Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 857–864

TETRAHEDRON

Stereoselective synthesis of (−)-malyngolide, (+)-malyngolide and (+)-tanikolide using ring-closing metathesis

Miguel Carda,[a,*] Santiago Rodríguez,[a] Encarnación Castillo,[a,†] Alejandro Bellido,[a] Santiago Díaz-Oltra[a] and J. Alberto Marco[b,*]

[a]*Depart. de Q. Inorgánica y Orgánica, Univ. Jaume I, Castellón, E-12080 Castellón, Spain*
[b]*Depart. de Q. Orgánica, Univ. de Valencia, D. Moliner, 50, E-46100 Burjassot, Valencia, Spain*

Received 25 October 2002; revised 25 November 2002; accepted 4 December 2002

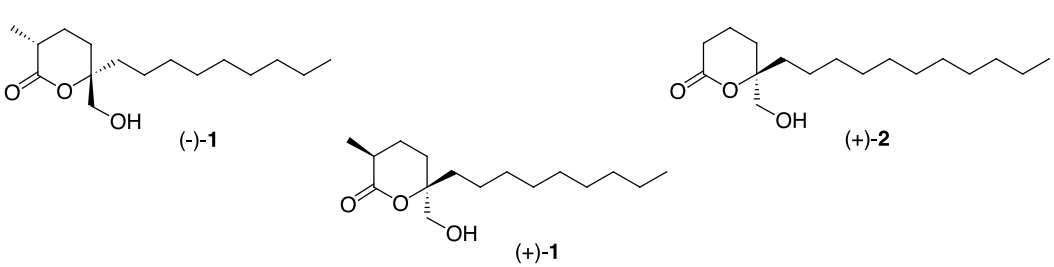
Abstract—The stereoselective syntheses of the naturally occurring δ-lactones (+)-tanikolide and (−)-malyngolide as well as of the unnatural (+)-enantiomer of the latter are described. Key steps in each of these syntheses were stereoselective additions of organometallic reagents to α-oxygenated ketones and olefin ring-closing metatheses.

1. Introduction

Investigations on the chemical components of the marine cyanobacterium *Lyngbya majuscula* Gomont have given rise to a plethora of new biologically active compounds.[1] One of these is malyngolide (−)-**1** (Scheme 1), a δ-lactone displaying antibiotic activity against pathogenic species of *Staphylococcus*, *Mycobacterium*, *Pseudomonas* and related genera.[1a] A further component isolated from the same source is tanikolide (+)-**2**, a structurally related lactone with antifungal and molluscicidal properties.[1b] Total syntheses of (−)-**1**, its unnatural antipode (+)-**1** and (+)-**2** have been published by several groups.[2–4] Two years ago, we described a further synthetic approach to (+)-**1** using a strategy which included an olefin ring-closing metathesis (RCM).[5] In the present report, we disclose in full the total syntheses of both enantiomers of malyngolide, (+)-**1** and (−)-**1**, and of the natural enantioner of tanikolide, (+)-**2**. All three syntheses are based on our recently described methodology of sequential allylation/RCM/allylic oxidation.[6] The chiral starting materials were D-glyceraldehyde acetonide and L-erythrulose, the latter being currently developed by our group as an useful C_4 chiron.[7]

2. Results and discussion

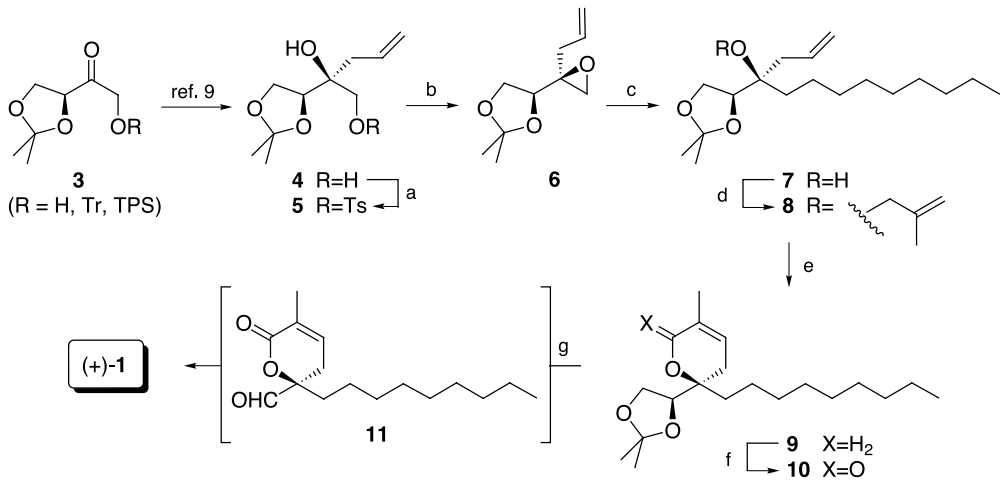
The synthetic sequence previously reported[5] for (+)-**1** (Scheme 2) relied upon a stereoselective nucleophilic allylation of protected L-erythrulose derivatives of general formula **3**.[8] This was performed under nonchelation control by means of allyl tributyltin in the presence of a Lewis acid. This generated the quaternary stereogenic carbon in alcohol **4**[9] with the configuration of the unnatural malyngolide enantiomer. Tosylation of **4** afforded **5**,[10] which was treated with base to yield epoxide **6**. Nucleophilic opening of the oxirane ring in **6** with a *n*-octylcuprate reagent[11] gave tertiary carbinol **7**, which was then *O*-alkylated with methallyl chloride to ether **8**. The latter underwent RCM[6] in the presence of ruthenium catalyst



Scheme 1.

Keywords: erythrulose; glyceraldehyde; ring-closing metathesis; lactones; malyngolide; tanikolide.
* Corresponding authors. Tel.: +34-96-3544337; fax: +34-96-3544328; e-mail: alberto.marco@uv.es
† Present address: Dept. Farm. y Tecn. Farm., Fac. C. Exp. y de la Salud, Univ. Cardenal Herrera-CEU, Moncada, Valencia, Spain.

0040–4020/03/$ - see front matter
PII: S0040-4020(02)01594-6

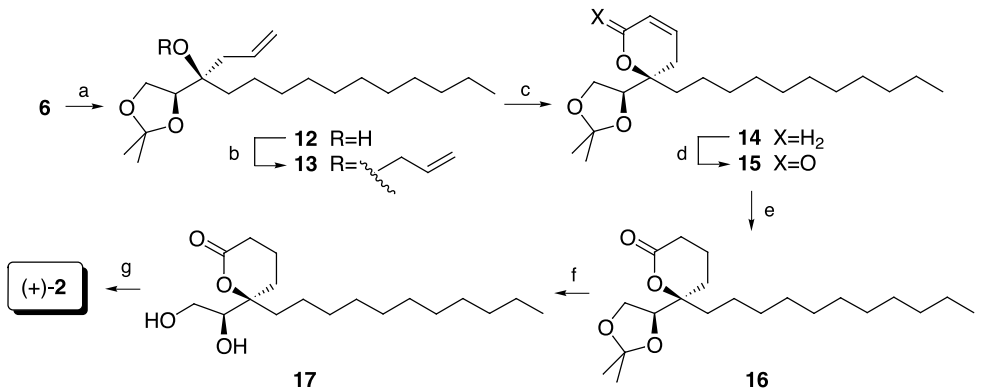


Scheme 2. Synthesis of (+)-malyngolide. *Reaction conditions*: (a) monotosylation. (b) base treatment (65–67% for the two steps, see details in the Section 3). (c) $Me(CH_2)_7MgBr$, CuI, THF, −30°C (80%). (d) KH, methallyl chloride, THF, △ (75%). (e) 3% $PhCH{=}RuCl_2(PCy_3)_2$, CH_2Cl_2, △ (92%). (f) CrO_3/3,5-DMP, CH_2Cl_2, −20°C (77%). (g) H_5IO_6, Et_2O, 6 h, rt, then L-Selectride, THF, 90 min, −78°C (65% overall) (Tr=trityl; TPS=*t*-butyldiphenylsilyl; *p*-Ts=*p*-toluenesulphonyl).

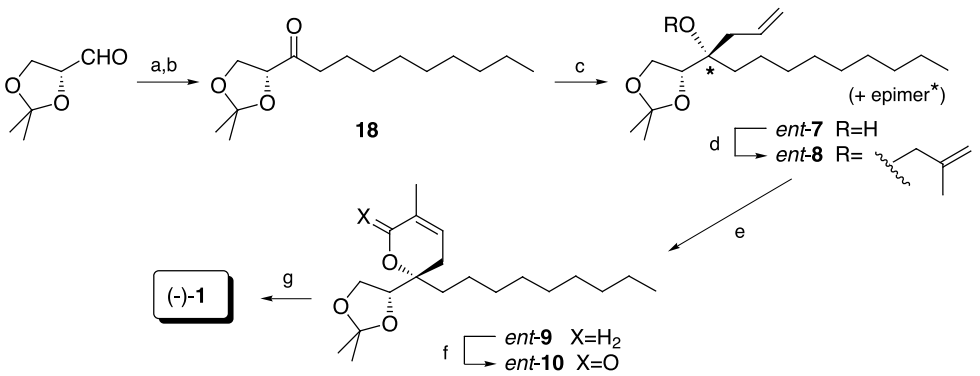
$PhCH{=}RuCl_2$-$(PCy_3)_2$[12] to furnish dihydropyran **9** in an excellent 92% yield. Allylic oxidation of **9** with the CrO_3/3,5-DMP complex[6,13] yielded the α,β-unsaturated δ-lactone **10**,[14] which was then subjected to oxidative cleavage of the dioxolane ring with periodic acid in Et_2O.[15] In our previous synthesis,[5] the intermediate unstable aldehyde **11** was not isolated but immediately reduced with $NaBH_4$ in isopropanol to yield dehydromalyngolide,[16] then converted into (+)-**1** through catalytic hydrogenation.[17] This procedure has now been improved in that crude **11** is treated with L-selectride at −78°C. This causes not only reduction of the aldehyde function but also saturation of the conjugated C=C bond[18] to afford (+)-**1** in 65% overall yield.[2c,19]

Tanikolide differs from malyngolide solely in lacking the α-carbonyl methyl group and in having a longer aliphatic chain (*n*-undecyl instead of *n*-nonyl). Furthermore, natural (+)-**2** has the same absolute configuration as (+)-**1** at the quaternary carbon center. Consequently, the same strategy was adapted without relevant changes to its synthesis (Scheme 3). Epoxide **6** was opened with a *n*-decylcuprate reagent[11] under the same conditions as above. This provided alcohol **12**, which was then *O*-allylated to ether **13**. RCM of the latter furnished dihydropyrane **14**, which was then subjected to allylic oxidation as above to yield lactone **15**.[13] The latter proved, however, more sensitive than **10** to the acidic conditions of oxidative acetal cleavage with periodic acid, as well as to those of acid hydrolysis.[20] Hydrogenation of the conjugated double bond afforded the saturated lactone **16**, the acetal group of which was amenable to acid hydrolysis to **17**. Oxidative cleavage of the diol moiety in **17** with lead tetraacetate, followed by immediate reduction of the intermediate unstable aldehyde[18] yielded (+)-**2**, with physical and spectral properties identical to those reported.[4]

In the syntheses of (+)-**1** and (+)-**2** described above, a derivative of the commercially available sugar L-erythrulose was the starting material. As described above, the synthesis relied on a stereoselective nucleophilic allylation of its carbonyl group under nonchelation control. The synthesis of the naturally occurring (−)-**1** would therefore demand either to start with a D-erythrulose derivative or to perform stereoselective allylations of L-erythrulose derivatives under chelation control. The reluctance of the more readily available erythrulose acetals to participate in chelation-controlled allylations of the carbonyl group[9] led us to discard the latter approach. While D-erythrulose



Scheme 3. Synthesis of (+)-tanikolide. *Reaction conditions*: (a) $Me(CH_2)_9MgBr$, CuI, THF, −30° (75%). (b) KH, allyl chloride, THF, △ (75%). (c) 3% $PhCH{=}RuCl_2(PCy_3)_2$, CH_2Cl_2, △ (85%). (d) CrO_3/3,5-DMP, CH_2Cl_2, −20°C (70%). (e) H_2, Pd/C (90%). (f) aq. AcOH, 40°C (87%). (g) $Pb(OAc)_4$, THF, then L-Selectride, THF, 90 min, −78°C (55% overall).



Scheme 4. Synthesis of (−)-malyngolide. *Reaction conditions*: (a) $Me(CH_2)_8MgBr$, THF, rt. (b) PCC, NaOAc, CH_2Cl_2, rt (60% for the two steps). (c) allyl bromide, indium powder, aq. THF, rt (73% of a 4.5:1 stereoisomeric mixture). Steps (d)–(g) as for (+)-**1** (Scheme 2).

derivatives can be prepared from D-isoascorbic acid,[8a] the somewhat lengthy synthetic procedure led us to explore an alternative way through chiral ketone **18**, readily prepared in two steps from D-glyceraldehyde acetonide (Scheme 4). This ketone proved unreactive towards allyl tributyltin and magnesium bromide etherate, even at room temperature, where decomposition started to take place.[21] Allyllithium and allylmagnesium bromide gave, however, an about 3:1 mixture of the enantiomer of alcohol **7** (*ent*-**7**, major compound) and its epimer at the starred carbon. A somewhat better stereoselectivity was observed under Barbier conditions.[22] Treatment of **18** with indium powder and allyl bromide in aqueous THF gave a 4.5:1 mixture of *ent*-**7** and its epimer, which could not be separated under normal chromatographic conditions. *O*-Methallylation of this mixture gave the corresponding epimeric ethers (*ent*-**8**+epimer), which were subjected to RCM under the same conditions as above. The major compound *ent*-**9** was separated at this stage from the minor epimer and found to be identical with compound **9** in all aspects except for the sign of the optical rotation. Compound *ent*-**9** was then converted as described above into natural malyngolide, (−)-**1**.

In summary, we have completed total, stereoselective syntheses of the naturally occurring, biologically active lactones (−)-malyngolide and (+)-tanikolide, as well as of the antipodal, unnatural form of the former. Precursors from the chiral pool were the starting materials. Further work related to the synthesis of natural lactones using RCM is underway and will be reported in due course.[23]

3. Experimental

NMR spectra (Varian Unity 400 and 500 NMR spectrometers) were measured in $CDCl_3$ solution at 25°C. ^{13}C NMR signal multiplicities were determined with the DEPT pulse sequence. Mass spectra were run by the electron impact (EIMS, 70 eV) on a VG AutoSpec mass spectrometer. IR spectra were recorded as oily films on NaCl plates (oils) or as KBr pellets (solids). Optical rotations were measured at 25°C. Reactions which required an inert atmosphere were carried out under argon with flame-dried glassware. Commercial reagents were used as received. THF and Et_2O were freshly distilled from sodium-benzophenone ketyl. Dichloromethane was freshly distilled from CaH_2. Hydrocarbons were freshly distilled from sodium wire. Tertiary amines were freshly distilled from KOH. Unless detailed otherwise, 'work-up' means pouring the reaction mixture into satd aqueous NH_4Cl, extraction with the solvent indicated in parenthesis, additional washing with 5% aq. $NaHCO_3$, (if acids had been utilized in the reaction) or with 5% aq. HCl (if bases had been utilized), drying over anhydrous Na_2SO_4 or $MgSO_4$ and solvent removal in vacuo. Where solutions were filtered through a Celite pad, the pad was additionally washed twice with the same solvent used, and the washings incorporated to the main organic layer. Column chromatography was performed on silica gel (Süd-Chemie AG, 60-200μ) with the eluent indicated in each case.

3.1. (2*S*,4′*S*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-hydroxypent-4-enyl *p*-toluenesulfonate, 5 and (4*S*,2′*S*)-4-(2-allyloxiranyl)-2,2-dimethyl-1,3-dioxolane, 6

Two alternative procedures A and B were used to convert diol **4** into epoxide **6** via tosylate **5**. While both gave comparable overall yields, method B was more comfortable of use.

Method A. Diol **4**[9] (2.02 g, 10 mmol) was dissolved under Ar in dry CH_2Cl_2 (50 mL) and treated sequentially with Et_3N (2.1 mL, 15 mmol), DMAP (60 mg, 0.5 mmol) and *p*-TsCl (2.1 g, ca. 11 mmol). The mixture was stirred for 24 h at reflux (TLC monitoring) and worked up (CH_2Cl_2). For analytical purposes, an aliquot of the residue was chromatographed on silica gel (hexanes–EtOAc, 7:3) to yield pure **5**. For synthetic purposes, the crude tosylate was used directly in the next step.

A 35% suspension of KH in mineral oil (1.15 g, equivalent to ca. 10 mmol of active hydride) was washed three times under Ar with dry hexane. Dry THF (25 mL) was then added, followed by a solution of the crude tosylate **5** in dry THF (40 mL). The solution was then stirred at room temperature for 30 min. Work-up (EtOAc) and column chromatography on silica gel (hexane–EtOAc 9:1) furnished **6** (1.23 g, 67% overall from **4**).

Method B. Diol **4** (2.02 g, 10 mmol) was dissolved under Ar in dry CH_2Cl_2 (25 mL) and treated sequentially with nBu_2SnO (50 mg, 0.2 mmol), Et_3N (2 mL, ca. 14 mmol) and *p*-TsCl (2.29 g, ca. 12 mmol).[24] The mixture was stirred

for 3–4 h at room temperature (TLC monitoring) and worked up (CH_2Cl_2). The crude tosylate was used directly in the next step and cyclized to **6** according to a literature procedure.[25]

NaOH (8 g, 200 mmol) and tetrabutylammonium hydrogen sulphate (6.8 g, 20 mmol) were dissolved in water (70 mL) and mixed with a solution of the crude tosylate in CH_2Cl_2 (40 mL). The biphasic reaction mixture was then vigorously stirred for 3 h at room temperature. Work-up (CH_2Cl_2) and column chromatography on silica gel (hexanes–EtOAc, 9:1) gave epoxide **6** (1.2 g, 65% overall yield from **4**).

3.1.1. (2*S*,4*S*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-hydroxypent-4-enyl *p*-toluenesulfonate, 5. Colorless needles, mp 59–60°C, $[\alpha]_D$=+6.8 (*c* 2.2; $CHCl_3$); IR ν_{max} (cm^{-1}): 3500 (br, OH), 3076, 2987, 2935, 1641, 1599, 1456, 1366, 1260, 1214, 1178, 1097, 1068, 983, 842, 815; ^1H NMR (400 MHz) δ 7.78 (2H, d, *J*=8 Hz), 7.34 (2H, d, *J*=8 Hz), 5.68 (1H, ddt, *J*=17, 11, 7 Hz), 5.10–5.00 (2H, m), 4.02 (1H, dd, *J*=8, 6.5 Hz), 3.93 (2H, br s), 3.92 (1H, dd, *J*=8, 6.5 Hz), 3.86 (1H, t, *J*=8 Hz), 2.80 (1H, br s, OH), 2.43 (3H, s), 2.20 (2H, m), 1.33 (3H, s), 1.26 (3H, s); ^{13}C NMR (100 MHz) δ 145.0, 132.5, 109.3, 72.1 (C), 131.1, 129.8, 128.1, 76.9 (CH), 119.8, 70.9, 64.0, 37.6 (CH_2), 26.1, 25.1, 21.6 (CH_3); EIMS, *m/z* (% rel. int.) 341.1047 [M^+−Me] (42), 315 (46), 155 (90), 101 (100), 91 (73). Calcd for $C_{17}H_{24}O_6S$–Me, *M*=341.1059. Anal. calcd for $C_{17}H_{24}O_6S$: C, 57.28; H, 6.79. Found, C, 57.34; H, 6.90.

3.1.2. (4*S*,2′*S*)-4-(2-Allyloxiranyl)-2,2-dimethyl-1,3-dioxolane, 6. Colorless oil, $[\alpha]_D$=−4.8 (*c* 7.2; $CHCl_3$); IR ν_{max} (cm^{-1}): 3079, 2988, 2936, 1457, 1436, 1381, 1372, 1260, 1219, 1158, 1071, 1000, 963, 920, 848; ^1H NMR (500 MHz) δ 5.72 (1H, ddt, *J*=17.3, 10, 7 Hz), 5.11 (1H, br d, *J*=17.3 Hz), 5.08 (1H, br d, *J*=10 Hz), 4.17 (1H, t, *J*=6.6 Hz), 4.02 (1H, dd, *J*=8.3, 6.6 Hz), 3.80 (1H, dd, *J*=8.3, 6.6 Hz), 2.82 (1H, d, *J*=5.2 Hz), 2.62 (1H, d, *J*=5.2 Hz), 2.42 (1H, dd, *J*=14.8, 7 Hz), 2.38 (1H, dd, *J*=14.8, 7 Hz), 1.36 (3H, s), 1.31 (3H, s); ^{13}C NMR (125 MHz) δ 109.7, 58.0 (C), 132.2, 76.3 (CH), 118.6, 65.6, 48.8, 36.0 (CH_2), 26.1, 25.4 (CH_3); EIMS, *m/z* (% rel. int.) 169.0870 [M^+−Me] (94), 101 (64), 81 (100). Calcd for $C_{10}H_{16}O_3$–Me, *M*=169.0864. Anal. calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found, C, 65.01; H, 8.94.

3.2. (4*R*,4′*S*)-4-(2,2-Dimethyl-1,3-dioxolan-4-yl)tridec-1-en-4-ol, 7

CuI (1.52 g, 8 mmol) was heated in vacuo in a three-necked flask until the solid turned light yellow. The flask was then filled with Ar and cooled to −30°C, followed by addition of dry Et_2O (30 mL). A 2 M solution of *n*-octylmagnesium bromide in Et_2O (10 mL, 20 mmol) was then added dropwise to the aforementioned CuI suspension. The resulting mixture was stirred for 20 min at −30°C. Epoxide **6** (921 mg, 5 mmol) was dissolved in dry Et_2O (10 mL) and added dropwise via syringe to the solution of the organocopper reagent. The reaction mixture was then stirred for 6–8 h at −30°C (TLC monitoring). The reaction was then quenched with satd aq. ammonium chloride and worked up (EtOAc). Column chromatography on silica gel (hexanes–EtOAc, 4:1) afforded alcohol **7** (1.19 g, 80%): oil, $[\alpha]_D$=+0.6 (*c* 3.8; $CHCl_3$); IR ν_{max} (cm^{-1}): 3480 (br, OH), 3076, 2980, 2928, 2855, 1457, 1371, 1216, 1160, 1069, 915, 861; ^1H NMR (500 MHz) δ 5.79 (1H, ddt, *J*=17.3, 10, 7 Hz), 5.10 (1H, br d, *J*=10 Hz), 5.08 (1H, br d, *J*=17.3 Hz), 4.00 (1H, dd, *J*=7.7, 6.6 Hz), 3.95 (1H, dd, *J*=8, 6.6 Hz), 3.86 (1H, dd, *J*=8, 7.7 Hz), 2.30 (1H, dd, *J*=14, 6.5 Hz), 2.05 (1H, dd, *J*=14, 8.2 Hz), 1.90 (1H, br s, OH), 1.55 (2H, m), 1.41 (3H, s), 1.35 (3H, s), 1.40–1.20 (14H, br m), 0.87 (3H, t, *J*=7 Hz); ^{13}C NMR (125 MHz) δ 108.9, 73.1 (C), 133.1, 80.1 (CH), 118.4, 64.6, 39.3, 37.3, 32.0, 30.2, 29.7, 29.6, 29.3, 23.2, 22.7 (CH_2), 26.4, 25.5, 14.1 (CH_3); EIMS, *m/z* (% rel. int.) 283.2273 [M^+−Me] (9), 257 (14), 197 (18), 171 (20), 155 (100). Calcd for $C_{18}H_{34}O_3$–Me, *M*=283.2273. Anal. calcd for $C_{18}H_{34}O_3$: C, 72.44; H, 11.48. Found, C, 72.69; H, 11.40.

3.3. (4*S*,1′*R*)-2,2-Dimethyl-4-[1-(2-methylallyloxy)-1-nonylbut-3-enyl]-1,3-dioxolane, 8

A 35% suspension of KH in mineral oil (0.69 g, equivalent to ca. 6 mmol of active hydride) was washed three times under Ar with dry hexane. Dry THF (5 mL) was then added, followed by a solution of **7** (895 mg, 3 mmol) in dry THF (20 mL). The solution was stirred at room temperature for 30 min. Methallyl chloride (590 μL, 6 mmol) was then added dropwise, followed by tetrabutylammonium iodide (37 mg, 0.1 mmol). The reaction mixture was then heated overnight at reflux. Work-up (EtOAc) and column chromatography on silica gel (hexanes–EtOAc, 19:1→9:1) furnished **8** (793 mg, 75%): oil, $[\alpha]_D$=−3.5 (*c* 3.2; $CHCl_3$); IR ν_{max} (cm^{-1}): 3077, 2970, 2921, 2853, 1640, 1458, 1379, 1210, 1159, 1068, 915, 861, 740; ^1H NMR (500 MHz) δ 5.82 (1H, ddt, *J*=17.3, 10, 7 Hz), 5.07 (1H, br d, *J*=17.3 Hz), 5.06 (1H, br d, *J*=10 Hz), 4.96 (1H, br s), 4.80 (1H, br s), 4.13 (1H, t, *J*=7.4 Hz), 4.06 (1H, br d, *J*=12.5 Hz), 3.95–3.90 (3H, m), 2.35 (1H, dd, *J*=14.5, 6.8 Hz), 2.18 (1H, dd, *J*=14.5, 7.8 Hz), 1.72 (3H, br s), 1.65 (2H, m), 1.42 (3H, s), 1.32 (3H, s), 1.40–1.20 (14H, br m), 0.88 (3H, t, *J*=7 Hz); ^{13}C NMR (125 MHz) δ 143.4, 108.6, 77.7 (C), 134.0, 80.4 (CH), 117.6, 110.2, 66.7, 65.1, 39.4, 32.8, 32.0, 30.3, 29.6, 29.5, 29.3, 23.1, 22.7 (CH_2), 26.4, 24.9, 19.7, 14.1 (CH_3); EIMS, *m/z* (% rel. int.) 337.2743 [M^+−Me] (2), 311 (4), 251 (33), 155 (100). Calcd for $C_{22}H_{40}O_3$–Me, *M*=337.2743. Anal. calcd for $C_{22}H_{40}O_3$: C, 74.95; H, 11.44. Found, C, 75.00; H, 11.66.

3.4. (2*R*,4′*S*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)-5-methyl-2-nonyl-3,6-dihydro-2*H*-pyran, 9

Compound **8** (705 mg, 2 mmol) and ruthenium complex PhCH=$RuCl_2$-$(PCy_3)_2$ (49 mg, 0.06 mmol) were dissolved under Ar in dry, degassed CH_2Cl_2 (100 mL) and heated at reflux for 12–18 h (TLC monitoring). After removal of all volatiles in vacuo, the residue was chromatographed on silica gel (hexanes–EtOAc, 9:1) to furnish cyclic ether **9** (597 mg, 92%): oil, $[\alpha]_D$=+31.9 (*c* 3.6; $CHCl_3$); IR ν_{max} (cm^{-1}): 2970, 2921, 2856, 1458, 1372, 1263, 1210, 1068, 857, 738; ^1H NMR (400 MHz) δ 5.42 (1H, m), 4.31 (1H, dd, *J*=8, 6.9 Hz), 3.96 (1H, dd, *J*=8, 6.9 Hz), 3.94 (2H, m), 3.69 (1H, t, *J*=8 Hz), 2.43 (1H, ddq, *J*=17, 2.5, 2.5 Hz), 1.80–1.70 (3H, br m), 1.58 (3H, br s), 1.42 (3H, s), 1.36 (3H, s), 1.35–1.20 (14H, br m), 0.86 (3H, t, *J*=7 Hz); ^{13}C NMR (100 MHz) δ 131.4, 109.5, 73.5 (C), 116.8, 78.6 (CH), 64.8,

64.3, 32.5, 31.9, 30.5, 29.6, 29.5, 29.3, 27.7, 22.8, 22.7 (CH_2), 26.3, 25.3, 18.6, 14.1 (CH_3); EIMS, *m/z* (% rel. int.) 324.2659 [M^+] (2), 309 (4), 223 (70), 155 (100), 101 (26). Calcd for $C_{20}H_{36}O_3$, *M*=324.2664. Anal. calcd for $C_{20}H_{36}O_3$: C, 74.03; H, 11.18. Found, C, 73.91; H, 11.00.

3.5. (6*R*,4′*S*)-6-(2,2-Dimethyl-1,3-dioxolan-4-yl)-3-methyl-6-nonyl-5,6-dihydropyran-2-one, 10

Finely powdered chromium trioxide (1.2 g, 12 mmol) was dried in vacuo in a dessicator containing P_2O_5. Then it was suspended under Ar in dry CH_2Cl_2 (10 mL), cooled to −20°C and treated rapidly at this temperature with 3,5-dimethylpyrazole (1.16 g, 12 mmol). After stirring the mixture for 15 min, ether **9** (325 mg, 1 mmol) dissolved in dry CH_2Cl_2 (5 mL) was added. The reaction mixture was then stirred for 1 h at −20°C, treated with 5 M aqueous NaOH (5 mL) and further stirred at 0°C for 1 h. The reaction mixture was then poured into diluted HCl, and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Filtration through Celite and solvent removal in vacuo were followed by column chromatography on silica gel (hexanes–EtOAc, 4:1) to yield **10** (260 mg, 77%): oil, $[\alpha]_D$=−9.9 (*c* 10; $CHCl_3$); IR ν_{max} 2941, 2856, 1720 (lactone C=O), 1121, 1058 cm^{-1}; ^1H NMR (500 MHz) δ 6.44 (1H, m), 4.33 (1H, dd, *J*=7.1, 6.3 Hz), 4.00 (1H, dd, *J*=9, 7.1 Hz), 3.91 (1H, dd, *J*=9, 6.3 Hz), 2.58 (1H, ddq, *J*=18.5, 2.5, 2.5 Hz), 2.45 (1H, ddq, *J*=18.5, 2.5, 2.5 Hz), 1.89 (3H, d, *J*=1.5 Hz), 1.70–1.60 (2H, m), 1.42 (3H, s), 1.32 (3H, s), 1.40–1.20 (14H, br m), 0.87 (3H, t, *J*=7 Hz); ^{13}C NMR (125 MHz) δ 164.4, 127.4, 109.9, 83.6 (C), 137.3, 77.9 (CH), 64.7, 34.4, 31.8, 30.0, 29.5 (×2), 29.2, 28.2, 23.5, 22.6 (CH_2), 26.1, 24.7, 17.0, 14.1 (CH_3); EIMS, *m/z* (% rel. int.) 323.2224 [M^+−Me] (26), 237 (100), 155 (55), 101 (68). Calcd for $C_{20}H_{34}O_4$–Me, *M*=323.2222. Anal. calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.12. Found, C, 71.01; H, 10.00.

3.6. (+)-Malyngolide, (+)-1

Lactone **10** (169 mg, 0.5 mmol) was dissolved under Ar in dry Et_2O (2 mL) and treated with periodic acid hydrate (171 mg, 0.75 mmol). The reaction mixture was then stirred for 6 h at room temperature, then diluted with Et_2O (10 mL) and filtered through Celite. The ethereal layer was then stirred for 15 min with solid K_2CO_3 (ca. 50 mg) to remove traces of acid and filtered again. Solvent removal in vacuo afforded crude **11**, which was dissolved under Ar in dry THF (5 mL) and cooled to −78°C. A 1 M solution of L-selectride in THF (1.25 mL, 1.25 mmol) was added via syringe. The reaction mixture was then stirred at −78°C for 90 min. Work-up (CH_2Cl_2) and column chromatography on silica gel (hexanes–EtOAc, 4:1→1:1) provided (+)-**1** (88 mg, 65% overall yield from **10**): oil, $[\alpha]_D$=+12.3 (*c* 1; $CHCl_3$), for synthetic (+)-malyngolide, lit.[2c] $[\alpha]_D$=+12.4 (*c* 2; $CHCl_3$). ^1H NMR (500 MHz) δ 3.66 (1H, d, *J*=12 Hz), 3.47 (1H, dd, *J*=12 Hz), 2.42 (1H, ddq, *J*=11, 7, 7 Hz), 2.00–1.60 (7H, br m), 1.35–1.20 (14H, br m), 1.24 (3H, d, *J*=7 Hz), 0.86 (3H, t, *J*=6.5 Hz); ^{13}C NMR (125 MHz) δ 175.0, 86.8 (C), 35.6 (CH), 67.8, 36.5, 31.9, 30.0, 29.5, 29.4, 29.3, 26.4, 23.7, 22.6, 17.1 (CH_2), 25.2, 14.1 (CH_3). EIMS, *m/z* (% rel. int.) 239.1999 [M^+−CH_2OH] (28), 237 (100), 155 (85). Calcd for $C_{16}H_{30}O_3$–CH_2OH, *M*=239.2011.

3.7. (4*R*,4′*S*)-4-(2,2-Dimethyl-1,3-dioxolan-4-yl)penta-dec-1-en-4-ol, 12

CuI (1.52 g, 8 mmol) was heated in vacuo in a three-necked flask until the solid turned light yellow. The flask was then filled with Ar and cooled to −30°C, followed by addition of dry Et_2O (20 mL). A 1 M solution of *n*-decylmagnesium bromide in Et_2O (20 mL, 20 mmol) was then added dropwise to the aforementioned CuI suspension. The resulting mixture was stirred for 20 min at −30°C. Epoxide **6** (921 mg, 5 mmol) was dissolved in dry Et_2O (10 mL) and added dropwise via syringe to the solution of the organocopper reagent. The reaction mixture was then stirred for 6–8 h at −30°C (TLC monitoring). The reaction was then quenched with satd aq. ammonium chloride and worked up (EtOAc). Column chromatography on silica gel (hexanes–EtOAc, 4:1) afforded alcohol **12** (1.22 g, 75%): oil, $[\alpha]_D$=−0.1 (*c* 3.8; $CHCl_3$); IR ν_{max} (cm^{-1}): 3480 (br, OH), 3077, 2984, 2930, 2854, 1457, 1380, 1371, 1251, 1216, 1161, 1069, 916, 861; ^1H NMR (400 MHz) δ 5.79 (1H, ddt, *J*=17.3, 10, 7 Hz), 5.10 (1H, br d, *J*=10 Hz), 5.08 (1H, br d, *J*=17.3 Hz), 3.99 (1H, dd, *J*=7.8, 6.4 Hz), 3.95 (1H, dd, *J*=7.8, 6.4 Hz), 3.87 (1H, t, *J*=7.8 Hz), 2.28 (1H, dd, *J*=14, 6.5 Hz), 2.04 (1H, dd, *J*=14, 8.2 Hz), 1.55 (2H, m), 1.41 (3H, s), 1.35 (3H, s), 1.40–1.20 (18H, br m), 0.87 (3H, t, *J*=7 Hz); ^{13}C NMR (100 MHz) δ 108.9, 73.1 (C), 133.1, 80.1 (CH), 118.5, 64.6, 39.3, 37.3, 32.0, 30.2, 29.8, 29.7 (×2), 29.6, 29.3, 23.2, 22.7 (CH_2), 26.5, 25.5, 14.2 (CH_3); EIMS, *m/z* (% rel. int.) 311.2530 [M^+−Me] (11), 285 (24), 225 (18), 183 (100). Calcd for $C_{20}H_{38}O_3$–Me, *M*=311.2586. Anal. calcd for $C_{20}H_{38}O_3$: C, 73.57; H, 11.73. Found, C, 73.69; H, 11.60.

3.8. (4*S*,1′*R*)-4-(1-Allyloxy-1-undecylbut-3-enyl)-2,2-dimethyl-1,3-dioxolane, 13

A 35% suspension of KH in mineral oil (0.69 g, equivalent to ca. 6 mmol of active hydride) was washed three times under Ar with dry hexane. Dry THF (5 mL) was then added, followed by a solution of **12** (980 mg, 3 mmol) in dry THF (20 mL). The solution was stirred at room temperature for 30 min. Methallyl chloride (590 μL, 6 mmol) was then added dropwise, followed by tetrabutylammonium iodide (37 mg, 0.1 mmol). The reaction mixture was then heated overnight at reflux. Work-up (EtOAc) and column chromatography on silica gel (hexanes–EtOAc, 19:1→9:1) furnished **13** (825 mg, 75%): oil, $[\alpha]_D$=−8.7 (*c* 2; $CHCl_3$); IR ν_{max} (cm^{-1}): 3077, 2983, 2931, 2855, 1640, 1458, 1379, 1370, 1261, 1211, 1159, 1067, 916, 862; ^1H NMR (400 MHz) δ 5.95–5.75 (2H, m), 5.25 (1H, dq, *J*=17, 1.5 Hz), 5.10–5.05 (3H, m), 4.20 (1H, ddt, *J*=12.7, 5.2, 1.6 Hz), 4.12 (1H, dd, *J*=8, 6.6 Hz), 4.06 (1H, ddt, *J*=12.7, 5.2, 1.6 Hz), 3.95–3.90 (2H, m), 2.36 (1H, dd, *J*=14.5, 6.8 Hz), 2.15 (1H, dd, *J*=14.5, 7.7 Hz), 1.70–1.60 (2H, m), 1.43 (3H, s), 1.31 (3H, s), 1.35–1.20 (18H, br m), 0.88 (3H, t, *J*=7 Hz); ^{13}C NMR (100 MHz) δ 108.7, 77.8 (C), 136.1, 133.9, 80.4 (CH), 117.7, 115.2, 65.0, 64.3, 39.4, 32.6, 32.0, 30.3, 29.7, 29.6 (×2), 29.5, 29.4, 23.1, 22.7 (CH_2), 26.4, 24.8, 14.2 (CH_3). EIMS, *m/z* (% rel. int.) 351.2890 [M^+−Me] (2), 325 (22), 265 (31), 183 (100), 101 (40). Calcd for $C_{23}H_{42}O_3$–Me, *M*=351.2899. Anal. calcd for $C_{23}H_{42}O_3$: C, 75.36; H, 11.55. Found, C, 75.20; H, 11.56.

3.9. (2*R*,4′*S*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-undecyl-3,6-dihydro-2*H*-pyran, 14

Compound **13** (733 mg, 2 mmol) and ruthenium complex PhCH=$RuCl_2$-$(PCy_3)_2$ (49 mg, 0.06 mmol) were dissolved under Ar in dry, degassed CH_2Cl_2 (100 mL) and heated at reflux for 12–18 h (TLC monitoring). After removal of all volatiles in vacuo, the residue was chromatographed on silica gel (hexanes–EtOAc, 19:1) to furnish cyclic ether **14** (575 mg, 85%): oil, $[\alpha]_D$=+24.4 (*c* 2.1; $CHCl_3$); IR ν_{max} (cm^{-1}): 3035, 2970, 2926, 2854, 1459, 1374, 1370, 1261, 1211, 1161, 1100, 1069, 859, 800; ^1H NMR (400 MHz) δ 5.77 (1H, dtt, *J*=10, 4.5, 2 Hz), 5.70 (1H, br d, *J*=10 Hz), 4.32 (1H, t, *J*=7.4 Hz), 4.16 (1H, br d, *J*=17 Hz), 4.10 (1H, br d, *J*=17 Hz), 3.97 (1H, dd, *J*=8, 7.4 Hz), 3.70 (1H, dd, *J*=8, 7.4 Hz), 2.48 (1H, dddt, *J*=17, 2.5, 2.5, 2.5 Hz), 1.90–1.70 (3H, br m), 1.44 (3H, s), 1.37 (3H, s), 1.35–1.20 (18H, br m), 0.87 (3H, t, *J*=7 Hz); ^{13}C NMR (100 MHz) δ 109.5, 73.7 (C), 125.0, 122.5, 78.7 (CH), 64.7, 61.1, 32.5, 31.9, 30.4, 29.7, 29.6 (×2), 29.5, 29.3, 27.7, 22.9, 22.7 (CH_2), 26.2, 25.2, 14.1 (CH_3). EIMS, *m*/*z* (% rel. int.) 338.2834 $[M]^+$ (1), 323 (5), 237 (58), 183 (100), 101 (22). Calcd for $C_{21}H_{38}O_3$, *M*=338.2821. Anal. calcd for $C_{21}H_{38}O_3$: C, 74.51; H, 11.31. Found, C, 74.72; H, 11.44.

3.10. (6*R*,4′*S*)-6-(2,2-Dimethyl-1,3-dioxolan-4-yl)-6-undecyl-5,6-dihydropyran-2-one, 15

Finely powdered chromium trioxide (1.2 g, 12 mmol) was dried in vacuo in a dessicator containing P_2O_5. Then it was suspended under Ar in dry CH_2Cl_2 (10 mL), cooled to −20°C and treated rapidly at this temperature with 3,5-dimethylpyrazole (1.16 g, 12 mmol). After stirring the mixture for 15 min, ether **14** (338 mg, 1 mmol) dissolved in dry CH_2Cl_2 (5 mL) was added. The reaction mixture was then stirred for 1 h at −20°C, treated with 5 M aqueous NaOH (5 mL) and further stirred at 0°C for 1 h. The reaction mixture was then poured into diluted HCl, and the organic layer was washed with brine, dried over anhydrous Na_2SO_4. Filtration and solvent removal in vacuo was followed by column chromatography on silica gel (hexanes–EtOAc, 9:1→4:1) to yield **15** (246 mg, 70%): oil, $[\alpha]_D$=−6.7 (*c* 1.9; $CHCl_3$); IR ν_{max} (cm^{-1}): 2985, 2932, 2854, 1721 (lactone C=O), 1459, 1382, 1263, 1215, 1159, 1072, 853, 811; ^1H NMR (400 MHz) δ 6.77 (1H, dt, *J*=10, 4.5 Hz), 6.00 (1H, dt, *J*=10, 2 Hz), 4.35 (1H, dd, *J*=7.1, 6.2 Hz), 4.02 (1H, dd, *J*=8.8, 7.1 Hz), 3.84 (1H, dd, *J*=8.8, 6.2 Hz), 2.64 (1H, ddd, *J*=19, 4.4, 2 Hz), 2.47 (1H, ddd, *J*=19, 4.1, 2 Hz), 1.70–1.60 (2H, m), 1.43 (3H, s), 1.33 (3H, s), 1.35–1.20 (18H, br m), 0.87 (3H, t, *J*=7 Hz); ^{13}C NMR (100 MHz) δ 163.0, 110.1, 83.8 (C), 143.6, 120.6, 78.0 (CH), 64.7, 34.5, 31.9, 30.0, 29.7, 29.6 (×2), 29.5, 29.4, 27.9, 23.5, 22.7 (CH_2), 26.1, 24.6, 14.2 (CH_3). EIMS, *m*/*z* (% rel. int.) 352.2605 $[M]^+$ (4), 337 (42), 251 (84), 183 (62), 101 (100). Calcd for $C_{21}H_{36}O_4$, *M*=352.2613. Anal. calcd for $C_{21}H_{36}O_4$: C, 71.55; H, 10.29. Found, C, 71.51; H, 10.30.

3.11. (6*R*,4′*S*)-6-(2,2-Dimethyl-1,3-dioxolan-4-yl)-6-undecyltetrahydropyran-2-one, 16

Paladium catalyst (5% Pd/C, 50 mg) was suspended in EtOH (5 mL) and stirred under an H_2 atmosphere for 5 min. A solution of lactone **15** (246 mmol, 0.7 mmol) in solvent (5 mL) was then added via syringe. The solution was stirred for 24 h at ambient pressure and temperature, then filtered through Celite. Solvent removal in vacuo and column chromatography on silica gel (hexanes–EtOAc, 4:1) furnished **16** (223 mg, 90%): oil, $[\alpha]_D$=+6.9 (*c* 4.3; $CHCl_3$); IR ν_{max} (cm^{-1}): 2965, 2925, 2855, 1737 (lactone C=O), 1459, 1371, 1329, 1259, 1158, 1068, 927, 856, 800; ^1H NMR (400 MHz) δ 4.23 (1H, dd, *J*=7.1, 6.5 Hz), 4.00 (1H, dd, *J*=8.8, 7.1 Hz), 3.79 (1H, dd, *J*=8.8, 6.5 Hz), 2.42 (2H, m), 2.00–1.70 (4H, m), 1.60–1.50 (2H, m), 1.43 (3H, s), 1.32 (3H, s), 1.35–1.20 (18H, br m), 0.86 (3H, t, *J*=7 Hz); ^{13}C NMR (100 MHz) δ 171.6, 109.7, 85.3 (C), 79.3 (CH), 64.8, 36.5, 31.9, 30.1, 30.0, 29.7, 29.6 (×2), 29.5, 29.3, 25.8, 22.9, 22.7, 17.0 (CH_2), 26.1, 24.6, 14.1 (CH_3); EIMS, *m*/*z* (% rel. int.) 354.2764 $[M^+]$ (3), 339 $[M^+-Me]$ (36), 253 (100), 225 (40), 101 (58). Calcd for $C_{21}H_{38}O_4$, *M*=354.2770. Anal. calcd for $C_{21}H_{38}O_4$: C, 71.14; H, 10.80. Found, C, 71.22; H, 10.66.

3.12. (6*R*,1′*S*)-6-(1,2-Dihydroxyethyl)-6-undecyltetrahydropyran-2-one, 17

Lactone **16** (177 mg, 0.5 mmol) was dissolved in 75% aqueous AcOH (2 mL) and stirred at 40°C for 48 h. The solvent was then azeotropically removed in vacuo (aided by addition of EtOAc), the residue dissolved in Et_2O (10 mL) and stirred in the presence of solid K_2CO_3 (ca. 100 mg) to remove traces of AcOH. Column chromatography of the oily residue on silica gel (hexanes–EtOAc, 1:1) afforded **17** (137 mg, 87%): oil, $[\alpha]_D$=+13.5 (*c* 1; $CHCl_3$); IR ν_{max} (cm^{-1}): 3430 (br, OH), 2950, 2921, 2854, 1722, 1459, 1337, 1254, 1036, 925; ^1H NMR (400 MHz) δ 3.86 (1H, dd, *J*=8.4, 3.2 Hz), 3.72 (1H, dd, *J*=11.2, 3.2 Hz), 3.55 (1H, dd, *J*=11.2, 8.4 Hz), 2.46 (2H, m), 2.05–1.90 (2H, br m), 1.85–1.60 (6H, br m), 1.35–1.20 (18H, br m), 0.88 (3H, t, *J*=6.8 Hz); ^{13}C NMR (100 MHz) δ 172.2, 87.2 (C), 75.5 (CH), 62.1, 37.1, 31.9, 30.1, 29.9, 29.7, 29.6 (x 2), 29.5, 29.4, 26.0, 23.1, 22.7, 16.9 (CH_2), 14.2 (CH_3); EIMS, *m*/*z* (% rel. int.) 253.2190 $[M^+-CHOHCH_2OH]$ (100), 225 (455). Calcd for $C_{18}H_{34}O_4-CHOHCH_2OH$, *M*=253.2167. Anal. calcd for $C_{18}H_{34}O_4$: C, 68.75; H, 10.90. Found, C, 68.92; H, 10.77.

3.13. (+)-Tanikolide, (+)-2

Diol **17** (125 mg, 0.4 mmol) was dissolved under Ar in dry CH_2Cl_2 (3 mL) and treated with lead tetraacetate (163 mg, 0.44 mmol). The reaction mixture was then stirred for 1–2 h at room temperature (TLC monitoring), then diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After solvent removal in vacuo, the residue was dissolved in Et_2O (10 mL) and treated with solid K_2CO_3 (ca. 100 mg) to remove traces of AcOH, followed by stirring at room temperature for 15 min. Filtration and solvent removal in vacuo afforded a crude aldehyde which was dissolved under Ar in dry THF (5 mL) and cooled to −78°C. A 1M solution of L-selectride in THF (0.6 mL, 0.6 mmol) was added via syringe. The reaction mixture was then stirred at −78°C for 90 min. Work-up (CH_2Cl_2) and column chromatography on silica gel (hexanes–EtOAc, 1:1) provided (+)-**2** (62 mg, 55% overall from **17**): oil, $[\alpha]_D$=+2.9 (*c* 0.8; $CHCl_3$); for natural (+)-tanikolide, lit.[1b] $[\alpha]_D$=+2.3 (*c* 0.65; $CHCl_3$); for synthetic (+)-tanikolide, lit.[4a] $[\alpha]_D$=+2.9 (*c* 0.65;

$CHCl_3$) and lit.[4c] $[\alpha]_D$=+3.0 (*c* 0.8; $CHCl_3$). IR ν_{max} (cm^{-1}): 3440 (br, OH), 2950, 2924, 2846, 1724, 1460, 1336, 1250, 1051, 927, 722; ^1H NMR (400 MHz) δ 3.65 (1H, br d, *J*=12 Hz), 3.55 (1H, br d, *J*=12 Hz), 2.48 (2H, m), 2.10 (1H, br s, OH), 2.00–1.60 (6H, br m), 1.35–1.20 (18H, br m), 0.87 (3H, t, *J*=6.8 Hz); ^{13}C NMR (100 MHz) δ 171.6, 86.5 (C), 67.6, 36.7, 31.9, 30.0, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 26.7, 23.5, 22.7, 16.7 (CH_2), 14.1 (CH_3); EIMS, *m/z* (% rel. int.) 285.2424 $[M+H]^+$ (1), 253 (100), 225 (45), 129 (20). Calcd for $C_{17}H_{33}O_3$, *M*=285.2429.

3.14. (*R*)-1-(2,2-Dimethyl-1,3-dioxolan-4-yl)decan-1-one, 18

Freshly prepared isopropylidene D-glyceraldehyde[26] (650 mg, 5 mmol) was dissolved at 0°C under Ar in dry Et_2O (10 mL) and treated dropwise with a 1 M solution of *n*-nonylmagnesium bromide in Et_2O (10 mL, 10 mmol). The cooling bath was then removed and the mixture was stirred for 1 h at room temperature. Work-up (Et_2O) and column chromatography on silica gel (hexanes–EtOAc, 9:1) provided a mixture of two diastereoisomeric *n*-nonylcarbinols, which was used directly in the next step.

Pyridinium chlorochromate (1.3 g, ca. 6 mmol) and NaOAc (246 mg, 3 mmol) were added under Ar to a solution of the alcohol mixture in dry CH_2Cl_2 (4 mL). The mixture was stirred overnight at room temperature, then diluted with Et_2O (10 mL) and filtered through Celite. Solvent removal in vacuo and column chromatography of the residue on silica gel (hexanes–EtOAc, 19:1→9:1) furnished ketone **18** (769 mg, 60% overall yield for the two steps): oil, $[\alpha]_D$=+4 (*c* 2.2; $CHCl_3$), IR ν_{max} (cm^{-1}): 2980, 2942, 2860, 1721 (ketone C=O), 1460, 1374, 1259, 1211, 1150, 1075, 818; ^1H NMR (400 MHz) δ 4.40 (1H, dd, *J*=7.7, 5.7 Hz), 4.17 (1H, dd, *J*=8.5, 8 Hz), 3.94 (1H, dd, *J*=8.5, 5.7 Hz), 2.56 (2H, td, *J*=7.5, 1.5 Hz), 1.55 (2H, m), 1.45 (3H, s), 1.36 (3H, s), 1.30–1.20 (12H, br m), 0.85 (3H, t, *J*=7 Hz); ^{13}C NMR (100 MHz) δ 211.0, 110.8 (C), 80.3 (CH), 66.5, 38.6, 31.8, 29.4, 29.3, 29.2, 29.1, 22.9, 22.6 (CH_2), 26.0, 25.0, 14.1 (CH_3); EIMS, *m/z* (% rel. int.) 241.1804 $[M^+-Me]$ (11), 173 (34), 155 (32), 129 (40), 101 (100), 73 (56). Calcd for $C_{15}H_{28}O_3$–Me, *M*=241.1803. Anal. calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found, C, 70.30; H, 11.20.

3.15. (4*S*,4′*R*)-4-(2,2-Dimethyl-1,3-dioxolan-yl)tridec-1-en-4-ol, *ent*-7 (+*R*,*R*-epimer)

Ketone **18** (769 mg, 3 mmol) was dissolved in 1:1 THF/H_2O (30 mL) and treated sequentially with allyl bromide (780 μL, 9 mmol), tetrabutylammonium bromide (2.3 g, 3 mmol) and indium powder (690 mg, 6 mmol). The mixture was stirred for 18 h at room temperature. Work-up (EtOAc) and column chromatography on silica gel (hexanes–EtOAc, 9:1) afforded *ent*-**7** as a 4.5:1 mixture with its epimer (653 mg, 73%). The NMR signals of the major component of the mixture were coincident with those of compound **7**.

3.16. (4*R*,1′*S*)-2,2-Dimethyl-4-[1-(2-methylallyloxy)-1-nonylbut-3-enyl]-1,3-dioxolane, *ent*-8 (+*R*,*R*-epimer)

It was obtained from *ent*-**7** as a 4.5:1 diastereoisomeric mixture under the same reaction conditions describe above for compound **8**. The NMR signals of the major component of the mixture were coincident with those of compound **8**.

3.17. (2*S*,4′*R*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)-5-methyl-2-nonyl-3,6-dihydro-2*H*-pyran, *ent*-9

Obtained through ring-closing metathesis (RCM) of compound *ent*-**8** (+epimer) under the same reaction conditions describe above for **9**. Separation of stereoisomers was feasible by means of column chromatography on silica gel (hexanes–EtOAc, 19:1, then 9:1). This afforded *ent*-**9** as an oil, $[\alpha]_D$=−30.6 (*c* 4.1; $CHCl_3$), with spectral data identical to those of **9**.

3.18. (6*S*,4′*R*)-6-(2,2-Dimethyl-1,3-dioxolan-4-yl)-3-methyl-6-nonyl-5,6-dihydropyran-2-one, *ent*-10

Obtained through allylic oxidation of *ent*-**9** under the same reaction conditions describe above for **10**: oil, $[\alpha]_D$=+10 (*c* 10; $CHCl_3$), with spectral data identical to those of **10**.

3.19. (−)-Malyngolide, (−)-1

Obtained through sequential periodic acid oxidation and L-selectride reduction of *ent*-**10** under the same reaction conditions describe above for (+)-**1**: oil, $[\alpha]_D$=−12.2 (*c* 1; $CHCl_3$), for natural (−)-malyngolide, lit.[1a] $[\alpha]_D$=−13 (*c* 2; $CHCl_3$); for synthetic (−)-malyngolide, lit.[2b] $[\alpha]_D$=−12.5 (*c* 0.8; $CHCl_3$) and lit.[3b] $[\alpha]_D$=−12.4 (*c* 2.5; $CHCl_3$). Spectral data identical to those of (+)-**1** (see above).

Acknowledgements

The authors acknowledge financial support by the Ministry of Science and Technology through DGI and FEDER funds (Project BQU2002-00468), by Fundació Caixa Castellò-Univ. Jaume I (project PI-1B2002-06) and by the Conselleria de Cultura de la Generalitat Valenciana (project GV-99-77-1-02). E. C. and S. D.-O. thank the latter institution for predoctoral fellowships. The authors further thank the S.C.S.I.E. at the University of Valencia for mass spectral measurements.

References

1. (a) Cardllina, II., J. H.; Moore, R. E.; Arnold, E. V.; Clardy, J. *J. Org. Chem.* **1979**, *44*, 4039–4042. (b) Singh, I. P.; Milligan, K. E.; Gerwick, W. H. *J. Nat. Prod.* **1999**, *62*, 1333–1335. (c) Luesch, H.; Yoshida, W. Y.; Moore, R. E.; Paul, V. J.; Mooberry, S. L. *J. Nat. Prod.* **2000**, *63*, 611–615. (d) Luesch, H.; Yoshida, W. Y.; Moore, R. E.; Paul, V. J. *J. Nat. Prod.* **2000**, *63*, 1437–1439. (e) Milligan, K. E.; Marquez, B. L.; Williamson, R. T.; Gerwick, W. H. *J. Nat. Prod.* **2000**, *63*, 1440–1443, see also references to previous work cited in these papers.
2. For two recent syntheses of (−)-**1** with a comprehensive account of previous work: (a) Winter, E.; Hoppe, D. *Tetrahedron* **1998**, *54*, 10329–10338. (b) Maezaki, N.;

Matsumori, Y.; Shogaki, T.; Soejima, M.; Ohishi, H.; Tanaka, T.; Iwata, C. *Tetrahedron* **1998**, *54*, 13087–13104. (c) For a synthesis of (+)-**1**: Kogure, T.; Eliel, E. L. *J. Org. Chem.* **1984**, *49*, 576–579.

3. For more recent syntheses of (−)-**1**, see: (a) Kanada, R. M.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2000**, *41*, 3631–3635. (b) Wan, Z. H.; Nelson, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 10470–10471. (c) Trost, B. M.; Tang, W. P.; Schulte, J. L. *Org. Lett.* **2000**, 4013–4015. (d) Date, M.; Tamai, Y.; Hattori, T.; Takayama, H.; Kamikubo, Y.; Miyano, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 645–653. (e) Suzuki, T.; Ohmori, K.; Suzuki, K. *Org. Lett.* **2001**, 1741–1744. (f) Ghosh, A. K.; Shirai, M. *Tetrahedron Lett.* **2001**, *42*, 6231–6233.
4. For syntheses of (+)-**2**, see: (a) Kanada, R. M.; Taniguchi, T.; Ogasawara, K. *Synlett* **2000**, 1019–1021. (b) Tanaka, H.; Kozuki, Y.; Ogasawara, K. *Tetrahedron Lett.* **2002**, *43*, 4175–4178. For syntheses of (±)-**2**, see: (c) Zhang, R. Z.; Wang, Z. Q.; Wei, F. P.; Huang, Y. R. *Synth. Commun.* **2002**, *32*, 2187–2194. (d) Krauss, J. *Nat. Prod. Lett.* **2001**, *15*, 393–399. A synthesis of the unnatural enantiomer of tanikolide, (−)-**2**, is described in the supplementary information of Ref. 3b.
5. Carda, M.; Castillo, E.; Rodríguez, S.; Marco, J. A. *Tetrahedron Lett.* **2000**, *41*, 5511–5513.
6. Carda, M.; Castillo, E.; Rodríguez, S.; Uriel, S.; Marco, J. A. *Synlett* **1999**, 1639–1641.
7. Marco, J. A.; Carda, M.; González, F.; Rodríguez, S.; Castillo, E.; Murga, J. *J. Org. Chem.* **1998**, *63*, 698–707.
8. (a) Marco, J. A.; Carda, M.; González, F.; Rodríguez, S.; Murga, J. *Liebigs Ann. Chem.* **1996**, 1801–1810. (b) Carda, M.; Rodríguez, S.; Murga, J.; Falomir, E.; Marco, J. A.; Röper, H. *Synth. Commun.* **1999**, *29*, 2601–2610.
9. Carda, M.; Castillo, E.; Rodríguez, S.; González, F.; Marco, J. A. *Tetrahedron: Asymmetry* **2001**, *12*, 1417–1429, and references cited therein.
10. The stereostructure of tosylate **5** has been further secured with the aid of an X-ray diffraction analysis. Crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Center as supplementary material with reference CCDC-195658. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
11. (a) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135–631. (b) In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley/VCH: Weinheim, 2002.
12. (a) Fürstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012–3043. (b) Trnka, T.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29.
13. This oxidation also produced small amounts (10–15%) of the oxygenation product (a cyclic ketone) at the alternative allylic position.
14. Attempts at preparing lactone **10** in a more direct way by RCM of the methacrylate of alcohol **7** with the standard ruthenium catalyst were unsuccessful (see Ref. 6). Very recently, a lactone with a conjugated trisubstituted C═C bond has been prepared by means of RCM with the aid of a second-generation ruthenium catalyst: (a) Cossy, J.; Bauer, D.; Bellosta, V. *Synlett* **2002**, 715–718. However, the unsatisfactory yield in the preparation of the aforementioned methacrylate led us to disregard this alternative. See, however: (b) Rodríguez, S.; Castillo, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2002**, *58*, 1185–1192.
15. (a) Wu, W.-L.; Wu, Y.-L. *J. Org. Chem.* **1993**, *58*, 3586–3588. (b) Xie, M.; Berges, D. A.; Robins, M. J. *J. Org. Chem.* **1996**, *61*, 5178–5179.
16. When the reduction of aldehyde **11** with $NaBH_4$ was conducted for 18 h at room temperature, (+)-malyngolide was formed in 15% yield, together with 60% of dehydromalyngolide. Attempts at achieving a complete saturation of the conjugated C═C bond by increasing the reaction time and/or the amount of $NaBH_4$ were unsuccessful, however, and led only to reduction of the lactone carbonyl group.
17. Hagiwara, H.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1157–1159.
18. The reduction of the aldehyde function in the intermediate products resulting from oxidative cleavage of **10**, ent-**10** and **17** has to be performed at low temperature, otherwise reductive opening of the lactone ring becomes competitive.
19. Part of the data presented here have been taken from the PhD Thesis of E. Castillo (Univ. Jaume I, Castellón, Spain, 2000).
20. Products of Michael addition to the conjugated double bond were detected during attempts at hydrolytic cleavage of the acetonide moiety in **15**. In view of this, acetal hydrolysis was performed in saturated lactone **16** under carefully controlled conditions, as this compound was prone to translactonization and/or hydrolytic ring opening in acidic media.
21. Stronger Lewis acids caused destruction of the acetonide moiety (see Refs. 7 and 9).
22. Li, C.-J.; Chan, T. H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997; Chapter 4.
23. For recent contributions of our group, see: (a) Carda, M.; González, F.; Castillo, E.; Rodríguez, S.; Marco, J. A.; Eur, *J. Org. Chem.* **2002**, 2649–2655. (b) Carda, M.; Rodríguez, S.; Segovia, B.; Marco, J. A. *J. Org. Chem.* **2002**, *67*, 6560–6563. (c) Murga, J.; Falomir, E.; García-Fortanet, J.; Carda, M.; Marco, J. A. *Org. Lett.* **2002**, 3447–3449. (d) Falomir, E.; Murga, J.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2003**, *44*, 539–541.
24. Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. *Org. Lett.* **1999**, *1*, 447–450.
25. Banfi, L.; Bernardi, A.; Colombo, C.; Gennari, C.; Scolastico, C. *J. Org. Chem.* **1984**, *49*, 3784–3790.
26. Dumont, A.; Pfander, H. *Helv. Chim. Acta* **1983**, *66*, 814–823.