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Atom transfer radical cyclization (ATRC) applied to a chemoenzymatic synthesis of Quercus lactones

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Abstract—The natural fragrances (+)-*trans* whisky lactone **2** and (+)-*trans* cognac lactone **4**, together with a minor amount of their (−)-*cis* stereoisomers, were prepared in 50% and 42% overall yield, respectively, starting from racemic 1-hepten-3-ol (±)-**5** and 1-octen-3-ol (±)-**6**. The procedure involved first the enantioconvergent, lipase mediated transformation of the secondary allylic alcohols derived dichloroacetates (±)-**7** and (±)-**8** into the corresponding homochiral (+)-**7** and (+)-**8**, combined with their cyclization under a transition metal catalyzed atom transfer process.

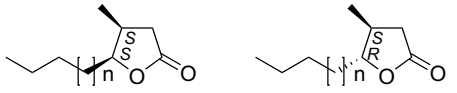
1. Introduction

Optically active γ-butyrolactones[1] are important heterocyclic aliphatic compounds. They are versatile building blocks for the synthesis of bioactive molecules, and are also widespread in nature, especially as pheromones and aroma components of many fruits and other natural products.[2]

As an example, *Quercus* lactones are known to be found in different types of wood and to be responsible for the sensory characteristics of wine and other alcoholic beverages,[3] such as whisky, brandy and cognac, in which they are extracted during their ageing in oak barrels.

Structurally, they are two pairs of diastereomeric optically active γ-butyrolactones (Fig. 1) characterized by the presence of a methyl group at C-(4), which is in *S* absolute configuration, while the C-(5) bears an aliphatic linear side chain, *cis* or *trans* to the C-(4) methyl substituent.

Compounds (−)-*cis* **1** and (+)-*trans* **2** are called whisky lactones, while the nickname of (−)-*cis* **3** and (+)-*trans* **4** is cognac lactones. A variety of syntheses of racemic and enantiomerically pure whisky[4] and cognac lactones[4e–u,5] in both diastereomeric forms can be found in the literature. Some of them make use of either a chiral auxiliary[4u] or a hydrolytic enzyme[4r,5b,c] in the enantiodifferentiating step. The biotransformation strategy was also applied by us[6] for the synthesis of the four stereoisomers of cognac lactones by means of baker's yeast reduction of 3-methyl-4-oxononanoic acid and its ethyl ester, or alternatively, through the lipase mediated kinetic resolution of this latter compound. The bioreduction of 3-methyl-4-oxononanoic acid to (+)-*trans* cognac lactone **4** was also reported by Fuganti[7] and coworkers in the same year, in a work aimed at the synthesis of (−)-*cis* and (+)-*trans* Aerangis lactone. Subsequently, several non-chemoenzymatic syntheses of racemic[8] and enantiomeric whisky[9] and cognac[9a,c,f] lactones have appeared in the literature.



n = 1: (-)-*cis*-**1** and (+)-*trans*-**2** whisky lactones
n = 2: (-)-*cis*-**3** and (+)-*trans*-**4** cognac lactones

Figure 1.

Transition metal catalyzed atom transfer radical cyclization (TMC-ATRC) reactions provide an especially useful means for the construction of rings.[10,11] Usually, the

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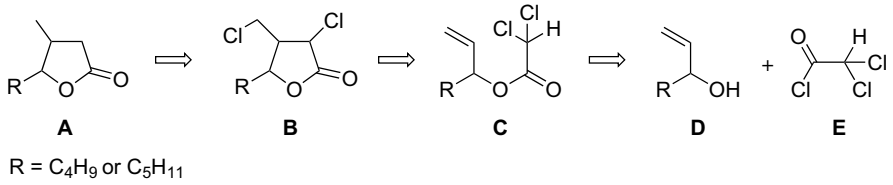


Scheme 1.

employed catalysts are Cu(I)/Cu(II) complexes, modulated in their reactivity by polydentate nitrogen ligands.[9f,12] The method presents some important advantages over other radical techniques, such as low cost of the catalyst, ease of work-up and high productivity.

From a retrosynthetic point of view, the application of the 'ATRC transform', on the Quercus lactones frame **A**, resolves, in just three steps, the γ-lactone ring into two simple and easily available fragments: 2,2-dichloroacetyl chloride **E** and allylic alcohol **D** (Scheme 1).

In this paper, we describe a new chemoenzymatic synthesis of Quercus lactones **A** (Scheme 1), based on an atom transfer radical cyclization of optically active α,α-dichloroacetates **C**, attained in very good enantiomeric excess from allylic alcohols **D** by the use of enzymes.

2. Results and discussion

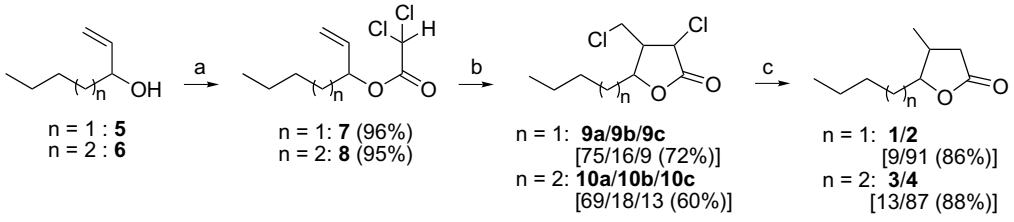
To test the viability of the retrosynthetic path, traced out in Scheme 1, the racemic allylic alcohols **5** and **6** (Scheme 2) were prepared by addition of commercial vinylmagnesiumbromide to pentanal or hexanal. The subsequent acylation of **5** and **6** with dichloroacetyl chloride afforded esters **7** and **8**, respectively, in excellent yields.

The TMC-ATRC works through the removal of an activated halogen atom (linked to a carbon atom bonded to strong electron acceptor groups) from the starting substrate by the complex Cu(I)Cl[ligand], which affords an electrophilic radical and a Cu(II)Cl[ligand] species (Scheme 3). The electrophilic radical then attacks the tethered radicophile C=C, generating the cycle and a new radical, now nucleophilic, which is trapped by Cl-transfer from the Cu(II) complex to provide the final product, with regeneration of the Cu(I)Cl[ligand] complex. For an efficient cyclization, it is crucial that the molecular frame is flexible enough to bring the radical centre and the radicophilic terminus at a distance suitable for their interaction. This is physically achieved when the two reacting extremities are connected by a single bond chain.[13]

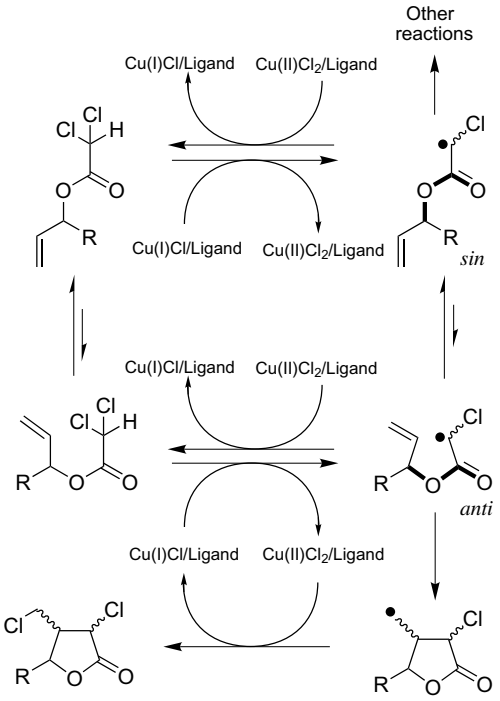
The situation is different when the open-chain starting material is an unsaturated amide or ester, as it is in the present case. In fact the estereal and peptidic bonds introduce an element of rigidity in the tethering chain, that is, a high rotational barrier, which restricts the interconversion of the *syn*- and *anti*-conformers (Scheme 3).[14] With secondary amides the drawback can be straight overcome replacing the amide hydrogen with any substituent. This increases the exchange rate between the two conformers or shifts the rotameric population, at the equilibrium, towards the *anti*-conformer, thus allowing the cyclization.[14b] For esters this option is impractical and the only simple way to foster the ring closure is to increase the reaction temperature.[14a] Another factor altering the conformers population of allylic ester or unsubstituted amide frames is the substitution at the carbon in α to the central heteroatom.[14c] Coincidentally this is achieved in our case. Anyway, to attain an acceptable cyclization yield for **7** and **8** (the γ-lactones **9** and **10** were obtained in 72% and 60% yield, respectively), the heating of the reaction mixture to 145 °C was required. Moreover, the catalyst concentration had to be increased to 30 mol % in comparison with the amount usually employed in the ATRC of *N*-allyl-N-substituted-2,2-dichloroamides.[15]

Owing to the high reaction temperature, there was no need to employ particular active Cu(I)Cl[ligand] species, the only condition being the robustness of the complex/ligand at harsh working conditions. Hence, the largely best reaction performances were, not astonishingly, secured by the Cu(I)Cl[bipyridine] species (Scheme 2).

Since the diastereomeric *cis*/*trans* ratios in the final lactones **1**,**2** and **3**,**4** are 9:91 and 13:87, respectively, it is evident that the relative configurations of the β- and γ-substituents in their precursors **9** and **10** are mainly *trans*, as already observed by Nagashima for the cyclization of trichloroacetates derived from secondary allylic alcohols.[16] This result



Scheme 2. Reagents and conditions: (a) $Cl_2CHCOCl$, DMAP, CH_2Cl_2, rt, 2 h; (b) BiPy/CuCl, 145 °C, CH_3CN; (c) TBSnH, AIBN, 80 °C, toluene.



Scheme 3.

is noteworthy being indicative of a potential 1,2-asymmetric induction in the case where enantiomerically pure allylic alcohols **5** and **6** were used.

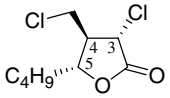
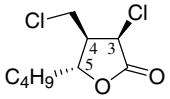
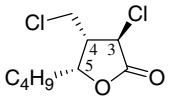
The ATRC of esters **7** and **8** gave three diastereomers in each case, [3α,4β,5α]-**9a**, [3α,4α,5β]-**9b** and [3α,4β,5β]-**9c**, and [3α,4β,5α]-**10a**, [3α,4α,5β]-**10b** and [3α,4β,5β]-**10c**, in the ratio 75/16/9 and 69/18/13, respectively. Their relative stereochemistry was assigned on the basis of difference NOE measurements (Table 1) carried out on the mixture of **9a**, **9b** and **9c**, and it agrees with previously reported data.[16]

Finally the racemic whisky **1**,**2** and cognac **3**,**4** lactones were effectively produced (86% and 88% yield, respectively), without loss of the stereochemical information (corresponding *cis*/*trans* ratio: 9/91 and 13/87), by hydrodehalogenation of the diastereomeric mixtures **9** and **10** with TBSnH/AIBN at 80 °C in toluene.

Having demonstrated the viability of the new pathway for the construction of Quercus lactones, our action was turned to the preparation of allylic dichloroacetates **7** and **8** in their optically active forms. For this purpose we planned two routes, either the kinetic resolution of the racemic secondary allylic alcohols (±)-**5** and (±)-**6**, followed by their esterification, or the enzymatic hydrolysis of the racemic dichloroacetates (±)-**7** and (±)-**8**.

The kinetic resolution of racemic allylic alcohols is a valuable alternative to the asymmetric catalytic reductions of α,β-unsaturated ketones,[17] when the synthesis of an enantiomerically pure allylic alcohol is required. It can be accomplished by Sharpless epoxidation,[18] and other chemical methods[19] or by the use of enzymatic transformations.

Table 1. The most meaningful data of difference NOE measurements carried out on lactones **9a**,**b**,**c**

	Irradiated proton (ppm)	Enhanced signal (% η)
 **9a**	H-3 (4.62) H-5 (4.43) CH_2Cl (3.77) (3.84)	H-5 (1), CH_2Cl (1) H-3 (2), CH_2Cl (4) H-3 (3), H-5 (1) H-3 (2), H-5 (1)
 **9b**	H-3 (4.57) H-4 (2.72)	H-4 (7) H-3 (6)
 **9c**	H-4 (2.98) H-5 (4.76) CH_2Cl (3.65)	H-5 (5) H-4 (7) H-3 (2)

Very high enantioselectivities have been achieved in particular in the biocatalytic enzymatic transesterification of racemic alcohols with enol acetates,[20] to give the corresponding acylated alcohols. Alternatively, acylated alcohols prepared as racemates can be enantiodifferentiated by hydrolytic enzymes.

Lipases have been frequently used as biocatalysts for these processes.[21] They are very flexible enzymes, for their wide acceptance of structurally different substrates and their ability to retain their activity and selectivity also in non-conventional media such as organic solvents[22a,b] and ionic liquids.[22c]

Specifically, Lipase B from *Candida antarctica*, (CAL-B) has shown a quite general enantioselectivity towards linear secondary alcohols,[23] and the origin of this behaviour has been fully explained from the knowledge of the protein structure.[24,25]

The enzymatic resolution of 1-octen-3-ol (Matsutake alcohol)[26] **6**, by transesterification with an equimolar amount of vinyl acetate, diethyl ether as solvent and immobilized CAL-B (Novozyme® 435), was described by Ohtani.[27] Under these conditions, alcohol *S*-(+)-**6** was found to be enantioselectively acylated with an E[28] of 46. Stopping the reaction at 37% conversion, the authors isolated ester (*S*)-(−)-**12** with 93% ee (30%yield), while the unreacted alcohol (*R*)-(−)-**6** was obtained with 46% ee. The same enzyme was recently reported to be very efficient in the acylation of **5** with vinyl crotonate.[29]

The hydrolysis of the corresponding racemic acetate (±)-**12**, catalyzed by the same lipase, and carried out in phosphate buffer, was also described by Ohtani and proceeds with a higher E (176), leading to alcohol (*R*)-(+)-**6**, while the unreacted starting ester (*S*)-(+)-**12** was recovered in 79% ee, by stopping the reaction at 39% conversion.[27]

Taking advantage of these results, we carried out the acylation of the racemic alcohols **5** and **6** with vinyl acetate in excess, with no use of diethyl ether. This little modification resulted in a significant improvement of the enantioselectivity of the enzyme compared to the above described literature data. In fact in the case of acylation of (±)-**6**, the enantiomeric ratio *E* was >200. A comparable result has been found for alcohol (±)-**5** (Table 2).

As an effect of this remarkable enantioselectivity, a dramatic slowdown of the reaction rate was observed at a conversion around 50%, when both diastereomeric pairs *R*-(−)-**5**,**6** and (*S*)-(−)-**11**,**12** could be isolated with excellent ee's.

We also carried out the hydrolyses of racemic acetates **11** and **12** as described in the literature.[27] The reaction occurred with a degree of enantioselectivity comparable to that reported (Table 3).

As a consequence of these good results, we tried Novozym 435 also for the kinetic resolution of dichloroacetates (±)-**7** and (±)-**8**. When run in buffer at pH 7.0 the hydrolyses of (±)-**7** and (±)-**8** turned out to occur with a lower enantioselectivity, when compared with the hydrolyses of the corresponding acetates carried out under the same conditions (Table 4). However, the addition of DME as a cosolvent increased the enantiomeric ratio to a value overcoming 200. This allowed the optically active esters *R*-(+)-**7** and *R*-(+)-**8** to be formed, at 50% conversion, as optically pure compounds. At the same conversion value, an approximately equimolar amount of alcohols (*S*)-(+)-**5** and (*S*)-(+)-**6** was formed, from which enantiomers (*R*)-(+)-**7** and (*R*)-(+)-**8** were recovered, after chromatographic separation.

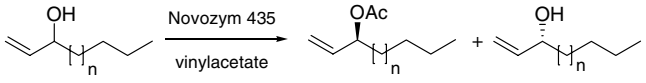
In that manner the above described biocatalytic processes provided both enantiomers of compounds **7** and **8** in high optical purity, giving thus access to both the enantiomers of the targeted γ-lactones, by the use of a single enzyme. On the other side, the intrinsically limited maximum theoretical yield of a kinetic resolution, together with the need for a chromatographic separation of the enantioresolved products, an ester and an alcohol in our case, represents a serious limitation for the entire synthetic process.

Therefore, starting from the results obtained, and with the aim of increasing the final yield we decided to use some enantioconvergent strategies for the transformation of a racemate into a single enantiomer. These strategies include, among the others, the chemoenzymatic dynamic kinetic resolution,[30] which combine an enzyme-mediated kinetic resolution with a transition metal catalyzed in situ racemization of the slow reacting enantiomer. Another method is based on the stereoinversion of one of the enantiomers resulting from the resolution process.

For the dynamic kinetic resolution of allylic substrates, both ruthenium[31] and palladium complexes[32,33] have been described in the literature as racemization catalysts, operating, respectively, under hydrogen transfer conditions or via π-allyl species formation. For instance a Pd(II)[33] complex, $PdCl_2(MeCN)_2$, was used for the epimerization of secondary cyclic allylic alcohol acetates, coupled with the PFL (Pseudomonas Fluorescens Lipase) mediated hydrolysis in 0.1 M phosphate buffer at 40 °C.

On the basis of these latter data, we run the hydrolysis of (±)-**7** in the presence of 5% $PdCl_2(PhCH_2CN)_2$. The result was disappointing, as the racemic substrate was converted,

Table 2. Enzymatic acylation of alcohols (±)-**5** and (±)-**6**



n = 1: (±)-**5**
n = 2: (±)-**6**

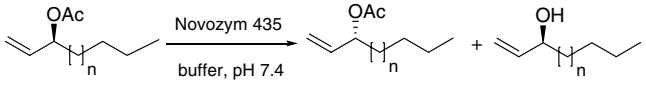
(*S*)-(−)-**11**
(*S*)-(−)-**12**

(*R*)-(−)-**5**
(*R*)-(−)-**6**

Substrate	Conversion	Time (h)	(*S*)-(−)-Ester ee[a] (%) [yield][b]	(*R*)-(−)-Alcohol ee[a] (%) [yield][b]	*E*
5	48	4	>99.9 [42]	93 [40]	>200
6	48	5	>99.9 [44]	91 [40]	>200 [lit.[27] 46]

[a] Enantiomeric excesses were determined by chiral HRGC.
[b] Isolated yield after chromatographic separation.

Table 3. Enzymatic hydrolysis of acetates (±)-**11** and (±)-**12**



n = 1: (±)-**11**
n = 2: (±)-**12**

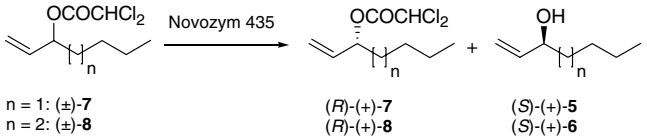
(*R*)-(+)-**11**
(*R*)-(+)-**12**

(*S*)-(+)-**5**
(*S*)-(+)-**6**

Substrate	Conversion	Time (h)	(*R*)-(+)-Ester ee[a] (%) [yield][b]	(*S*)-(+)-Alcohol ee[a] (%) [yield][b]	*E*
11	51	24	98 [40]	95 [38]	179
12	50	24	94 [42]	95 [40]	139 [lit.[27] 176]

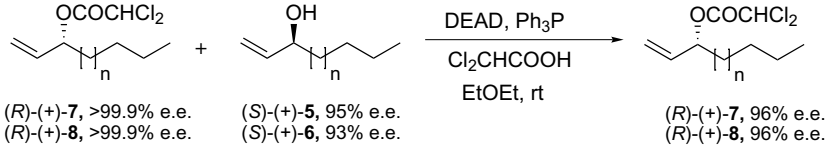
[a] Enantiomeric excesses were determined by chiral HRGC.
[b] Isolated yield after chromatographic separation.

Table 4. Enzymatic hydrolysis of dichloroacetates (±)-**7** and (±)-**8**



Substrate	Conditions	Conversion calcd (%)	Time (h)	(*R*)-(+)-Ester ee[a] (%) [yield][b]	(*S*)-(+)-Alcohol ee[a] (%) [yield][b]	*E*
7	Buffer pH 7.0	53	8	99 [40]	95 [38]	90
7	Buffer/DME 1:2	52	12	>99.9 [40]	95 [40]	>200
7	Buffer pH 7.0/Pd(II)	95	30	—	37	
7	Buffer pH 7.0/DME-Pd(II)[c]	92	48	—	69	
8	Buffer pH 7.0	56	24	99 [38]	79	61
8	Buffer/DME 1:2	52	30	>99.9 [40]	93	200

[a] Enantiomeric excesses were determined by chiral HRGC.
[b] Isolated yield after chromatographic separation.
[c] Pd(II) is $PdCl_2(PhCH_2CN)_2$.



Scheme 4.

under these conditions into (*S*)-(+)-**7** but with a modest 69% ee (Table 4).

As a consequence, we resorted to the stereoinversion of the secondary alcohol by means of the Mitsunobu procedure.[34] The reaction of the crude enzymatic hydrolysis mixtures with DEAD, PPh_3 and dichloroacetic acid resulted in the quantitative conversion of the alcohols (*S*)-(+)-**5** and (*S*)-(+)-**6** into their dichloroacetate opposite enantiomers (*R*)-(+)-**7** and (*R*)-(+)-**8**, with overall one-pot conversion of the racemic substrates into a single enantiomeric product. Esters (*R*)-(+)-**7** and (*R*)-(+)-**8** were isolated in yields largely overcoming 50%, although their ee's were slightly lower when compared with those obtained after their above mentioned kinetic resolutions (Scheme 4).

Clean samples of homochiral allyl dichloroacetates (*R*)-(+)-**7** and (*R*)-(+)-**8** were subjected to the TMC-ATRC process, as delineated in Scheme 2. The next defunctionalization step secured enantiopure (+)-*trans* whisky lactone **2** (yield 53%) and (+)-*trans* cognac lactone **4** (yield 40%), together with a minor amount of the corresponding *cis* isomers (**1** and **3**, respectively).

3. Conclusions

In conclusion, we have developed a new protocol for the chemoenzymatic synthesis of optically active β-methyl-γ-alkyl-γ-butyrolactones, addressed at the obtainment of the natural fragrances *Quercus* lactones.

The starting materials were optically active dichloroacetyl esters of secondary allylic alcohols, which underwent a Cu(I) catalyzed, radical cyclization to dichlorosubstituted γ-lactone intermediates, subsequently transformed to the targeted products by reductive dehalogenation.

The asymmetric step of the synthesis involved a very efficient lipase catalyzed kinetic resolution of the racemic dichloroacetates, followed by the Mitsunobu transformation/stereoinversion of the unreacted alcohols into the opposite enantiomers of the dichloroacetates.

The combination of the highly enantioselective kinetic resolution with the Mitsunobu stereoinversion allowed the enantioconvergent and quantitative conversion of the racemic ester substrate into a single enantiomer.

The subsequent cyclization and dehalogenation steps proceeded smoothly to provide the desired products in high enantiomeric excess and good overall yield, mainly as *trans* diastereoisomers, which formed in the absolute configuration of the natural products. A very minor amount of the *cis* diastereoisomers was also present in the final mixture.

Being aware of the environmental unfriendly properties of organotin reagents, we are seeking a cleaner procedure for the hydrodechlorination, which is compatible with our strategy.

4. Experimental

4.1. General

IR spectra were recorded on a Jasco FT-IR 200 spectrometer. ^1H NMR and ^{13}C NMR spectra were run on a Jeol EX-400 (400 MHz for proton, 100.1 MHz for carbon), using deuterochloroform as a solvent and tetramethylsilane

as an internal standard. Optical rotations were determined on a Perkin Elmer Model 241 polarimeter, at 25 °C. MS were performed on an ion trap Finnigan GCQ (70 eV) spectrometer. HRMS were run on a Finnigan MAT95XP spectrometer. Enzymatic hydrolyses were performed using a pH-stat Controller PHM290 Radiometer, Copenhagen. Chiral High Resolution GLC analyses were run on a Shimadzu GC-14B instrument, the capillary columns being Chiraldex™ type G-TA, γ-cyclodextrin (40 m × 0.25 mm) (carrier gas helium, 180 kPa, split 1:100), or DiMePe β-cyclodextrin (25 m × 0.25 mm) (carrier gas He, 110 kPa, split 1:50); TLC's were performed on Polygram® Sil G/UV_{254} silica gel pre-coated plastic sheets (eluent: light petroleum/ethyl acetate). Flash chromatography was run on silica gel, 230–400 mesh ASTM (Kieselgel 60, Merck), using mixtures of light petroleum 40–70 °C and ethyl acetate as the eluent.

Novozym 345 (CalB) was purchased from Novo Nordisk Bioindustrial A/S, Denmark.

4.2. General procedure for the synthesis of the allylic alcohols

To a cold solution of freshly distilled pentanal (8.6 g, 100 mmol) or hexanal (9.8 g, 100 mmol) in dry THF, 110 ml (110 mmol) of a 1 M solution of vinylmagnesiumbromide was slowly added under vigorous magnetic stirring, at −15 °C and in an inert atmosphere. After the addition was complete, the temperature was left to rise spontaneously to rt and the mixture stirred until disappearance of the starting material (TLC, eluent: light petroleum/ethyl acetate 9:1). 1 M HCl was added at 0 °C, the organic layer separated and the aqueous phase extracted with diethylether. The organic phase was dried, the solvent evaporated and the residue was distilled to give the pure alcohols.

4.2.1. 1-Hepten-3-ol 5. Colourless oil, yield 81%; bp 48 °C/4 mmHg. IR (neat) 3355 (OH), 1644 (C=C) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 (ddd, 1H, H-2, $^3J_{trans} = 17.2$, $^3J_{cis} = 10.5$, $^3J_{2,3} = 6.0$ Hz), 5.16 (ddd, 1H, $^2J = 1.6$, $^4J = 1.3$, $^3J_{trans} = 17.2$ Hz, H-1), 5.08 (ddd, 1H, $^2J = 1.6$, $^4J = 1.3$, $^3J_{cis} = 10.5$ Hz, H-1), 4.04 (br q, 1H, H-3), 2.18 (s, 1H, OH), 1.51 (m, 2H), 1.31 (m, 4H), 0.88 (br t, 3H, CH_3CH_2). ^{13}C NMR (100.1 MHz, $CDCl_3$) δ 141.3 (d, C-2), 114.4 (t, C-1), 73.1 (d, C-3), 36.6 (t), 27.4 (t), 22.5 (t), 13.9 (q). HRMS (EI) calcd for $C_7H_{14}O$ ($M^{+\cdot}$) 114.1045, found 114.1033. MS, *m/z*: 96 ($[M-H_2O]^{+\cdot}$, 5%), 81 (10), 72 (18), 57 (100), 43 (15), 41 (21), 29 (20). HRGC: Compounds (+)-**5** and (−)-**5** were not separable. They were analyzed as the corresponding acetates (see Section 4.3.1).

4.2.2. 1-Octen-3-ol 6. Colourless oil, yield 74%; bp 58 °C/10 mmHg. IR (neat) 3370 (OH), 1640 (C=C) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (ddd, 1H, $^3J_{trans} = 17.1$, $^3J_{cis} = 10.2$, $^3J = 6.0$ Hz, H-2), 5.16 (ddd, 1H, $^3J_{trans} = 17.1$, $^4J = 1.3$, $^2J = 1.6$ Hz, H-1), 5.05 (ddd, 1H, $J_{cis} = 10.2$, $^2J = 1.0$, $^4J = 1.3$ Hz, H-1), 4.08 (br q, 1H, H-3), 1.51 (m + br s, 3H, CH_2 and OH), 1.34 (m, 6H), 0.89 (br t, 3H, CH_3CH_2). ^{13}C NMR (100.1 MHz, $CDCl_3$) δ 141.3 (d, C-2), 114.4 (t, C-1), 73.2 (d, C-3), 37.0 (t), 31.7 (t), 25.0 (t), 22.6 (t), 14.0 (q). HRMS (EI) calcd for $C_8H_{16}O$ ($M^{+\cdot}$) 128.1201, found 128.1214. MS, *m/z* 127 ($[M-H]^{+\cdot}$, 3%), 111 (3), 99 (10), 83 (100), 71 (10), 57 (12), 55 (53), 43 (25).

HRGC: Compounds (+)-**6** and (−)-**6** were not separable. They were analyzed as the corresponding acetates (see Section 4.3.2).

4.3. General procedure for the synthesis of the racemic acetates 11,12 and dichloroacetates 7,8

A solution of **5** (3.0 g, 26.3 mmol) and **6** (3.4 g, 26.3 mmol) in dichloromethane was added of DMAP (3.4 g, 28.0 mmol) and freshly distilled acetylchloride (2.0 ml, 28.0 mmol), or freshly distilled dichloroacetylchloride (2.7 ml, 28 mmol).

The white suspension formed was stirred until complete disappearance of the starting alcohol (TLC, eluent: light petroleum/ethyl acetate 9:1), then washed with 1 N HCl, water and brine. The organic phase was dried on Na_2SO_4, the solvent evaporated and the residue eluted with petroleum ether through a short silica gel column, giving the pure acetates **11** and **12**, and the pure dichloroacetates **7** and **8**.

4.3.1. 1-Butyl-2-propenyl acetate 11. Colourless oil, 3.8 g, 97% yield. IR (neat) 1740 (C=O), 1632 (C=C) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.77 (ddd, 1H, $^3J_{trans} = 17.2$, $^3J_{cis} = 10.3$, $^3J = 6.2$ Hz, H-2), 5.21 (ddd, 1H, $^3J_{trans} = 17.2$, $^4J = 1.2$, $^2J = 1.4$ Hz, H-1), 5.21 (m, 1H, H-3), 5.14 (ddd, 1H, $^3J_{cis} = 10.3$, $^4J = 1.3$, $^2J = 1.4$ Hz, H-1), 2.0 (s, 3H, CH_3CO), 1.62 (m, 2H), 1.31 (m, 4H), 0.79 (br t, 3H, CH_3CH_2). ^{13}C NMR (100.1 MHz, $CDCl_3$) δ 170.4 (s, CO), 136.7 (d, C-2), 116.45 (t, C-1), 74.8 (d, C-3), 33.9 (t), 27.2 (t), 22.4 (t), 21.2 (q), 13.9 (q). MS, *m/z* 114 (11%), 99 (13), 81 (10), 72 (10), 55 (14), 54 (18), 43 (100). HRMS (EI) calcd for $C_9H_{16}O_2$ ($M^{+\cdot}$) 156.1150, found 156.1160. HRGC 70 °C (1 min) 1 °C/min to 150 °C, γ-cyclodextrines (*R*)-enantiomer: 10.6 min, (*S*)-enantiomer 11.9 min.

4.3.2. 1-Pentyl-2-propenyl acetate 12. Colourless oil, 4.0 g, yield 95%. IR (neat) 1736 (C=O), 1632 (C=C) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.76 (ddd, 1H, $^3J_{trans} = 17.2$, $^3J_{cis} = 10.2$, $^3J = 6.2$ Hz, H-2), 5.21 (ddd, 1H, $^3J_{trans} = 17.2$, $^4J = 1.1$, $^2J = 1.4$ Hz, H-1), 5.21 (m, 1H, H-3), 5.14 (ddd, 1H, $^3J_{cis} = 10.2$, $^4J = 1.3$, $^2J = 1.4$ Hz, H-1), 2.0 (s, 3H, CH_3CO), 1.60 (m, 2H), 1.28 (m, 6H), 0.79 (br t, 3H, CH_3CH_2). ^{13}C NMR (100.1 MHz, $CDCl_3$) δ 170.3 (s, CO), 136.65 (d, C-2), 116.4 (t, C-1), 74.8 (d, C-2), 34.1 (t), 31.5 (t), 24.7 (t), 22.5 (t), 21.2 (q), 13.9 (q). MS, *m/z* 138 (14%), 113 (8), 99 (12), 85 (10), 71 (9), 54 (22), 43 (100). HRMS (EI) calcd for $C_{10}H_{18}O_2$ ($M^{+\cdot}$) 170.1307, found 170.1300. HRGC 70 °C (1 min) 1 °C/min to 150 °C, γ-cyclodextrines (*R*)-enantiomer: 14.2 min, (*S*)-enantiomer 15.3 min.

4.3.3. 1-Butyl-2-propenyl dichloroacetate 7. Colourless oil 5.7 g, yield 96%; bp 60–62 °C (0.05 mmHg). IR (neat) 1763, 1746 (C=O), 1669 (C=C), 817 (C–Cl) cm^{-1}. ^1H NMR

(400 MHz, $CDCl_3$) δ 5.94 (s, 1H, $CHCl_2$), 5.81 (ddd, 1H, $^3J_{trans} = 17.1$, $^3J_{cis} = 10.5$, $^3J = 6.7$ Hz, H-2), 5.34 (ddd, 1H, $^3J_{trans} = 17.1$, $^4J = 1.1$, $^2J = 1.1$ Hz, H-1), 5.32 (m, 1H, H-3), 5.25 (ddd, 1H, $^3J_{cis} = 10.5$, $^4J = 1.1$, $^2J = 1.1$ Hz, H-1), 1.71 (m, 2H, CH_2), 1.32 (m, 4H $(CH_2)_2$), 0.90 (br t, 3H, CH_3). ^{13}C NMR (100.1 MHz, $CDCl_3$) δ 163.8 (s, CO), 134.9 (d, C-2), 118.1 (t, C-1), 78.6 (d, C-3), 64.6 (d, $CHCl_2$), 33.6 (t), 26.9 (t), 22.3 (t), 13.9 (q). HRMS (EI) calcd for $C_9H_{14}Cl_2O_2$ 224.0371, found 224.0382. MS, *m/z* 97 (22%), 85 (18), 83 (22), 81 (33), 67 (20), 57 (34), 55 (100), 54 (46), 41 (50). HRGC 100 °C (2 min) 3 °C/min to 150 °C, β-cyclodextrine (*R*)-enantiomer: 13.45 min, (*S*)-enantiomer 14.18 min.

4.3.4. 1-Pentyl-2-propenyl dichloroacetate 8. Colourless oil, yield 95%, bp 68–9 °C (0.07 mmHg). IR (neat) 1764, 1746 (C=O), 1669 (C=C), 816 (C–Cl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (s, 1H, $CHCl_2$), 5.79 (ddd, 1H, $^3J_{trans} = 17.1$, $^3J_{cis} = 10.5$, $^3J = 6.7$ Hz, H-2), 5.34 (ddd, 1H, $^3J_{trans} = 17.1$, $^4J = 1.1$, $^2J = 1.1$ Hz, H-1), 5.31 (m, 1H, H-3), 5.21 (ddd, 1H, $^3J_{cis} = 10.5$, $^4J = 1.1$, $^2J = 1.1$ Hz, H-1), 1.68 (m, 2H, CH_2), 1.30 (m, 6H $(CH_2)_3$), 0.87 (br t, 3H, CH_3). ^{13}C NMR (100.1 MHz, $CDCl_3$) δ 163.9 (s, CO), 134.8 (d, C-2), 118.1 (t, C-1), 78.6 (d, C-3), 64.5 (d, $CHCl_2$), 33.8 (t), 31.3 (t), 24.4 (t), 22.4 (t), 13.9 (q). MS, *m/z* 110 (15), 95 (16), 85 (20), 83 (31), 81 (40), 69 (100), 57 (47), 55 (85), 54 (78), 43 (66), 41 (92). HRMS (EI) calcd for $C_{10}H_{16}Cl_2O_2$ 238.0527, found: 238.0520. HRGC 100 °C (2 min) 3 °C/min to 150 °C, β-cyclodextrine (*R*)-enantiomer: 13.20 min, (*S*)-enantiomer 17.85 min.

4.4. General procedure for the radical cyclization of the dichloroacetates

CuCl (149 mg, 1.5 mmol) and bipyridine (234 mg, 1.5 mmol) were weighted in a Schlenk tube fitted with a perforatable septum (blocked by a screw cap) and a magnetic stirrer bar. Dry acetonitrile (20 ml) was added under argon, followed by addition of the dichloroesters **7** and **8** (5 mmol) after 30 min. The mixture was stirred at 145 °C for 15 h and, after cooling, diluted with 10% HCl (30 ml) and extracted with CH_2Cl_2 (2 × 15 ml). The combined organic layers were concentrated and the crude product was purified by flash chromatography on silica gel (eluent: petroleum ether/diethyl ether gradient from 10/0 to 8/2). The yellow oil collected were identified as dichlorolactones **9** and **10**, formed as mixtures of diastereoisomers, which were not separated.

4.4.1. 5-Butyl-3-chloro-4-(chloromethyl)dihydrofuran-2(3*H*)-one 9. This was obtained as a 75:16:9 mixture of diastereoisomers [3α,4β,5α]-**9a**, [3α,4α,5β]-**9b** and [3α,4β,5β]-**9c** (72% overall yield). IR (neat) 1788 (C=O), 1176 (C–O) cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra of **9a** and the resonances of **9b**,**9c** not overlapped to those of **9a** are given. ^{1}H NMR diastereoisomer **9a** (400 MHz, $CDCl_3$), δ 4.62 (d, $^3J_{3,4} = 10.3$ Hz, 1H, H-3), 4.43 (dt, $^3J_{4,5} = 2.9$, $J = 9.6$ Hz, 1H, H-5), 3.85 (part A of an ABX system, $J_{AB} = 12.2$, $J_{AX} = 4.0$ Hz, CHCl), 3.75 (part B of an ABX system, $J_{AB} = 12.2$, $J_{BX} = 3.3$ Hz, CHCl), 2.62 (tdd, $^3J_{4,5} = 2.9$, $^3J_{3,4} = 10.3$, $J_3 = 3.3$, $J_4 = 4.0$ Hz, H-4), 1.78, 1.70, 1.55, 1.42 (4m, $(CH_2)_3$), 0.91 (t, CH_3CH_2). ^{1}H NMR diastereoisomer **9b**, δ 4.59 (d, $^3J_{3,4} = 6.2$ Hz, H-3), 4.46 (ddd, $J = 8.1$, 3.3, 2.9 Hz, H-5), 3.72 (part A of an ABX, $J_{AB} = 11.3$, $J_{AX} = 2.9$ Hz, CHCl), 3.57 (part B of an ABX system, $J_{AB} = 11.3$, $J_{BX} = 5.9$ Hz, CHCl), 2.72 (m, H-4). ^{1}H NMR diastereoisomer **9c**, δ 4.75 (ddd, J 3.6, 4.0, 6.6 Hz, H-5), 4.38 (d, J 6.6 Hz, H-3), 3.65 (part AB of an ABX system, $J_{AB} = 11.7$, $J_{AX} = 3.3$, $J_{BX} = 4.0$ Hz, CH_2Cl), 2.98 (m, H-4). ^{13}C NMR diastereoisomer **9a** (100.1 MHz, $CDCl_3$) δ 170.4 (s, CO), 79.6 (d, C-5), 52.9 (d, C-4), 52.1 (d, C-3), 40.8 (t, CH_2Cl), 33.3 (t), 27.2 (t), 22.3 (t), 13.7 (q). ^{13}C NMR diastereoisomer **9b** 170.3 (s, CO), 81.4 (d, C-5), 54.3 (d, C-3), 48.5 (d, C-4), 40.0 (t, CH_2Cl), 33.0 (t), 27.3 (t). ^{13}C NMR diastereoisomer **9c** 170.6 (s, CO), 80.2 (d, C-5), 53.6 (d, C-3), 50.0 (d, C-4), 40.2 (t, CH_2Cl), 32.6 (t). MS, *m/z* 225 ($[M+H]^{+\cdot}$, 0.5%), 171 (1), 169 (6), 167 (10), 131 (12), 133 (4), 109 (12) 95 (27), 75 (38), 70 (100), 55 (53), 42 (56), 41 (45), 39 (34).

4.4.2. 3-Chloro-4-(chloromethyl)-5-pentyldihydrofuran-2(3*H*)-one 10. This was obtained as a 69:18:13 mixture of diastereoisomers [3α,4β,5α]-**10a**, [3α,4α,5β]-**10b** and [3α,4β,5β]-**10c** (60% overall yield). IR (neat) 1788 (C=O), 1176 (C–O) cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra of **10a** and the resonances of **10b**,**10c** not overlapped to those of **10a** are given: ^{1}H NMR diastereoisomer **10a** (400 MHz, $CDCl_3$) δ 4.62 (d, $^3J_{3,4} = 10.3$ Hz, H-3), 4.43 (dt, $^3J_{4,5} = 2.9$, $J = 9.6$ Hz, H-5), 3.85 (part A of an ABX system, $J_{AB} = 12.2$, $J_{AX} = 4.0$ Hz, CHCl), 3.75 (part B of an ABX system, $J_{AB} = 12.2$, $J_{BX} = 3.3$ Hz, CHCl), 2.62 (tdd, $^3J_{3,4} = 10.3$, $^3J_{4,5} = 2.9$, $J_3 = 3.3$, $J_4 = 4.0$ Hz, H-4), 1.78, 1.70, 1.55, 1.42, 1.31 (5m, $(CH_2)_4$), 0.91 (t, CH_3CH_2). ^{1}H NMR diastereoisomer **10b**, δ 4.58 (d, $^3J_{3,4} = 6.2$ Hz, H-3), 4.43 (ddd, $J = 8.1$, 3.3, 2.9 Hz, H-5), 3.73 (part A of an ABX, $J_{AB} = 11.3$, $J_{AX} = 2.9$ Hz, CHCl), 3.57 (part B of an ABX system, $J_{AB} = 11.3$, $J_{BX} = 5.9$ Hz, CHCl), 2.72 (m, H-4). ^{1}H NMR diastereoisomer **10c**, δ 4.76 (ddd, $J = 3.6$, 4.0, 6.6 Hz, H-5), 4.40 (d, $J = 6.6$ Hz, H-3), 3.65 (part AB of an ABX system, $J_{AB} = 11.7$, $J_{AX} = 3.3$, $J_{BX} = 4.0$ Hz, CH_2Cl), 2.98 (m, H-4). ^{13}C NMR diastereoisomer **10a** (400 MHz, $CDCl_3$) δ 170.4 (s, CO), 79.6 (d, C-5), 52.9 (d, C-4), 52.1 (d, C-3), 40.8 (t, CH_2Cl), 33.3 (t), 27.3 (t), 22.2 (t), 13.7 (q). ^{13}C NMR diastereoisomer **10b** 170.3 (s, CO), 81.4 (d, C-5), 54.4 (d, C-3), 48.8 (d, C-4), 40.0 (t, CH_2Cl), 33.5 (t), 25.0 (t). ^{13}C NMR diastereoisomer **10c** 170.6 (s, CO), 80.3 (d, C-5), 53.6 (d, C-3), 50.1 (d, C-4), 40.2 (t, CH_2Cl), 33.1 (t), 25.3 (t). MS, *m/z*: 239 ($M+H^{+\cdot}$, 0.5%), 171 (0.8), 169 (5), 167 (8), 131 (10), 109 (21), 103 (20), 84 (38), 75 (32), 69 (47), 56 (100), 43 (70), 41 (50), 39 (45).

4.5. Reductive dehalogenation of compounds 9 and 10

To a solution of dichlorolactones **9** (0.8 g, 3.6 mmol) or **10** (0.9 g, 3.6 mmol) in dry toluene (7 ml), Bu_3SnH (2.1 ml, 8 mmol) was added under argon. The resulting solution was heated to 80 °C and AIBN (25 mg), dissolved in toluene (0.5 ml), was added stepwise (170 μl every 1.5 h). After 7 h, the reaction mixture was allowed to cool to rt, and eluted through a flash silica gel column packed with petroleum ether, without preliminary concentration. This allowed the rough separation of the whisky and cognac

lactone mixtures from the organotin byproducts. A second separation (as indicated below) was necessary for the purification of the γ-lactones mixtures **1**,**2** (ratio 9:91) and **3**,**4** (ratio 13:87).

4.5.1. 5-Butyl-4-methyldihydrofuran-2(3*H*)-one (whisky lactone). Pale yellow oil. (0.478 g, 3.1 mmol, *cis*/*trans* = 9/91). Diastereoisomers **1** and **2** were separated by flash chromatography (eluent: gradient of petroleum ether/ethyl acetate from 0% up to 5%). All analytical and spectroscopic data are in accordance with those reported in the literature.[7]

4.5.2. 5-Pentyl-4-methyldihydrofuran-2(3*H*)-one (cognac lactone). Pale yellow oil (0.536 g, 3.15 mmol, *cis*/*trans* 13/87). Diastereoisomers **3** and **4** were separated by flash chromatography (eluent: gradient of petroleum ether/ethyl acetate from 0% up to 5%). All analytical and spectroscopic data are in accordance with those reported in the literature.[4]

4.6. General procedure for lipase acetylation of the allylic alcohols

To a solution of the racemic alcohol **5** or **6** (30 mmol) in vinylacetate (50 ml), Novozyme 435 (1.0 g) was added under stirring. The reaction was monitored by HRGC. After stirring vigorously at room temperature for the time indicated below, the enzyme was filtered off and washed with diethyl ether. The organic phases were combined and evaporated to give in each case an approximately 1:1 mixture of alcohols (*R*)-(−)-**5** and (*R*)-(−)-**6** and acetates (*S*)-(−)-**11** and (*S*)-(−)-**12**, respectively. The mixtures were separated on silica gel column (eluent: light petroleum/ethyl acetate, gradient from 0% to 5%).

4.6.1. Lipase acetylation of alcohol (±)-5. This gave after 3.5 h an approx. 1:1 mixture of ester (*S*)-(−)-**11**, >99.9% ee, $[\alpha]_D^{25} = -5.5$ (*c* 1.5, pentane), $[\alpha]_D^{25} = -15$ (*c* 3.1, $CHCl_3$), and the unreacted alcohol (*R*)-(−)-**5**, 93% ee, 51% calcd conversion, $E > 200$.

4.6.2. Lipase acetylation of alcohol (±)-6. This gave after 4 h an approx. 1:1 mixture of ester (*S*)-(−)-**12**, >99.9% ee, $[\alpha]_D^{25} = -3.0$ (*c* 1.0, *n*-pentane), [lit.:[27] −2.73 (*c* 0.95, pentane)], $[\alpha]_D^{25} = -11.5$ (*c* 2.8, $CHCl_3$), and the unreacted alcohol (*R*)-(−)-**6**, 94% ee, at 50% calcd conversion, $E > 200$.

4.7. General procedure for enzymatic hydrolyses of the allylic acetates and dichloroacetates

A suspension of the appropriate ester (30 mmol) in phosphate buffer (0.1 M, pH 7) (40 ml), or in a 2:1 mixture of DME/buffer, was hydrolyzed with Novozym 435 (0.5 g) at room temperature under vigorous stirring. The pH was kept at its initial value by automatic continuous addition of 1 M NaOH. After addition of 0.5 equiv of NaOH, the mixture was centrifuged and extracted with diethyl ether (2 × 10 ml). The combined organic layers were dried over Na_2SO_4 and evaporated to give a crude reaction mixture, which was chromatographed as indicated above.

4.7.1. Enzymatic hydrolysis of acetate (±)-11. This gave after 4.0 h an approx. 1:1 mixture of alcohol (*S*)-(+)-**5**, 95% ee, $[\alpha]_D^{25} = +10.3$ (*c* 1.45, pentane), +6.1 (*c* 1.2, $CHCl_3$). The unreacted ester (*R*)-(+)-**11** was recovered with 98% ee, 51% calcd conversion, $E = 179$.

4.7.2. Enzymatic hydrolysis of acetate (±)-12. This gave after 2.5 h an approximately 1:1 mixture of alcohol (*S*)-(+)-**6**, 95% ee, +6.1 (*c* 1.0, $CHCl_3$); $[\alpha]_D^{25} = +7.0$ (1.0, *n*-pentane); [lit.:[27] +7.16 (*c* 1.38, pentane)], and the unreacted ester (*R*)-(+)-**12**, 94% ee, 50% calcd conversion $E = 139$ (lit.:[27] $E = 176$).

4.7.3. Enzymatic hydrolysis of dichloroacetate (±)-7. When carried out in a DME/buffer 2:1 mixture, it gave after 24 h an approximately 1:1 mixture of alcohol (*S*)-(+)-**5** (94% ee), and the unreacted ester (*R*)-(+)-**7**, (>99.9% ee), $[\alpha]_D^{25} = +2.8$ (*c* 2.4 *n*-pentane), $[\alpha]_D^{25} = +9.5$ (*c* 1.35, $CHCl_3$), 52% calcd conversion, $E = 243$.

4.7.4. Enzymatic hydrolysis of dichloroacetate (±)-8. When carried out in a DME/buffer 2:1 mixture, gave after 24 h an approximately 1:1 mixture of alcohol (*S*)-(+)-**6** (93% ee) and the unreacted ester (*R*)-(+)-**8** (>99.9% ee) $[\alpha]_D^{25} = +1.4$ (*c* 1.35 *n*-pentane), $[\alpha]_D^{25} = +7.2$ (*c* 1.2, $CHCl_3$), 52% calcd conversion, $E = 206$.

4.8. General procedure for Mitsunobu reaction

A 1.0 g amount of crude, unseparated enzymatic 1:1 hydrolysis mixture, containing (*R*)-(+)-**7** with >99.9% ee and (*S*)-(+)-**5** having 94% ee, was dissolved in 5 ml diethyl ether. PPh_3 and dichloroacetic acid in equimolar amount with respect to the alcohol were added at room temperature. The mixture was cooled at 0 °C and an equimolar amount of diethylazodicarboxylate (DEAD) was slowly added dropwise under vigorous stirring. The yellow suspension was allowed to warm to room temperature and left to stir until disappearance of the alcohol (TLC).

After evaporation of the solvent the mixture was chromatographed on column, to give only (*R*)-(+)-**7** in a 97% ee, in a 82% overall yield starting from the racemic mixture.

The identical procedure allowed to obtain (*R*)-(+)-**8** in a 96% ee and 84% yield, starting from the crude hydrolysis mixture of (*R*)-(+)-**8** (>99.9% ee) and (*S*)-(+)-**6** (93% ee).

4.9. (4*S*,5*R*)-(+)-*trans* Whisky lactone 2

This was obtained in 91:9 admixture with (4*R*,5*R*)-(+)-*cis* whisky lactone **1** starting from a sample of (*R*)-(+)-**7** dichloroacetate, and following the procedure previously described. The mixture was separated on column. Compound (+)-**1** had optical data in accordance with the literature,[9e] 53% overall yield from (*R*)-(+)-**7**.

4.10. (4*S*,5*R*)-(+)-*trans* Cognac lactone 4

This was obtained in 87:13 admixture with (4*R*,5*R*)-(+)-*cis* cognac lactone **3** starting from a sample of (*R*)-(+)-**8** dichloroacetate, and following the procedure previously

described. The mixture was separated on column. Compound (+)-**4** had optical data in accordance with the literature.[6] 40% overall yield from (*R*)-(+)-**8**.

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References

1. Koch, S. S. C.; Chamberlin, A. R. In *Enantiomerically Pure γ-Butyrolactones in Natural Products Synthesis*; Attaur-Rahman, Ed.; Elsevier Science: Amsterdam, 1995; pp 687–725.
2. (a) Mori, K. In *Techniques in Pheromone Research*; Hummel, H. H., Miller, T., Eds.; Springer: New York, 1989; (b) Silverstein, R. M. In *Semiochemistry Flavours and Pheromones, Proceedings ACS Symposium*; Acree, T., Ed.; Walter de Gruyter: Berlin, 1985.
3. (a) Carrillo, J. D.; Garrido-Lopez, A.; Tena, M. T. *J. Chromatogr., A* **2006**, *1102*, 25–36; (b) Cerdan, T. G.; Ancin-Azpilicueta, C. *Food Science and Technology* **2006**, *9*, 199–205; (c) De Souza, M. D. C. A.; Vasquez, P.; Del Mastro, N. L.; Acree, T. E.; Lavin, E. H. *J. Agric. Food Chem.* **2006**, *54*, 485–488.
4. (a) Masuda, M.; Nishimura, K. *Chem. Lett.* **1981**, 1333–1336; (b) Nishikori, H.; Ito, K.; Katsuki, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1165–1170; (c) Tsuboi, S.; Sakamoto, J.; Yamashita, H.; Sakai, T.; Utaka, M. *J. Org. Chem.* **1998**, *63*, 1102–1108; (d) Ito, K.; Yoshitake, M.; Katsuki, T. *Tetrahedron* **1996**, *52*, 3905–3920; (e) Takahata, H.; Uchida, Y.; Momose, T. *J. Org. Chem.* **1995**, *60*, 5628–5633; (f) Taber, D. F.; Houze, J. B. *J. Org. Chem.* **1994**, *59*, 4004–4006; (g) Bloch, R.; Gilbert, L. *J. Org. Chem.* **1987**, *52*, 4603–4605; (h) Sarmah, B. K.; Barua, N. C. *Tetrahedron* **1993**, *49*, 2253–2260; (i) Zschage, O.; Hoppe, D. *Tetrahedron* **1992**, *48*, 5657–5666; (j) Miyata, O.; Shinada, T.; Kawakami, N.; Taji, K.; Ninomiya, I.; Naito, T.; Date, T.; Okamura, K. *Chem. Pharm. Bull.* **1992**, *40*, 2579–2581; (k) Casey, M.; Manage, A. C.; Murphy, P. J. *Tetrahedron Lett.* **1992**, *33*, 965–968; (l) Sharma, G. V.; Vepachdu, S. R.; Chandrasekhar, S. *Synth. Commun.* **1990**, *20*, 3403–3410; (m) Beckmann, M.; Hildebrandt, H.; Winterfeldt, E. *Tetrahedron: Asymmetry* **1990**, *1*, 335–345; (n) Marino, J. P.; de la Pradilla, R. F. *Tetrahedron Lett.* **1985**, *26*, 5381–5384; (o) Shengming, M.; Zhangjie, S.; Zhanqian, Y. *Tetrahedron* **1999**, *55*, 12137–12148; (p) Suzuki, Y.; Mori, W.; Ishizone, H.; Naito, K.; Honda, T. *Tetrahedron Lett.* **1992**, *33*, 4931–4932; (q) Salaun, B.; Karkour, B.; Olliver, J. *Tetrahedron* **1989**, *45*, 3151–3162; (r) Pai, Y.-C.; Fang, J.-M.; Wu, S. H. *J. Org. Chem.* **1994**, *59*, 6018–6025; (s) Ebata, T.; Matsumoto, K.; Yoshikoshi, H.; Koseki, K.; Kawakami, H.; Okano, K.; Matsushita, H. *Heterocycles* **1993**, *36*, 1017–1026; (t) Günther, C.; Mosandl, A. *Liebigs Ann. Chem.* **1986**, 2112–2122; (u) Fukuzawa, S.; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997**, *119*, 1482–1483.
5. (a) Ortuño, R. M.; Merce, R.; Font, J. *Tetrahedron* **1987**, *43*, 4497–4506; (b) Rojo, J.; García, M.; Carretero, J. C. *Tetrahedron* **1993**, *49*, 9787–9800; (c) Ha, H.-J.; Yoon, K.-N.; Lee, S.-Y.; Park, Y.-S.; Lim, M.-S.; Yim, Y.-G. *J. Org. Chem.* **1998**, *63*, 8062–8066.
6. Benedetti, F.; Forzato, C.; Nitti, P.; Pitacco, G.; Valentin, E.; Vicario, M. *Tetrahedron: Asymmetry* **2001**, *12*, 305–311.
7. Brenna, E.; Dei Negri, C.; Fuganti, C.; Serra, S. *Tetrahedron: Asymmetry* **2001**, *12*, 1871–1879.
8. Armstrong, A.; Chung, H. *Tetrahedron Lett.* **2006**, *47*, 1617–1619.
9. (a) Ozeki, M.; Hashimoto, D.; Nishide, K.; Kajimoto, T.; Node, M. *Tetrahedron: Asymmetry* **2005**, *16*, 1663–1671; (b) Evans, P.; Leffray, M. *Tetrahedron* **2003**, *59*, 7973–7981; (c) Schleth, F.; Vogler, T.; Harms, K.; Studer, A. *Chem. Eur. J.* **2004**, *10*, 4171–4185; (d) Kerrigan, N. J.; Hutchison, P. C.; Heightman, P. D.; Procter, D. J. *Org. Biomol. Chem.* **2004**, *2*, 2476–2482; (e) Suzuki, K.; Shoji, M.; Kobayashi, E.; Inomata, K. *Tetrahedron: Asymmetry* **2001**, *12*, 2789–2792; (f) Schlapbach, A.; Hoffmann, R. W. *Eur. J. Org. Chem.* **2001**, 323–328; (g) Brown, R. C.; Taylor, D. K.; Elsey, G. M. *Org. Lett.* **2006**, *8*, 463–466; (h) Zhang, Y.; Wang, Y.; Dai, W.-M. *J. Org. Chem.* **2006**, *71*, 2445–2455.
10. Clark, A. *Chem. Soc. Rev.* **2002**, *31*, 1–11.
11. (a) Motoyama, Y.; Hanada, S.; Shimamoto, K.; Nagashima, H. *Tetrahedron* **2006**, *62*, 2779–2788; (b) Edlin, C. D.; Faulkner, J.; Helliwell, M.; Knight, C. K.; Parker, J.; Quayle, P.; Raftery, J. *Tetrahedron* **2006**, *62*, 3004–3015; (c) Bellesia, F.; Danieli, C.; De Buyck, L.; Galeazzi, R.; Ghelfi, F.; Mucci, A.; Orena, M.; Pagnoni, U. M.; Parsons, A. F.; Roncaglia, F. *Tetrahedron* **2006**, *62*, 746–757; (d) Cagnoli, R.; Ghelfi, F.; Pagnoni, U. M.; Parsons, A. F.; Schenetti, L. *Tetrahedron* **2003**, *59*, 9951–9960; (e) De Buyck, L.; Forzato, C.; Ghelfi, F.; Mucci, A.; Nitti, P.; Pagnoni, U. M.; Parsons, A. F.; Pitacco, G.; Roncaglia, F. *Tetrahedron Lett.* **2006**, *47*, 7759–7762; (f) Clark, A. J.; Geden, J. V.; Thom, S. *J. Org. Chem.* **2006**, *71*, 1471–1479; (g) Kobrakov, K. I.; Ivanov, A. V. *Chem. Heterocycl. Compd.* **2001**, *37*, 529–539.
12. Pintauer, T.; Matyjaszewski, K. *Coord. Chem. Rev.* **2005**, *249*, 1155–1184.
13. (a) Itoh, T.; Sakabe, K.; Kudo, K.; Ohara, H.; Takagi, Y.; Kihara, H.; Zagatti, P.; Renou, M. *J. Org. Chem.* **1999**, *64*, 252–326; (b) Bart, F.; O-Yang, C. *Tetrahedron Lett.* **1990**, *31*, 1121–1124; (c) Itoh, T.; Ohara, H.; Emoto, S. *Tetrahedron Lett.* **1995**, *36*, 3531–3534.
14. (a) Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746–2750; (b) Ghelfi, F.; Parsons, A. F. *J. Org. Chem.* **2000**, *65*, 6249–6253; (c) Bryans, J. S.; Large, J. M.; Parsons, A. F. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2897–2904.
15. Benedetti, M.; Forti, L.; Ghelfi, F.; Pagnoni, U. M.; Ronzoni, R. *Tetrahedron* **1997**, *53*, 14031–14042.
16. Nagashima, H.; Seki, N.; Ozaki, N.; Wakamatsu, H.; Itoh, K.; Tomo, Y.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 985–990.
17. Ohkuma, T.; Ikehira, H.; Ihariya, T.; Noyori, R. *Synlett* **1997**, 467–468.
18. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
19. Tiecco, M.; Testaferri, L.; Santi, C.; Tomassini, C.; Bonini, R.; Marini, F.; Bagnoli, L.; Temperini, A. *Org. Lett.* **2004**, *6*, 4751–4753.
20. Faber, K. *Biotransformations in Organic Chemistry*, 5th ed.; Springer: Berlin, 2004; pp 336–383.
21. Schmid, R. D.; Verger, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1608–1633.
22. (a) Bornscheuer, U. T.; Kazlaukas, R. J. *Hydrolases in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 1999; (b) Koskinen, A. M. P.; Klibanov, A. M. *Enzymatic Reactions in Organic Media*; Blackie Ed.; London, 1996; (c) Itoh, T.; Akasaki, E.; Nishimura, Y. *Chem. Lett.* **2002**, 154–155.
23. Orrenius, C.; Öhrner, N.; Rotticci, D.; Mattson, A.; Hult, K.; Norin, T. *Tetrahedron: Asymmetry* **1995**, *6*, 1217–1220.

24. (a) Mccabe, R. W.; Rodger, A.; Taylor, A. *Enzyme Microb. Technol.* **2005**, *36*, 70–74; (b) Uppenberg, J.; Hansen, M. T.; Patkar, S.; Jones, T. A. *Structure* **1994**, *2*, 293–308.
25. Uppenberg, J.; Ohrner, N.; Norin, M.; Hult, K.; Kleywegt, G. J.; Patkar, S.; Waagen, V.; Anthonsen, T.; Jones, T. A. *Biochemistry* **1994**, *34*, 16838–16851.
26. Takano, S.; Yanase, M.; Takahashi, M.; Ogasawara, K. *Chem. Lett.* **1987**, 2017–2020.
27. Ohtani, T.; Nakatsukasa, H.; Kamezawa, M.; Tachibana, H.; Naoshima, Y. *J. Mol. Catal. B: Enzym.* **1998**, *4*, 53–60.
28. *E* symbolizes the enantiomeric ratio; see: Chen, C.-S.; Fujimoto, Y.; Gilrdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.
29. Fuji, M.; Fukumura, M.; Hory, Y.; Hirai, Y.; Akita, H.; Nakamura, K.; Toriizuka, K.; Ida, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 2292–2298.
30. (a) Faber, K. *Chem. Eur. J.* **2001**, *7*, 5005–5007; (b) Pamies, O.; Bäckwall, J. E. *Chem. Rev.* **2003**, *103*, 3247–3262.
31. Lee, D.; Huh, E. A.; Kim, M.-J.; Jung, H. M.; Koh, J. H.; Park, J. *Org. Lett.* **2000**, *2*, 2377–2379.
32. Choi, Y. K.; Suh, J. H.; Lee, D.; Lim, I. T.; Jung, J. Y.; Kim, M.-J. *J. Org. Chem.* **1999**, *64*, 8423–8424.
33. Allen, J. V.; Williams, J. M. J. *Tetrahedron Lett.* **1996**, *37*, 1859–1862.
34. (a) Huges, D. L. *Org. React. (NY)* **1992**, *42*, 333–395; (b) Huges, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127–164.