- 3) E. Profft and W. Georgi, *Ann.*, **643**, 136 (1961).
- 4) D. Klemann and E. Schaffer, *Chem. Ber.*, **87**, 1294 (1954); J.A. Montgomery and H.J. Thomas, *J. Org. Chem.*, **30**, 3235 (1965).
- 5) T. Hisano and M. Ichikawa, *Yakugaku Zasshi*, **91**, 1136 (1971).
- 6) M. Ichikawa, C. Yamamoto, and T. Hisano, *Org. Prep. Proced. Int.*, in press.

[Chem. Pharm. Bull.]
[29(10)3047—3050(1981)]

Total Synthesis of ($\pm$)-Malyngolide

KEIZO MATSUO,* TOSHIYUKI KINUTA and KUNIYOSHI TANAKA

*Faculty of Pharmaceutical Sciences, Kinki University, 3-4-1
Kowakae, Higashiosaka, Osaka, 577, Japan*

(Received February 27, 1981)

($\pm$)-Malyngolide, which is an antibiotic isolated from a marine blue-green alga, was synthesized starting from 2-ethoxycarbonylcyclopentanone.

Keywords—malyngolide; antibiotic; selective oxidation; selective reduction; Baeyer–Villiger oxidation

Malyngolide is a recently discovered antibiotic isolated from the marine blue-green alga, *Lyngbya majuscula* GOMONT,¹⁾ and its structure was determined as **1**. Recently, an elegant total synthesis of (–)-malyngolide has been reported by Mukaiyama *et al.*²⁾

1

Fig. 1

As a part of a general project aimed at the elucidation of the structure-activity relationships of antimicrobial substances³⁾, we selected malyngolide as a parent compound and firstly planned to synthesize it by a route which is applicable to the synthesis of its analogs.

The synthetic route to ($\pm$)-malyngolide is illustrated in Chart 1.

2-Ethoxycarbonyl-2-nonylcyclopentanone (**3**) was prepared by the reaction of 2-ethoxycarbonylcyclopentanone (**2**)⁴⁾ with nonyl bromide in the presence of sodium hydride in N,N-dimethylformamide at 100–110°C in 82.5% yield.

For conversion of the keto ester (**3**) to a ketol (**5**), it is necessary to reduce the ester group selectively in the presence of the keto group. There is no good method so far available for that purpose, although many procedures are available for the reduction of a ketone or aldehyde in the presence of an ester or lactone.⁵⁾ Therefore, we examined firstly reduction of both keto and ester groups and successive selective oxidation of the secondary alcohol in the diol (**4**). Thus, reduction of the keto ester (**3**) with lithium borohydride gave the diol (**4**) in 71.4% yield, and this product was oxidized selectively with bromine and hexamethylphosphoramide (HMPA)⁶⁾ to give the ketol (**5**) in 72.2% yield. Secondary, we employed the method of enolate formation in combination with hydride reduction which was first developed by Barton for the reduction of steroidal ketones.⁷⁾ Thus, the keto ester (**3**) was treated with lithium diisopropylamide (LDA) at –76°C in tetrahydrofuran (THF) to form a lithium enolate, which was reduced with lithium aluminum hydride at the same temperature to afford the desired ketol (**5**) in 63.5% yield.

Baeyer–Villiger oxidation of the ketol (**5**) with *m*-chloroperbenzoic acid in the presence of sodium bicarbonate in chloroform gave a lactone (**6**) as a sole product in 81.8% yield. The protection of the hydroxyl group in **6** was accomplished in 78.6% yield by treatment with

Chart 1

dihydropyran in the presence of a catalytic amount of *p*-toluenesulfonic acid in methylene chloride. The lactone (7) was treated with LDA at -76°C in the presence of HMPA in THF, and alkylated with methyl iodide to afford a diastereomeric mixture of methyl lactones 8 and 9.²⁾ Removal of the protecting group of the crude products with acetic acid gave a diastereomeric mixture of ($\pm$)-malyngolide (1) and its C-2 epimer (10) in 58% yield. The ratio of 1:10 was 5:4. The diastereomers 1 and 10 were separated by silica gel column chromatography. Moore *et al.* reported that malyngolide was the most stable C-2 epimer, since epimerization at C-2 did not occur during the saponification of 1.¹⁾ Therefore, isomerization of 10 to 1 was examined.²⁾ When pure 10 was treated with LDA in THF at -76°C and then quenched with water, a ratio of 1:10 of approximately 9:4 was obtained. The IR, NMR and mass spectra of 1 were superimposable on those of the natural product.

Antimicrobial activity testing of both 1 and 10, and syntheses of malyngolide analogs are in progress.

Experimental

Infrared (IR) spectra were measured with a Hitachi EPI-S infrared spectrometer and nuclear magnetic resonance (NMR) spectra were taken on a Hitachi Perkin-Elmer R-20B or a JEOL PS-100 spectrometer using tetramethylsilane (TMS) as an internal standard. Mass spectra (MS) were measured with a Hitachi M-70 spectrometer and relative ratios of diastereomers in mixtures were determined by use of a Shimadzu CS-910 dual-wavelength chromatogram scanner.

2-Ethoxycarbonyl-2-nonylcyclopentanone (3)—A solution of 2-ethoxycarbonylcyclopentanone (2)⁴⁾ (20.0 g, 0.128 mol) in dry DMF (15 ml) was added dropwise to a suspension of NaH (6.415 g, 0.147 mol as 55% purity) in dry DMF (200 ml) with stirring under an N₂ atmosphere at room temperature, and the obtained mixture was stirred at the same temperature for 2 h. A solution of nonyl bromide (30.76 g, 0.147 mol) in dry DMF (15 ml) was added dropwise, then the mixture was heated in an oil bath at 100–110°C for 2.5 h.

It was cooled to room temperature, poured into a mixture of ice and water, and extracted three times with ether. The extracts were washed with water and saturated brine, and dried over Na_2SO_4 . Removal of the solvent and fractional distillation gave 29.78 g (82.5%) of 3. bp 108–112°C (0.2 mmHg). IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} : 1758 (C=O), 1725 (COO), 1218, 1145, 1025. NMR (CDCl_3) δ : 0.89 (3H, br. t, $J=5$ Hz, CH_2CH_3), 1.25 (16H, s, $(\text{CH}_2)_8\text{CH}_3$), 1.25 (3H, t, $J=7$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.7–2.7 (6H, m, $\text{COCH}_2\text{CH}_2\text{CH}_2\text{C}-$), 4.16 (2H, q, $J=7$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$). MS m/e : 282 (M^+), 237 (M^+-45), 209 (M^+-73), 156 (M^+-126), 110. Anal. Calcd for $\text{C}_{17}\text{H}_{30}\text{O}_3$: C, 72.30; H, 10.72. Found: C, 72.58; H, 11.01.

2-Hydroxymethyl-2-nonylcyclopentanol (4)—A solution of 3 (20.0 g, 71 mmol) in dry THF (20 ml) was added dropwise to a suspension of LiBH_4 (2.008 g, 92 mmol) in dry THF (80 ml) with stirring and ice cooling. The mixture was stirred at room temperature for 4 h, then more LiBH_4 (0.309 g, 14 mmol) was added and the whole was stirred at the same temperature for 1 h. Ethyl acetate and water were added to destroy excess LiBH_4 under cooling. The solution was acidified by the addition of 10% H_2SO_4 solution to give pH 1–2 and extracted three times with ether. The extracts were washed with saturated brine, dried over Na_2SO_4 , and concentrated to leave an oil, which was purified by SiO_2 column chromatography (methanol–chloroform=3: 97) to afford 12.256 g (71.4%) of 4 as a viscous oil. IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} : 3370 (OH), 1040. NMR (CDCl_3) δ : 0.89 (3H, br. t, $J=5$ Hz, $(\text{CH}_2)_8\text{CH}_3$), 1.29 (16H, s, $(\text{CH}_2)_8\text{CH}_3$), 1.40–1.90 (6H, m, $\text{COCH}_2\text{CH}_2\text{CH}_2\text{C}-$), 2.18 (2H, s, $\text{OH} \times 2$), 3.32, 3.64 (each 1H, d, $J=11$ Hz, CH_2OH), 4.13 (1H, br. t, $J=5$ Hz, CHOH). MS m/e : 211 (M^+-31), 206 (M^+-36), 180 (M^+-62), 135, 121. Anal. Calcd for $\text{C}_{15}\text{H}_{28}\text{O}_2$: C, 74.33; H, 12.47. Found: C, 74.41; H, 12.62.

2-Hydroxymethyl-2-nonylcyclopentanone (5) from 4—A solution of bromine (0.102 ml, 1.99 mmol) in dichloromethane (10 ml) was added dropwise to a vigorously stirred heterogeneous mixture of 4 (300 mg, 1.24 mmol) and HMPA (66 mg, 0.37 mmol) in dichloromethane (8 ml) and 8% NaHCO_3 solution (4.2 ml) at 5°C. Stirring was continued at 0–5°C for 75 min. After separation of the dichloromethane phase, the water layer was extracted six times with dichloromethane. The combined organic phase was washed with 5% $\text{Na}_2\text{S}_2\text{O}_3$ solution and saturated brine, and dried over Na_2SO_4 . Removal of the solvent *in vacuo* gave an oil, which was purified by SiO_2 column chromatography (methanol–chloroform=2: 98) to furnish 215 mg (72.2%) of 5 as an oil. bp 108–110°C (0.15 mmHg). IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} : 3420 (OH), 1727 (C=O), 1460, 1160, 1045. NMR (CDCl_3) δ : 0.89 (3H, br. t, $J=5$ Hz, $(\text{CH}_2)_8\text{CH}_3$), 1.25 (16H, s, $(\text{CH}_2)_8\text{CH}_3$), 1.5–2.3 (7H, m, $\text{COCH}_2\text{CH}_2\text{CH}_2\text{C}-$ and CH_2OH), 3.30, 3.66 (each 1H, d, $J=11$ Hz, CH_2OH). MS m/e : 210 (M^+-30), 128, 114, 97, 84. Anal. Calcd for $\text{C}_{15}\text{H}_{28}\text{O}_2$: C, 74.95; H, 11.74. Found: C, 74.60; H, 12.24.

2-Hydroxymethyl-2-nonylcyclopentanone (5) from 3—A solution of *n*-butyllithium in hexane (14.5% solution, 3.49 ml, 5.33 mmol) was added dropwise to a cooled solution (–76°C) of dry diisopropylamine (0.74 ml, 5.33 mmol) in dry THF (8 ml) with stirring under an N_2 atmosphere. After the mixture had been stirred at –76°C for 30 min, a solution of 3 (1.0 g, 3.55 mmol) in dry THF (3 ml) was added dropwise, and the whole was stirred at –76°C for 1 h. LiAlH_4 (0.135 g, 3.55 mmol) was added portionwise at –76°C and the mixture was warmed slowly to –40°C and stirred at that temperature for 1 h. The mixture was poured into cooled 2N HCl solution (50 ml) and then extracted three times with ether. The combined ether layer was washed with saturated brine and dried over Na_2SO_4 . Removal of the solvent *in vacuo* and purification of the residue by SiO_2 column chromatography (benzene–ethyl acetate=1: 1) gave 0.541 g (63.5%) of 5 as an oil.

δ -Hydroxymethyl- δ -nonyl- δ -valerolactone (6)—*m*-Chloroperbenzoic acid (1.691 g, 9.8 mmol) and NaHCO_3 (0.823 g, 9.8 mmol) were added to a solution of 5 (1.567 g, 6.53 mmol) in dry chloroform (60 ml), and the mixture was stirred at room temperature for 16.5 h in the dark. Saturated NaHCO_3 solution was added, then the chloroform layer was separated, washed with NaHCO_3 solution and saturated brine, and dried over Na_2SO_4 . Removal of the solvent and purification of the residue by SiO_2 column chromatography (benzene–ethyl acetate=1: 1) furnished 1.368 g (81.8%) of 6 as an oil. IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} : 3420 (OH), 1730 (COO), 1240, 1145. NMR (CDCl_3) δ : 0.89 (3H, br. t, $J=5$ Hz, $(\text{CH}_2)_8\text{CH}_3$), 1.27 (16H, s, $(\text{CH}_2)_8\text{CH}_3$), 1.73–1.95 (4H, m, $\text{COCH}_2\text{CH}_2\text{CH}_2\text{C}-$), 2.3–2.6 (2H, m, COCH_2CH_2), 3.01 (1H, s, OH), 3.50, 3.70 (each 1H, d, $J=11$ Hz, CH_2OH). MS m/e : 225 (M^+-31), 197 (M^+-59), 129 (M^+-127), 112.

Malyngolide (1) and C-2 Epimalyngolide (10)—Dihydropyran (0.53 ml, 6.85 mmol) was added to a mixture of 6 (1.0 g, 3.91 mmol) and *p*-toluenesulfonic acid (0.156 g, 0.91 mmol) in dichloromethane (39 ml) with stirring at 0°C, and the mixture was stirred at 0°C for 3.5 h and then at room temperature for 2 h. After saturated NaHCO_3 solution had been added with cooling, the organic layer was separated, washed with saturated NaHCO_3 solution and saturated brine, and dried over Na_2SO_4 . After removal of the solvent *in vacuo*, the residue was purified by SiO_2 column chromatography (ether–hexane=8: 1) to give 1.044 g (78.6%) of 7 as an oil.

A solution of *n*-butyllithium in hexane (14.5% solution, 2.16 ml, 3.3 mmol) was added dropwise to a cooled solution (–76°C) of dry diisopropylamine (0.46 ml, 3.3 mmol) in dry THF (8 ml) with stirring under an N_2 atmosphere. The mixture was stirred at –76°C for 30 min, then HMPA (5 ml), followed by a solution of 7 (0.93 g, 2.75 mmol) in dry THF (10 ml), was added dropwise. Stirring was continued for 5 min, then a solution of methyl iodide (0.19 ml, 3.05 mmol) in dry THF (3 ml) was added dropwise and the whole was stirred at –76°C for 3 h and then at room temperature for 1 h. The mixture was diluted with water with cooling, acidified with 2N HCl solution to pH 2–3 and then concentrated *in vacuo*. After being heated

on a water bath at 60–70°C for 20 min, the mixture was extracted three times with ether and the extracts were washed with saturated brine. Sodium sulfate was used for drying, and removal of the solvent gave a crude mixture of **8** and **9** as an impure oil. This was used as such for the next hydrolysis reaction. The crude mixture of **8** and **9** was dissolved in 60% aqueous acetic acid (10 ml) and allowed to stand at 45°C for 5 h. The mixture was cooled to room temperature, neutralized by the addition of saturated NaHCO₃ solution and extracted three times with ethyl acetate. The extracts were washed with saturated brine and dried over Na₂SO₄. Removal of the solvent gave 0.897 g of an oil, which was purified by SiO₂ column chromatography (chloroform–acetone=4:1) to furnish 0.431 g (58.0%) of a diastereomeric mixture of **1** and **10**. The ratio of **1**:**10** was 5:4, as determined by the use of a dual-wavelength chromatogram scanner. When the diastereomeric mixture of **1** and **10** was carefully chromatographed on an SiO₂ column (chloroform–acetone=4:1), pure **10** was eluted from the column first followed by pure **1**. The IR, NMR and mass spectra of **1** were identical with those of the natural product. **1**: IR $\nu_{\text{max}}^{\text{CCl}_4}$ cm⁻¹: 3450 (OH), 1721, 1715 (COO), 1210, 1115. NMR (CDCl₃) δ : 0.89 (3H, br. t, $J=5$ Hz, (CH₂)₈CH₃), 1.27 (16H, s, (CH₂)₈CH₃), 1.27 (3H, d, $J=7$ Hz, COCHCH₃), 1.5–2.2 (4H, m, COCH(CH₃)CH₂CH₂C–), 2.40 (1H, m, COCH(CH₃)CH₂), 2.52 (1H, s, CH₂OH), 3.45, 3.71 (each 1H, d, $J=12$ Hz, CH₂OH). MS m/e : 239 (M⁺–31), 211 (M⁺–58), 155 (M⁺–115), 143 (M⁺–127), 115, 95, 85. **10**: IR $\nu_{\text{max}}^{\text{CCl}_4}$ cm⁻¹: 3450 (OH), 1725, 1708 (COO). NMR (CDCl₃) δ : 0.89 (3H, br. t, $J=5$ Hz, (CH₂)₈CH₃), 1.28 (16H, s, (CH₂)₈CH₃), 1.28 (3H, d, $J=7$ Hz, COCHCH₃), 1.50–2.20 (4H, m, COCH(CH₃)CH₂CH₂C–), 2.30–2.65 (1H, m, COCH(CH₃)CH₂), 2.32 (1H, br. s, CH₂OH), 3.60 (2H, s, CH₂OH).

Isomerization of 10 to 1—A solution of *n*-butyllithium in hexane (14.5% solution, 3.92 ml, 6.0 mmol) was added dropwise to a solution of diisopropylamine (0.84 ml, 6.0 mmol) in dry THF (8 ml) with stirring and cooling (–76°C), and the mixture was stirred for 30 min. A solution of **10** (0.406 g, 1.5 mmol) in dry THF (3 ml) was added dropwise over a period of 4 min, and the mixture was stirred at –76°C for 1 h, warmed to room temperature and then stirred for 1 h. Water and 2*N* HCl solution were added with ice-cooling and THF was removed by evaporation *in vacuo*. After the mixture had been warmed at 60–70°C on a water bath for 30 min, it was extracted three times with ethyl acetate. The extracts were washed with saturated brine and dried over Na₂SO₄. Removal of the solvent gave 0.394 g (97.0%) of a mixture of the diastereomeric isomers **1** and **10** in the ratio of 9:4.

Acknowledgement The authors are indebted to Prof. T. Mukaiyama, Department of Chemistry, Tokyo University, for providing copies of IR, NMR and mass spectra of natural malynolide, and to Prof. T. Tokoroyama, Department of Chemistry, Osaka City University, and Mrs. T. Minematsu, Faculty of Pharmaceutical Sciences, Kinki University, for NMR spectral measurement. Thanks are also due to Mr. M. Kan, Chemical Research Laboratories, Central Research Division, Takada Chemical Industries Ltd., for microanalysis and to Dr. O. Muraoka, Faculty of Pharmaceutical Sciences, Kinki University, for GC–MS.

References and Notes

- 1) J.H. Cardellina II, R.E. Moore, E.V. Arnold, and J. Clardy, *J. Org. Chem.*, **44**, 4039 (1979).
- 2) Y. Sakito, S. Tanaka, M. Asami, and T. Mukaiyama, *Chem. Lett.*, **1980**, 1223.
- 3) K. Tanaka, K. Matsuo, Y. Nakaizumi, Y. Morioka, Y. Takashita, Y. Tachibana, Y. Sawamura, and S. Kohda, *Chem. Pharm. Bull.*, **27**, 1901 (1979); K. Matsuo, I. Kitaguchi, Y. Takata, and K. Tanaka, *ibid.*, **28**, 2494 (1980).
- 4) P.S. Pinkney, "Organic Syntheses," Coll. Vol. II, ed. by A.H. Blatt, John Wiley and Sons, Inc., New York, 1943, p. 116.
- 5) H.O. House, "Modern Synthetic Reactions," 2nd ed., W.A. Benjamin, Inc., Menlo Park, Ca, 1972, Chapter 2.
- 6) M.A. Neirabeyeh, J.-C. Ziegler, B. Gross, and P. Caubire, *Synthesis*, **1976**, 811.
- 7) D.H.R. Barton, R.H. Hesse, C. Wilshire, and M.M. Pechet, *Chem. Commun.*, **1972**, 1017; *idem*, *J. Chem. Soc., Perkin Trans. I.*, **1977**, 1075; G.R. Kieczkowski and R.H. Schlessinger, *J. Am. Chem. Soc.*, **100**, 1938 (1978); D.J. Goldsmith, A.J. Lewis, and W.C. Still, Jr., *Tetrahedron Lett.*, **1973**, 4807; G.A. Kraus and K. Frazier, *J. Org. Chem.*, **45**, 4262 (1980).