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An Improved Total Synthesis of (±)-Malyngolide

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(±)-Malyngolide, which is an antibiotic isolated from a marine blue-green alga, was synthesized stereoselectively in four steps starting from 2-ethoxycarbonylcyclopentanone.

Keywords——malyngolide; antibiotic; marine product; 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] and we have synthesized (±)-malyngolide.[3]

We wish to report here a four-steps stereoselective total synthesis of (±)-malyngolide starting from 2-ethoxycarbonylcyclopentanone. The synthetic route to (±)-malyngolide is illustrated in Chart 1.

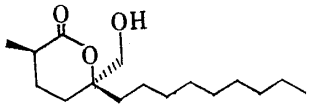

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Fig. 1

2-Ethoxycarbonyl-2-nonylcyclopentanone (**3**) was prepared in the same manner as described before,[3] starting from 2-ethoxycarbonylcyclopentanone[4] and nonyl bromide in 82.5% yield. In the previous paper,[3] we chose the reaction sequence of selective reduction of the ester group in **3**, Baeyer–Villiger oxidation and then methylation for the transformation of **3** to **1**. In that case, it was necessary to protect the hydroxy group before methylation and the methylation product was found to be a mixture of two diastereomeric isomers. We therefore examined the reaction sequence of methylation of **3**, selective reduction and then Baeyer–Villiger oxidation. In this case, no protection of the hydroxy group should be necessary at all. Thus, the keto ester (**3**) was treated with methyl iodide in the presence of lithium diisopropylamide (LDA) in a mixture of tetrahydrofuran (THF) and hexamethylphosphoramide (HMPA) to afford **4**, which was not purified but was used directly for the next reaction. The crude keto ester (**4**) was treated with LDA at −76° in THF to form a lithium enolate which was reduced with lithium aluminum hydride to give

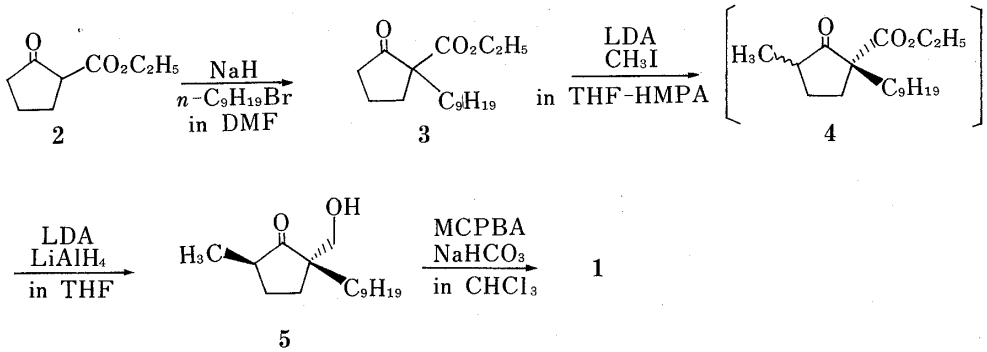

Chart 1

the desired ketol **5** as a sole product in 74.2% yield from **3**.[5] Baeyer–Villiger oxidation of the ketol (**5**) with *m*-chloroperbenzoic acid (MCPBA) in the presence of sodium bicarbonate in chloroform at room temperature in the dark gave **1** in 83.7% yield. The infrared (IR), nuclear magnetic resonance (NMR) and mass spectra of **1** were identical with those of the natural product. This represents a stereoselective total synthesis of (±)-malyngolide in 51.2% overall yield in four steps starting from 2-ethoxycarbonylcyclopentanone.

Experimental

The boiling point is uncorrected. IR spectra were recorded on a Hitachi EPI-S infrared spectrometer and NMR spectra were taken on a Hitachi Perkin-Elmer R-20A, a JEOL PS-100 or a JEOL JNM-FX 200 spectrometer using tetramethylsilane as an internal standard. The mass spectrum (MS) was measured with a Hitachi M-70 spectrometer.

2-Hydroxymethyl-5-methyl-2-nonylcyclopentanone (**5**)——A solution of *n*-butyllithium in hexane (14.5% solution, 2.76 ml, 4.26 mmol) was added dropwise to a cooled solution (−76°C) of dry diisopropylamine (0.6 ml, 4.26 mmol) in dry THF (10 ml) with stirring under an N_2 atmosphere. After the mixture had been stirred at −76°C for 30 min, a solution of **3**[3] (1.0 g, 3.55 mmol) in dry THF (3 ml) was added dropwise, and the whole was stirred at −76°C for 3 h. EMPA (2 ml) was added, then a solution of methyl iodide (0.44 ml, 7.1 mmol) in dry THF (2 ml) was added dropwise at the same temperature. The mixture was allowed to warm to room temperature and stirred at ambient temperature overnight. The mixture was acidified with 2 N HCl solution to pH 2 with cooling and then extracted three times with ether. The combined extract was washed twice with water, once with $Na_2S_2O_3$ solution and once with saturated brine, then dried over Na_2SO_4. Removal of the solvent *in vacuo* gave 1.113 g of a crude keto ester (**4**) as a slightly yellow oil.

A solution of the crude keto ester (**4**) (1.113 g) in dry THF (3 ml) was added dropwise at −76°C under an N_2 atmosphere to a solution of LDA (4.26 mmol) in THF prepared by the same method as described above, and the mixture was stirred at the same temperature for 1.5 h. $LiAlH_4$ (0.135 g, 3.55 mmol) was added at −76°C and the mixture was warmed slowly to −25°C over a period of 2.5 h. The mixture was acidified with 2 N HCl solution to pH 3 with cooling and then extracted three times with ether. The combined extract was washed with water and 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=2:1) gave 0.668 g (74.2% from **3**) of **5** as an oil. An analytical sample was obtained by distillation; bp 115—120°C (0.3 mmHg). IR ν_{max}^{neat} cm^{-1}: 3400 (OH), 1725 (C=O), 1040 (C–OH). NMR ($CDCl_3$) δ: 0.87 (3H, t, J=6 Hz, $CH_2C\underline{H}_3$), 1.05 (3H, d, J=7 Hz, $CHCl_3$), 1.24 (16H, s, $C(C\underline{H}_2)_8CH_3$), 1.3—2.3 (6H, m, $COC\underline{H}(CH_3)C\underline{H}_2C\underline{H}_2C$ and OH), 3.43 and 3.64 (each 1H, d, J=11 Hz, CCH_2OH). *Anal.* Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89. Found: C, 75.48; H, 12.08.

(±)-Malyngolide (**1**)——*m*-Chloroperbenzoic acid (0.316 g, 1.28 mmol as 70% purity) and $NaHCO_3$ (0.108 g, 1.28 mmol) were added to a solution of **5** (0.271 g, 1.07 mmol) in dry $CHCl_3$ (10 ml), and the mixture was stirred at room temperature for 4 d in the dark. After addition of more MCPBA (0.105 g, 0.43 mmol as 70% purity) and $NaHCO_3$ (0.036 g, 0.43 mmol), the mixture was stirred under the same conditions for 1.5 d. Saturated $NaHCO_3$ solution was added to the reaction mixture and the $CHCl_3$ layer was separated. The organic 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 ($CHCl_3$–acetone=4:1) furnished 0.241 g (83.7%) of pure **1** as an oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3450 (OH), 1721, 1715 (COO), 1210, 1115. NMR ($CDCl_3$) δ: 0.89 (3H, br. t, J=5 Hz, $CH_2C\underline{H}_3$), 1.27 (16H, s, $(C\underline{H}_2)_8CH_3$), 1.27 (3H, d, J=7 Hz, $COCHC\underline{H}_3$), 1.5—2.2 (4H, m, $COCH(CH_3)C\underline{H}_2C\underline{H}_2C$), 2.40 (1H, m, $COC\underline{H}(CH_3)CH_2$), 2.52 (1H, s, $CH_2O\underline{H}$), 3.45 and 3.71 (each 1H, d, J=12 Hz, $C\underline{H}_2OH$). MS *m/e*: 239 (M^+-31), 211 (M^+-58), 155 (M^+-115), 143 (M^+-127), 115, 95, 85.

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