An Efficient Synthetic Method for ($\pm$)-Malyngolide and Its Optical Resolution[†]

KOZO MACHIYA,* ITSUO ICHIMOTO, KENOSUKE TONARI,
MITSUNORI KIRIHATA and HIROO UEDA

*Department of Agricultural Chemistry, College of Agriculture,
University of Osaka Prefecture, Sakai, Osaka 591, Japan*

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A convenient synthetic method for ($\pm$)-malyngolide (**1**), an antibiotic from the marine blue-green alga *Lyngbya majuscula* GOMONT, is described. The compound ($\pm$)-**1** was synthesized from 2-methylglutaric anhydride (starting material) in four steps, involving the TBHP-based osmium-catalyzed procedure for vicinal dihydroxylation of the methylene unit in unsaturated carboxylic acid as the key step. The optical resolution of ($\pm$)-**1** was accomplished by HPLC, in which diastereomeric (+)-2-(4-chlorophenyl)isovaleric acid [(+)-CPIA] esters of ($\pm$)-**1** derived from (+)-CPIA-Cl could be easily separated, and subsequent hydrolysis of each ester gave the enantiomerically pure (–)-**1** and (+)-**1**, respectively. A synthetic method for α -methylene malyngolide, which is to be expected for biological activity, is also described.

Malyngolide (**1**), an antibiotic effective against *Mycobacterium smegmatis* and *Streptococcus pyogenes*, was isolated from a shallow water variety of the blue-green alga *Lyngbya majuscula* GOMONT.¹⁾ The structure and absolute configuration of this novel δ -lactone was determined by a combination of chemical and physical techniques.¹⁾ The unique structural feature of malyngolide (**1**) coupled with its biological activity against bacteria has prompted several research groups to explore synthetic approaches to this compound.^{2~7)} During the past few years, we have also been attempting to develop the synthesis of **1** and its derivatives, and we now report some detail of our progress.

Retrosynthetic analysis of the malyngolide

(**1**) molecule reveals the need for simultaneous introduction of the two hydroxyl groups into olefinic acid as the key step of the synthesis (Scheme 1).

In planning the synthetic route for **1**, 2-methylglutaric anhydride (**2**) seemed to be the most attractive starting material (Scheme 2). A Michael addition of ethyl malonate to ethyl methacrylate in the presence of sodium ethoxide and followed by hydrolysis, decarboxylation and dehydration with acetyl chloride gave **2** in a 67% yield.⁸⁾ Treatment of **2** with *n*-nonylmagnesium bromide in THF afforded the keto acid (**3**), which was treated with methyltriphenylphosphonium iodide ($\text{Ph}_3\text{P}^+\text{CH}_3\text{I}^-$) in DMSO in the presence of NaH to give the olefinic acid (**4**) in a 61.4%

SCHEME 1.

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* To whom correspondence should be addressed.

SCHEME 2.

SCHEME 3.

yield from **2**. A facile conversion of **4** to the key intermediate (**5**) could be accomplished by modification of the method of Sharpless, who revealed the osmium-catalyzed vicinal dihydroxylation of olefin with *tert*-butylhydroperoxide (TBHP) into the corresponding diol.⁹ This procedure was much more reliable than the earlier ClO_3^- ¹⁰ and H_2O_2 ¹¹ based osmium-catalyzed procedure. Namely, treatment of **4** with 2 equiv. of 70% TBHP aqueous solution and a catalytic amount of OsO_4 (1/500 equiv.) in acetone in the presence of $\text{Et}_4\text{N}^+ \text{OAc}^-$ as a nucleophile gave **5** in a 69% yield. Lactonization of **5** was accomplished by treating with *p*-TsOH in refluxing ben-

zene to give a 1 : 1 mixture of $(\pm)$ -malyngolide (**1**) and its diastereoisomer $(\pm)\text{-1'}$, which could be readily separated by silica-gel column chromatography to afford the individual isomers $(\pm)\text{-1}$ and $(\pm)\text{-1'}$ in an almost quantitative yield. The overall yield was 35%.

The optical resolution of $(\pm)\text{-1}$ was performed by the following procedure: the reaction of $(\pm)\text{-1}$ with (+)-2-(4-chlorophenyl)isovaleric acid chloride ((+)-CPIA-Cl)¹² gave the diastereoisomeric mixture of (+)-CPIA esters (**6a** and **6b**), which could be readily separated by HPLC using a μ Porasil column to give **6a** and **6b** in the pure state (Fig. 1). Each diastereoisomer was sub-

 FIG. 1. Chromatographic Separation of the Diastereomeric Esters **6a** and **6b**.

SCHEME 4.

sequently subjected to hydrolysis with KOH-MeOH, followed by lactonization to afford the corresponding lactones (–)-**1**, $[\alpha]_D^{22} - 13.03^\circ$ (CHCl₃) and (+)-**1**, $[\alpha]_D^{22} + 13.06^\circ$ (CHCl₃), respectively. The IR and NMR spectra of these products were identical with those previously reported for the natural product.

In general, α -methylene lactones are of interest because of their biological activities as an antibiotic. Therefore, we planned the synthesis of lactones containing an exo-methylene group as depicted in Scheme 4. Treatment of glutaric anhydride with *n*-nonylmagnesium bromide

gave the keto acid (**7**), which was allowed to react with Wittig reagent (Ph₃P=CH₂) to afford **8** in a 49% yield from glutaric anhydride. Vicinal dihydroxylation of the methylene unit of **8** gave **9**, subsequent lactonization with *p*-TsOH in benzene afforded the lactone (**10**). Silylation of **10** with *tert*-butyldimethylsilyl chloride (BDMCS) and imidazole afforded a silyl ether (**11**). Treatment of **11** with ethyl oxalate and formalin gave the α -methylene lactone (**12**) and subsequent deprotection with AcOH-THF-H₂O provided the desired lactone (**13**) in a 54% yield from **8**. The com-

pound **13** was hydrogenated over 5% Pd-C to give ($\pm$)-malyngolide (**1**) and its C-2 epimer (**1'**). Each enantiomer of ($\pm$)-**1** and ($\pm$)-**1'** could be easily separated by the same procedure as described above.

The details of antibacterial activity of these products against bacteria (*Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*) will be reported in the next paper.

EXPERIMENTAL

Infrared spectra were taken with a JASCO IRA-2 spectrometer. Proton NMR spectra and carbon 13 NMR spectra were recorded with JEOL JNM-MH60, JNM-FX90Q and JNM-FX100 spectrometers, respectively. Mass spectra were measured with a Hitachi RMU-6MG instrument. Melting points were determined on a Yanaco MP-S3 melting point apparatus and are uncorrected.

2-Methylglutaric anhydride (2). To a solution of sodium metal (14.1 g, 0.61 mol) dissolved in ethanol (250 ml) was added ethyl malonate (115 g, 0.72 mol) and ethyl methacrylate (68.4 g, 0.6 mol), and the mixture was refluxed for 1 hr. After removing the solvent, water (200 ml) and conc. HCl (450 ml) were added to the residue and the resulting mixture was refluxed for 8–10 hr. After evaporating the solvent, the residue was heated at 180°C until the evolution of CO₂ had ceased, and the reaction mixture was distilled *in vacuo* to afford 2-methylglutaric acid (73 g), bp 188°C/0.4 mmHg, mp 73–74°C (83.3%).

A mixture of 2-methylglutaric acid (15.6 g, 0.1 mol) and acetyl chloride (23.4 g, 0.3 mol) was heated under reflux for 15–20 min. The reaction mixture was distilled *in vacuo* to afford 12.6 g (98.4%) of **2**, bp 136°C/13 mmHg. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1810, 1750, 1080, 1040, 1020. NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 1.31 (3H, d, $J = 7$ Hz), 1.73–2.13 (2H, m), 2.16–3.03 (3H, m). Anal. Found: C, 56.20; H, 6.21. Calcd. for C₆H₈O₃: C, 56.24; H, 6.29%.

2-Methyl-5-oxotetradecanoic acid (3). To a cooled solution of **2** (12.8 g, 0.1 mol) in dry ether (160 ml) was added dropwise a solution prepared from Mg (2.64 g, 0.11 mol) and 1-bromononane (22.8 g, 0.11 mol) in dry ether, and the mixture was stirred for 4 hr at room temperature. After being cooled, the reaction mixture was treated with 3N-HCl and crushed ice, and extracted with ether. The ethereal extract was washed with brine and dried over Na₂SO₄. Evaporation of the solvent afforded 19.8 g of a light yellowish oil, which was purified by column chromatography (silica-gel, ether-*n*-hexane = 1:1) to give 17.3 g of **3**, mp 58–60°C (67.6%). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3600–2400 (br), 2900, 1690, 1240. NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.87 (3H, br. t), 1.13 (3H, d), 1.26 (14H, br. s), 1.53–2.10 (3H, m), 2.13–2.63

(4H, m). MS m/z : Me ester of **3**; 270 (M⁺), 158, 126 (base peak), 88. Anal. Found: C, 70.21; H, 10.98. Calcd. for C₁₅H₃₀O₃: C, 70.27; H, 11.01%.

2-Methyl-5-methylenetetradecanoic acid (4). A mixture of NaH (50% in oil, 1032 mg, 21.5 mmol) and anhydrous DMSO (65 ml) was heated at 75°C for 45 min, and the mixture was cooled to 20°C. To the mixture was added PhP₃⁺CH₃I⁻ (9.6 g, 23.5 mmol) and stirring continued at room temperature for 30 min. A solution of **3** (1.1 g, 4.3 mmol) in dry THF (60 ml) was added to the reaction mixture and stirring continued for 4 hr. The reaction mixture was poured into dil. HCl and extracted with ether. The extract was washed with water and brine, and dried over Na₂SO₄. Evaporation of the solvent afforded an oily residue, which was subsequently applied to silica-gel column chromatography. Elution of the column with ether-*n*-hexane (1:1) gave 1.0 g of **4** (90.9%). IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 3500–2400 (br.), 2930, 1710, 1470, 890. NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.87 (3H, br. t), 1.13 (3H, d), 1.23 (16H, br. s), 1.70–2.63 (5H, m), 4.63 (2H, br. s), 12.33 (1H, br. s). MS m/z : Me ester of **4**; 268 (M⁺), 156, 124, 88 (base peak). Anal. Found: C, 75.49; H, 11.80. Calcd. for C₁₆H₃₀O₂: C, 75.53; H, 11.89%.

5-Hydroxy-5-hydroxymethyl-2-methyltetradecanoic acid (5). A mixture of **4** (900 mg, 3.54 mmol), 70% TBHP (0.85 ml, 6 mmol) and Et₄NOAc-4H₂O (230 mg, 0.885 mmol), prepared from Et₄NBr and acetic acid, in acetone (10 ml) was stirred until the salt had dissolved. The solution was cooled in an ice bath and OsO₄ (1.77 mg, 0.007 mmol) was added. After stirring for 1 hr, the ice bath was removed, ethyl acetate (20 ml) and 10% NaHSO₃ (1.7 ml) was added to the mixture, stirring being continued for 1 hr at room temperature. The reaction mixture was saturated with solid NaCl, which was then extracted with two 10 ml portions of ethyl acetate. The combined organic layers were dried over Na₂SO₄ and concentrated to afford a brownish oil, which was purified by silica-gel column chromatography. Elution of the column with CHCl₃-EtOH (1:1) gave 700 mg of white crystal (**5**) (68.7%), mp 79–81.5°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3400, 2950, 1710, 1470, 1280, 1040. NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.86 (3H, br. t), 1.06 (3H, br. d), 1.20 (14H, br. s), 1.40–1.89 (6H, m), 1.89–2.60 (1H, m), 3.33 (2H, br. s), 5.37 (3H, br. s). MS m/z : 302 (M⁺), 239 (base peak), 211, 155, 143. Anal. Found: C, 66.59; H, 11.13. Calcd. for C₁₆H₃₂O₄: C, 66.63; H, 11.18%.

($\pm$)-Malyngolide (**1**) and its C-2 epimer (**1'**). A solution of **5** (140 mg, 0.49 mmol) and a catalytic amount of *p*-TsOH in benzene (20 ml) was refluxed for 1 hr. After removing the solvent, the residue was diluted with ether, washed with sat. NaHCO₃ and brine, and dried over Na₂SO₄. After evaporating the solvent, the residue was purified by silica-gel column chromatography. Elution of the column with AcOEt-benzene (4:6) gave 58.1 mg of ($\pm$)-malyngolide (**1**) as a colorless oil. On the other hand, elution of the column with AcOEt-benzene (2:8) gave

47.4 mg of the (±)-C-2 epimer (**1'**) as a colorless oil. (Elution of the column with AcOEt–benzene (3:7) gave 26.3 mg of a mixture of **1** and **1'**.)

(±)-*Malyngolide* (**1**). IR $\nu_{\max}^{\text{film}}$ cm⁻¹: 3400, 2920, 1710, 1460, 1080. NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.88 (3H, br t), 1.27 (16H, br. s), 1.27 (3H, d, $J=6$ Hz), 1.49~2.10 (4H, m), 2.31 (1H, br. s), 2.48 (1H, m), 3.46 (1H, dd, $J=12$ Hz, 7 Hz), 3.69 (1H, dd, $J=12$ Hz, 7 Hz). ¹³C-NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 14.1 (CH₃), 17.2 (CH₃), 22.7, 23.7, 25.3, 26.4, 29.3, 29.5, 30.1, 31.9, 35.6, 36.6 (CH₂), 67.8 (CH₂–O–), 86.9 (C–O), 175.2 (C=O). MS m/z : 239 (base peak), 223, 211, 155, 143, 115, 111, 95. *Anal.* Found: C, 71.04; H, 11.15. Calcd. for C₁₆H₃₀O₃: C, 71.07; H, 11.18%.

(±)-C-2 epimer (**1'**). IR $\nu_{\max}^{\text{film}}$ cm⁻¹: 3400, 2910, 1710, 1460, 1210, 1110, 1090. NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.88 (3H, br. t), 1.26 (16H, br. s), 1.27 (3H, d, $J=6$ Hz), 1.48~2.07 (4H, m), 2.07~2.71 (1H, m), 2.40 (1H, br. s), 3.60 (2H, br. s). ¹³C-NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 14.2 (CH₃), 17.3 (CH₃), 22.7, 23.3, 25.5, 27.2, 29.3, 29.6, 30.0, 31.9, 35.3, 37.6 (CH₂), 67.7 (CH₂–O–), 86.4 (C–O), 175.2 (C=O). MS m/z : 239 (base peak), 155, 143. *Anal.* Found: C, 71.03; H, 11.12. Calcd. for C₁₆H₃₀O₃: C, 71.07; H, 11.18%.

Optical resolution of (±)-**1** and (±)-**1'**.

Preparation of (+)-CPIA-Cl. This compound was prepared by the procedure reported by Itaya *et al.*¹²⁾ A mixture of (+)-CPIA (2.13 g, 0.01 mol) and one drop of dry DMF in SOCl₂ (14.4 ml, 0.2 mol) was stirred for 18 hr at room temperature. The reaction solution was concentrated *in vacuo* at room temperature. After separating the green crystals by filtration, the residue was dried over P₂O₅ to give 2.25 g of a pale-yellow oil of (+)-CPIA-Cl (97.4%). NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.73 (3H, d, $J=7$ Hz), 1.13 (3H, d, $J=7$ Hz), 2.00~2.63 (1H, m), 3.57 (1H, d, $J=7$ Hz), 7.25 (4H, m).

(+)-CPIA ester of (±)-**1**. To a cooled solution of (±)-**1** (82 mg, 0.3 mmol) in dry pyridine (3.5 ml) was added a solution of (+)-CPIA-Cl (105 mg, 0.45 mmol) in dry pyridine (1.5 ml), and the mixture was stirred for 8 hr at 0~5°C. The reaction mixture was dissolved in ether (10 ml) and the ether solution was successively washed with 1 N-HCl, sat. NaHCO₃ and brine, and then dried over Na₂SO₄. After removing the solvent, the residue was purified by preparative TLC, developing with ether–*n*-hexane (1:2). A positive spot on the UV spectrum was isolated and extracted with acetone. Removal of the solvent gave 95 mg of a 1:1 mixture of **6a** and **6b** as a colorless oil. NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 3.10 (1H, dd, $J=18$ Hz, 3 Hz), 4.00 (2H, br. s), 7.20 (4H, s). *Anal.* Found: C, 69.71; H, 8.85. Calcd. for C₂₇H₄₄O₄Cl: C, 69.73; H, 8.89%.

(+)-CPIA ester of (±)-**1'**. In the same manner as with the preparation of **6a** and **6b**, **1'** and (+)-CPIA-Cl gave **6'a** and **6'b**. NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 3.12 (1H, dd, $J=18$ Hz, 3 Hz), 4.06 (2H, br. s), 7.20 (4H, s). *Anal.* Found: C, 69.71; H, 8.84. Calcd. for C₂₇H₄₄O₄Cl: C, 69.73; H, 8.89%.

Separation of (+)-CPIA esters **6a** and **6b** and (+)-CPIA

esters **6'a** and **6'b**. The separation of (+)-CPIA esters **6a** and **6b**, and (+)-CPIA esters **6'a** and **6'b** was carried out by HPLC using a Waters HPLC apparatus (Pump 6000A) with a Model 440 absorbance detector (254 nm); column, μ Porasil (3.9 mm × 30 cm); eluent, AcOEt–*n*-hexane = 1:9; flow rate, 1.0 ml/min (Fig. 1).

Hydrolysis of the (+)-CPIA ester (**6a**) and lactonization.

The separated (+)-CPIA ester (**6a**) (33 mg, 0.07 mmol) in 5% KOH–MeOH (10 ml) was stirred for 3 hr at room temperature. The reaction mixture was then acidified with 1N-HCl and extracted with ether. The ethereal solution was washed with brine and dried over Na₂SO₄. After evaporating the solvent, the residue was purified by silica-gel column chromatography. Elution of the column with CHCl₃–EtOH (1:1) gave 11 mg of **5**. A mixture of **5** and a catalytic amount of *p*-TsOH in benzene (5 ml) was refluxed for 1 hr. After removing the solvent, the residue was diluted with ether, washed with sat. NaHCO₃ and brine, and dried over Na₂SO₄. After evaporating the solvent, the residue was purified by silica-gel column chromatography. Elution of the column with AcOEt–benzene (4:6) gave 8 mg of (2*R*,5*S*)-(–)-malyngolide. $[\alpha]_D^{22}$ –13.0° ($c=0.8$, CHCl₃) (natural malyngolide, $[\alpha]_D^{22}$ –13° ($c=2$, CHCl₃)). The spectroscopic data of (2*R*,5*S*)-(–)-**1** were identical with those of natural malyngolide.¹⁾

*Hydrolysis of (+)-CPIA esters (**6b**), (**6'a**) and (**6'b**), and lactonization.* By the same procedure as that above, the separated (+)-CPIA esters (**6b**), (**6'a**) and (**6'b**) gave (2*S*,5*R*)(+)-**1**, (2*R*,5*R*)-(–)-**1'** and (2*S*,5*S*)-(–)-**1'**, respectively.

(2*S*,5*R*)-(–)-**1**: $[\alpha]_D^{22}$ +13.1° ($c=0.7$, CHCl₃).

(2*R*,5*R*)-(–)-**1'**: $[\alpha]_D^{22}$ –21.2° ($c=0.8$, CHCl₃).

(2*S*,5*S*)-(–)-**1'**: $[\alpha]_D^{22}$ +21.2° ($c=0.8$, CHCl₃).

5-Oxotetradecanoic acid (7). To a stirred solution of glutaric anhydride (6.8 g, 0.06 mol) in dry ether (100 ml) was added dropwise a solution of Grignard reagent prepared from 1-bromononane (13.7 g, 0.066 mol) and Mg (1.6 g, 0.066 mol) in dry ether (50 ml) at 0~5°C. After stirring for 4 hr at room temperature, the reaction mixture was cooled in an ice bath treated with 3 N-HCl and ice, and then extracted with ether. The ethereal extract was washed with 5% KOH, the washing solution being acidified with dil. HCl and extracted with ether. The extract was washed with brine and dried over Na₂SO₄. Evaporation of the solvent gave 10.2 g of **7** as a white crystal (68.9%), mp 76~77°C. IR $\nu_{\max}^{\text{KBr}}$ cm⁻¹: 3600~2400 (br), 2850, 1700, 1290. NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.88 (3H, br. t), 1.31 (16H, br. s), 1.87~2.76 (6H, m), 11.15 (1H, br. s). *Anal.* Found: C, 69.31; H, 10.77. Calcd. for C₁₄H₂₆O₃: C, 69.38; H, 10.81%.

5-Methylenetetradecanoic acid (8). A mixture of NaH (50% in oil, 556 mg, 11.6 mmol) and anhydrous DMSO (40 ml) was heated at 75°C for 45 min, and the mixture was then cooled to 20°C. To the mixture was added

$\text{Ph}_3\text{P}^+\text{CH}_3\text{I}^-$ (5.2 g, 12.8 mmol) and stirring continued at room temperature for 30 min. A solution of **7** (1.4 g, 5.8 mmol) in dry THF (40 ml) was added and the reaction mixture stirred for 4 hr. The reaction mixture was poured into dil. HCl and extracted with ether. The extract was washed with water and brine, and dried over Na_2SO_4 . Evaporation of the solvent afforded a brown oil. The residue was chromatographed on a silica-gel column with ether-*n*-hexane-acetone (1 : 1 : 0.2) as an eluent to give 1 g of **8** as oil (71%). IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 3600~2400 (br), 2940, 1710, 1650, 1420, 1250, 890. NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.87 (3H, br. t), 1.23 (16H, br. s), 1.67~2.50 (6H, m), 4.69 (2H, br. s), 12.50 (1H, br. s). *Anal.* Found: C, 74.89; H, 11.72. Calcd. for $\text{C}_{15}\text{H}_{28}\text{O}_2$: C, 74.95; H, 11.74%.

5-Hydroxy-5-hydroxymethyltetradecanoic acid (9). A mixture of **8** (1.2 g, 5 mmol), 70% TBHP (1.2 ml, 8.5 mmol) and $\text{Et}_4\text{NOAc} \cdot 4\text{H}_2\text{O}$ (330 mg, 1.25 mmol) in acetone (10 ml) was stirred until the salt had dissolved. The solution was cooled in an ice bath and OsO_4 (2.5 mg, 0.01 mmol) was added. After stirring for 1 hr, the ice bath was removed and ethyl acetate (25 ml) and 10% NaHSO_3 (2.4 ml) were added to the mixture, which was then stirred for 1 hr at room temperature. The reaction mixture was saturated with solid NaCl, and then extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated to afford a brown oil, which was purified by silica-gel column chromatography. Elution of the column with CHCl_3 -EtOH (5 : 1) gave 1.1 g of **9** as a colorless oil (73%). IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 3400, 2930, 1710, 1150. NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.88 (3H, br. t), 1.27 (14H, br. s), 1.57 (4H, br. s), 2.33 (2H, br. s), 3.26~3.80 (4H, m), 5.63 (3H, br. s). *Anal.* Found: C, 65.61; H, 11.00. Calcd. for $\text{C}_{15}\text{H}_{30}\text{O}_4$: C, 65.65; H, 11.02%.

5-Hydroxymethyl-5-tetradecanolide (10). A mixture of **9** (900 mg, 3.28 mmol) and a catalytic amount of *p*-TsOH in benzene (90 ml) was refluxed for 1 hr. After removing the solvent, the residue was diluted with ether, washed with sat. NaHCO_3 and brine, and dried over Na_2SO_4 . Evaporation of the solvent gave 790 mg of an oil (**10**) (94%). This was employed for the next step without further purification. IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 3350, 2910, 1700, 1080, 1050. NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.89 (3H, br. t), 1.27 (16H, br. s), 1.70~2.13 (4H, m), 2.30~3.05 (3H, m), 3.58 (2H, br. s). *Anal.* Found: C, 70.23; H, 10.98. Calcd. for $\text{C}_{15}\text{H}_{28}\text{O}_3$: C, 70.27; H, 11.01%.

5-*t*-Butyldimethylsilyloxymethyl-5-tetradecanolide (11). A mixture of **10** (486 mg, 1.9 mmol), $\text{Bu}^t\text{Si}(\text{Me})_2\text{Cl}$ (316 mg, 2.1 mmol) and imidazole (323 mg, 4.75 mmol) in dry DMF (1 ml) was stirred for 6 hr at room temperature. The resulting mixture was treated with 3*N*-HCl and extracted with ether. The extract was washed with brine and dried over Na_2SO_4 . Evaporation of the solvent gave 733 mg of **11** (quantitative yield), which was employed for the next step without further purification. IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} :

2920, 1740, 1250, 1110, 830, 770. NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.03 (6H, s), 0.87 (12H, s), 1.24 (16H, br. s), 1.70~2.03 (4H, m), 2.23~2.80 (2H, m), 3.52 (2H, br. s). MS m/z : 370 (M^+), 313, 295, 225 (base peak), 221, 203, 197.

2-Methylene-5-*t*-butyldimethylsilyloxymethyl-5-tetradecanolide (12). To a suspension of NaH (50% in oil, 115 mg, 2.4 mmol) in dry THF (20 ml) was added dropwise a mixture of **11** (716 mg, 1.94 mmol) and ethyl oxalate (438 mg, 3 mmol) in dry THF (20 ml) under an N_2 atmosphere at 0°C. After adding EtOH (1~2 ml), the mixture was stirred for 4 hr at room temperature. The resulting mixture was cooled in an ice bath, and in turn, a solution of K_2CO_3 (828 mg, 6 mmol) in water (1.2 ml) and 37% formalin (1.6 g, 20 mmol) was added. After stirring for 1.5 hr at 0°C, brine was added and the mixture extracted with ether. The extract was washed with brine and dried over Na_2SO_4 . After removing the solvent, the residue was purified by silica-gel column chromatography (ether-*n*-hexane = 2 : 8) to give 590 mg of **12** (79.6%). IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 2920, 1720, 1610, 1300, 1150, 1110, 830. NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.06 (6H, s), 0.88 (12H, s), 1.27 (16H, br. s), 1.90~2.08 (2H, m), 2.33~2.90 (2H, m), 3.59 (2H, br. s), 5.50 (1H, br. s), 6.39 (1H, br. s). MS m/z : 382 (M^+), 307, 281, 237, 205, 75 (base peak).

2-Methylene-5-hydroxymethyl-5-tetradecanolide (13). A mixture of **12** (156 mg, 0.4 mmol) in AcOH (3 ml), THF (1 ml) and water (1 ml) was stirred for 3 days at room temperature. To the reaction mixture was added water, followed by extraction with ethyl acetate. The extract was washed with sat. NaHCO_3 and brine, and dried over Na_2SO_4 . After evaporating the solvent, the residue was purified by silica-gel column chromatography (AcOEt-benzene = 3 : 7) to afford 87 mg of **13** (79.8%). IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 3400, 2920, 1700, 1610, 1300, 1170, 1060. NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.87 (3H, br. t), 1.21 (16H, br. s), 1.70~2.23 (2H, m), 2.47~3.17 (3H, m), 3.60 (2H, br. s), 5.51 (1H, br. s), 6.38 (1H, br. s). *Anal.* Found: C, 71.55; H, 10.48. Calcd. for $\text{C}_{16}\text{H}_{28}\text{O}_3$: C, 71.60; H, 10.52%.

(±)-Malyngolide (1) and its C-2 epimer (1'). A solution of **13** (47 mg, 0.175 mmol) in EtOH (10 ml) was hydrogenated over 5% Pd-C (40 mg) at room temperature. The reaction mixture was filtered to remove the catalyst, and after removing the solvent, the residue was purified by silica-gel column chromatography to give 21 mg of **1** (AcOEt-benzene = 4 : 6) and 19 mg of **1'** (AcOEt-benzene = 2 : 8) (85%). Satisfactory elemental analyses and IR, NMR and MS spectra were obtained for these products.

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