A Stereoselective Synthesis of (±)-Malyngolide

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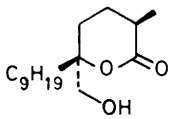
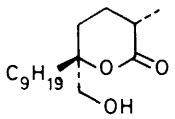
A stereoselective synthesis of (±)-malyngolide (**1**) has been accomplished by applying a cross-aldol condensation of the dianion of ethyl 2-methyl-3-oxobutyrate (**3**) with 1-(tetrahydropyran-2-yloxy)-undecan-2-one (**4**). Reduction of the 3-oxo group of the resulting 3-oxopentanolide (**6**), followed by dehydration of the alcohol (**7**) and catalytic hydrogenation of the unsaturated hydroxy lactone (**10**), furnished (±)-malyngolide (**1**) in 34% overall yield.

Malyngolide is the major antibiotic in the lipid extract of a shallow-water variety of *Lyngbya majuscula* from Kahala Beach, Oahu, which is active against *Mycobacterium smegmatis* and *Micrococcus pyogenes*.[1] In connection with our studies on the synthetic utility of the cross-aldol condensation product between the regioselectively generated enolates of ketones and protected α-ketols, which have been applied to the synthesis of several natural products,[2] we disclose here our investigations which have resulted in an alternative, stereoselective, short-step synthesis of (±)-malyngolide (**1**).[3,4] The lack of stereocontrol at C-2 [formation of both malyngolide (**1**) and 2-*epi*-malyngolide (**2**)], which was a main disadvantage in some of the earlier syntheses, has been resolved by taking advantage of hydroxy-group participation in catalytic hydrogenation at the final step.



(**1**)

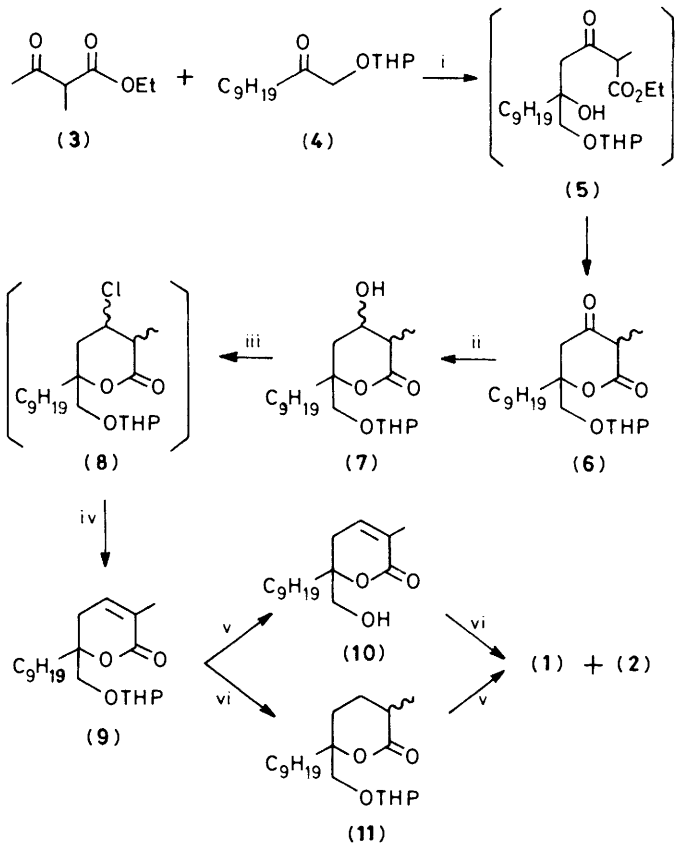


(**2**)

If the dianion of ethyl 2-methyl-3-oxobutyrate (**3**) reacts with 1-(tetrahydropyran-2-yloxy)undecan-2-one (**4**), analogous to the case of ethyl acetoacetate,[2b] subsequent treatment of the resulting cross-aldol adduct (**5**) with base[5] would give the δ-lactone (**6**), having all three substituents of malyngolides (**1**) and (**2**) at the proper positions (Scheme). Indeed, treatment of the dianion of the β-oxo ester (**3**) with the protected α-ketol (**4**), and then with water *in situ*, afforded somewhat unstable 2-methyl-3-oxo-5-[(tetrahydropyran-2-yloxy)methyl]tetradecan-5-olide(**6**) in 74% yield. Introduction of unsaturation between C-2 and C-3 was achieved through the following three-step procedure.

Reduction of the carbonyl group at C-3 proceeded with borane–t-butylamine complex in aqueous citric acid (pH *ca.* 1)[6] to yield the hydroxylactone (**7**) in 83% yield. The use of other reducing agents such as sodium borohydride or sodium cyanoborohydride in acidic media gave none of the desired product. Treatment of compound (**7**) with thionyl chloride in hot pyridine furnished the chloride (**8**) which, without purification, was dehydrochlorinated with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in refluxing benzene to give the unsaturated lactone (**9**) in 72% overall yield from (**6**). Catalytic hydrogenation of the lactone (**9**) over 5% Pd–carbon in ethanol gave the tetrahydropyranyloxylactone (**11**), whose tetrahydropyranyl ether (THP) was hydrolysed on treatment with a catalytic amount of toluene-*p*-sulphonic acid monohydrate (PTSA) in hot aqueous ethanol, furnishing a mixture of almost equal amounts of malyngolide (**1**) and 2-*epi*-malyngolide (**2**) in 90% overall yield.

In order to enhance the stereoselectivity of the catalytic



Scheme *Reagents*: i, NaH–n-BuLi–THF, then H_2O; ii, Bu^tNH_2–BH_3–MeOH–aq. Citric acid; iii, $SOCl_2$–pyridine; iv, DBU–benzene; v, PTSA–aq. EtOH; vi, 5% Pd–C, H_2

hydrogenation leading to malyngolide (**1**), we examined catalytic hydrogenation of the free hydroxymethyl lactone (**10**), which was prepared by hydrolysis of the THP ether (**9**) in 97% yield, in a variety of solvents. Among the solvents examined, hexane gave the best result (76% yield), as anticipated, the ratio being 15:1 in favour of malyngolide (**1**) (see the Table in the Experimental section). This preferential formation of the desired stereochemistry at C-2 of malyngolide (**1**) is accounted for by the hydroxy-group-assisted hydrogen transfer from the same side as the hydroxymethyl group. Both malyngolide (**1**) and 2-*epi*-malyngolide (**2**) had spectral data identical with those of authentic samples. Thus, stereoselective total synthesis of (±)-malyngolide (**1**) has been accomplished in 34% overall yield in 6 steps from readily available precursors.

Experimental

I.r. spectra were recorded for solutions in carbon tetrachloride on a Jasco A-3 spectrophotometer. ^{1}H N.m.r. spectra were obtained for solutions in deuteriochloroform with a Jeol PS-100 (100 MHz) instrument with tetramethylsilane as internal standard. Mass spectra were obtained on a Jeol JMS-DX 300 spectrometer. High-pressure liquid chromatography (h.p.l.c.) was carried out on a Jasco PRC-50 instrument. Microanalyses were carried out in the microanalytical laboratory of this Institute. Ether for extractions refers to the use of diethyl ether.

2-Methyl-3-oxo-5-(tetrahydropyran-2-yloxy)methyl tetradecan-5-olide (**6**).—The dianion of ethyl 2-methyl-3-oxobutyrate (**3**) was prepared according to the procedure for the preparation of the dianion of ethyl acetoacetate by Huckin and Weiler.[7] To a stirred suspension of sodium hydride (26 mg, 1.08 mmol) in tetrahydrofuran (THF) (0.5 ml) cooled with an ice-bath and under nitrogen was added the β-oxo ester (**3**) (148 mg, 1.03 mmol) and the mixture was stirred for 10 min. A solution of n-butyl-lithium (1 mmol) in hexane (0.57 ml) was then added and the mixture was stirred for 10 min at an ice-bath temperature. A solution of 1-(tetrahydropyran-2-yloxy)-undecan-2-one (**4**)[2b,4b] (143 mg, 0.53 mmol) in THF (2 ml) was added to the above dianion solution, and the resulting mixture was stirred at an ice-bath temperature for 25 min. Water (20 ml) was added carefully, and the mixture was stirred at room temperature overnight. After addition of 1M HCl, the product was extracted with ether (2 × 30 ml). Evaporation of the ether and preparative thin-layer chromatography (p.l.c.) [developer hexane–ethyl acetate (1:1)] of the residue gave the *keto lactone* (**6**) (148 mg, 74%), which partially decomposed at room temperature overnight; $\nu_{max.}$ 1 765, 1 730, 1 135, 1 045, and 970 cm^{-1}; δ 0.90 (3 H, t, *J* 6 Hz, CH_2*Me*), 1.10—1.50 (16 H, br s, $[CH_2]_8$), 1.43 (3 H, d, *J* 8 Hz, 2-Me), 1.40—1.90 (7 H, br s, $OCHOCH_2[CH_2]_3$ and 2-H), 2.60—2.80 (2 H, m, 4-H_2), 3.1—4.0 (4 H, m, $OCHOCH_2[CH_2]_3$ and CH_2OTHP), and 4.54 (1 H, br s, $OCHO[CH_2]_4$); *m/z* 367 (0.2%), 253 (14), 155 (13), and 85 (100) (Found: C, 68.2; H, 10.2 $C_{21}H_{36}O_5$ requires C, 68.4; H, 9.9%).

3-Hydroxy-2-methyl-5-(tetrahydropyran-2-yloxy)methyltetradecan-5-olide (**7**).—To a stirred solution of the oxo lactone (**6**) (43 mg, 0.11 mmol) in methanol (2 ml) were added borane–t-butylamine complex (22 mg, 0.22 mmol) and then aqueous citric acid (0.5 ml, 1M-solution). The resulting solution was stirred at room temperature for 1 h, and poured into water. The product was extracted with ether (2 × 30 ml). Evaporation of the ether and p.l.c. [developer hexane–ethyl acetate (1:1)] of the residue gave the *hydroxy lactone* (**7**) (36 mg, 83%); $\nu_{max.}$ 3 450, 1 745, 1 250, 1 145, 1 085, and 1 045 cm^{-1}; δ 0.88 (3 H, t, *J* 6 Hz, CH_2*Me*), 1.10—1.50 (20 H, br s, $[CH_2]_8$, OH, and 2-Me), 1.40—1.80 (6 H, br s, $OCHOCH_2[CH_2]_3$), 2.00—2.50 (3 H, m, 4-H_2 and 2-H), 3.20—4.00 (5 H, m, 3-H, $OCHOCH_2[CH_2]_3$ and CH_2OTHP), and 4.60 (1 H, br s, $OCHO[CH_2]_4$) (Found: C, 68.1; H, 10.6. $C_{21}H_{38}O_5$ requires C, 68.1; H, 10.3%).

2-Methyl-5-(tetrahydropyran-2-yloxy)methyltetradec-2-en-5-olide (**9**).—To a stirred solution of the hydroxy lactone (**7**) (88 mg, 0.23 mmol) in pyridine (2 ml) was added thionyl chloride (90 μl, 1.23 mmol), and the resulting solution was heated at 60—90 °C for 40 min under nitrogen. After having cooled to room temperature, the mixture was poured into water and the products were extracted with ether. Evaporation of the ether left the crude chloro lactone (**8**) (101 mg) which was used without further purification.

To a stirred solution of the chloride (**8**) in benzene (4 ml) was added DBU (70 μl, 0.47 mmol), and the solution was heated under reflux for 2 h. After being cooled to room temperature, the solution was diluted with ether (30 ml), and the organic layer was washed successively with water and brine. Evaporation of the solvent, followed by h.p.l.c. separation of the residue, gave the *unsaturated pyranyloxy lactone* (**9**) (60 mg, 72%); $\nu_{max.}$ 1 725, 1 370, 1 145, 1 045, and 920 cm^{-1}; δ 0.88 (3 H, t, *J* 7 Hz, CH_2*Me*), 1.10—1.50 (16 H, br s, $[CH_2]_8$), 1.30—1.90 (6 H, br, $OCHOCH_2[CH_2]_3$), 1.92 (3 H, br s, 2-Me), 2.35—2.66 (2 H, br, $w_{\frac{1}{2}}$ 13 Hz, 4-H_2), 3.25—3.92 (4 H, m, $OCHOCH_2[CH_2]_3$ and CH_2OTHP), 4.56 (1 H, br s, $OCHO[CH_2]_4$), and 6.40 (1 H, br s, $w_{\frac{1}{2}}$ 10 Hz, 3-H); *m/z* 267 (9%), 236 (43), 155 (22), and 85 (100) (Found: C, 71.4; H, 10.3. $C_{21}H_{36}O_4$ requires C, 71.6; H, 10.3%).

5-Hydroxymethyl-2-methyltetradec-2-en-5-olide (**10**).—A solution of the unsaturated pyranyloxy lactone (**9**) (53 mg, 0.15 mmol) and a catalytic amount of PTSA in a mixture of ethanol (2 ml) and water (0.5 ml) was heated at 80 °C for 40 min. After having cooled to room temperature, the resulting mixture was poured into brine, and the product was extracted with ether (2 × 20 ml). Evaporation of the solvent, followed by h.p.l.c. separation of the residue, gave the *unsaturated hydroxy lactone* (**10**) (38 mg, 97%); $\nu_{max.}$ 3 600, 3 400, 1 720, 1 360, and 1 130 cm^{-1}; δ 0.94 (3 H, t, *J* 6 Hz, CH_2*Me*), 1.08—1.52 (15 H, br s) and 1.52—1.87 (2 H, br) (together $[CH_2]_8$ and OH), 1.93 (3 H, br s, 2-Me), 2.29 (1 H, *J* 18 Hz, B part of AB-type q) and 2.72 (1 H, *J* 18 Hz, A part of AB-type q) (together 4-H_2), 3.56 (1 H, *J* 12 Hz, B part of AB-type q) and 3.69 (1 H, *J* 12 Hz, A part of AB-type q) (together CH_2OH), and 6.52 (1 H, br s, $w_{\frac{1}{2}}$ 9 Hz, 3-H); *m/z* 268 (M^+, 0.5%), 237 (100), 155 (88), 141 (34), and 85 (34) (Found: C, 71.9; H, 10.8. $C_{16}H_{28}O_3$ requires C, 71.6; H, 10.5%).

Malyngolide (**1**) *and* 2-epi-*Malyngolide* (**2**) via *Catalytic Hydrogenation of Compound* (**9**).—The unsaturated pyranyloxylactone (**9**) (24.7 mg, 0.068 mmol) in ethanol (2 ml) was hydrogenated over 5% Pd–C (20 mg) under one atomosphere of hydrogen at room temperature overnight. After filtration of the catalyst, evaporation of the solvent gave the pentanolide (**11**) (26.2 mg), which was used for the next reaction without purification. Compound (**11**) had $\nu_{max.}$ 1 735, 1 460, 1 205, 1 135, and 1 045 cm^{-1}; δ 0.88 (3 H, t, *J* 6 Hz, CH_2*Me*), 1.1—1.5 (19 H, br, $[CH_2]_8$ and 2-Me), 1.5—1.9 (6 H, $OCHOCH_2[CH_2]_3$), 1.9—2.1 (5 H, br, 2-H, 3-H_2, and 4-H_2), 3.20—4.10 (4 H, br, $OCHOCH_2[CH_2]_3$ and CH_2OTHP), and 4.63 (1 H, br, $OCHO[CH_2]_3$).

A solution of the pentanolide (**11**) (26.2 mg) and PTSA (a catalytic amount) in a mixture of ethanol (2 ml) and water (0.5 ml) was heated at 80 °C for 40 min. After having cooled to room temperature, the mixture was poured into brine, and the product was extracted with ether (2 × 20 ml). Evaporation of the solvent followed by h.p.l.c. separation of the residue gave malyngolide (**1**) (9.0 mg, 55% overall) and 2-*epi*-malyngolide (**2**) (7.4 mg, 45% overall).

Malyngolide (**1**) *and* 2-epi-*Malyngolide* (**2**) via *Catalytic Hydrogenation of Compound* (**10**).—The unsaturated hydroxy lactone (**10**) (21 mg, 0.078 mmol) in hexane (2 ml) was hydrogenated over 5% Pd–C (10 mg) under one atmosphere of hydrogen at room temperature overnight. After removal of the catalyst by filtration and evaporation of the hexane, h.p.l.c. separation of the residue gave malyngolide (**1**) (15 mg, 71%) and 2-*epi*-malyngolide (**2**) (1 mg, 5%). Malyngolide (**1**) had $\nu_{max.}$ 3 600, 3 400, 1 730, and 1 460 cm^{-1}; δ 0.88 (3 H, t, *J* 6 Hz, CH_2*Me*), 1.24 (19 H, br, $[CH_2]_8$ and 2-Me), 1.45—2.08 (4 H, m, 3- and 4-H_2), 2.40 (1 H, m, 2-H), 2.96 (1 H, br, OH, exchangeable

Table.

Solvent	Ratio of malyngolide (**1**)/ 2-*epi*-malyngolide (**2**)	Yield (%)[a]
Hexane	15	76
Methylene dichloride	8	85
Ethanol	4	89
Ethyl acetate	3	90
Ethanol	1.2	90[b]

[a] Yields are for the isolated and combined malyngolides. [b] The tetrahydropyranyl ether (**9**) was employed.

identical with those of an authentic sample;[3] *m/z* 270 (M^+, 0.3%), 239 (100), 211 (42), 155 (30), 143 (31), and 71 (39). 2-*epi*-malyngolide (**2**) had $\nu_{max.}$ 3 600, 3 400, 1 730, 1 720, and 1 460 cm^{-1}, δ 0.88 (3 H, t, *J* 6 Hz, CH_2Me), 1.28 (19 H, br, $[CH_2]_8$ and 2-Me), 1.50—2.20 (5 H, 2 × CH_2 and OH), 2.10—2.60 (1 H, m, 2-H), and 3.59 (2 H, s, CH_2OH) identical with those of an authentic sample;[3] *m/z* 270 (M^+, 0.1%), 239 (64), 211 (29), 155 (19), and 143 (14).

According to the same procedure on the same reaction scale, hydrogenation of the unsaturated hydroxy lactone (**10**) was examined in various solvents, and the results are listed in the Table.

Acknowledgements

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