Total Synthesis of (−)-Malyngolide and of Its Three Stereomers

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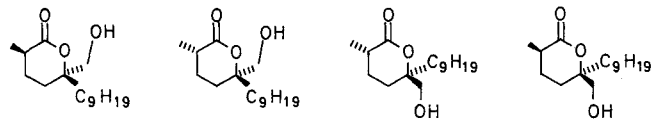
(−)-Malyngolide (1a) and its three stereomers 1b–d are synthesized from the allylic alcohol 4 in total yields of about 10% each. The key reaction steps are Sharpless epoxidation of the allylic alcohol 4 and radical C–C bond formation with the iodide 3 and methyl methacrylate (2). This radical chain reaction needs only small amounts of organotin compounds.

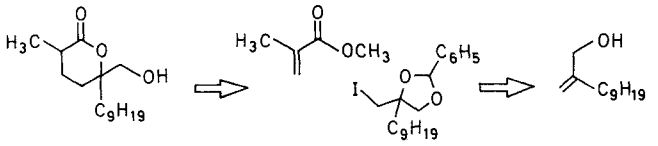
Totalsynthese von (−)-Malyngolid und seinen drei Stereomeren

(−)-Malyngolid (1a) und seine drei Stereomeren 1b–d werden aus dem Allylalkohol 4 in jeweils 10% Gesamtausbeute synthetisiert. Schlüsselstufen der Synthese sind die Sharpless-Epoxidierung des Allylalkohols 4 und die radikalische C–C-Bindungsbildung mit dem Iodid 3 und Methacrylsäure-methylester (2). Diese radikalische C–C-Bindungsbildung benötigt nur geringe Mengen an Organozinnverbindungen.

(−)-Malyngolide (**1a**) is the major antibiotic in the lipid extract of a shallow-water variety of *Lyngbya majuscula* which is active against *Streptococcus pyogenes*[1]. Malyngolide has been the target molecule of several syntheses[2]; we describe here a short and efficient synthesis of (−)-malyngolide (**1a**) and its three stereomers **1b–d** using Sharpless epoxidation[3] and radical C–C bond formation[4] as key reaction steps.

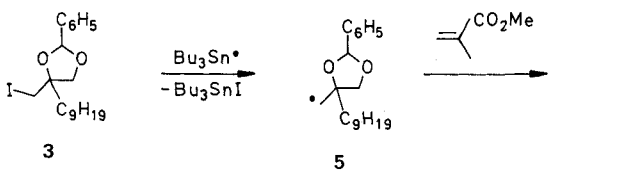


1a **1b** **1c** **1d**

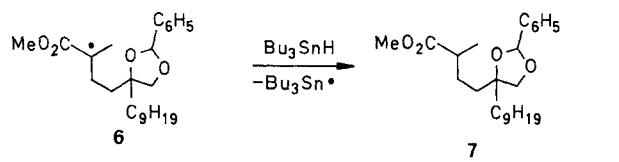


1 **2** **3** **4**

The C–C bond formation between methyl methacrylate (**2**) and the iodide **3** occurs via a radical chain reaction with iodine abstraction from **3** by tributyltin radicals (**3**→**5**), addition of radical **5** to methyl methacrylate (**5**→**6**) and hydrogen abstraction from tributyltin hydride (**6**→**7**) as chain propagation steps. The hydrogen abstraction yields tributyltin radicals which again react with the iodide **3**.

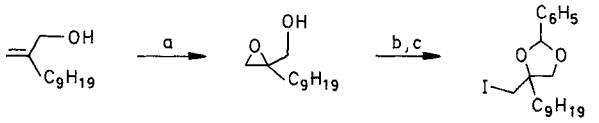


3 **5**



6 **7**

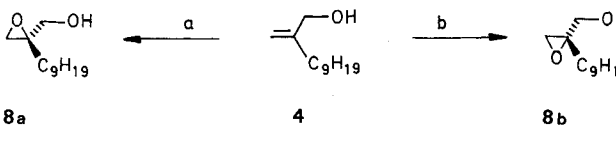
The radical precursor **3** was synthesized via Sharpless epoxidation of the allylic alcohol **4** (**4**→**8**), epoxide ring opening, and acetal formation (**8**→**3**).



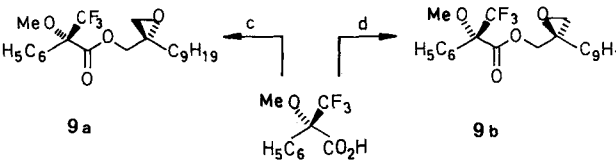
4 **8** **3**

a: Sharpless epoxidation; b: LiI, ether; c: $C_6H_5CH(OMe)_2$, Amberlyst 15

The Sharpless epoxidation carried out with (*S,S*)-diethyl tartrate (*S,S*-DET) gave the *R*-(+)-epoxide **8a** in 41% yield, the reaction with (*R,R*)-diethyl tartrate (*R,R*-DET) led to the (*S*)-(−)-epoxide **8b** in 53% yield. Esterification of **8a** and **8b**, respectively, with Mosher's acid[5] and NMR analysis of the resulting diastereomeric esters **9a** and **9b** showed that the enantioselectivity of the Sharpless epoxidation of the allylic alcohol **4** is higher than 96%.



8a **4** **8b**



9a **9b**

a: $Ti(OPr^i)_4$, *S,S*-DET, Bu^tOOH; b: $Ti(OPr^i)_4$, *R,R*-DET, Bu^tOOH; c: 1) $SOCl_2$, 2) **8a**; d: 1) $SOCl_2$, 2) **8b**

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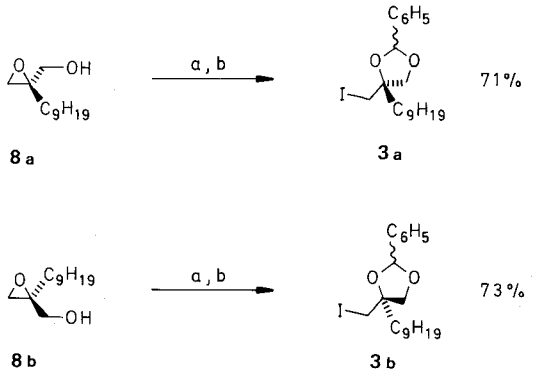
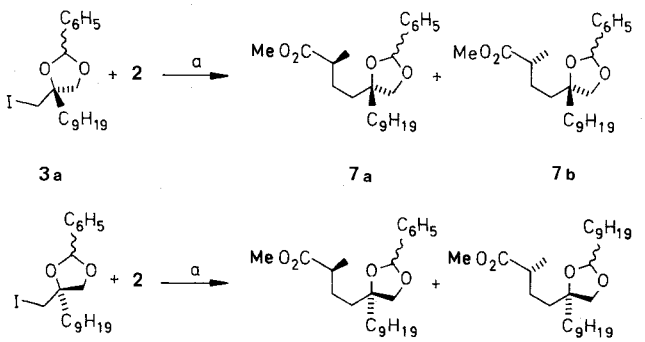
Ring opening of epoxides **8a** and **8b** with LiI and acetalization with dimethoxytoluene led to the iodides **3a** and **3b** in 71 and 73% yield, respectively.



a: LiI, ether; b: $C_6H_5CH(OMe)_2$, Amberlyst 15

The radical C–C bond formation between methyl methacrylate (**2**) and the iodide **3** was carried out with 0.2 equivalents of tributyltin chloride and an excess of $NaBH_4$. Tributyltin chloride and tributyltin iodide, generated in the iodine abstraction step, were in situ transformed into tributyltin hydride by an excess of $NaBH_4$[6]. The photolytically initiated radical chain reaction of iodides **3a** and **3b** with the alkene **2** yields 70% of the 1:1 mixtures (**7a** + **7b**) and (**7c** + **7d**), respectively. This means that the hydrogen donation from tributyltin hydride to the adduct radical **6** is unselective.



7a + **7b** $\xrightarrow{b,c}$ **1a**(37%) + **1b**(40%)

7c + **7d** $\xrightarrow{b,c}$ **1c**(37%) + **1d**(33%)

a: Bu_3SnCl, $NaBH_4$, hv, EtOH; b: H_2, Pd/C; c: 1) KOH, EtOH, 2) Amberlyst 15, CH_3CN

Hydrogenation and solvolysis of the diastereomeric mixtures (**7a** + **7b**) and (**7c** + **7d**), respectively, gave the malyngolides **1a–d** which could easily be separated by column chromatography on silica gel.

This procedure therefore leads to enantiomerically pure malyngolide (**1a**) and to each of its stereomers **1b–d** in about 10% total yield starting from the allylic alcohol **4**.

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Experimental

The instrumentation for the spectroscopic and chromatographic work was listed recently[7].

(2R)-2-Hydroxymethyl-2-nonyloxirane (**8a**): At −20 °C a solution of titanium tetraisopropylate (14.20 g, 50.0 mmol) in dichloromethane (200 ml) was treated under argon successively with (*S,S*)-diethyl tartrate (11.34 g, 55.0 mmol) in dichloromethane (50 ml) and 2-hydroxymethyl-1-undecen[8] (**4**) (9.22 g, 50.0 mmol) in 50 ml of dichloromethane. After 30 min the solution was cooled to −40 °C and treated with 1.5 equivalents of anhydrous *tert*-butyl hydroperoxide (3 M solution in dichloromethane). The reaction mixture was poured after standing for 48 h at −40 °C into ether (500 ml, −30 °C), and 50 ml of a saturated sodium sulfate solution was added drop by drop under rigorous stirring. The mixture was warmed to room temperature and the stirring continued for 3 h. Filtration through celite and two flash chromatographies (hexane: ethyl acetate = 7:3) gave 4.10 g (41%) of **8a**. – $[\alpha]_D^{20}$ = 11.0 (*c* = 13.0, $CHCl_3$). – IR (film): 3420 cm^{-1} (OH), 3020 (CH). – ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, 3H, *J* = 6.7 Hz, CH_3), 1.26 (b.s, 16H, CH_2), 1.95 (b.s, 1H, OH), 2.67, 2.89 (2d, *J* = 4.7 Hz, 2H), 3.63, 3.78 (2d, *J* = 12.3 Hz, 2H). – MS (70 eV): *m/z* (%) = 200 (1, M^+), 170 (6, M − CH_2O), 169 (30, M − CH_2OH), 127 (6, C_9H_{19}), 101 (22, M − C_7H_{15}), 71 (78, $C_3H_3O_3$), 57 (93), 55 (51), 43 (62, C_3H_7), 41 (100, C_3H_5).

$C_{12}H_{24}O_2$ (200.3) Calcd. C 71.95 H 12.08
8a: Found C 71.79 H 12.05
8b: Found C 71.86 H 12.15

(2S)-2-Hydroxymethyl-2-nonyloxirane (**8b**): Using the conditions of the synthesis of **8a** the reaction with (*R,R*)-diethyl tartrate gave 5.3 g (53%) of **8b**. – $[\alpha]_D^{20}$ = −11.9 (*c* = 13.4, $CHCl_3$).

For the detection of the enantiomeric purity (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (92.7 mg, 0.396 mmol) was heated under reflux with thionyl chloride (2 ml) for 12 h, the thionyl chloride was removed in vacuo, the residue solved in dry pyridine (1 ml), and tetrachloromethane (1 ml) and 72 mg (0.36 mmol) of the epoxide **8a** or **8b**, respectively, was added. After 12 h at room temperature, water (1 ml) and ether (20 ml) were added and after another 2 h the ether layer was washed 4 times with diluted sulfuric acid (10%, 1 ml), two times with saturated hydrogen carbonate solution (1 ml), and with water (1 ml), and dried with $MgSO_4$. After distillation of the ether, a residue of esters **9a** or **9b**, respectively, remained.

9a: ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.5 Hz, 3H, CH_3), 1.25 (m, 16H, CH_2), 2.66, 2.73 (2d, *J* = 4.6 Hz, 2H), 3.55 (m_c, 3H, OCH_3), 4.27, 4.49 (2d, *J* = 12.0 Hz, 2H), 7.40 (m_c, 3H), 7.50 (m_c, 2H).

9b: ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.5 Hz, 3H, CH_3), 1.25 (b.s, 16H, CH_2), 2.66, 2.73 (2d, *J* = 4.6 Hz, 2H), 3.55 (m_c, 3H, OCH_3), 4.17, 4.55 (2d, *J* = 11.9 Hz, 2H), 7.40 (m_c, 3H), 7.50 (m_c, 2H).

By NMR spectroscopy the esters **9a** and **9b**, respectively, were free of their diastereomers.

(2RS,4R)-4-Iodomethyl-4-nonyl-2-phenyl-1,3-dioxolane (**3a**): At −20 °C **8a** (3.50 g, 17.7 mmol) was added to a solution of lithium iodide (3.40 g, 25.0 mmol) in ether (30 ml). Stirring was continued for 30 min at room temperature, and diluted acetic acid (2.0 g in 10 ml of water) was added at 0 °C. The aqueous phase was extracted with ether (10 ml), and the combined ether solutions were treated with concentrated sodium chloride solution (20 ml) and water (10 ml). After drying with $MgSO_4$ the ether was distilled off, the residue was treated twice with toluene (20 ml), evaporated, and the

residue dissolved in dimethoxytoluene (10.0 g, 66 mmol). The solution was stirred with H^+-resin (Amberlyst 15; 100 mg), and the methanol was distilled off. After 7 h the excess of dimethoxytoluene was distilled in a kugelrohr (50°C/0.05 Torr), and chromatography (silica gel, hexane:methyl acetate = 8:2) gave 5.38 g (73%) of **3a** which was a 1:1 mixture of diastereomers. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (3H, t, *J* = 7.0 Hz, CH_3), 1.27 (m, 16H), 3.2–3.6 (m, 2H), 3.84 (d, 0.5H, *J* = 9.0 Hz), 4.00 (s, 1H), 4.23 (d, 0.5H, *J* = 9.0 Hz), 5.90, 5.96 (2s, 1H), 7.3–7.5 (m, 5H). – MS (70 eV): *m/z* (%) = 416 (23%, M^+), 415 (26, M − H), 289 (19, M − I), 275 (36, M − CH_2I), 183 (25, M − I − C_6H_5CHO), 121 (18, $C_6H_5CH_2OCH_2$), 105 (100, C_6H_5CO).

$C_{19}H_{29}IO_2$ Calcd. 416.1211 **3a**: Found 416.1222
3b: Found 416.1218

(2RS,4S)-4-Iodomethyl-4-nonyl-2-phenyl-1,3-dioxolane (**3b**): The procedure for the synthesis of **3a** applied to the epoxide **8b** gave 71% of **3b**.

Methyl (2RS)-2-Methyl-4-[(4R)-4-nonyl-2-phenyl-1,3-dioxolan-4-yl]butanolate (**7a**): A solution of **3a** (1.30 g, 3.10 mmol), methyl methacrylate (**2**) (2.64 g, 30.0 mmol), and $NaBH_4$ (190 mg, 5.0 mmol) in ethanol (130 ml) was treated with tributyltin chloride (101 mg, 0.31 mmol) in 10 ml of ethanol, and irradiated under argon. After 30 min another portion of tributyltin chloride (101 mg, 0.31 mmol) was added. The irradiation was stopped after 60 min, the solution evaporated, the residue dissolved in ether (150 ml), 2 g of potassium fluoride and two drops of water added and stirred for 10 h. The mixture was filtered over $MgSO_4$ and celite, the solvent distilled off and the remaining oil flash-chromatographed (first hexane; then hexane: ethyl acetate = 3:1). Vacuum distillation in a kugelrohr (210°C bath temperature/0.07 Torr) gave 847 mg (70%) of **7a** which was a mixture of diastereomers. – IR (film): 1735 cm^{-1} (C=O), 760, 695. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (m_c, 3H, CH_3), 1.10–1.25 (m, 3H, CH_3), 1.27 (b.s, 16H, CH_2), 2.60–2.80 (m, 4H, CH_2), 2.40–2.60 (m, 1H), 3.60–3.70 (m, 3H, OCH_3), 3.76, 3.92 (2m_c, 2H), 5.83 (m_c, 1H), 7.38 (m_c, 3H), 7.48 (m_c, 2H). – MS (70 eV): *m/z* (%) = 391 (11, M + H), 390 (40, M^+), 359 (5, M − OCH_3), 263 (24, M − 127), 275 (68, M − $C_4H_8CO_2CH_3$), 157 (95, 263 − C_6H_5CHO), 127 (27, C_9H_{19}), 120 (31), 105 (91, C_6H_5CO), 43 (100).

$C_{24}H_{38}O_4$ (390.6) Calcd. C 73.81 H 9.81
7a: Found C 73.62 H 9.77
7b: Found C 73.55 H 9.74

Methyl (2RS)-2-Methyl-4-[(4S)-4-nonyl-2-phenyl-1,3-dioxolan-4-yl]butanoate (**7b**): The procedure for the synthesis of **7a** applied to the iodide **3b** gave 70% of **7b**. The spectroscopical data are the same as for **7a**.

Malyngolide (**1a**) *and Epimalyngolide* (**1b**): A mixture of palladium (50 mg, 10% Pd on C) and **7a** (1.00 g, 2.60 mmol) in ethanol (25 ml) was treated for 15 h with H_2 at room temperature. After filtration KOH (560 mg, 10 mmol) was added, the solution was stirred for 1 h at 40°C, and acidified to pH = 5 with cold sulfuric acid in methanol (10% solution). The mixture was filtered, evaporated, the crystalline residue dissolved in acetonitrile and treated for 10 h with 100 mg of H^+-resin (Amberlyst 15). Filtration and chromatography (silica gel, hexane:ethyl acetate = 3:1) gave 260 mg (37%) of malyngolide (**1a**) and 280 mg (40%) epimalyngolide (**1b**).

Malyngolide (**1a**): $[\alpha]_D^{20}$ = −12.1 (*c* = 4.0, $CHCl_3$). – IR (film): 3440 cm^{-1} (OH), 1735, 1705 (C=O). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, 3H, *J* = 6.0 Hz, CH_3), 1.27 (b.s, 19H), 1.5–2.0 (m, 4H), 2.3–2.4 (m, 1H, 2H), 2.65 (b.s, 1H, OH), 3.46, 3.65 (2d, *J* = 12.0 Hz). – MS (70 eV): *m/z* (%) = 240 (19), 239 (100, M − CH_2OH), 211 (33), 155 (24), 143 (29).

$C_{16}H_{30}O_3$ (270.4) Calcd. C 71.07 H 11.18
1a: Found C 70.82 H 11.31
1b: Found C 70.96 H 11.28
1c: Found C 70.77 H 11.27
1d: Found C 70.28 H 11.25

Epimalyngolide (**1b**): $[\alpha]_D^{20}$ = 19.5 (*c* = 6.8, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, 3H, *J* = 6.5 Hz, CH_3), 1.27 (b.s, 19H), 1.5–2.0 (m, 4H), 2.3–2.4 (m, 1H, 2H), 2.48 (b.s, 1H, OH), 3.54 (s, 2H, CH_2). – MS (70 eV): *m/z* (%) = 240 (17), 239 (100, M − CH_2OH), 211 (26), 155 (20), 143 (15).

Enantiomalyngolide (**1c**) *and Epienantiomalyngolide* (**1d**): The procedure for the synthesis of **1a** and **1b** applied to 350 mg (0.90 mmol) of **7b** gave 90 mg (37%) of enantiomalyngolide (**1c**) and 81 mg (33%) of enantioepimalyngolide (**1d**).

Enantiomalyngolide (**1c**): $[\alpha]_D^{20}$ = 12.4 (*c* = 2.8, $CHCl_3$). – The spectroscopic data are the same as for **1a**.

Enantioepimalyngolide (**1d**): $[\alpha]_D^{20}$ = −18.7 (*c* = 2.2, $CHCl_3$). – The spectroscopic data are the same as for **1b**.

CAS Registry Numbers

1a: 71582-80-4 / **1b**: 76023-93-3 / **1c**: 88643-05-4 / **1c**: 88643-05-4 / **1d**: 88643-06-5 / **2**: 80-62-6 / **3a** (isomer 1): 105122-25-6 / **3a** (isomer 2): 105122-31-4 / **3b** (isomer 1): 105122-26-7 / **3b** (isomer 2): 105122-32-5 / **4**: 103680-89-3 / **7a** (isomer 1): 105122-27-8 / **7a** (isomer 2): 105181-89-3 / **7b** (isomer 1): 105181-90-6 / **7b** (isomer 2): 105181-91-7 / **8a**: 105122-28-9 / **8b**: 103680-90-6 / **9a**: 105122-29-0 / **9b**: 105122-30-3 / titanium tetraisopropylate 546-68-9 / (*S,S*)-diethyl tartrate 13811-71-1 / (*R,R*)-diethyl tartrate 87-91-2 / (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid 17257-71-2 / (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride 39637-99-5

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[158/86]