# STUDIES ON THE SYNTHESIS OF MACROCYCLIC COMPOUNDS STARTING FROM LONG CHAIN FATTY ACIDS

(高級脂肪酸を原料とする大環状化合物の合成)

**ATSUSHI MAKITA**

NARA INSTITUTE of SCIENCE and TECHNOLOGY

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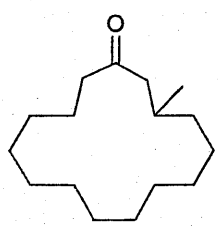
# Contents

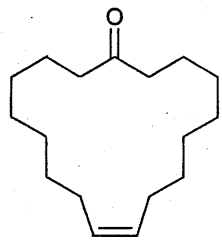
# General Introduction

Natural macrocyclic compounds including macrocyclic musks[1,2] and macrolides antibiotics[3] have been the one of the most challenging synthetic target of academic and industrial organic chemists for an interest in their characteristic cyclic structures and highly commercial value.[3]

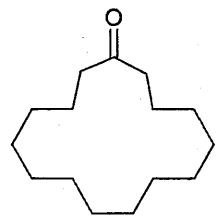
Macrocyclic musks are important perfumes used for over 900 years. The term musk, which derives from the name of an animal, the musk deer, is used to designate this entire group of odorants.[1] Muscone (**1**), civetone (**2**), cyclopentadecanone (**3**), and cyclopentadecanolide (**4**) are representative macrocyclic musks.



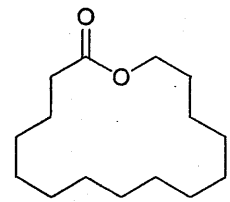
muscone (**1**)



civetone (**2**)

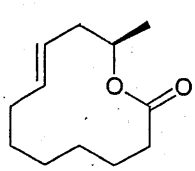


cyclopentadecanone (**3**)

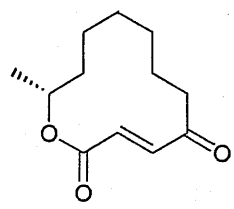


cyclopentadecanolide (**4**)

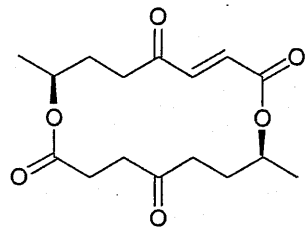
Macrolides are used to express the macrocyclic lactones that have antibacterial and/or antifungal activities. The macrolides that I mention in this thesis contain recifeiolide (**5**), patulolide A (**6**), pyrenophorin (**7**).



recifeiolide (**5**)

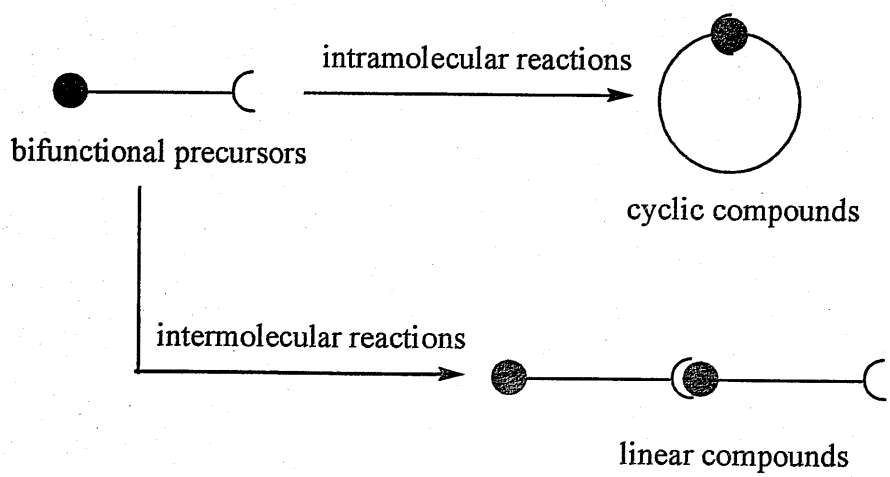


patulolide (**6**)



pyrenophorin (**7**)

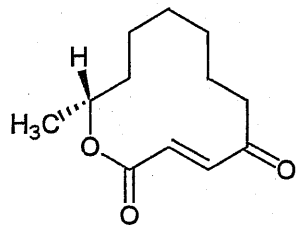
Two strategies are used for the synthesis of macrocyclic compounds. One is an intramolecular ring closure of the bifunctional precursors and the other is a ring expansion of smaller ring compounds. In the former strategy, intramolecular reactions with bifunctional precursors are usually in competition with intermolecular reactions. How to ring-close the bifunctional precursors intramolecularly with higher efficiency and how to prepare the bifunctional precursors are the key points in the synthesis of the macrocyclic compounds. Long chain fatty acids can use as starting materials for the bifunctional precursors of the macrocyclic compounds that need long methylene chain.




From these viewpoints, I have studied on the synthesis of some macrocyclic compounds starting from long chain fatty acids using intramolecular ring closure methods of the bifunctional precursor, and the practical synthesis of the bifunctional precursors for the intermediate of macrocyclic compounds since 1986. My work was published as papers and patents.[4-19] This thesis is a selective part of my work that was mainly reported by papers, and consists of the following 5 chapters.

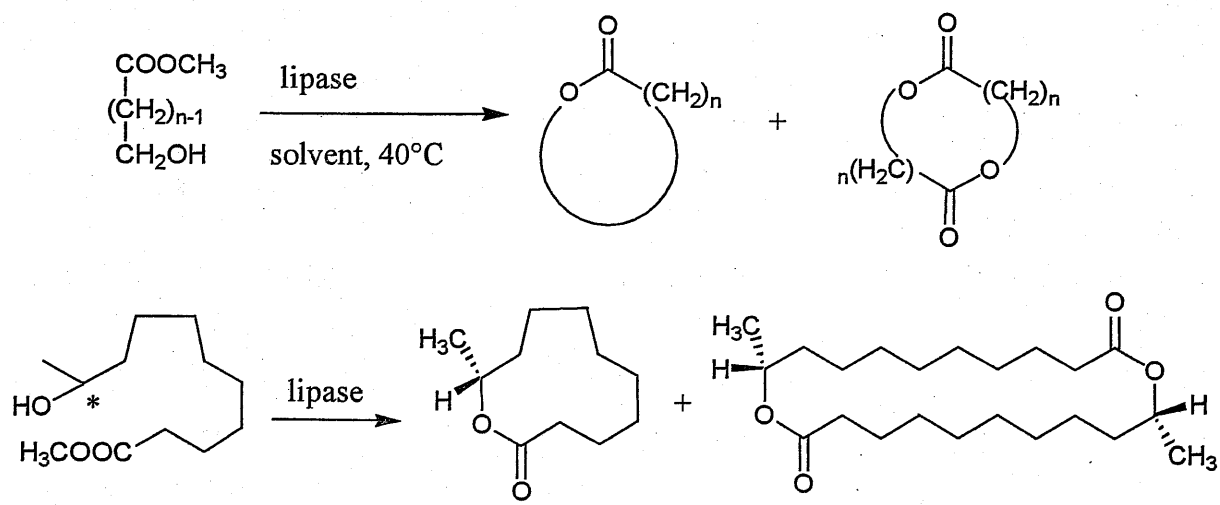
Chapter 1 deals with the synthesis of (±)-Patulolide A (**6**), a macrolide isolated from a

*Penicillium urtcae* mutant, from 12-hydroxydodecanoic acid. This was the first total synthesis of Patulolide A, and the structure of the natural compound was confirmed by this work.



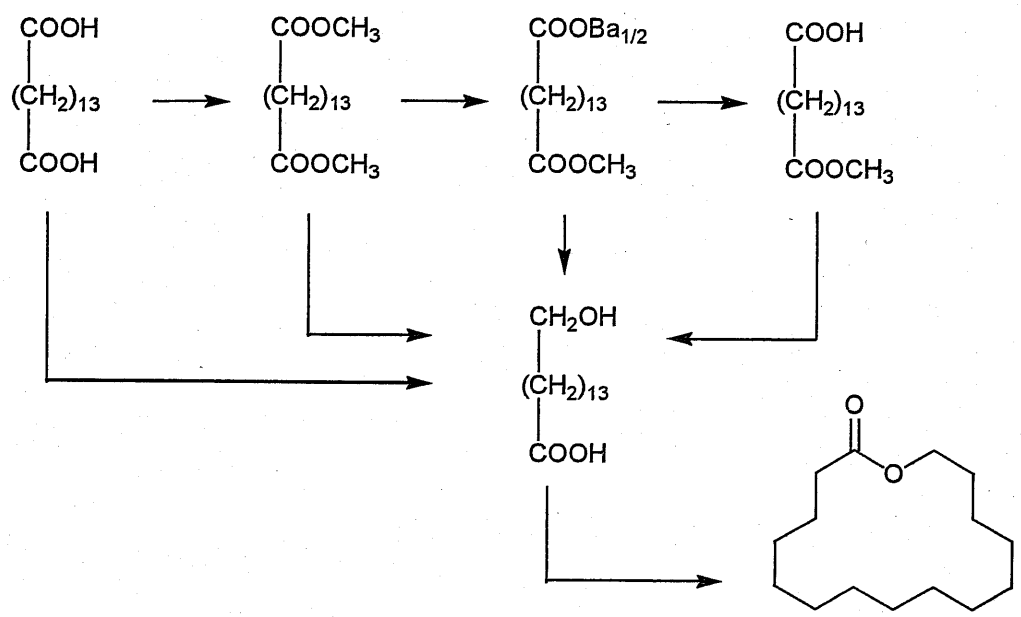
(+) - Patulilide A

Chapter 2 deals with the novel synthetic method at that time of cyclopentadecanolide (**4**),[1,2] a macrocyclic musk, and other related lactones from methyl ω-hydroxyalcanoates by using lipase in organic solvents, and kinetic resolution of racemic methyl (ω-1)-hydroxyalcanoate stereospecific leading to the formation of (*R*)-isomer of lactones. The lipase-catalyzed lactonization in organic solvents was a pioneer work and the related studies have been done extensively after this work.[20]

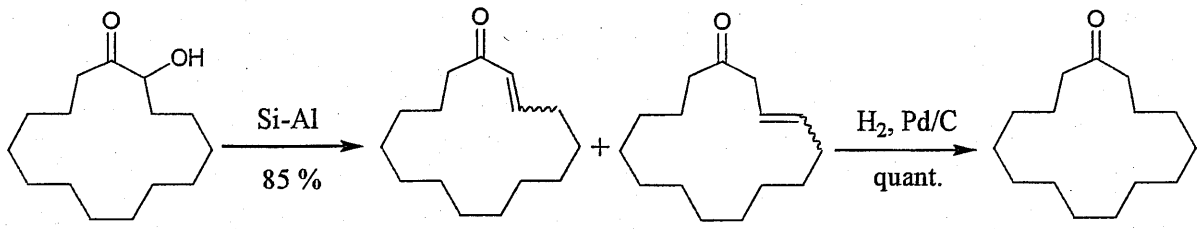



Chapter 3 deals with the practical synthetic methods of 15-hydroxypentadecanoic acid, the

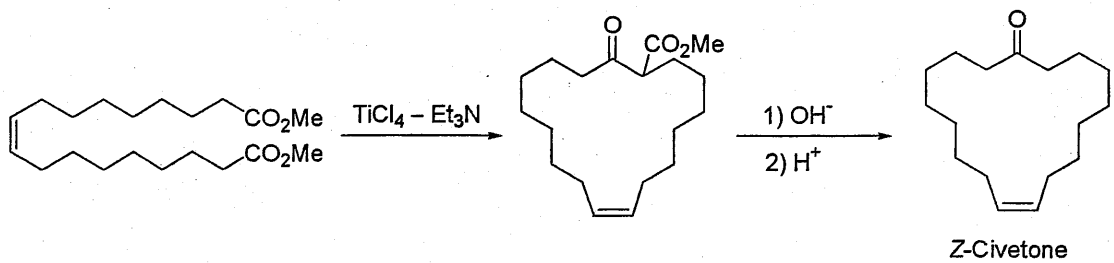
precursor of cyclopentadecanolide (**4**), from 1,15-pentadecanedioic acid by using selective hydrogenation with the Ru-Sn-$Al_2O_3$ or Re-Sn-$Al_2O_3$ catalysts. A practical synthesis of 15-hydroxypentadecanoic acid is a key point of the industrial production of cyclopentadecanolide (**4**) because there are excellent intramolecular ring closure methods for synthesis of cyclopentadecanolide (**4**) include my work.




Chapter 4 deals with the synthetic methods of cyclopentadecanone (**3**),[1,2] a macrocyclic musk, from dimethyl 1,15-pentadecanedioate by using catalytic liquid-phase dehydration of 2–hydroxycyclopentadecanone as the key step. The catalytic liquid-phase dehydration could work at considerably lower reaction temperature than the conventional vapor-phase reaction; therefore, this dehydration would be preferable to be used in multi-purpose plant for producing fine chemicals. Cyclopentadecanone was given by a catalytic hydrogenation of the products of this dehydration, 2- and 3-cyclopentadecenones. Because the new route is carried out in catalytic manner, this protocol is more ecofriendly and green than the present process.




Chapter 5 deals with the synthetic methods of *Z*-civetone (**2**),[1,2] a macrocyclic musk, from dimethyl 9-octadecenedioate by using a $TiCl_4$ mediated Dieckmann condensation (intramolecular Claisen condensation). This method seems to be one of the most practical synthetic methods of *Z*-civetone. This cyclization reaction has some advantages compared with the traditional basic Dieckmann condensation such as higher concentration (100–300 mM), lower reaction temperature (0–5 °C), shorter reaction time (1–3 h), use of environmentally benign (low toxicity and safe) reagents ($TiCl_4$ and $Et_3N$ or $Bu_3N$), and economical reagents and solvents. 15-, 17- and 19-membered saturated β-keto esters were also prepared by the present method.

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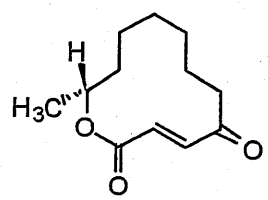
# Chapter 1. The Total Synthesis of (±)-Patulolide A

## 1-1. Summary

The first total synthesis of (±)-patulolide A, a new macrolide isolated from a *Penicillium urtcae* mutant, was achieved from 12-hydroxydodecanoic acid. The structure of the natural product was confirmed by this synthesis.

## 1-2. Introduction

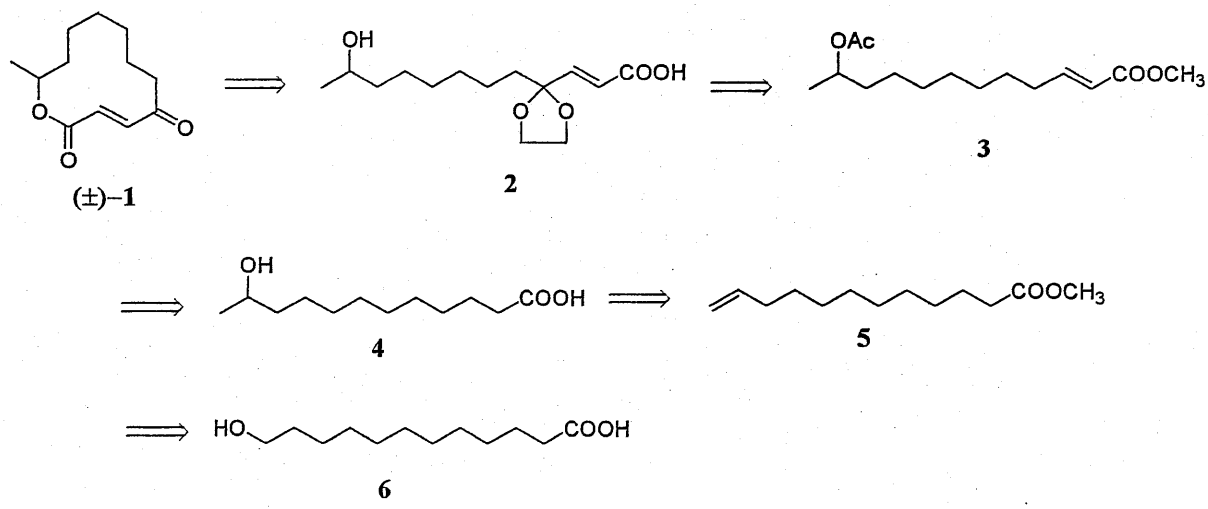
A new 12-membered macrolide, (+)-patulolide A (**1**), was isolated from the culture broth of *Penicillium urtcae* S11R59[1] that is a patulin-minus mutant of *P. urtcae* NRRL 2159A.[2] Patulolide A shows weak antibacterial activities and relatively high antifungal activities.[3] The structure of patulolide A is rather simple but it has a characteristic structural feature, one double bond flanked with lactone carbonyl and ketone group, which is common with some antifungal metabolites such as pyrenophorin[4], pyrenolides[5, 6], vermiculine[7], and A26771B.[8] Thus it is interesting to synthesize this new 12-membered macrolide in order to provide some knowledge of the chemistry of these compounds. From this viewpoint, I undertook the first total synthesis of (±)-patulolide A (**1**), from 12-hydroxydodecanoic acid (**2**), and therefore ascertained the chemical structure of the natural product as shown below.




(+) - Patulilide A (**1**)

### 1-3. Results and Discussion

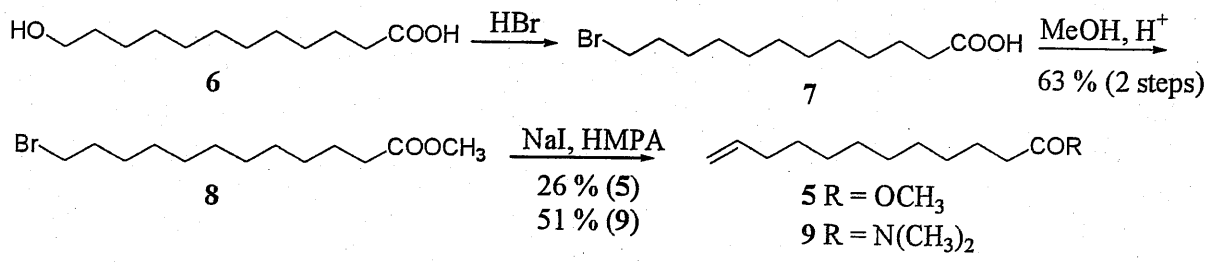
First the retrosynthetic analysis of (±)-Patulolide A (**1**) was done. Macrolide **1** could be obtained by the intramolecular cyclization of corresponding seco-acid **2** using Yamaguchi lactonization[9]. The seco-acid **2** could be derived from 11-acetoxy-2-dodecenoate **3** by allylic oxidation, the protection with ketal, and hydrolysis of acetyl and methyl ester groups. The acetate **3** could be prepared from 11-hydroxydodecanoic acid (**4**) by using selenoxide elimination as a key step. The acid **4** could be yielded from methyl 11-dodecenoate **5** by oxymercuration followed by reduction of $NaBH_4$. Then the ester **5** could synthesize from 12-hydroxydodecanoic acid **6** by bromination, esterification and dehydrobromination (Scheme 1).




**Scheme 1** Retrosynthetic analysis of (±)-Patulolide A (**1**)

According the retrosynthetic study, first the hydroxyacid (**6**) was converted to 12-bromododecanoic acid (**7**) by refluxing in hydrobromic acid solution.[10] The bromo acid **7** was transformed to the methyl ester **8** by refluxing with hydrochloric acid in methanol.

Overall yield of **8** from **6** was 63 %. The ester **6** was dehydrobrominated by heating with sodium iodide (1 equiv.) in hexamethylphosphoramide (HMPA)[11] at 170 °C for 3 h to give methyl 11-dodecenoate (**5**) and *N,N*-dimethyl-11-dodecenamide (**9**) in 26 and 51 % yields respectively. The amide **9** would be obtained by the reaction with HMPA (Scheme 2).

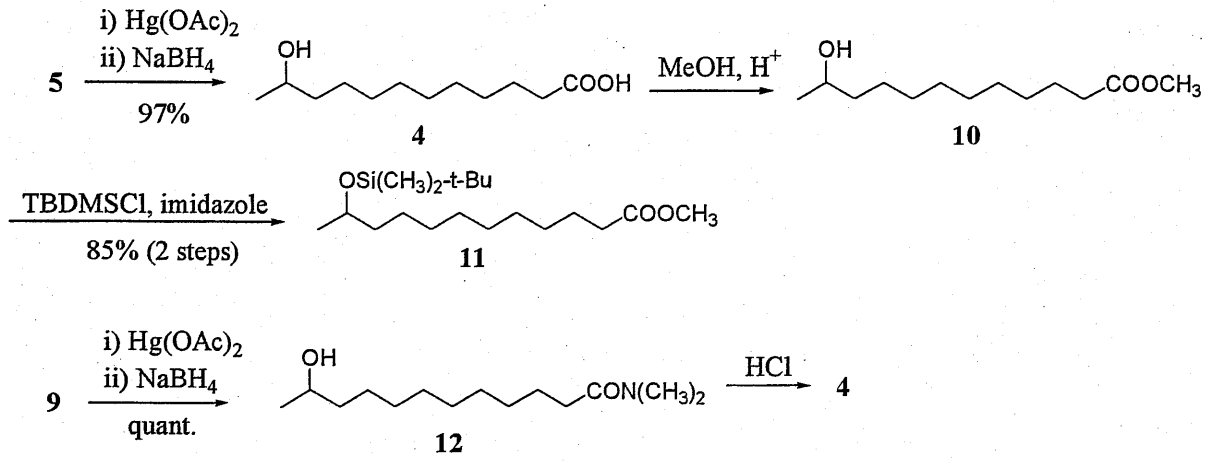



**Scheme 2** Synthetic route to **5**.

The dodecenoate **5** was treated with $Hg(OAc)_2$ (1.03 equiv) in THF-$H_2O$ (1:1) at room temperature for 0.5 h followed by rection with $NaBH_4$ (1.9 equiv) to give 11-hydroxydodecanoicacid (**4**) in 97% yield.[12] Reaction of the hydroxy acid **4** with methanol-hydrochloric acid gave the methyl ester **10**, which was transformed to *tert*-butyldimethylsilyl ether (**11**)[13] in 85% overall yield from **4**. The amide **9** was converted to 11-hydroxydodecanamide **12** by the same procedure as the ester **5**. The amide **12** was hydrolyzed to the hydroxy acid **4** by refluxing in 3N-HCl solution (Scheme 3).

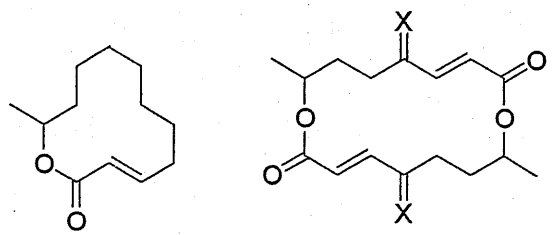
The ester **11** was converted to α,β-unsaturated ester **13** by using selenoxide elimination. Treatment of **11** with lithium diisopropylamine (LDA) (1.2 equiv) in tetrahydrofuran (THF) at −78°C for 1 h and then with benzeneselenenyl bromide (1.2 equiv) at -78 - -40°C for 2 h gave the phenyl selenide, which was subjected to reaction with hydrogen peroxide solution (30%) and acetic acid at 0 °C to give 11 in 63% oveall yield.[14] As the *tert*-butyldimethylsilyl ether did not resist the next oxidation step, this protective group was replaced to an acetyl group in

90% yield by treating **13** with anhydrous $FeCl_3$ (0.15 equiv) in acetic anhydride at 5°C for 20




**Scheme 3** Synthetic route to **11**.

minutes.[15] The acetate **3** thus obtained was oxidized to the ketone **14** with $CrO_3$ (5equiv) in acetic anhydride-acetic acid-benzene (1:1:2) at 20°C for 1 hour in 42% yield.[16] It is noteworthy that application of the chromic anhydride oxidation to 12-membered α,β-unsaturated macrolide **17** to give patulolide A was unsuccessful whereas Seebach successfully oxidized the 16-membered α,β-unsaturated diolide **18** to pyrenophorin (**19**)[17].

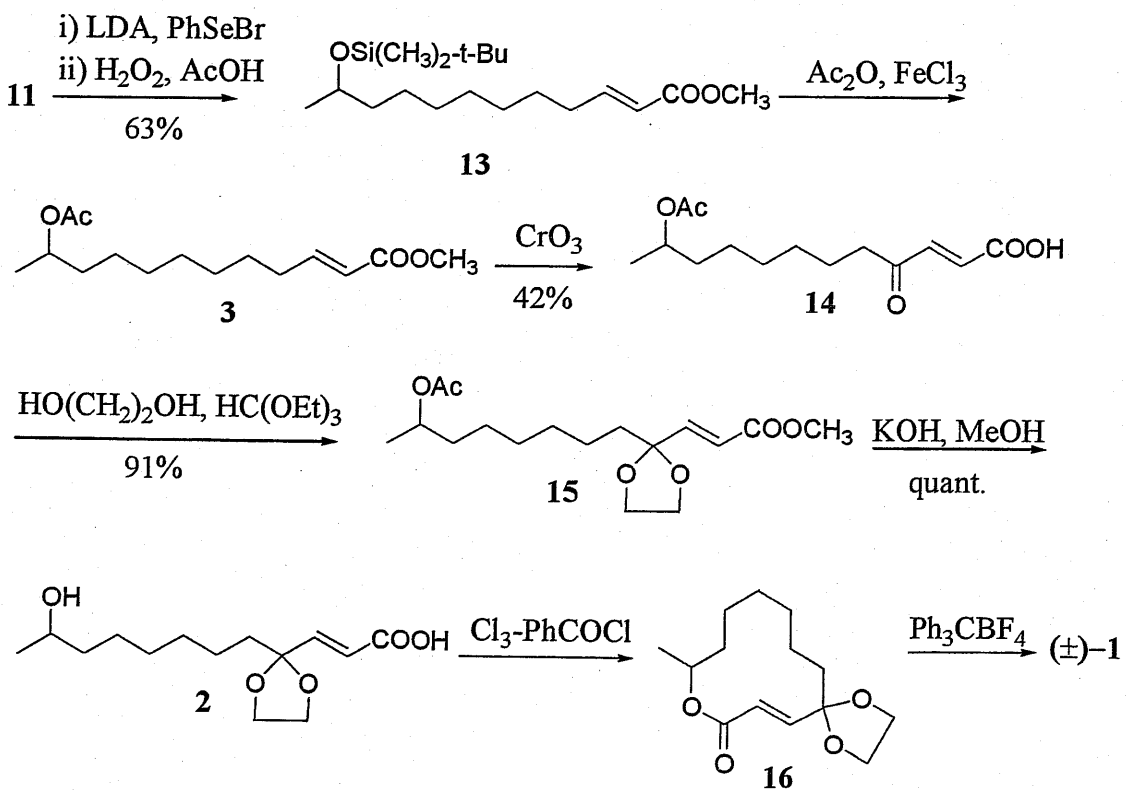



**17**

X = $H_2$ (**18**)
X = O (**19** Pyrenophorin)

The carbonyl group of **14** was protected as an ethylene ketal to give **15** by treating with

ethyleneglycol (1.5 equiv), triethyl orthoformate (1.03 equiv) and a catalytic amount of boron trifluoride-etherate in boiling benzene for 24 h in 91% yield.[18] The ketal ester was quantitatively hydrolyzed to the hydroxy acid **2** in 2N-KOH-methanol at room temperature for 5 h. The hydroxy acid **2** was cyclized to the lactone **16** by reaction with trichlorobenzoyl chloride (1 equiv) and triethylamine (1.1 equiv) in THF at room temperature for 2 h then after the removal of triethylamine hydrochloride and THF, the resulting mixed anhydride in toluene was added to refluxing toluene by high dilution method.[9] The cleavage of cyclic ketal to patulolide A (**1**) in acetone with *p*-toluenesulfonic acid gave a complex mixture, although this procedure was successful in pyrenophorin synthesis.[19] Deprotection of the ketal group was successfully carried out by Barton's method[20] using trityl fluoroborate (1.1 equiv) in dichloromethane in 32% (Scheme 4).




**Scheme 4** Final synthetic route to (±)-**1**.

The spectroscopy and Rf values on TLC of synthetic patulolide A were identified with those of the natural product.

## 1-4. Conclusion

In conclusion, I achieved the first total synthesis of (±)-Patulolide A (**1**), from 12-hydroxydodecanoic acid (**2**). The structure of the natural product was confirmed by this synthesis.

After my thesis,[21] the synthesis of (±)-Patulolide A[22, 23] and the asymmetric synthesis of (+)-Patulolide A[24-29] have been reported.

## 1-5. Experimental section

### General

Melting points are uncorrected. $^1$H NMR spectra were recorded on a JEOL (100 MHz) spectrometer. $^1$H NMR spectra were reported as chemical shifts in parts-per-million (ppm) based on a TMS internal standard in $CDCl_3$. Coupling constants (*J*) are reported in Hertz (Hz). Silica gel column chromatography was performed on a Merck 70 - 230 mesh. Commercially available reagents were used without further purification.

### Starting Materials.

12-Hydroxydodecanoicacid (**6**) was purchased from Aldrich. The other reagents were purchased from Wako.

**Bromination and esterification of 12-hydroxydodecanoicacid (6)**

12-Hydroxydodecanoicacid (**6**; 25 g, 0.116 mol) was refluxed with 6.3 mL of sulfuric acid in 24.7 mL of hydrobromic acid solution (47 %) at 160 °C for 7.5 h with stirring. The reaction product was extracted with $CH_2C1_2$ and dried over anhydrous sodium sulfate and the solvent was evaporated to give crude brownish oil of 12-bromododecanoic acid (**7**). This crude oil was dissolved in 300 mL of MeOH and dry HCl gas (15 g) was introduced into the solution. The solution was refluxed at 80 °C for 1.5 h. The reaction mixture was poured into 300 mL of $H_2O$ and extracted with $CH_2C1_2$. The extract was dried over anhydrous sodium sulfate and concentrated to give 30.8 g of crude oil. The product was purified on silica gel column chromatography using hexane-EtOAc as solvent system to give methyl 12-bromododecanoate (**8**; 21.4 g). $^1$H NMR (100 MHz, $CDCl_3$) δ 3.65 (3H, S), 3.38 (2H, t, J = 6 Hz), 2.1 - 2.7 (2H, m). IR $cm^{-1}$ 1740.

**Debromination of methyl 12-bromododecanoate (8)**

The bromo ester **8** (21 g, 71.7 mmol) was heated with sodium iodide (10.75 g) in 50 mL of HMPA at 170 °C for 3 h. To the reaction mixture 200 mL of water was added and was extracted with hexane. The extract was washed with sodium thiosulfate solution, HCl solution and water. After drying over anhydrous sodium sulfate the solvent was evaporated to give 12.3 g of crude oil. The crude product was purified by silica gel column chromatography using hexane-EtOAc (10:1). The first fraction was methyl 11-dodecenoate (**5**; 4.0 g) and the second fraction was *N, N*-dimethyl 11-dodecenamide (**9**; 8.2 g).

**5**: $^1$H NMR (100 MHz, $CDCl_3$) δ 5.6 - 6.0 (1H, m), 4.8 - 5.1 (2H, m), 3.62 (3H, s), 2.29 (2H, t), 1.85 - 2.15 (2H, m). IR $cm^{-1}$ 1740, 1650. MS *m/z* 212 ($M^+$), 180. Anal. Calcd for $C_{13}H_{24}O_2$:

C, 73.52; H, 11.40. Found: C, 73.21; H, 11.56.

**9**: $^1$H NMR (100 MHz, $CDCl_3$) δ 5.6 - 5.95 (1H, m), 4.8 - 5.1 (2H, m), 3.0 and 2.95 (3H, s, $CH_3N$), 2.28 (2H, t), 1.8 - 2.2 (2H, m). MS *m/z* 225 ($M^+$). Anal. Calcd for $C_{14}H_{27}NO$: C, 73.76; H, 12.33; N, 6.09. Found: C, 74.60; H, 12.09; N, 6.22.

**Oxymercuration and reduction of methyl 11-dodecenoate (5)**

To the THF solution of methyl dodecenoate (**5**) (1 g in 10 mL), 1.56 g of $Hg(OAc)_2$ in 20 mL of THF-$H_2O$ (1:1) was added in one portion and the mixture was stirred for 0.5 h. Then 20 mL of 3N NaOH solution was added to the reaction mixture and stirred for 0.5 h. $NaBH_4$ (0.36 g) was added portionwise and after 1 h the reaction mixture was acidified with 6 N HCl solution. THF was evaporated and the solution was extracted with EtOAc. The extract was dried over anhydrous sodium sulfate and evaporated to give 11-hydroxydodecanoic acid (**4**; 0.99 g). White crystals: mp 39 – 41 °C. MS *m/z* 216 ($M^+$), 198, 183, 172, 129; $^1$HNMR (100 MHz, $CDCl_3$) δ 3.1 - 4.1 (1H, m), 2.35 (2H, t), 2.20 (3H, d).

**Oxymercuration, reduction and hydrolysis of *N, N*-Dimethyl 11-dodecenamide (9)**

The amide **9** (1.0 g) was treated with $Hg(OAc)_2$ and $NaBH_4$ in THF and $H_2O$ according to the same procedure with that of the ester **5**. The hydroxy amide **12** was obtained quantitatively (1.08 g). White crystals: mp 48 – 49°C. MS *m/z* 243 ($M^+$), 225, 100, 88; $^1$HNMR (100 MHz, $CDCl_3$) δ 3.75 (1H, m), 3.01 and 2.91 (3H, s, $CH_3N$), 2.30 (2H, t), 1.18 (3H, d). Anal. Calcd for $C_{14}H_{29}NO_2$: C, 69.07; H, 12.02; N, 5.76. Found: C, 68.51; H, 11.94; N, 5.52.

The hydroxy amide **12** was hydrolyzed in refluxing 3N HCl solution to give the hydroxy

acid **4**.

**Esterification of 11-hydroxydodecanoic acid (4)**

Anhydrous HCl (5.7 g) was introduced into the MeOH solution of 11-hydroxydodecanoic acid (**4**) (3.0 g in 100 mL MeOH) and the solution was kept at room temperature overnight. The reaction mixture was poured into $H_2O$ and extracted with dichloromethane. The extract was dried over anhydrous sodium sulfate and evaporated to give crystalline methyl ester (**10**; 3.0 g, 93.9%). IR $cm^{-1}$ 3350, 1730; MS *m/z* 230 ($M^+$), 186, 143, 87, 74; $^1$HNMR (100 MHz, $CDCl_3$) δ 3.8 (1H, m), 3.7 (3H, s), 2.4 (2H, t), 1.22 (3H, d). Anal. Calcd for $C_{13}H_{26}O_3$: C, 67.77; H, 11.39. Found: C, 67.64; H, 11.27.

**Protection of methyl 11-hydroxydodecanoate (10)**

The hydroxy methyl ester **10** (5.31 g) was dissolved in 10.62 mL of DMF and *tert*-butyldimethylsilylchloride (4.19 g, 1.2 equiv) and imidazole (3.93 g, 2.5 equiv) was added. The reaction mixture was kept at room temperature for overnight. $H_2O$ was added to the solution and it was extracted with EtOAc. The extract was dried over anhydrous sodium sulfate and evaporated to give 8.8 g of crude oil. The oil was distilled under reduced pressure and methyl 11-*tert*-Butyldimethylsilyloxydodecanoate (**11**) was obtained (7.76 g, 90.2 %). Colorless oil (bp 147 - 148 °C/ 2 mmHg). MS *m/z* 344 ($M^+$), 329, 314, 287, 256, 159, 107, 75; $^1$HNMR (100 MHz, $CDCl_3$) δ 3.75 (1H, m), 3.68 (3H, s), 2.30 (2H, t), 1.10 (3H, d), 0.9 (9H, s). Anal. Calcd for $C_{19}H_{40}O_3Si$: C, 66.22; H, 11.71. Found: C, 66.09; H, 11.76.

**Dehydrogenation of methyl 11-*tert*-Butyldimethylsilyloxydodecanoate (11)**

Lithium diisopropylamide (1.2 equiv) was prepared in 20 mL of THF from 0.56 mL of diisopropylamine and butyllithium (1.06 M in hexane, 3.85 mL) at -78 °C for 20 minutes with stirring. The ester **11** (1.15 g, 3.4 mmol in 4.5 mL of THF) was added dropwise to the solution. Benzeneselenenyl bromide (4.08 mmol, in 4.5 mL of THF) that was freshly prepared from 0.63 g of diphenyldiselenide and 110 μl of $Br_2$, was added to the reaction mixture. It was stirred at -78 °C for 1 h and then at -40 °C for 2 h. The temperature of the solution was raised to 0 °C and 2 mL of $H_2O$, 0.4 mL of acetic acid and 1.67 mL of $H_2O_2$ (30 %) was added to it. After stirring for 30 minutes, the solution was neutralized with diluted $NaHCO_3$ solution and extracted with dichloromethane. The extract was washed with $H_2O$, 0.1 N HCl, and again $H_2O$ and then dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was purified by silica gel column chromatography using hexane-EtOAc (500:1) to give Methyl 11-*tert*-Butyldimethylsilyloxy-2-dodecenoate (**13**; 0.72 g, 62.6 %). $^1$HNMR (100 MHz, CDCl3) δ 6.9 - 7.2 (1H, m), 5.9 (1H, d, J = 16 Hz), 2.25 (2H, m), 3.75 (3H, s), 1.12 (3H, d), 0.93 (9H, s). IR $cm^{-1}$ 1730, 1660. MS *m/z* 342 ($M^+$), 327, 311, 295, 285, 254, 159, 75. Anal. Calcd for $C_{19}H_{38}O_3Si$: C, 66.61; H, 11.19. Found: C, 65.72; H, 11.17.

**Acetylation of Methyl 11-*tert*-Butyldimethylsilyloxy-2-dodecenoate (13)**

*tert*-Butyldimethylsilyloxy ester (**13**; 1.06 g, 3.1 mmol) was dissolved in 2 mL of acetic anhydride and stirred under argon with ice-bath cooling. To the solution 76 mg of anhydrous $FeCl_3$ was added and it was stirred for 20 minutes. $H_2O$ was added to the solution and it was extracted with hexane. After drying over anhydrous sodium sulfate and evaporation of the solvent, 0.99 g of crude oil was obtained. It was purified by middle pressure column chromatography (Licroprep Si 60) using hexane-EtOAc (20:1) to give methyl

11-Acetoxy-2-dodecenoate (**3**; 0.77 g, 89.9 %): $^1$HNMR (100 MHz, CDCl3) δ 6.65 - 7.10 (1H, m), 5.79 (1H, d), 4.9 (1H, m), 3.72 (3H, s), 2.20 (2H, m), 2.0 (3H, s), 1.20 (3H, d). IR cm$^{-1}$ 1740, 1735, 1660. MS *m/z* 270 ($M^+$), 238, 195, 177, 150, 136, 113, 105, 87.

**Oxidation of methyl 11-Acetoxy-2-dodecenoate (3)**

To the mixture of acetic anhydride (11.12 mL) and acetic acid (22.25 mL), chromic anhydride (4.45 g, 5 equiv) was added portionwise with stirring under ice-cooling. After adding 22.25 mL of benzene to it, the acetoxy ester (**3**; 2.40 g, 8.9 mmol) in 4.45 mL of benzene was added dropwise to the reaction mixture keeping the temperature under 20 °C. After the addition, it was stirred for 1 h at room temperature. $H_2O$ was added to the reaction mixture and it was neutralized with 1 N NaOH solution and extracted with EtOAc. After drying over anhydrous sodium sulfate and evaporation of the solvent, 2.60 g of crude oil was obtained. It was purified by silica gel column chromatography using hexane-EtOAc to give methyl 11-Acetoxy-4-oxo-2-dodecenoate (**14**; 1.07 g, 42.4 %). $^1$HNMR (100 MHz, CDCl3) δ 7.08 and 6.65 (1H, d, J = 16 Hz), 4.90 (1H, m), 3.82 (3H, s), 2.64 (2H, t), 2.04 (3H, s), 1.21 (3H, d). IR cm$^{-1}$ 1730, 1705, 1650. UV nm () 221 (11,000). MS *m/z* 284 ($M^+$). Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.34; H, 8.51. Found: C, 63.11; H, 8.85.

**Protection with ethylene ketal of methyl 11-Acetoxy-4-oxo-2-dodecenoate (14)**

The keto ester (**14**; 1.07 g, 3.77 mmol) was refluxed with ethylene glycol (323 μl, 5.80 mmol), triethyl orthoformate (643μl, 3.87 mmol) and trace amount of boron trifluoride etherate in 14.5 mL of benzene for 24 h. $H_2O$ was added to the reaction mixture and it was extracted with EtOAc. The extract was dried and concentrated to give ethylene ketal of

methyl 11-acetoxy-4-oxo-2-dodecenoate (**15**; 1.12 g, 90.6 %). $^1$HNMR (100 MHz, CDCl3) δ 6.75 and 6.04 (1H, d, J = 16 Hz), 4.89 (1H, m), 3.86 (4H, m), 3.72 (3H, s), 2.0 (3H, s), 1.20 (3H, d). MS *m/z* 328 ($M^+$), 297, 270, 243, 157, 113.

**Hydrolysis of ethylene ketal of methyl 11-Hydroxy-4-oxo-2-dodecenoate (15)**

The ester (**15**; 1.13g) was dissolved in 23.4 mL of MeOH and 11.7 mL of 2N KOH solution was added to it. After 5 h reaction at room temperature, the reaction mixture was poured into the ice water and pH was adjusted to 3 with 1N HCl. The solution was extracted with dichloromethane and it was dried over anhydrous sodium sulfate. Evaporation of the solvent gave 11-hydroxy-4-oxo-2-dodecenoic acid (**2**; 0.95 g). Crystals (mp 55 - 56 °C). $^1$HNMR (100 MHz, CDCl3) δ 6.80 and 6.11 (1H, d, J = 16 Hz), 3.9 (4H, m), 1.12 (3H, d). IR $cm^{-1}$ 1700, 1640; MS *m/z* 254, 239, 227, 201, 99. Anal. Calcd for $C_{14}H_{24}O_5$: C, 61.74; H, 8.87. Found: C, 61.12; H, 8.90.

**Lactonization of 11-hydroxy-4-oxo-2-dodecenoic acid (2)**

The hydroxy acid (**2**; 0.11 g, 0.4 mmol), triethylamine (0.44 mmol) and 2, 4, 6-trichlorobenzoyl Chloride (0.1 g, 0.4mmol) were dissolved in 4.4 mL of THF and stirred for 2 h at room temperature. The precipitate of triethylamine hydrochloride was removed by filtration and THF was evaporated by flushing with nitrogen gas. The residue was dissolved in 220 mL of toluene and it was added dropwise for 8 h to the refluxing solution of 4-dimethylaminopyridine (0.27 g, 2.2 mmol) in 44 mL of toluene. The reaction mixture was diluted with ether and washed with 3 % HCl, $H_2O$, $NaHCO_3$ solution and $H_2O$. The solvent layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by

silica gel column chromatography and ethylene ketal of (±)-Patulolide A (**16**; 70 mg, 68.1 %) was obtained. $^1$HNMR (100 MHz, CDCl3) δ 6.72 and 6.10 (1H, d, J = 16 Hz), 5.1 (1H, m), 3.9 (4H, m), 1.3 (3H, d). MS *m/z* 254, 239, 210, 199, 182, 143, 125, 113, 98.

**Deprotection of ethylene ketal of (±)-Patulolide A (1)**

The ketal (**16**; 37 mg) and 53 mg of $Ph_3CBF_4$ was dissolved in 6 mL of dichloromethane and the solution was stirred at room temperature under nitrogen for 4 h. $H_2O$ was added to the solution and it was extracted with dichloromethane. After drying over anhydrous sodium sulfate, that was concentrated and the residue was purified on preparative TLC using dichloromethane to give (±)-Patulolide A (**1**; 12.6 mg). [1] Crystals (mp 78 - 79 °C).

**1-6. References and Notes**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# Chapter 2. Lipase Catalyzed Synthesis of Macrocyclic Lactones in Organic Solvents

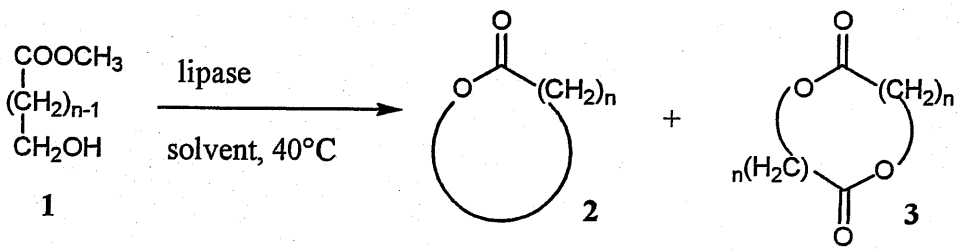
## 2-1. Summary

A new method for the preparation of macrocyclic lactones from ω-hydroxyacid methyl esters is developed. This method utilizes intramolecular transesterification catalyzed by lipase in organic solvents. A chiral lactone is prepared by this procedure.

## 2-2. Introduction

The potential of enzymes as practical catalysts for organic synthesis especially for asymmetric synthesis is becoming increasingly recognized.[1] Among enzymes so far investigated, lipases are one of the most advantageous, because it does not require any cofactor regeneration, and are commercially available, stable and inexpensive. Lipases have been widely used for the resolution of racemic alcohols and carboxylic acids through asymmetric hydrolyses of the corresponding esters.[2] In addition to hydrolysis, lipases can also catalyze different reactions where compound other than water serve as nucleophiles. Actually, lipases are reported to catalyze transesterification,[3] esterification,[4] aminolysis or oximolysis.[5] This property prompted me to investigate intramolecular transesterification instead of intermolecular one catalyzed by lipase, leading stereospecific synthesis of macrocyclic lactones. Following this proposal, the catalytic potential of lipase toward methyl esters of ω- and (ω-1)-hydroxyalkanoic acid in organic solvents was examined. As a result, I found that lipase can be used for facile, preparative and efficient catalyst in synthesizing macrocyclic lactones, and for preparation of a chiral lactone through kinetic resolution of a racemic

(ω-1)-hydroxyalkanoic acid. This lactone-synthesis, especially asymmetric lactone-synthesis has some important advantages over the conventional chemical synthesis of lactones utilizing a pyridinethiol ester (Mukaiyama-Corey method),[6a] a halopyridinium salt (Mukaiyama method),[6b] a mixed anhydride with 2,4,6-trichlorobenzoyl chloride (Yamaguchi method),[6c] a mixed anhydride of 2,4,6-trichlorobenzoyl chloride with a high concentration of DMAP (modified Yamaguchi method),[6d, 6e] diethyl azodiformate (Mitsunobu method)[6f] and the recently developed chemical synthesis of lactones utilizing *p*-(trifuluoromethyl)benzoic anhydride and a catalytic amount of titanium salt together with chlorotrimethylsilane,[6g] *p*-nitrobenzoic anhydride and a catalytic amount of scandium trifluoromethanesulfonate,[6h] dealuminated HY zeolite,[6i] a polymer bound carbodiimide,[6j] ethoxyacetylene and a catalytic amount of $[RuCl_2(p\text{-cymene})]_2$,[6k] and 2-methyl-6-nitrobenzoic anhydride.[6l]




**2-3. Results and Discussion**

At first several lipases for their lactone synthesizing activity using methyl 16-hydroxyhexadecanoate (**1a**) (n = 15) in benzene were surveyed. To the substrate solution (1 mM in benzene) was added a powder of each lipase (5 mg/mL), and the suspension was stirred vigorously at 40 °C. The reaction was monitored by gas chromatography of the periodically withdrawn samples. These results are summarized in Table 1. The lipase P from *Pseudomonas sp.* and the porcine pancreatic lipase could catalyze lactonization efficiently to

give the lactone **2a** in 78% and 73 % yields, respectively (entries 1 and 2). The other lipases such as *Rhizopus japonicu*, *Rhizopus delmer*, *Candida cylindracea*, and Wheat germ, however, showed little or no activity (entries 3-6). These results indicate that the lactonization activity is not the common feature of lipases but seemed a specific character of some lipases. The character might be caused by the difference of the structure of lipases that shows the good stability in organic solvents. Lactone formation by Lipase P in benzene proceeded linearly up to 10 h, and reached plateau at ca. 25 h with 79 % conversion, probably due to the low concentration of the substrate. Judging from the fact that lactone formation ended at c.a. 80 % yield with 1 mM substrate, catalytic activity of Lipase P becomes negligible at the substrate concentration lower than 0.2 mM. Actually, Lipase P catalyzed lactonization in benzene obeyed Michaelis-Menten kinetics[7] with $K_m$ for methyl 16-hydroxyhexadecanoate of 9.61 mM, indicating that at 0.2 mM substrate, reaction rate decreased to 1/100 of the maximal velocity. Michaelis-Menten kinetics is based on two assumptions. 1) The reaction between the enzyme and its substrate remains in equilibrium (eq. 1), any effect of the equation 2 on this equilibrium being assumed to be negligible. These conditions will be achieved when the rate of breakdown of the ES complex back to the free enzyme and substrate is much greater than the rate of its breakdown to free enzyme and products ($k_{-1} >> k_{+2}$). 2) The concentration of free substrate remains essentially unchanged during the initial period of the reaction, so that in eq. 1 and eq. 2 the concentration of free substrate can be taken as being equal to the total substrate concentration. The rate of the overall reaction (v) will be determined by the rate of breakdown of the enzyme-substrate complex according to eq. 2 as eq. 3, where Vmax is the maximum velocity obtained when the enzyme is saturated with substrate, Km is the value of substrate which is experimentally found to give half the maximum velocity. This phenomenon

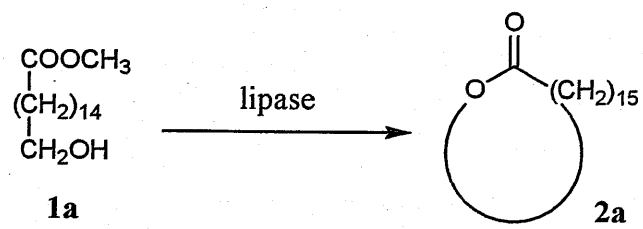
is discussed later agin.

$$E + S \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} ES \qquad \text{eq. 1}$$

$$ES \xrightarrow{k_{+2}} E + \text{products} \qquad \text{eq. 2}$$

$$v = Vmax\,[S] / (Km + [S]) \qquad \text{eq. 3}$$

**Table 1.** Efficiency of several lipases in lactone synthesis from methyl 16-hydroxyhexadecanoate (**1a**)[a]




**1a** **2a**

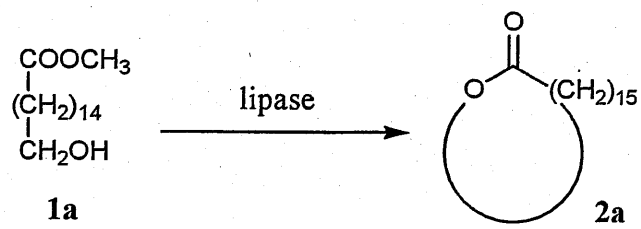
| Entry | Origin of lipase | **2a**, Yield / %[b] |
|---|---|---|
| 1 | *Pseudomonas sp.* | 78 |
| 2 | Porcine pancreas | 73 |
| 3 | *Rhizopus japonicus* | 2 |
| 4 | *Rhizopus delmer* | 0 |
| 5 | *Candida cylindracea* | 0 |
| 6 | Wheat germ | 0 |

a) Reactions were performed at 40 °C in 100 ml dry benzene with 500 mg of each lipase and 1 mM of methyl 16-hydroxyhexadecanoate (**1a**) for 72 hr. b) Yields were determined by GLC.

Because enzyme-catalyzed reactions in organic solvents are reported to be affected by solvents used,[8] the effect of solvents on the lactonization was examined. Lactonizaction yields of **2a** for 4 h in various solvents are summarized in Table 2. Among of the solvents used, cyclohexane showed the best yield (35%, entry 1). The order of the other solvents were as follows, tetrachloromethane (33%, entry 2), hexane (20%, entry 3), 1,1,1,-trichloroethane (19%, entry 4), heptane(16%, entry 5), benzene (12%, entry 6), toluene(7%, entry 7), *iso*-octane (6%, entry 8), 1,4-dioxane (2%, entry 9), trichloroethylene (0.8%, entry 10), and 1,1,2,2-Tetrachloroethane (0.4%, entry 11). The lactonizations in ethyl acetate and dimethylesulfoxide were not observed (entries 12, 13).

From the Table 2, more than 87-fold difference in the yield of **2a** for 4 h was observed (entry 1 vs. entry 11). The yields related roughly the dielectric constants of solvents. Polar solvents, such as ethyl acetate, seemed badly for the lactonization, which agreed well with the tendency in lipase catalyzed ester synthesis.[9] The low activity of lactonization with lipase in some polar solvents might be due to the loss of the water from lipase in polar solvents, which need to keep its proper conformation, by polar solvents. The reason why the polar solvent, 1,1,1,-trichloroethane, showed 19 % yield is not clear.

**Table 2.** Survey of Solvents for Lipase P Catalyzed Lactonization of Methyl 16-Hydroxyhexadecanoate (**1a**)[a]




**1a** **2a**

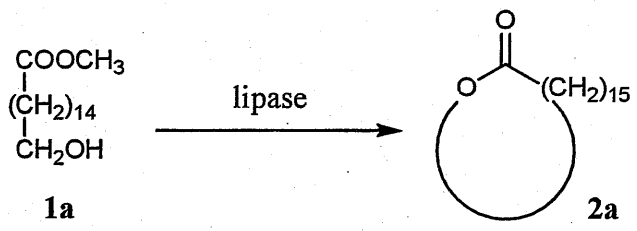
| Entry | Solvent | Dielectric constant[b] | **2a**, Yield / %[c] |
|---|---|---|---|
| 1 | Cyclohexane | 2.052 (20°C) | 35 |
| 2 | Tetrachloromethane | 2.238 (20°C) | 33 |
| 3 | Hexane | 1.890 (20°C) | 20 |
| 4 | 1,1,1-Trichloroethane | 7.53 (20°C) | 19 |
| 5 | Heptane | 1.924 (25°C) | 16 |
| 6 | Benzene | 2.283 (20°C) | 12 |
| 7 | Toluene | 2.24 (20°C) | 7 |
| 8 | *iso*-Octane | 1.943 (20°C) | 6 |
| 9 | 1,4-Dioxane | 2.235 (25°C) | 2 |
| 10 | Trichloroethylene | 3.409 | 0.8 |
| 11 | 1,1,2,2-Tetrachloroethane | 8.00 (20°C) | 0.4 |
| 12 | Ethyl acetate | 6.02 (20°C) | 0 |
| 13 | Dimethylsulfoxide | 48.9 (20°C) | 0 |

a) Reactions were performed at 30 °C in 10 ml solvent with 50 mg of lipase P and 1 mM of methyl 16-hydroxyhexadecanoate (**1a**) for 4 hr. b) "Handbook of Solvents", ed. by T. Asahara et al., Kodan-sya Scientific Tokyo, 1998 b) Yields were determined by GLC.

To know more about the effect of solvents, the time course of the lactone formation was analyzed using some good solvents for the lipase catalyzed lactonization (Table 3). The initial rate was 0.67 nmoles $mg^{-1}$ $min^{-1}$ in heptane (entry 1), 0.65 in hexane (entry 2), 0.59 in

cyclohexane (entry 3), and 0.09 in benzene (entry 4). As shown in the Table 3, the initial rate in heptane was more than 7-fold higher than that in benzene, while the same lactone yield was obtained in both cases in sufficient reaction time. The initial rate might be determined by the rate of breakdown of the enzyme-substrate complex, which is changed by the solvent.

**Table 3**. Effect of Solvents on the Reaction Rate and the Yield in Lipase Catalyzed Lactonization of Methyl 16-Hydroxyhexadecanoate (**1a**)[a]




**1a** **2a**

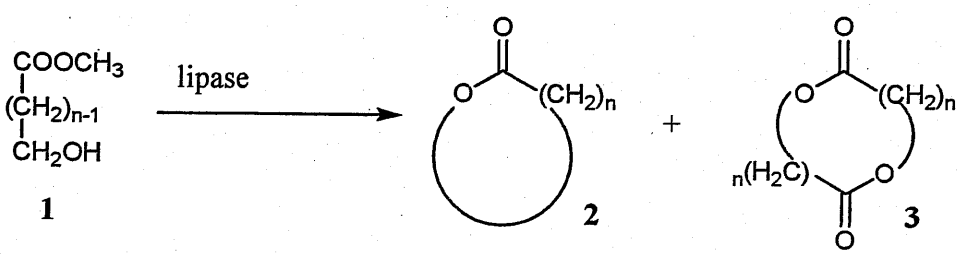
| Entry | Solvent | Reaction rate[b] / nmole $mg^{-1}$ $min^{-1}$ | Reaction time / h | **2a**, Yield / %[c] |
|---|---|---|---|---|
| 1 | Heptane | 0.67 | 10 | 78 |
| 2 | Hexane | 0.65 | 6 | 80 |
| 3 | Cyclohexane | 0.59 | 8 | 79 |
| 4 | Benzene | 0.09 | 30 | 78 |

a) Reactions were performed at 40 °C in 300 ml solvent with 1.5 g of lipase P and 1 mM of methyl 16-hydroxyhexadecanoate (**1a**). b) Reaction rate was calculated from the initial linear part of the synthesis. c) Yields were determined by GLC.

Next, the lipase-catalyzed lactonization of other ω-hydroxyacid methyl esters (**1b – 1d**) was carried out. The results are summarized in Table 4. The reaction of methyl 13-hydroxytridecanoate (**1b**) gave lactone **2b** in 38% yield together with the corresponding diolide **3b** in 25% yield (entry 1). In the case of methyl 14-hydroxytetradecanoate (**1c**), the

yield of lactone **2c** was 64% and the yield of corresponding diolide **3c** was 9% (entry 2). Methyl 15-hydroxypentadecanoate (**1d**) gave lactone **2d** in 78% yield with no detection of corresponding diolide **3d** (entry 3). In the case of methyl 16-hydroxyhexadecanoate (**1a**), the yield of lactone **2a** was 78% and the yield of corresponding diolide **3a** was 3% (entry 4). The yield of lactone **2** increased with the increase of the chain length, and on the other hands, the diolide **3** formation decreased with the increase of the chain length, and become negligible in the cases of methyl 15-hydroxypentadecanoate (**1d**; not detected) and methyl 16-hydroxyhexadecanoate (**1a**; 3 % yield). Therefore, with Lipase P, some proper distance between ester and free OH group would need for the efficient intramolecular transesterification.

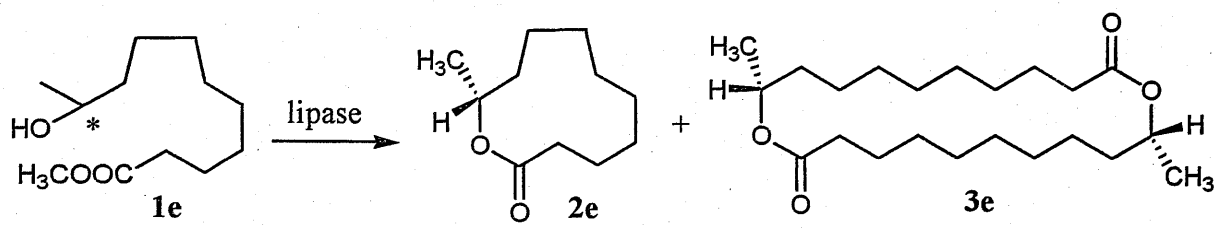
**Table 4**. Lactonization of ω-Hydroxyacid Methyl Esters **1** with Lipase[a]



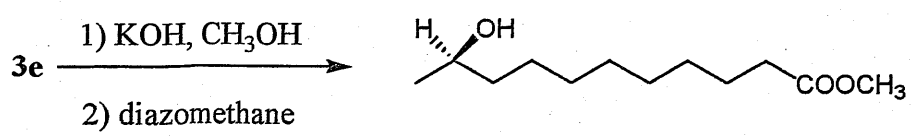

| Entry | $HOCH_2$-$(CH_2)_{n-1}$-$COOCH_3$ | **2**, Yield / %[b] | **3**, Yield / %[b] |
|---|---|---|---|
| 1 | n = 12 (**1b**) | 38 | 25 |
| 2 | n = 13 (**1c**) | 64 | 9 |
| 3 | n = 14 (**1d**) | 78 | ND |
| 4 | n = 15 (**1a**) | 78 | 3 |

a) Reactions were performed at 40 °C in 300 ml solvent with 3 g of lipase P and 1 mM of each ester for 72 h. b) Isolated yield.

To ascertain the asymmetric nature of the lipase-catalyzed lactonization, I used racemic methyl 10-hydroxyundecanoate, (*R,S*)-**1e**, as a substrate. Because diolide formation is greater with shorter chain length (n = 8) as mentioned table 4, I only isolated 45 mg of the corresponding diolide **3e** from 108 mg of (*R,S*)-**1e**. In order to estimate absolute configulation of the product, **3e** was hydrolyzed with KOH/ MeOH and methylated with diazomethane. The resulting **1e** was found to be (*R*)-isomer by comparison of the specific rotation ($[\alpha]_D^{25}$ = -6.3°, c = 1.4 in MeOH) with that reported ($[\alpha]_D^{25}$ = -5.8°, c = 2.5 in MeOH for (*R*)-**1e**).[10] The optical purity of (*R*)-**1e** was 97 % ee, which was determined by $^1$H-NMR of the MTPA ester using Eu(fod)$_3$. The recovered **1e** of the lactonization was rich in (*S*)-isomer ($[\alpha]_D^{25}$ = +1.8°, c = 2.9 in MeOH). Therefore, it can be concluded that lipase P can catalyze stereospecific intramolecular transesterification leading to the formation of (*R*)-isomer lactone through kinetic resolution of a racemic (ω-1)-hydroxyacid methyl ester. A 12-membered macrolide, (+)-patulolide A, which discussed in chapter 1, could not synthesized by this method, but the diolide was obtained.[11]




**1e** **2e** **3e**




(R)-**1e**

## 2-4. Conclusion

In summary, it was revealed that lipase could be used for facile, preparative and efficient catalyst in synthesizing macrocyclic lactones in organic solvents. Also the effect of the solvent and the effect of the methylene chain length of hydroxyester on lactonization was elucidated. Lipase P can catalyze stereospecific intramolecular transesterification leading to the formation of (*R*)-isomer through kinetic resolution of a racemic (ω-1)-hydroxyacid methyl ester.

Since my initial report,[12] the lipase-catalyzed intramolecular transesterification of ω-hydroxy esters has been investigated extensively.[13-21] Shorter-chain γ -hydroxy esters (n=3) underwent lactonization with a high yield.[13,14] With a medium-sized hydroxy ester (n=9) the product gave a complex, consisting of a mixture of di-, tri-, tetra-, and pentalactones.[15] Macrocyclic lactones via direct condensation of diacids with diols were reported.[16] Mevinic acid analogue[17], (R)-recifeiolide[18], and several macrolide pheromones[19] were synthesized by using enantioselective lactonization. Lipase catalyzed formation of lactones via irreversible intramolecular acyltransfer (vinyl esters)[20] and the utilization of immobilized lipase[21] were also investigated.

## 2-5. Experimental Section

### General

Melting points are uncorrected. $^1$H NMR spectra were recorded on a JEOL (100 MHz) spectrometer. $^1$H NMR spectra were reported as chemical shifts in parts-per-million (ppm) based on a TMS internal standard in $CDCl_3$. Coupling constants (*J*) are reported in Hertz (Hz). Silica gel column chromatography was performed on a Merck 70 - 230 mesh. Commercially available reagents were used without further purification. Lipases of *Pseudomonas sp.* and

*Rhizopus japonicus* were supplied by Nagase Biochemicals Ltd., Osaka. Lipases of porcine pancreas, *Candida cylindracea* and wheat germ were purchased from Sigma. Lipases of *Rhizopus delmer* were purchased from Seikagaku Kogyo Co., Ltd., Tokyo. Lactones and diolides were determined by Hitachi 163 gas chromatograph equipped with FID. For lactones, a glass column (5 mm, 1 m) packed with Silicone OV-17 was used. Column and injection temperatures were 190 and 250 °C, respectively. For diolides, a glass column (5 mm, 1 m) packed with Silicone DC-QF-1 was used. Column and injection temperatures were 250 °C.

**Starting Materials.**

16-Hydroxyhexadecanoic acid was purchased from Aldrich. 1,13-Tridecanedioic acid, 1,14-tetradecanedioic acid and 1,15-pentadecanedioic acid were kindly provided by Nippon Mining Co., Ltd., Tokyo.

**Methyl 16-hydroxyhexadecanoate (1a)**

Anhydrous HCl (2 g, generated from NaCl and sulfuric acid) was introduced into a solution of 16-hydroxyhexadecanoic acid (4.16 g, 15.3 mmol) in MeOH (40 mL). The solution was refluxed for 1.5 h, and kept at room temperature overnight. The reaction product was extracted with $CH_2Cl_2$ and dried over anhydrous sodium sulfate and the solvent was evaporated *in vacuo* to give **1a** (4.56 g, 100%). **1a**: white solid mp 54 °C. IR (nujol) 3260, 2950, 2915, 2845, 1745, 1740 $cm^{-1}$; MS *m/z* 287 ($M^+$+1); ). $^1H$ NMR (100 MHz, $CDCl_3$) δ 3.52-3.76 (2H, m), 3.67 (3H, s), 2.31 (2H, t), 1.16-1.80 (26H, m). Anal. Calcd for $C_{17}H_{34}O_3$: C, 71.26; H, 11.97. Found: C, 71.38; H, 12.01.

**Methyl 13-hydroxytridecanoate (1b)**

Red Al solution (82 mmol) diluted with toluene (40 mL) was added dropwise to a solution of 1,13-tridecanedioic acid (5.0 g, 20 mmol) in THF (200 mL) at 0 °C during 2.5 h under a nitrogen atmosphere. The mixture was further stirred for 2.5 h at the same temperature. Then, 3 N HCl (300 mL) was added carefully to the stirring mixture. The resulting mixture was extracted with $CH_2Cl_2$, washed with water, and dried over anhydrous sodium sulfate and the solvent was evaporated *in vacuo* to give crude hydroxytridecanoic acid (4.79 g) that was used next reaction without any purification. Esterification of the product was carried out as described for **1a**. Column chromatography of the crude product ($CH_2Cl_2$ : AcOEt = 20 : 1) gave **1b** (1.26 g, 25 %). **1b**: white solid mp 37 °C. IR (nujol) 3275, 1740 $cm^{-1}$. MS *m/z* 245 ($M^+$+1). $^1H$ NMR (100 MHz, $CDCl_3$) δ 3.52-3.70 (2H, m), 3.67 (3H, s), 2.31 (2H, t), 1.16-1.84 (20H, m). Anal. Calcd for $C_{14}H_{28}O_3$: C, 68.80; H, 11.56. Found: C, 68.47; H, 11.47.

**Methyl 14-hydroxytetradecanoate (1c)**

Reaction of 1,14-tetradecanedioic acid (5.0 g, 19.4 mmol) similar to that for **1b** gave **1c** (2.07 g, 41%) after column chromatography ($CH_2Cl_2$ : AcOEt = 20 : 1). **1c**: white solid mp 43 °C. IR (nujol) 3300, 2920, 2840, 1740 $cm^{-1}$; MS *m/z* 259 ($M^+$+1). $^1H$ NMR (100 MHz, $CDCl_3$) δ 3.52-3.70 (2H, m), 3.67 (3H, s), 2.31 (2H, t), 1.12-1.84 (22H, m). Anal. Calcd for $C_{15}H_{30}O_3$: C, 69.71; H, 11.71. Found: C, 69.69; H, 11.70.

**Methyl 15-hydroxypentadecanoate (1d)**

Reaction of 1,15-pentadecanedioic acid (1.71 g, 6.3 mmol) similar to that for **1b** gave **1d** after column chromatography ($CH_2Cl_2$ : AcOEt = 20 : 1). **1d**: white solid. mp 50.5 °C. IR

(nujol) 3275, 1740 $cm^{-1}$. MS *m/z* 273 ($M^+$+1). $^1H$ NMR (100 MHz, $CDCl_3$) δ 3.52-3.76 (2H, m), 3.66 (3H, s), 2.30 (2H, t), 1.12-1.84 (24H, m). Anal. Calcd for $C_{16}H_{32}O_3$: C, 70.53; H, 11.85. Found: C, 70.11; H, 11.79.

**Methyl 10-hydroxyundecanoate (1e)**

Esterification of 10-undecenoic acid (5.0 g, 27.2 mmol) as described for **1b** gave the crude ester (5.77 g).

To a solution of the ester (5.77 g) in THF (50 mL), $Hg(OAc)_2$ (9.08 g, 28.5 mmol) in THF-$H_2O$ (1:1, 100 mL) was added in one portion and the mixture was stirred for 1 h. Then 3N NaOH solution (100 mL) was added to the reaction mixture and stirred for 30 min. $NaBH_4$ (1.96 g, 51.8 mmol) was added portionwise. After stirring for1 h, the reaction mixture was acidified with 6 N HCl solution. THF was evaporated in vacuo and the solution was extracted with EtOAc, dried over anhydrous sodium sulfate and the solvent was evaporated *in vacuo* to give the hydroxyacid (5.45 g). Estrifiaction of the hydroxyacid (5.45 g) as described for **1b** gave **1e** (5.33g, 91% in three steps) after column chromatography ($CH_2Cl_2$ : AcOEt = 50 : 1). **1e**: colorless oil IR (neat) 3350, 1740 $cm^{-1}$. MS *m/z* 217 ($M^+$+1). $^1H$ NMR (100 MHz, $CDCl_3$) δ $^1$HNMR ($CDCl_3$) δ 3.5-4.0 (4H, m), 2.1-2.5 (2H, m), 1.1-2.0 (14H, m), 1.16 (3H, d). Anal. Calcd for $C_{12}H_{24}O_3$: C, 66.61; H, 11.19. Found: C, 66.62; H, 11.26.

**Typical Procedure for Macrocyclic Lactonization with Lipase in Organic Solvent**

To a solution of methyl 16-hydroxyhexadecanoate (**1a**; 85.8 mg, 0.3 mmol) in benzene (300 mL) was added a powder of Lipase P from *Pseudomonas sp* (3.0 g), and the suspension was stirred vigorously at 40 °C for 58-72 h. After separation of lipase by filtration, filtrate was

concentrated to give the crude product. The insoluble compound in hexane was filtrated to give cyclohexadecanediolide (**3a**; 2.0 mg). Soluble product was purified by column chromatography (hexane : AcOEt = 20 : 1) to give cyclohexadecanolide (**2a**; 60.9 mg). Similar reactions of **1a** as well as those of **1b-e** were carried out. Reactions using other lipase and solvents for the different reaction time are summarized in Tables 1-4.

**Cyclohexadecanolide (2a)**

Yield 80%: white solid mp 28.5-30 °C (lit.[13] 35°C). IR (nujol) 2930, 2850, 1740 $cm^{-1}$. MS *m/z* 254 ($M^+$). $^1H$ NMR (100 MHz, $CDCl_3$) δ 3.9-4.2 (2H, m), 2.1-2.4 (2H, m), 1.1-1.9 (26H, m). Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.52; H, 11.89. Found: C, 75.09; H, 11.82.

**Cyclohexadecanediolide (3a)**

Yield 3%: white solid mp 109-110 °C (lit.[13] 108°C); IR (nujol) 1730 $cm^{-1}$. $^1H$ NMR (100 MHz, $CDCl_3$) δ 3.9-4.2 (4H, m), 2.1-2.5 (4H, m), 1.1-1.9 (52H, m). Anal. Calcd for $C_{32}H_{60}O_4$: C, 75.52; H, 11.89. Found: C, 74.09; H, 11.80.

**Cyclotridecanolide (2b)**

Purified by column chromatography (hexane : AcOEt = 50 : 1). Yield 32%: faint yellow oil; MS *m/z* 212 ($M^+$); $^1H$ NMR (100 MHz, $CDCl_3$) δ 4.15 (2H, m), 2.36 (2H, m), 1.1-1.8 (20H, m).

**Cyclotridecanediolide (3b)**

Purified by column chromatography (hexane : AcOEt = 50 : 1). Yield 28%: white solid;

MS *m/z* 424 ($M^+$); $^1$HNMR ($CDCl_3$) δ 4.09 (4H, m), 2.29 (4H, m), 1.08-1.80 (40H, m).

**Cyclotetradecanolide (2c)**

Purified by column chromatography (hexane : AcOEt = 20 : 1). Yield 64 %: colorless oil; MS *m/z* 226 ($M^+$).

**Cyclotetradecanediolide (3c)**

The insoluble compound in hexane; Yield 9%: white solid; MS *m/z* 452 ($M^+$).

**Cyclopentadecanolide (2d)**

Purified by column chromatography ($CH_2Cl_2$). Yield 78%: white solid; mp 30-32 °C (lit.[13] 32°C); IR (nujol) 1727 $cm^{-1}$. MS *m/z* 240 ($M^+$). $^1$H NMR (100 MHz, $CDCl_3$) δ 4.14 (2H, m), 2.35 (2H, m), 1.37 (24H, m). Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.93; H, 11.75. Found: C, 74.50; H, 11.71.

**Asymmetric Lactonization from Racemic Methyl 10-Hydroxyundecanoate (1e)**

To the solution of methyl 10-hydroxyundecanoate (**1e**; 108 mg, 0.5 mmol) in hexane (500 mL) was added a powder of Lipase P from *Pseudomonas sp* (2.5 g), and the suspension was stirred vigorously at 40 °C for 31 h. After separation of lipase by filtration, filtrate was concentrated to give the crude product. The product was purified by column chromatography (hexane : AcOEt = 10 : 1) to give (3*R*, 14*R*)-3,14-dimethyl-2,13-dioxadocosane-1,12-dione **3e** (45 mg, 0.12 mmol, 14 %). **3e**: white solid; MS *m/z* 368 ($M^+$); $^1$H NMR (100 MHz, $CDCl_3$) δ 4.95 (4H, m), 2.26 (4H, m), 1.10-1.80 (28H, m), 1.19 (6H, d); $[\alpha]_D^{25}$ = -14.8 ° (c 0.63,

MeOH).

**Alkali Hydrolysis of 3e followed by Treatment with Diazomethane**

To the solution of **3e** (40 mg) in MeOH (2 mL) was added 2N KOHaq (1 mL), and stirred at room temperature for 6 days. Then, 3 N HClaq was added to the stirring mixture, the resultant mixture was extracted with $CH_2Cl_2$ , and the organic phase was washed with water, dried over anhydrous sodium sulfate and the solvent was evaporated *in vacuo* to give the crude hydroxyacid (white crystals, 30.4 mg).

To the solution of the crude product in ether was added carefully a solution of diazomethane in ether. The reaction mixture was stirred at room temperature overnight and concentrated *in vacuo*. The crude product of methyl ester was purified by column chromatography ($CH_2Cl_2$ : AcOEt = 20 : 1) to give methyl (10*R*)-10-hydroxyundecanoate **1e** (28.0 mg, 70 % from **3e**). **1e**: $[\alpha]_D^{25}$ = -6.3°, c = 1.4 in MeOH (lit.[10] (*R*)-**1**, $[\alpha]_D^{25}$ = -5.8°, c = 2.5 in MeOH).

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# Chapter 3. Practical Synthesis of 15-Hydroxypentadecanoic Acid, the Precursor of Cyclopentadecanolide, by Using Selective Hydrogenation with Ruthenium or Rhenium Catalysts

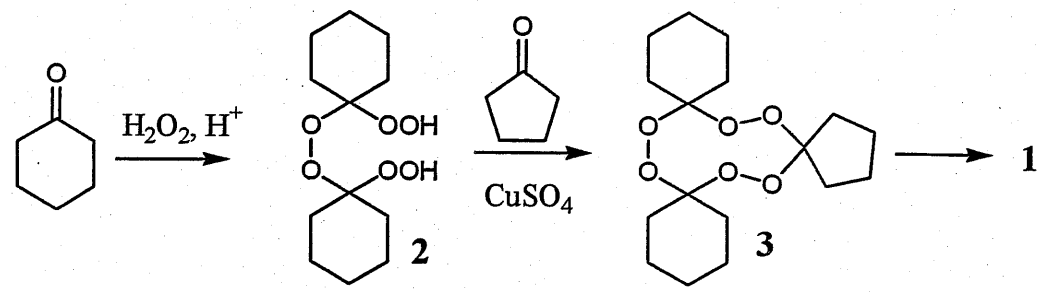
## 3-1. Summary

The selective hydrogenation of 1,15-pentadecanedioic acid derivatives (1,15-pentadecanedioic acid, methyl hydrogen 1,15-pentadecanedioate, and dimethyl 1,15-pentadecanedioate) to 15-hydoxypentadecanoic acid, which is an important precursor of macrocyclic musk cyclopentadecanolide, has been studied using Ru-Sn-Al or Re-Sn-Al catalysts prepared by the sol-gel method. The ability of the selective hydrogenation catalysts and reaction conditions were evaluated by an apparent hydrogenated ratio of the two terminal functional groups, which was termed $k_1/k_2$ value, determined by comparison of the experimental results and the calculation under an estimated kinetic model. Serendipitously it was found that 1,15-pentadecanedioic acid, which has the same terminal functional groups, gave 15-hydoxypentadecanoic acid with high selectivity.

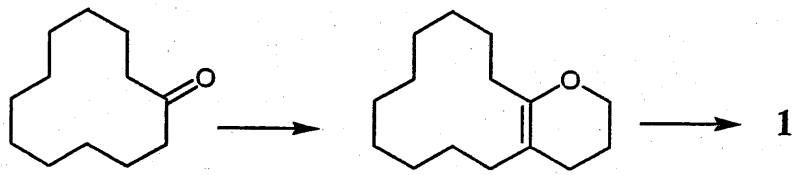
## 3-2. Introduction

New practical synthesis of natural macrocyclic musks is one of the most important topics in the perfume industry because the natural macrocyclic musks are known to be safer and more biodegradable than the others, polycyclic musks and nitro-musks.[1] Cyclopentadecanolide (**1**) is one of the represented macrocyclic musk perfumes isolated from the *Angelica* root.[2] Three industrial routes are known for the manufacture of **1**. The first industrial route for the synthesis of **1** is known as the Story synthesis[3, 4] (Scheme 1). The next

route is using the ring enlargement of cyclododecanone (**4**)[5] (Scheme 2). The last one is achieved using 15-hydoxypentadecanoic acid (**6**) as an important intermediate (Scheme 3).



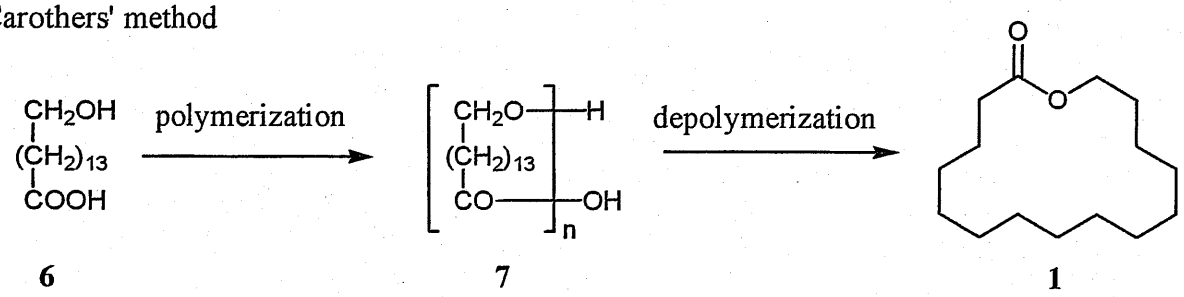

**Scheme 1** The first industrial route for the synthesis of **1** known as the Story synthesis




**Scheme 2** The second industrial route for the synthesis of **1** started from cyclododecanone (**4**)

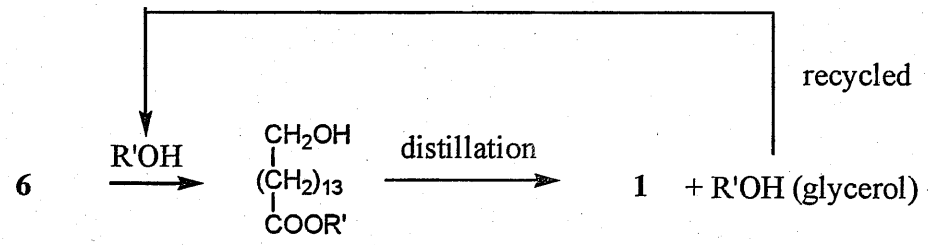
In the last route, the synthesis of **1** from **6** is achieved in excellent yield by Carothers' method[6, 7] that uses the polymerization of **6** to the polyester **7** and the depolymerization of **7** to **1** or by Collaud's method[8, 9, 10, 11] that uses vacuum distillation of glycerol ester **8**. Therefore, the economical synthesis of **6** is the major problem in this route[5].

Carothers' method




**6** **7** **1**

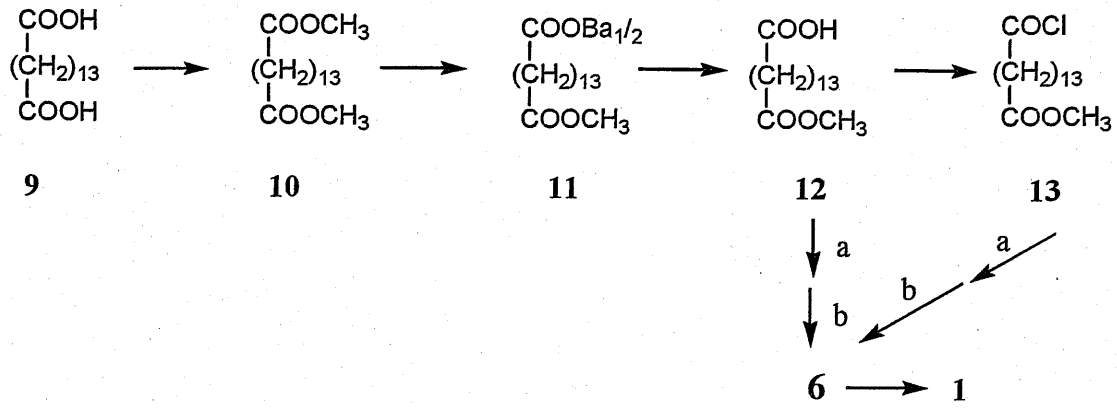
Collaud's method




**8**

**Scheme 3** The third industrial route for the synthesis of **1** using intramolecular cyclization started from 15-hydroxypentadecanoic acid (**6**).

The hydroxy acid **6** can be prepared from 1,15-pentadecanedioic acid derivatives (**12**, **13**) (Scheme 4). It has been reported that the selective reduction of methyl hydrogen 1,15-pentadecanedioate (**12**) to **6** with reducing agents or hydrogenation catalysts ($Bu_4NBH_4$[12], Cu-Cr[13], Co-La-Pd[14]), where the difference of the reduction rate between the acid group and the methyl ester group is utilized. Similarly, the selective reduction of acid chloride **13** to **6** with a reducing agent or a hydrogenation catalyst ($NaBH_4$[15], Pd/C[15]) has been reported using the difference of the reduction rate between the acid chloride functional group and the methyl ester group. I believed that a catalytic hydrogenation of these derivatives is an appropriate way to prepare **6** economically.




**Scheme 4** The synthesis of 15-hydroxypentadecanoic acid (**6**) from 1,15-pentadecanedioic acid derivatives. a; reduction or hydrogenation, b; hydrolysis.

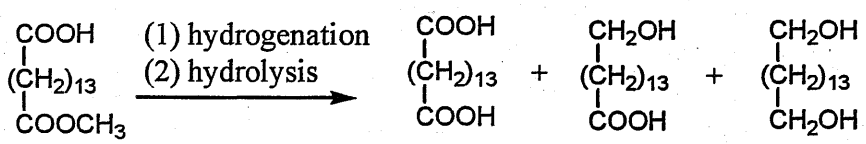
Recently, Mizukami and Niwa have developed a Ru-Sn-alumina[16] and Re-Sn-alumina[17] catalysts that could reduce oleic acid to oleyl alcohol. These precious metal catalysts would be better than the popularly used Cu-Cr catalyst because the precious metal catalysts can hydrogenate a carboxylic acid and an ester group at lower hydrogen pressure. Moreover, these catalysts are more ecofriendly because they do not use heavy metal such as Cr.

Based on these points of view, I studied on the behavior of these Ru-Sn-alumina and Re-Sn-alumina catalysts in the selective hydrogenation of methyl hydrogen 1,15-pentadecanedioate (**12**) to **6**. In this study, I evaluated the ability of the selective hydrogenation catalysts and reaction conditions using an apparent hydrogenated ratio of two terminal functional groups, which was termed $k_1/k_2$ value, determined by comparison of the experimental results and the calculation under an estimated kinetic model. Moreover I found that 1,15-pentadecanedioic acid, which has same terminal functional groups, gave 15-hydoxypentadecanoic acid with high selectivity. This new method would be effective route of industrial preparation of 15-hydoxypentadecanoic acid.

### 3-3. Results and Discussion

Dicarboxylic acid **9** has been industrially available by the fermentation of pentadecane with *Candida*[18]. Esterification of **9** with methanol and a catalytic amount of sulfuric acid gave dimethyl eater **10**. Half saponification of **10** with barium hydroxide in methanol furnished barium methyl 1,15-pentadecanedioate **11**[19] as a white precipitate, and the subsequent acidification afforded methyl hydrogen 1,15-pentadecanedioate **12** (Scheme 4).

The hydrogenation reaction was carried out in a 100-mL or 500-mL autoclave reactor at the required temperature that was charged with the starting material, solvent and catalyst, and pressurized with hydrogen to the reaction pressure. After the appropriate time, the reactor was cooled and the reaction mixture was recovered for analysis. The reaction mixture was analyzed as the trimethylsillyl ether and/or ester by gas chromatography after the hydrolyzed with sodium hydroxide in methanol-water solution to give hydroxy acid **6**, diol **14** and dicarboxylic acid **9**, followed by treatment with trimethylsillyl chloride/pyridine (Scheme 5).




**12** **9** **6** **14**

**Scheme 5** Hydrogenation of **12**.

The typical concentration-time profile for hydrogenation of methyl hydrogen 1,15-pentadecanedioate (**12**) to 15-hydroxypentadecanoic acid (**6**) with Ru-Sn-alumina catalyst is shown in Figure 1. The concentration of **9** (○), which is the hydrolyzed product of **12**, fell monotonously, while the concentration of the intermediate **6** (■) rose maximum and

then fell. On the other hand, the concentration of the final product, diol **14** (●), rose monotonously.

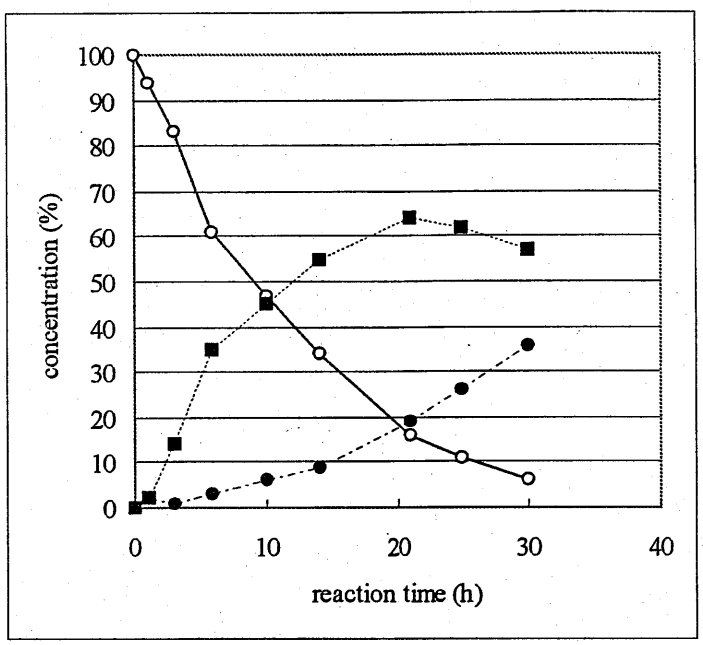
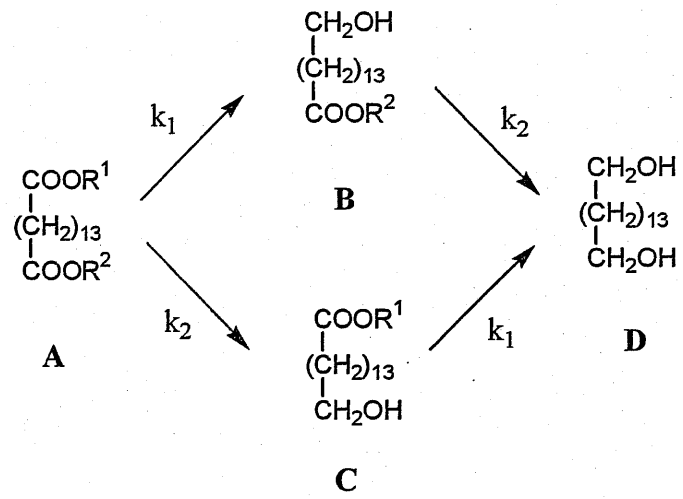



**Figure 1** Typical concentration-time profile for hydrogenation of methyl hydrogen 1,15-pentadecanedioate (**12**) to 15-hydroxypentadecanoic acid (**6**) with 3.0 wt% Ru and 3.5 wt% Sn-alumina catalyst at 6.4 Mpa (65 kg/cm$^2$). Reaction conditions: **6**, 50 g; catalyst, 6 g; decaline, 100 g; temp., 250 °C. ○ **9** (hydrolyzed product of recovered **12**); ■ **6**; ● 1,15-pentadecanediol (**14**).

I assumed that hydrogenation of **12** obeys the 2-steps successive first-order reaction path shown in Scheme 7.




**Scheme 7** Proposed hydrogenation path of pentadecanedioic acid derivatives.

It is known that the concentration of an intermediate in a 2-steps successive first-order reaction depends on the conversion of starting material and the ratio of the 2-steps rate constants of each step[20]. The yield of the intermediate can be derived from them. I applied these relationships to analyze the selective hydrogenation of **12** with a modification as shown below. To simplify the model, I supposed also that the reaction rate constant of the same functional group was always same, and independent of the other terminal functional group of the compound itself in this path. Based on the postulated model, the reaction rate constants of both A to B and C to D are represented by $k_1$, and that of both A to C and B to D by $k_2$.

When a starting material A is methyl hydrogen 1,15-pentadecanedioate (**12**), the concentration of the recovered starting material **12** that is measured as **9** ([A]), 15-hydroxypentadecanoic acid (**6**) ([B] + [C]), and 1,15-pentadecanediol (**14**) ([D]) in reaction mixture is given as function of time;

$$\textbf{[12]}\ (\textbf{[9]}) = [A] = [A]_0 \exp\{-(k_1+k_2)t\} \qquad \text{(eq. 1)}$$

$[\mathbf{6}] = [B] + [C] = [A]_0 [\exp(-k_1t) + \exp(-k_2t) - 2\exp\{-(k_1+k_2)t\}]$ (eq. 2)

$[\mathbf{14}] = [D] = [A]_0 [1 - \exp(-k_1t) - \exp(-k_2t) + 2\exp\{-(k_1+k_2)t\}]$ (eq. 3)

where $k_1$ = hydrogenation rate constant of the terminal group, $k_2$ = hydrogenation rate constant of the other terminal group, $k_1 \geqq k_2$, $[A] = [A]_0$, $[B] = [C] = [D] = 0$ at $t = 0$.

Therefore, the conversion of **12** and the yield of **6** were given as;

Conversion of **12** $= [[A]_0 - [A]_0 \exp\{-(k_1+k_2)t\}] / [A]_0 = 1 - \exp\{-(k_1+k_2)t\}$ (eq. 4)

Yield of **6** $= ([B] + [C]) / [A]_0 = \exp(-k_1t) + \exp(-k_2t) - 2\exp\{-(k_1+k_2)t\}]$ (eq. 5)

Then a hydrogenated ratio of the two terminal functional groups is given as $k_1/ k_2$ value. Because of the definition, $k_1/ k_2$ value is larger than 1.

The relationships between the yield of **6** and the conversion of **12**, which is calculated for $k_1/ k_2$ values = 1, 5 and infinity, are shown in Figure 2. These relationships are called the time-independent plots[21].

The time-independent plot of the experimental result of Figure 1, which is superposed on Figure 2, showed good agreement with that of the calculation with $k_1/ k_2$ value = 5. Therefore, I used the $k_1/ k_2$ value, which is determined by comparison of the experimental results and the calculation under an estimated kinetic model, to evaluate the results of experiments. The $k_1/ k_2$ value is time-independent and could be determined by single data point when the conversion is from c.a. 40 to 90%, consequently, the $k_1/ k_2$ value is convenient for the direct comparison of the result of various screenings.

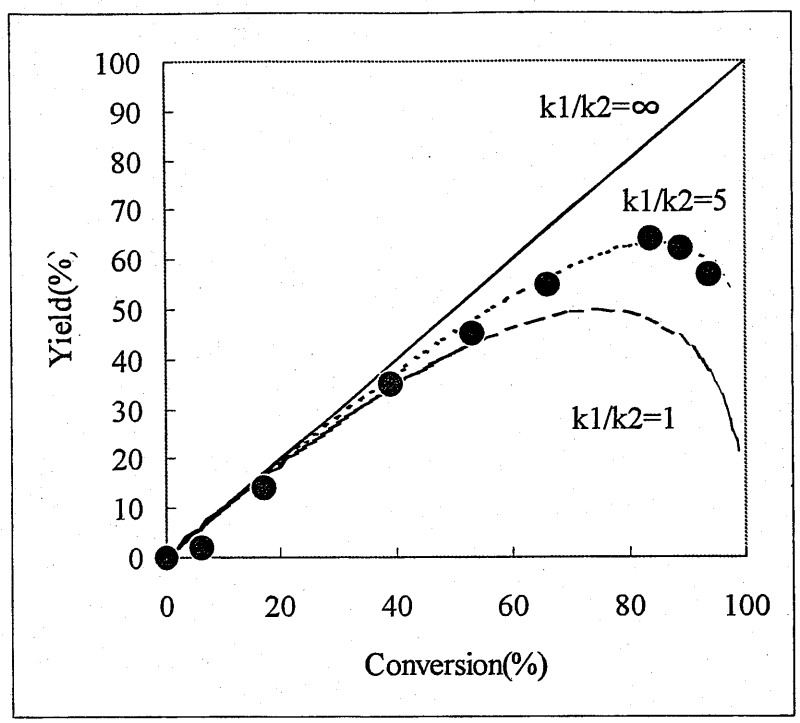


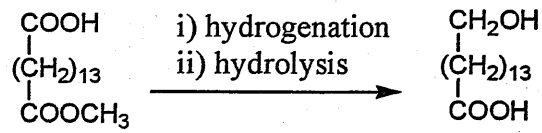

**Figure 2** Relationship between yield and conversion for given $k_1/k_2$ values. The data points are the same result shown on Figure 1.

A higher $k_1/ k_2$ value is preferable to the economical preparation of **6**. When a $k_1/ k_2$ value is high, each the maximum yield of **6** and the conversion of starting material is high. Therefore, the high conversion of starting material would not need to separate 1,15-pentadecanedioic acid (**9**) from reaction mixture after the hydrolysis. On the other hand, when a $k_1/ k_2$ value is low, the conversion of starting material needs to be low in order to avoid obtaining unwanted **14** instead of **6**. Because the low conversion of starting material leads a large amount of **9**, the necessity of a separation of **9** would hurt economical merit of the hydrogenation route.

In order to explore better catalysts and conditions for the preparation of **6**, I studied that the effect of the temperature on the hydrogenation of methyl hydrogen 1,15-pentadecanedioate (**12**) using Re-Sn-Al catalysts (Table 1), the effect of the hydrogen

pressure on the hydrogenation of **12** using Re-Sn-Al catalysts (Table 2), the effect of atomic ratio of Re to Sn on the hydrogenation of **12** using Re-Sn-Al catalysts (Table 3), the effect of calcination and activation condition of Ru-Sn-Al catalysts on the hydrogenation of **12** (Table 4), the effect of the second metal additive for Re-Al catalysts on the hydrogenation of **12** (Table 5), and the effect of starting materials using Ru-Sn-Al catalyst (Table 6).

**Table 1**. Effect of the temperature on the hydrogenation of methyl hydrogen 1,15-pentadecanedioate (**12**) using Re-Sn-Al catalysts[a].




**12** **6**

| Entry | Temp. / °C | Conversion of **12** / %[b] | Selectivity[c] of **6** / %[b] | Yield of **6** / %[b] | $k_1/k_2$ |
|---|---|---|---|---|---|
| 1 | 220 | 3 | 94 | 3 | -[d] |
| 2 | 250 | 15 | 93 | 14 | -[d] |
| 3 | 265 | 23 | 90 | 21 | -[d] |
| 4 | 280 | 28 | 91 | 25 | -[d] |

a) Reaction conditions: catalyst, $Re_2O_7$ (2 wt%)/ $Sn(OEt)_4$ (Re / Sn = 1 / 0.5) / aluminum isopropoxide. activated at 400 °C for 4 h in a stream of hydrogen. 4.0 g; pressure, 6.5 MPa; reaction time, 3 h; methyl hydrogen 1,15-pentadecanedioate **12**, 50.0 g; decaline, 100.0 g. b) Yields were determined by GLC. c) Selectivity = Yield / Conversion. d) The k1/k2 value could not be determined because of low conversion.

Using the Re-Sn-Al catalyst, the effect of the hydrogenation temperature was examined (Table 1). The conversion at 220 °C was low at 3.4 % (entry 1). Increasing the hydrogenation temperature to 280 °C led to the increased conversion and decreased selectivity (entries 2-4).

The effect on $k_1/k_2$ value of these conditions could not be determined because of the low conversion of them. I chose 250 or 280 °C for the experiment hereafter.

Moreover the effect of the hydrogenation pressure was investigated (Table 2). As shown Table 2, increasing the hydrogenation pressure from 3.0 to 12.0 MPa improved the conversion (entries 1-3). The effect on $k_1/k_2$ value of these conditions could not be determined because of the low conversion of them in these cases. I chose 6.5 or 10.0 MPa for the experiment hereafter.

**Table 2**. Effect of the hydrogen pressure on the hydrogenation of **12** using Re-Sn-Al catalysts[a].

| Entry | Pressure / MPa | Conversion of **12** / %[b] | Selectivity[c] of **6** / %[b] | Yield of **6** / %[b] | $k_1/k_2$ |
|---|---|---|---|---|---|
| 1 | 3.0 | 10 | 90 | 9 | -[d] |
| 2 | 6.5 | 15 | 93 | 14 | -[d] |
| 3 | 12.0 | 23 | 89 | 21 | -[d] |

a) Reaction conditions: catalyst, $Re_2O_7$ (2 wt%)/ $Sn(OEt)_4$ (Re / Sn = 1 / 0.5) / aluminum isopropoxide. activated at 400 °C for 4 h in a stream of hydrogen. 4.0 g; temperature, 250 °C; reaction time, 3 h; methyl hydrogen 1,15-pentadecanedioate **12**, 50.0 g; decaline, 100.0 g. b) Yields were determined by GLC. c) Selectivity = Yield / Conversion. d) The k1/k2 value could not be determined because of low conversion.

Next, the effect of atomic ratio of Re to Sn on the conversion, selectivity, yield and a $k_1/k_2$ value in the hydrogenation of monoester **12** was investigated (Table 3). In the absence and very low ratio (1:0.01 - 0.1) of Sn, the catalyst was highly active and showed a conversion of about 60 - 80 % with $k_1/k_2$ value = 1(entries 1-3). The increasing incorporation of Sn into the catalyst clearly modified the activity of the catalyst, and the conversion decreased under 20 %

and so $k_1/k_2$ value could not be determined (entries 5 – 7). The prolonged reaction time (24 h) with modified reaction condition using Re/Sn = 1:0.5 catalyst showed the $k_1/k_2$ value = 4 (entry 4), Therefore, the atomic ratio of Re/Sn of 1:0.5 - 2 might show $k_1/k_2$ value > 1. The source of Sn did not affect the results ($Sn(OEt)_4$: entry 6, $SnCl_4$: entry 7).

**Table 3**. Effect of the atomic ratio of Re to Sn on the hydrogenation of **12** using Re-Sn-Al catalysts[a].

| Entry | Atomic ratio of Re/ Sn | Conversion of **12** / %[b] | Selectivity[c] of **6** / %[b] | Yield of **6** / %[b] | $k_1/k_2$ |
|---|---|---|---|---|---|
| 1 | 1 / 0 | 74 | 63 | 47 | 1 |
| 2 | 1 / 0.01[d] | 79 | 55 | 44 | 1 |
| 3 | 1 / 0.1[d] | 61 | 63 | 38 | 1 |
| 4 | 1 / 0.5[f] | 85 | 71 | 60 | 4 |
| 5 | 1 / 0.5[e] | 21 | 95 | 20 | -[g] |
| 6 | 1 / 1[e] | 20 | 96 | 19 | -[g] |
| 7 | 1 / 2[d] | 15 | 97 | 15 | -[g] |
| 8 | 1 / 2[e] | 12 | 96 | 11 | -[g] |

a) Reaction conditions: catalyst, $ReCl_3$ (2 wt%)/ $Sn(OEt)_4$ or $SnCl_4$ / aluminum isopropoxide. activated at 400 °C for 4 h in a stream of hydrogen. 1.5 g; temperature, 280 °C; Pressure, 10.0 MPa, reaction time, 3 h; methyl hydrogen 1,15-pentadecanedioate **12**, 15.0 g; decaline, 30.0 g. b) Yields were determined by GLC. c) Selectivity = Yield / Conversion. d) Sn source is $Sn(OEt)_4$. e) Sn source is $SnCl_4$. f) Reaction conditions: catalyst, $ReCl_3$ (2 wt%)/ $Sn(OEt)_4$ / aluminum isopropoxide. activated at 400 °C for 4 h in a stream of hydrogen. 4.0 g; temperature, 250 °C; Pressure, 6.5 MPa, reaction time, 24 h; **12**, 50.0 g; decaline, 100.0 g. g) The $k_1/k_2$ value could not be determined because of low conversion.

Moreover it was studied that the effect of calcination and activation conditions of the

Ru-Sn-Al catalysts on the hydrogenation of methyl ester **12** (Table 4). As shown in Table 4, the calcination of Ru-Sn catalyst at 400 to 600 °C gave the $k_1/k_2$ value of 4 (entries 4, 5), and the activation of the catalyst at 400 to 800 °C also gave the $k_1/k_2$ value of 4 (entries 1-3). Activation and calcination conditions of catalysts were found hardly to affect the catalytic activity and selectivity.

**Table 4**. Effect of calcination and activation condition of Ru-Sn-Al catalysts on the hydrogenation of **12**[a].

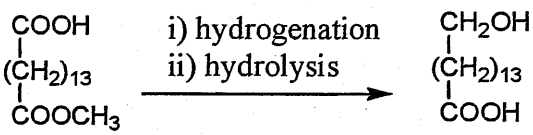
| Entry | Calcination / °C[b] | Activation / °C[c] | Conversion of **12** / %[d] | Selectivity[e] of **6** / %[d] | Yield of **6** / %[d] | $k_1/k_2$ |
|---|---|---|---|---|---|---|
| | Ru (2.0 wt%) | | | | | |
| 1 | 600 | 400 | 45 | 90 | 40 | 4 |
| 2 | 600 | 600 | 48 | 89 | 42 | 4 |
| 3 | 600 | 800 | 55 | 87 | 48 | 4 |
| | Ru (3.0 wt%) | | | | | |
| 4 | 400 | 400 | 81 | 73 | 59 | 4 |
| 5 | 600 | 400 | 75 | 80 | 60 | 5 |

a) Reaction conditions: catalyst, $Ru(acac)_3$ or $RuCl_3$ / $Sn(OEt)_4$ (Ru / Sn = 1 / 1) / aluminum isopropoxide. 1.5 g; temperature, 280 °C; Pressure, 10.0 MPa, reaction time, 3 h; methyl hydrogen 1,15-pentadecanedioate **12**, 15.0 g; decaline, 30.0 g. b) The catalyst is calcinated in air. c) The catalyst is activated in hydrogen. d) Yields were determined by GLC. e) Selectivity = Yield / Conversion.

It is examined that the effect of the second metal additive for Re-Al catalysts on the hydrogenation of methyl hydrogen 1,15-pentadecanedioate (**12**) (Table 5). Under these conditions, the catalyst containing transition metals such as Fe (entry 2), Co (entry 3), Ni (entry 4), Cu (entry 5), Zn (entry 6) did not show any effects compared to the Re catalyst

(entry 1). The catalysts containing group IV elements such as Sn (entry 7), Pb (entry 8) and group V elements such as Sb (entry 9), Bi (entry 10) decreased the conversion. I chose Sn as the second metal for my study according to the catalyst for the hydrogenation of oleic acid[xx]; however, Pb, Sb, and Bi would show good selectivity from this result.

**Table 5**. Effect of the second metal additive for Re-Al catalysts on the hydrogenation of **12**[a].




**12** **6**

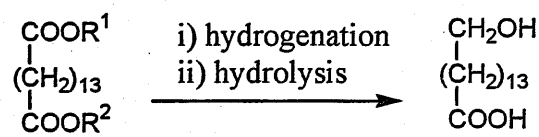
| Entry | Second metal | Conversion of **12** / %[b] | Selectivity[c] of **6** / %[b] | Yield of **6** / %[b] | $k_1/k_2$ |
|---|---|---|---|---|---|
| 1 | none | 74 | 63 | 47 | 1 |
| 2 | Fe | 82 | 53 | 43 | 1 |
| 3 | Co | 79 | 54 | 43 | 1 |
| 4 | Ni | 68 | 64 | 43 | 1 |
| 5 | Cu | 62 | 69 | 43 | 1 |
| 6 | Zn | 79 | 55 | 43 | 1 |
| 7 | Sn | 20 | 46 | 9 | -[d] |
| 8 | Pb | 8 | 57 | 4 | -[d] |
| 9 | Sb | 6 | 50 | 3 | -[d] |
| 10 | Bi | 29 | 84 | 25 | -[d] |

a) Reaction conditions: catalyst, $Re_2O_7$ or $ReCl_3$ (2 wt%)/ metal ethoxide (Re / Sn = 1 / 1) / aluminum isopropoxide. activated at 400 °C for 4 h in a stream of hydrogen. 1.5 g; temperature, 280 °C; pressure, 10.0 MPa; reaction time, 3 h; methyl hydrogen 1,15-pentadecanedioate **12**, 15.0 g; decaline, 30.0 g. b) Yields were determined by GLC. c) Selectivity = Yield / Conversion. d) The $k_1/k_2$ value could not be determined because of low conversion.

Finally dicarboxylic acid **9** and dimethyl ester **10** were examined to confirm that the reaction mechanism shown above could be extrapolated to them (Table 6). I had expected that both dicarboxylic acid **9** and dimethyl ester **10** should show $k_1/k_2$ value = 1 because these compounds have same functional groups at their terminals respectively. Dimethyl ester **10** showed that $k_1/k_2$ value = 1, however, dicarboxylic acid **9** showed that $k_1/k_2$ value = 6 against my expectation. The hydrogenation of **9** gave one of the best yields of **6** (62 %) (entry 1).

The preparation of **6** from **9** is much advantageous for industrially against the conventional route from **12** because of shortening the reaction step.

**Table 6**. Hydrogenation result of 1,15-pentadevanedioic acid derivatives, dicarboxylic acid **9**, dimethyl ester **10** and methyl hydrogen 1,15-pentadecanedioate **12**[a].



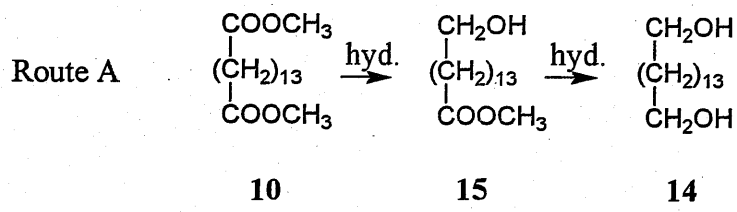

**9** $R^1 = R^2 = H$
**10** $R^1 = R^2 = CH_3$
**12** $R^1 = H$, $R^2 = CH_3$

**6**

| Entry | Starting material | Conversion of starting material / %[b] | Selectivity[c] of **6** / %[b] | Yield of **6** / %[b] | $k_1/k_2$ |
|---|---|---|---|---|---|
| 1 | **9** | 94 | 66 | 62 | 6 |
| 2 | **10** | 43 | 80 | 34 | 1 |
| 3 | **12** | 48 | 88 | 42 | 4 |

a) Reaction conditions: catalyst, $RuCl_3$ / $Sn(OEt)_4$ / ( Ru / Sn = 1 / 1) aluminum isopropoxide. 1.5 g; temperature, 280 °C; Pressure, 10.0 MPa, reaction time, 3 h; starting material, 15.0 g; decaline, 30.0 g. b) Yields were determined by GLC. c) Selectivity = Yield / Conversion.

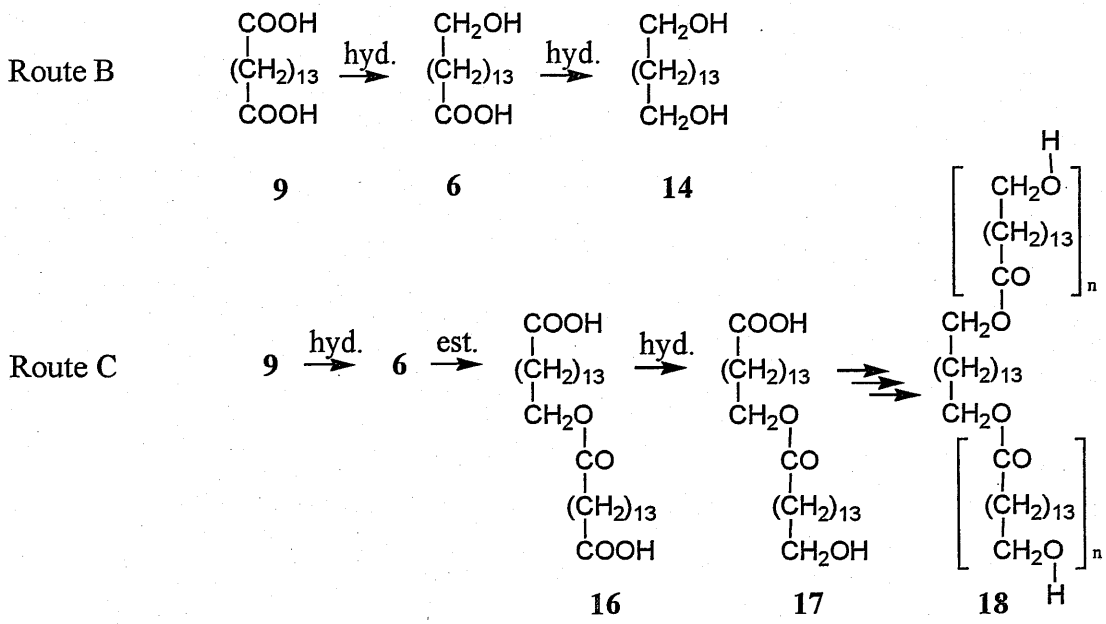
These results can be explained reasonably by two hypotheses. The first one is described below. Dimethyl ester **10** is hydrogenated by the route A shown in Scheme 9. The hydrogenation of **10** by the Route A shows that $k_1/ k_2$ value = 1 because the terminal functional group is same.




**10** **15** **14**

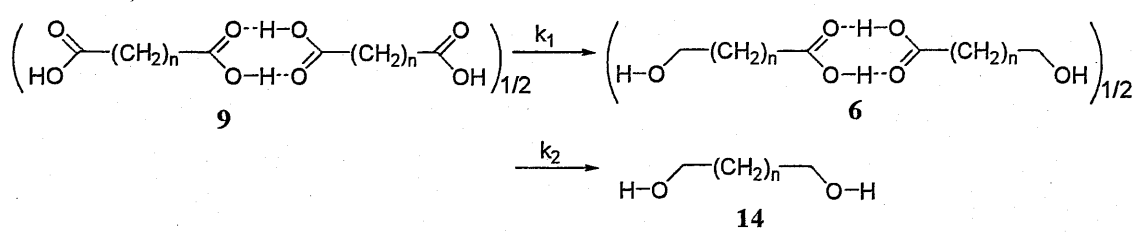
**Scheme 9** Proposed reaction pathway on hydrogenation of **10** based on the first hypothesis.

On the other hand, dicarboxylic acid **9** is hydrogenated by 2 routes, B and C shown in Scheme 10. The route B is the 2-steps successive first-order reaction discussed above. The hydrogenation of **9** by the route B shows that $k_1/ k_2$ value = 1 because the terminal functional group is same. The route C is the pathway that the esterification is concerned. The hydroxy group of **6** reacts a carboxylic group of **9** to give the ester **16**. Next, one carboxylic group of **16** is hydrogenated to give **17**. Then the hydroxy group of **17** reacts a carboxylic group of another **9** by the esterification. The repeated these reactions give polyester **18**, which is composed of a diol **14** and 2n of **6**. Therefore, the products of the route B are mainly **6**, and it seems apparently that the selective hydrogenation is done after hydrolysis of **18**. Thus while the hydrogenation of **9** shows that $k_1/ k_2$ value > 1 apparently by the contribution of the route C.




**Scheme 10** Proposed reaction pathways of hydrogenation of **9** based on the first hypothesis.

These results can be also explained reasonably by the other hypothesis that the hydrogenation rate of the carboxyl group of **9** and **6** would not be equal by the difference of the intermolecular hydrogen bonds (Scheme 11). The hydrogenation rate of the carboxyl group, which does not make the intermolecular hydrogen bond would be faster than the hydrogenation rate of the carboxyl group, which make the intermolecular hydrogen bond. Therefore, the hydrogenation of **9** shows that $k_1/ k_2$ value > 1. The hydrogenation rate of the ester group of **10** and **15** are equal, because they are not affected by the hydrogen bonds.




**Scheme 11** Proposed reaction pathways of hydrogenation of **9** based on the second hypothesis.

### 3-4. Conclusion

The selective hydrogenation of 1,15-pentadecanedioic acid derivatives (1,15-pentadecanedioic acid (**9**), methyl hydrogen 1,15-pentadecanedioate (**12**), and dimethyl 1,15-pentadecanedioate (**10**)) to 15-hydoxypentadecanoic acid (**6**), which is an important precursor of macrocyclic musk cyclopentadecanolide, has been studied using Ru-Sn-Al or Re-Sn-Al catalysts prepared by the sol-gel method. The ability of the selective hydrogenation catalysts and reaction conditions were evaluated by an apparent hydrogenated ratio of the two terminal functional groups determined by comparison of the experimental results and the calculation under an estimated kinetic model. I found that 1,15-pentadecanedioic acid (**9**), which has same terminal functional groups, gave 15-hydoxypentadecanoic acid (**6**) with high selectivity. This new method would be effective route of industrial preparation of **6**.

### 3-5. Experimental section

#### General

Silica gel column chromatography was performed on a Merck Art. 7734 and 9385. Commercially available reagents were used without further purification.

#### Starting Materials.

1,15-pentadecanedioic acid (**9**) was prepared by the microbial oxidation (*Candida Tropicalis*) of n-pentadecane. Dimethyl 1,15-pentadecanedioate (**10**) was prepared by the esterification of **9** with methanol and sulfuric acid. Saponification of **10** with barium hydroxide in methanol gave methyl hydrogen 1,15-pentadecanedioate-Ba salt **11** as a

precipitate, and following acidification gave methyl hydrogen 1,15-pentadecanedioatemethyl ester **12**.

## Catalyst Preparation

### Sol-gel Ru-Sn Alumina Catalysts

Sol-gel Ru-Sn alumina catalysts were prepared using Mizukami and co-workers protocol. Metal precursors were $RuCl_3 \cdot 3H_2O$, $SnCl_2 \cdot 2H_2O$ and aluminum iso-propoxide. Solvents used were ethanol and hexylene glycol (Kanto Reagents).

Solutions of 1.5 g of $RuCl_3 \cdot 3H_2O$ and 2.55 g of $SnCl_2 \cdot 2H_2O$ in 10 mL and 30 mL ethanol, respectively, were added to 123.5 g of hexylene glycol. Then 106.5 g of aluminum iso-propoxide was added to this solution, and the mixture was stirred for 4 h at 80-90 °C. To a homogeneous solution obtained, 42 g of water was added and the resultant mixture was aged for 3 h at the same temperature. The gel obtained was dried at 170 °C under vacuum.

### Sol-gel Ru-Sn Alumina Catalysts (Chloride Free)

Thirty grams of concentrated nitric acid was added to 30mL of suspended solution of ethanol containing 3 g of $Ru(acac)_3$, and the mixture was stirred for 2 h at 80-90 °C. An additional 23 g of concentrated nitric acid was then added, and the complex adhering to the wall of the vessel was washed out into the solution with as small an amount of acetic acid as possible. After heating for another 3-4 h at 90-100 °C, the solution became red and clear. Nitrogen oxide was generated during heating. After the solution was evaporated, 163.7 g of hexylene glycol and 142 g of aluminum iso-propoxide were added to the residue, and the mixture was stirred for 4 h at 80-90 °C. Then 4.5 g of $Sn(OEt)_4$ was added, and the mixture

was stirred for another hour at the same temperature. Then 42 g of water was added, and the gel obtained was aged for 2 h at the same temperature before being dried at 160 °C under vacuum.

**Sol-gel Re-Sn Alumina Catalysts**

Sol-gel Re-Sn alumina catalysts were prepared using Mizukami and co-workers protocol. Metal precursors were Re chloride ($ReCl_3$), and ammonium perrhenate ($NH_4ReO_4$) for Re; stannous chloride hydrate ($SnCl_2 \cdot 2H_2O$), stannic chloride hydrate ($SnCl_4 \cdot nH_2O$) and stannic tetraethoxide ($Sn(OEt)_4$) for Sn; and aluminum iso-propoxide. Solvents used were ethanol and hexylene glycol (Kanto Reagents).

Solutions of 0.94 g of $ReCl_3$ and 2.25 g of $SnCl_4 \cdot nH_2O$ in 300 mL and 300 mL ethanol, respectively, were added to 132.8 g of hexylene glycol. Then 114.8 g of aluminum iso-propoxide was added to this solution, and the mixture was stirred for 3 h at 80-90 °C. To a homogeneous solution obtained, 46 g of water was added and the resultant mixture was aged for 1 h at the same temperature. The gel obtained was dried at 170 °C under vacuum.

**Hydrogenation Reaction**

The hydrogenation reaction was carried out in a 100-mL or 500-mL reacter equipped with a pressure regulator. The reactor was charged with starting material, catalyst, solvent and additive together and purged with hydrogen four times to remove air. The reactor was then heated to the required temperature and pressurized with hydrogen to the reaction pressure, which was maintained throughout the reaction. Stirring was maintained at about 1000 rpm. At the end of the specified time, the reactor was cooled and the reaction product was recovered

for analysis.

**Analysis of Products**

The aliquot (200 mg) of reaction products was hydrolyzed with a 1 ml of 6 N sodium hydroxide solution and 2 ml of methanol at 70 °C for 2 h. Then, 1 ml of 6 N hydrochloric acid was added to the hydrolyzed mixture, and the mixture was extracted with ether, and concentrated. About 10 mg of crude solid was derivatized with 250 μl of trimethylsillyl chloride/pyridine (GL Sciences Inc., Tokyo) at 150 °C. The derivatized reaction products were analyzed by gas chromatography with a 25 m and 0.25 mm OV-1 column (GL Sciences Inc., Tokyo) operated with 200 °C and with helium as a carrier gas. A flame ionization detector was used.

**3-6. References and Notes**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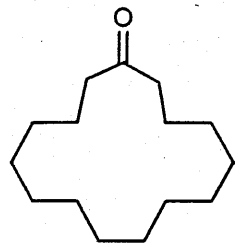
# Chapter 4. Practical Synthesis of Cyclopentadecanone by Using Catalytic Liquid-Phase Dehydration of 2-Hydroxycyclopentadecanone

## 4-1. Summary

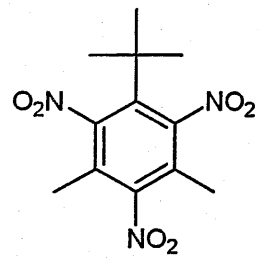
A new and efficient synthesis of cyclopentadecanone, one of the representative macrocyclic musk perfumes, was achieved by means of catalytic liquid-phase dehydration of 2-hydroxycyclopentadecanone (acyloin) under 300 °C as the key step. This dehydration reaction is practical with respect to availability of equipment compared with the conventional vapor-phase method requiring a higher reaction temperature (540–560 °C). Using a silica-alumina solid acid catalyst, I obtained a mixture of 2-cyclopentadecenones and 3-cyclopentadecenones in 85% combined yield under optimized conditions, and the subsequent hydrogenation of them gave cyclopentadecanone quantitatively. This 2-step synthesis, which was carried out in a catalytic manner, can be said to be more ecofriendly than the presently used process. Furthermore, this route opens a practical synthetic way of muscone.

## 4-2. Introduction

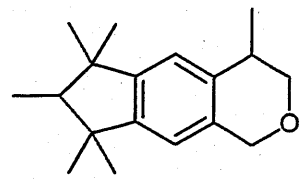
A new practical method for the synthesis of natural macrocyclic musks is one of the most important topics in the perfume industry because the natural macrocyclic musks are known to be safer and more biodegradable than the others, i.e., polycyclic musks and nitro-musks.[1]



macrocyclic musks
(ex. Cyclopentadecanone)

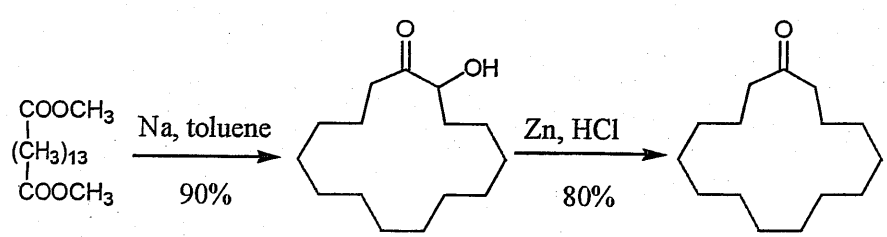


nitro-musks
(ex. musk xylol)



polycyclic musks
(ex. Galaxolide)

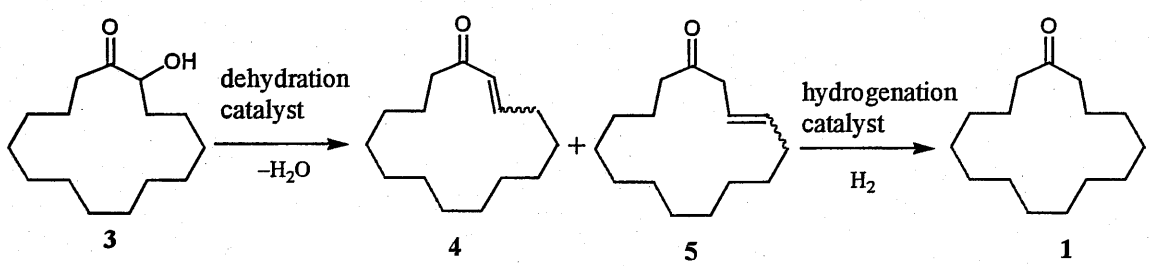
Cyclopentadecanone (**1**)[2], one of the representative macrocyclic musks isolated from the muskrat by Stevens and Erickson,[3] has been produced in an industrial process using a modification of Prelog's method[4,5] since the 1980's by the acyloin condensation of dimethyl pentadecanedioate (**2**) and the Clemmensen-type reduction[6] of 2-hydroxycyclopentadecanone (**3**) (Scheme 1). The diester **2** was derived from the esterification of pentadecanedioic acid which was the fermentation product of pentadecane obtained with *Candida maltosa*.[5] Since the Clemmensen-type reduction using zinc and hydrochloric acid is a stoichiometric reaction and, moreover, a part of the zinc and hydrochloric acid is consumed regardless of the reduction, this step suffers from much waste as $ZnCl_2$ and acidic water. From the viewpoint of atom efficiency and an environmentally benign process, the industrial process for synthesis of **1** would be better if the zinc reduction step were replaced by an alternative method, e.g., catalytic dehydration and catalytic hydrogenation.




**2** **3** **1**

**Scheme 1**. Industrial process of **1** using a modification of Prelog's method.

To my best knowledge, the synthesis of cyclopentadecenone by the one-step dehydration of acyloin **3**, which does not use a protective and a leaving group for the synthesis, was only reported by Stoll in the 1940's for the preparation of 2-cyclopentadecenone[7], the key intermediate of muscone, and related compounds[8]. While a catalytic hydrogenation of cyclopentadecenone would be an interesting approach for the synthesis of cyclopentadecanone (**1**), the necessity of the special equipment for the Stoll one-step dehydration, which was achieved by using alumina at high temperature (540–560 °C) in vapor-phase, hampers adopting it. Therefore, I developed an efficient synthesis of **1** by using a practical catalytic liquid-phase dehydration of **3** at a lower temperature as a key reaction in order to use a multi-purpose plant for industrial production. (Scheme 2).



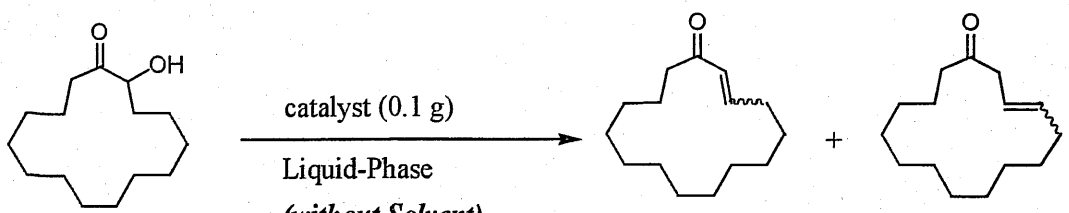

**Scheme 2**. Synthetic route to cyclopentadecanone (**1**)

### 4-3. Results and Discussion

First, I screened various acid catalysts for the liquid-phase dehydration of **3** under reaction conditions shown in Table 1. Acyloin **3** was prepared by the acyloin condensation of **2** in an industrial process and used without purification (purity 68%, by-products were mostly oligomers arising from intermolecular condensations). The yield, based on acyloin **3**, was determined by internal standard (eicosane) method of GLC analysis using a SE30-packed column.

The catalytic dehydration with phosphoric acid at 240 °C for 0.3 h gave *cis*- and *trans*-2-cyclopentadecenone **4**[9] together with *cis*- and *trans*-3-cyclopentadecenone **5**[9] in 64% combined yield (entry 1). The crude products with low boiling points were separated in 2 fractions by column chromatography on silica gel. One fraction, at the earlier retention time in GLC analysis using a SE30-packed column, contained *cis*-**4**, *cis*-**5** and *trans*-**5** as an inseparable mixture. The other, at the later retention time, contained *trans*-**4**. Formation of the 4 isomers is not troublesome because the following hydrogenation of these isomers can afford only the desired ketone, **1**. Prolongation of the reaction time (1 h) caused a decrease in the yield (entry 2). Polyphosphoric acid was also effective to give **4** and **5** in 65% yield (entry 3). In the case of metaphosphoric acid, phosphorus pentoxide, and boric acid, the yields decreased considerably (entries 4–6). Moreover, the reaction with *p*-toluenesulfonic acid gave **4** and **5** in only 7% combined yield (entry 7). The low yield might be due to formation of by-products with high boiling points. Similar treatment with oxalic acid resulted in no increase in the yield (entry 8). The catalytic dehydration using a solid acid catalyst such as sulfated zirconia alumina (SZA291/03)[10] also furnished **4** and **5** in 49% yield with 5.0 g of the catalyst (entry 9). Thereafter, I chose solid acid catalysts for this research because they seemed to be preferable with respect to green chemistry.

**Table 1**. Catalytic dehydration of 2-hydroxycyclopentadecanone (**3**)




**3** (6.0 g, 17 mmol) **4** **5**

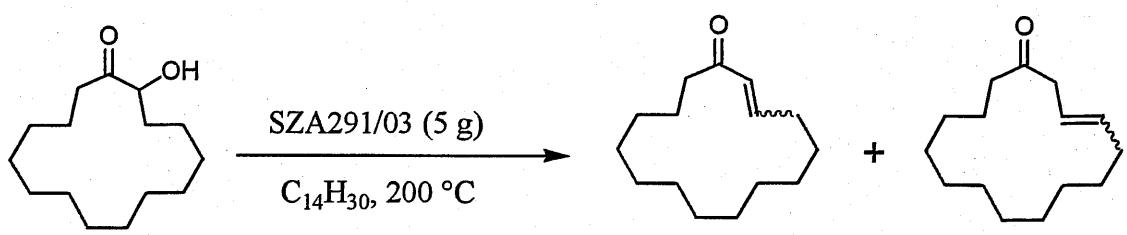
| entry | catalyst | temp (°C) | time (h) | conv (%) | yield (%) 4 and 5[a)] |
|---|---|---|---|---|---|
| 1 | $H_3PO_4$ | 240 | 0.3 | 93 | 64 |
| 2 | $H_3PO_4$ | 240 | 1 | 97 | 39 |
| 3 | $H_4P_2O_7$ | 240 | 0.3 | 96 | 65 |
| 4 | $HPO_3$ | 240 | 1 | 36 | 38 |
| 5 | $P_2O_5$ | 180 | 1 | 71 | 14 |
| 6 | $HBO_3$ | 290 | 1 | 64 | 44 |
| 7 | *p*-TsOH | 120 | 1 | 73 | 7 |
| 8 | $(COOH)_2$ | 180 | 1 | 11 | 5 |
| 9 | SZA291/03[b)] | 200 | 1 | 99 | 49 |

a) Determined by GLC analysis. b) Sulfated zirconia alumina (solid-acid) (5 g).

Next, I examined the effect of the concentration of **3** using the SZA291/03 catalyst was used. The lower the concentration of **3** by diluting with tetradecane, the better the yield, as shown in Table 2. It is reasonable that lowering the concentration would prevent the formation of by-products derived from intermolecular side reactions. The catalytic dehydration with homogeneous catalyst such as phosphoric acid might show the same effect.

Compared with homogeneous acid catalysts, heterogeneous (solid) acid catalysts would have several advantages such as easy separation, re-use of recovered catalysts, no need for neutralization, and the resultant decrease in waste. Thus, I investigated the dehydration activity of some solid acid catalysts. Since I found that the lower the concentration of **3**, the better the yield, I used a solvent such as tetradecane and toluene as shown in Table 2.

**Table 2.** Effect of concentration of acyloin **3** on dehydration using SZA catalyst.



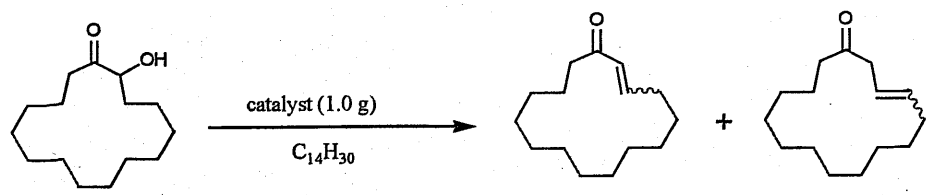

**3** (6.0 g, 17 mmol) **4** **5**

| entry | $C_{14}H_{30}$ (g) | time (h) | conv (%) | yield (%) **4** and **5**[a)] |
|---|---|---|---|---|
| 1 | 0 | 1 | 99 | 49 |
| 2 | 12 | 3 | 99 | 64 |
| 3 | 24 | 5 | 99 | 70 |
| 4 | 54 | 4 | 97 | 73 |
| 5 | 114 | 6 | 97 | 77 |

a) Determined by GLC analysis.

As a result, commonly used solid acids such as silica-alumina (Si-Al HA® and LA®) and zeolite (Zeolyte® CBV720) showed fair to good dehydration activity (Table 3; entries 2-7) in addition to the sulfated zirconia alumina (SZA291/03; entry 1). Under optimized conditions, the dehydration with Si-Al HA® gave **4** and **5** in 85% yield (entry 3). The dehydration catalyst (Si-Al HA®) could be easily recovered by filtration and re-used (entries 4, 5). The dehydration with the re-used catalyst resulted in slightly lower yield. Si-Al LA® gave **4** and **5** in 76% yield and zeolite (Zeolyte® CBV720) gave **4** and **5** in 41% yield (entries 6, 7)

**Table 3.** Dehydration activity of silica-alumina and zeolite




3 (6.0 g, 17 mmol) 4 5

| entry | catalyst[a)] | $C_{14}H_{30}$ (g) | temp (°C) | time (h) | conv (%) | yield (%) 4 and 5[b)] |
|---|---|---|---|---|---|---|
| 1 | SZA291/03 | 114 | 200 | 6 | 97 | 77 |
| 2 | Si-Al HA™ | 12 | 220 | 2 | 93 | 66 |
| 3 | Si-Al HA™ | 54 | 220 | 7 | 93 | **85** |
| 4[c)] | Si-Al HA™ | 108 | 240 | 3 | 100 | 76 |
| 5[c,d)] | Si-Al HA™ | 108 | 240 | 3 | 98 | 57 |
| 6 | Si-Al LA™ | 54 | 200 | 2 | 96 | 76 |
| 7 | Zeolyte CBV720™ | 12 | 220 | 12 | 81 | 41 |

a) Commercially available from Catalysts & Chemicals Industries Co., Ltd. and Zeolyst International. b) Determined by GLC analysis. c) 3 (12 g, 34 mmol), catalyst (2.0 g), and toluene as solvent.
d) The recovered catalyst of entry 4 was used.

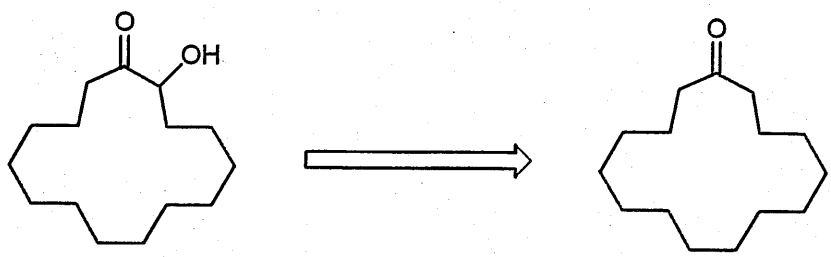
Finally, catalytic hydrogenation of a mixture of **4** and **5** with 5% Pd/C under a hydrogen atmosphere at room temperature for 6 h gave **1** quantitatively.

Larger scale dehydration in toluene was carried out in a 500 ml autoclave reactor to isolate the ketone **1**. The yield of dehydration determined by GLC was 77 %, and after the hydrogenation, the concentrated reaction mixture was purified by spinning band distillation to give **1** in 63 % overall isolated yield based on **3**.

The catalytic dehydration-dehydrogenation protocol shows improved atom efficiency over the zinc-hydrochloric acid protocol. The process gives only water as by-product, while the zinc-hydrochloric acid protocol gives $ZnCl_2$ other than water (Scheme 3).

In addition to the improvement of atom efficiency and an environmental issue which is

already described, this process has the advantage of being able to produce *trans*-2-cyclopentadecenone (**4**) that is the key compound for a synthesis of muscone (**6**). Naturally occurring (*R*)-muscone can be synthesized by asymmetric Michel addition[11] of the methyl group to *trans*-**4**, and (*R,S*)-muscone can be also synthesized by Michel addition[9] (Scheme 4).




**3** **1**

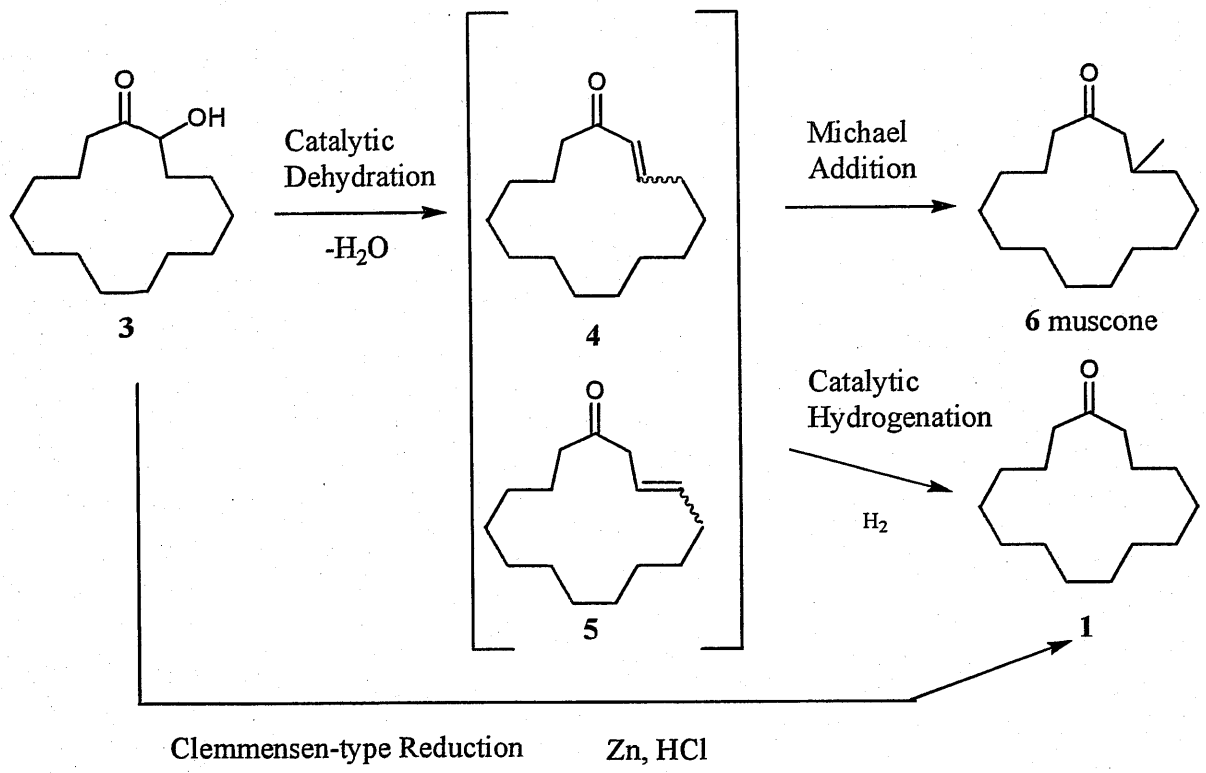
**Catalytic Dehydration-Hydrogenation Protocol**

$$\mathbf{3} + H_2 \longrightarrow \mathbf{1} + H_2O$$

**Zinc-Hydrochloric acid Protocol**

$$\mathbf{3} + Zn + HCl \longrightarrow \mathbf{1} + H_2O + ZnCl_2$$

**Scheme 3**. Comparison of an atom efficiency of the catalytic dehydration-hydrogenation protocol and the zinc-hydrochloric acid protocol.




**Scheme 4**. Advantage of the catalytic dehydration-hydrogenation over the zinc-hydrochloric acid; the synthetic route for muscone (**6**) from enone **4**.

## 4-4. Conclusion

In conclusion, I have developed a new efficient route for the synthesis of cyclopentadecanone (**1**) by using the catalytic liquid phase dehydration of 2-hydroxycyclopentadecanone (**3**) as a key reaction instead of stoichiometric zinc reduction. Since the 2-step transformation of the acyloin **3** to the ketone **1** was carried out in a catalytic manner, the waste was reduced, and, therefore, the process can be said to be ecofriendly. Furthermore, this route opens a practical synthetic way of muscone (**6**)

## 4-5. Experimental Section

### General

Yields of dehydration and hydrogenation were determined by internal standard (eicosane) method of GLC analysis using a SE30-packed column with Shimazu GC 9A.

**Starting Materials.**

Acyloin **3** was prepared by the acyloin condensation of **2** in an industrial process and used without purification. The sample has 68% purity, including by-products which consist of mostly oligomers by intermolecular condensations.

**Catalytic Dehydration of 2-Hydroxycyclopentadecanone (3)**

In a 100 ml three-necked round-bottomed flask equipped with a thermometer, a cooler, and a magnetic stirring bar were charged **3** (6.0 g, 17.1 mmol), acid, and solvent shown in Tables 1 to 3 under nitrogen. The mixture was stirred at the temperature for the period also shown in Tables 1 to 3. In the cases of using toluene as a solvent, **3** (12.0 g, 34.2 mmol) was subjected to dehydration using a 300 ml autoclave with an automatic temperature control and an agitator. Then the mixture was analyzed by GLC. In the case of solid acids, the filtrate was analyzed after a separation of the catalyst by a filtration. The results are summarized in Tables 1 to 3. *Cis*-2-cyclopentadecenone (**4**) and *cis*- and *trans*-3-cyclopentadecenone (**5**) did not separate clearly by GLC.

**Catalytic Hydrogenation of Cyclopentadecenones (4 and 5)**

In a 100 ml round-bottomed flask equipped with a magnetic stirring bar were charged the tetradecane solution containing **4** and **5** (14.5 mmol) obtained by reaction shown in Table 3, entry 3, and 5% palladium-C catalyst (0.10 g) under hydrogen. The mixture was stirred at

room temperature for 6 h. After a separation of the catalyst by a filtration, the filtrate was analyzed by GLC, showing cyclopentadecanone (**1**) (14.3 mmol, 99%).

**Isolation of Cyclopentadecanone (1)**

Dehydration of **3** (209.1 mmol) in toluene carried out in two pots as described above using a 500 ml autoclave reactor to give the solution of **4** and **5** (161.8 mmol, 77%) in toluene. A part of the solution was used in the next dehydrogenation without purification. Using a 500 ml round-bottomed flask, hydrogenation of the above solution (395.2 g) containing **4** and **5** (130.6 mmol) with 5 % palladium-C catalyst (0.36 g) were undertaken under hydrogen as described above. After stirring for 5 h, the mixture was filtered and the filtrate was concentrated under reduced pressure to give a red brown oil (60.2 g), which was purified by spinning band distillation (135-137°C/ 3 mmHg) to afford **1** (23.9 g, 106.7 mmol, 82% isolated yield from **4** and **5**, 63% isolated yield from **3**). The spectral data of **1** were consistent with those of the authentic sample.

**4-6. References and Notes**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# Chapter 5. Practical Synthesis of *Z*-Civetone Utilizing $TiCl_4$ Mediated Dieckmann Condensation

## 5-1. Summary

An efficient, practical, and stereocontrolled synthesis of *Z*-civetone, a representative musk perfume, has been performed utilizing a $TiCl_4$ mediated Dieckmann condensation (intramolecular Claisen condensation) of dimethyl *Z*-9-octadecanedioate as the key step. This cyclization reaction has some advantages compared with the traditional basic Dieckmann condensation such as higher concentration (100–300 mM), lower reaction temperature (0–5 °C), shorter reaction time (1–3 h), use of environmentally benign (low toxicity and safe) reagents ($TiCl_4$ and $Et_3N$ or $Bu_3N$), and economical reagents and solvents. 15-, 17- and 19-membered saturated β-keto esters were also prepared by the present method.

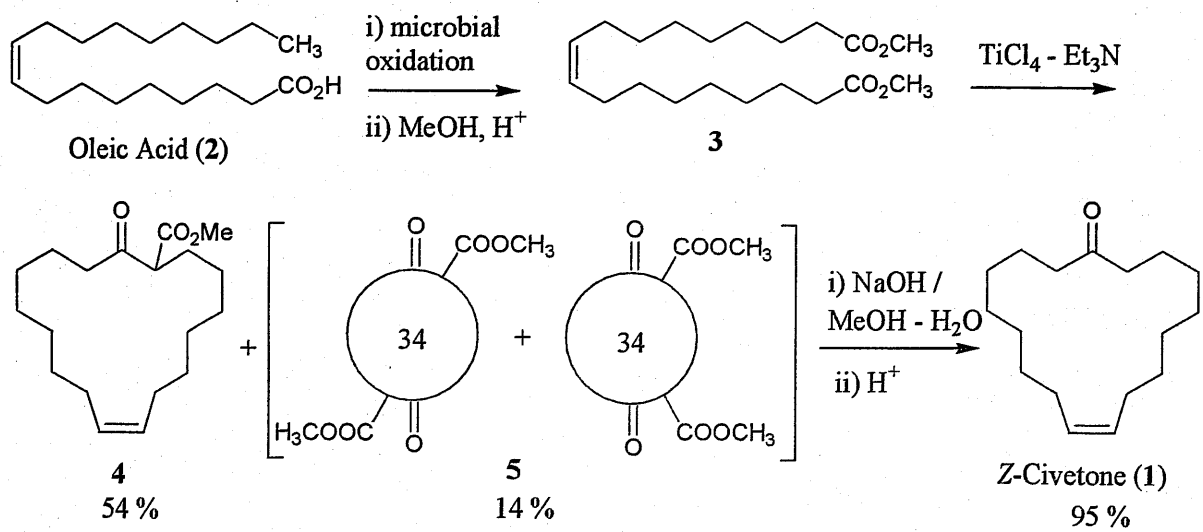
## 5-2. Introduction

Practical synthesis of natural macrocyclic musks, especially muscone and civetone, is one of the most important topics in the perfume industry.[1] These two representative natural musks originally come from glandular secretions of musk deer and civet cat, respectively. The Washington treaty, Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES), however, claims that harvesting musk constitutes ill treatment of wild animals. *Z*-Civetone (**1**) is an attractive ingredient of civet cat musk[2] and has been one of the most challenging synthetic targets for producing macrocyclic musks due to its unique symmetric 17-membered structure. Several hitherto reported syntheses of **1**, however, are limited by the laboratory methods used because of their low yields and/or multistep

procedures.[3]

Recently, Tanabe reported a short step synthesis of *E*-rich civetone utilizing the $TiCl_4$ mediated Claisen condensation and ring-closing metathesis.[4] However, the Grubbs' metathesis catalyst is expensive and this method requires high dilution conditions (ca. 4 mM ), which are undesirable for large scale production. Moreover, most of the known syntheses, including Tanabe's work, are not stereocontrolled. There are only two stereocontrolled examples to my knowledge. One is Tsuji and Mandai's method,[5] which requires 17 steps starting from nitromethane and butadiene, and the other is Fürstner and Seidel's method,[6] which seems to be one of the most efficient to date (5 steps), but requires a high dilution technique of ring-closing metathesis.

From these points of view, I studied on a practical synthesis of *Z*-civetone (**1**) utilizing the $TiCl_4$ mediated Dieckmann condensation[7] (Scheme 1).




**Scheme 1** Synthetic route to *Z*-civetone (1)

## 5-3. Results and Discussion

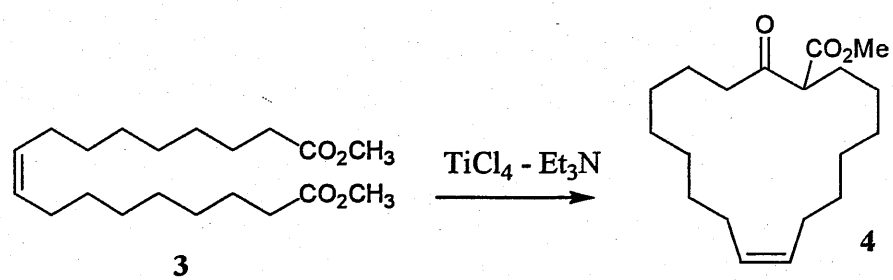
Dimethyl *Z*-9-octadecanedioate (**3**) was prepared by the known microbial oxidation (*Candida Tropicalis*) of cheap and available oleic acid (*Z*-9-octadecenoic acid, **2**), followed by esterification in MeOH with the complete retention of *Z*-geometry.[8] $TiCl_4$ and $ZrCl_4$ has exhibited powerful reactivity in Claisen-type condensations between various carboxylic esters.[9] This characteristic merit would promise a large ring closing with higher concentrations and speed. Therefore, I carried out reactions of **3** with $TiCl_4$ in the presence of tertiary amine under a variety of conditions. The results are summarized in Table 1.

An important technical note is that conformity of the molar ratio should be maintained to realize smooth condensation using a microfeeder apparatus equipped with dual syringes. That is, two lots of solutions were prepared: one was a mixture of dimethyl ester **3** and amine in solvent and the other was $TiCl_4$ in the same solvent. To keep the molar ratio balance of the reactants and reagents, these solutions were simultaneously and proportionally added to a solution placed beforehand in the reaction vessel. If this protocol was not followed, significant competitive intermolecular origomerization occurred.

Reactions of **3** (100 mM) with $TiCl_4$ (1.2 eq.) and $Bu_3N$ (1.4 eq.) in $CH_2Cl_2$ at 0 - 5 °C gave the 17-membered ring β-ketoester **4** in 23% yield, and the double-sized, 34-membered ring diester **5** in 5% yield, together with 45% of the recovery **3** (entry 1). Using more amounts of $TiCl_4$ and $Bu_3N$ caused an increase in the yield of **3** (2.4 eq. of $TiCl_4$, 3.0 eq. of $Bu_3N$, 41%, entry 2; 2.8 eq. of $TiCl_4$, 3.0 eq. of $Bu_3N$, 52%, entry 3). Similar reaction of **3** with $TiCl_4$ (2.8 eq.) and $Et_3N$ instead of $Bu_3N$ (3.0 eq.) gave **4** in 54% yield (entry 4). The reaction in toluene gave lower yield of **4** compared to that in $CH_2Cl_2$ (entry 5). The yield of **4** was decreased with higher (300 mM) and lower (50 mM) concentrations (entries 6, 7) compared to 100 mM, and

with lower (-15 – -10 °C) and higher (10 – 15 °C) reaction temperatures (entries 8, 9) compared to at 0 – 5 °C. Prolonged adding time (reaction time) from 1 to 3 h did not effect the yield of **4** (entry 10).

**Table 1.** $TiCl_4$ mediated Dieckmann condensation of dimethyl *Z*-9-octadecanedioate (**3**).




**3** **4**

| entry | Eqiv of $TiCl_4$ | Amine / Equiv | Solvent | Conc (mM) | temp (°C) | Adding time (h) | yield (%) [a] **3**[b] | **4** | **5** |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1.2 | $Bu_3N$ / 1.4 | $CH_2Cl_2$ | 100 | 0 - 5 | 1 | 45 | 23 | 5 |
| 2 | 2.4 | $Bu_3N$ / 3.0 | $CH_2Cl_2$ | 100 | 0 - 5 | 1 | 7 | 41 | 22 |
| 3 | 2.8 | $Bu_3N$ / 3.0 | $CH_2Cl_2$ | 100 | 0 - 5 | 1 | trace | 52 | 13 |
| 4 | 2.8 | $Et_3N$ / 3.0 | $CH_2Cl_2$ | 100 | 0 - 5 | 1 | trace | 54 | 14 |
| 5 | 2.8 | $Et_3N$ / 3.0 | toluene | 100 | 0 - 5 | 1 | 5 | 44 | 17 |
| 6 | 2.8 | $Et_3N$ / 3.0 | $CH_2Cl_2$ | 300 | 0 - 5 | 3 | trace | 47 | 16 |
| 7 | 2.8 | $Et_3N$ / 3.0 | $CH_2Cl_2$ | 50 | 0 - 5 | 1 | 15 | 37 | 22 |
| 8 | 2.8 | $Et_3N$ / 3.0 | $CH_2Cl_2$ | 100 | -15 - -10 | 1 | trace | 42 | 33 |
| 9 | 2.8 | $Et_3N$ / 3.0 | $CH_2Cl_2$ | 100 | 10 - 15 | 1 | 22 | 34 | 17 |
| 10 | 2.8 | $Et_3N$ / 3.0 | $CH_2Cl_2$ | 100 | 0 - 5 | 3 | trace | 54 | 12 |

a) Isolated yields. b) Recovery.

There are some advantages compared with the traditional Dieckmann condensations using the basic system (KH or KHMDS reagent / THF solvent); (a) higher concentrations (100~300

mM), lower reaction temperature (0-5 °C), and shorter reaction time (1-3 h), than those of the basic methods[10] (25 mM, 60 °C, 2-10 h); (b) use of environmentally benign (low toxicity and safe) reagents; and (c) more economical and practical reagents and solvents (it is not necessary to use the strict dryness conditions required for the THF solvent). Yield of the $TiCl_4$ mediated Dieckmann condensations, however, slightly lower than the basic method (63%).[10b]

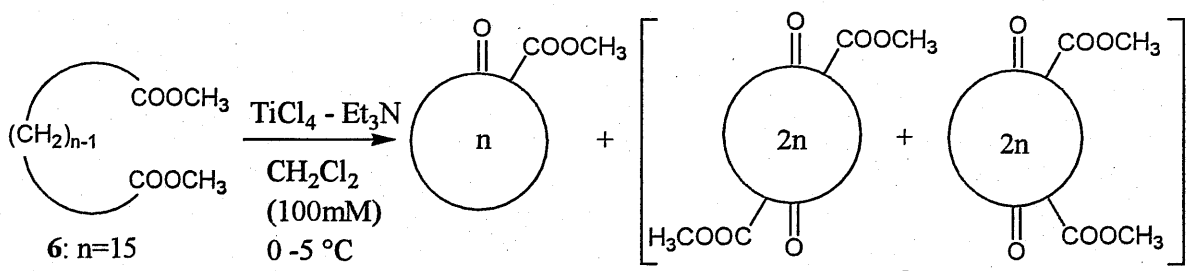
Finally, hydrolysis and decarboxylation of β-keto esters **4** gave the desired *Z*-civetone (**1**) in 95% yield according to the reported method.[4, 10b]

$TiCl_4$ mediated Dieckmann condensations of 15-, 17- and 19-membered saturated β-keto esters (**6a-8a**) were also performed by the present method (Table 2).

Dieckmann condensation of dimethyl hexadecanedioate (**6**) with the best reaction condition determined by the reaction of **3** gave the 15-membered ring β-ketoester **6a** in 8% yield, and the double-sized, 30-membered ring diester **6b** in 31% yield (entry 1). Using more equivalents of $TiCl_4$ and $Bu_3N$ and prolonged reaction time caused a slightly increase in the yield of **6a** (entry 2). The similar treatment of dimethyl octadecanedioate (**7**) gave the 17-membered ring β-ketoester **7a** in 33% yield, and the double-sized, 34-membered ring diester **7b** in 18% yield (entry 3). Further usage of $TiCl_4$ and $Bu_3N$ and prolonged reaction time caused a slightly increase in the yield of **7a** (entry 4). The condensation of dimethyl eicosanedioate (**8**) gave the 19-membered ring β-ketoester **8a** in 46% yield, and the double-sized, 38-membered ring diester **8b** in 11% yield (entry 5).

In the case of **6**, the 30-memberd diester predominated over the 15-memberd β-keto ester. Major by-products in the other cases of **7** and **8** were double-sized, 34- and 38-membered diesters, respectively.

**Table 2.** Ti-Dieckmann condensation of saturated dimethyl carboxylic esters (**6-8**).




**6**: n=15
**7**: n=17
**8**: n=19

**a** **b**

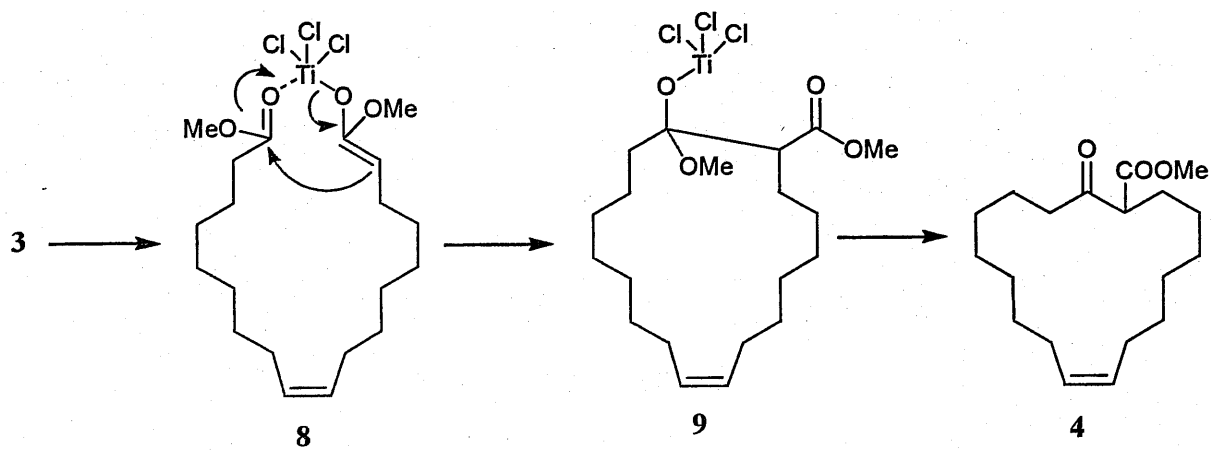
| entry | Ester | Eqiv of $TiCl_4$ | Eqiv of $Et_3N$ | Adding time (h) | yield (%)[a] **a** | **b** |
|---|---|---|---|---|---|---|
| 1 | **6** (n=15) | 2.8 | 3.0 | 1 | 8 | 31 |
| 2 | **6** (n=15) | 3.5 | 3.7 | 3 | 15 | 41 |
| 3 | **7** (n=17) | 2.8 | 3.0 | 1 | 33 | 18 |
| 4 | **7** (n=17) | 3.5 | 3.7 | 3 | 45 | 12 |
| 5 | **8** (n=19) | 3.5 | 3.7 | 3 | 46 | 11 |

a) Isolated yields.

The reasons for $TiCl_4$ mediated Dieckmann condensation working in higher concentrations compared with traditional basic system might be explained by faster condensation reaction rate. One of a plausible reaction path in $TiCl_4$ mediated Dieckmann condensation is shown in Scheme 2. The titanium enolate **8** generated by the abstraction of α-hydrogen of **3** attacks the nucleophilic carbon of the second ester group to form the intermediate **9**. Elimination of the methoxide ion gives the desired compound **4**. The nucleophilic attack to an ester group of the other diester molecule would lead the undesired linear product. Therefore, it is important to be consumed the unreacted diester in the reaction system as soon as possible before accumulation of it in order to surpress the intermolecular

reaction. Since the carbonyl oxygen is well-known to coordinate strongly to titanium atom of $TiCl_4$, it is reasonable to consider that the other ester group would coordinate to the titanium atom of the enolate moiety in the intermediate **8**. If another molecule does not exist near the titanium atom, the coordination mentioned above causes the more smooth Claisen-type bond formation than that in traditional basic system. In this reaction system, the almost equimolar amounts of the diester and $TiCl_4$ are loaded into the reaction vessel at the same time. Therefore, a chance for other molecule to access the titanium moiety would be low.

Because the $TiCl_4$ mediated Dieckmann condensation was considerably faster than the Dieckmann condensation of traditional basic system,[9] the amount of treated diester with the $TiCl_4$ mediated Dieckmann condensation within a unit time is larger, and hence the final concentration of diester used within reasonable reaction time could increase.




**Scheme 2** Plausible reaction path of $TiCl_4$ mediated Dieckmann condensation.

### 5-4. Conclusion

In conclusion, we achieved the first simple and practical synthesis of *Z*-civetone (**1**) utilizing the $TiCl_4$ mediated Dieckmann condensations, which is a promising candidate for the

industrial production of *Z*-civetone (**1**) and provide a novel methodology for construction of large carbon ring compound.

## 5-5. Experimental Section

### General

Melting points were determined on a hot stage microscope apparatus (Yanagimoto) and are uncorrected. $^{1}$H NMR spectra were recorded on a JEOL α (400 MHz) or Varian UNITY Plus (300 MHz) spectrometer. $^{1}$H NMR spectra were reported as chemical shifts in parts-per-million (ppm) based on a TMS internal standard in $CDCl_3$. Coupling constants (*J*) are reported in Hertz (Hz). $^{13}$C NMR spectra were reported as chemical shifts in ppm based on the middle peak of chloroform-*d* (77.0 ppm). IR spectra were recorded on a JASCO FT/IR-8000 spectrophotometer; absorption peaks are reported in reciprocal centimeters. Silica gel column chromatography was performed on a Merck Art. 7734 and 9385. Commercially available reagents were used without further purification.

### Starting Materials.

Dimethyl *Z*-9-octadecanedioate (**3**) was prepared by the microbial oxidation (*Candida Tropicalis*) of oleic acid (*Z*-9-octadecenoic acid, **2**), followed by esterification in MeOH with the complete retention of *Z*-geometry.[8] Dimethyl hexadecanedioate (**6**), dimethyl octadecanedioate (**7**), and dimethyl eicosanedioate (**8**) were also prepared by the microbial oxidation of corresponding n-alkane and esterification

**General Procedure of TiCl4 Mediated Dieckmann Condensation of Dimethyl Z-9-Octadecenedioate (3)**

Two lots of solutions (A) and (B) were prepared; (A) $TiCl_4$ (9.23 mL, 84.0 mmol) diluted with $CH_2Cl_2$ (147 mL) under an argon atmosphere and (B) mixed solution of dimethyl *Z*-9-octadecenedioate (**3**; 10.21 g, 30 mmol) and $Et_3N$ (9.11 g, 90 mmol) in $CH_2Cl_2$ (133 mL). Solutions of (A) and (B) were simultaneously and proportionally added to a stirred $CH_2Cl_2$ solvent (30 mL) at 0-5 °C during 1 h under an argon atmosphere, using a microfeeder apparatus equipped with dual syringes (Note: this procedure is critical as described in the text.). After completion of the feed, the mixture was further stirred for 15 min at the same temperature. Then, water (100 mL) was added to the stirring mixture for 5 min with vigorously stirring, which was evaporated using a rotary evaporator to remove $CH_2Cl_2$. The resultant mixture was extracted with toluene (150 mL x 3), and the combined organic phase was washed with water, brine, dried ($Na_2SO_4$) and concentrated. The obtained crude oil (9.83 g) was purified by $SiO_2$-column chromatography (hexane : AcOEt = 20 : 1) to give 2-methoxycarbonyl-*Z*-cycloheptadecen-9-one (**4**; 4.83 g, 52%) and 2,17(or 19)-bis(methoxycarbonyl)-*Z*,*Z*-cyclotetratriacota-9,26-diene-1,17-dione (**5**; 1.27 g, 14%).

**4**: Colorless oil. $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.18-1.44 (16H, m), 1.53-1.71 (2H, m), 1.75-1.87 (1H, m), 1.88-2.09 (5H, m), 2.52 (2H, t, J = 6.8 Hz), 3.49 (0.93H, dd, J = 9.0 Hz, 5.4 Hz; keto form), 3.70 (2.79H, s; keto form), 3.75 (0.21H, s; enol form), 5.28-5.40 (2H, m), 12.72 (0.07H, s; enol form). $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 23.34, 26.58, 26.79, 27.05, 27.95, 27.99, 28.08, 28.15, 28.35, 28.45, 28.98, 29.01, 41.54, 52.24, 58.42, 130.07, 130.14, 170.22 (keto form), 175.51 (enol form), 206.34. IR (neat) 2928, 1748, 1713, 1437, 1242 $cm^{-1}$.

**5**: Colorless oil. $^1$H NMR (300 MHz, $CDCl_3$ ) δ 1.18-1.41 (32H, m), 1.47-1.68 (4H, m), 1.77-1.89 (4H, m), 1.93-2.08 (8H, m), 2.40-2.62 (4H, m), 3.45 (1H, t, J = 7.3 Hz), 3.45 (1H, t, J = 7.3 Hz), 3.71 (6H, s), 5.26-5.40 (4H, m). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 23.36, 27.01, 27.03, 27.38, 28.21, 28.74, 28.77, 28.87, 28.90, 28.95, 29.03, 29.04, 29.43, 29.49, 41.77, 41.89, 52.19, 58.78, 58.84, 129.78, 129.83, 129.86, 129.90, 170.35, 205.51. IR (neat) 2928, 1746, 1715, 1437, 1200 $cm^{-1}$.

**6a**: Pale yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.20-1.43 (20H, m), 1.54-2.04 (4H, m), 2.56 (2H, t, *J* = 6.9 Hz), 3.54 (1H, dd, *J* = 9.1 Hz, 5.4 Hz), 3.70 (3H, s). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 22.71, 26.17, 26.34, 26.51, 26.61, 26.77, 27.01, 27.33, 27.97, 41.56, 52.26, 58.01, 170.27, 206.55. IR (neat) 2930, 2857, 1750, 1717, 1460, 1240 $cm^{-1}$.

**6b**: Colorless crystals; mp 69.5-71.5 °C. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.18-1.37 (40H, m), 1.48-1.69 (4H, m), 1.76-1.96 (4H, m), 2.42-2.62 (4H, m), 3.47 (1H, t, *J* = 7.3 Hz), 3.48 (1H, t, *J* = 7.3 Hz), 3.71 (6H, s). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 23.35, 27.21, 27.27, 28.28, 28.75, 28.80, 28.98, 29.01, 29.06, 29.13, 29.18, 29.22, 29.30, 29.33, 41.76, 41.94, 52.21, 58.56, 58.62, 170.34, 205.85.

**7a**: Colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.21-1.42 (24H, m), 1.52-1.73 (2H, m), 1.76-1.99 (2H, m), 2.54 (2H, t, *J* = 7.1 Hz), 3.51 (0.89H, dd, *J* = 8.8 Hz, 5.9 Hz; keto form), 3.70 (2.67H, s; keto form), 3.75 (0.33H, s; enol form), 12.76 (0.11H, s; enol form). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 23.10, 26.54, 26.67, 26.78, 27.00, 27.09, 27.12, 27.38, 27.61, 27.74, 28.05, 28.07, 28.11, 41.77, 52.24, 58.23, 170.24, 206.34. IR (neat) 2920, 1750, 1715, 1460, 1246 $cm^{-1}$.

**7b**: Colorless crystals; mp 69.5-72.0 °C. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.18-1.36 (48H, m), 1.52-1.68 (4H, m), 1.77-1.93 (4H, m), 2.42-2.62 (4H, m), 3.46 (1H, t, *J* = 7.4 Hz), 3.47 (1H, t,

$J$ = 7.4 Hz), 3.71 (6H, s). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 23.36, 27.22, 27.27, 28.26, 28.78, 28.81, 29.02, 29.07, 29.18, 29.21, 29.27, 29.33, 29.39, 41.79, 41.86, 52.20, 58.62, 58.67, 170.34, 205.80.

**8a**: Colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.22-1.37 (28H, m), 1.52-1.72 (2H, m), 1.76-1.98 (2H, m), 2.46-2.61 (2H, m), 3.50 (0.96H, dd, $J$ = 8.5 Hz, 6.1 Hz; keto form), 3.70 (2.88H, s; keto form), 3.75 (0.12H, s; enol form), 12.75 (0.04H, s; enol form). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 23.27, 26.86, 27.27, 27.44, 27.47, 27.57, 27.65, 27.83, 27.95, 28.15, 28.19, 28.22, 28.26, 28.53, 41.95, 52.25, 58.33, 170.28, 206.31. IR (neat) 2928, 1748, 1717, 1460, 1242 $cm^{-1}$.

**8b**: Colorless crystals; mp 89.0-91.0 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.19-1.33 (56H, m), 1.51-1.66 (4H, m), 1.78-1.92 (4H, m), 2.43-2.59 (4H, m), 3.46 (1H, t, $J$ = 7.3 Hz), 3.46 (1H, t, $J$ = 7.3 Hz), 3.71 (6H, s). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 23.39, 27.25, 27.28, 28.26, 28.81, 28.84, 29.07, 29.12, 29.22, 29.25, 29.30, 29.33, 29.38, 29.41, 29.45, 29.48, 41.80, 41.85, 52.20, 58.68, 58.71, 170.36, 205.75.

**Hydrolysis and Decarboxylation of 2-Methoxycarbonyl-Z-9-cycloheptadecenone (4)**

Aqueous 10%-NaOH (36 mL, 90 mmol) was added to a stirred solution of 2-methoxycarbonyl-*Z*-9- cycloheptadecenone (**4**; 9.25 g, 30 mmol) in MeOH (36 mL) at 20-25 °C, and the mixture was refluxed for 1 h. After cooling down, the mixture was made slightly acidic (pH ~ 1) with 10% $H_2SO_4$, followed by refluxed for 30 min. The mixture was evaporated under reduced pressure to remove MeOH. Then residue was extracted with ether (100 mL x 3), and the combined organic phase was washed with water, brine, dried ($Na_2SO_4$) and concentrated. The obtained crude oil (7.60 g) was purified by $SiO_2$-column

chromatography (hexane : AcOEt = 40 : 1) to give the desired *Z*-civetone (**1**; 7.12 g, 95%). Colorless crystals. mp 31.0-32.0 °C. $^{1}$H NMR (400 MHz, CDCl3) δ 1.24-1.39 (16H, m), 1.57-1.67 (4H, m), 1.96-2.06 (4H, m), 2.40 (4H, t, J = 6.7 Hz), 5.30-5.39 (2H, m). $^{13}$C NMR (100 MHz, CDCl3) δ 23.84, 26.68, 28.11, 28.19, 28.58, 29.01, 42.41, 130.12, 212.50. IR (neat) 2926, 1713, 1460, 1364, 718 cm$^{-1}$.

**5-6. References and Notes**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# General Conclusion

In this thesis, synthesis of the natural macrocyclic compounds including some macrocyclic musks and a macrolide antibiotic has been described. The results mentioned in each chapter of this thesis are summarized as follows.

In Chapter 1, it has been described that the first total synthesis of (±)-Patulolide A, a macrolide isolated from a *Penicillium urtcae* mutant, from 12-hydroxydodecanoic acid. The structure of the natural product was confirmed by this synthesis.

In Chapter 2, it has been described that the novel synthetic method at that time of cyclopentadecanolide and other related lactones from methyl ω-hydroxyalcanoates, and stereospecific intramolecular transesterification leading to the formation of (*R*)-isomer from methyl (ω-1)-hydroxyalcanoate by using lipase in organic solvents. The lipase-catalyzed lactonization in organic solvents has been investigated extensively after this work.

In Chapter 3, it has been described that the practical synthetic methods of 15-hydroxypentadecanoic acid, the precursor of cyclopentadecanolide, from 1,15-pentadecanedioic acid by using selective hydrogenation with the Ru-Sn or Re-Sn catalysts. The practical synthesis of 15-hydroxypentadecanoic acid is the key point of the industrial production of cyclopentadecanolide.

In Chapter 4, it has been described that the synthetic methods of cyclopentadecanone from dimethyl 1,15-pentadecanedioate by using catalytic liquid-phase dehydration of 2–hydroxycyclopentadecanone as the key step. The catalytic liquid-phase dehydration could work at considerably lower reaction temperature than the conventional vapor-phase reaction; therefore, this dehydration would be preferable to be used in multi-purpose plant for producing fine chemicals. Cyclopentadecanone was given by a catalytic hydrogenation of the products of this dehydration, 2- and 3-cyclopentadecenones. Because the new route is carried out in catalytic manner, this method is more ecofriendly and green than present process.

In Chapter 5, it has been described that the synthetic methods of *Z*-civetone from dimethyl 9-octadecenedioate by using a $TiCl_4$ mediated Dieckmann condensation. This method seems

to be one of the most practical synthetic methods of *Z*-civetone. This cyclization reaction has some advantages compared with the traditional basic Dieckmann condensation such as higher concentration, lower reaction temperature, shorter reaction time, and economical reagents and solvents.

Present studies on this synthesis of macrocyclic compounds starting from long chain fatty acids might offer some new approaches of industrial production, an efficient method of lactonization for natural compounds, and an insight of new compounds.

# List of Publications

The contents of this thesis are composed of the following papers.

Chapter 1. A. Makita, Y. Yamada, H. Okada, "The Total Synthesis of (±)-Patulolide A," *J. Antibiot.* **39** (*9*), 1257-1262 (1986).

Chapter 2. A. Makita, T. Nihira, Y. Yamada, "Lipase Catalyzed Synthesis of Macrocyclic Lactones in Organic Solvents," *Tetrahedron Lett.*, **28**, *7*, 805-808 (1987).

Chapter 3. S. Niwa, F. Mizukami, H. Yokochi, T. Makoto, K.-Y. Cheah, T.-S. Tang, T. Shimizu, A. Makita, T. Fufii, "Selective hydrogenation of carboxylic acids to alcohols with sol-gel Ruthenium/Tin catalysts," *Chemical Industries series.* **62**, 451-455 (1994).

A. Makita, S. Niwa, F. Mizukami, "Practical Synthesis of 15-Hydroxypentadecanoic Acid, the Precursor of Cyclopentadecanolide, by Using Selective Hydrogenation," *Applied Catalysis A* (preparation).

Chapter 4. A. Makita, H. Matsuda, K. Furuhashi, K. Kakiuchi, "Practical Synthesis of Cyclopentadecanone by Using Catalytic Liquid-Phase Dehydration of 2-Hydroxycyclopentadecanone," *Green Chemistry* (to be submitted).

Chapter 5. Y. Tanabe, A. Makita, S. Funakoshi, R. Hamasaki, T. Kawakusu, "Practical Synthesis of *Z*-Civetone Utilizing Ti-Dieckmann Condensation," *Advanced Synthesis and Catalysis* **344**, 507-510 (2002).

# Supplementary list of Publications

1 牧田淳, "クレオパトラの香りをつくる 分子内閉環反応によるジカルボン酸からの大環状ムスク合成", 化学と生物, **40** (*10*), 660-664 (2002).

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