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Articles

Practical Chemo-Enzymatic Process for the Preparation of (1*R*,*cis*)-2-(2,2-Dihaloethenyl)-3,3-dimethylcyclopropane Carboxylic Acids

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Abstract:

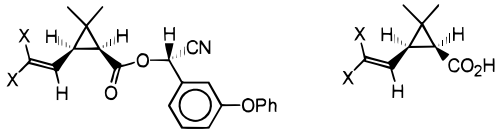
A practical chemo-enzymatic process for the preparation of optically active (1*R*,*cis*)-2-(2,2-dichloro (or dibromo)ethenyl)-3,3-dimethylcyclopropane carboxylic acids (permethrinic or deltamethrinic acids) from racemic 1,1,1-trichloro-2-acetoxy-4-methyl-3-pentene is described. The key intermediate, enantiopure (*R*)-1,1,1-trichloro-2-hydroxy-4-methyl-3-pentene, is prepared by a lipase catalysed kinetic resolution of the racemic acetate. The reaction mixture, containing (*R*)-alcohol and the unreacted (*S*)-acetate, is directly acetylated by a haloacetyl halide, and the products are separated by distillation. The (*S*)-acetate is racemized, and the (*R*)-haloacetate is transformed to the corresponding glycinate hydrochloride, followed by diazotization to (*R*)-1,1,1-trichloro-4-methyl-3-penten-2-yl diazoacetate. The stereoselective carbenic dediazotization of the (*R*)-diazoacetate furnishes the optically active (1*R*,4*R*,5*S*)-6,6-dimethyl-4-trichloromethyl-3-oxobicyclo[3.2.0]hexan-2-one, which is transformed to the desired enantiopure (1*R*,*cis*)-permethrinic or deltamethrinic acid in high optical yield (>99% ee) and overall chemical yield of 10−15%.

Introduction

Pyrethroids, photostable and highly effective derivatives of the natural insecticides, pyrethrins, are widely used in agriculture and the public health sector for the control of many kinds of undesired insects, mites, and spiders.[1] The most important insecticides of this class are deltamethrin and cypermethrin (Scheme 1).

Extensive research has demonstrated that from the eight possible stereoisomers, the one with the (1*R*,*cis*,α*S*)-configuration has the highest biological activity both for cypermethrin and deltamethrin.[2−4] The synthesis of these esters was usually carried out by coupling the corresponding cyclopropane carboxylic acids: 2-(2,2-dichloroethenyl)-3,3-dimethylcyclopropane carboxylic acid (**1a**, permethrinic acid) or 2-(2,2-dibromoethenyl)-3,3-dimethylcyclopropane carboxylic acid (**1b**, deltamethrinic acid), with an alcohol component containing an α-cyano-3-phenoxybenzylic fragment.[5]

Scheme 1. **Synthetic pyrethroids and pyrethroid acids**



The aim of this work was to design a practical generic process with industrial potential for the preparation of (1*R*,*cis*)-**1a** and (1*R*,*cis*)-**1b**. The main advantages of the process are the application of selective and nonhazardous procedures using readily available, commercial starting materials and full utilization of the undesired enantiomer.

Industrial Synthesis of (1*R*,*cis*)-1b and Generic Strategy. The industrial process for manufacturing (1*R*,*cis*)-**1b** is depicted in Scheme 2.[6] It starts from racemic *trans*-2-(2-methyl-2-propenyl)-3,3-dimethyl cyclopropane carboxylic acid (chrysanthemic acid). A key stage of the procedure is the resolution of the racemic chrysanthemic acid, followed by further complicated transformations of both the (1*R*,3*S*)- and (1*S*,3*R*)-stereoisomers, including hazardous ozonization processes.

In our opinion a competitive generic process should satisfy the following criteria: (i) induction of chirality should be carried out in the early steps with a high ee (>95%); (ii) a minimum number of steps should be included (one-pot procedures are preferred); (iii) the high output procedures should be safe and simple; (iv) nonhazardous and available reagents should be used, and (v) minimum auxiliary materials (solvents, etc.) should be used.

In the search for a suitable generic process, we evaluated a method developed by Kondo and Hatch for FMC Corp. (Scheme 3).[7] This comprised the stereoselective intramolecular cyclization of the chiral (*R*)-1,1,1-trichloro-4-methyl-3-penten-2-yl diazoacetate, **2**, into the chiral (1*R*,4*R*,5*S*)-6,6-dimethyl-4-trichloromethyl-3-oxobicyclo[3.2.0]hexan-2-

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(7) Hatch, C. E., III; Baum, J. S.; Takashima, T.; Kondo, K. *J. Org. Chem.* **1980**, *45*, 3281−3285.

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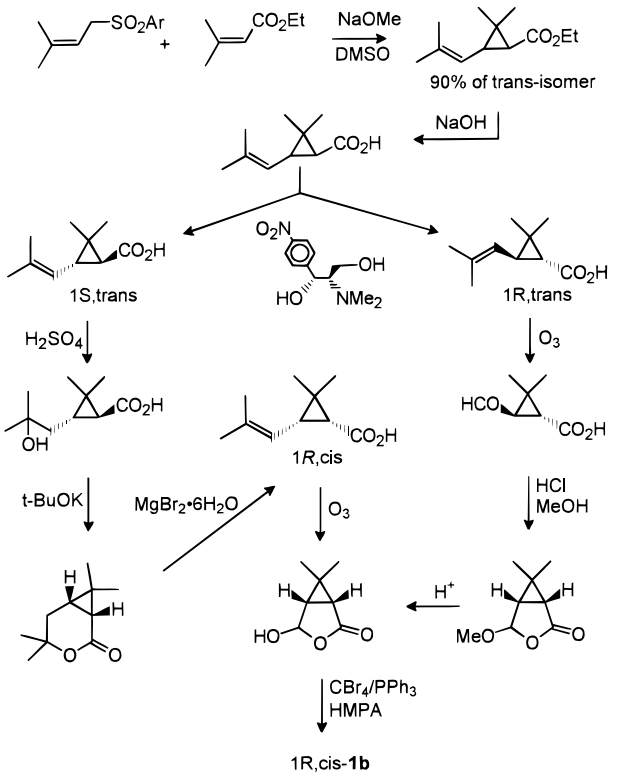
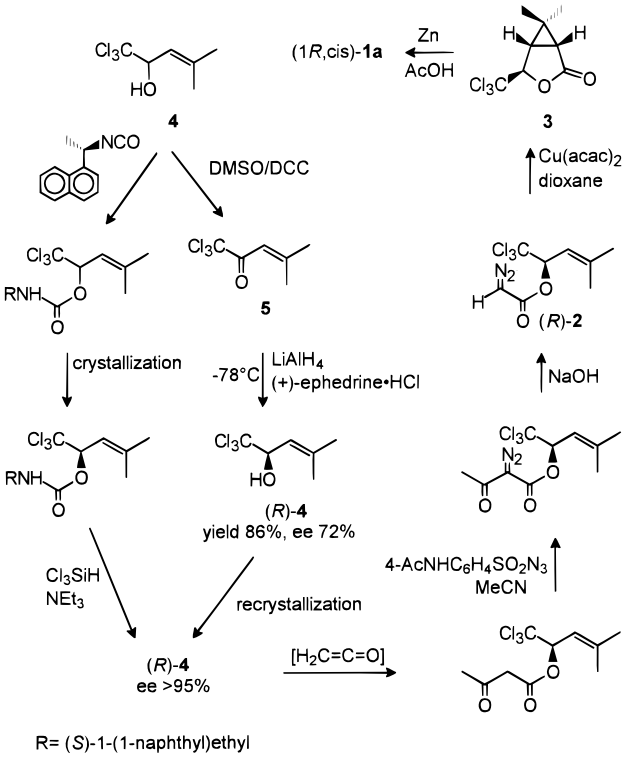
Scheme 2. **Industrial method for the preparation of (1*R*,*cis*)-1b (Roussel-Uclaf-Hoechst)**



Scheme 3. **Intramolecular carbenic dediazotization as a method for producing (1*R*,*cis*)-1a (FMC Corp.)**



one, **3**, which was then transformed into (1*R*,*cis*)-**1a** in one step.

Synthesis of the optically active diazo compound was performed by a multistep procedure, starting from the chiral (*R*)-1,1,1-trichloro-2-hydroxy-4-methyl-3-pentene, (*R*)-**4**. This was obtained by resolution of the racemic alcohol, the unwanted enantiomer being discarded, or by an asymmetric reduction of 1,1,1-trichloro-2-oxo-4-methyl-3-pentene, **5**, with a chiral ligand−lithium aluminum hydride complex, followed by an additional crystallization to increase the low enantiopurity from 72 to >95%.

Both of these procedures make this approach unfeasible for practical use. Nevertheless, this scheme does not contain a dangerous ozonization step and could be improved in the stages of the introduction of optical activity and the preparation of the chiral diazoester, **2**.

Introduction of Chirality. Among the numerous methods of introduction of optical activity, the biocatalytic kinetic resolution of a racemic precursor frequently provides the highest enantioselectivity. Earlier work of Indian scientists demonstrated the feasibility of the biosynthesis of the enantiopure (*R*)-**4** by fermentation of 1,1,1-trichloro-2-acetoxy-4-methyl-3-pentene, **6**, in a culture broth of *Bacillus subtilis* under aerobic conditions for 24−48 h.[8] The desired optically active alcohol (*R*)-**4** was isolated by extraction and separated from the unhydrolyzed (*S*)-**6** by crystallization. The main disadvantages of this method are the requirement for a microorganism cultivation and unsutisfactory output due to the low substrate concentration (0.5−1%).

In an effort to develop a more practical enzymatic process we tested several enzyme preparations to find one which could be used as a biocatalyst. Two options were tested: enzymatic hydrolysis of racemic **6** and enzymatic transesterification with *n*-butanol.

Enzyme-Mediated Hydrolysis. Screening experiments were performed with enzyme preparations from various sources (mammalian, plant, microbial) and suppliers, in a medium of a phosphate buffer of pH 7. The results are summarized in Table 1. The results indicate that lipases from different sources were able to hydrolyze the substrate, although only a few of them catalysed the reaction in a stereospecific way, affording **4** with the desired R-configuration at the asymmetric center. Only enzymes from Baker's yeast catalyzed the formation of (*S*)-**4** (entry 6). Among the four most selective enzyme preparations, providing an ee >98% (entries 8, 12, 23, and 24), porcine liver acetone powder (PLAP) exhibited the highest conversion (>38%). It was also the cheapest enzyme preparation at the time of inquiry. Therefore, further studies were carried out using this enzyme.

Enzyme-Mediated Transesterification. The possiblity of using an organic medium for the selective transformation of **6** was evaluated by PLAP-promoted transesterification with *n*-butanol (Scheme 4). It was discovered that the transesterification was normally promoted with a 2−5-molar excess of *n*-butyl alcohol in the presence of 0.5−2 g of enzyme powder per g of racemic **6**. An acceptable conversion was only reached in the presence of 1−3% water. In the absence of water, only 8−15% conversion was obtained for all of the solvents studied. Above a concentration of 3%, the water suppresses the enzyme's activity. Among the

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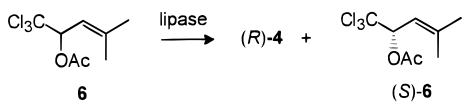
Table 1. **Enzyme-mediated hydrolysis of 6[a]**

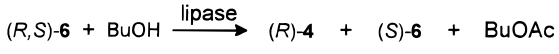


6 (S)-6

entry	enzyme origin	supplier	**4** (%)	ee (*R*)-**4** (%)
1	α-chymotrypsin	Sigma	0	
2	*Achromobacter sp.* (AL)	Meito Sangyo	0	
3	*Alcaligenes*	Biocatalyst	0	
4	Alcaligenes (QL)	Meito Sangyo	0	
5	*Aspergillus niger*	Fluka	27	87
6	Baker's yeast	IMI stock	29	30[b]
7	bovine liver acetone powder	Sigma	63	61
8	*Candida antarctica* A (L-5)	Boehringer Mannheim[c]	16	>98
9	*Candida cylindracea*	Biocatalyst	84	62
10	*Candida cylindracea*	Sigma	18	77
11	*Candida cylindracea* (AY)	Amano	26	85
12	*Candida cylindracea* (L-3)	Boehringer Mannheim[c]	21	>98
13	*Candida cylindracea* (MY)	Meito Sangyo	30	64
14	*Candida cylindracea* (OF)	Meito Sangyo	12	35
15	*Candida lipolytica*	Fluka	5	0
16	*Chromobacterium viscosum*	Biocatalyst	10	0
17	horse liver acetone powder	Sigma	66	54
18	*Mucor javanicus*	Fluka	0	
19	*Mucor miehei*	Biocatalyst	0	
20	*Mucor miehei*	Fluka	0	
21	pancreatic lipase	Biocatalyst	25	0
22	*Penicillum roquefortii*	Fluka	0	
23	pig liver esterase	Sigma	32	>98
24	porcine liver acetone powder	Sigma	38	> 98
25	porcine pancreatic lipase	Sigma	26	0
26	*Pseudomonas fluorescens*	Biocatalyst	60	0
27	*Pseudomonas sp.*	Amano	0	
28	*Pseudomonas sp.*	Boehringer Mannheim[c]	33	0
29	*Rhizopus arhizus*	Fluka	0	
30	*Rhizopus delmar*	Fluka	0	
31	*Rhizopus nereus*	Fluka	0	
32	*Subtilisin carlsberg*	Sigma	0	
33	wheat germ	Sigma	46	83
34	wheat germ	Fluka	60	72

[a] Conditions: 0.8 mmol of **6**; 50 mg of enzyme; total volume = 10 mL; 0.1 M phosphate buffer pH = 7.0; T = 30 °C; time −24 h. [b] ee of (*S*)-**4**. [c] Roche Diagnostics at present.

Scheme 4. **Enzymatic transesterification of 6 with *n*-butanol**



various solvents investigated, hexane was preferable in terms of enzyme selectivity. In a more polar medium, such as toluene, tetrahydrofuran, dioxane, methylisopropylketone, and di-isopropyl ether, conversion of the acetate, **6**, was drastically reduced, to 8−12%. In *n*-butanol the selectivity was very poor (only 60% ee). A conversion of 45% and an ee of more than 98% was reached under the optimal conditions. Unfortunately, the enormous enzyme consumption made the transesterification inappropriate as a practical method. Thus, PLAP-promoted hydrolysis was chosen for further optimization.

Table 2. **Effect of cosolvent on conversion of 6[a]**

entry	cosolvent	conversion (%)
1	diglyme	15
2	THF	22
3	ethylene glycol	23
4	none	23
5	di(ethylene glycol) methyl ether	25
6	2-methoxyethanol	25
7	1-methyl-2-pyrrolidone (NMP)	29
8	DMF	31
9	dioxane	32

[a] Conditions: 1 mmol of **6**; 100 mg of enzyme; 10% v/v cosolvent; total volume = 10 mL; 0.1 M phosphate buffer pH = 7.0; T = 35 °C; time −4 h.

Optimization of the PLAP mediated hydrolysis of 6. *pH.* The hydrolysis of **6** was examined under pH values of 4−8.5. It was found that the optimal pH for PLAP activity was 6.5−7.0. For the lab-scale experiments, phosphate buffer was used, and for the bench-scale trials, pH control was achieved by periodic addition of a sodium hydroxide solution.

Cosolvent. One of the major problems encountered with hydrolytic reactions, is the poor solubility of the substrate in the aqueous medium. An alternative method, to overcome this problem, is to incorporate water-miscible solvents (cosolvents).[9] The use of cosolvents offers several advantages, such as increased solubility and the need for gentler mixing. However, inhibitory effects on the enzyme were also reported.[10] It is assumed that the major cause of the loss of enzymatic activity in the presence of a cosolvent is its effect on the hydrophobic pockets of the enzyme.

Several potential cosolvents were examined for their ability to improve the hydrolysis of **6** (Table 2).

Addition of 10% v/v dioxane to the reaction mixture improved the conversion by nearly 50% (entry 9), with DMF and NMP also giving good results (entries 7 and 8). The reaction rate was nearly the same within a cosolvent range of 5−20%. However, addition of 30% dioxane resulted in almost complete loss of enzymatic activity. THF, ethylene glycol, di(ethylene glycol) methyl ether, and 2-methoxyethanol did not effect the conversion of **6** (entries 2, 3, 5, and 6). Diglyme (entries 1) demonstrated an inhibiting effect on PLAP. Due to safety considerations, it was decided to use DMF at a concentration of 5% in further studies.

Substrate Concentration. A low concentration of **6** in the reaction mixture was found to be important for achieving high conversion rates to (*R*)-**4**. When a concentration of 10% substrate was used, 0.12 g PLAP per g of **6** was needed to reach 30% conversion within 100 h. When concentrations of <5% substrate were used, 0.05 g of the enzyme powder per g of the substrate was sufficient to reach 40% conversion in 24 h.

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(10) Plank-Koblenc, T.; Tor, R.; Freeman, A. *Biotechnol. Appl. Biochem.* **1988**, *10*, 32−41; Smidt, H.; Fisher, A.; Fisher P.; Schmidt, R. *Appl. Microbiol. Biotechnol.* **1987**, *25*, 495−501.

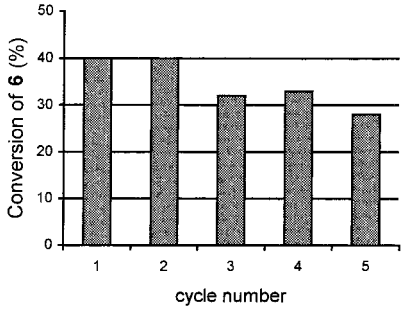


Figure 1. **Activity of recovered PLAP. Conditions: 1 mmol of 6; 100 mg of enzyme; 0.5 mL of DMF, 9.5 mL of a 0.1 M phosphate buffer pH = 7.0; *T* = 38 °C; time − 5 h.**

Temperature. The best temperature was 38−40 °C. Below this temperature the reaction rate was slow, and at elevated temperatures the enzyme underwent deactivation.

Amount of Enzyme and Recycling. The lowest ratio of enzyme-to-substrate was found to be 5:95, yielding 40% conversion within 48 h. An increase of this amount accelerated the reaction rate. Thus, using 8.7% enzyme provided 40% conversion of **6** after 14 h at 38 °C at pH 7. Nevertheless, because of the relatively high cost of the enzyme preparation, such consumption of biocatalyst is unacceptable.

To improve the economical feasibility of the process, we studied the possibility of re-using the enzyme preparation. After the first cycle was complete, the reaction products were extracted with toluene, and the aqueous phase, comprising a suspension of the enzyme preparation in a DMF−water solution, was separated and charged with a fresh portion of substrate. Data depicted in Figure 1 demonstrate that a significant lowering of the enzyme activity (30%) was observed only in the fifth cycle.

No attempts were made to immobilize the enzyme although it is assumed that immobilization can further improve the enzymatic activity.

Purity of Substrate. The results of the enzyme recycling study also showed that the enzyme was not sensitive to residues of toluene present in the substrate. In addition, we discovered that a residual amount of acetic acid and acetic anhydride did not influence the enzymatic reaction. It is concluded that crude **6** can be used instead of distilled substrate.

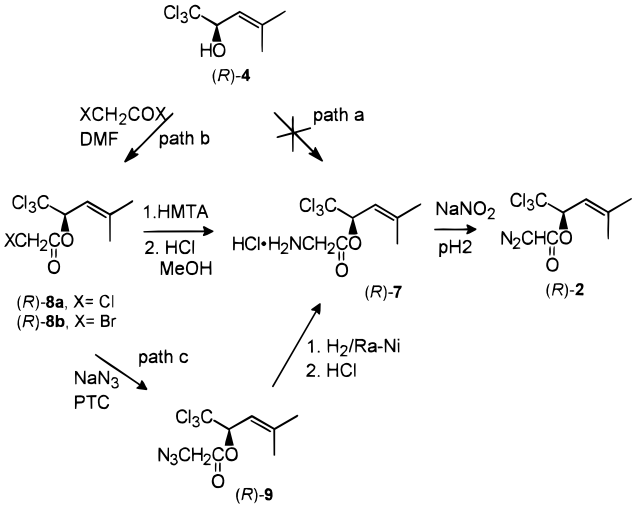
Summary of Optimum Conditions. The best results in the hydrolysis reaction were reached using a 5−9% enzyme: substrate ratio, 5−6% substrate concentration in the medium, a constant pH of 6.5−7.0, a temperature of 38−40 °C, and with the presence of 5% (v/v) dioxane or DMF as cosolvent.

Under these conditions, on a 50 g scale, a conversion of 40−45% is reached within 15 h with >98% ee of (*R*)-**4**.

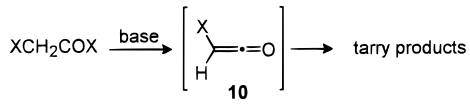
Synthesis of Enantiopure Diazoester (*R*)-2. The successful solution to the problem of chirality led to the following challenges: separation of (*R*)-**4** and its conversion to the enantiopure diazoester, (*R*)-**2**, racemization of (*S*)-**6**, and the synthesis of racemic **6**.

The shortest classical route to diazoesters from alcohols comprises the esterification of the alcohol with glycine, followed by diazotization of the glycine ester with nitrous acid (path a, Scheme 5).

Scheme 5. **Routes to diazoester 2 from (*R*)-4**



Scheme 6. **Dehydrohalogenation of haloacetyl halide**



Unfortunately, this approach was unfeasible for the alcohol, **4**, due to the low activity of the alcohol moiety attached to the strong electron-withdrawing trichloromethyl group. We tested two alternative strategies for the preparation of enantiopure (*R*)-1,1,1-trichloromethyl-3-methyl-3-penten-2-yl glycinate hydrochloride, (*R*)-**7**. The first comprised the acylation of enantiopure (*R*)-**4** with haloacetyl halide, followed by amination of 1,1,1-trichloromethyl-3-methyl-3-penten-2-yl haloacetate, (*R*)-**8a,b**, by splitting the quaternary salt with hexamethylenetetramine (HMTA) and concentrated hydrochloric acid (path b). The second involved the preparation of (*R*)-**7** via hydrogenation of the corresponding 1,1,1-trichloromethyl-3-methyl-3-penten-2-yl azidoacetate, (*R*)-**9**, followed by treatment with HCl (path c).

Acylation. For the acylation study, a sample of essentially pure (*R*)-**4** was separated from the reaction mixture at the end of the enzymatic hydrolysis stage by crystallization from toluene, *o*-xylene, or carbon tetrachloride. Bromoacetyl bromide (BAB) and chloroacetyl chloride (CAC), in the presence of a base, were used for the acylation. It was found that the reaction was sensitive to the nature of the base and the order of mixing the reagent. Inorganic bases, e.g., anhydrous potassium carbonate, were noneffective.

Strong organic bases (pyridine and triethylamine) induced dehydrohalogenation of the haloacetyl halide, releasing an unstable haloketene, **10**, which gave tarry products (Scheme 6). As a result, the yield of the desired product, **8**, was not more than 50−60%.

As an alternative, the simultaneous addition of the haloacetyl halide and base to the alcohol solution could be carried out. However, the best solution was the application of organic amides as bases, in particular, DMF and *N*-methylpyrrolidone.

We found that acylation of a toluene extract of the crude reaction products (containing (*R*)-**4**, (*S*)-**6** and a residual amount of DMF) after enzymatic hydrolysis, proceeded

smoothly and afforded the desired **8** in excellent yield (more than 90%). Experiments with pure (*R*)-**4** showed that a maximum yield of (*R*)-**8b** with >99% conversion of the starting alcohol was reached using a 1.0−1.2 molar excess of BAB and a 1.0−1.2 molar excess of DMF, at 50−80 °C. Filtration of the reaction mixture through Celite, followed by distillation at 130−135 °C/10 mbar afforded the (*R*)-**8b** with a purity of >95% and >98% ee, in 90−92% isolated yield, and a crude product, containing the remaining (*S*)-**6** and residual amounts of (*R*)-**6** and (*R*)-**4**.

The chloroacetylation with CAC proceeded under more severe conditions. A 2−3 molar excess of DMF and CAC, and heating to 110 °C were required to reach ∼90% conversion of the starting alcohol and a 65−75% yield of (*R*)-**8a**.

The optically active haloacetate, (*R*)-**8**, was then used for preparing the diazoacetate, (*R*)-**2**, while the unreacted (*S*)-**6** underwent racemization and recycling to the process.

Amination. (*R*)-**8** was transformed to the hexamethylenetetramine quaternary salt by heating with a 1−1.5 molar excess of HMTA in the presence of 20−30% v/v inert solvent at 35−110 °C. The mixing order of the reagents was not critical. The reaction can be carried out by heating a mixture of the reagents, as well as by the addition of one reagent after the other. Dilution of the reaction mixture with a solvent prolonged the reaction and decreased the conversion of the reactants. However, in the absence of a solvent the reaction mixture solidified. Thus, the addition of 20−50% v/v of solvent is required. Heat evolved from the exothermic reaction, but additional heating was needed to complete the process. Heating above 110 °C induced a partial decomposition of the reaction products. A small excess of HMTA promoted the reaction, but was not critical. Examples of suitable solvents are alcohols, halogenated hydrocarbons, and ethers. The most preferable solvents were dibromomethane, methanol, or dimethoxymethane, which were already used in other stages of the process.

The salt, after removal of the solvent, was then split by treatment with a strong acid. Splitting of hexamethylenetetramine quaternary salts is known in the art as a method for preparing amines from halogen derivatives, the so-called Delepine reaction. Various α-amino acids can be prepared in this way.[11] However, this transformation has never been applied to the preparation of aminoesters, apparently due to the possibility of hydrolysis occurring easily, brought about by the strong acids.

We found that splitting can be achieved by heating with a solution of hydrogen halide, for example, hydrogen chloride or hydrogen bromide, or a concentrated hydrohalic acid, for example, 32% hydrochloric or 47% hydrobromic acid, in a protic polar solvent such as an alcohol, preferably methanol, at 50−70 °C, to give the glycinate (*R*)-**7**.

The reaction also resulted in the formation of formaldehyde diacetal (dialkoxymethane), which, after recovering by distillation, was used as a solvent in the quaternization stage. Another side product was ammonium halide. Potentiometric titration with 0.1 N $AgNO_3$ indicated that more than 92% of the halogen atoms in the quaternary salt were bonded to the glycinate in the form of an addition salt, whereas the precipitating ammonium halide originated from the acid used for the splitting. An equimolar quantity of acid was preferable, although no decrease in the yield of the product was observed, even with a 2 molar excess of the acid. The presence of a protic solvent was critical. In the absence of solvent, splitting with concentrated acid had place in low yields. However, no glycinate ester was detected when the reaction was carried out in chloroform.

After the ammonium salt and solvents were removed, the crude reaction product contained mainly the desired glycinate, **7**, which was used directly in the diazotization step.

Azidotization. According to an alternative approach to the glycine ester, (*R*)-**7**, the bromoacetate, (*R*)-**8b**, was treated with sodium azide in the presence of a phase transfer catalyst, for example, tetrabutylammonium bromide (TEBA),[12] followed by hydrogenation of the azidoacetate, (*R*)-**9**, in the presence of 2−5% Lindlar catalyst[13] and treatment of the hydrogenated product with an ethanolic solution of concentrated hydrochloric acid. In this route, a diazoester of >94% purity (ee >98%), was obtained in an overall isolated yield of 70%. The relatively low yield, the requirement for hydrogenation, and the use of the hazardous reagent, sodium azide, do not favor this method over the Delepine reaction.

Diazotization. The crude glycinate, (*R*)-**7**, was diazotized in accordance with the traditional procedure, comprising treatment with an excess of sodium nitrite in an organic solvent immiscible with water, in the presence of water, at pH 2−4, and at low temperature.[14] This method was earlier used for diazotization of alkyl glycinates, not of glycinates with a complex alcohol moiety, bearing functional groups, whose behaviour is unpredictable under the action of strong acids.

We found that the diazotization can be carried out smoothly using a 1−1.1 molar excess of a 30−50% aqueous solution of sodium nitrite, under controlled pH (2−3) at 0−5 °C. The presence of water was critical for successful diazotization, as, according to a generally accepted mechanism, the diazoester formation occurs in the aqueous phase. Subsequent extraction of the diazoester into the organic solvent prevented its decomposition. Halogenated hydrocarbons were preferable solvents because of their stabilizing effect on the diazoester. In this work, dibromomethane was the preferred solvent and was also suitable for the subsequent dediazotization stage and the stage of preparing (*R*)-**1b**.

The temperature and pH were also critical for reaching a high yield of diazoester. At temperatures above 20 °C, a slow decomposition of the reaction product was observed. Under strongly acidic conditions (pH <2), decomposition of the diazoester also took place. At pH >5, the diazoester formation became slower and was accompanied by the formation of side products. The pH of the reaction medium can be adjusted by the continuous (or occasional) addition

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of acid, preferably dilute sulfuric acid, or a base, for example, sodium bicarbonate, or by the use of a buffer with the appropriate pH value, for instance, acetate buffer or citrate buffer. Ammonium halides, such as ammonium chloride or ammonium bromide, or their mixtures do not interfere with the diazotization under these conditions. This enables the use of the crude reaction product from the quaternary salt-splitting stage after separation of most of the ammonium halide by filtration and evaporation of MeOH, for the diazotization.

No racemization of the optically active compounds occurred under these conditions. The corresponding diazoester was prepared from (*R*)-**8b** in a 70−75% overall yield with >98% ee. Using (*R*)-**8a** slightly decreased the yield but not the purity or ee of the product.

The diazoester was a fairly stable compound and was isolated by column chromatography on silica gel. However, to avoid any possibility of uncontrolled dediazotization, the original reaction solution, containing 3−5% of the diazoester, was used directly.

Synthesis of (1*R*,4*R*,5*S*)-3 by Carbenic Cyclization. The diazoacetate, (*R*)-**2**, was converted, by intramolecular cyclization, into the optically active bicyclolactone, (1*R*,4*R*,5*S*)-**3**, according to the Kondo method (Scheme 3), by heating with a copper catalyst in an organic solvent.

This intramolecular catalytic transformation was found to be very sensitive to the type of catalyst and its concentration, the temperature, and the substrate concentration. Despite the large amount of information on this topic, there are no reliable recommendations concerning each specific case. Hence, we decided to carry out a preliminary optimization of this reaction.

Catalyst. In contrast to Kondo, we found that copper(II) perchlorate hexahydrate was a better catalyst than copper-(II) acetylacetonate, because it provided reliable results with a crude wet solution of the diazoester, even in relatively concentrated solutions. The cyclization was promoted with 0.005−5 mol % of copper(II) perchlorate hexahydrate, in a moderately dilute (1 g of the diazoacetate per 10−40 mL of solvent) solution of a halogenated hydrocarbon at 80−110 °C.

Solvent and Temperature. These parameters were critical. The use of halogenated hydrocarbons with a boiling point below 80 °C, such as chloroform, drastically reduced the yield of the product. The cyclization in toluene at 82 °C led only to carbene adducts of the aromatic ring. In diisopropyl ether at 69 °C, the carbenic dediazotization afforded mainly C−H bond carbene insertion products. No bicyclolactone was found. The best result was obtained when the dediazotization was carried out in dibromomethane at 85−90 °C. A solution of the crude diazoacetate could also be used.

Substrate Concentration. This is a very important parameter for a practical process. Dilution favors the target reaction but decreases the volume yield of the product. To solve this dilemma, we designed a special apparatus for working with dilute solutions (Figure 2).

To reduce the concentration of the diazoester, the working solution, with a substrate concentration of 3−5%, was fed, via an intermediate vessel (diluter) filled with solvent, to a boiling suspension of the catalyst in the solvent, at a rate which ensured a constant volume in the reactor. Part of the evaporating solvent was directed back into the diluter. Such a simple scheme enabled an increase in the volume yield to a reasonable value of 60 g/L.

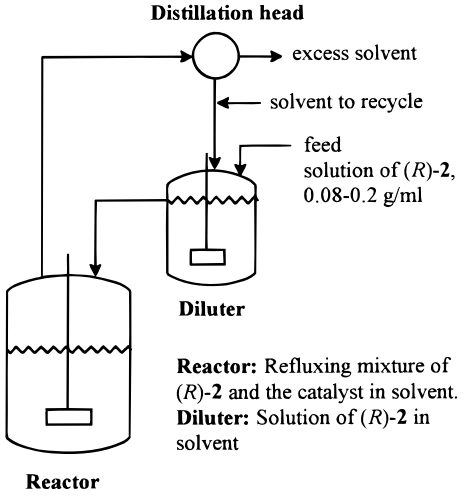


Figure 2. **Unit for a low-concentration reactant process.**

When the feeding was completed, most of the solvent was evaporated, the microcrystalline catalyst was filtered off, and the filtrate was passed through Celite to remove tarry products. The desired bicyclic lactone, (1*R*,4*R*,5*S*)-**3**, with a purity of 90% and an ee >98% was isolated by distillation at 150 °C/5 mbar or by crystallization from hexane in 40−45% yield with respect to (*R*)-**8b**.

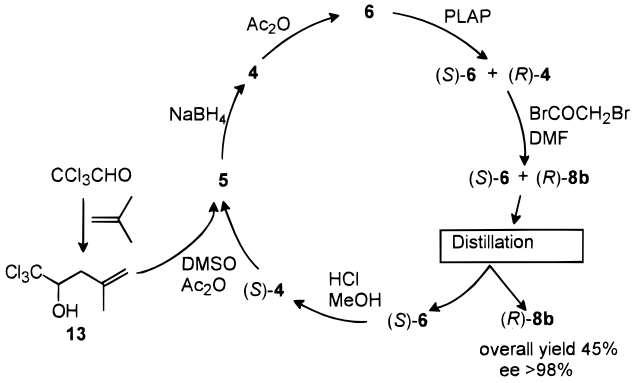
Synthesis of (1R,*cis*)-1a and (1R,*cis*)-1b. The optically active oxabicyclolactone, (1*R*,4*R*,5*S*)-**3**, was opened by a Boord-type reaction using zinc powder. Methanol simplified the isolation of the reaction product and was therefore used as solvent instead of acetic acid.[7] Refluxing in methanol afforded the desired permethrinic acid, (1*R*,*cis*)-**1a**, in 93% yield and with more than 98% ee of the 1*R*,3*S*-enantiomer.

The acid was then transformed to deltamethrinic acid, (1*R*,*cis*)-**1b**, by a halogen-exchange reaction according to a literature method.[15] Only one reaction was tested. Aluminum bromide in dibromomethane at 0 °C gave the desired deltamethrinic acid, (1*R*,*cis*)-**1b**, in 68% yield and with more than 98% ee of the 1*R*,3*S*-enantiomer after two crystallizations from hexane.

Racemization of (*S*)-6. The entire process can only be considered practical if the feasibility of recovering the (*S*)-**6** enantiomer can be demonstrated. Unfortunately, the direct racemization of the undesired enantiomer, which would enable recycling of the racemic acetate, **6**, failed. Heating the substrate with hydrohalic acids or transition metal catalysts, such as PdO or Pd(II) acetate, only induced hydrolysis of the ester and led to tarry products. Racemization did not occur under this treatment. Activation of the hydroxyl group by tosylation or mesylation only facilitated these undesired side reactions. Such behavior of the alcohol was not surprising in view of the easy dechlorination of the

(15) Kondo, K.; Takashima, T.; Negishi, A.; Matsui, K.; Fujimoto, T.; Sugimoto, K.; Hatch, C. E., III; Baum, J. S. *Pestic. Sci.* **1980**, *11*, 180−189.

Scheme 7. **Racemization of (*S*)-6**



trichloromethyl group under the influence of a partial negative charge on the adjacent carbon atom. For instance, the dechlorodeacylation of the acetate, **6**, is an industrial method for preparing the corresponding 1,1-dichloro-4-methyl-1,3-pentadiene.[1]

Thus, we faced the problem of developing an indirect method for the racemization of (*S*)-**6**. The most obvious method was oxidation of the chiral alcohol, (*S*)-**4**, to the ketone, **5**, followed by reduction to the racemic alcohol, **4**, and then acetylation to racemic **6**.

Such a major addition to the reaction sequence required an additional experimental study, followed by optimization.

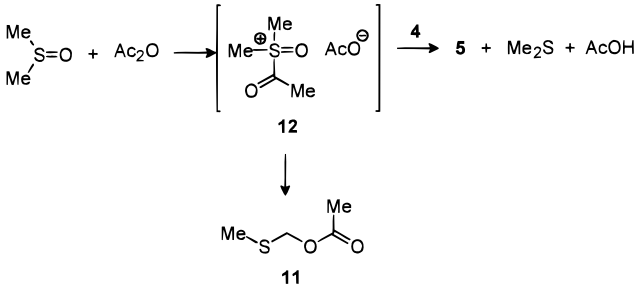
Hydrolysis of 6. Hydrolysis of (*S*)-**6** was readily performed by treatment of the crude product, obtained as the first fraction during the distillation of (*R*)-**8**, with hydrohalic acids. The product contained mainly (*S*)-**4** (~85%) along with residual amounts of (*R*)-**6** and (*R*)-**8**. Complete hydrolysis was achieved by heating with concentrated hydrochloric acid in methanol or ethanol at 65−75 °C. After cooling and diluting with water, precipitation occurred to give (*S*)-**4** in >93% yield (Scheme 7).

Oxidation. Since the Moffat-type oxidation of **4** to secondary alcohols with DMSO in the presence of DCC, applied by Kondo in the prototype, was unfeasible in practice, we decided to test an alternative approach[16] using readily available and nonhazardous acetic anhydride instead of DCC. It was found that the DMSO−acetic anhydride oxidation readily took place with a 3−20 molar excess of acetic anhydride and a 3−50 molar excess of DMSO, optionally in the medium of an organic solvent at 20−150 °C. The type of solvent is not critical. The reaction proceeded even in the absence of a solvent. The use of equimolar quantities of the reagents or of an excess of only one of them (DMSO or acetic anhydride) did not give the product, **5**, in acceptable yields. Elevated temperatures accelerated the reaction and decreased the reagent excess requirement for DMSO and acetic anhydride to 3−4-fold. This made recovering and re-utilization of the reagents unnecessary.

The desired reaction was accompanied by the formation of two side-products: dimethyl sulfide and methylthiomethyl acetate, **11**, (Scheme 8). Dimethyl sulfide, formed in a stoichiometric amount with respect to the ketone, **5**, is the expected by-product. According to known data[16] the ester,

(16) Albright, J. D.; Goldman, L. *J. Am. Chem. Soc.* **1967**, *89*, 2416−2423.

Scheme 8. **Formation of side-products during oxidation**



11, originates from the rearrangement of an active intermediate species, the acetylsulfonium salt **12** (Pummerer reaction), further reaction of which, with the alcohol, affords the desired ketone, **5**.

All attempts to eliminate this side reaction by a change of temperature or reagent mixing order, failed. Nevertheless, the target ketone was obtained in good yield (more than 85−90%) and was readily separated from **11** by distillation.

Reduction. The next two stages, reduction with sodium borohydride in ethanol and acetylation with acetic anhydride, were carried out in one stage, without separating the carbinol, **4**, from the borate ester. Treatment of the reduction products, after removal of the ethanol, with an equimolar amount of acetic anhydride, in the presence of 5−10 mol % triethylamine, at 50−95 °C, was found to give the acetate, **6**, in 87% yield (based on **5**). It is important to note that a crude reaction mixture can be used directly in the enzymatic hydrolysis stage. As mentioned above, the enzymatic hydrolysis was not affected by the presence of toluene, acetic acid, or acetic anhydride, as it was carried out under controlled pH. Apparently boric acid was also neutralized by the sodium hydroxide and did not interfere with the target reaction.

Synthesis of Ketone 5. The racemization procedure developed provided the transformation of (*S*)-**6** to a racemic acetate in 3 steps, in 70−72% overall yield. However, to balance the material flow we needed to find simple methods for preparing fresh portions of any of the racemic products from the racemization cycle: ketone **5**, alcohol **4**, or acetate **6**. Surprisingly we found that 1,1,1-trichloro-2-hydroxy-4-methyl-4-pentene, **13**, can be transformed directly to the conjugated ketone, **5**, under conditions of the DMSO−acetic anhydride oxidation process, apparently due to an easy isomerization of the initially formed nonconjugated 1,1,1-trichloro-4-methyl-4-penten-2-one, **14**, to **5**. To complete the isomerization, distillation of **5** was performed in the presence of a catalytic amount of an organic base, for example, triethylamine.

The starting alcohol, **13**, can be prepared according to any well-known procedure,[17] such as by the condensation reaction known as the Prins reaction, by treating 1,1,1-trichloroacetaldehyde (TCA) with isobutene in the presence of Lewis acids. The presence of impurities at the end of the Prins reaction, and the type of catalyst, is not critical for the

(17) Colonge, J.; Perrot, A. *Bull. Soc. Chim. Fr.* **1957**, 204; Soos, R.; Nemes, J.; Szelestey, M.; Vidra, L.; Schler, I.; Szekely, I. HU 31,623 (Chinoin) [*Chem. Abstr.* **1985**, *102*: 95240q].

tandem oxidation-isomerization, therefore a crude reaction product was directly used.

Summary

According to the method developed, (1*R*,*cis*)-**1a** and **1b** were prepared at >98% ee and an overall chemical yield of 10−15% using 10 chemical steps and 5 essential auxiliary operations (distillations of **5**, **8**, and **3**, crystallizations of **1a** and **1b**). The list of raw materials was limited to twelve inexpensive and nonhazardous compounds: TCA, isobutene, DMSO, acetic anhydride, sodium borohydride, DMF, BAB (or CAC), HMTA, methanol, sodium nitrite, zinc dust, and aluminum bromide. The most uncommon material, bromoacetyl bromide, is a readily available reagent in Israel. According to literature data,[15] aluminum bromide could be replaced by cheaper combinations of aluminum−HBr or $AlCl_3$−HBr. Solvents used were toluene, methanol, hexane, and dibromomethane. The latter is a rather expensive material but is produced from dichloromethane under conditions of halogen exchange in the last stage of the process.

The overall essential raw material consumption was a moderate 25 kg per 1 kg product. The major parameter, the biocatalyst consumption was within a reasonable value of 40 g per 1 kg product. No doubt this may be further decreased. The essential raw material cost (for deltamethrinic acid) was within an acceptable range of $100−150 per kg. For permethrinic acid the cost is lower.

In conclusion, a practical chemo-enzymatic process was developed with an industrial potential, which can compete with existing industrial processes after further optimization and improvement.

Experimental Section

In the examples which follow, temperatures are in degrees Celsius and pressures are in mmHg or in mbar. Melting points were determined on an Electrothermal 9100 instrument. All of the melting points and boiling points are uncorrected. Specific rotation [α] values were determined on a JASCO polarimeter DIP-360 for 1% solutions in chloroform at 25 °C, using a standard cylindrical glass cell 10 × 100 mm. ^{1}H NMR spectra were measured with a Bruker WP200 spectrometer using TMS as an internal standard. Mass spectra were recorded on a Hewlett-Packard HP 5971A gas chromatography mass spectrometer (GC columns 20 m × 0.18 mm, RESTEK Rtx-1 or RESTEK Rtx-20).

Analytical determinations by GC were performed on a Hewlett-Packard 5890 series II gas chromatograph using the same columns. Enantiopurity of the products was established by chiral GC analysis using CHIRALDEX B-PH (30 m × 0.25 mm) and CHIRALDEX G-TA (30 m × 0.25 mm) columns. Analytical determinations by HPLC were performed on a Hewlett-Packard HP 1050 liquid chromatograph, supplied with a Jasco detector model UV-975, on a Kromasil C-18 column, 250 mm × 4.6 mm, loop 20 mL at λ 200 nm, using acetonitrile/water (70:30) as eluent.

Porcine liver acetone powder (PLAP) was purchased from Sigma. Suppliers of the enzymes used for screening are specified in Table 1.

The yields and equivalents of reagents are corrected for their purity.

Ketone 5 (1,1,1-Trichloro-4-methyl-3-penten-2-one). A cooled (−10 °C) and well-stirred solution of TCA (74.3 g, 0.5 mol), iron(III) chloride hexahydrate (0.23 g, 1.4 mmol) and trichloroacetic acid (0.23 g, 1.4 mmol) in 75 mL of dichloromethane, was saturated with gaseous isobutene (total 37.6 g, 0.67 mol) for ∼1 h (volume rate 200 mL/min.), while the temperature was kept in a range of −12 to −8 °C by means of a cooling bath supplied with a dry ice−acetone mixture. The excess isobutene was removed by nitrogen, and the reaction mixture was allowed to warm to room temperature.

To the reaction vessel was connected a Claisen distillation adapter, condenser and receiver (**CAUTION:** the following operations must be carried out in a well-ventilated hood!). Acetic anhydride (153.1 g; 1.5 mol) and DMSO (117.2 g; 1.5 mol) were added to the reaction mixture all at once. The mixture was gradually heated to 55−60 °C, under stirring, until the low boiling fraction (dichloromethane and dimethyl sulfide) started to distill off. At the end of the distillation the temperature was raised to 85 °C and the reaction mixture was stirred for 3.3−3.5 h. The reaction mixture was allowed to cool to 30 °C and treated with 3% NaClO solution. The organic phase was transferred to a distillation apparatus supplied with a distillation column. Triethylamine (1.45 g; 0.0143 mol) was introduced into the still, and the mixture was heated at 70 °C for 2 h. The pressure was gradually decreased to 12 mbar, and the crude **5** (61.8 g; yield = 70%; purity = 88%) was distilled off and used in the next stage without additional purification.

Part of the product was redistilled at 80 °C/10 mm to give a sample with 98% purity for analysis: $C_6H_7Cl_3O$; MW = 201.47; ^{1}H NMR ($CDCl_3$, ppm) δ 2.08 (d, J = 1 Hz, 3H); 2.28 (d, J = 1 Hz, 3H); 6.61 (m, 1H); MS, *m*/*z* 201, 203, and 205 (M^+).

Oxidation of the (*S*)-**4** was performed according to the same procedure, but without the addition of triethylamine in the distillation step.

Racemic Acetate 6 (1,1,1-Trichloro-2-acetoxy-4-methyl-3-pentene). A solution of the crude **5** (4.93 g; 21.2 mmol; purity = 88%) in methanol (5 mL) was added gradually to a heated (38 °C) mixture of sodium borohydride (0.2 g) and methanol (3 mL) over 30 min, not allowing the temperature to rise above 44 °C. More sodium borohydride (0.11 g) was introduced in three stages, over 10 min, to complete the conversion of **5** (total amount 0.31 g; 8.2 mmol). The mixture was heated at 60 °C for 0.5 h, under stirring, and then then the solvent was removed at 67 °C/10 mm.

To the hot viscous residue, acetic anhydride (2.55 g; 21.2 mmol) and triethylamine (0.1 g; 1 mmol) were added all at once. The reaction mixture was heated at 95 °C for 1.3 h. After cooling to 30 °C the reaction mixture can be used directly in the enzymatic hydrolysis step. Yield 87% (based on **5**).

To separate a sample for analysis, the reaction products were diluted with 10 mL of water. The crude **6** (5 g; purity = 90%) separated as an oil. Distillation at 121 °C/25 mm

afforded **6** with 98% purity: $C_8H_{11}O_2Cl_3$; MW= 245.5, ^{1}H NMR ($CDCl_3$, ppm) δ 1.89 (s, 3H); 1.92 (s, 3H); 2.15 (s, 3H); 5.32 (dm, J = 9.2 Hz, 1H); 6.06 (d, J = 9.2 Hz, 1H); MS m/z 246 (M^+).

Enantiopure Alcohol (*R*)-4 ((*R*)-1,1,1-Trichloro-2-hydroxy-4-methyl-3-pentene) via Enantioselective Enzymatic Hydrolysis. The reaction mixture, after the process described in the previous experiment, was diluted with water (140 mL) and homogenized with DMF (7.5 mL). The solution was neutralized with NaOH pellets to pH 7 and heated to 38 °C. PLAP (0.5 g) was added, and the reaction mixture was heated at 38 °C, under stirring, for 20 h, while the pH was kept at 7.0−7.2 by the addition of 0.2 N NaOH solution, using a pH-controller and peristaltic pump. An additional amount of PLAP (0.38 g) was added to complete the hydrolysis, while heating and stirring was continued for another 26 h at pH 7.0−7.2 (total amount of NaOH solution was ca. 78 mL).

The reaction products were extracted with toluene. Drying the extracts by a partial evaporation of toluene at 60 °C/30 mm afforded a colored solution, containing the desired optically active alcohol, (*R*)-**4**. This product can be used directly in the acylation step.

For characterization of the product, the crude solution was evaporated completely to afford a crystallizing oil. Crystallization from hexane gave (*R*)-**4** (0.93 g; yield = 36%; ee >98%; conversion of (*R*)-**6** = 84%): $[\alpha]^{20}_D$ −12.6 ± 0.3. These data correspond to those in the literature.[7,8]

Alcohol (*R*)-4 via Enantioselective Enzymatic Transesterification. To a solution of racemic **6** (50 mg; 0.2 mmol) in hexane (5 mL), which contained *n*-butanol (55 mg; 0.7 mmol), and 50 mg of distilled water, was added 100 mg of PLAP. After 24-hour heating at 38 °C, 86% conversion of the (*R*)-**6** (according to chiral GC) was attained.

Alcohol (*R*)-4 (Preparative Synthesis). Into a mixture of 0.1 M phosphate buffer, pH 7 (1 L) and DMF (40 mL) were added racemic **6** (51.8 g; 0.21 mol) and the 3.5 g of PLAP. The mixture was heated at 38° for over 6 h, and 20% NaOH solution (∼14 g) was added dropwise for 35 min to adjust the pH from 6.0 to 6.97. After the addition of more PLAP (1.0 g) the heating was continued for 8 h. Extraction with toluene (2 × 200 mL) at 38 °C, washing with brine (200 mL), and removal of solvent at 80 °C in vacuo, gave 50.2 g of a colorless crystallizing oil with an (*R*)-**4** content of 36%, according to chiral GC (yield of racemic **6** = 42%, selectivity of the (*R*)-**6** to (*R*)-**4** transformation = 84%). This mixture was used in the next stage without any additional treatment.

Bromoacetate (*R*)-8b ((*R*)-1,1,1-Trichloro-4-methyl-3-penten-2-yl 2-Bromoacetate). The reaction product (130 g) after the enzymatic hydrolysis of racemic **6** (150 g; 0.61 mol) with an (*R*)-**4** content of 38.2% (50 g; 0.24 mol) was used as starting material.

To a heated (65 °C) solution of the enzymatic reaction product and DMF (28 mL) in toluene (175 mL), was introduced a solution of bromoacetyl bromide (74.5 g; 0.37 mol) in toluene (70 mL) dropwise over 2.3 h, with vigorous stirring. After additional heating for 1.5 h, the reaction product was cooled to 25 °C, and the amorphous residue was coagulated with silica gel (0.040−0.063 mm). After filtration, the solvent was removed at 60 °C under reduced pressure, and the remaining colored oil (162 g) was distilled to give two fractions. The first (84.7 g), with a bp 99−128 °C/8 mbar, contained mainly the enantiomers of **6** (total content = 80%, *S*/*R*-ratio = 75:25) along with the desired product, (*R*)-**8b** (14%), and small quantities of side products. The second fraction (60.5 g), with a bp 128−131 °C/8 mbar was the desired product, in the form of a colorless oil with an (*R*)-**8b** content of 93% and an excess of *R*-enantiomer >98%. This was used in the next stage without additional purification. The first fraction was directed to the hydrolysis stage for recovery of the alcohol, **4**. The selectivity of the transformation of (*R*)-**6** to (*R*)-**8b** was 75%.

Repeated distillation afforded a sample for analysis, (*R*)-**8b** (purity = 97%; ee > 98%): $C_8H_{10}O_2BrCl_3$; MW = 324.4; bp = 135°−136 °C/10 mbar, $[\alpha]^{20}_D$ +7.2 ± 0.6; ^{1}H NMR ($CDCl_3$, ppm) δ 1.84 (d, J = 1 Hz, 3H); 1.87 (d, J = 1 Hz, 3H); 3.92 (dd, J = 1.3 Hz, 2H); 5.35 (dm, J = 9.3 Hz, 1H), 6.05 (d, J = 9.3 Hz, 1H); MS m/z 324 and 326 (M^+).

Chloroacetate 8a (1,1,1-Trichloro-4-methyl-3-penten-2-yl 2-Chloroacetate). The chloroacetylation of **4** was carried out on the racemic sample according to the same procedure as for the bromoacetate but using excess DMF and chloroacetyl chloride instead of bromoacetyl bromide (molar ratio **4**/chloroacetyl chloride/DMF = 1:2.0:3.5) and with prolonged (9 h) heating at 110 °C. The above-described treatment and distillation yielded the desired racemic product, **8a**, (yield 65%; purity = 95%): $C_8H_{10}O_2Cl_4$; MW = 279.97; bp = 126−128 °C/10 mbar; ^{1}H NMR ($CDCl_3$, ppm) δ 1.84 (d, 3H); 1.87 (d, 3H); 4.16 (d.d., 2H), 5.35 (d, 1H); 6.08 (d, 1H); MS m/z 280 and 282 (M^+).

Alcohol (*S*)-4. To the solution of crude (*S*)-**6** (49 g; 0.2 mol) in methanol (200 mL), obtained in the previous experiment, was added 40 mL of 32% HCl all at once. The mixture was heated under reflux for 1.5 h until 98% conversion of **6** was achieved (GC monitoring). The reaction product was cooled to 25 °C and diluted with 300 mL water to precipitate the desired product, which was filtered and dried in air to give **4** (38.2 g; yield 93%; purity >98%), enriched with the *S*-enantiomer.

Diazoacetate (*R*)-2 ((*R*)-1,1,1-Trichloro-4-methyl-3-penten-2-yl Diazoacetate) via Bromoacetate (*R*)-8b. To a mixture of HMTA (7.1 g; 0.05 mol) and dibromomethane (15 mL) was added a mixture of (*R*)-**8b** (16.4 g; 0.05 mol) with dibromomethane (5 mL), all at once. After heating at 65 °C for 25 min, the reaction mixture was converted into a viscous, colorless oil. The pressure of the reaction system was then gradually reduced to 10 mm, and the solvent was evaporated, to yield the quaternary ammonium salt as a white amorphous solid.

Normal pressure was restored, and a solution of 32% HCl (15 mL) in methanol (50 mL) was introduced into the flask all at once. The heating at 65 °C was continued for 10 min. After 5 min, the residue of the quaternary salt completely dissolved, and ammonium salts precipitated, with the simultaneous commencement of dimethoxymethane evolution. To

promote the dimethoxymethane evolution, the pressure was reduced to 300 mm, and the reaction mixture was maintained under these conditions for 15 min. The pressure was restored to normal, and more methanol (50 mL) was added. The reaction mixture was cooled to 5 °C and stirred for an additional 15 min to complete precipitation of the ammonium salts. The reaction mixture was filtered, and the precipitate was washed with cold methanol (15 mL) and discarded.

The filtrates were combined and mixed with citrate buffer of pH 3 (75 mL), then the methanol was evaporated at 65 °C/40 mm. To the clear, colorless solution of (*R*)-1,1,1-trichloro-4-methyl-3-penten-2-yl 2-aminoacetate hydrochloride (glycinate (*R*)-**7**) was added dibromomethane (100 mL), and the reaction mixture was cooled to 0−2 °C. A solution of sodium nitrite (3.66 g; 0.053 mol) in water (6 mL) was introduced over 1.5 h at 2−5 °C. After the addition was complete, the reaction mixture was stirred at 2 °C for an additional 10 min, and the temperature was allowed to rise to 15 °C. The lower, yellow organic layer was separated, and the upper, aqueous layer was extracted with dibromomethane. The organic extracts were combined, neutralized with 10% sodium bicarbonate solution, and dried with anhydrous sodium sulfate, to give a clear yellow solution (272 g) of the desired product with an (*R*)-**2** content of 3.7% (according to calibrated HPLC), which corresponds to a 76% yield from the starting (*R*)-**8b**. The solution was used in the next stage without purification.

A sample of the (*R*)-**2** (purity = 96% according to HPLC): $[\alpha]^{20}_D$ +67.4 ± 0.5 [lit. data:[7] $[\alpha]_D$ +63.0 (*c* 1; $CHCl_3$)], was isolated by column chromatography on silica gel (eluent: hexanes/ethyl acetate, 98/2 (v/v)). **CAUTION**: The pure diazoacetate can explode in the presence of strong mineral acids or upon heating above 150 °C.

Diazoacetate (*R*)-2 via Chloroacetate (*R*)-8a. A quaternary ammonium salt of (*R*)-**8a** with HMTA, in the form of a white amorphous solid, was prepared as described in the previous experiment, from HMTA (3.37 g; 0.024 mol), chloroacetate, (*R*)-**8a**, (5.6 g; 0.02 mol) and dibromomethane (10 mL). Treatment of the salt with a solution of 32% HCl (6.8 g; 5.9 mL; 0.06 mol) in methanol (20 mL) at 65 °C, followed by cooling and filtration, gave 3.14 g of ammonium chloride, which was discarded. The filtrate was evaporated; extraction of the residue with hot hexane (2 × 20 mL) separated a crude glycinate (*R*)-**7**. The hexane extracts were evaporated to give 2.67 g of a colorless oil, which contained 75% of the starting (*R*)-**8a** (conversion = 66%).

The crude glycinate, (*R*)-**7**, was dissolved in citrate buffer of pH 3 (75 mL), and the rest of the methanol was evaporated at 65 °C/40 mm. Diazotization, in dibromomethane, with sodium nitrite solution (1.1 g; 0.016 mol) at 0−5 °C and pH 2−3, which was maintained by the occasional addition of 5% sulfuric acid, led to a dibromomethane solution of (*R*)-**2**. Evaporation of the solution furnished the crude (*R*)-**2**, as a yellow viscous oil (2.47 g; content = 60% (according to HPLC); yield = 30% of starting (*R*)-**8a**).

Glycinate (*R*)-7 via Azidoacetate (*R*)-9 ((*R*)-1,1,1-Trichloro-4-methyl-3-penten-2-yl 2-Azidoacetate). A mixture of (*R*)-**8b** (5.2 g; 0.016 mol), sodium azide (2.05 g; 0.032 mol), tetrabutylammonium bromide (0.075 g; 0.23 mmol) and toluene (25 mL) was heated at 90 °C for 10 h. The reaction product was filtered and evaporated to give 5.19 g of a pink solid, which was decolorized by treatment with silica gel in hexane solution. The removal of solvents afforded (*R*)-**9** (3.9 g; yield = 78%; purity = 94%; ee >98%): $C_8H_{10}N_3O_2Cl_3$; MW = 286.54; $[\alpha]^{20}_D$ −18.7 ± 0.5; ^{1}H NMR ($CDCl_3$, ppm) δ 1.85 (d, J = 1.3 Hz, 3H); 1.89 (d, J = 1.3 Hz, 3H); 3.97 (dd, J = 15 Hz, 2H), 5.34 (dm, J = 9.3 Hz, 1H); 6.11 (d, J = 9.3 Hz, 1H).

A solution of (*R*)-**9** (10.0 g; 0.035 mol) in absolute ethanol (50 mL) was hydrogenated in the presence of 0.24 g of Lindlar catalyst at 20 °C and normal pressure for 10 h. The reaction mixture was filtered and treated with a solution of 32% HCl (30 mL) in 50 mL of ethanol. The clear solution was evaporated to dryness to give 14 g of crude (*R*)-**7**, as a white solid.

Several crystallizations from water furnished a sample of the pure (*R*)-**7**: $C_8H_{13}NO_2Cl_4$; MW = 297.0; mp = 174−176 °C (with decomposition); ^{1}H NMR (DMSO-d_6, ppm) δ 1.92 (s, 3H); 1.95 (s, 3H); 4.07 (brs., 2H), 5.44 (dm, J = 9.3 Hz, 1H); 6.19 (d, J = 9.3 Hz, 1H); 8.7 (brs, 3H).

Bicyclic Lactone (1*R*,4*R*,5*S*)-3 ((1*R*,4*R*,5*S*)-6,6-Dimethyl-4-trichloromethyl-3-oxobicyclo[3.2.0]hexane-2-one). To a suspension of copper(II) perchlorate, hexahydrate (0.143 g; 0.385 mmol; 0.5 mol %) in dibromomethane (200 mL) refluxing at 98 °C was added 560 g of a solution of the crude product, having an (*R*)-**2** content of 3.7% (21 g; 0.0775 mol), and the mixture was held for 5 h with vigorous stirring, dibromomethane (450 g) being distilled off. The heating was continued for an additional 0.5 h, and the reaction product was allowed to cool to 40 °C. The microcrystalline residue was filtered off, and the filtrate was evaporated to dryness to give 31.5 g of a clear brown oil. The crude product was purified by flash column chromatography on a column with an internal diameter of 40 mm packed with 150 g of silica gel SG 60 (0.063−0.200 mm). Eluting with a mixture of hexanes−ethyl acetate (95/5 v/v) gave 20.7 g of a crude product, which was finally purified by "bulb-to-bulb" distillation to yield (1*R*,4*R*,5*S*)-**3** (12.1 g; yield = 44% (based on (*R*)-**8b**); purity = 90%), which was used in the next stage without additional purification.

Crystallization from hexane gave a pure sample with >99% purity (ee >98%): bp = 100−118 °C/0.75 mbar; mp = 77−78 °C; $[\alpha]^{20}_D$ −27.0 ± 0.7 [lit. data:[7] mp = 74−76 °C (hexane), $[\alpha]_D$ −28.27 (*c* 1; $CHCl_3$)].

Acid (1*R*,*cis*)-1a ((1*R*,*cis*)-2-(2,2-Dichloroethenyl)-3,3-dimethylcyclopropane Carboxylic Acid). To a suspension of zinc powder (8.0 g; 0.12 mol) in 55 mL methanol heated under reflux, was added a solution of (1*R*,4*R*,5*S*)-**3** (22.4 g; 0.091 mol) in methanol, dropwise over 2 h. The heating was continued an additional hour, and the reaction mixture was allowed to cool to 40 °C. The hot mixture was decanted from the residue of the zinc, and the solvent was evaporated to dryness to give 32.73 g of white solid. The residue was partitioned between ethyl acetate and 5% HCl. The organic layer was separated, and the aqueous layer, after extraction with ethyl acetate, was discarded. The organic extracts were

combined, washed with 5% HCl, dried with anhydrous sodium sulfate, and evaporated to dryness to give (1*R*,*cis*)-**1a**, as a clear crystallizing oil (19.6 g; yield = 93%; purity = 93%). Crystallization from hexane gave a product with >99% purity (ee >98%), as colorless prisms: $C_8H_{10}O_2Cl_2$; MW = 209.07; mp = 90.5−91.5 °C, $[\alpha]^{20}_D$ +33.4 ± 0.5 (lit. data:[7] mp = 90−91 °C, $[\alpha]^{20}_D$ +28.9 (*c* 1; $CHCl_3$)); ^{1}H NMR ($CDCl_3$, ppm) δ 1.27 (s, 3H); 1.28 (s, 3H); 1.85 (d, *J* = 8.5 Hz, 1H), 2.11 (t, *J* = 8.5 Hz, 1H); 6.21 (d, *J* = 8.5 Hz, 1H); MS *m*/*z* 208, 210 and 212 (M^+).

Acid (1*R*,*cis*)-1b ((1*R*,*cis*)-2-(2,2-Dibromoethenyl)-3,3-dimethylcyclopropane Carboxylic Acid). To a solution of aluminum bromide (30.2 g; 0.113 mol) in dibromomethane (50 mL) was added a solution of (1*R*,*cis*)-**1a** (17.0 g; 0.0756 mol) in dibromomethane (35 mL) dropwise over 1 h under ice−water cooling. Ar was introduced into the deep purple mixture for 15 min. The pressure of the reaction system was then gradually reduced to 37 mm under Ar bubbling, and the mixture was kept at 4 °C for 2.5 h. The reaction product was poured on ice and treated with 32% HCl and ethyl acetate. The aqueous layer was separated, extracted with ethyl acetate, and discarded. The organic extracts were combined, washed with brine, dried with anhydrous sodium sulfate, and evaporated to give 26.4 g of a black crystallizing oil, which was crystallized twice from hexane to give the desired product (15.4 g; yield = 68%; purity = 93%; ee >98%): $C_8H_{10}O_2Br_2$; MW = 297.97; mp = 124−126 °C, $[\alpha]^{20}_D$ +10.0 ± 0.5; ^{1}H NMR ($CDCl_3$, ppm) δ 1.28 (s, 3H); 1.30 (s, 3H); 1.87 (d, *J* = 8.5 Hz, 2H), 2.05 (t, *J* = 8.5 Hz, 1H); 6.74 (d, *J* = 8.5 Hz, 1H); MS *m*/*z* 296, 298, and 300 [M^+].

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