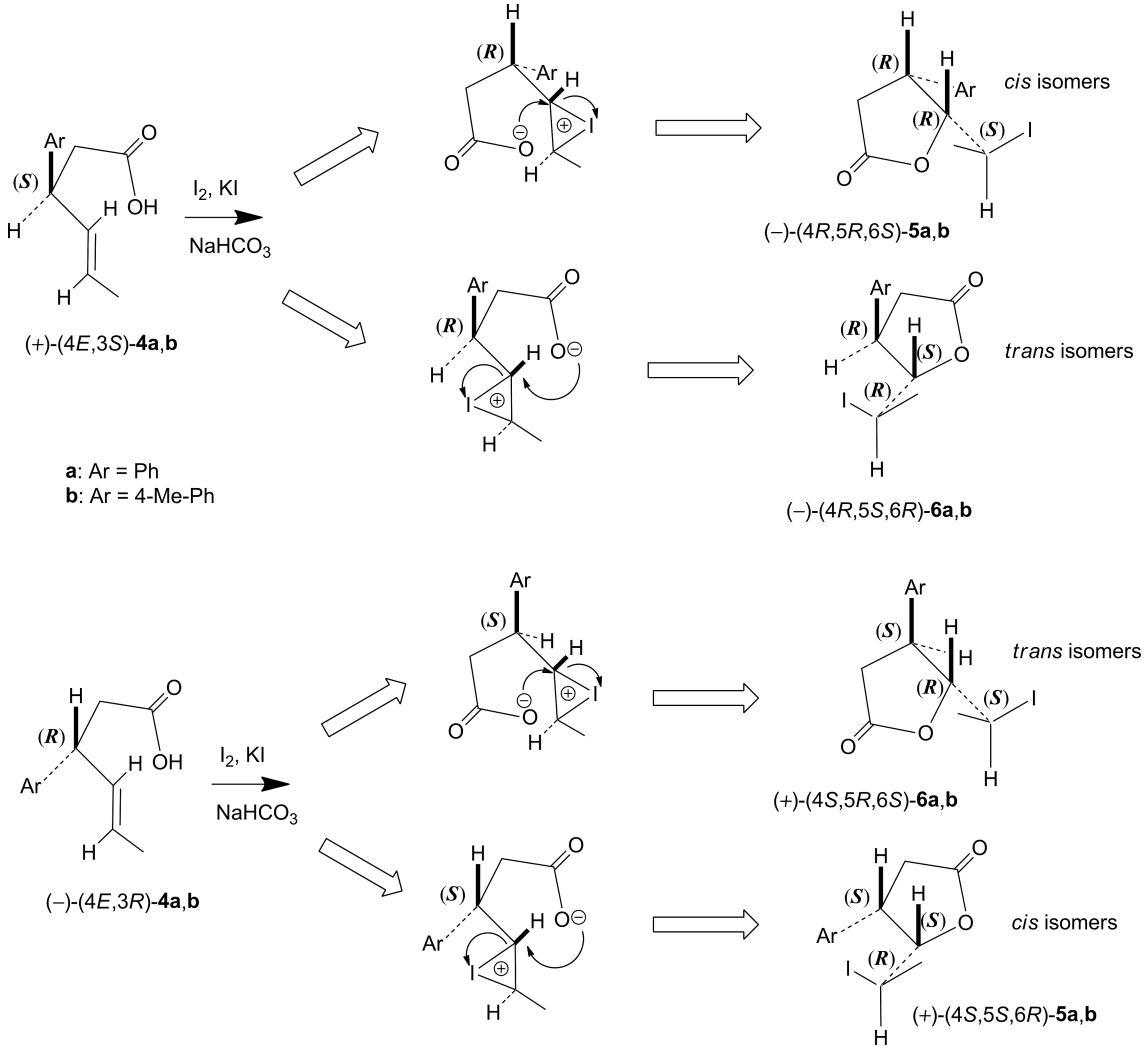


Figure 2. Crystal structures of γ-iodo-δ-lactones: (a) (–)-(4*S*,5*S*,6*R*)-**7a**, (c) (–)-(4*S*,5*S*,6*R*)-**7b**, and their enantiomers: (b) (+)-(4*R*,5*R*,6*S*)-**7a** and (d) (+)-(4*R*,5*R*,6*S*)-**7b**.



Scheme 4. Formation of δ-iodo-γ-lactones during iodolactonization of enantiomeric acids **4a**,**b**.

and 6*R*). Overall, *trans*-γ-lactones **6a**,**b** obtained from (+)-(*S*)-acids **4a**,**b** possessed configurations 4*R*, 5*S*, and 6*R*. For *trans*-γ-lactones **6a**,**b** obtained from (–)-(*R*)-acids **4a**,**b**, parallel reasoning led to the assignment of configurations of stereogenic centers as 4*S*, 5*R*, and 6*S*.

The *cis*-γ-lactones were obtained in higher yields (36–41%). Chiral GC analysis of all synthesized iodolactones revealed their high optical purity, with enantiomeric excesses of 97–99%.

Conclusions

An efficient synthetic pathway leading to chiral β-aryl-substituted iodolactones was developed. From the stereochemical point of view, the crucial steps of the presented pathway were lipase-catalyzed resolution of starting racemic allyl alcohols and transfer of the chirality to the benzylic atom C-3 of γ,δ-unsaturated esters formed by the Johnson–Claisen rearrangement. Six new enantiomeric pairs of iodolactones with high to excellent enantiomeric excesses were obtained as the final products of this pathway. Configurations of their stereogenic centers, which were predicted on the basis of iodolactonization mechanism, were confirmed by X-ray analysis. The presented chemoenzymatic strategy constitutes a universal approach to the synthesis of enantiomerically pure or enriched δ-iodo-γ-lactones and γ-iodo-δ-lactones containing different aromatic rings at the β-position of the lactone ring. Moreover, it may be employed for the synthesis of other halolactones, for example chloro- or bromolactones. The enantiomers of halolactones may be further transformed into other chiral lactone derivatives with clearly defined stereogenic centers, which is important in the context of testing their biological activities.

Experimental Section

Chemicals: Triethyl orthoacetate (purity 97%), vinyl propionate (purity 98%), diisopropyl ether (DIPE, purity ≥ 98.5%), acetyl chloride (purity ≥ 99%), diatomaceous earth (Celite 560) and lipase B from *Candida antarctica* immobilized in a macroporous acrylic resin (> 5,000 U/g) were purchased from Sigma–Aldrich (USA). Propionic acid, sodium hydrogen carbonate, potassium iodide, iodine, anhydrous magnesium sulfate, organic solvents (diethyl ether, methanol, ethanol), sodium hydroxide, and sodium chloride, all of analytical grade, and hydrochloric acid (35–37%) were purchased from P.P.H. Stanlab (Poland), Chempur (Poland), or POCH (Poland). Racemic alcohols (*E*)-4-phenylbut-3-en-2-ol (*rac*-**1a**) and (*E*)-4-phenylbut-3-en-2-ol (*rac*-**1b**) were synthesized as described earlier.[19]

Chromatographic Separations: Column chromatography was performed on silica gel (Kieselgel 60, 230–400 mesh, Merck) using mixtures of hexane and acetone in various ratios as the eluents. Analytical thin-layer chromatography (TLC) was performed on silica gel coated aluminum plates (DC-Alufolien Kieselgel 60 F_{254}, Merck) with mixtures of hexane and acetone (different ratios) as developing systems. Compounds were visualized by spraying the plates with a solution of 1% $Ce(SO_4)_2$ and 2% $H_3[P(Mo_3O_{10})_4]$ in 10% H_2SO_4.

Gas Chromatography Analysis: Analysis was performed with an Agilent Technologies 6890N instrument equipped with autosampler, split injection (50:1) and FID detector. The progress of reactions were monitored on DB-17 column [(50%-phenyl)-methylpolysiloxane, 30 m×0.25 mm × 0.25 μm] with hydrogen as carrier gas. Temperature programme for the analysis of alcohols **1a**,**b**, propionates **2a**,**b**, esters **3a**,**b** and acids **4a**,**b** was as follows: 80 °C (1 min), 80–200 °C (20 °C min^{-1}), 200–300 °C (30 °C min^{-1}), 300 °C (2 min); for iodolactones **5a**,**b**–**7a**,**b**: injector 280 °C, detector (FID) 280 °C, column temperature: 220 °C, 220–240 °C (3 °C min^{-1}), 240–280 °C (30 °C min^{-1}), 280 °C (2 min). The enantiomeric excesses were determined by chiral gas chromatography (CGC) using Varian CP Chirasil-DEX CB column (25 m × 0.25 mm × 0.25 μm) with following temperature programs: for products of transesterification of alcohol **1a**: 80 °C, 80–130 °C (0.5 °C min^{-1}), 130–200 °C (30 °C min^{-1}), 200 °C (2 min), for products of transesterification of alcohol **1b**: 80 °C, 80–150 °C (2 °C min^{-1}), 150–200 °C (10 °C min^{-1}), 200 °C (2 min), for iodolactones **5b**–**7b**: 80 °C, 80–200 °C (2 °C min^{-1}), 200 °C (3 min), for esters **3a**,**b**, acids **4a**,**b** and iodolactones **5a**–**7a**: 50 °C, 50–200 °C (0.5 °C min^{-1}), 200 °C (1 min). Enantiomers of alcohol **1b** were analyzed as acetate derivatives after treating with acetyl chloride. Racemic compounds **1**–**7 a**,**b**[19] were used as the standards.

Spectroscopic Analysis: ^1H, ^{13}C NMR (including DEPT 135 experiment) and HMQC spectra were recorded for $CDCl_3$ solutions with a Bruker Avance AMX 300 spectrometer. Residual solvent signals (δ_H = 7.26, δ_C = 77.0) were used as references for chemical shifts. IR spectra were determined with a Mattson IR 300 Thermo Nicolet spectrophotometer using KBr pellets or in liquid films. Mass spectra were recorded at the Structural Research Laboratory of the UJK University in Kielce by using the electron spray ionization (ESI) technique with a Bruker micrOTOF-Q II system. Melting points were determined with a Boetius apparatus. Refraction indexes were measured with a Carl Zeiss Jena refractometer. Optical rotations were measured with a Jasco P-2000-Na digital polarimeter with intelligent Remote Module (iRM) controller. Compounds were dissolved in dichloromethane, concentrations are denoted in g × 100 mL^{-1}.

General Protocol for Kinetic Resolution of *rac*-1a,b by Enzymatic Transesterification: Lipase B from *C. antartica* (50 wt.-% of alcohol) was placed in a 250 mL round-bottom flask containing a mixture of racemic alcohol (33 mmol) and vinyl propionate (46 mmol) in diisopropyl ether (50 mL). The reaction was stirred at room temperature for 2 h, then the enzyme was filtered off and the organic solvent was removed by rotary evaporation in vacuo. Enantiomerically enriched products were separated by column chromatography (hexane/acetone, 5:1).

Process of transesterification of racemic alcohol **1a** (4.98 g, 33 mmol) gave the following products:

(–)-(2*S*,3*E*)-4-Phenylbut-3-en-2-ol [(–)-1a]: Yield 2.3 g (46%); colorless crystals; m.p. 54–56 °C; *ee* > 99%; t_R = 60.18 min; R_f = 0.23 [hexane/acetone (4:1 v/v)]; $[\alpha]_D^{20}$ = –23.7 (*c* = 2.6, CH_2Cl_2) [ref.[20] $[\alpha]_D^{20}$ = –19.9 (*c* = 1.0, CH_2Cl_2), *ee* > 99%]. Spectral data are identical to the reported values.[21]

(+)-(2*R*,3*E*)-4-Phenylbut-3-en-2-yl Propionate [(+)-2a]: Yield 3.1 g (45%); pale-brown liquid; n_D^{20} = 1.5160; *ee* = 99%; t_R = 71.12 min; R_f = 0.64 [hexane/acetone (4:1 v/v)]; $[\alpha]_D^{20}$ = +115.9 (*c* = 2.1, CH_2Cl_2) [ref.[26] $[\alpha]_D^{20}$ = +70.0 (*c* = 0.6, $CHCl_3$); *ee* = 66%]. Spectral data are identical to the reported values.[35]

Process of transesterification of racemic alcohol **1b** (5 g, 31 mmol) gave the following products:

(–)-(2*S*,3*E*)-4-(4′-Methylphenyl)but-3-en-2-ol [(–)-1b]: Yield 2.45 g (47%); colorless crystals; m.p. 36–42 °C; *ee* = 95% (determined after derivatization into acetate); t_R = 27.00 min; R_f = 0.23 [hexane/acetone (4:1 v/v)]; $[\alpha]_D^{20}$ = –22.8 (*c* = 1.8, CH_2Cl_2) [ref.[25] $[\alpha]_D^{25}$ = –22.8 (*c* = 1, $CHCl_3$); *ee* = 99%]. Spectral data are identical to reported values.[36]

(+)-(2*R*,3*E*)-4-(4′-Methylphenyl)but-3-en-2-yl Propionate [(+)-2b]: Yield 2.55 g (38%); pale-brown liquid; n_D^{20} = 1.5348; *ee* = 88%; t_R = 31.30 min; R_f = 0.65 [hexane/acetone (4:1 v/v)]; $[\alpha]_D^{20}$ = +111.8 (*c* = 1.7, CH_2Cl_2). IR (film): $\tilde{\nu}_{max}$ = 1736 (s), 1610 (w), 1514 (m), 1187 (s), 1039 (m), 969 (m), 801 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.18 [t, *J* = 7.5 Hz, 3 H, C(O)CH_2CH_3], 1.43 (d, *J* = 6.6 Hz, 3 H, CH_3-1), 2.35 (s, 3 H, CH_3-8), 2.36 [q, *J* = 7.5 Hz, 2 H, C(O)CH_2CH_3], 5.57 (m, 1 H, 2-H), 6.17 (dd, *J* = 15.9, 6.6 Hz, 1 H, 3-H), 6.60 (d, *J* = 15.9 Hz, 1 H, 4-H), 7.12–7.15 (m, 2 H, 2′-H and 6′-H), 7.28–7.31 (m, 2 H, 3′-H and 5′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.9 [C(O)CH_2CH_3], 20.2 (C-1), 20.9 (C-8), 27.6 [C(O)CH_2CH_3], 70.6 (C-2), 126.2 (C-2′ and C-6′), 129.0 (C-3′ and C-5′), 127.6 (C-3), 131.2 (C-4), 133.4 (C-1′), 137.4 (C-4′), 173.3 (C-5) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{14}H_{18}O_2$ [M + Na]$^+$ 241.1204; found 241.1212.

General Protocol for Hydrolysis of Esters (+)-2a,b: The ester (12 mmol) was heated to reflux in a mixture of 5% solution of NaOH in EtOH (100 mL) and water (20 mL). When the substrate reacted completely (3 h, TLC), the ethanol was evaporated in vacuo and the residue was diluted with water. The product was extracted with dichloromethane (3 × 40 mL) and the combined organic fractions were washed with brine until neutral and dried with anhydrous $MgSO_4$. After evaporation of solvent in vacuo, pure alcohol was obtained.

(+)-(2*R*,3*E*)-4-Phenylbut-3-en-2-ol [(+)-1a]: Obtained from propionate (+)-**2a** (3 g, 15 mmol), yield 2.1 g (96%); colorless crystals; m.p. 53–55 °C; *ee* = 99%; t_R = 59.27 min; $[\alpha]_D^{20}$ = +22.9 (*c* = 1.6, CH_2Cl_2) [ref.[20] $[\alpha]_D^{20}$ = +19.9 (*c* = 1, CH_2Cl_2); *ee* > 99%]. Spectral data are identical to the reported values for (–)-**1a**.[21]

(+)-(2*R*,3*E*)-4-(4′-Methylphenyl)but-3-en-2-ol [(+)-1b]: Obtained from propionate (+)-**2b** (2.5 g, 11 mmol), yield 1.81 g (98%); colorless crystals; m.p. 46–49 °C; *ee* = 96% (determined after derivatization to the acetate); t_R = 27.75 min; $[\alpha]_D^{20}$ = +22.5 (*c* = 1.5, CH_2Cl_2) [ref.[37] $[\alpha]_D^{25}$ = +20.9 (*c* = 0.8, $CHCl_3$); *ee* = 98%]. Spectral data are identical to the reported values for (–)-**1b**.[36]

General Protocol for the Synthesis of γ,δ-Unsaturated Esters (+)-3a,b and (–)-3a,b: Allyl alcohol (15 mmol) was dissolved in triethyl orthoacetate (273 mmol) and one drop of propionic acid was added. The mixture was heated at 138 °C with simultaneous removal of ethanol by distillation. When the reaction was finished (24 h, TLC, GC), the crude product was purified by column chromatography (hexane/acetone, 10:1) to afford the pure ester.

(+)-(3*S*,4*E*)-Ethyl 3-Phenylhex-4-enoate [(+)-3a]: Obtained from alcohol (–)-**1a** (2.2 g, 15 mmol), yield 2.6 g (80%); yellow liquid; n_D^{20} = 1.5030; *ee* > 99%; t_R = 119.83 min; $[\alpha]_D^{20}$ = +8.0 (*c* = 2.1, CH_2Cl_2). IR (film): $\tilde{\nu}_{max}$ = 3028 (w), 2979 (m), 1735 (s), 1159 (s), 757 (m), 699 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.15 (t, *J* = 6.9 Hz, 3 H, -OCH_2CH_3), 1.63 (d, *J* = 6.0 Hz, 3 H, CH_3-6), 2.66 (m, 2 H, CH_2-2), 3.78 (m, 1 H, 3-H), 4.05 (q, *J* = 6.9 Hz, 2 H, -OCH_2CH_3), 5.47 (dq, *J* = 15.3, 6.0 Hz, 1 H, 5-H), 5.58 (dd, *J* = 15.3, 7.5 Hz, 1 H, 4-H), 7.18–7.35 (m, 5 H, -C_6H_5) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (C-8), 17.9 (C-6), 41.0 (C-2), 44.9 (C-3), 60.2 (C-7), 125.6 (C-5), 126.4 (C-4′), 127.4 (C-2′ and C-6′), 128.5 (C-3′ and C-5′), 133.1 (C-4), 143.3 (C-1′), 172.0 (C-1) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{14}H_{18}O_2$ [M + Na]$^+$ 241.1204; found 241.1200.

(–)-(3*R*,4*E*)-Ethyl 3-Phenylhex-4-enoate [(–)-3a]: Obtained from alcohol (+)-**1a** (2.0 g, 13.5 mmol), yield 2.32 g (79%); yellow liquid; n_D^{20} = 1.5030; *ee* = 99%; t_R = 119.01 min; $[\alpha]_D^{20}$ = –8.3 (*c* = 2.55, CH_2Cl_2). Spectral data identical to those of (+)-**3a**.

(+)-(3*S*,4*E*)-Ethyl 3-(4′-Methylphenyl)-hex-4-enoate [(+)-3b]: Obtained from alcohol (–)-**1b** (2.40 g, 15 mmol), yield 2.99 g (87%); yellow liquid; n_D^{20} = 1.5050; *ee* = 95%; t_R = 138.14 min; $[\alpha]_D^{20}$ = +8.9 (*c* = 1.25, CH_2Cl_2). IR (film): $\tilde{\nu}_{max}$ = 1736 (s), 1514 (m), 1248 (s), 1158 (m), 1037 (s), 968 (m), 816 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.18 (t, *J* = 7.2 Hz, 3 H, -OCH_2CH_3), 1.65 (d, *J* = 6.6 Hz, 3 H, CH_3-6), 2.31 (s, 3 H, Ph-CH_3), 2.65 (dd, *J* = 15.0, 7.2 Hz, 1 H, one of CH_2-2), 2.68 (dd, *J* = 15.0, 8.4 Hz, 1 H, one of CH_2-2), 3.77 (m, 1 H, 3-H), 4.08 (q, *J* = 7.2 Hz, 2 H, -OCH_2CH_3), 5.49 (dq, *J* = 15.0, 6.6 Hz, 1 H, 5-H), 5.58 (ddq, *J* = 15.0, 7.2, 1.2 Hz, 1 H, 4-H), 7.09–7.13 (m, 4 H, *p*-C_6H_4) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (-OCH_2CH_3), 17.9 (C-6), 21.0 (Ph-CH_3), 41.0 (C-2), 44.5 (C-3), 60.2 (-OCH_2CH_3), 125.3 (C-5), 127.2 (C-2′ and C-6′), 129.2 (C-3′ and C-5′), 133.3 (C-4), 135.9 (C-1′), 140.4 (C-4′), 172.0 (C-1) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{15}H_{20}O_2$ [M + Na]$^+$ 255.1361; found 255.1336.

(–)-(3*R*,4*E*)-Ethyl 3-(4′-Methylphenyl)-hex-4-enoate [(–)-3b]: Obtained from alcohol (+)-**1b** (1.8 g, 11 mmol), yield 2.16 g (84%); yellow liquid; n_D^{20} = 1.5050; *ee* = 88%; t_R = 137.72 min; $[\alpha]_D^{20}$ = –8.7 (*c* = 0.25, CH_2Cl_2). Spectral data identical to those of (+)-**3b**.

General Protocol for the Synthesis of γ,δ-Unsaturated Acids (+)-4a,b and (–)-4a,b: The ester (11 mmol) was heated to reflux in 5% ethanol solution of NaOH (100 mL). When the reaction was completed (3 h, TLC, GC), ethanol was evaporated in vacuo. The residue was diluted with water and washed with diethyl ether (3 × 40 mL) to remove organic impurities. After separation of the layers, the aqueous layer was acidified with 1 M HCl and the acid was extracted with diethyl ether (3 × 40 mL). The ethereal fractions were combined, washed with brine and dried with anhydrous $MgSO_4$. After evaporation of the solvent in vacuo, pure acid was obtained.

(+)-(3*S*,4*E*)-3-Phenylhex-4-enoic Acid [(+)-4a]: Obtained from ester (+)-**3a** (2.5 g, 11 mmol), yield 1.90 g (87%); brown liquid; n_D^{20} = 1.5162; *ee* > 99%; t_R = 184.39 min, $[\alpha]_D^{20}$ = +6.2 (*c* = 2.0, CH_2Cl_2) [ref.[28] $[\alpha]_D^{20}$ = +7.3 (*c* = 1.0, CH_2Cl_2]. Spectral data in accordance with reported values.[28]

(–)-(3*R*,4*E*)-3-Phenylhex-4-enoic Acid [(–)-4a]: Obtained from ester (–)-**3a** (2.3 g, 10.5 mmol), yield 1.78 g (89%); brown liquid; *ee* = 99%; t_R = 184.91 min; $[\alpha]_D^{20}$ = –5.4 (*c* = 2.4, CH_2Cl_2). Spectral data identical to the reported values for the (*S*)-enantiomer [(+)-**4a**].[28]

(+)-(3*S*,4*E*)-3-(4′-Methylphenyl)hex-4-enoic Acid [(+)-4b]: Obtained from ester (+)-**3b** (2.9 g, 12.5 mmol), yield 1.83 g (72%); brown liquid; n_D^{20} = 1.5233; *ee* = 95%; t_R = 197.77 min; $[\alpha]_D^{20}$ = +4.6 (*c* = 1.1, CH_2Cl_2). IR (film): $\tilde{\nu}_{max}$ = 2700–3550 (b, s), 1710 (s), 1514 (m), 1439 (s), 1266 (s), 968 (s), 815 (s), 738 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.68 (d, *J* = 5.4 Hz, 3 H, CH_3-6), 2.33 (s, 3 H, Ph-CH_3), 2.73 (m, 2 H, CH_2-2), 3.78 (m, 1 H, 3-H), 5.51 (dq, *J* = 15.3, 5.4 Hz, 1 H, 5-H), 5.60 (dd, *J* = 15.3, 7.2 Hz, 1 H, 4-H), 7.09–7.15 (m, 4 H, *p*-C_6H_4) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.9 (C-6), 21.0 (C-7), 40.6 (C-2), 44.0 (C-3), 125.6 (C-5), 127.2 (C-2′ and C-6′), 129.3 (C-3′ and C-5′), 133.0 (C-4), 136.1 (C-1′), 140.0 (C-4′), 178.0 (C-1) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{13}H_{16}O_2$ [M + Na]$^+$ 227.1048; found 227.1074.

(–)-(3*R*,4*E*)-3-(4′-Methylphenyl)hex-4-enoic Acid [(–)-4b]: Obtained from ester (–)-**3b** (2.1 g, 9 mmol), yield 1.70 g (91%); brown liquid; *ee* = 88%; t_R = 198.70; $[\alpha]_D^{20}$ = –4.4 (*c* = 0.95, CH_2Cl_2). Spectral data identical to those of (+)-**4b**.

General Protocol for the Synthesis of Iodolactones (–)-5a–b, (–)-6a–b, (+)-7a–b and (+)-5a–b, (+)-6a–b, (–)-7a–b: A mixture of acid (10 mmol) dissolved in a mixture of diethyl ether (20 mL) and a saturated solution of $NaHCO_3$ (20 mL) was stirred for 1 h at room temperature and then a solution of I_2 (20 mmol) and KI (60 mmol) in water (6 mL) was added dropwise. When the acid reacted completely (24 h, TLC, GC), the mixture was washed with saturated $Na_2S_2O_3$ solution. The two layers were separated and the organic fraction was washed with saturated $NaHCO_3$, brine, and dried with anhydrous $MgSO_4$. After vacuum evaporation of diethyl ether, the products were separated by column chromatography (hexane/acetone, 20:1).

From acid (+)-**4a** (1.85 g, 10 mmol) the following iodolactones were obtained:

(–)-*cis*-(4*R*,5*R*,6*S*)-5-(1-Iodoethyl)-4-phenyldihydrofuran-2-one [(–)-5a]: Yield 1.1 g (36%); colorless crystals (crystallization from mixture hexane/acetone, 20:1); m.p. 104–106 °C; *ee* > 99%; t_R = 199.09 min; R_f = 0.43 [hexane/acetone (4:1 v/v)]; $[\alpha]_D^{20}$ = –15.7 (*c* = 1.4, CH_2Cl_2). IR (KBr): $\tilde{\nu}_{max}$ = 1779 (s), 1416 (s), 1183 (s), 1136 (s), 1005 (s), 755 (s), 706 (s), 535 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.01 (d, *J* = 6.6 Hz, 3 H, CH_3-7), 2.71 (dd, *J* = 17.7, 0.9 Hz, 1 H, one of CH_2-3), 3.14 (dd, *J* = 17.7, 8.7 Hz, 1 H, one of CH_2-3), 3.47 (dq, *J* = 10.8, 6.6 Hz, 1 H, 6-H), 3.91 (dd, *J* = 8.4, 5.1 Hz, 1 H, 4-H), 4.82 (dd, *J* = 10.8, 5.1 Hz, 1 H, 5-H), 7.25–7.35 (m, 5 H, -C_6H_5) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.3 (C-6), 25.5 (C-7), 38.9 (C-3), 45.0 (C-4), 87.8 (C-5), 128.0 (C-4′), 128.5 (C-2′ and C-6′), 128.7 (C-3′ and C-5′), 137.3 (C-1′), 176.4 (C-2) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{12}H_{13}IO_2$ $[M + Na]^+$ 338.9858; found 338.9874.

(–)-*trans*-(4*R*,5*S*,6*R*)-5-(1-Iodoethyl)-4-phenyldihydrofuran-2-one [(–)-6a]: Yield 0.61 g (20%); brown liquid; *ee* = 95%; t_R = 212.11 min; R_f = 0.35 [hexane/acetone (4:1 v/v)]; $[\alpha]_D^{20}$ = –16.3 (*c* = 1.1, CH_2Cl_2). IR (KBr): $\tilde{\nu}_{max}$ = 1781 (s), 1494 (m), 1200 (s), 1149 (s), 1027 (s), 768 (s), 700 (s), 524 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.86 (d, *J* = 6.9 Hz, 3 H, CH_3-7), 2.68 (dd, *J* = 18.3, 6.6 Hz, 1 H, one of CH_2-3), 3.16 (dd, *J* = 18.3, 10.2 Hz, 1 H, one of CH_2-3), 3.64 (ddd, *J* = 10.2, 6.6, 5.4 Hz, 1 H, 4-H), 4.26 (t, *J* = 5.4 Hz, 1 H, 5-H), 4.38 (qd, *J* = 6.9, 5.4 Hz, 1 H, 6-H), 7.26–7.41 (m, 5 H, -C_6H_5) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.4 (C-7), 28.4 (C-6), 37.7 (C-3), 45.4 (C-4), 89.4 (C-5), 127.0 (C-2′ and C-6′), 127.7 (C-4′), 129.3 (C-3′ and C-5′), 141.2 (C-1′), 174.8 (C-2) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{12}H_{13}IO_2$ $[M + K]^+$ 354.9597; found 354.9653.

(+)-(4*R*,5*R*,6*S*)-5-*t*-Iodo-6-*c*-methyl-4-*r*-phenyltetrahydropyran-2-one [(+)-7a]: Yield 0.21 g (7%); colorless crystals (crystallization from mixture hexane/acetone, 20:1); m.p. 78–80 °C; *ee* > 99%; t_R = 217.99 min; R_f = 0.31 [hexane/acetone (4:1 v/v)]; $[\alpha]_D^{20}$ = +7.5 (*c* = 0.7, CH_2Cl_2). IR (KBr): $\tilde{\nu}_{max}$ = 1721 (s), 1453 (m), 1253 (s), 1226 (s), 1043 (s), 968 (m), 759 (s), 701 (s), 538 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.75 (d, *J* = 6.3 Hz, 3 H, CH_3-7), 2.68 (dd, *J* = 17.7, 10.2 Hz, 1 H, one of CH_2-3), 2.99 (dd, *J* = 17.7, 6.3 Hz, 1 H, one of CH_2-3), 3.50 (td, *J* = 10.2, 6.3 Hz, 1 H, 4-H), 4.05 (t, *J* = 10.2 Hz, 1 H, 5-H), 4.78 (dq, *J* = 10.2, 6.3 Hz, 1 H, 6-H), 7.16–7.41 (2m, 5 H, -C_6H_5) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.3 (C-7), 34.3 (C-5), 37.8 (C-3), 48.6 (C-4), 81.1 (C-6), 126.8 (C-2′ and C-6′), 128.0 (C-4′), 129.1 (C-3′ and C-5′), 142.3 (C-1′), 169.5 (C-2) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{12}H_{13}IO_2$ $[M + Na]^+$ 338.9858; found 338.9889.

From acid (–)-**4a** (1.72 g, 9 mmol) the following iodolactones were obtained:

(+)-*cis*-(4*S*,5*S*,6*R*)-5-(1-Iodoethyl)-4-phenyldihydrofuran-2-one [(+)-5a]: Yield 1.1 g (39%); colorless crystals (crystallization from mixture hexane/acetone, 20:1); m.p. 100–103 °C; *ee* = 97%; t_R = 198.23 min; $[\alpha]_D^{20}$ = +14.8 (*c* = 1.3, CH_2Cl_2). Retardation factor and spectroscopic data were identical to those of (–)-**5a**.

(+)-*trans*-(4*S*,5*R*,6*S*)-5-(1-Iodoethyl)-4-phenyldihydrofuran-2-one [(+)-6a]: Yield 0.6 g (21%); brown liquid; *ee* = 98%; t_R = 214.26 min; $[\alpha]_D^{20}$ = +6.7 (*c* = 1.1, CH_2Cl_2). Retardation factor and spectroscopic data were identical to those of (–)-**6a**.

(–)-(4*S*,5*S*,6*R*)-5-*t*-Iodo-6-*c*-methyl-4-*r*-phenyltetrahydropyran-2-one [(–)-7a]: Yield 0.22 g (8%); colorless crystals (crystallization from mixture hexane/acetone, 20:1); m.p. 85–88 °C; *ee* = 99%; t_R = 218.91 min; $[\alpha]_D^{20}$ = –7.2 (*c* = 0.95, CH_2Cl_2). Retardation factor and spectroscopic data were identical to those of (+)-**7a**.

From acid (+)-**4b** (1.7 g, 8 mmol) following iodolactones were obtained:

(–)-*cis*-(4*R*,5*R*,6*S*)-5-(1-Iodoethyl)-4-(4′-methylphenyl)dihydrofuran-2-one [(–)-5b]: Yield 1.04 g (38%); colorless crystals (crystallization from mixture hexane/acetone, 20:1); m.p. 87–90 °C; *ee* = 98%; t_R = 46.17 min; R_f = 0.45 [hexane/acetone (4:1 v/v)]; $[\alpha]_D^{20}$ = –6.5 (*c* = 0.7, CH_2Cl_2). IR (KBr): $\tilde{\nu}_{max}$ = 1791 (s), 1449 (s), 1180 (s), 1139 (s), 960 (s), 829 (s), 498 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.01 (d, *J* = 6.9 Hz, 3 H, CH_3-7), 2.34 (s, 3 H, Ph-CH_3), 2.68 (d, *J* = 17.4 Hz, 1 H, one of CH_2-3), 3.13 (dd, *J* = 17.4, 8.4 Hz, 1 H, one of CH_2-3), 3.46 (dq, *J* = 10.8, 6.9 Hz, 1 H, 6-H), 3.86 (dd, *J* = 8.4, 5.1 Hz, 1 H, 4-H), 4.80 (dd, *J* = 10.8, 5.1 Hz, 1 H, 5-H), 7.10–7.17 (m, 4 H, *p*-C_6H_4) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 (Ph-CH_3), 23.5 (C-6), 25.5 (C-7), 38.9 (C-3), 44.5 (C-4), 87.8 (C-5), 128.4 (C-2′ and C-6′), 129.4 (C-3′ and C-5′), 134.2 (C-1′), 137.7 (C-4′), 176.6 (C-2) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{13}H_{15}IO_2$ $[M + Na]^+$ 353.0014; found 352.9989.

(–)-*trans*-(4*R*,5*S*,6*R*)-5-(1-Iodoethyl)-4-(4′-methylphenyl)dihydrofuran-2-one [(–)-6b]: Yield 0.52 g (19%); oily liquid; *ee* = 97%; t_R = 86.61 min; R_f = 0.39 [hexane/acetone (4:1 v/v)]; $[\alpha]_D^{20}$ = –8.4 (*c* = 3.9, CH_2Cl_2). IR (film): $\tilde{\nu}_{max}$ = 1782 (s), 1516 (m), 1149 (s), 1185 (s), 1030 (s), 814 (m), 539 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.85 (d, *J* = 7.2 Hz, 3 H, CH_3-7), 2.34 (s, 3 H, Ph-CH_3), 2.65 (dd, *J* = 18.3, 6.6 Hz, 1 H, one of CH_2-3), 3.13 (dd, *J* = 18.3, 10.2 Hz, 1 H, one of CH_2-3), 3.59 (ddd, *J* = 10.2, 6.6, 5.4 Hz, 1 H, 4-H), 4.23 (t, *J* = 5.4 Hz, 1 H, 5-H), 4.37 (qd, *J* = 7.2, 5.4 Hz, 1 H, 6-H), 7.13–7.20 (m, 4 H, *p*-C_6H_4) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1 (C-7), 23.4 (Ph-CH_3), 28.5 (C-6), 37.9 (C-3), 45.1 (C-4), 89.6 (C-5), 127.0 (C-2′ and C-6′), 130.0 (C-3′ and C-5′), 137.6 (C-4′), 138.33 (C-1′), 175.0 (C-2) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{13}H_{15}IO_2$ $[M + K]^+$ 368.9754; found 368.9796.

(+)-(4*R*,5*R*,6*S*)-5-*t*-Iodo-6-*c*-methyl-4-*r*-(4′-methylphenyl)tetrahydropyran-2-one [(+)-7b]: Yield 0.19 g (7%); colorless crystals (crystallization from mixture hexane/acetone, 20:1); m.p. 74–76 °C; *ee* > 99%; t_R = 88.57 min; R_f = 0.34 [hexane/acetone (4:1 v/v)]; $[\alpha]_D^{20}$ = +19.7 (*c* = 0.7, CH_2Cl_2). IR (KBr): $\tilde{\nu}_{max}$ = 1724 (s), 1516 (m), 1257 (s), 1233 (s), 1095 (s), 527 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.74 (d, *J* = 6.3 Hz, 3 H, CH_3-7), 2.35 (s, 3 H, Ph-CH_3), 2.65 (dd, *J* = 17.7, 10.2 Hz, 1 H, one of CH_2-3), 2.96 (dd, *J* = 17.7, 6.6 Hz, 1 H, one of CH_2-3), 3.45 (td, *J* = 10.5, 6.6 Hz, 1 H, 4-H), 4.04 (t, *J* = 10.5 Hz, 1 H, 5-H), 4.77 (dq, *J* = 10.5, 6.3 Hz, 1 H, 6-H), 7.04–7.06 (m, 2 H, 2′-H and 6′-H), 7.18–7.20 (m, 2 H, 3′-H and 5′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2 (C-7), 22.4 (Ph-CH_3), 34.8 (C-5), 38.0 (C-3), 48.2 (C-4), 81.2 (C-6), 126.8 (C-2′ and C-6′), 129.8 (C-3′ and C-5′), 137.8 (C-4′), 139.4 (C-1′), 169.7 (C-2) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{13}H_{15}IO_2$ $[M + K]^+$ 368.9754; found 368.9745.

From acid (–)-**4b** (1.65 g, 8 mmol), the following iodolactones were obtained:

(+)-*cis*-(4*S*,5*S*,6*R*)-5-(1-Iodoethyl)-4-(4′-methylphenyl)dihydrofuran-2-one [(+)-5b]: Yield 1.09 g (41%); colorless crystals (crystallization from mixture hexane/acetone, 20:1); m.p. 90–93 °C; *ee* > 99%; t_R = 45.85 min; $[\alpha]_D^{20}$ = +6.1 (*c* = 0.9, CH_2Cl_2). Retardation factor and spectroscopic data were identical to those of (–)-**5b**.

(+)-*trans*-(4*S*,5*R*,6*S*)-5-(1-Iodoethyl)-4-(4′-methylphenyl)dihydrofuran-2-one [(+)-6b]: Yield 0.48 g (18%); oily liquid; *ee* = 97%; t_R = 87.14; $[\alpha]_D^{20}$ = +8.0 (*c* = 3.7, CH_2Cl_2). Retardation factor and spectroscopic data were identical to those of (–)-**6b**.

(–)-(4*S*,5*S*,6*R*)-5-*t*-Iodo-6-*c*-methyl-4-*r*-(4′-methylphenyl)tetrahydropyran-2-one [(–)-7b]: Yield 0.11 g (4%); colorless crystals (crystallization from mixture hexane/acetone, 20:1); m.p. 70–72 °C; *ee* = 98%; t_R = 88.96 min; $[\alpha]_D^{20}$ = –17.7 (*c* = 0.7, CH_2Cl_2). Retardation factor and spectroscopic data were identical to those of (+)-**7b**.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H, ^{13}C NMR (including DEPT 135) and HMQC spectra of all new products.

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