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TETRAHEDRON: *ASYMMETRY*

Synthesis of (1*R*,*cis*,α*S*)-cypermethrine via lipase catalyzed kinetic resolution of racemic *m*-phenoxybenzaldehyde cyanohydrin acetate[1]

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Abstract

A technical scale preparation of optically active (1*R*,*cis*,α*S*)-cypermethrine **4** from racemic *m*-phenoxybenzaldehyde cyanohydrin acetate (*RS*)-**1** and (1*R*,*cis*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid chloride (1*R*,*cis*)-**3** is described. Key steps of the new procedure are a lipase catalyzed enantioselective transesterification of (*RS*)-**1** with *n*-butanol and direct acylation of the mixture of (*R*)-**1** and (*S*)-cyanohydrin (*S*)-**2** with (1*R*,*cis*)-**3** to give enantiomerically pure (1*R*,*cis*,α*S*)-**4**. The unchanged (*R*)-**1** is removed from (1*R*,*cis*,α*S*)-**4** by distillation, and is racemized with triethylamine to give (*RS*)-**1** which is returned to the process. The total yield of (1*R*,*cis*,α*S*)-**4** referred to (*RS*)-**1** is 80%.

1. Introduction

Plant extracts of *Chrysanthemum cinerariefolium* are known to have strong insecticidal activities.[2] For a long time it has been known that pyrethrine I is the most active compound in these plant extracts.[2b] A disadvantage of pyrethrine I for practical applications as an insecticide is its relatively low stability.[3a] Specific variations of both the alcohol and the acid component gave photostable and highly efficient derivatives.[3b] Previous investigations showed strongly increased stability in the presence of cyano substituents in the α-position of the alcohols. Cypermethrine is one of the most important insecticides of this type.[2]

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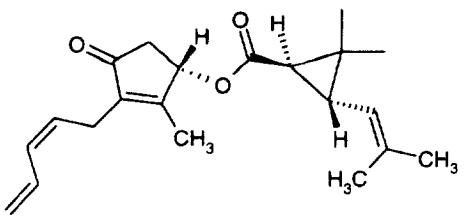
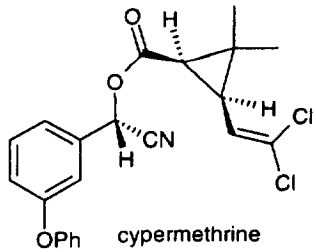


pyrethrine I



cypermethrine

From the eight possible stereoisomers, cypermethrine which has the (1*R*,*cis*,α*S*)-configuration, has by far the highest biological activity.[2a,b,4] Many efforts for the stereoselective syntheses of cypermethrine have therefore been made.

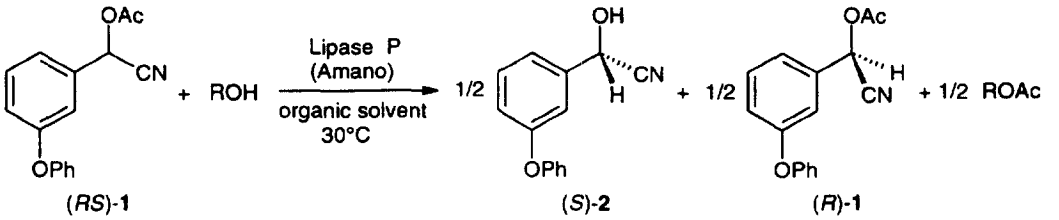
For the stereoselective preparation of (*S*)-*m*-phenoxybenzaldehyde cyanohydrin, the alcohol component of cypermethrine, many procedures have been developed. *m*-Phenoxybenzaldehyde cyanohydrin is accessible, for example, by enantioselective addition of HCN to *m*-phenoxybenzaldehyde catalyzed by cyclic dipeptides.[5] Further methods are the (*S*)-oxynitrilase catalyzed addition of HCN to the aldehyde[6] and the enantioselective cleavage of racemic *m*-phenoxybenzaldehyde cyanohydrin with (*R*)-oxynitrilase,[7] respectively. Lipase catalyzed preparations applied are the enantioselective transesterification of racemic cyanohydrin esters[8] and the esterification of racemic cyanohydrins[8a,9] as well as the enantioselective transesterification of racemic cyanohydrin esters using primary alcohols.[8a,10] Kinetic resolutions of racemates for technical applications require in any case racemization of the undesired stereoisomer. This could be realized by enantioselective acetylation of racemic cyanohydrins with isopropenyl acetate in an organic solvent and in the presence of a basic ion exchange resin that is sufficiently basic to cause racemization of the cyanohydrin enantiomers but not the optically active cyanohydrin acetate formed.[9a] Unfortunately, this procedure cannot be applied to the preparation of enantiomerically pure cyanohydrins.

In the present publication we report on the preparation of (1*R*,*cis*,α*S*)-cypermethrine **4** for technical scale application involving a lipase catalyzed transesterification of the racemic acetate with high boiling alcohols as the key reaction.

2. Enantioselective transesterification of acetylated (*RS*)-*m*-phenoxybenzaldehyde cyanohydrin (*RS*)-1

Former investigations of lipase catalyzed transesterification of racemic cyanohydrin esters have demonstrated that lipase P from Amano gave the best results using acetylated aromatic cyanohydrins.[8a] The reactions were carried out with the primary alcohols *n*-butanol or *n*-octanol in *n*-hexane and dichloromethane, respectively, as solvents. We have now optimized the parameters for the lipase catalyzed transesterification of (*RS*)-**1** to give (*S*)-*m*-phenoxybenzaldehyde cyanohydrin **2** as outlined in Scheme 1.

Preliminary investigations of the application of lipase P have shown that the reaction times could be significantly shortened by enzyme immobilization on Celite.[11] Furthermore, the phosphate buffer (0.05 M, pH 7)[11] used for the treatment of Celite was replaced by sodium acetate buffer (0.01 M, pH 4.5) resulting in enhanced enantiomeric excesses. Finally, the amount of the primary alcohol has been found to influence both reaction time and *ee* values. While a molar ratio of alcohol: (*RS*)-**1**=1:1 resulted in short reaction times and high *ee* values, a molar ratio of alcohol: (*RS*)-**1**=0.5:1 decelerated drastically the lipase catalyzed transesterification, and lower enantiomeric excesses were obtained (Table 1).



Scheme 1.

Table 1
Lipase P catalyzed transesterification of (*RS*)-**1** (0.50 mmol) with *n*-octanol in *n*-hexane at 30°C

Octanol (mmol)	Lipase P	React. time (h)	Conversion (%)[a]	(*S*)-**2** *ee* (%)[b]
0.50	native	52	46	91
0.50	immobilized[c]	11	48	95
0.25	immobilized[c]	38	43	63
0.50	immobilized[d]	4	48	98
0.25	immobilized[d]	46	44	92

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by gas chromatography after derivatization with (*R*)-α-methoxy-α-trifluoromethylphenylacetic acid chloride according to ref.[12] [c] Treatment of celite with phosphate buffer, pH 7. [d] Treatment of celite with sodium acetate buffer, pH 4.5.

Table 2
Application of different primary alcohols and solvents, respectively, in the lipase catalyzed transesterification of (*RS*)-**1** (7.5 mmol) to (*S*)-*m*-phenoxybenzaldehyde cyanohydrin (*S*)-**2** at 30°C

Solvent	ROH[a]	React.-time (h)	Conversion (%)[b]	(*S*)-**2** *ee* (%)[c]	(*R*)-**1** *ee* (%)[c]
n-hexane	*n*-octanol	16	47	96	93
n-hexane	*n*-butanol	6	49	>99	97
CH_2Cl_2	*n*-butanol	6	30	>99	43

[a] Addition in equimolar amounts (7.5 mmol) referred to (*RS*)-**1**. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by gas chromatography.

Considering these results with respect to a technical application, we have increased the batch size of (*RS*)-**1** from 0.5 mmol (Table 1) to 7.5 mmol and have varied the organic solvent and the primary alcohol as listed in Table 2.

As can be seen from Table 2, (*S*)-*m*-phenoxybenzaldehyde cyanohydrin (*S*)-**2** was obtained in all cases with high enantiomeric excess. With respect to reaction times, butanol is more advantageous than octanol, and moreover, the excess of butanol and butyl acetate can easily be removed in vacuo. Since (*S*)-**2** subsequently should be acylated directly from the reaction mixture without further purification, it is important to remove the unreacted alcohol before acylation. The transesterification proceeded faster in *n*-hexane than in dichloromethane resulting in 49% conversion in 6 hours reaction time compared with only 30% in dichloromethane (Table 2).

The lipase can be applied for several reaction cycles. Thereby the enzymatic activity of the lipase decreases continuously with the number of cycles. The enantiomeric excess of (*S*)-**2**, however, is not influenced by reduced activity as shown in Table 3, summarizing the results of four reaction cycles.

The disadvantage of kinetic resolutions of racemates generally is a maximum yield of the desired

Table 3
Multiple application of lipase P in the transesterification of (*RS*)-**1** with butanol in *n*-hexane at 30°C

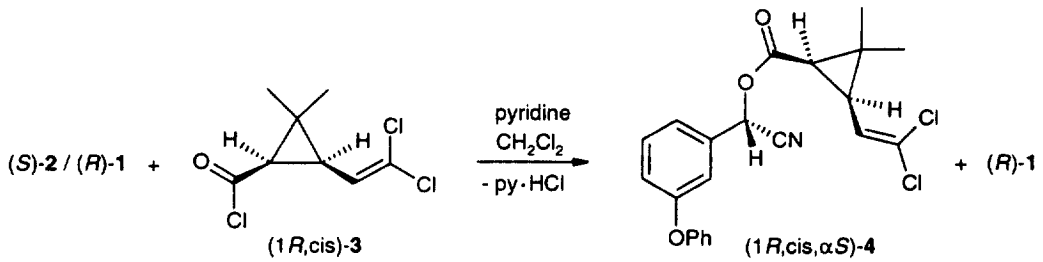
Cycle	React.-time (h)	Conversion (%)[a]	(*S*)-**2** *ee* (%)	(*R*)-**1** *ee* (%)
1	6	48.5	98	94
2	9	45.4	>99	83
3	12	43.6	>99	77
4	15	39.7	>99	66

[a] Determined from *ee*-values of (*R*)-**1**.

product of only 50%. For technical applications it is therefore necessary to racemize the undesired enantiomer (*R*)-**1** and to return the resulting racemic (*RS*)-**1** to the process.

3. Acylation of (*S*)-2 with the cyclopropanecarboxylic acid derivative (1*R*,*cis*)-3 to (1*R*,*cis*,α*S*)-cypermethrine 4 and racemization of (*R*)-1

(*R*)-Cyanohydrin acetate (*R*)-**1** could be separated from (*S*)-**2** only by a time-consuming chromatography.[8b] In order to avoid this difficult separation, we have directly acylated the mixture of (*S*)-**2**/(*R*)-**1** with (1*R*,*cis*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid chloride (1*R*,*cis*)-**3**[13] to give a mixture of (1*R*,*cis*,α*S*)-**4** and (*R*)-**1** as outlined in Scheme 2.



Scheme 2.

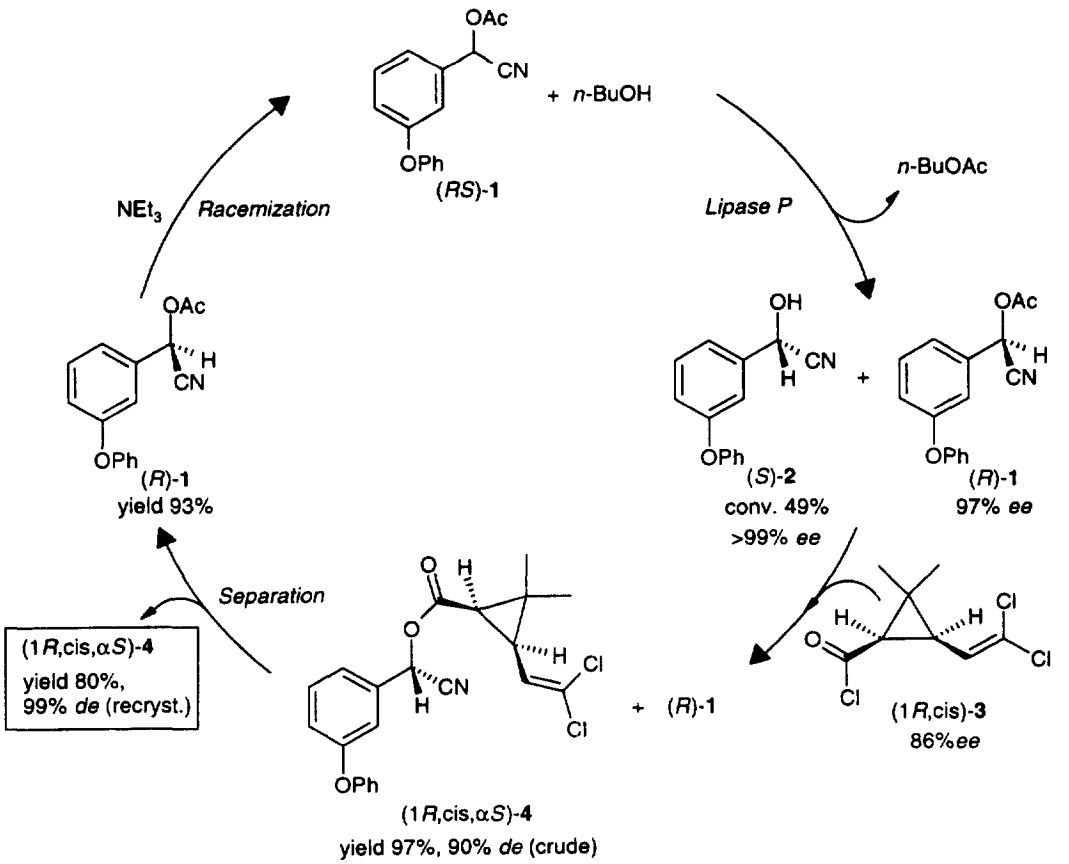
The salts formed during the reaction were filtered off. Unchanged (*R*)-**1** could now be separated by bulb-to-bulb distillation. The residue consists of crude (1*R*,*cis*,α*S*)-cypermethrine **4**. After recrystallization from petroleum ether, pure (1*R*,*cis*,α*S*)-**4** (99% *de*) was obtained in 82% yield based on (*S*)-**2**.

The distilled (*R*)-**1** was racemized based on a literature-known procedure.[8b] In contrast to the described method,[8b] equimolar amounts of triethylamine were used, and the reaction mixture was heated in toluene until completion of the reaction. Based on the reaction sequence outlined in Schemes 1 and 2, (*RS*)-**1** could be reisolated in 91% yield and returned to the process.

4. Summary

The reactions described allow a continuous process for the preparation of (1*R*,*cis*,α*S*)-cypermethrine **4** from racemic (*RS*)-**1**, involving four reaction steps as illustrated in Scheme 3.

The lipase P catalyzed transesterification of racemic *m*-phenoxybenzaldehyde cyanohydrin acetate (*RS*)-**1** with butanol in *n*-hexane gave enantiomerically pure (*S*)-*m*-phenoxybenzaldehyde cyanohydrin (*S*)-**2** in a maximum yield of nearly 50% and >99% *ee* (step 1). After removal of the excess of butanol and



Scheme 3.

butyl acetate, the mixture of (*S*)-**2** and (*R*)-**1** was acylated directly with (1*R*,*cis*)-**3** to give cypermethrine (1*R*,*cis*,α*S*)-**4** and unchanged (*R*)-**1** (step 2). Compound (*R*)-**1** was separated from (1*R*,*cis*,α*S*)-**4** by distillation (step 3) and racemized with triethylamine to (*RS*)-**1** (step 4). By this procedure (1*R*,*cis*,α*S*)-**4** could be obtained in high optical yield (99% *de*) and a total chemical yield of 80% referred to (*RS*)-**1**.

5. Experimental

5.1. Materials and methods

Lipase P (30 units/mg) was purchased from Amano, Celite 503 from Roth and (1*R*,*cis*)-**3** from FMC Corp. Racemic *m*-phenoxybenzaldehyde cyanohydrin acetate (*RS*)-**1** was prepared according to a literature method.[13] Melting points were determined on a Büchi SMP-20 and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC 250 F (250 MHz) and ARX 500 (500 MHz) with TMS as an internal standard. Optical rotations were determined in a Perkin–Elmer polarimeter 241 LC. GC for determination of enantiomeric and diastereomeric excess: (a) Hewlett–Packard 5890 Series II with FID, 0.45 bar hydrogen, column 30 m×0.32 mm, phase OV 1701; (b) Hewlett–Packard 6890 Series with FID, 0.9 bar hydrogen, column 30 m×0.32 mm, phase Chiraldex B-TA (ITC). GC–MS was performed on a

Varian Star 3400 CX (carrier gas helium) and Varian Saturn 4 D GC/MS/MS, column 30 m×0.25 mm, phase DB-5MS.

5.2. *Enantioselective transesterification of* (RS)-**1**; *general procedure*

Immobilized lipase P [2 g Celite was washed with 0.01 M sodium acetate buffer (pH 4.5) and added to 0.5 g lipase in 10 ml 0.01 M sodium acetate buffer (pH 4.5). This mixture was dried at room temperature[11]] was added to a solution of (*RS*)-**1** (2.0 g, 7.48 mmol) in 25 ml of organic solvent and the respective alcohol (7.45 mmol). The reaction mixture was stirred at 30°C for the times given in Tables 1 and 2. Then the lipase was filtered off, and the filtrate was concentrated *in vacuo* to remove the solvent, alcohol and acetylated alcohol. The residue was used for the determination of *ee* values.

5.3. *Determination of enantiomeric excesses*

Pyridine (10 μl) in 0.5 ml dichloromethane and chloroacetic anhydride (65 mg) were added to 10 mg of the crude mixture (*S*)-**2**/(*R*)-**1**. After heating to 60°C for 4 h, the reaction mixture was filtered through a silica gel column (3×0.5 cm) with ca 3 ml dichloromethane. The enantiomeric excess of (*R*)-**1** and chloroacetylated (*S*)-**2** was determined by GC directly from the filtrate. The enantiomers were assigned by coinjection of the racemate. [2-Chloroacetyloxy-2-(3′-phenoxy)phenylacetonitrile: ^{1}H NMR ($CDCl_3$) δ 4.14 and 4.15 (2s, 2H, CH_2Cl), 6.41 (s, 1H, CH), 7.02–7.41 (m, 9H, Ph); GC–MS: *m/z* (%): 301 (52) [M^+], 225 (100), 206 (9), 197 (36), 181 (32), 169 (10), 152 (14), 141 (11)].

5.4. *Acylation of* (S)-**2** *using* (*1*R,cis)-**3**

To a solution of the mixture (*S*)-**2**/(*R*)-**1** in 25 ml of dichloromethane (1*R*,*cis*)-**3**[13] (86% *ee*, 0.92 g, 4.04 mmol) was added followed by pyridine (0.33 ml, 4.1 mmol) under ice cooling. After stirring for 6 h at room temperature, the reaction mixture was filtered through a silica gel column (4×5 cm) with dichloromethane. The filtrate was concentrated and distilled bulb-to-bulb (130°C/0.001 torr) to give 0.95 g (93%) (*R*)-**1**. The residue was recrystallized from petroleum ether yielding 1.25 g (82%) (1*R*,*cis*,α*S*)-**4**, mp 53–55°C; 99% *de*, $[\alpha]_D^{20}$ = +29.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.19 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.90 (d, *J*=8.5 Hz, 1H, CHCO), 2.15 (dd, 1H, C*H*CH=), 6.18 (d, *J*=8.8 Hz, 1H, CH=), 6.39 (s, 1H, CHCN), 7.02–7.42 (m, 9H, Ph). Anal. calcd for $C_{22}H_{19}Cl_2NO_3$: C, 63.47; H, 4.60; N, 3.36; Cl, 17.03. Found: C, 63.45; H, 4.60; N, 3.31; Cl, 16.75. The data correspond with those in the literature.[13]

5.5. *Racemization of* (R)-**1** *according to Mitsuda et al.*[8b]

A solution of (*R*)-**1** (0.95 g, 3.54 mmol) and triethylamine (0.5 ml, 3.6 mmol) in 10 ml toluene was heated to 80°C for 3 h (control by optical rotation). Then the reaction mixture was concentrated and distilled *in vacuo* to give 0.93 g (98%) (*RS*)-**1**, bp 150°C/0.005 torr.

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