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Lipase-catalyzed kinetic resolution of 3-chloro-2-hydroxyalkanoates. Its application for the synthesis of (−)-disparlure

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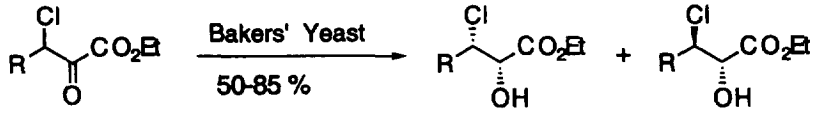
Abstract: Reduction of 3-chloro-2-oxoalkanoates **1** with $NaBH_4$ gave predominantly *syn*-3-chloro-2-hydroxyalkanoates **2** (*syn*/*anti*=91/9–99/1) in 50–97% yields. Resolution of *syn*-**2** by lipase-catalyzed transesterification gave (2*S*,3*S*)-**2** and (2*R*,3*R*)-2-acetoxy-3-chloroalkanoates (2*R*,3*R*)-**3**. Total synthesis of (−)-disparlure, the pheromone of the gypsy moth was established from (2*S*,3*S*)-**2g** via 4 steps in 34.9% overall yield.

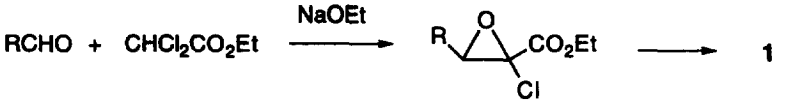
Recently we have reported that the reduction of 3-chloro-2-oxoalkanoates **1** with baker's yeast gave optically active 3-chloro-2-hydroxyalkanoates **2** (*syn*-(2*S*,3*S*)/*anti*-(2*S*,3*R*)=48/52–10/90).[1]



1 *syn*-**2** >95 % ee *anti*-**2** >95 % ee

In this paper we wish to report the synthesis of (2*S*,3*S*)-3-chloro-2-hydroxyalkanoates ((2*S*,3*S*)-**2**) and (2*R*,3*R*)-2-acetoxy-3-chloroalkanoates ((2*R*,3*R*)-**3**) with the combination of the reduction of 3-chloro-2-oxoalkanoates **1** with $NaBH_4$ and lipase-catalyzed kinetic resolution of the products. Furthermore, the total synthesis of (−)-disparlure[2] from a resolved product, ethyl 2-hydroxy-3-chlorotridecanoate ((2*S*,3*S*)-**2g**) is described.

The starting material **1** can be easily obtained by Darzens' type condensation of aldehydes and dichloroacetate[2f] and the following thermal rearrangement of 2-chloro-2,3-epoxyalkanoates to **1** promoted with alumina which has been recently developed by us.[3]



First, the reduction of several 3-chloro-2-oxoalkanoates **1** with $NaBH_4$ was studied, and the results are tabulated in Table 1. The reduction afforded predominantly *syn*-**2** in 50–97% yields with high stereoselectivity (*syn*/*anti*=91/9–99/1).

Lipase-catalyzed kinetic resolution of these *syn*-**2** was carried out for obtaining enantiomerically pure (2*S*,3*S*)-**2** and (2*R*,3*R*)-**3**, and the result was shown in Table 2. In almost all cases the reactions gave both of hydroxyester **2** and acetoxyester **3** with high enantiomeric excesses. Absolute configuration of (2*S*,3*S*)-**2** was determined by comparison of the sign of the specific rotation in the literature.[1] Enantiomeric excesses were determined by HPLC equipped with a chiral stationary phase. The E

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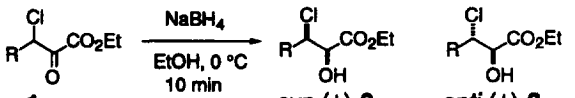
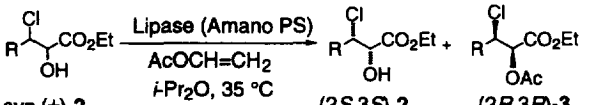
Table 1. Reduction of 3-chloro-2-oxoalkanoates with $NaBH_4$



1 *syn*-(±)-**2** *anti*-(±)-**2**

entry	R	Yield (%)	*syn*/*anti*
a	C_2H_5	85	97/3
b	*n*-C_3H_7	50	99/1
c	*n*-C_4H_9	64	96/4
d	*n*-C_5H_{11}	69	94/6
e	*n*-C_6H_{13}	97	91/9
f	*n*-C_7H_{15}	85	95/5
g	*n*-$C_{10}H_{21}$	92	91/9

Table 2. Lipase-catalyzed kinetic resolution of *syn*-(±)-**2**



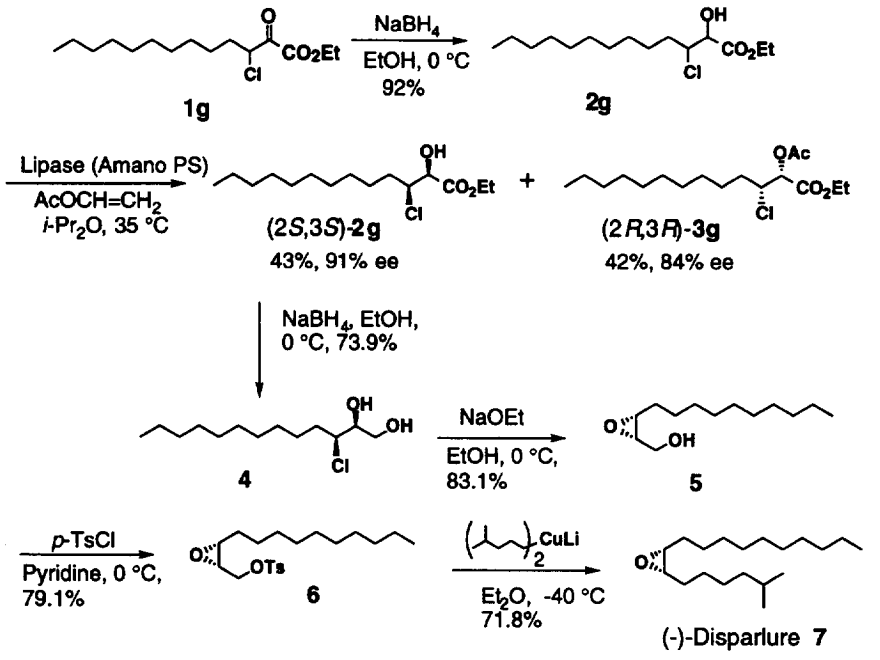
syn-(±)-**2** (2*S*,3*S*)-**2** (2*R*,3*R*)-**3**

entry	R	(2*S*,3*S*)-**2** yield (%)	ee (%)	(2*R*,3*R*)-**3** yield (%)	ee (%)	*E*
a	C_2H_5	17	53	74	30	3
b	*n*-C_3H_7	27	96	59	88	61
c	*n*-C_4H_9	40	98	54	95	180
d	*n*-C_5H_{11}	33	97	44	46	10
e	*n*-C_6H_{13}	41	99	46	78	41
f	*n*-C_7H_{15}	18	95	42	98	371
g	*n*-$C_{10}H_{21}$	43	91	42	84	36

values[4] were calculated although the reaction conditions were not optimized, and tabulated in Table 2. This lipase (Amano PS) seems to be practically suitable for the kinetic resolution of racemic esters **2** because E values[4] in most cases showed more than 36 except those for R=C_2H_5 and *n*-C_5H_{11}. Lipase-catalyzed kinetic resolution of α-hydroxy esters was reported by several groups.[5–9] These reports show that the reaction of (*S*)-isomers proceeds much faster than that of (*R*)-isomers in the acylation of the hydroxy group as well as in the hydrolysis of its acetate. The present kinetic resolution also gives the same result as those of the literatures.[5,6]

The success of the lipase-catalyzed resolution prompted us the total synthesis of (−)-disparlure and the synthetic sequence is shown in Scheme 1. This synthesis was essentially followed by that of (±)-disparlure, which had been reported by ourselves.[2f]

The synthetic scheme is shown in Scheme 1.[2f] Reduction of (2*S*,3*S*)-**2g**, which was obtained by the reduction of **1g** with sodium borohydride and the kinetic resolution of the racemate **2g** by lipase, with sodium borohydride at 0°C gave *syn*-3-chloro-1,2-tridecanediol (**4**) in 73.9% yield. Dehydrochlorination of **4** with sodium ethoxide in ethanol gave *cis*-2,3-epoxy-1-tridecanol (**5**) in 83.1% yield, and the subsequent reaction of **5** with tosyl chloride afforded tosylate **6** in 79.1% yield. Treatment of **6** with lithium bis(4-methylpentyl)cuprate(I)[2e] gave (−)-disparlure **7** in 71.8% yield. Overall yield was 13.8% from **1**.



Scheme 1. Total synthesis of (−)-disparlure.

Experimental

IR spectra were measured as films for oils or KBr method for solids on a Jasco A-102 spectrometer. ^{1}H-NMR spectra were recorded with TMS as an internal standard at 60 MHz on a JEOL JNM-PMX60SI and at 200 MHz on a Varian Gemini 200. ^{13}C-NMR spectra were obtained with $CDCl_3$ as an internal standard at 50 MHz on a Varian Gemini 200. Specific rotations were recorded on a Jasco DIP 370 polarimeter. Enantiomeric excesses were determined by HPLC apparatus (Shimazu LC-9A) fitted with Daicel Chiralcel OB-H (4.6 mmϕ×250 mm). Preparative HPLC was performed on a HITACHI 655 Liquid Chromatography apparatus.

The starting material **1** was prepared by the method similar to that reported previously by us[1] and the yield was improved. Synthesis of **1g** was shown representatively.

Ethyl 2-chloro-2,3-epoxytridecanoate (8)

To a mixture of ethyl dichloroacetate (4.10 g, 26 mmol) and dry ether (80 ml) was slowly added sodium ethoxide (1.89 g, 28 mmol) at 0°C. The mixture was stirred for 30 min, and then undecanal (4.43 g, 26 mmol) was added. After stirred for 30 min, the mixture was heated at reflux temperature for 3 h. Then the mixture was poured into ice water and neutralized with 10% HCl. The organic materials were extracted with ether. The combined extracts were washed with water, dried over $MgSO_4$, and the solvent was evaporated. The residual oil (9.24 g) was distilled, giving 6.461 g (85.7%) of **8**: Bp 220°C/1 mmHg.

Ethyl 3-chloro-2-oxotridecanoate (1g)

A mixture of **8** (9.00 g, 31 mmol), alumina (12 g), and xylene (20 ml) was heated at reflux temperature with stirring for 3 h. After filtration, the solvent was removed with distillation, giving 8.03 g (89.2%) of **1g**.

Reduction of **1** with $NaBH_4$ was representatively shown below.[1,2f]

Ethyl 3-chloro-2-hydroxytridecanoate (2g)[2f]

To a mixture of $NaBH_4$ (126 mg, 3.3 mmol) and dry ethanol (3 ml) was added a solution of **1g** (2.9 g, 10 mmol) in dry ethanol (2 ml) at 0°C. The mixture was stirred for 10 min at 0°C, then poured into ice water and neutralized with 10% HCl. The organic materials were extracted with ethyl acetate. The combined extracts were washed with water and dried over $MgSO_4$. The solvent was removed and the residual oil (3.11 g) was chromatographed on SiO_2 (hexane–ethyl acetate, 20:1), giving 2.68 g (92%) of **2g**: *syn/anti* (91/9)[10] by HPLC [column, YMC-PACK S-5 60A SIL 6 mmϕ×250 mm; eluent, hexane–ethyl acetate (10:1), 1.3 ml/min^{-1}]. Preparative HPLC gave 1.81 g of *syn*-**2g** (Rt=13.5 min) and 270 mg of *anti*-**2g** (Rt=19.4 min).

Lipase-catalyzed kinetic resolution

A mixture of *syn*-**2g** (1.00 g, 3.42 mmol), Lipase (amano-PS, 1.47 g), vinyl acetate (0.888 g, 10.35 mmol), isopropyl ether (5 ml) was stirring for 7 h at 35°C. The reaction was monitored by TLC and continued until the half of the starting material would be consumed. After the reaction mixture was filtered, the solvent of the filtrate was evaporated and the residual oil (1.66 g) was chromatographed on SiO_2 (hexane–ethyl acetate, 50:1), giving 0.481 g (42.2%, 84% ee)[11] of (2*R*,3*R*)-**3g** and 0.434 g (43.4%, 91% ee)[11] of (2*S*,3*S*)-**2g**.

(2S,3S)-3-Chloro-1,2-tridecanediol (4)[2f]

To a mixture of $NaBH_4$ (45 mg, 1.18 mmol) and dry ethanol (3 ml) was added a solution of *syn*-**2g** (316 mg, 1.08 mmol) in dry ethanol (2 ml) at 0°C. The mixture was stirred for 6 h at room temperature, then poured into ice water and neutralized with 10%-HCl. The organic materials were extracted with ethyl acetate. The combined extracts were washed with water and dried over $MgSO_4$. The solvent was removed and the residual oil (295 mg) was chromatographed on SiO_2 (hexane–ethyl acetate, 20:1), giving 200 mg (73.9%) of **4**.

(2S,3S)-2,3-Epoxy-1-tridecanol (5)[2f]

To a mixture of NaOEt (40 mg, 0.6 mmol) and dry ethanol (1 ml) was added a solution of **4** (150 mg, 0.6 mmol) in dry ethanol (1 ml) at 0°C. The mixture was stirred for 6.5 h at 0°C, then poured into water and neutralized with 10% HCl. The organic materials were extracted with ethyl acetate. The combined extracts were washed with water and dried over $MgSO_4$. The solvent was removed and the residual oil (131 mg) was chromatographed on SiO_2 (hexane–ethyl acetate, 10:1), giving 84 mg (65.6%) of **5** ($[\alpha]_D^{25}$ −1.87 (c 1.0, CCl_4)) and recovered 32 mg (21.3%) of **4**. The yield from the consumed **4** is 83.1%.

(2S,3S)-2,3-Epoxytridecyl p-*toluenesulfonate (6)*[2f]

To 151 mg (0.82 mmol) of *p*-toluenesulfonyl chloride was added a solution of **5** (70 mg, 0.32 mmol) in pyridine (2 ml) at 0°C. The mixture was stirred for 12 h at 0°C and then poured into ice water. The organic materials were extracted with ether. The combined extracts were washed with saturated $CuSO_4$, brine, and water, and dried over $MgSO_4$. The solvent was removed and the residual oil (95 mg) was chromatographed on SiO_2 (hexane–ethyl acetate, 50:1), giving 68 mg (56.7%) of **6** and recovered 20 mg (28.6%) of **5**. The yield from the consumed **5** is 79.1%.

(−)-Disparlure (7)

To a mixture of CuI (170 mg, 0.900 mmol) and dry ether (10 ml) was slowly added 3.80 ml (1.80 mmol) of 0.475 M 4-methylpentyllithium in ether at −30°C. After the mixture was stirred for 30 min at −30°C, a solution of **6** (68 mg, 0.18 mmol) in dry ether (4 ml) was added dropwise. The mixture was stirred for 30 min at −30°C, then the ice bath was removed. After saturated NH_4Cl (15 ml) was added, the mixture was stirred for 1 h. The organic materials were extracted with ether. The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed and the residual oil (271 mg) was chromatographed on SiO_2 (hexane–ethyl acetate, 50:1), giving 49 mg of desired product

7 (74% purity). Preparative HPLC gave 15 mg (30% isolated yield; 72% yield by HPLC analysis) of **7**: $[\alpha]_D^{20}$ −0.8±0.4 (c=0.5, CCl_4) (lit.[2e] +0.6±0.2). ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50 MHz) data were identical with those of the literature.[2e]

Acknowledgements

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10. Determination of *syn*- and *anti*-isomer was established by comparison of HPLC and spectral data with those of the literature (ref. 1). *syn*-Isomer eluted faster than the corresponding *anti*-isomer.
11. Enantiomeric excess was determined by HPLC analysis (column: Daicel Chiralcel OB-H (4.6 mm ϕ×250 mm), eluent: hexane/isopropanol (10/1), 0.5 ml/min).

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