An Enantiocontrolled Synthesis of (−)-Malyngolide

Toshio Honda,* Minako Imai, Katsuyuki Keino, and Masayoshi Tsubuki
Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

Enantioselective synthesis of (−)-malyngolide (**1**) was accomplished by employing diastereoselective addition of nonylmagnesium bromide to the 2-acylfuran derivative (**4**), followed by a ring transformation of the resulting optically active 2-furylalcohol (**5**) to give the pyranone derivative (**7**) as key steps.

(−)-Malyngolide (**1**), isolated from the lipid extract of a shallow-water variety of *Lyngbya majuscula*, exhibits antimicrobial activity against *Streptococcus pyogenes*.[1] This antibiotic has been the target molecule for the application of newly developed synthetic methods and strategies to give δ-lactone ring systems with a chiral quaternary carbon centre.[2]

In line with our interest in the use of oxidative conversion of 2-furylalcohols into pyranones as a method for synthesis of physiologically active natural compounds,[3] we describe herein an enantioselective synthesis of (−)-malyngolide.

The key step in this total synthesis is the introduction of the stereogenic centre at the carbon bearing the lactonic oxygen. This was accomplished by employing the highly diastereoselective addition of organometallic reagents to carbonyl compounds, in which the chelation effect played an important role in controlling the stereochemistry.[4]

The requisite starting material for the key reaction was prepared as follows. Treatment of (*R*)-2,3,-*O*-isopropylideneglyceraldehyde (**2**)[5] with 2-lithio-4-methylfuran[6] in diethyl ether afforded the alcohol (**3**), in 69.2% yield, as a diastereoisomeric mixture which, without separation, was subjected to Swern oxidation[7] to give the ketone (**4**).

The nucleophilic addition of nonylmagnesium bromide to (**4**) as a key step was carried out in diethyl ether at ambient temperature to provide the alcohols (**5**) and (**6**), in 72.5 and 12.1% yield from (**3**), respectively. Although the stereochemistry of the products (**5**) and (**6**) could not be determined at this stage, the major compound was assumed to be the desired alcohol (**5**) because the chelation model can be proposed as a transition state in this reaction as shown in the Figure.[4c]

Oxidation of compound (**5**) with *m*-chloroperbenzoic acid (MCPBA)[8] in chloroform in the presence of sodium acetate brought about the ring transformation to afford the pyranone derivative (**7**) which, on further oxidation with pyridinium chlorochromate (PCC), furnished the δ-lactone derivative (**8**) in 69.9% yield from alcohol (**5**). As a basic skeleton for the target molecule had thus been constructed, we embarked on the conversion of lactone (**8**) into the natural product.

Reduction of compound (**8**) with sodium borohydride in methanol–dichloromethane (5:1, v/v) in the presence of cerium(III) chloride[9] gave the alcohol (**9**) as a diastereoisomeric mixture in 94.2% yield. The alcohol (**9**) was used in the following step without determination of the stereochemistry at C-5 since this stereogenic centre was removed in the later step of the synthesis. Acetylation of the alcohol (**9**) with acetic anhydride provided the acetate (**10**). After removal of the acetonide group of compound (**10**) by acid treatment, the resulting diol (**11**) was converted into the primary alcohol (**13**), *via* the aldehyde (**12**), by treatment with sodium periodate and subsequently with sodium borohydride in the presence of cerium(III) chloride in 46.6% overall yield from the acetate (**10**). Reductive deacetoxylation of compound (**13**) with zinc amalgam in

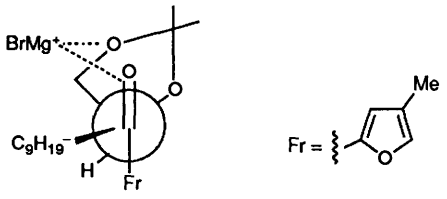


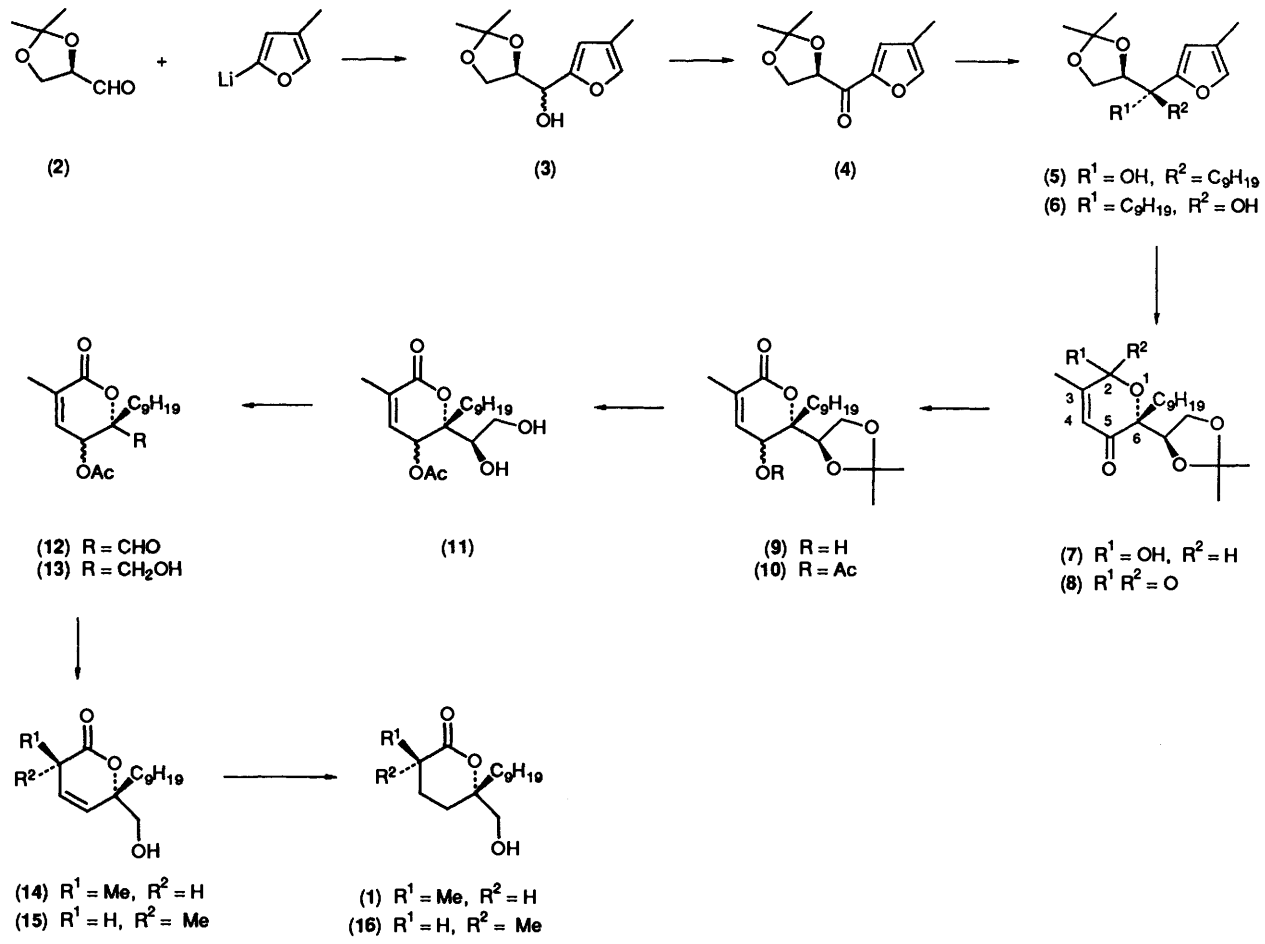
Figure.

ethereal hydrogen chloride[10] afforded the olefins (**14**) and (**15**) in 59.5 and 29.7% yield, respectively. Finally, hydrogenation of compound (**14**) over platinum oxide provided (−)-malyngolide (**1**), $[\alpha]_D^{25}$ −12.4° (*c* 0.306 $CHCl_3$) {lit. $[\alpha]_D$ −13.0°,[1] $[\alpha]_D^{22}$ −12.3°,[2a] $[\alpha]_D$ −12.7°,[2f] $[\alpha]_D^{20}$ −13.4°,[2i] $[\alpha]_D^{20}$ −12.1°[2k]}, whose spectroscopic data were in agreement with those reported.[1,2a,2k] Moreover the epimer (**15**) was also hydrogenated under similar reaction conditions as above to give (+)-epimalyngolide (**16**).[2a,2k] (Scheme).

Experimental

General Methods.—M.p.s were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrophotometer. ^1H NMR spectra were obtained for solutions in $CDCl_3$ on a JEOL PMX 270 instrument, and chemical shifts are reported in ppm on the δ-scale from internal Me_4Si. Mass spectra were measured with a JEOL JMS D-300 spectrometer. Optical rotations were taken with a JASCO-DIP-340 polarimeter. All new compounds described in the Experimental section were homogeneous on TLC and HPLC.

(2R)-1,2-O-*Isopropylidene*-3-(4-*methyl*-2-*furyl*)*glycerol* (**3**).—To a stirred solution of 2-lithio-4-methylfuran[6] [prepared from 2-bromo-4-methylfuran (69.8 g, 434 mmol) and 1.6M-butyllithium (250 ml, 400 mmol) in Et_2O (100 ml)] was added dropwise a solution of (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**2**)[5] (47 g, 362 mmol) in Et_2O (50 ml) at −78 °C and the reaction mixture was allowed to warm to 0 °C. Brine (10 ml) was added and the organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave an oil, which was purified by column chromatography on silica gel with hexane–AcOEt (5:1, v/v) as eluant to afford the *alcohol* (**3**) (53 g, 69.2%) as an oil; $\nu_{max}(CHCl_3)$ 3 380 cm^{-1}; δ 1.36, 1.38, 1.43, and 1.46 (each 1.5 H, each s, CMe_2), 2.00 (3 H, br s, 4′-Me), 3.74 (0.5 H, dd, *J* 8.6 and 6.1 Hz, 1-*H*H), 3.91 (1.5 H, m, 1-H_2), 4.34 and 4.37 (each 0.5 H, each q, *J* 6.1 Hz, 2-H), 4.50–4.55 and 4.70–4.75 (each 0.5 H, each m, 3-H), 6.17 and 6.18 (each 0.5 H, each br s, 3′-H), and 7.13 (1 H, br s, 5′-H); *m/z* 212 (M^+) (Found: M^+, 212.1042. $C_{11}H_{16}O_4$ requires *M*, 212.1047).



Scheme.

(2R,3R)-1,2-O-*Isopropylidene*-3-(4-*methyl*-2-*furyl*)*dodecane*-1,2,3-*triol* (**5**) *and its* (2R,3S)-*Isomer* (**6**).—To a stirred solution of oxalyl dichloride (1.85 ml, 21.2 mmol) in CH_2Cl_2 (50 ml) was added dropwise a solution of dimethyl sulphoxide (2 ml, 28.3 mmol) in (5 ml) at −50 °C. The reaction mixture was stirred for 5 min and a solution of the alcohol (**3**) (3 g, 14.2 mmol) in CH_2Cl_2 (10 ml) was added to the mixture and the mixture was stirred for 20 min. Et_3N was added and the reaction mixture was stirred for 5 min and then allowed to warm to room temperature. Water (50 ml) was added and the organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude ketone (**4**) (*ca.* 3 g) which was used in the next reaction without further purification owing to its instability.

To a stirred solution of nonylmagnesium bromide [prepared from nonyl bromide (4.06 ml, 21.2 mmol) and magnesium (0.61 g, 25.5 mmol) in Et_2O (50 ml)] was added dropwise a solution of the ketone (**4**) in Et_2O (5 ml) at 0 °C and the reaction mixture was stirred for 30 min. Brine (10 ml) was added and the organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave an oil, which was purified by column chromatography on silica gel with hexane–AcOEt (20:1, v/v) as eluant to afford the (2R,3R)-*alcohol* (**5**) [3.47 g, 72.5% from (**3**)] as an oil; $[\alpha]_D^{25}$ +13.8° (*c* 1.64, $CHCl_3$); $\nu_{max}(CHCl_3)$ 3 350 cm^{-1}; δ 0.87 (3 H, t, *J* 6.7 Hz, CH_2*Me*), 1.23 (14 H, br s, CH_2 × 7), 1.37 and 1.40 (each 3 H, each s, CMe_2), 1.83 (2 H, dd, *J* 9.1 and 7.0 Hz, 4-H_2), 2.00 (3 H, br s, 4′-Me), 3.75 and 3.84 (each 1 H, dd, *J* 8.5 and 6.7 Hz, 1-H_2), 4.29 (1 H, t, *J* 6.7 Hz, 2-H), 6.12 (1 H, br, 3′-H), and 7.08 (1 H, br s, 5′-H); *m*/*z* 388 (M^+) (Found: M^+, 338.2457. $C_{20}H_{34}O_4$ requires *M*, 338.2457).

The second fraction gave the (2R,3S)-*epimer* (**6**) [0.58 g, 12.1% from (**3**)] as an oil; $\nu_{max}(CHCl_3)$ 3 350 cm^{-1}; δ 0.87 (3 H, t, *J* 6.7 Hz, CH_2*Me*), 1.21 (14 H, br s, CH_2 × 7), 1.36 and 1.39 (each 3 H, each s, CMe_2), 2.01 (3 H, d, *J* 1.2 Hz, 4′-Me), 3.94 and 4.01 (each 1 H, dd, *J* 8.5 and 6.7 Hz, 1-H_2), 4.40 (1 H, t, *J* 6.7 Hz, 2-H), 6.15 (1 H, br s, 3′-H), and 7.12 (1 H, br s, 5′-H); *m*/*z* 388 (M^+) (Found: M^+, 338.2451).

(2R)-2-[(4R)-2,2-*Dimethyl*-1,3-*dioxolan*-4-*yl*]-6-*hydroxy*-5-*methyl*-2-*nonyl*-2H-*pyran*-3(6H)-*one* (**7**).—To a stirred suspension of the alcohol (**5**) (100 mg, 0.296 mmol) and anhydrous sodium acetate (29.1 mg, 0.355 mmol) in $CHCl_3$ (2 ml) was added portionwise MCPBA (*ca.* 70% purity; 87.5 mg, 0.355 mmol) at 0 °C and the reaction mixture was stirred for 30 min at the same temperature. Brine (2 ml) was added and the organic layer was washed successively with 5% aq. sodium hydroxide and brine, and dried over Na_2SO_4. Evaporation of the solvent gave an oil, which was purified by column chromatography on silica gel with hexane–AcOEt (15:1, v/v) as eluant to afford the lactol (**7**) (95 mg, 90.6%) as an oil; $\nu_{max}(CHCl_3)$ 3 350 and 1 675 cm^{-1}; δ 0.87 (3 H, t, *J* 6.7 Hz, CH_2*Me*), 1.23 (16 H, br s, CH_2 × 8), 1.23 and 1.37 (each 3 H, each s, CMe_2), 2.05 (3 H, d, *J* 1.8 Hz, 5-Me), 4.05 and 4.07 (each 1 H, each d, *J* 6.7 Hz, 5′-H_2), 4.19 (1 H, t, *J* 6.7 Hz, 4′-H), 5.28 (1 H, br s, 6-H), and 5.95 (1 H, d, *J* 1.8 Hz, 4-H); *m*/*z* 339 (M^+ − 15).

(6R)-[(4R)-2,2-*Dimethyl*-1,3-*dioxolan*-4-*yl*]-3-*methyl*-6-*nonyl*-2H-*pyran*-2,5(6H)-*dione* (**8**).—To a stirred suspension of the lactol (**7**) (3 g, 8.48 mmol) and anhydrous sodium acetate (556 mg, 6.78 mmol) in CH_2Cl_2 (100 ml) was added portionwise

PCC (7.3 g, 33.9 mmol) at room temperature and the reaction mixture was stirred for 2 h at the same temperature. Et_2O (100 ml) was added and the mixture was decanted. Evaporation of the solvent gave an oil, which was purified by column chromatography on silica gel with hexane–AcOEt (30:1, v/v) as eluant to afford the lactone (**8**) (2.3 g, 77.2%) as an oil; $[\alpha]_D^{25}$ +17.0° (*c* 2.94, $CHCl_3$); ν_{max}($CHCl_3$) 1 680 cm^{-1}; δ 0.87 (3 H, t, *J* 6.1 Hz, CH_2*Me*), 1.23 (16 H, br s, CH_2 × 8), 1.27 and 1.29 (each 3 H, each s, CMe_2), 2.20 (3 H, d, *J* 1.8 Hz, 3-Me), 3.99 (2 H, d, *J* 6.7 Hz, 5′-H_2), 4.30 (1 H, t, *J* 6.7 Hz, 4′-H), and 6.58 (1 H, d, *J* 1.8 Hz, 4-H); *m/z* 337 (M^+ − 15) [Found: (M^+ − 15), 337.2016. $C_{19}H_{29}O_5$ requires *m/z* 337.2016].

(6R)-6-[(4R)-2,2-*Dimethyl*-1,3-*dioxolan*-4-*yl*]-5-*hydroxy*-3-*methyl*-6-*nonyl*-5,6-*dihydro*-2H-*pyran*-2-one (**9**).—To a stirred suspension of the enone (**8**) (2.66 g, 7.56 mmol) and cerium(III) chloride (3.38 g, 9.01 mmol) in MeOH (5 ml)–CH_2Cl_2 (1 ml) at 0 °C was added portionwise sodium borohydride (314 mg, 8.31 mmol) and the reaction mixture was stirred for 10 min at the same temperature. Brine (1 ml) was added and the product was extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave an oil, which was purified by column chromatography on silica gel with hexane–AcOEt (4:1, v/v) as eluant to afford the allylic alcohol (**9**) (2.52 g, 94.2%) as an oily, diastereoisomeric mixture (2:3, less polar:more polar isomer). A small amount of product was separated carefully by further column chromatography on silica gel with hexane–AcOEt (4:1, v/v) as eluant to afford the less polar compound; $[\alpha]_D^{25}$ −3.1° (*c* 0.32, $CHCl_3$); ν_{max}($CHCl_3$) 3 550 and 1 720 cm^{-1}; δ 0.88 (3 H, t, *J* 6.7 Hz, CH_2*Me*), 1.25 (16 H, br s, CH_2 × 8), 1.36 and 1.50 (each 3 H, each s, CMe_2), 1.92 (3 H, d, *J* 1.8 Hz, 3-Me), 4.07 (1 H, d, *J* 9.2 and 7.3 Hz, 5′-H), 4.13 (1 H, dd, *J* 9.2 and 4.9 Hz, 5′-H), 4.34 (1 H, dd, *J* 7.3 and 4.9 Hz, 4′-H), 4.87 (1 H, br s, 5-H), and 6.40 (1 H, t, *J* 1.8 Hz, 4-H); *m/z* 355 (M^+ + 1) [Found: (M^+ + 1), 355.2475. $C_{20}H_{35}O_5$ requires *m/z*, 355.2482].

The second fraction afforded the more polar compound; $[\alpha]_D^{25}$ −19.8° (*c* 2.56, $CHCl_3$); ν_{max}($CHCl_3$) 3 430 and 1 695 cm^{-1}; δ 0.88 (3 H, t, *J* 7.3 Hz, CH_2*Me*), 1.26 (16 H, br s, CH_2 × 8), 1.35 and 1.48 (each 3 H, each s, CMe_2), 1.95 (3 H, d, *J* 1.5 Hz, 3-Me), 4.09 (1 H, dd, *J* 9.2 and 7.3 Hz, 5′-H), 4.16 (1 H, dd, *J* 9.2 and 5.5 Hz, 5′-H), 4.42–4.52 (1 H, m, 5-H), 4.61 (1 H, dd, *J* 7.3 and 5.5 Hz, 4′-H), and 6.58 (1 H, distorted d, *J* 1.5 Hz, 4-H); *m/z* 339 (M^+ − 15).

(6R)-5-*Acetoxy*-6-[(4R)-2,2-*dimethyl*-1,3-*dioxolan*-4-*yl*]-3-*methyl*-6-*nonyl*-5,6-*dihydro*-2H-*pyran*-2-*one** (**10**).—A solution of the alcohol (**9**) (1 g, 2.83 mmol) in acetic anhydride (5 ml)–pyridine (10 ml) was stirred for 2 h at room temperature and poured into water (20 ml). The product was extracted with AcOEt and the extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave an oil, which was purified by column chromatography on silica gel with hexane–AcOEt (30:1, v/v) as eluant to afford the acetate (**10**) (1.06 g, 95.1%) as an oily, diastereoisomeric mixture (2:3, less polar:more polar isomer). A small amount of the product was separated carefully by further column chromatography on silica gel with hexane–AcOEt (30:1, v/v) as eluant to afford the less polar compound; $[\alpha]_D^{25}$ +76.2° (*c* 0.216, $CHCl_3$); ν_{max}($CHCl_3$) 1 715 cm^{-1}; δ 0.88 (3 H, t, *J* 6.7 Hz, CH_2*Me*), 1.26 (16 H, br s, CH_2 × 8), 1.31 and 1.41 (each 3 H, each s, CMe_2), 1.95 (3 H, d, *J* 1.2 Hz, 3-Me), 2.11 (3 H, s, MeCO), 3.95 (1 H, dd, *J* 9.2 and 6.1 Hz, 5′-H), 4.00 (1 H, dd, *J* 9.2 and 7.3 Hz, 5′-H), 4.30 (1 H, dd, *J* 7.3 and 6.1 Hz, 4′-H), 5.73 (1 H, dd, *J* 4.3 and 1.2 Hz, 5-H), and 6.40 (1 H, dd, *J* 4.3 and 1.2 Hz, 4-H); *m/z* 396 (M^+).

The second fraction afforded the more polar compound; $[\alpha]_D^{25}$ −123.1° (*c* 0.495, $CHCl_3$); ν_{max}($CHCl_3$) 1 710 cm^{-1}; δ 0.88 (3 H, t, *J* 7.3 Hz, CH_2*Me*), 1.25 (16 H, br s, CH_2 × 8), 1.34 and 1.45 (each 3 H, each s, CMe_2), 1.98 (3 H, d, br s, 3-Me), 2.08 (3 H, s, MeCO), 4.05 (1 H, dd, *J* 9.2 and 7.3 Hz, 5′-H), 4.15 (1 H, dd, *J* 9.2 and 6.1 Hz, 5′-H), 4.35 (1 H, dd, *J* 7.3 and 6.1 Hz, 4′-H), 5.26 (1 H, d, *J* 5.5 Hz, 5-H), and 6.58 (1 H, distorted dd, *J* 5.5 and 1.2 Hz, 4-H); *m/z* 397 (M^+ + 1).

(6R)-5-*Acetoxy*-6-[(1R)-1,2-*dihydroxyethyl*]-3-*methyl*-6-*nonyl*-5,6-*dihydro*-2H-*pyran*-2-*one*† (**11**).—To a stirred solution of the acetonide (**10**) (971.4 mg, 2.45 mmol) in MeOH (15 ml) at 0 °C was added dropwise 10% H_2SO_4 (4.9 ml, 17.6 mmol) and the reaction mixture was stirred for 2 h at room temperature. Saturated aq. $NaHCO_3$ was added (to pH 7) and the product was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave an oil, which was purified by column chromatography on silica gel with hexane–AcOEt (2:1, v/v) as eluant to afford the diol (**11**) (632 mg, 72.4%) as an oily, diastereoisomeric mixture (2:3, less polar:more polar isomer). A small amount of the product was separated carefully by further column chromatography on silica gel with hexane–AcOEt (2:1, v/v) as eluant to afford the less polar compound; $[\alpha]_D^{25}$ +39.1° (*c*. 1.667, $CHCl_3$); ν_{max}($CHCl_3$) 3 340 and 1 710 cm^{-1}; δ 0.88 (3 H, t, *J* 6.7 Hz, CH_2*Me*), 1.26 (16 H, br s, CH_2 × 8), 1.94 (3 H, br s, 3-Me), 2.11 (3 H, s, MeCO), 3.49 (1 H, dd, *J* 11.6 and 7.9 Hz, 2′-H), 3.73 (1 H, dd, *J* 11.6 and 2.4 Hz, 2′-H), 3.90 (1 H, dd, *J* 7.9 and 2.4 Hz, 1′-H), 5.86 (1 H, dd, *J* 3.7 and 1.8 Hz, 5-H), and 6.40 (1 H, dd, *J* 3.7 and 1.8 Hz, 4-H); *m/z* 356 (M^+).

The second fraction afforded the more polar compound; $[\alpha]_D^{25}$ −111.0° (*c* 0.172, $CHCl_3$); ν_{max}($CHCl_3$) 3 340 and 1 690 cm^{-1}; δ 0.88 (3 H, t, *J* 6.7 Hz, CH_2*Me*), 1.24 (16 H, br s, CH_2 × 8), 1.98 (3 H, br s, 3-Me), 2.12 (3 H, s, MeCO), 3.72 (1 H, dd, *J* 11.0 and 7.9 Hz, 2′-H), 3.98 (1 H, dd, *J* 11.0 and 3.1 Hz, 2′-H), 4.06 (1 H, dd, *J* 7.9 and 3.6 Hz, 1′-H), 5.40 (1 H, d, *J* 6.1 Hz, 5-H), and 6.60 (1 H, dd, *J* 6.1 and 1.8 Hz, 4-H); *m/z* 356 (M^+).

(6R)-5-*Acetoxy*-6-*hydroxymethyl*-3-*methyl*-6-*nonyl*-5,6-*dihydro*-2H-*pyran*-2-*one*‡ (**13**).—To a stirred solution of the diol (**11**) (697.7 mg, 1.96 mmol) in CH_2Cl_2 (7 ml) was added portionwise sodium periodate (1.38 g, 7.84 mmol). Water (2 ml) was added and the reaction mixture was stirred for 1 h. The organic layer was separated, washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave the crude aldehyde (**12**) (*ca.* 635 mg) as a diastereoisomeric mixture (2:3, less polar:more polar isomer), which was used in the next reaction without further purification. A small amount of the product was separated carefully by column chromatography on silica gel with hexane–AcOEt (10:1, v/v) as eluant to afford the less polar compound; δ 0.88 (3 H, t, *J* 6.7 Hz, CH_2*Me*), 1.25 (16 H, br s, CH_2 × 8), 1.97 (3 H, d, *J* 1.8 Hz, 3-Me), 2.13 (3 H, s, MeCO), 5.45 (1 H, d, *J* 5.5 Hz, 5-H), 6.55 (1 H, dd, *J* 5.5 and 1.8 Hz, 4-H), and 9.54 (1 H, s, CHO).

The second fraction afforded the more polar compound; δ 0.87 (3 H, t, *J* 6.7 Hz, CH_2*Me*), 1.23 (16 H, br s, CH_2 × 8), 1.99 (3 H, d, *J* 1.8 Hz, 3-Me), 2.06 (3 H, s, MeCO), 5.42 (1 H, d, *J* 4.9 Hz, 5-H), 6.53 (1 H, dd, *J* 4.9 and 1.8 Hz, 4-H), and 9.70 (1 H, s, CHO).

The same procedure as for the preparation of compound (**9**) from dione (**8**) was applied to the aldehyde (**12**) to afford the alcohol (**13**) [419.8 mg, 64.3% from (**11**)] as an oily, diastereoisomeric mixture (2:3, less polar : more polar isomer).

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* (2R)-2-[(4R)-2,2-*Dimethyl*-1,3-*dioxolan*-4-*yl*]-5-*methyl*-2-*nonyl*-6-*oxo*-3,6-*dihydro*-2H-*pyran*-3-*yl Acetate*.

† (2R)-2-[(1R)-1,2-*Dihydroxyethyl*]-5-*methyl*-2-*nonyl*-6-*oxo*-3,6-*dihydro*-2H-*pyran*-3-*yl Acetate*.

‡ (2R)-2-*Hydroxymethyl*-5-*methyl*-2-*nonyl*-6-*oxo*-3,6-*dihydro*-2H-*pyran*-3-*yl Acetate*.

A small amount of the product was separated carefully by column chromatography on silica gel with hexane–AcOEt (4:1, v/v) as eluant to afford the less polar compound; $[\alpha]_D^{25}$ +73.7° (*c* 0.263, $CHCl_3$); $\nu_{max}(CHCl_3)$ 3 450 and 1 720 cm^{-1}; δ 0.88 (3 H, t, *J* 6.7 Hz, CH_2*Me*), 1.26 (16 H, br s, CH_2 × 8), 1.95 (3 H, br s, 3-Me), 2.12 (3 H, s, MeCO), 3.60 and 3.73 (each 1 H, each d, *J* 12.2 Hz, 1′-H_2), 5.72 (1 H, br s, 5-H), and 6.46 (1 H, dd, *J* 3.7 and 1.8 Hz, 4-H); *m/z* 325 (M^+ − 1).

The second fraction afforded the more polar compound; $[\alpha]_D^{25}$ −26.3° (*c* 0.334, $CHCl_3$); $\nu_{max}(CHCl_3)$ 3 470 and 1 715 cm^{-1}; δ 0.88 (3 H, t, *J* 6.7 Hz, CH_2*Me*), 1.26 (16 H, br s, CH_2 × 8), 1.94 (3 H, t, *J* 1.8 Hz, 3-Me), 2.07 (3 H, s, MeCO), 4.25 and 4.50 (each 1 H, each d, *J* 12.2 Hz, 1′-H_2), 4.28–4.35 (1 H, m, 5-H), and 6.49 (1 H, dd, *J* 4.3 and 1.8 Hz, 4-H); *m/z* 325 (M^+ − 1).

(3R,6S)-6-*Hydroxymethyl*-3-*methyl*-6-*nonyl*-3,6-*dihydro*-2H-*pyran*-2-*one* (**14**) *and its* (3S,6S)-*Epimer* (**15**).—To a stirred suspension of the allylic alcohol (**13**) (26.3 mg, 0.08 mmol) and zinc amalgam (78.5 mg, 1.2 mmol) in Et_2O (2 ml) at −15 °C was added dropwise ethereal 2.6M-hydrogen chloride (0.0611 ml, 0.16 mmol) during 2 h. Further Et_2O (20 ml) was added and the inorganic compound was filtered off. The filtrate was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave an oil, which was purified by column chromatography on silica gel with hexane–AcOEt (4:1, v/v) as eluant to afford the β,γ-unsaturated lactone (**15**) (6.4 mg, 29.7%) as an oil; $\nu_{max}(CHCl_3)$ 3 350 and 1 715 cm^{-1}; δ 0.88 (3 H, t, *J* 6.7 Hz, CH_2*Me*), 1.25 (16 H, br s, CH_2 × 8), 1.41 (3 H, d, *J* 7.3 Hz, 3-Me), 3.08–3.14 (1 H, m, 3-H), 3.54 and 3.65 (each 1 H, each d, *J* 12.2 Hz, CH_2OH), 5.63 (1 H, dd, *J* 10.4 and 3.1 Hz, 5-H), and 5.86 (1 H, dd, *J* 10.4 and 3.1 Hz, 4-H).

The second fraction afforded the desired compound (**14**) (12.9 mg, 59.5%) as an oil; $[\alpha]_D^{25}$ −10.2° (*c* 0.244, $CHCl_3$); $\nu_{max}(CHCl_3)$ 3 360 and 1 715 cm^{-1}; δ 0.88 (3 H, t, *J* 6.7 Hz, CH_2*Me*), 1.25 (16 H, br s, CH_2 × 8), 1.39 (3 H, d, *J* 7.9 Hz, 3-Me), 3.06–3.09 (1 H, m, 3-H), 3.58 and 3.69 (each 1 H, each d, *J* 12.2 Hz, CH_2OH), and 5.62 and 5.87 (each 1 H, each dd, *J* 10.4 and 2.4 Hz, 5- and 4-H); *m/z* 237 (M^+ − 31).

(−)-*Malyngolide* (**1**).—A mixture of the olefin (**14**) (19.3 mg, 0.0714 mmol) and platinum(IV) oxide (5 mg) in AcOEt (1 ml) was hydrogenated for 1 h. After filtration to remove the catalyst, the filtrate was concentrated to give an oil, which was purified by column chromatography on silica gel with hexane–AcOEt (3:1, v/v) as eluant to afford (−)-malyngolide (**1**) (17.6 mg, 90.7%); $[\alpha]_D^{25}$ −12.4° (*c* 0.306, $CHCl_3$) (lit. $[\alpha]_D$ −13.0°,[1] $[\alpha]_D^{22}$ −12.3 °,[2a] $[\alpha]_D$ −12.7°,[2f] $[\alpha]_D^{20}$ −13.4°,[2i] $[\alpha]_D^{20}$ −12.1°[2k]). Its spectroscopic data were identical with those previously reported.[1,2a,2k]

(+)-*Epimalyngolide* (**16**).—The same procedure as for compound (**14**) was applied to the olefin (**15**) to afford epimalyngolide (**16**) (90.5%); $[\alpha]_D^{25}$ +18.9° (*c* 0.036, $CHCl_3$) (lit. $[\alpha]_D^{22}$ +19.1°,[2a] $[\alpha]_D$ +17.0°,[2f] $[\alpha]_D^{20}$ +19.5°[2k]). Its spectroscopic data were identical with those previously reported.[2a,2k]

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