ALTERNATIVE SYNTHESIS OF (-)-MALYNGOLIDE UTILIZING (-)-QUINIC ACID

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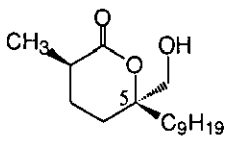
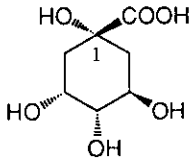
Abstract - (-)-Malyngolide, an antibiotic isolated from a blue-green algae, was synthesized starting from (-)-quinic acid.

(-)-Malyngolide is an antibiotic isolated from the marine blue-green algae, *Lyngbya majuscula* GOMONT,[1] and its structure was determined as **1**. Although more than thirty methods for its synthesis have so far been appeared, [2] in the course of our synthetic studies[3] on biologically active natural products using (-)-quinic acid (**2**)[4] as a chiral source,[5] we planned to synthesize (-)-**1**. (-)-Quinic acid (**2**) has four asymmetric centers, of which one is quaternary and the others are secondary. We thought that it might be possible to introduce the stereogenic center at *C1 of (-)-2 into the C5 asymmetric center of (-)-1*.

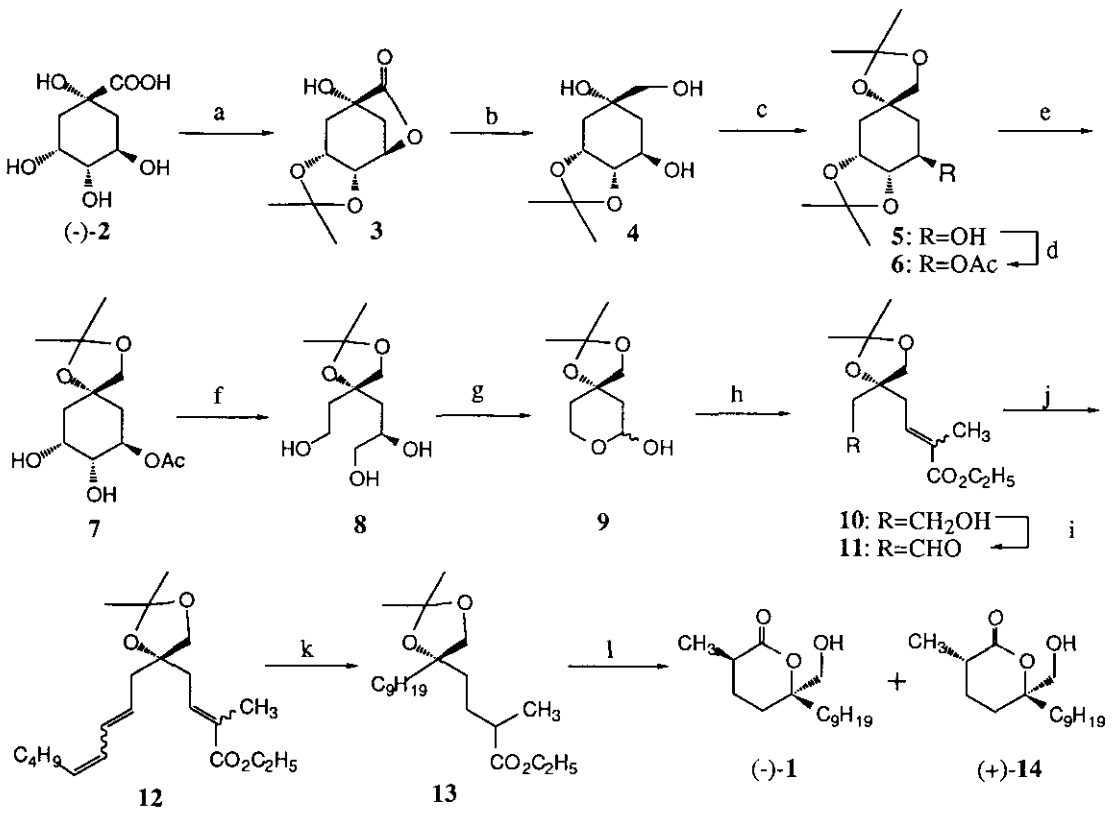


(-)-Malyngolide (**1**)



(-)-Quinic acid (**2**)

Although the triol (**4**) is known,[6] we synthesized **4** with a modified method from (-)-**2**. Thus, (-)-**2** was treated with 2,2-dimethoxypropane in acetone in the presence of a catalytic amount of *p*-toluenesulfonc acid (*p*-TsOH) to give the protected γ–lactone (**3**) in 87% yield.[4] Lithium aluminum hydride reduction of **3** gave the triol (**4**) in 83% yield. Protection of the glycol part in **4** as an acetonide was first tried with 2,2-dimethoxypropane in acetone in the presence of a catalytic amount of *p*-TsOH,[7] but a complex mixture was formed. The desired alcohol (**5**) was obtained in quantitative yield, when 2,2-dimethoxypropane was used instead of acetone as the solvent.[8] Acetylation of **5** was performed by treatment with acetic anhydride and pyridine to give **6** in 94% yield. Selective deprotection of the acetonide groups in **6** with aqueous acetic acid in methanol gave the diol (**7**) in 54% yield (80% based on recovery of **6** in 27%). Oxidative cleavage of the glycol portion of **7** was carried out using sodium metaperiodate in a mixture of methanol and water, and the crude dialdehyde was reduced successively with sodium borohydride in ethanol followed by hydrolysis of the ester group by addition of water to the reaction mixture and stirring the mixture at room temperature to afford the triol (**8**) in 67% yield from **7**. Lithium aluminum hydride



Scheme 1. *Reagents and coditions*: a. 2,2-dimethoxypropane, acetone, *p*-TsOH (87%); b. $LiAlH_4$ (83%); c. 2,2-dimethoxypropane, DMF, *p*-TsOH (quant.); d. Ac_2O, pyr (94%); e. AcOH, H_2O, MeOH (54%; 80% based on recovery of material); f. 1) $NaIO_4$, H_2O, MeOH; 2) $NaBH_4$; 3) H_2O (67%); g. $NaIO_4$, H_2O, MeOH (88%); h. ethyl 2-(triphenylphosphoranylidene)propionate, MeCN (66%; 74% based on recovery of material); i. TEMPO, KBr, aq. NaOCl (quant.); j. 2-heptenyltriphenylphosphonium bromide, *n*-BuLi, ether (74%); k. H_2, Ra Ni, EtOH (quant.); l. 1) KOH, H_2O; 2) HCl, H_2O.

reduction of the intermediary dialdehyde in tetrahydrofuran gave **8** in only 39% yield. Again, oxidative glycol cleavage of **8** was performed with sodium metaperiodate in a mixture of methanol and water to furnish the lactol (**9**) in 88% yield. Wittig reaction of **9** with ethyl 2-(triphenylphosphoranylidene)-propionate in acetonitrile gave the conjugate ester (**10**) as a stereoisomeric mixture in 66% yield (74% based on recovery of **9** in 11% yield). Oxidation of the primary alcohol (**10**) to the aldehyde (**11**) was carried out in a quantitative yield by the treatment with a catalytic amount of 2,2,6,6-tetramethylpiperidine-1-oxyl, free radical (TEMPO), potassium bromide and aqueous sodium hypochlorite in a mixture of dichloromethane and water.[9] Pyridinium dichromate oxidation of **10** gave **11** in low yield (42%). Wittig reaction of **11** with 2-heptenyltriphenylphosphonium bromide[10] in the presence of *n*-butyllithium in ether gave the crude triene (**12**), which was hydrogenated directly using Raney Nickel (W-7) as a catalyst to form the known ester (**13**)[2w] as a diastereomeric mixture in 74% yield from **11**. Thus, the known ester

(**13**) was synthesized in 11 steps and 18% overall yield from (-)-quinic acid (**2**). This is superior to our method reported previously starting from D-lactose (13 steps and 2% overall yield).[2w] Finally, hydrolysis of the ester group of **13** with potassium hydroxide in aqueous ethanol followed by acidic work-up gave (-)-malyngolide (**1**); $[\alpha]_D^{20}$ -13.1° (lit.,[1] $[\alpha]_D$ -13°) and (+)-2-epimalyngolide (**14**) in 38 and 37% yields, respectively. It is known that the base treatment of (+)-**14** followed by acidic work-up furnished a mixture of (-)-**1** and (+)-**14** in a ratio of 9:4.[2c] IR, ^{1}H-NMR and MS spectral data of the synthesized (-)-**1** are identical to those of the natural one.[1]

EXPERIMENTAL SECTION

Unless otherwise stated the following procedures were adopted. Melting points were determined using a Yanagimoto micro-melting point apparatus, model MP-S3, and are uncorrected. IR spectra were measured with a Hitachi 260-30 infrared spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-GSX270 (270 MHz) spectrometer using tetramethylsilane as the internal standard. High resolution mass spectra (HRMS) were measured with a JEOL JMS-HX100 instrument at 70 eV. Optical rotations were recorded on a JASCO DIP-370 polarimeter.

(1*S*,3*R*,4*S*,5*R*)-1,3,4-Trihydroxy-3,4-*O*-isopropylidene-6-oxabicyclo[3.2.1]octan-7-one (3)

A solution of (-)-quinic acid (**2**) (0.500 g, 2.60 mmol), 2,2-dimethoxypropane (0.58 mL, 4.68 mmol), and *p*-TsOH (0.016 g, 0.09 mmol) in dry acetone (9.3 mL) was heated to reflux for 6 h. After cooling to rt, the mixture was concentrated to give a residue, which was dissolved in saturated aqueous $NaHCO_3$ solution. The aqueous solution was extracted with AcOEt and the extract was washed with brine. After drying over anhydrous Na_2SO_4, the organic solution was concentrated to give a residue, which was chromatographed on SiO_2 (acetone : *n*-hexane=1 : 1) to furnish **3** (0.485 g, 87%)[6] as colorless needles; mp 144-146 °C ($CHCl_3$-*n*-hexane).

(1*R*,2*S*,3*R*,5*R*)-1,2,3,5-Tetrahydroxy-5-hydroxymethyl-2,3-*O*-isopropylidenecyclohexane (4)

A solution of **3** (0.860 g, 4.02 mmol) in dry THF (3 mL) was added dropwise to a mixture of $LiAlH_4$ (0.191 g, 5.02 mmol) and dry THF (17 mL) and the reaction mixture was heated to reflux for 8 h. After cooling to rt, H_2O (1 mL) and Celite were added and the mixture was stirred at rt for 2 h. The mixture was filtered and the residue was washed with a mixture of $CHCl_3$ and EtOH. The combined filtrate was concentrated to leave a residue, which was chromatographed on SiO_2 (acetone : *n*-hexane=3 : 1) to give **4** (0.727 g, 83%)[6] as a colorless crystalline powder; mp 117-118 °C ($CHCl_3$-*n*-hexane).

(5*R*,7*R*,8*R*,9*R*)-7,8,9-Trihydroxy-8,9-*O*-isopropylidene-2,2-dimethyl-1,3-dioxaspiro-[4.5]decane (5)

2,2-Dimethoxypropane (50 mL) and *p*-TsOH (0.392 g, 2.06 mmol) were added to a solution of **4** (4.500 g, 20.62 mmol) in dry DMF (3.0 ml) and the whole was stirred at rt for 2 h. The mixture was concentrated and the residue was dissolved in ether and the solution was washed successively with saturated $NaHCO_3$ solution, H_2O, and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give **5**

(5.465 g, quant.) as colorless crystalline powder; mp 69.5-70.0 °C. IR (Nujol): 3400 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (6H, s, 2 x CH_3), 1.52 (3H, s, CH_3), 1.48-1.59 (1H, m, $CHCH_2C$), 1.94 (1H, dd, *J*=15.0, 5.0 Hz, $CHCH_2C$), 2.02-2.12 (2H, m, $CHCH_2C$), 2.13 (1H, 1H, br s, OH), 3.75 (1H, d, *J*=8.5 Hz, OCH_2C), 3.82 (1H, d, *J*=8.5 Hz, OCH_2C), 3.88 (1H, t, *J*=6.0 Hz, OCH), 4.08-4.18 (1H, m, $OCHCH_2C$), 4.32 (1H, dd, *J*=10.5, 5.0 Hz, OCH). HRMS (*m/z*): Calcd for $C_{12}H_{19}O_5$ (M^+-CH_3): 243.1233. Found: 243.1203. *Anal.* Calcd for $C_{13}H_{22}O_5$: C, 60.44; H, 8.58. Found: C, 60.26; H, 8.38. $[\alpha]_D^{21}$ -24.3° (*c*=0.970, MeOH).

(5*S*,7*R*,8*R*,9*R*)-7-Acetoxy-8,9-dihydroxy-8,9-*O*-isopropylidene-1,3-dioxaspiro[4.5]-decane (6)

To a mixture of acetic anhydride (1.4 mL, 14.84 mmol) and dry pyridine (3.5 mL, 43.28 mmol) was added under ice cooling a solution of **5** (0.100 g, 0.39 mmol) in dry CH_2Cl_2 (1.4 mL) and the whole was stirred under ice cooling for 8 h. After addition of H_2O (1 mL), the organic layer was separated and the H_2O layer was extracted with $CHCl_3$. The combined organic layer was washed successively with H_2O and brine, and dried over anhydrous Na_2SO_4. The organic layer was concentrated to give a residue, which was chromatographed on SiO_2 (AcOEt : benzene=1 : 1) to furnish **6** (0.109 g, 94%) as a colorless oil. IR (neat): 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.35, 1.40, 1.42, 1.54 (each 3H, s, 4 x CH_3), 1.60 (1H, dd, *J*=13.5, 8.5 Hz, $CHCH_2C$), 1.95 (1H, dd, *J*=15.0, 5.0 Hz, $CHCH_2C$), 2.04-2.14 (1H, m, $CHCH_2C$), 2.07 (3H, s, $OCOCH_3$), 2.19 (1H, ddd, *J*=15.0, 3.5, 1.5 Hz, $CHCH_2C$), 3.74 (2H, s, OCH_2C), 4.01 (1H, t, *J*=5.5 Hz, $OCHCH_2$), 4.36 (1H, dd, *J*=10.0, 5.0 Hz, OCH), 5.25 (1H, ddd, *J*=8.0, 5.5, 3.5 Hz, $OCHCH_2C$). HRMS (*m/z*): Calcd for $C_{14}H_{21}O_6$ (M^+-CH_3): 285.1338. Found 285.1357. $[\alpha]_D^{21}$ -17.9° (*c*=1.025, MeOH).

(5*S*,7*R*,8*R*,9*R*)-7-Acetoxy-8,9-dihydroxy-2,2-dimethyl-1,3-dioxaspiro[4.5]decane (7)

Acetic acid (4 mL) was added to a solution of **6** (0.245 g, 0.81 mmol) in MeOH (4 mL) and H_2O (2 mL) and the mixture was stirred at rt for 14 h. After neutralization with 2N NaOH solution and then salting out, the mixture was extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ solution and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was chromatographed on SiO_2 (AcOEt : benzene=1 : 1) to give **7** (0.114 g, 54%, 80% based on recovery of material) as an colorless oil and the starting **6** (0.066 g, 27%). IR (neat): 3350, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (6H, s, 2 x CH_3), 1.46-1.76 (2H, m, $CHCH_2C$), 2.07-2.27 (2H, m, $CHCH_2C$), 2.10 (3H, s, $OCOCH_3$), 2.63 (1H, d, *J*=10.0 Hz, OH), 3.48 (1H, td, *J*=10.0, 3.5 Hz, $OCHCH_2$), 3.57 (1H, d, *J*=10.0 Hz, OH), 3.80 (2H, s, OCH_2C), 4.08 (1H, ddd, *J*=10.0, 7.0, 3.0 Hz, OCH), 5.22 (1H, ddd, *J*=11.0, 10.0, 5.0 Hz, $OCHCH_2$). HRMS (*m/z*): Calcd for $C_{11}H_{17}O_6$ (M^+-CH_3): 245.1025. Found: 245.1018.

(4*S*)-4-[(2*R*)-2,3-Dihydroxypropyl]-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane (8)

To a mixture of **7** (8.016 g, 30.80 mmol), MeOH (290 mL), and H_2O (200 mL) was added portionwise $NaIO_4$ (16.468 g, 76.99 mmol) and the whole was stirred at rt for 1 h. During the reaction proceed, the mixture was maintained neutral by addition of 1M $NaHCO_3$ solution. After addition of H_2O, the most of MeOH was evaporated, and the resulting aqueous solution was salted out and then extracted with AcOEt. The extract was washed successively with H_2O and brine, and dried over anhydrous Na_2SO_4. Evaporation

of the solvent gave the crude dialdehyde (7.435 g) as colorless oil, which was used for the following reaction without further purification.

To a solution of the crude dialdehyde (7.435 g) in EtOH (325 mL) was added gradually $NaBH_4$ (2.342 g, 61.91 mmol) under ice cooling and the whole was stirred at rt for 1 h. After addition of H_2O, the mixture was stirred at rt for 1 h and neutralized with 10% HCl solution. After the most of EtOH was evaporated and the residue was salted out, the whole was extracted continuously with ether. The extract was concentrated to give a residue, which was chromatographed on SiO_2 (acetone-*n*-hexane=1:1) to yield **8** (4.517g, 67% from **7**) as a colorless oil. IR (neat): 3270 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.43, 1.47 (each 3H, s, 2 x CH_3), 1.70 (1H, dd, *J*=15.0, 2.0 Hz, $CHCH_2C$), 1.88 (1H, dd, *J*=15.0, 10.0 Hz, $CHCH_2C$), 2.00 (2H, dd, *J*=11.5, 6.0 Hz, CCH_2CH_2), 2.30 (1H, br s, OH), 3.48 (1H, dd, *J*=11.0, 6.2 Hz, $CHCH_2OH$), 3.61 (1H, dd, *J*=11.0, 3.0 Hz, $CHCH_2OH$), 3.78 (1H, s, OH), 3.79 (2H, dd, *J*=11.5, 5.5 Hz, CH_2CH_2OH), 3.89 (1H, d, *J*=9.0 Hz, OCH_2C), 3.99 (1H, d, *J*=9.0 Hz, OCH_2C), 3.86-4.07 (1H, m, $OCHCH_2$). HRMS (*m/z*): Calcd for $C_9H_{17}O_5$ (M^+-CH_3): 205.1076. Found: 205.1054.

(5*S*)-7-Hydroxy-2,2-dimethyl-1,3,8-trioxaspiro[4.5]decane (9)

To a mixture of **8** (1.513 g, 6.87 mmol), MeOH (55 mL), and H_2O (38 mL) was added portionwise $NaIO_4$ (3.673 g, 17.17 mmol) at rt and the whole was stirred for 1.5 h. During the reaction proceed, 1M $NaHCO_3$ solution was added to keep the mixture being neutral. After addition of H_2O, the most of MeOH was evaporated and the resulting solution was salted out. The mixture was extracted with AcOEt and the organic layer was washed with brine. After drying over anhydrous Na_2SO_4, the solvent was evaporated to give a stereoisomeric mixture (2:1) of **9** (1.143 g, 88%) as colorless crystals after recrystallization from AcOEt-*n*-hexane; mp 63-70 °C. IR ($CHCl_3$): 3300 cm^{-1}. HRMS (*m/z*): Calcd for $C_8H_{13}O_4$ (M^+-CH_3): 173.0808. Found: 173.0814. Major isomer: ^1H-NMR ($CDCl_3$) δ: 1.37, 1.405 (each 3H, s, 2 x CH_3), 1.66-2.04 (4H, m, $CH_2CH_2CCH_2CH$), 2.78 (1H, m, OH), 3.76-3.84 (1H, m, OCH_2CH_2), 3.85 (1H, d, *J*=9.0 Hz, OCH_2C), 3.93 (1H, d, *J*=9.0 Hz, OCH_2C), 3.89 -3.99 (1H, m, OCH_2CH_2), 5.18-5.22 (1H, m, OCHOH). Minor isomer: ^1H-NMR ($CDCl_3$) δ: 1.42, 1.45 (each 3H, s, 2 x CH_3), 1.66-2.04 (4H, m, $CH_2CH_2CCH_2CH$), 3.70 (1H, m, OH), 3.76 (1H, d, *J*=9.0 Hz,OCH_2C), 3.80 (1H, d, *J*=9.0 Hz, OCH_2C), 4.18 (1H, td, *J*=11.5, 3.5 Hz, OCH_2CH_2), 5.04 (1H, d, *J*=10.5 Hz, OCH_2CH_2), 5.14-5.19 (1H, m, OCHOH).

(4*R*)-4-(3-Ethoxycarbonyl-2-butenyl)-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane (10)

Ethyl 2-(triphenylphosphoranylidene)propionate (0.558 g, 1.54 mmol) was added to a solution of **9** (0.200 g, 1.06 mmol) in dry MeCN (7 mL) and the mixture was heated to reflux for 4.5 h. After addition of more ethyl 2-(triphenylphosphoranylidene)propionate (0.212 g, 0.58 mmol), refluxing the mixture was continued further for 1.5 h. The mixture was concentrated and the residue was treated with ether. The insoluble material was removed by filtration and the filtrate was concentrated to give a residue, which was chromatographed on SiO_2 (AcOEt:*n*-hexane=1 : 1) followed by preparative thin layer SiO_2 chromatography with the same solvent system to furnish **10** (0.192 g, 66%; 74% based on recovery of material) as a colorless oil and the starting **9** (0.021 g, 11%). IR (neat): 3400, 1705 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.30 (3H, t, *J*=7.0 Hz, $CO_2CH_2CH_3$), 1.44 (6H, s, 2 x CH_3), 1.80-1.92 (4H, m, $CH_2CH_2CCH_2CH$), 2.55

(3H, dd, *J*=7.5, 1.0 Hz, =CCH$_3$), 3.70-3.90 (2H, m, CH$_2$CH$_2$OH), 3.86 (2H, s, OCH$_2$C), 4.20 (2H, q, *J*=7.0 Hz, CO$_2$CH$_2$CH$_3$), 6.75 (1H, tq, *J*=7.5, 1.5 Hz, CH$_2$CH=). HRMS (*m/z*): Calcd for $C_{13}H_{21}O_5$ (M^+-CH$_3$): 257.1389. Found: 257.1366.

(4*R*)-4-(3-Ethoxycarbonyl-2-butenyl)-4-formylmethyl-2,2-dimethyl-1,3-dioxolane (11)

A solution of KBr (0.007 g, 0.06 mmol) in H$_2$O (0.03 mL) and TEMPO (0.001 g, 0.01 mmol) were added to a solution of **10** (0.166 g, 0.61 mmol) in CH$_2$Cl$_2$ (0.2 mL). Sodium hypochlorite solution (7 mL) was added dropwise to the above mixture at -15 °C under vigorous stirring. The organic layer was separated and the water layer was extracted with CH$_2$Cl$_2$, and the combined organic layer was washed successively with saturated NH$_4$Cl solution pregnated with KI, saturated Na$_2$S$_2$O$_3$ solution and brine. After drying over anhydrous Na$_2$SO$_4$, the organic layer was concentrated to give **11** (0.174 g, quant.) as an yellow oil. IR (neat): 1720, 1705 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 1.30 (3H, t, *J*=7.0 Hz, CO$_2$CH$_2$CH$_3$), 1.41, 1.425 (each 3H, s, 2 x CH$_3$), 1.83 (3H, m, =CCH$_3$), 2.58 (2H, dd, *J*=8.0, 1.0 Hz, =CCH$_2$), 2.67 (1H, dd, *J*=16.5, 2.0 Hz, CH$_2$CHO), 2.80 (1H, dd, *J*=16.5, 2.0 Hz, CH$_2$CHO), 3.90 (1H, d, *J*=9.0 Hz, OCH$_2$C), 3.95 (1H, d, *J*=9.0 Hz, OCH$_2$C), 4.20 (2H, q, *J*=7.0 Hz, CO$_2$CH$_2$CH$_3$), 6.79 (1H, tq, *J*=8.0, 1.5 Hz, =CHCH$_2$), 9.79 (1H, t, *J*=2.0 Hz, CHO). HRMS (*m/z*): Calcd for $C_{13}H_{19}O_5$ (M^+-CH$_3$): 255.1232. Found: 255.1233.

(4*S*)-4-(3-Ethoxycarbonyl-2-butenyl)-2,2-dimethyl-4-(2,4-nonadienyl)-1,3-dioxolane (12)

n-Butyllithium (1.47 M in *n*-hexane solution, 0.45 mL, 0.67 mmol) was added to a solution of 2-heptenyltriphenylphosphonium bromide (0.321 g, 0.73 mmol) in dry THF (2 mL) under ice cooling and the mixture was stirred at rt for 1.5 h. A solution of **11** (0.165 g, 0.61 mmol) in dry THF (4 mL) was added to the above reaction mixture under ice cooling and the whole was stirred at rt for 20 min. The mixture was concentrated to leave a residue, which was treated with ether. The insoluble material separated by filtration was treated again with ether and filtered. The combined filtrate was washed successively with H$_2$O and brine, and then dried over anhydrous Na$_2$SO$_4$. Evaporation of the solvent gave the residue, which was chromatographed on SiO$_2$ (AcOEt : *n*-hexane=1 : 10) to afford **12** (0.159 g, 74%) as a colorless oil. IR (neat): 1710, 1650 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 0.89 (3H, t, *J*=7.0 Hz, CH$_2$CH$_3$), 1.29 (3H, t, *J*=7.0 Hz, CO$_2$CH$_2$CH$_3$), 1.30-1.38 (4H, m, CH$_2$CH$_2$), 1.40, 1.41 (each 3H, s, 2 x CH$_3$), 1.83 (3H, dd, *J*=4.0, 1.5 Hz, =CCH$_3$), 2.06 (2H, q, *J*=7.0 Hz, =CHCH$_2$), 2.26-2.51 (4H, m, 2 x CCH$_2$CH=), 3.76 (1H, dd, *J*=9.0, 6.5 Hz, OCH$_2$C), 3.84 (1H, dd, *J*=9.0, 2.5 Hz, OCH$_2$C), 4.19 (2H, q, *J*=7.0 Hz, CO$_2$CH$_2$CH$_3$), 5.24-6.48 (4H, m, =CH), 6.83 (1H, tq, *J*=7.0, 1.5 Hz, =CHCH$_2$C). HRMS (*m/z*): Calcd for $C_{21}H_{34}O_4$ (M^+): 350.2457. Found: 350.2483.

(4*S*)-4-(3-Ethoxycarbonylbutyl)-2,2-dimethyl-4-nonyl-1,3-dioxolane (13)

A solution of **12** (0.153 g, 0.44 mmol) in EtOH (3 mL) was stirred under hydrogen atmosphere in the presence of Ra Ni (prepared from 1 g of Al-Ni alloy; W-7) at rt for 4.5 h. The catalyst was removed by filtration and the filtrate was concentrated to give **13** (0.160 g, quant.) as a colorless oil. IR (neat): 1735 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 0.88 (3H, t, *J*=7.0 Hz, CH$_2$CH$_3$), 1.16 (3H, d, CHCH$_3$), 1.26 (3H, t, *J*=7.0 Hz, CO$_2$CH$_2$CH$_3$), 1.27 (14H, s, (CH$_2$)$_7$), 1.38 (6H, s, 2 x CH$_3$), 1.40-1.80 (6H, m, CCH$_2$CH$_2$, CHCH$_2$CH$_2$C), 2.33-2.47 (1H, m, CHCH$_3$), 3.71, 3.75 (each 1H, d *J*=8.5 Hz, OCH$_2$C), 4.13 (2H, q,

J=7.8 Hz, $CO_2C\underline{H}_2CH_3$). HRMS (m/z): Calcd for $C_{20}H_{37}O_4$ (M^+-CH_3): 341.2692. Found: 341.2672. $[\alpha]_D^{21}$ +18.5° (c=1.05, MeOH).

(-)-Malyngolide (1) and (+)-2-Epimalyngolide (14)

To a solution of **13** (0.158 g, 0.44 mmol) in EtOH (4 mL) was added a solution of KOH (1.095 g, 19.52 mmol) in H_2O (4 mL) under ice cooling and the mixture was stirred at rt for 5 h. The mixture was acidified with 10% HCl solution to pH 3 under ice cooling and the whole was stirred at rt for 1 h. After salting out, the mixture was extracted with AcOEt, and the extract was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was dissolved in MeCN (5 mL). Amberlyst 15 (0.03 g) was added to the mixture and the whole was stirred at rt for 1.5 h. After filtration, the filtrate was concentrated to afford a residue, which was dissolved in ether and the whole was washed successively with saturated $NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified with preparative SiO_2 thin layer chromatography ($CHCl_3$: acetone=4 : 1) to give (-)-**1** (0.44g, 37%) and (+)-**14** (0.045 g, 38%) as colorless oils. (-)-Malyngolide (**1**): IR (neat): 3400, 1720, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.7 Hz, $CH_2C\underline{H}_3$), 1.26 (14H, s, $(CH_2)_7$), 1.29 (3H, d, J=7.0 Hz, $CHC\underline{H}_3$), 1.51-1.82 (4H, m, $CHC\underline{H}_2C\underline{H}_2C$), 1.88-2.06 (2H, m, $CC\underline{H}_2CH_2$), 2.36-2.52 (1H, m, $C\underline{H}CH_3$), 3.48 (1H, d, J=12.0 Hz, $CC\underline{H}_2OH$), 3.67 (1H, d, J=12.0 Hz, $CC\underline{H}_2OH$). HRMS (m/z): Calcd for $C_{15}H_{27}O_2$ (M^+-CH_2OH): 239.2011. Found: 239.1987. $[\alpha]_D^{20}$ -13.1° (c=2.185, $CHCl_3$) [lit.,[1] $[\alpha]_D$ -13° (c=2, $CHCl_3$)]. (+)-2-Epimalyngolide (**14**): IR (neat): 3340, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz, $CH_2C\underline{H}_3$), 1.26 (14H, s, $(C\underline{H}_2)_7CH_3$), 1.29 (3H, d, J=7.0 Hz, $CHC\underline{H}_3$), 1.62-1.84 (4H, m. $CHC\underline{H}_2C\underline{H}_2C$), 1.86-2.02 (2H, m., $CC\underline{H}_2CH_2$), 2.26 (1H, t, J=6.0 Hz, OH), 2.37-2.51 (1H, m, $C\underline{H}CH_3$), 3.61 (2H, d, J=6.0 Hz, $C\underline{H}_2OH$). $[\alpha]_D^{21}$ +20.14° (c=2.185, $CHCl_3$).

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Received, 13th March, 1998