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LIPASE-CATALYZED KINETIC RESOLUTION OF METHYL 4-HYDROXY-5-TETRADECYNOATE AND ITS APPLICATION TO A FACILE SYNTHESIS OF JAPANESE BEETLE PHEROMONE

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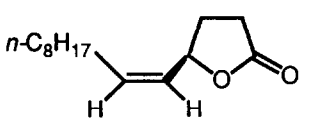
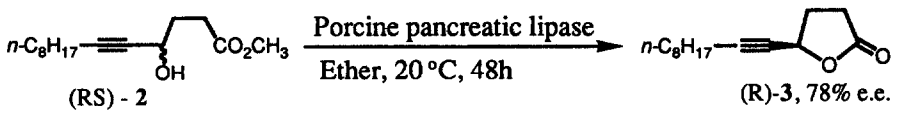
Abstract: A kinetic resolution of methyl 4-hydroxy-5-tetradecynoate is accomplished by a lipase-catalyzed enantioselective acylation in organic solvent. Acylation of methyl 4-hydroxy-5-tetradecynoate with succinic anhydride in an organic solvent yields methyl (R)-4-succinoyloxy-5-tetradecynoate with over 90% e.e.. Furthermore, this optically active diester was converted to (R)-5-(1-decynyl)oxacyclopentan-2-one by lipase-catalyzed enantioselective lactonization which enhanced its e.e. over 99%. The Japanese beetle pheromone (R,Z)-(-)-5-(1-decenyl)oxacyclopentan-2-one is synthesized in one step from this optically active lactone.

The Japanese beetle, *Popillia japonica* Newman, is a devastating pest of a variety of trees and crops in the United States. Tumlinson *et al.* have isolated its pheromone from virgin females and identified it as (R,Z)-(-)-5-(1-decenyl)oxacyclopentan-2-one (**1**). This pheromone has a unique feature whereby a small amount of unnatural (S,Z)-isomer strongly inhibits the male response to it. Indeed, 2% contamination of (S,Z)-isomer causes the mixture to be three times less active than optically pure pheromone.[1] Therefore, extremely high optical purity is essential for the practical use of this pheromone.



(R,Z) - **1**

In the original synthesis of Doolittle *et al.* (R)-(-)-glutamic acid was used as its starting material.[2] Since then, a number of other syntheses have been reported.[3-13] In several of these studies, the acetylenic lactone (R)-**3** has been established as the key-intermediate.[4-9] Recently, a synthesis involving the lipase-catalyzed enantioselective lactonization of (RS)-**2** to yield (R)-**3** as the key-reaction (Scheme 1) was reported by Sugai *et al.*[12]

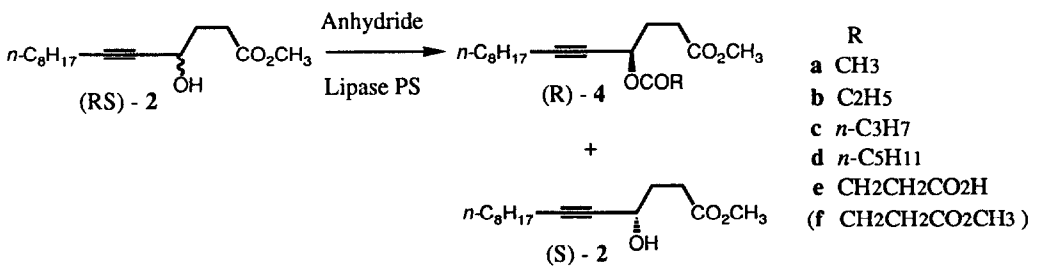


Scheme 1

In Sugai's synthesis, optically active lactone (R)-3 of 97% e.e. was prepared by repetitions of the above reaction . Although this method was very efficient for the optical enrichment of (R)-3, it could not raise the optical purity sufficiently high for practical use because the enantioselectivity of the above reaction was not so high (E=20)[14].

Recently, lipases have been successfully used for resolutions of racemic alcohols, either *via* enantioselective hydrolysis of the corresponding esters in aqueous media or *via* enantioselective esterifications and transesterifications in organic solvents.[15] Reported here in a practical chemicoenzymatic synthesis of Japanese beetle pheromone (R,Z)-1 of over 99% e.e. which involves two lipase-catalyzed crucial steps : enantioselective acylation of γ-hydroxy ester 2 and enantioselective lactonization of γ-acyloxy ester 4 . In addition, it was found that the repetition of the first process, lipase-catalyzed enantioselective acylation, was also successful to obtain (R)-3 over 99% e.e.. The starting material, methyl 4-hydroxy-5-tetradecynoate (2), was easily prepared by the reduction of methyl 4-oxo-5-tetradecynoate[9] with sodium borohydride.[12]

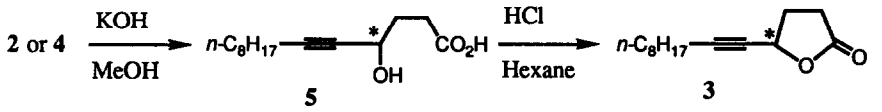
First, several commercially available lipases were surveyed for the acylation of 2 in organic solvent. Lipase PS from *Pseudomonas* sp. (Amano Pharm. Co., Japan) was found to catalyze the enantioselective acylation of 2 with several anhydrides[16] as acylating reagents in diisopropyl ether (Scheme 2). As acyclic acid anhydrides, acetic, propionic, *n*-butyric, and *n*-caproic anhydride were



Scheme 2

examined for acylating activity. Cyclic acid anhydrides such as succinic anhydride, glutaric anhydride, and phthalic anhydride were also examined. The reactions were carried out at 30°C and the conversion was monitored by HPLC. When the conversion reached ca. 50%, the reaction was stopped by the removal of enzyme by filtration. Then, acyloxy esters 4 and unreacted substrate 2

were separated by silica gel column chromatography. To determine the e.e. of **2** and **4**, they were hydrolyzed with KOH in methanol to yield hydroxy acid **5**. After acidification with HCl, **5** was



Scheme 3

Table 1 Acylation of (RS)-2 by Lipase PS

entry[a]	anhydride	conv.(%)[b]	time(h)	product , ee(%)[c]		E[d]
1	acetic	51	18	(R)-**4a** , 85	(S)-**2** , 90	36
2	propionic	51	18	(R)-**4b** , 86	(S)-**2** , 91	40
3	*n*-butyric	50	18	(R)-**4c** , 93	(S)-**2** , 93	94
4	*n*-caproic	50	18	(R)-**4d** , 92	(S)-**2** , 92	79
5	succinic	50	24	(R)-**4e** , 94	(S)-**2** , 94	115

a The substrate at 40mM concentration in diisopropyl ether was stirred with epual weight of enzyme (lipase PS) and equal equiv. of acid anhydride for indicated time at 30°C.

b Determined by HPLC analysis (ODS column , acetonitrile/distilled water (70/30) , 2ml/min, 215nm). In entry 5, the product **4e** was methylated with diazomethane to yield **4f** , which was measured by HPLC.

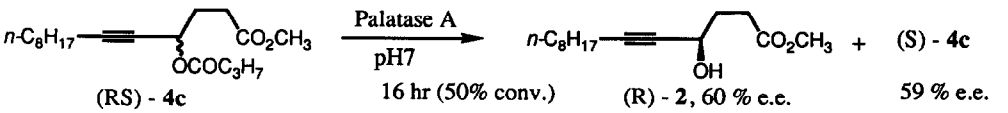
c Determined by HPLC analysis (Chiralcel OD column, hexane/propanol (99/1), 1 ml/min, 215nm) of **3** derived from **4** and **2** .

d E value[14] [E=ln[1-c(1+ee(P))] / ln[1-c(1-ee(P))]] was calculated on the basis of the ee of **4**.

converted to the corresponding lactone **3** by heating in hexane at 60°C (Scheme 3). The e.e. of **3** was determined by HPLC equipped with a column with a chiral stationary phase, Chiralcel OD (Daicel Chemical Co., Japan). The absolute configuration was determined by comparing the HPLC data of **3** with that of (R)-**3** prepared by a previously reported procedure.[9] Results are summarized in Table 1. The best result was obtained, when succinic anhydride was used as the acylating reagent (E=115). On the contrary, glutaric anhydride and phthalic anhydride provided very poor yields (data not shown).

Among acyclic anhydrides, *n*-butyric anhydride was proved to be the best acylating reagent (E=94). As for solvents, toluene and isooctane, which are recognized as suitable for enzymatic reactions in non-aqueous media[17], were also examined as reaction solvents. Diisopropyl ether was selected as the best solvent because the reaction was faster than toluene, and lactone **3** was formed as a by-product in isooctane. Acylation with enol esters[18] such as vinyl acetate were examined, but the reaction rates were too slow for practical application.

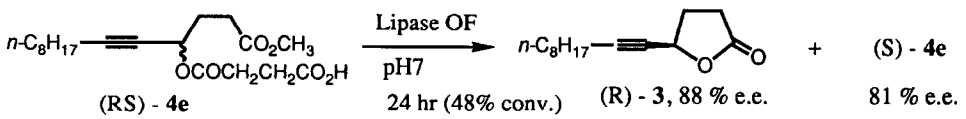
To further enrich the e.e. of desired (R)-enantiomer, asymetric hydrolysis of ester **4** was attempted. First, hydrolysis of butanoate **4c** was examined. After surveying of several commercially available lipases, Palatase A, a lipase from *Aspergillus niger* (Novo Ind. Co., Denmark), was found to catalyze the hydrolysis of **4c** (Scheme 4). It hydrolyzed (RS)-**4c** in 0.1M phosphate buffer



(RS) - **4c** 16 hr (50% conv.) (R) - **2**, 60 % e.e. 59 % e.e.

Scheme 4

(pH 7) to give (R)-**2** (60% e.e.) and (S)-**4c** (59% e.e.). The reaction was moderately stereoselective (E=7). These results, however, were unsatisfactory for preparing the extremely pure target lactone (R)-**3** . Higher stereoselectivity was then expected by using succinoate **4e** as the substrate. Although the enzymatic hydrolysis of **4e** was unsuccessful, we found that lipase OF from *Candida cylindracea* (Meito Sangyo Co., Japan) catalyzed the lactonization of **4e** to yield (R)-**3** (88% e.e.) (Scheme 5). The E value in this case was 39. Lipase catalyzed lactonization of hydroxy esters in organic solvents have been previously reported.[19,20] Following those procedures, lactonization of (RS)-**4c** or (RS)-**4e** was tried in organic solvents such as toluene, isooctane, diethyl ether and diisopropyl ether. Those



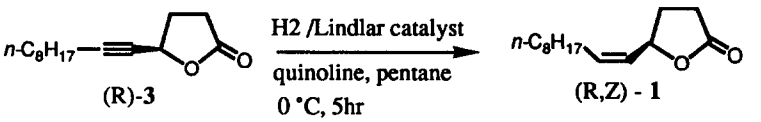
(RS) - **4e** 24 hr (48% conv.) (R) - **3**, 88 % e.e. 81 % e.e.

Scheme 5

attempts, however, were not successful. In order to refine the methodology to obtain highly optically pure lactone (R)-**3**, this lipase OF-catalyzed reaction was applied to (R)-**4e**, which was prepared in 94% e.e. with Lipase PS (Scheme 5). The reaction was stopped after 23 hr and (R)-**3** was isolated with over 99% e.e. (83% yield).

Another successful way to increase the e.e. of **4** was the repetition of lipase PS-catalyzed esterification (Scheme 2). These reactions with *n*-butyric anhydride or succinic anhydride as acyl donor are so highly enantioselective (E values is 94 and 115 respectively) that one repetition of these reactions was enough to obtain the optically active (R)-**4** with over 99% e.e.. For example, **4c** (92% e.e.) obtained by the first enzymatic reaction was converted to (R)-**2** by hydrolysis with KOH in methanol followed by methylation with diazomethane. That (R)-**2** was then subjected to the second enzymatic esterification. The second reaction was stopped after a shorter period (10 hr) and (R) - **4c** was isolated with over 99% e.e.(80% yield). (R)-**4c** was hydrolyzed with KOH to yield hydroxy acid (R)-**5**, which was distilled to give optically pure lactone (R)-**3**.

Semihydrogenation of (R)-**3** by a previously reported procedure[9] (Scheme 6) gave the Japanese beetle pheromone (R,Z)-**1** , $[\alpha]_D^{25}$ -73.9° (chloroform). Among the reported $[\alpha]_D$ values in a chloroform solution (-70.82°,[11] -70.4°,[9,10] -70.0°,[2,3] -69.93°,[7] -69.7°,[8] -68.1°,[12] -63.1°,[13]), this result (-73.9°) provided the highest value.



(R)-**3** (R,Z) - **1**

Scheme 6

In conclusion, a new synthesis of the Japanese beetle pheromone (R,Z)-**1** was established by combining enzymatic and chemical methods without using any chiral auxiliaries.

EXPERIMENTAL

Boiling points are uncorrected. IR spectra were recorded in neat on JASCO A-810 spectrophotometer. ^{1}H-MNR spectra were measured at 400MHz on a JEOL GX-400. ^{13}C-NMR spectra were measured at 100MHz on a JEOL GX-400. Optical rotations were measured on JASCO DIP-181. Column chromatography was effected using Merck Kieselgel 60 (70-230 mesh). Lipase PS was purchased from Amano Pharm. Co. Palatase A was purchased from Novo Ind. Co. Lipase OF was purchased from Meito Sangyo Co. Solvent for enzymatic reaction was distilled before use.

Methyl (RS)-4-butanoyloxy-5-tetradecynoate (RS)-4c : (RS)-**2**[12] (10.0g, 39mmol) was acylated with butyryl chloride (5.0g, 47mmol) in pyridine (50ml) in the usual manner and purified by silica gel column chromatography [Elution with hexane/EtOAc (9/1)] to give (RS)-**4c** (11.1g, 88% yield). vmax 2940, 2860, 2230, 1740, 1180 cm^{-1} ; δ (^{1}H, 400 MHz, $CDCl_3$) 0.87(3H, t, J=6.6 Hz), 0.94(3H, t, J=7.3Hz), 1.25-1.35(10H, bm), 1.47(2H, m), 1.65(2H, m), 2.06(2H, m), 2.17(2H, m), 2.28(2H, m), 2.47 (2H, t, J=7.0Hz), 3.67(3H, s), 5.42(1H, deformed t, J=6.1Hz) ; δ (^{13}C, 100 MHz, $CDCl_3$) 13.45, 14.13, 18.43, 18.70, 22.68, 28.48, 28.86, 29.08, 29.19, 29.72, 30.27, 31.85, 36.21, 51.73, 63.22, 76.78, 86.99, 172.51, 173.19 ; (Found: C, 70.15 ; H, 9.95 %. Calc for $C_{19}H_{32}O_4$: C, 70.33 ; H, 9.94 %)

Methyl (RS)-4-succinoyloxy-5-tetradecynoate (RS)-4e : (RS) - **2** (10.0g, 39mmol) was acylated with succinic anhydride (4.7g, 47mmol) in pyridine (50ml) in the usual manner and purified by silica gel column chromatography [Elution with hexane/EtOAc (5/1)] to give (RS)-**4e** (11.5g, 83% yield). vmax 3300, 2940, 2850, 2240, 1740, 1710,1160 cm^{-1} ; δ (^1H, 400 MHz, $CDCl_3$) 0.85 (3H, t, J=7.0 Hz), 1.24 (8H, m), 1.32 (2H, m), 1.46 (2H, m), 2.05 (2H, td, J=7.3, 6.2 Hz), 2.46 (2H, t, J=7.6Hz), 2.61 (2H, m), 2.66 (2H, m), 3.66 (3H, s), 5.42 (1H, t, J=6.2Hz); δ (^{13}C, 100 MHz, $CDCl_3$) 14.07, 18.65, 22.64, 28.40, 28.84, 28.91, 29.02, 29.15, 29.57, 30.15, 31.81, 51.74, 63.97, 76.36, 87.38, 170.98, 173.20, 177.86 ; (Found: C, 64.22 ; H, 8.51%. Calc for $C_{19}H_{30}O_6$: C, 64.39 ; H, 8.53 %)

General procedure for acylation of (RS)-2 using lipase PS : (RS)-**2** (30mg, 0.118 mmol) and acid anhydride (0.12 mmol) were dissolved in diisopropyl ether (3ml). Lipase PS (30 mg) was added to the solution and the suspension was stirred at 30 °C for indicated time in Table 1. The conversion of the reactions were determined by HPLC analysis on the system consisting of pump [JASCO 880-PU] and UV detector [JASCO 875-UV] equipped with ODS column [NUCLEOSIL 7C-18, 4.6 x 250mm; acetonitrile/distilled water (70/30), 2ml/min, 215nm]. The retention times of **2**, **3**, and **4** were: **2**, 3 1min; **3**, 3.7min; **4a**, 4.9min; **4b**, 6.1min; **4c**, 7 6min, **4d**, 12.4min; **4f**, 4.8min. In monitoring of acylation of **2** with succinic anhydride, product **4e** was methylated to yield **4f**, which was analyzed by HPLC analysis. After the lipase powder had been removed by filtration, the filtrate was evaporated and chromatographed on a silica gel column [hexane/EtOAc (9/1)] to give **4** and **2**. To determine the enantiomeric excess(e.e.) of **2**, and **4**, they were hydrolyzed with 5 % KOH in methanol to yield hydoroxy acid **5**, and **5** was converted to **3** by heating in hexane/2N-HCl (1/2) at 60°C for 30min. And then **3** derived from **2** and **4** was subjected to HPLC analysis on the system consisting of pump [JASCO 880-PU] and UV detector [JASCO 875-UV] equipped with a column with a chiral stationary phase [Chiralcel OD, 4.6 x 250mm; hexane/2-propanol(99/1), 1ml/min, 215nm]. The retention times of (R)-**3** and (S)-**3** were 17.1 min and 19.6 min respectively. Results were summarized in Table 1.

Lipase catalyzed hydrolysis of (RS)-4c : (RS)-**4c** (500 mg, 1.54 mmol) was suspended in 50 ml of phosphate buffer (pH 7). Palatase A (500mg) was added to the solution and the suspension was stirred at 25 °C for 16 hr. The reaction mixture was extracted with ether. The extract was washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purifed by silica gel column chromatography (10g). Elution with hexane/EtOAc (9/1) gave (R)-**2** (165 mg, 43% yield, 60% e.e.) . vmax 3480, 2940, 2860, 2230, 1740, 1440, 1250, 1165, 1160 cm^{-1} ; δ (^1H, 400 MHz, $CDCl_3$) 0.86 (3H, t, J=6.2 Hz), 1.25-1 33(10H, bm), 1.45(2H, m), 1.98(2H, m), 2.17(2H, m), 2.25(1H, bs), 2.51(2H, m), 3.66(3H, s), 4.44(1H, t, J=6 2 Hz) Further elution gave (S)-**4c** (219 mg, 45% yield, 59% e.e.). Its IR and NMR spectra were identical with those of (RS)-**4c** obtained above respectively.

Lipase catalyzed lactonization of (RS)-4e to yield (R)-5-(1-decynyl)oxacyclopentan-2-one (R)-3 : (RS)-**4e** (500 mg, 1.41 mmol) was suspended in 50ml of phosphate buffer (pH 7). Lipase OF (500mg) was added to the solution and the suspension was stirred at 25 °C for 24 hr. The reaction mixture was extracted with ether. The extract was washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (10g). Elution with hexane/EtOAc (9/1) gave (R) - **3** (128 mg, 41% yield, 88% e.e.) bp 130-134 °C at 0.3 mmHg , vmax 2940, 2860, 2240, 1790, 1185, 1150, 1020 cm^{-1} ; δ (^1H, 400 MHz, $CDCl_3$) 0.89 (3H, t, J=7.1 Hz), 1 26-1.39 (10H, m), 1 49 (2H, tt, J=7 1 Hz), 2.19-2.27 (1H, m), 2.21 (2H, td, J=7 1, 2.0 Hz), 2.43-2 53 (2H, m), 2 59-2.69 (1H, m), 5.2 (1H, m) , δ (^{13}C, 100 MHz, $CDCl_3$) 14 00, 18 60, 22.56, 27.90, 28.20, 28.74, 28 96, 29.07, 30.07, 31 74, 69.69, 76 46, 88.78,

176.23. Further elution with hexane/EtOAc(5/1) gave (S) - **4e** (195mg, 39% yield, 81% e.e.). Its IR and NMR spectra were identical with those of racemic one obtained above.

Large scale preparation of methyl (R)-4-succinoyloxy-5-tetradecynoate (R)-4e : (RS)-2 (30.0g, 118.1mmol) and succinic anhydride (5.9g, 59.1mmol) were dissolved in diisopropyl ether (1000ml). Lipase PS(10 g) was added and the suspension was stirred at room temp for 48hr. After lipase powder had been removed by filtration, the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (800 g). Elution with hexane/EtOAc(9:1) gave (S)-2 (12.7 g, 43% yield, 88% e.e.). Its IR and NMR spectra was identical with those of racemic one obtained above. Further elution with hexane/EtOAc(5/1) gave (R)-**4e** (17.1 g, 41% yield, 94% e.e.). Its IR and NMR spectra were identical with those of racemic one obtained above.

Preparation of (R)-5-(1-decynyl)oxacyclopentan-2-one (R)-3 by lactonization of (R)-4e: (R)-**4e** (94 % e.e., 500 mg, 1.41 mmol) was suspended in 50ml of 0.1M phosphate buffer (pH 7). Lipase OF (500mg) was added to the solution and the suspension was stirred at 25 °C for 23 hr. The reaction mixture was extracted with ether. The extract was washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (10g). Elution with hexane/EtOAc(9/1) gave (R) - **3** (260 mg, 83% yield, >99% e.e.). bp 135-140 °C at 0.6 mmHg ; Its IR and NMR spectra were identical with those of racemic one obtained above.

Large scale preparation of methyl (R)-4-butanoyloxy-5-tetradecynoate (R)-4c : (RS) - **2** (20.0 g, 78.7mmol) and *n*-butyric anhydride (6.2 g, 39.4mmol) were dissolved in diisopropyl ether (200ml). Lipase PS (5g) was added and the suspension was stirred at room temp for 30 hr. After lipase powder had been removed by filtration, the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (300g). Elution with hexane/EtOAc(9:1) gave (R)-**4c** (11.0g, 43% yield, 92% e.e.). Its IR and NMR spectra were identical with those of racemic one obtained above. Further elution gave (S)-2 (9.2 g, 46% yield, 94% e.e.). Its IR and NMR spectra were identical with those of racemic one obtained above.

Methyl (R)-4-hydroxy-5-tetradecynoate (R)-2: (R)-**4c** (92% e.e., 10.0 g, 30.9 mmol) in 5% KOH in MeOH(100 ml) was stirred and heated under reflux for 15 min. The reaction mixture was concetrated *in vacuo*, diluted with water, adjusted to pH 4 with ice-cooled 1N-HCl, and extrated with ether. The aqueous layer was again extracted with ether. The organic layers were combined, dried over sodium sulfate, and treated with diazomethane. The solution was concetrated *in vacuo* The residue was purified by silica gel column chromatography (200g). Elution with hexane/EtOAc (9:1) gave (R)-2 (7.1 g, 91% yield). Its IR and NMR spectra was identical with those of racemic one obtained above.

Second acylation of (R)-2 to yield (R)-4c: (R) 2 (92 % e.e., 7.10 g, 28.0 mmol) and butyric anhydride (4.15g, 26.2 mmol) were dissolved in diisopropyl ether (100 ml). Lipase PS (2 g) was added to the solution. The suspension was stirred at room temp for 10 hr. Work up and purification were performed in the same manner descrived above to give (R)-**4c** (7.30 g, 80% yield, >99% e e.) Its IR and NMR spectra were identical with those of the primary acylation product.

Preparation of (R)-5-(1-decynyl)oxacyclopentan-2-one (R)-3 from (R)-4c : (R)-**4c** (>99% e.e., 7.30g, 22.5mmol) was hydrolyzed in 5% KOH in MeOH(80ml) was stirred and heated under reflux for 15 min. The reaction mixture was concetrated *in vacuo*, diluted with water, adjusted to pH 4 with ice-cooled 1N-HCl, and extracted with ether. The

aqueous layer was again extracted with ether. The organic layers were combined, dried over sodium sulfate and concentrated *in vacuo*. The residue was heated at 110-120 °C for 30 min to effect lactonization. Distillation gave 4.03g of (R)-3 (81% yield). bp 135-140 °C (0.6 mmHg). Its IR and NMR spectra were identical with those of (R) - 3 obtained above. Its ee was determined to be more than 99%.

(R,Z)-(-)-5-(1-Decenyl)oxacyclopentan-2-one (R,Z)-1: Following the reported prodedure,[9] semihydrogenation of (R)-3 (>99% e.e., 4.03g, 18.2mmol) was accomplished. The crude material was purifed by silica gel column chromatography [hexane/ether(9/1)]. The organic solvent was removed under reduced pressure. The residue was distilled to give (R,Z)-1 (3.71 g, 91% yield). bp 100-105 °C (0.5 mmHg) ; n_D^{24}=1.4618 ;$[\alpha]_D^{25}$=-73.9° (c=1.004, $CHCl_3$) ; vmax 2940, 2860, 1780, 1660, 1460, 1420, 1380, 1330, 1295, 1220, 1180, 1125, 1015, 980, 910, 870, 810, 720 cm^{-1} ; δ (^1H, 400 MHz, $CDCl_3$) 0.87 (3H, t, J=6.8 Hz), 1.26 (10H, m), 1.36-1.48 (2H, m), 1.88-1.98 (1H, m), 2.02-2.18 (2H, m), 2.32-2.41 (1H, m), 2.52-2.57 (2H, m), 5.24 (1H, dddd, J=11.7, 11.7, 9.8, 1.2 Hz), 5.44 (1H, ddt, J=9.8, 9.8, 1.7 Hz), 5.65 (1H, dtd, J=10.7, 7.8, 1.2 Hz) ; δ (^{13}C, 100 MHz, $CDCl_3$) 14.08, 22.65, 27.83, 28.99, 29.19, 29.22, 29.32, 29.40, 29.43, 31.85, 76.42, 127.27, 135.83, 177.07 ; (Found: C, 74.70 ; H, 10.74 %. Calc for $C_{14}H_{24}O_2$: C, 74.95 ; H, 10.78 %)

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