Synthesis of (+)-Malyngolide from (+)-Tartaric Acid

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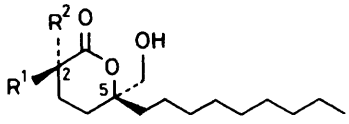
(+)-Malyngolide (+)-(**1**), the antipode of natural malyngolide, was synthesized in 9 steps from dimethyl (2*R*,3*R*)-(−)-tartrate acetonide (**3**) *via* (2*R*)-(−)-2-nonylbutane-1,2,4-triol (**8**) in 5.1% overall yield.

Since (−)-malyngolide (−)-(**1**), an antibiotic active against *Mycobacterium smegmatis* and *Streptococcus pyogenes*, has been isolated from the blue-green marine alga *Lyngbya majuscula* Gomont,[1] six asymmetric total syntheses of (−)-(**1**)[2] and nine syntheses of the racemic form[3] have hitherto been reported.



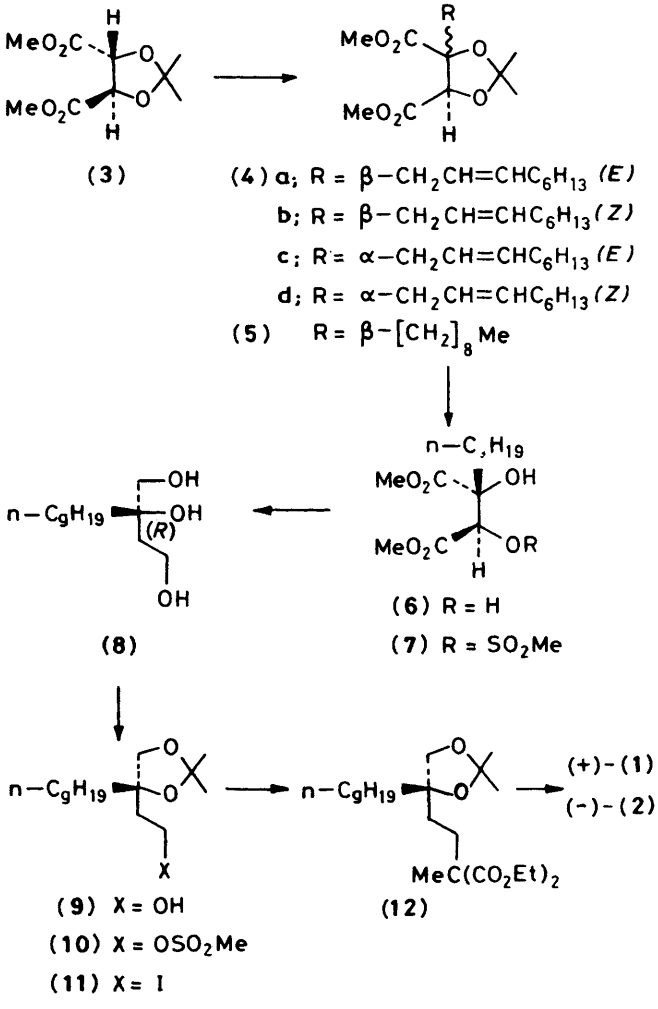
(−)-(**1**) R^1 = Me, R^2 = H
(+)-(**2**) R^1 = H, R^2 = Me

We now report an asymmetric synthesis of (+)-malyngolide (+)-(**1**), the antipode of natural malyngolide, starting from dimethyl (2*R*,3*R*)-(−)-tartrate acetonide (**3**), a readily available chiral synthon. The synthetic route is illustrated in Scheme 1.

Following the alkylation method of dimethyl (2*R*,3*R*)-(−)-tartrate acetonide (**3**) developed by Seebach,[4] the enolate derived from (**3**) was treated with 1-bromonon-2-ene (*E*:*Z* = 4:1)† to give an inseparable mixture of monoalkylated diastereoisomers (**4a**) and (**4b**) (4:1; 39%), together with the dialkylated product (20—30%). The isolation of the former products was easily performed by silica gel column chromatography. The minor diastereoisomers, (**4c**) and (**4d**), were not isolated. The *R* configuration at the newly formed quaternary carbon atom (C-2) in compounds (**4a**) and (**4b**) is tentatively assigned based on precedent.[4,5] However, in order to confirm the stereochemistry unambiguously the transformation of the diastereoisomers into malyngolide was needed.

Catalytic hydrogenation of the mixture (**4a**) and (**4b**) over 10% Pd–C followed by hydrolysis in refluxing aqueous acetic acid afforded diol (**6**) in 70% yield. Mesylation of the diol (**6**) with methanesulphonyl chloride in pyridine gave monomesylate (**7**), m.p. 51.5—52.0 °C, in 89% yield.

Reduction of compound (**7**) with lithium triethylborohydride gave (2*R*)-2-nonylbutane-1,2,4-triol (**8**) as an oil, $[\alpha]_D$ −5.1° (*c* 2 in $CHCl_3$), in 98% yield. To determine the optical purity of the chiral tertiary alcohol, its acetonide derivative (**9**) was submitted to ^1H (270 MHz) and ^{13}C (67.8 MHz) n.m.r. spectral investigation in the presence of the chiral shift reagent Eu(tfc)$_3$ {tfc = 3-[trifluoromethyl(hydroxy)methylene]-d-camphorato}, [(**9**):Eu(tfc)$_3$ = 20:1 and 3:1 molar ratio; $CDCl_3$]. For comparison, n.m.r. spectra of the racemic acetonide (±)-(**9**) prepared from γ-butyrolactone and nonanal (Scheme 2) were

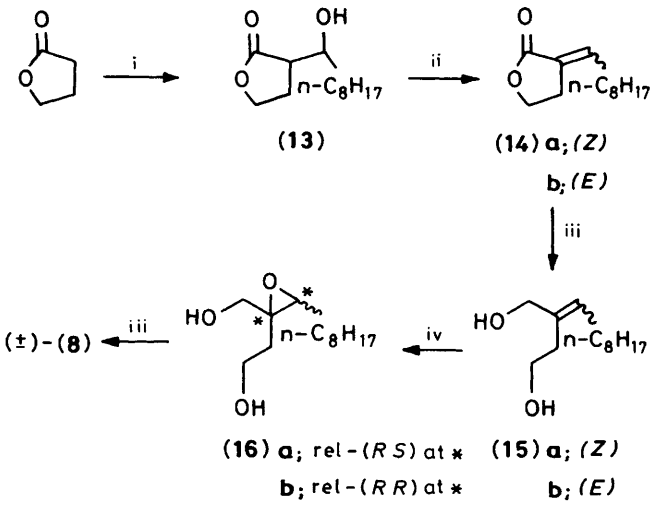


Scheme 1.

also recorded. The enantiomeric shift differences were sufficiently large for the separation of the enantiomers, and the high optical purity of chiral (**9**) was ascertained since no peak due to the minor antipode was detected.

The chiral alcohol (**9**) was then transformed into the iodide (**11**) *via* the mesylate (**10**). Attempts to introduce a three-carbon unit into the iodide (**11**) using either the dianion of propionic acid or the enolate of ethyl propionate were not successful. However, the enolate of diethyl methylmalonate was efficiently alkylated with the iodide (**11**) to give diester (**12**) in 89% yield. The diester (**12**) was, after acid hydrolysis of the acetal group, saponified and decarboxylated to give (+)-malyngolide (+)-(**1**) and (−)-epimalyngolide (−)-(**2**) in 40 and 30% yield, respectively. The spectral properties (i.r., ^1H and ^{13}C n.m.r., and

† H. Nii, K. Furukawa, and M. Iwakiri, *Nippon Kagaku Kaishi*, 1971, **92**, 1214. 1-Bromonon-2-ene, prepared following the procedure described by Nii *et al.*, was found to be a mixture of diastereoisomers (*E*:*Z* = 4:1), based on the ^1H n.m.r. spectrum (270 MHz).



Scheme 2. *Reagents:* i, LDA, $Me[CH_2]_7CHO$; ii, $MeSO_2Cl$, then heat; iii, $LiAlH_4$; iv, MCPBA

m.s.) of compounds (+)-(**1**) and (−)-(**2**) were completely identical with those previously reported.[1,2d] The specific rotations of compounds (+)-(**1**) and (−)-(**2**) were $[\alpha]_D^{22}$ +12.5° (*c* 0.73 in $CHCl_3$) and $[\alpha]_D^{23}$ −18.5° (*c* 0.60 in $CHCl_3$), respectively. This shows that the antipode of natural malyngolide has been synthesized from (+)-tartaric acid. The optical purity of (+)-malyngolide (+)-(**1**) was 96% e.e. It follows that natural (−)-malyngolide could be synthesized similarly, starting from commercially available (−)-tartaric acid.

This synthetic study shows that chiral 2-alkylbutane-1,2,4-triols are potentially useful intermediates for the syntheses of various types of naturally occurring chiral tertiary alcohols, $R^1R^2R^3COH$, because an arbitrary substituent at C-2 can be introduced by alkylation of tartaric acid, and the two primary hydroxy functions in the butanetriols can be differentiated by converting these compounds into 1,2-*O*-isopropylidene derivatives.

Experimental

I.r. spectra were taken on a JASCO A-3 spectrometer as thin-layer films on sodium chloride plates unless stated otherwise. ^1H N.m.r. spectra were recorded on JEOL GX-270 (270 MHz) or JEOL C-60 (60 MHz) spectrometers with $CDCl_3$ as solvent and $SiMe_4$ as internal standard. ^{13}C N.m.r. spectra were recorded on a JEOL GX-270 (67.8 MHz) instrument with $CDCl_3$ as internal standard. Mass spectra were obtained by direct introduction on a JEOL DX-300 mass spectrometer using either electron impact (e.i.; 70 eV) or chemical ionization (c.i.; isobutane) modes. Accurate mass measurements (e.i.) were recorded on the mass spectrometer. Optical rotations were determined on a JASCO DIP-181 polarimeter. Pre-coated Merck Kieselgel 60 F_{254} was used for general analytical purposes and silica gel (Wakogel C-200) was used for column chromatography.

Dimethyl (2R,3R)-2,3-O-*Isopropylidene*-2-(*non*-2-*enyl*)*tartrates* (**4a**) *and* (**4b**).—To a solution of dimethyl (2*R*,3*R*)-2,3-*O*-isopropylidenetartrate (**3**) (5.90 g) and 1-bromonon-2-ene (*E*:*Z* = 4:1; 7.37 g) in dry tetrahydrofuran (THF) (65 ml)–hexamethylphosphoric triamide (13.5 ml), stirred under nitrogen at −78 °C, was added a solution of lithium di-isopropylamide (LDA) (30 mmol) in dry THF (43 ml). The reaction mixture was stirred overnight at −30 °C and then poured into diethyl ether (500 ml). The resulting solution was washed successively with water and saturated brine, and dried over anhydrous sodium sulphate. Chromatography on silica gel (250 g) with hexane–ethyl acetate (15:1–5:1 v/v) as eluant yielded dialkylated product (5.3 g) and a mixture of monoalkylated diesters (**4a**) and (**4b**) (4:1; 3.56 g, 39%). Spectral data of the mixture (**4a**) and (**4b**) are as follows: $\nu_{max.}$ 1 760 and 1 738 cm^{-1}; δ_H (270 MHz) 0.87 (3 H, t, *J* 7 Hz, Me), 1.25 (8 H, br s, 4 × CH_2), 1.42 (3 H, s, Me), 1.62 (3 H, s, Me), 1.97 (2 H, m, $=CHCH_2$), 2.44 (2 H, m, $=CHCH_2$), 3.79 (3 H, s, CO_2Me), 3.80 (3 H, s, CO_2Me), and 5.4 (2 H, m, CH=CH). Two singlet peaks due to the C-3 methine protons of (**4a**) and (**4b**) were observed at δ_H 4.98 and 5.01 in the ratio of 4:1; δ_C 14.06 (Me), 22.60 (CH_2), 25.94 (25.89) (Me), 27.50 (27.38) (Me), 28.81 (28.96), 29.30 (29.37), 31.71, 32.61 (32.37), and 37.91 (CH_2), 52.24 (CO_2Me), 52.60 (CO_2Me), 79.43 (C-3), 85.95 (85.62) (C-2), 112.56 (O–C–O), 122.19 (121.30) (CH=), 135.91 (CH=), 168.86 (C=O), and 172.08 (C=O) [the values shown in parentheses are the chemical shifts of the minor diastereomer (**4b**)]; *m/z* (e.i.) 342 (1.3%, M^+), 327 (14, M^+ − Me), 283 (27, M^+ − CO_2Me), and 193 (100) (Found: M^+ − Me, 327.1845. $C_{17}H_{27}O_6$ requires *m/z* 327.1808). ^1H N.m.r. spectral data (60 MHz) of the dialkylated product; δ 0.86 (6 H, t-like, Me), 1.47 (6 H, s, 2 × Me), 3.62 (6 H, s, 2 × CO_2Me), and 5.30 (4 H, m, 2 × CH=CH).

Dimethyl (2R,3R)-2,3-O-*Isopropylidene*-2-*nonyltartrate* (**5**).—The mixture of compounds (**4a**) and (**4b**) (3.64 g) was hydrogenated over 10% Pd–C (398 mg) in methanol (250 ml) to give the *saturated diester* (**5**) (3.30 g, 90%) as an oil, $\nu_{max.}$ 1 760 and 1 740 cm^{-1}; δ_H (270 MHz) 0.88 (3 H, t, *J* 7 Hz, Me), 1.24 (14 H, br s, 7 × CH_2), 1.42 (3 H, s, Me), 1.61 (3 H, s, Me), 3.80 (3 H, s, CO_2Me), 3.82 (3 H, s, CO_2Me), and 4.94 (1 H, s, 3-H); δ_C 13.99 (Me), 22.56 and 23.73 (CH_2), 25.94 (Me), 27.56 (Me), 29.14, 29.23, 29.34, 29.61, 31.76, and 34.19 (CH_2), 52.14 (CO_2Me), 52.62 (CO_2Me), 79.89 (C-3), 85.95 (C-2), 112.41 (O–C–O), 168.88 (C=O), and 172.53 (C=O) (Found: M^+ − Me, 329.1951. $C_{17}H_{29}O_6$ requires *m/z* 329.1963).

Dimethyl (2R,3R)-2-*Nonyltartrate* (**6**).—The acetonide (**5**) (1.04 g) was hydrolysed in acetic acid–water (4:1 v/v) at reflux temperature. Chromatography on silica gel (50 g) with hexane–ethyl acetate (6:1 v/v) as eluant gave the *deprotected tartrate* (**6**) (607 mg, 78%) as a solid, m.p. 45—49 °C, together with recovered compound (**5**) (163 mg). Spectral data of diester (**6**): $\nu_{max.}$ 3 500 and 1 742 cm^{-1}; δ_H (270 MHz) 0.88 (3 H, t, *J* 7 Hz, Me), 1.25 (14 H, br s, 7 × CH_2), 1.80 (2 H, m, CH_2), 3.29 (1 H, d, *J* 9 Hz, CHO*H*), 3.57 (1 H, s, OH), 3.842 (3 H, s, CO_2Me), 3.845 (3 H, s, CO_2Me), and 4.33 (1 H, d, *J* 9 Hz, C*H*OH); *m/z* (c.i.) 305 (M^+ + 1); *m/z* (e.i.) 245 (M^+ − CO_2Me), 227 (M^+ − CO_2Me − H_2O), 215 [$MeO_2CC(OH)C_9H_{19}^+$], and 155 ($HOC{=}CHC_8H_{17}^+$) (Found: M^+ − CO_2Me, 245.1730. $C_{13}H_{25}O_4$ requires *m/z* 245.1752).

Dimethyl (2R,3R)-2-O-*Mesyl*-3-*nonyltartrate* (**7**).—The diol (**6**) (3.09 g) was dissolved in dry pyridine (13 ml) and mesylated with methanesulphonyl chloride (2.0 g) at room temperature. Chromatography of the crude product [silica gel 30 g; eluant hexane–ethyl acetate (7:1—3:1 v/v)] gave the *mesylate* (**7**) (3.46 g, 89%) as needles, m.p. 51.5—52.0 °C (from hexane); $[\alpha]_D^{30}$ + 0.9° (*c* 1.4 in $CHCl_3$); $\nu_{max.}$(KBr) 3 550, 1 766, 1 740, 1 370, 1 180, 1 160, 970, 870, and 825 cm^{-1}; δ_H (270 MHz) 0.88 (3 H, t, *J* 7 Hz, Me), 1.25 (14 H, br s, 7 × CH_2), 1.8—2.0 (2 H, m, CH_2), 3.14 (3 H, s, SMe), 3.60 (1 H, s, OH), 3.87 (6 H, s, 2 × CO_2Me), and 5.20 (1 H, s, *H*COMs); *m/z* (c.i.) 383 (M^+ + 1); *m/z* (e.i.) 323 (22%, M^+ − CO_2Me), 291 (11, M^+ − CO_2Me − OMe), 227 (32, M^+ − CO_2Me − $MeSO_3H$), 215 [22, $MeO_2CC(OH)$-

$C_9H_{19}^+$], 155 (42, $HOC{=}CHC_8H_{17}^+$), and 89 (100) (Found: $M^+ - CO_2Me$, 323.1458. $C_{14}H_{27}O_6S$ requires *m/z* 323.1527).

(2R)-2-*Nonylbutane*-1,2,4-*triol* (**8**).—To a solution of diester (**7**) (919 mg, 2.40 mmol) in dry THF (8 ml), stirred at 0 °C under nitrogen, was added a solution of lithium triethylborohydride (34 mmol) in THF (34 ml). The reaction mixture was warmed gradually to room temperature and left overnight at this temperature. To the solution, again cooled to 0 °C, was added dropwise water to decompose an excess of the hydride. A solution of sodium hydroxide (2.3 g) in water (8 ml) and 30% hydrogen peroxide (10 ml) were then successively added dropwise. The reaction mixture was stirred at 50 °C. The course of the reaction was monitored by t.l.c. and a few portions of 30% hydrogen peroxide (total 39 ml) were further added. After neutralization with dil. hydrochloric acid, the organic layer was separated and concentrated to *ca.* 5 ml. The aqueous layer was extracted with three portions of diethyl ether. The combined organic layers were washed successively with water and saturated brine, and dried over anhydrous sodium sulphate. Purification of the crude product by chromatography on silica gel (50 g) with hexane–ethyl acetate (1:1—1:4 v/v) as eluant gave *triol* (**8**) (546 mg, 98%) as an oil; $[\alpha]_D^{30}$ −5.1° (*c* 2.0 in $CHCl_3$) and −4.3° (*c* 2 in hexane); $\nu_{max.}$ 3 350 cm^{-1}; δ_H (270 MHz) 0.88 (3 H, t, *J* 7 Hz, Me), 1.26 (14 H, br s, 7 × CH_2), 1.45—1.65 (2 H, br s, CH_2), 3.4 (3 H, br s, 3 × OH), 3.48 [1 H, A part of an AB-type quartet, *J* (−)11 Hz, 1-H], and 3.52 [1 H, B part of an AB-type quartet, *J* (−)11 Hz, 1-H]. The multiplet at δ_H 1.65—1.9 (3-H_2) was changed to an AB-type quartet [δ_H 1.73 and 1.80, *J* (−)15 Hz] on irradiation of the signal at δ_H 3.75—3.95. The multiplet at δ_H 3.75—3.95 (4-H_2) was changed to an AB-type quartet [δ_H 3.80 and 3.88, *J* (−)12 Hz] on irradiation of the C-3 methylene protons; δ_C 14.06 (Me), 22.63, 23.50, 29.28, 29.55, 30.13, 30.25, 31.85, 37.76, and 37.85 (CH_2), 58.89 (CH_2OH), 68.09 (CH_2OH), and 74.70 (C-2); *m/z* (e.i.) 201 (65%, $M^+ - CH_2OH$), 187 (13, $M^+ - CH_2CH_2OH$), 183 (16), 155 (35), 105 (37, $M^+ - C_9H_{19}$), and 43 (100) (Found: $M^+ - CH_2OH$, 201.1868. $C_{12}H_{25}O_2$ requires *m/z* 201.1855).

(2R)-1,2-O-*Isopropylidene*-2-*nonylbutane*-1,2,4-*triol* (**9**).—A solution of the triol (**8**) (106 mg) in dry acetone (20 ml) was stirred for 3 h at room temperature in the presence of a catalytic amount of toluene-*p*-sulphonic acid to give the *acetonide* (**9**) (95 mg, 76%), as an oil, after silica gel chromatography [eluant hexane–ethyl acetate (9:1—3:1 v/v]; $[\alpha]_D^{18}$ +5.9° (*c* 1.33 in hexane); $\nu_{max.}$ 3 450 cm^{-1}; δ_H (270 MHz) 0.88 (3 H, t, *J* 7 Hz, Me), 1.27 (12 H, br s, 6 × CH_2), 1.40 (3 H, s, Me), 1.43 (3 H, s, Me), 1.5—1.8 (4 H, m, 2 × CH_2), 1.84 (2 H, m, CH_2), 2.73 (1 H, br s, OH), and 3.7—3.9 (4 H, m, 1- and 4-H_2); δ_C 14.06 (Me), 22.63, 24.45, 26.89 (Me), 27.02 (Me), 29.26, 29.50 (2 × C), 30.07, 31.85, 37.80, and 38.19 (CH_2), 59.34 (C-4), 73.10 (C-1), 83.85 (C-2), and 109.29 (O–C–O); *m/z* (e.i.) 257 (25%, $M^+ - Me$), 227 (24, $M^+ - CH_2CH_2OH$), and 145 (100, $M^+ - C_9H_{19}$) (Found: $M^+ - Me$, 257.2037. $C_{15}H_{29}O_3$ requires *m/z* 257.2106).

(2R)-1,2-O-*Isopropylidene*-4-O-*mesyl*-2-*nonylbutane*-1,2,4-*triol* (**10**).—Mesylation of compound (**9**) (81 mg) in dry pyridine (1 ml) with methanesulphonyl chloride (328 mg) gave the *mesylate* (**10**) (94 mg, 90%), $\nu_{max.}$ 1 360, 1 180, 980, and 960 cm^{-1}; δ_H (270 MHz) 0.88 (3 H, t, *J* 7 Hz, Me), 1.27 (12 H, br s, 6 × CH_2), 1.37 (3 H, s, Me), 1.40 (3 H, s, Me), 1.56 (4 H, m, 2 × CH_2), 2.05 (1 H, t, *J* 7 Hz, 3-H), 3.01 (3 H, s, O_3SMe), an AB-type quartet centred at δ_H 3.80 [2 H, *J ca.* (−)10 Hz, 1-H_2], and 4.36 (2 H, m, 4-H_2); *m/z* (c.i.) 351 ($M^+ + 1$); *m/z* (e.i.) 335 (16%, $M^+ - Me$), 227 (19, $M^+ - CH_2CH_2OMs$), 223 (30, $M^+ - C_9H_{19}$), and 72 (100) (Found: $M^+ - Me$, 335.1889. $C_{16}H_{31}O_5S$ requires *m/z* 335.1891).

(2R)-2-(2-*Iodoethyl*)-1,2-O-*isopropylideneundecane*-1,2-*diol* (**11**).—The mesylate (**10**) (206 mg) was dissolved in butan-2-one (15 ml) and refluxed with sodium iodide (412 mg) to give *iodide* (**11**) (209 mg, 93%), $\nu_{max.}$ 1 210 and 1 063 cm^{-1}; δ_H (270 MHz) 0.88 (3 H, t, *J* 7 Hz, Me), 1.27 (12 H, br s, 6 × CH_2), 1.36 (3 H, s, Me), 1.40 (3 H, s, Me), 1.4—1.65 (4 H, m, 2 × CH_2), 2.21 (2 H, m, CH_2CH_2I), 3.18 (2 H, m, CH_2CH_2I), and 3.75 (2 H, s, 1-H_2); *m/z* (c.i.) 383 ($M^+ + 1$); *m/z* (e.i.) 367 (24%, $M^+ - Me$), 255 (32, $M^+ - C_9H_{19}$), 227 (100, $M^+ - CH_2CH_2I$), and 197 (29) (Found: $M^+ - Me$, 367.1181. $C_{15}H_{28}IO_2$ requires *m/z* 367.1136).

Diethyl [(3R)-3,4-*Isopropylidenedioxy*-3-*nonylbutyl*]*methylmalonate* (**12**).—To a suspension of hexane-washed sodium hydride (32 mg of a 60% dispersion in oil) in dry THF (1 ml) stirred under nitrogen was added a solution of diethyl methylmalonate (155 mg) in dry THF (1.5 ml). The reaction mixture was stirred for 30 min at room temperature, and to the resulting colourless solution was added a solution of the iodide (**11**) (58 mg) in dry THF (3 ml). The reaction mixture was heated under reflux for 10 h. After work-up as usual, the crude product was purified by chromatography on silica gel (7 g) with hexane–diethyl ether (60:1—15:1 v/v) as eluant to give *compound* (**12**) (58 mg, 89%) as an oil, $\nu_{max.}$ 1 740 cm^{-1}; δ_H (270 MHz) 0.88 (3 H, t, *J* 7 Hz, Me), 1.25 (6 H, t, *J* 7 Hz, 2 × CO_2CH_2Me), 1.26 (12 H, br s, 6 × CH_2), 1.37 (3 H, s, Me), 1.38 (3 H, s, Me), 1.40 (3 H, s, Me), 1.4—1.7 (6 H, m, 3 × CH_2), 3.74 (2 H, s, CH_2O), and 4.18 (4 H, q, *J* 7 Hz, 2 × CO_2CH_2Me); δ_C 14.06 (3 × Me), 19.87 (Me), 22.65 and 24.13 (CH_2), 26.98 (Me), 27.23 (Me), 29.28 and 29.53 (2 × CH_2), 30.05, 30.11, 31.69, 31.87, and 37.03 (CH_2), 53.32 [$C(CO_2Et)_2$], 61.17 (CO_2CH_2Me), 73.05 (OCH_2), 83.09 (O–C), 108.98 (O–C–O), and 172.19 (C=O) (these were assigned based on the completely decoupled and INEPT spectra); *m/z* (e.i.) 413 (7%, $M^+ - Me$), 383 (6), 353 (53), 325 (8), 301 (26), 279 (16), 243 (100), 227 (84), and 174 (90) (Found: $M^+ - Me$, 413.2872. $C_{23}H_{41}O_6$ requires *m/z* 413.2902).

(2S,5R)-(+)-*Malyngolide* (+)-(**1**) *and* (2R,5R)-(−)-*Epimalyngolide* (−)-(**2**).—A solution of compound (**12**) (84 mg) in acetic acid–water (4:1; 2.5 ml) was refluxed for 4 h under nitrogen. Evaporation of the solvent gave an oil (86 mg), which was then hydrolysed with sodium hydroxide (750 mg) in ethanol–water (9:1; 7.4 ml) at room temperature. After neutralization with acetic acid, the product was extracted with diethyl ether. The crude product was then dissolved in toluene (5 ml) and the solution was heated at reflux temperature for 3 h under nitrogen. The product was submitted to chromatography on silica gel (2 g) with hexane–ethyl acetate (4:1 v/v) as eluant to give (−)-epimalyngolide (−)-(**2**) (16 mg) and (+)-malyngolide (+)-(**1**) (20 mg) together with a mixture of the diastereoisomers (4 mg). All the spectral data of the diastereoisomers were identical with those reported in the literature. A characteristic ^1H n.m.r. pattern [AB-type quartet, δ_H 3.48 and 3.66, *J* (−)12 Hz; $CDCl_3$; 270 MHz] due to the CH_2OH group in (+)-(**1**) was observed as reported by Eliel.[2d] The ^1H n.m.r. spectral data (270 MHz) of (+)-malyngolide (+)-(**1**) and (−)-epimalyngolide (−)-(**2**) determined in C_6D_6 are as follows. (+)-(**1**): δ_H 0.93 (3 H, t, *J* 7 Hz, Me), 1.13 (3 H, d, *J* 7 Hz, Me), 1.27 (br s, CH_2), 2.05—2.2 (1 H, m, 2-H), 2.7—3.0 (1 H, br s, OH), 3.25 [1 H, A part of an AB-type quartet, *J* (−)12 Hz, C*H*OH], and 3.51 [1 H, B part of an AB-type quartet, *J* (−)12 Hz, C*H*OH]. (−)-(**2**): δ_H 0.93 (3 H, t, *J* 7 Hz, Me), 1.19 (3 H, d, *J* 7 Hz, Me), 1.29 (br s, CH_2), 1.85—2.0 (1 H, m, 2-H), 2.5—2.8 (1 H, br s, OH), 3.36 [1 H, A part of an AB-type quartet, *J* (−)12 Hz, C*H*OH], and 3.40 [1 H, B part of an AB-type quartet, *J* (−)12 Hz, C*H*OH].

(±)-α-(1-*Hydroxynonyl*)-γ-*butyrolactone* (**13**).—To a solution of LDA (59.2 mmol) in dry THF (173 ml), stirred at

−78 °C under nitrogen, was added dropwise during 30 min a solution of γ-butyrolactone (4.5 g) in dry THF (30 ml). A solution of nonanal (8.5 g) in dry THF (10 ml) was added dropwise during 30 min. The reaction mixture was then stirred for 1 h at −78 °C and overnight at −60 °C. An aqueous solution of ammonium chloride was added dropwise at −60 °C. After work-up as usual, the crude pale yellow oil was purified by dry silica gel column chromatography [silica gel 500 g; eluant hexane–ethyl acetate (2:1 v/v)] to give compound (**13**) (7.68 g, 64%) as an oil, $\nu_{max.}$ 3 450 and 1 760 cm^{-1}; δ_H (60 MHz) 0.88 (3 H, t-like, Me), 1.30 (12 H, br s, 6 × CH_2), 1.7—1.9 (4 H, m, 2 × CH_2) 3.75 (2 H, m, CHOH), and 4.0—4.5 (2 H, m, O=$COCH_2$); *m/z* (e.i.) 210 (14%, $M^+ - H_2O$), 115 (38), and 86 (100).

(±)-(Z)- *and* (±)-(E)-α-*Nonylidene*-γ-*butyrolactone* (**14a**) *and* (**14b**).—To a solution of compound (**13**) (3.71 g) in dry CH_2Cl_2 (70 ml) and triethylamine (2.45 g), stirred at 0 °C, was added dropwise during 40 min a solution of methanesulphonyl chloride (2.46 g) in dry CH_2Cl_2 (20 ml). The reaction mixture was further stirred at 0 °C for 1 h. Methanol (1 ml) and then ice–water were added and the product was extracted with CH_2Cl_2. The crude mesylate was dissolved in pyridine (70 ml) and was heated at reflux temperature for 2 h. After decantation the colourless precipitate was washed with diethyl ether. The combined washings and filtrate were concentrated to *ca.* 20 ml. Diethyl ether was added and the ethereal solution was washed successively with dil. hydrochloric acid, water, aqueous sodium hydrogen sulphate, water, and saturated brine, and dried over anhydrous sodium sulphate. The crude product was submitted to chromatography [eluant hexane–ethyl acetate (20:1—1:1)] to give the *Z*-alkene (**14a**) (13%) and the *E*-alkene (**14b**) (50%). Alkene (**14a**): $\nu_{max.}$ 1 750 and 1 668 cm^{-1}; δ_H (60 MHz) 0.88 (3 H, t-like, Me), 1.30 (12 H, br s, 6 × CH_2), 2.5—3.1 (4 H, m, 2 × CH_2), 4.30 (2 H, t, *J* 7 Hz, γ-H_2), and 6.25 (1 H, m, =CH). Alkene (**14b**): $\nu_{max.}$ 1 760 and 1 680 cm^{-1}; δ_H (60 MHz) 0.88 (3 H, t-like, Me), 1.30 (12 H, br s, 6 × CH_2), 2.0—2.4 (2 H, t-like, CH_2), 2.6—3.0 (2 H, t-like, CH_2), 4.35 (2 H, t, *J* 7 Hz, γH_2), and 6.8 (1 H, m, =CH).

(±)-(Z)-2-*Nonylidenebutane*-1,4-*diol* (**15a**).—To a suspension of lithium aluminium hydride (450 mg) in dry diethyl ether (50 ml), stirred at 0 °C under argon, was added dropwise during 1.5 h a solution of lactone (**14a**) (1.24 g) in dry diethyl ether (55 ml). The reaction mixture was stirred for a further 5.5 h at room temperature. After work-up as usual, the crude product was purified by chromatography on silica gel (200 g) with hexane–ethyl acetate (11:5 v/v) as eluant to give *diol* (**15a**) (794 mg, 63%) as an oil, $\nu_{max.}$ 3 300 cm^{-1}; δ_H (60 MHz) 0.88 (3 H, t-like, Me), 1.25 (12 H, br s, 6 × CH_2), 1.7—2.0 (2 H, m, CH_2), 2.38 (2 H, t, *J* 6 Hz, CH_2CH_2OH), 2.9 (2 H, br, s, 2 × OH), 3.67 (2 H, t, *J* 6 Hz, 4-H_2), 4.00 (2 H, s, CH_2OH), and 5.52 (1 H, t, *J* 8 Hz, =CH); *m/z* (e.i.) 214 (3%, M^+), 196 (8, $M^+ - H_2O$), and 83 (100) (Found: M^+, 214.1873. $C_{13}H_{26}O_2$ requires *M*, 214.1932).

(±)-(E)-2-*Nonylidenebutane*-1,4-*diol* (**15b**).—The γ-lactone (**14b**) (905 mg) was reduced similarly with lithium aluminium hydride (313 mg) to give diol (**15b**) (590 mg, 64%) as an oil, δ_H (60 MHz) 0.88 (3 H, t-like, Me), 1.30 (12 H, br s, 6 × CH_2), 1.7—2.3 (2 H, m, CH_2), 2.33 (2 H, t, *J* 6 Hz, CH_2CH_2OH), 2.9 (2 H, br s, 2 × OH), 3.71 (2 H, t, *J* 6 Hz, 4-H_2), 4.13 (2 H, s, CH_2OH), and 5.40 (1 H, t, *J* 8 Hz, =CH).

(±)-2-*Nonylbutane*-1,2,4-*triol* (±)-(**8**).—To a solution of diol (**15a**) (1.17 g) in dry CH_2Cl_2 (50 ml), stirred at room temperature, was added dropwise during 30 min a solution of *m*-chloroperbenzoic acid (MCPBA) (1.33 g, 1.3 mol equiv.) in dry CH_2Cl_2 (60 ml). The reaction mixture was stirred for 5 h at room temperature. The excess of the peracid was decomposed by addition of aqueous sodium sulphite. The organic layer was washed successively with aqueous sodium hydrogen carbonate, water, and saturated brine, and dried over anhydrous sodium sulphate. The crude product oxirane (**16a**) (1.6 g) was submitted to the following reduction without further purification.

Epoxidation of alkene (**15b**) (550 mg) with MCPBA (632 mg) gave the oxirane (**16b**) (540 mg).

To a suspension of lithium aluminium hydride (960 mg) in dry diethyl ether (50 ml), stirred at 0 °C under nitrogen, was added a solution of the above crude epoxide (**16a**) (1.6 g) in dry diethyl ether (50 ml). The reaction mixture was stirred for 5 h at room temperature. After work-up as usual, the crude triol was purified by chromatography on silica gel (110 g) with hexane–ethyl acetate (1:1 v/v) as eluant to give (±)-(**8**) (969 mg, 76%) as an oil. All the spectra (i.r., ^1H n.m.r., and m.s.) were identical with those of (−)-(**8**) prepared above.

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