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# Malyngolide Analogues. Synthesis of (±)-Dehydromalyngolide and (±)-Isomalyngolide

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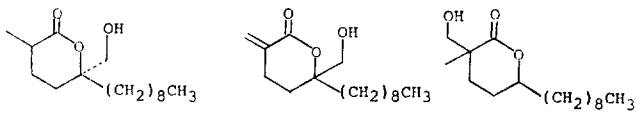
Two novel malyngolide analogues, (±)-dehydromalyngolide and (±)-isomalyngolide, of (−)-malyngolide antibiotic have been synthesized by application of our previously developed synthetic sequence for the synthesis of (±)-malyngolide. Dehydromalyngolide was synhtesized from the known lactone (4) in a 55 % overall yield in six steps, while isomalyngolide was synthesized from the readily available keto ester (11) in a 56 % overall yield in four steps.

(−)-Malyngolide (1), an antibiotic active against Mycobacterium smegmatis and Streptococcus pyogenes, was isolated from a shallow water variety of the blue-green alga Lyngbya majuscula Gomont and its structure was originally determined by Clardy.[1] In view of its biological properties and to further confirm the assigned structure, many reports on the synthesis of malyngolide have been appeared.[2-10] We have prepared two closely related analogues with malyngolide which we designate hereim (±)-dehydromalyngolide (2) and (±)-isomalyngolide (3). Our interest in dehydromalyngolide stemmed from the observation that the α-methylene lactone and ketone functional groups are the active functionality in a great number of antural products with antitumor and anticancer activity.[11-14] Furthermore, the synthesis of isomalyngolide would allow further exploration of its relative biological properties and structureactivity relationship. Since our previous synthesis of (±)-malyngolide[8] is very efficient in terms of the high yield, the few steps required, the use of readily available starting material, and the versatility for the synthesis of its analogues, we adopted the similar syntheic scheme for the ysnthesis of dehydromalyngolide and isomalyngolide.




1 2 3

## Results and Discussion

The known lactone ester (4), which was prepared in a high yield from readily available 2-(carbomethoxy)-cyclopentanone in two steps,[8] was hydrolyzed with lithium iodide in pyridine at reflux for 6 hrs to afford the acid (5) in 95 % yield. Reduction of the acid (5) with equimolar amounts of borane-tetrahydrofuran in tetrahydrofuran or borane-dimethyl sulfide complex in methylene chloride resulted in 30-40 % of the triol, resulting from overreduction of the δ-lactone ring, along with the hydroxy lactone (6) and the original acid. Thus, the acid (5) was converted to the mixed anhydride with equimolar amounts of ethyl chloroformate

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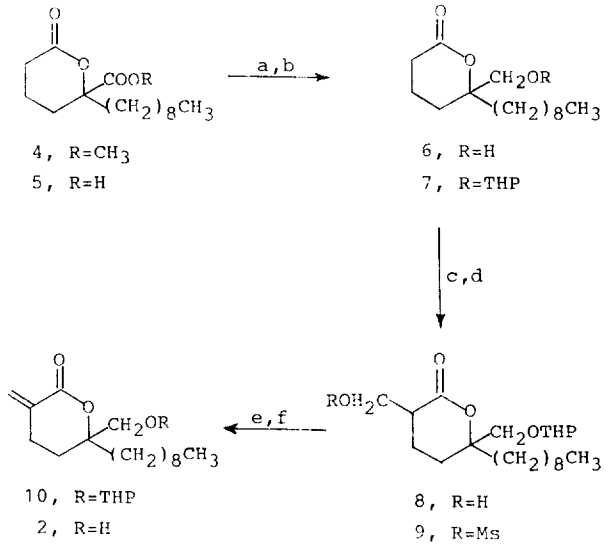
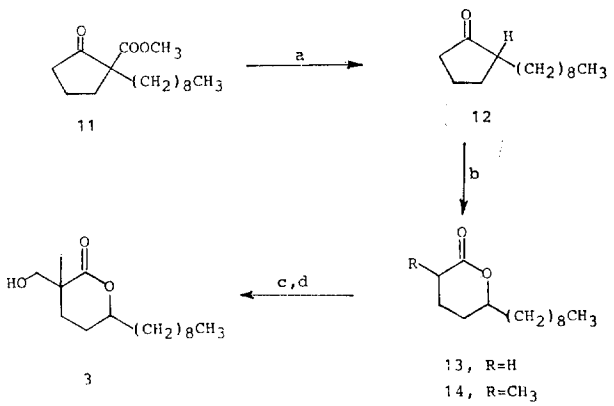
and triethylamine in diethyl ether at 0 °C, followed by the reduction with zinc borohydride in diethyl ether to afford the desired alcohol (6) in 80 % yield after purification by silica gel column chromatography. The hydroxy lactone (6) was quantitatively tetrahydropyranylated with dihydropyran in the presence of a catalytic amount of pyridinium tosylate[15] in methylene chloride at room temperature for 3 hrs.[6] At this point all that remained to complete the synthsis of dehydromalyngolide is the introduction of the $\alpha$-methylene group to the lactone group.[16] Thus, the lactone (7) was treated with 1.1 equiv of lithium diisopropylamide in tetrahydrofuran at −78 °C, followed by the addition of anhydrous formaldehyde at −20 °C to afford 60 % of the desired $\beta$-hydroxy lactone (8) and 25 % of the recovery of the starting material after separation by silica gel column chromatography. Dehydration was achieved by converting the $\beta$-hydroxy lactone (8) into the corresponding mesylate (9) and subsequent elimination of the mesylate group. Thus, the $\alpha$-methylene lactone (10) was obtained in 98 % yield by the reaction of the $\beta$-hydroxy lactone (8) with 1.1 equiv of methanesulfonyl chloride and 3 equiv of triethylamine in methylene chloride at −78 °C for 0.5 hr and then at room temperature for 6 hrs. Finally, dehydromalyngolide was prepared in a quantitative yield by removing the tetrahydropyranyl protective group with a catalytic amount of pyridinium tosylate in ethanol at 55 °C for 3 hrs. Its nmr spectrum showed doublets ($J$=2 Hz) for the $\alpha$-methylene group at 5.55 and 6.40 ppm, respectively, and ir spectrum showed a carbonyl absorption at 1725 $cm^{-1}$ for the $\delta$-lactone group. The synthetic pathway for the synthesis of dehydromalyngolide is summarized in Scheme 1.

For the synthesis of isomalyngolide (3), the introduction of the hydroxymethylene group at $C_2$ instead of at $C_5$ is required and the removal of the carbomethoxy group at $C_5$ at the early stage of the synthesis appeared to be desirable. Thus, decarboxylation of the alkylated keto ester (11) was carried out with aqueous methanolic sulfuric acid at 80 °C for 2 day to provide 2-nonylcyclopentanone in 89 % yield. Cyclopentanone (12) was subjected to Baeyer-Villiger oxidation condition with *m*-chloroperoxybenzoic acid and sodium bicarbonate in chloroform at room temperature for 2 day to afford the lactone (13) in 84 % yield. The lactone (13) was treated with 1.1 equiv of litihum diisopropylamide in tetrahydrofuran at −78 °C and methylated with 7 equiv of methyl iodide and 1.2 equiv of hexamethylphosphoramide at −45 °C to afford the methylated lactone (14) in 92 % yield. The hydroxymethylene group was introduced in the same manner as described above. Thus, the lithium enolate of the methylated lactone (14), generated via addition of 1.1 equiv of lithium diisopropylamide in tetrahydrofuran at −78 °C, was reacted with anhydrous formaldehyde to afford 58 % of isomalyngolide along with the recovery of 27 % of the starting material. Isomalyngolide was obtained as a mixture of diasteroisomers in a ratio of approximately 1:1. The synthetic pathway for the synthesis of isomalyngolide is summarized in Scheme 2.




**Scheme 1**[a].

[a] (a) LiI/pyridine (95 %); (b) ClCOOEt/$Et_3N$, $Zn(BH_4)_2$ (80 %); (c) DHP/PPTS (98 %); (d) LDA/THF, HCHO (80 %); (e) MsCl/$Et_3N$ (98 %); (f) PPTS/EtOH (98 %).




**Scheme 2**[a].

[a] (a) $H_2SO_4$/MeOH (89 %); (b) MCPBA, $NaHCO_3$ (84 %); (c) LDA, MeI/HMPA-THF (92 %); (d) LDA/THF, HCHO (81 %).

## Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 267, and the frequences are given in reciprocal centimeters. Proton nuclear magnetic resonance spectra were recorded with a Varian T-60A spectrometer, and chemical shifts are expressed as $\delta$ units relative to tetramethylsilane. Analytical thin-layer chromatography was performed on precoated silica gel glass plates (0.25 mm, 60F-254, E. Merck), and silica gel (Art. 9385, Kiesegel 60, 230-400 mesh) was used for column chromatography. Elemental analyses were performed by Korea Research Institute for Chemical Technology.

*5-Nonyl-5-carboxypentanolide* (*5*). To a solution of the lactone ester (4) (0.95 g, 3.3 mmol) in dry pyridine (20 m*l*) was added lithium iodide (3.1 g,23.4 mmol). The resuting solution was refluxed for 6 h, poured into water, acidified with 0.1*N* HCl, and extracted with ethyl ether. The ether extracts were washed with water, dried ($MgSO_4$) and evaporated to yield the acid

(5) (860 mg) in 95 % yield as a colorless oil: NMR ($CDCl_3$) $\delta$ 0.89 (*br t*, $J$=5 Hz, 3H, $CH_3$), 1.27 (*br s*, 16H, $CH_2$), 1.45–2.20 (*m*, 4H, $CH_2$), 2.25–2.70 (*m*, 2H, $CH_2CO$), 9.40 (*br s*, 1H, COOH); IR (NaCl) 1730, 1690 (C=O) $cm^{-1}$.

*5-Nonyl-5-(hydroxymethyl) pentanolide (6)*. To a solution of the acid (5) (259 mg, 1.0 mmol) in ethyl ether (3 m*l*) at 0 °C were added triethylamine (107 mg, 1.1 mmol) and ethyl chloroformate (115 mg, 1.1 mmol). After 0.5 h of stirring at 0 °C, freshly prepared zinc borohydride in ethyl ether (0.9*M*, 1.2 m*l*, 1.1 mmol) was added. The resulting solution was stirred at 0 °C for 0.5 h, allowed to warm to room temperature for 0.5 h, poured into saturated $NH_4Cl$ solution, and extracted with ethyl ether. The ether extracts were washed with water, dried ($MgSO_4$), and evaporated. The residue was subjected to silica gel column chromatography with hexane-ethyl acetate (6:4) to yield the hydroxy lactone (197 mg) in 80 % yield: NMR ($CDCl_3$) $\delta$ 0.89 (*br t*, $J$=5 Hz, 3H, $CH_3$), 1.27 (*br s*, 16H, $CH_2$), 1.65–2.00 (*m*, 4H, $CH_2$), 2.30–2.65 (*m*, 3H, $CH_2CO$, OH), 3.60 (*br s*, 2H, $CH_2O$); IR (NaCl) 3420 (OH), 1730 (C=O) $cm^{-1}$

*5-Nonyl-5-(tetrahydropyranyloxymethyl) pentanolide (7)*. A solution of the hydroxy lactone (6) (1.10 g, 4.4 mmol) and dihydropyran (540 mg, 6.3 mmol) in methylene chloride (10 m*l*) containing pyridium *p*-toluenesulfonate (108 mg, 0.4 mmol) was stirred for 4 h at room temperature. The solution was diluted with ethyl ether and washed with brine, dried ($MgSO_4$). After evaporation of solvents, the THP-ether (7) was obtained in an essentailly quantitative yield (1.43 g, 98 %): NMR ($CDCl_3$) $\delta$ 0.89 (*br t*, $J$=5 Hz, 3H, $CH_2$), 1.26 (*br s*, 16H, $CH_2$), 1.50–1.70 (*m*, 6H, $CH_2$), 2.15–2.45 (m, 2H, $CH_2CO$), 3.20–3.90 (*m*, 4H, $OCH_2$), 4.55 (m, 1H, OCHO); IR (NaCl) 1735 (C=O) $cm^{-1}$.

*2-Hydroxymethyl-5-nonyl-5-(tetrahydropyranyloxymethyl) pentanolide (8)*. To a solution of the lactone (7) (401 mg, 1.2 mmol) in THF (3 m*l*) at −78 °C under nitrogen was added lithium diisopropylamide (1.0*M*, 1.3 m*l*, 1.3 mmol) in THF. The reaction mixture was stirred at −78 °C for 0.5 h, was raised to −20 °C, and then was treated with formaldehyde vapors (paraformaldehyde (1.0 g) was heated at 180°C to generate formaldehyde and the vapors were carried by a nitrogen flow into the reaction mixture). After all the paraformaldehyde has been consumed, stirring was continued for an additional 0.5h. The reaction mixture was quenched with oxalic acid and extracted with ethyl ether. The ether extracts were washed with brine, dried ($MgSO_4$) and condensed in vacuo to give the hydroxymethylated lactone (8) (261 mg) in 60 % yield and the recovered starting material (101 mg, 25 %) after separation by silica gel column chromatography with hexane-ethyl acetate (1: 1) as an eluant: NMR ($CDCl_3$) $\delta$ 0.89 (*br t*, $J$=5 Hz, 3 H, $CH_3$), 1.27 (*br s*, 16 H, $CH_2$), 1.50–1.70 (*m*, 6H, $CH_2$), 1.72–2.00 (*m*, 4H, $CH_2$), 2.10–2.40 (m, 1H, CHC=O), 3.20–3.80 (*m*, 7 H, $OCH_2$, OH), 4.55 (*m*, 1H, OCHO); IR(NaCl) 3450 (OH), 1730(C=O) $cm^{-1}$

*Anal.* Calcd for $C_{21}H_{38}O_5$: C, 68.07; H, 10. 34. Found: C, 67.30; H, 10.35.

*2-Methylene-5-nonyl-5-(tetrahydropyranyloxymethyl) pentanolide (10)*. To a solution of the hydroxymethyl lactone (8) (371 mg, 1.0 mmol) in methylene chloride (5 ml) containing triethylamine (304 mg, 3.0 mmol) at −78 °C was added dropwise methanesulfonyl chloride (126 mg, 1.1 mmol). After 0.5 h of stirring at −78 °C, the reaction mixture was allowed to warm to room temperature, stirred for 6 h, poured into water, and extracted with ethyl ether. The ether extracts were washed with brine, dried, and evaporated to yield the $\alpha$-methylene lactone (335 mg) in 95 % yield: NMR ($CDCl_3$) $\delta$ 0.89 (*br t*, $J$=5 Hz, 3H, $CH_3$), 1.27 (*br s*, 16H, $CH_2$), 1.50–1.70 (*m*, 6H, $CH_2$), 1.80–2.15 (*m*, 2H, $CH_2$), 2.50–2.85 (*m*, 2H, $CH_2$), 3.30–3.95 (*m*, 4H, $CH_2O$), 4.62 (m, 1H, OCHO), 5.55 (*br s*, 1H, HC=C), 6.42 (*br s*, 1H, HC=C); IR (NaCl) 1725 (C=O) $cm^{-1}$.

*2-Methylene-5-nonyl-5-(hydroxymethyl) pentanolide, dehydro malyngolide (2)*. A solution of the $\alpha$-methylene lactone (10) (120 mg, 0.3 mmol) and pyridinium p-toluenesulfonate (9mg, 0.03 mmol) in ethanol (3 m*l*) was stirred at 55 °C for 3 h. The solvent was evaporated under reduced pressure and the residue was subjected to silica gel column chromatography with hexane-ethyl acetate (3:1) as an eluant to afford pure dehydromalyngolide (89 mg) in 98 % yield as a colorless oil. NMR ($CDCl_3$) $\delta$ 0.89 (*br t*, $J$=5 Hz, 3H, $CH_3$), 1.27 (*br s*, 16H, $CH_2$), 1.80–2.20 (*m*, 2H, $CH_2$), 2.75 (*m*, 3H, $CH_2$, OH), 3.65 (*br s*, 2H, $CH_2O$), 5.62 (*d*, $J$=2 Hz, 1H, HC=C), 6.25 (*d*, $J$=2 Hz, 1 H, HC=C); IR (NaCl) 3450 (OH), 1725 $cm^{-1}$.

*Anal.* Calcd for $C_{16}H_{28}O_3$: C, 71.61; H, 10.51. Found: C, 71.67; H, 10.39

*2-Nonylcyclopentanone (12)*. A solution of the keto ester (11) (400 mg, 1.5 mmol) in 35 % methanolic sulfuric acid (6 m*l*) was refluxed at 80 °C for 48 h, poured into saturated $NaHCO_3$ solution, and extracted with ethyl ether. The ether extracts were washed with water, dried, and evaporated to dryness. The residue was subjected to silica gel column chromatography with hexane-ethyl acetate (5:1) as an eluant to yield 2-nonylcyclopentanone (276 mg) in 89 % yield: NMR ($CDCl_3$) $\delta$ 0.89 (*br t*, $J$=5 Hz, 3H, $CH_3$), 1.27 (*br s*, 16H, $CH_2$), 1.80–2.40 (*m*, 7H, CH, $CH_2$); IR (NaCl) 1740 (C=O) $cm^{-1}$.

*5-Nonylpentanolide (13)*. To a solution of 2-nonylcyclopentanone (1.03 g, 4.9 mmol) in chloroform (10 m*l*) were added *m*-chloroperoxybenzoic acid (1.69 g, 9.9mmol) and sodium bicarbonate (0.83 g, 9.9 mmol). After the reaction mixture was stirred at room temperature for 48 h, hexane (20 m*l*) was added to the reaction mixture and the precipitate was filtered off. The filtrate was washed with 1N NaOH, saturated $NaHSO_3$, and water. The organic layer was dried over $MgSO_4$ and evaporated to dryness. The residue was subjected to silica gel column chromatography with hexane-ethyl acetate (3:1) as an eluant to yield the lactone (13) (0.93 g) in 84 % yield: NMR ($CDCl_3$) $\delta$ 0.89 (*br t*, J=5 Hz, 3H, $CH_3$), 1.27 (*br s*, 16H, $CH_2$), 1.70–2.10 (m, 4H, $CH_2$), 2.30–2.65 (*m*, 2H, $CH_2CO$), 4.00–4.40 (m, 1H, OCH); IR (NaCl) 1735 (C=O) $cm^{-1}$.

*Anal.* Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 74.10; H, 11.68.

*2-Methyl-5-nonylpentanolide (14)*. To a solution of the

lactone (13) (200 mg, 0.9 mmol) in THF (2 ml) at −78 °C under nitrogen was added lithium diisopropylamide (1.0*M*, 1.0 ml, 1.0 mmol) in THF. The reaction mixture was stirred at −78 °C for 10 min and allowed to warm to −45 °C over 0.5 h. A mixture of dry HMPA (192 mg, 1.1 mmol) and methyl iodide (890 mg, 6.3 mmol) in THF (1 ml) was added dropwise to the enolate solution at −45 °C and the resulting solution was warmed to −20 °C for 0.5 h, and quenched with saturated $NH_4Cl$, dried ($MgSO_4$), and evaporated to dryness. The residue was subjected to silica gel column chromatography with hexane–ethyl acetate (3:2) as an eluant to yield the methylated lactone (224 mg) in 92 % yield: NMR ($CDCl_3$) $\delta$ 0.89 (br t, J=5 Hz, 3H, $CH_3$), 1.27 (br s, 19H, $CH_2$, $CH_3$), 1.45–2.10 (*m*, 4H, $CH_2$), 2.25–2.65 (*m*, 1H, CHC=O), 4.00–4.40 (*m*, 1 H, OCH); IR (NaCl) 1735 (C=O) $cm^{-1}$.

*2-Methyl-2-hydroxymethyl-5-nonylpentanolide, isomalyngoli de (3).* To a solution of the lactone (14)(200 mg, 0.8 mmol) in THF (3 ml) at −78 °C under nitrogen was added lithium diisopropylamide (1.0*M*, 0.9 ml, 0.9 mmol) in THF. The reaction mixture was stirred at −78 °C for 0.5 h, warmed to −20 °C, and treated with formaldehyde generated from paraformaldehyde (0.5 g) at 180 °C. After all the paraformaldehyde was consumed, stirring was continued for an additional 0.5 h. The reaction mixture was quenched with oxalic acid and extracted with ethyl ether. The ether extracts were washed with brine, dried, and condensed under reduced pressure. The residue was subjected to silica gel column chromatography with hexane–ethyl acetate (2:1) as an eluant to give isomalyngolide (135 mg, 59 %) along with the starting material (54 mg, 27 %): NMR ($CDCl_3$) $\delta$ 0.89 (*br t*, *J*=5 Hz, 3 H, $CH_3$), 1.27 (*br s*, 19H, $CH_2$, $CH_3$), 1.45–2.20 (m, 4H, $CH_2$), 2.95 (br s, 1H, OH), 3.59 (*br s*, 2H, $OCH_2$), 4.15–4.60 (m, 1 H, CHC=O); IR (NaCl) 3450 (OH), 1720 (C=O) $cm^{-1}$.

*Anal.* Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 71.42; H, 11.43.

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# Determination of Rate Constants in Competitive Consecutive (Series)Second-Order Reaction

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The kinetics of the reactions of the type $A + B \xrightarrow{k_1} C + E$ and $B + C \xrightarrow{k_2} D + F$ has been analyzed and a method of obtaining approximate values of $k_1$ and $k_2$ for the cases where $k_2 \gg k_1$ is proposed.

## Introduction

Several detailed numerical procedures have been given for the experimental determination of the individual rate stants $k_1$ and $k_2$ in the kinetic systems consisting of two comconpetitive consecutive (series) irreversible second-order reactions.

$$A+B \xrightarrow{k_1} C+E$$
$$C+B \xrightarrow{k_2} D+F$$

Frost and Schwemer[1] developed a method for extracting