FULL PAPER

Biocatalytic Approach for the Total Synthesis of (–)-Malyngolide and Its C(5)-Epimer

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An enzymatic approach has been successfully utilized in the total synthesis of (–)-malyngolide and its C(5)-epimer. The required configuration was established by an enzymatic kinetic resolution and *Sharpless* asymmetric dihydroxylation.

Keywords: Malyngolide, Antibiotic activity, Enzymatic resolution, Asymmetric dihydroxylation, δ-Lactone.

Introduction

The six-membered *δ*-lactone-containing natural products, *e.g.*, (–)-malyngolide (**1a**) and its diastereoisomers **1b** – **1d** and (*R*)-tanikolide (*Fig.*), were isolated as marine metabolites from the lipid extract of marine cyanobacterium, *Lyngbya majuscula*, which was collected from the coast of Hawai [1]. Marine cyanobacteria are considered as a rich source of secondary metabolites, which are evaluated as potent anticancer agents. The cytotoxicity of these marine metabolites against tumor cell lines is under clinical trials. In addition, some of them have been used as templates for the development of new anticancer drugs [2]. Furthermore, many chemically diverse *δ*-lactone-containing compounds are known to exhibit diverse biological activities such as cytotoxicity, anti-inflammatory, and antibacterial behavior. Among them, (–)-malyngolide (**1a**) shows potential antibiotic activity against *Staphylococcus*, *Pseudomonas*, and *Mycobacterium smegmatis*, but no activity against *Escherichia coli* and *Pseudomonas aeruginosa. Gerwick* and co-workers [3] recently isolated a dimer of **1a**, which also shows antimalarial activity against *Plasmodium falciparum.* (–)-Malyngolide (**1a**) has drawn our interest toward its synthesis, because of its superior biological activity as compared to its other diastereoisomers (*Fig.*). Consequently, *Mukaiyama* and co-workers [4] reported the first total synthesis of (–)-malyngolide. Later on, a large number of syntheses of **1a** have been reported by various groups employing chiron approach, asymmetric induction, and RCM strategy [5], Subsequently, *Trost et al.* [6] also reported its asymmetric version by enantioselective ring opening of an epoxide using a chiral Pd(0) complex.

Results and Discussion

Following our interest in the total synthesis of natural products [7], we herein report an efficient synthetic route for the total synthesis of (–)-malyngolide (**1a**) and its epimer **1b**. In our retrosynthetic analysis, we proposed

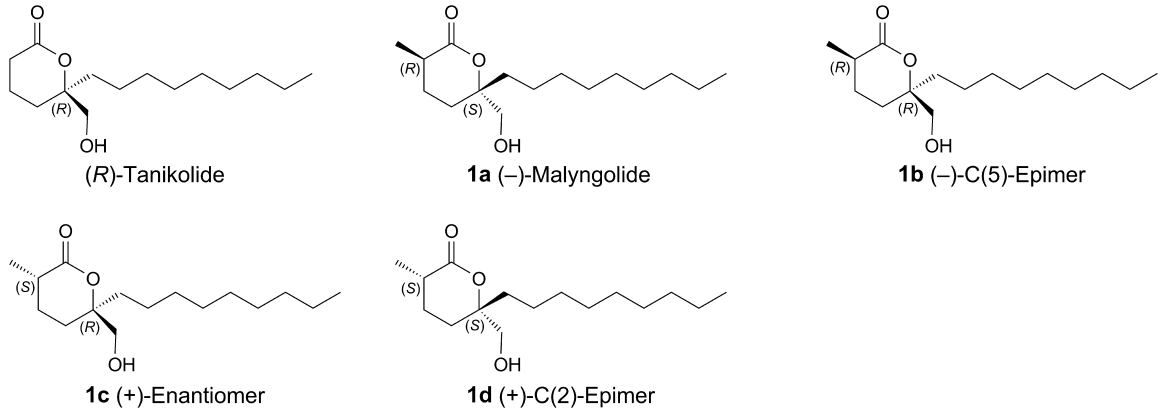

Figure. Examples of *δ*-lactone-containing natural products.

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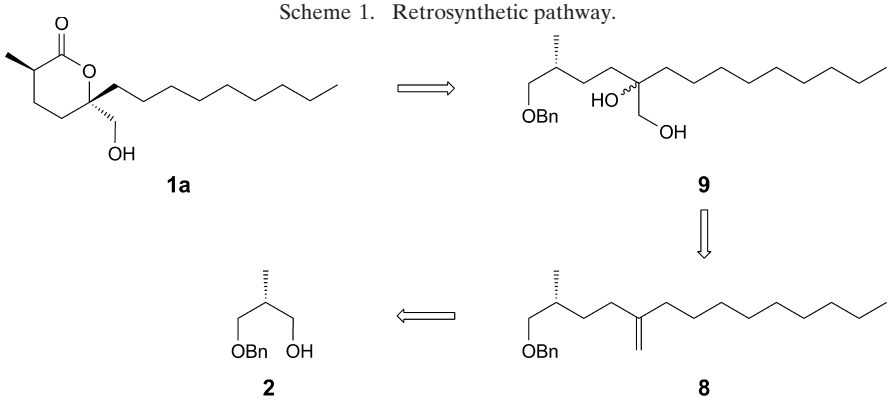
that the target molecule can be synthesized from the intermediate **9**, which in turn could be prepared by the dihydroxylation of olefin **8**. The intermediate **8** might be synthesized from a chiral alcohol **2**, which in turn could be prepared by enzymatic kinetic resolution (*Scheme 1*).

Our synthetic sequence began with a known precursor, *i.e.*, mono-benzyl alcohol **2**, which was synthesized by the kinetic resolution of racemic 2-methylpropane-1,3-diol using *Pseudomonas fluorescens* as reported by *Santaniello* and co-workers [8]. The required alcohol **2** was obtained with 90% ee. Oxidation of **2** under *Swern* conditions [9] followed by *Horner–Wadsworth–Emmons* reaction with triethyl phosphonoacetate afforded the α,β-unsaturated ester **3** with a ratio of (*E*)/(*Z*) 98:2 in 80% yield [10]. Hydrogenation of the C=C bond in compound **3** using $NiBH_4$ (generated *in situ* from $NiCl_2 \cdot 6\ H_2O$ and $NaBH_4$ in MeOH) afforded the saturated ester **4** in 96% yield [11]. Treatment of the saturated ester **4** with $LiAlH_4$ gave the mono-benzyl alcohol **5** in 90% yield [12]. Oxidation of the later under *Swern* conditions afforded the aldehyde, which was further treated with nonylmagnesium bromide (2.0 equiv., 1M in Et_2O) to give the alcohol **6** as a mixture of two diastereoisomers in 66% yield [13]. Subsequent oxidation of **6** under *Swern* conditions gave the ketone **7** in 77% yield and *Wittig* olefination of **7** with (methyl)triphenylphosphonium bromide using LiHMDS furnished the olefin **8** in 70% yield (*Scheme 2*).

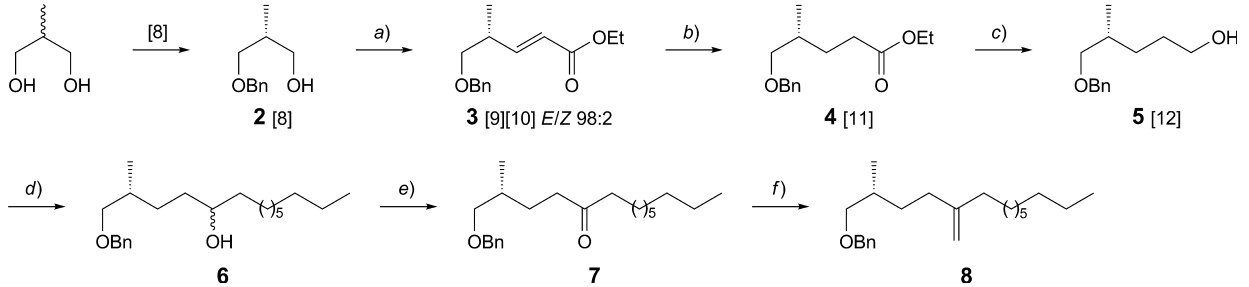
Asymmetric dihydroxylation of **8** using *AD-mix-α* (prepared *in situ* from chiral ligand $(DHQ)_2PHAL$, OsO_4, $K_3[Fe(CN)_6]$, and methanesulfonamide) gave a mixture of two diasteoisomeric diols **9a**/**9b** in a ratio of 6:4, which was confirmed by the ^{1}H-NMR spectrum [14]. Protection of diols **9a**/**9b** with TBDPSCl gave a mixture of monosilyl ethers **10a**/**10b**. Debenzylation of the latter using Pd/C (10% *w*/*w*) under H_2 atmosphere afforded the diols **11a**/**11b**. Subsequent oxidative lactonization of diols **11a**/**11b** using TEMPO/BAIB led to a mixture of δ-lactones **12a**/**12b** in 60% yield. Eventual deprotection of TBDPS group from the δ-lactone gave the target molecules, (–)-malyngolide (**1a**) in 55% and its C(5)-epimer (**1b**) in 33% yield, which were successfully separated by flash chromatography (*Scheme 3*). The spectroscopic data for both diastereoisomers were identical with the data reported in [5e][15].

In summary, we have successfully achieved the required configuration of the methyl center with good enantiomeric excess by an enzymatic kinetic resolution approach, which is one of the imperative criteria for the biological activity of (–)-malyngolide (**1a**), which differentiates it from other diastereoisomers. In earlier reports,

Scheme 1. Retrosynthetic pathway.

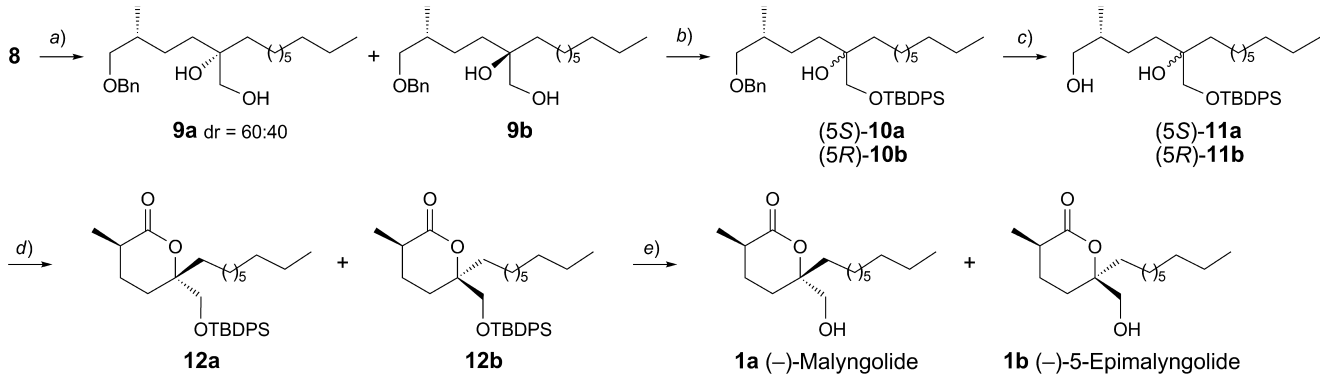


Scheme 2. Synthesis of olefin **8**.



a) 1) $(COCl)_2$ (2.0 equiv.), DMSO (4.0 equiv.), −78 °C, 2 h, (2*R*)-3-(benzyloxy)-2-methylpropanal; 2) $(EtO)_2P(O)CH_2COOEt$ (1.2 equiv.), EtN(^{i}Pr)$_2$ (1.5 equiv.), LiBr (1.6 equiv.), MeCN, 20 °C to r.t., 12 h; 80%. b) $NaBH_4$ (2.0 equiv.), $NiCl_2 \cdot 6\ H_2O$, (0.2 equiv.) MeOH, 0 °C to r.t., 1 h; 96%. c) $LiAlH_4$, 0 °C, 15 min; 90%. d) 1) $(COCl)_2$ (2.0 equiv.), DMSO (4.0 equiv.), −78 °C, 2 h; 2) nonylmagnesium bromide (1.0M in Et_2O, 45 ml, 2.0 equiv.) at 0 °C to r.t., 0.3 h; 66%. e) DMSO (4.0 equiv.), $(COCl)_2$ (2.0 equiv.), −78 °C, 2 h; 77%. f) $MePh_3PBr$ (3.0 equiv.), LiHMDS (1.0M in THF, 3.0 equiv.), 0 °C to r.t., 5 h; 70%.

Scheme 3. Synthesis of (–)-malyngolide and its (–)-C(5)-epimer.



a) $(DHQ)_2PHAL$ (5 mol%), OsO_4 (0.5 mol%), $K_3[Fe(CN)_6]$ (3.0 equiv.), K_2CO_3 (3.0 equiv.), $MeSO_2NH_2$ (1.0 equiv.), $^tBuOH/H_2O$ (1:1), 0 °C, 12 h; 80% (**9a**/**9b** 60:40 dr, inseparable). b) TBDPSCl, imidazole, CH_2Cl_2; 82%. c) Pd/C (10% *w*/*w*), AcOEt, H_2, r.t., 5 h; 84%. d) TEMPO (0.2 equiv.), BAIB (2.5 equiv.), CH_2Cl_2/H_2O (2:1), 1 h; 80%. e) TBAF, dry THF, r.t., 0.3 h.

the required configuration of the Me center was achieved by chiral induction approach [5]. For the construction of the chiral quaternary center, *Sharpless* dihydroxylation approach has been utilized to accomplish the total synthesis of (–)-malyngolide and its C(5)-epimer.

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Experimental Part

General

Column chromatography (CC): silica gel (SiO_2; *E. Merck*, 100 – 200 mesh). Optical rotations: *Anton Paar MCP 200* digital polarimeter using a 1 ml cell with a 1 dm path length. IR Spectra: *Thermo Nicolet Nexus 670* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H-NMR Spectra: *Bruker-300* and *Varian Unity 500* spectrometer in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. ^{13}C-NMR Spectra: *Bruker-300* and *Varian Unity 500* spectrometer at 75 or 125 MHz in $CDCl_3$; δ in ppm rel. to $CDCl_3$ as internal standard (δ (C) 77 ppm). ESI-MS: *Finnigan MAT1020B* or *micromass VG 70-70H* spectrometer operating at 70 eV using a direct inlet system; in *m*/*z*.

(2*R*)-3-(Benzyloxy)-2-methylpropan-1-ol (**2**) [8]. Viscous liquid. $[\alpha]_D^{25}$ = –2.6 (*c* = 2.2, EtOH). IR (neat): 3398, 2959, 2871, 1454, 1364, 1096, 1038, 739, 698. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.88 (*d*, *J* = 6.8, 3 H): 2.03 – 2.15 (*m*, 1 H); 3.43 (*t*, *J* = 8.2, 1 H); 3.52 – 3.58 (*m*, 1 H); 3.59 – 3.66 (*m*, 2 H); 4.52 (*s*, 2 H); 7.26 – 7.40 (*m*, 5 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 13.4; 35.5; 67.6; 73.2; 75.2; 127.5; 127.6; 128.3; 137.9. ESI-MS: 203 ($[M + Na]^+$). HR-ESI-MS: 203.10468 ($[M + Na]^+$, $C_{11}H_{16}NaO_2^+$; calc. 203.10425).

Ethyl (4*R*,2*E*)-5-(Benzyloxy)-4-methylpent-2-enoate (**3**). To a stirred soln. of oxalyl chloride (7.8 ml, 111.1 mmol) in anh. CH_2Cl_2 (150 ml) was added dry DMSO (15.7 ml, 222.2 mmol) at –78 °C. After stirring at –78 °C for 20 min, a soln. of **2** (10 g, 56.1 mmol) in anh. CH_2Cl_2 (70 ml) was added dropwise. After stirring for another 20 min at the same temperature, Et_3N (56 ml, 392.0 mmol) was added, and the mixture was stirred at –30 °C for an additional 30 min. The mixture was poured into H_2O (200 ml) and extracted thrice with Et_2O (400 ml). The combined org. layers were washed with brine (250 ml), dried ($MgSO_4$), and concentrated *in vacuo* to afford (2*R*)-3-(benzyloxy)-2-methylpropanal [9] as pale-yellow oil. A mixture of triethyl phosphonoacetate (13.8 g, 62.0 mmol), MeCN (150 ml), and LiBr (7.1 g, 82.6 mmol) was stirred at 20 °C for 15 min, and then EtN $(^iPr)_2$ (14.2 ml, 77.5 mmol) was added portionwise. After stirring for 15 min, a soln. of (2*R*)-3-(benzyloxy)-2-methylpropanal (9.2 g, 51.6 mmol) in MeCN (60 ml) was added, and the resulting mixture was stirred at 20 °C for 12 h. After completion, as indicated by TLC, the mixture was then poured into 1M aq. HCl soln. (300 ml) under vigorous stirring, and the aq. layer was extracted with AcOEt. The combined org. layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash chromatography over SiO_2 (100 – 200 mesh) afforded the product **3** [10] as colorless liquid (11.5 g, 80% yield). R_f (10% AcOEt/petroleum ether (PE)) 0.35. $[\alpha]_D^{25}$ = +7.0 (*c* = 0.2, $CHCl_3$). IR (neat): 2978; 2867; 1718; 1653; 1454; 1270; 1185; 1097; 1035; 739; 698. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.90 (*d*, *J* = 6.8, 3 H); 1.29 (*t*, *J* = 7.1, 3 H); 2.61 – 2.71 (*m*, 1 H); 3.35 – 3.45 (*m*, 2 H); 4.19 (*q*, *J* = 7.1, 2 H); 4.52 (*s*, 2 H); 5.83 – 5.89 (*dd*, *J* = 15.7, 1.3, 1 H); 6.92 – 6.93 (*dd*, *J* = 15.7, 8.8, 1 H); 7.26 – 7.38 (*m*, 5 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.1; 15.9; 36.6; 60.1; 72.9; 73.7; 120.8; 127.4; 127.4; 128.2; 138.0; 151.0; 166.5. ESI-MS: 271 ($[M + Na]^+$). HR-ESI-MS: 271.13016 ($[M + Na]^+$, $C_{15}H_{20}NaO_3^+$; calc. 271.13047).

Ethyl (4*R*)-5-(Benzyloxy)-4-methylpentanoate (**4**). To an ice-cooled soln. of **3** (11.5 g, 46.3 mmol) and $NiCl_2 \cdot 6\ H_2O$ (2.1 g, 9.2 mmol) in MeOH (200 ml) was added

$NaBH_4$ (3.4 g, 92.7 mmol) in small portions [11]. The reaction temperature was kept at 0 °C. After complete addition, the mixture was stirred for 1 h at room temperature. The resulting black precipitate was filtered and washed with MeOH (2 × 75 ml). The solvent was removed under reduced pressure, and the residual mixture was diluted with H_2O (100 ml) and extracted with AcOEt (2 × 100 ml). The combined org. layers were washed with H_2O and brine, and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash chromatography over SiO_2 (100 – 200 mesh) afforded **4** as colorless liquid (10.5 g, 96% yield). R_f (10% AcOEt/PE) 0.37. $[\alpha]_D^{25}$ = +2.7 (*c* = 0.39, $CHCl_3$). IR (neat): 2959, 2931, 2866, 1788, 1733, 1454, 1372, 1179, 1098, 737, 698. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.94 (*d*, *J* = 6.7, 3 H); 1.25 (*t*, *J* = 7.0, 3 H); 1.43 – 1.56 (*m*, 1 H); 1.73 – 1.87 (*m*, 2 H); 2.25 – 2.42 (*m*, 2 H); 3.25 – 3.36 (*m*, 2 H); 4.11 (*q*, *J* = 7.1, 2 H); 4.49 (*s*, 2 H); 7.26 – 7.38 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.1; 16.7; 28.7; 31.9; 32.9; 60.1; 72.8; 75.2; 127.3; 127.3; 128.2; 138.4; 173.7. ESI-MS: 273 ([*M* + Na]$^+$). HR-ESI-MS: 273.14553 ([*M* + Na]$^+$, $C_{15}H_{22}NaO_3^+$; calc. 273.14612).

(4*R*)-5-(Benzyloxy)-4-methylpentan-1-ol (**5**). To a stirred suspension of $LiAlH_4$ (2.2 g, 60.4 mmol) in dry THF (120 ml) at 0 °C was added dropwise a soln. of **4** (10.0 g, 40.3 mmol) in dry THF (80 ml). The resulting mixture was allowed to stir for 15 min at the same temperature, and then reaction was quenched with a sat. soln. of Na_2SO_4. The resulting precipitate was filtered and washed with AcOEt (2 × 100 ml). The combined org. extracts were dried (Na_2SO_4), concentrated *in vacuo*, and purified by flash chromatography over SiO_2 (100 – 200 mesh) to afford **5** [12] as colorless liquid (8.0 g, 90% yield). R_f (30% AcOEt/PE) 0.35. $[\alpha]_D^{25}$ = +4.0 (*c* = 1, CH_2Cl_2). IR (neat): 3382, 2932, 2864, 1731, 1454, 1364, 1098, 1071, 738, 698. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.94 (*d*, *J* = 6.7, 3 H); 1.09 – 1.33 (*m*, 1 H); 1.42 – 1.71 (*m*, 4 H); 1.72 – 1.92 (*m*, 1 H); 3.18 – 3.41 (*m*, 2 H); 3.62 (*t*, *J* = 6.0, 2 H); 4.50 (*s*, 2 H); 7.27 – 7.44 (*m*, 5 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 16.9; 29.5; 29.9; 33.1; 62.8; 72.9; 75.7; 127.3; 127.4; 128.2; 138.4. ESI-MS: 231 ([*M* + Na]$^+$). HR-ESI-MS: 209.15293 ([*M* + H]$^+$, $C_{13}H_{21}O_2^+$; calc. 209.15361).

(2*R*)-1-(Benzyloxy)-2-methyltetradecan-5-ol (**6**). To a stirred soln. of oxalyl chloride (4.0 ml, 57.6 mmol) in anh. CH_2Cl_2 (150 ml) was added DMSO (8.1 ml, 115.3 mmol) at −78 °C. After 20 min, a soln. of **5** (6.0 g, 28.8 mmol) in CH_2Cl_2 (50 ml) was added dropwise at −78 °C. After stirring for another 20 min, Et_3N (28 ml) was added and the resulting mixture was allowed to stir at −30 °C for 30 min. Upon completion, the mixture was poured into H_2O (150 ml) and extracted thrice with Et_2O (200 ml). The combined org. extracts were washed with brine (150 ml), dried ($MgSO_4$), and concentrated *in vacuo*. This crude aldehyde (4*R*)-5-(benzyloxy)-4-methylpentanal (5.2 g, 25.2 mmol) was then dissolved in dry THF (80 ml) and cooled to 0 °C. To this mixture, nonylmagnesium bromide (1.0M in Et_2O, 45 ml, 2.0 equiv.) was added within 10 min. After addition, the ice bath was removed, and the mixture was allowed to warm to room temperature over 30 min, and then quenched with a sat. aq. NH_4Cl soln., and extracted thrice with AcOEt. The combined org. extracts were dried (Na_2SO_4), concentrated *in vacuo* and purified by CC to give two diastereoisomeric secondary alcohols (2*R*,5*S*)- and (2*R*,5*R*)-1-(benzyloxy)-2-methyltetradecan-5-ol (**6**) [13] (4.0 g, 66% yield from **5**). R_f (10% AcOEt/PE) 0.20. Liquid. $[\alpha]_D^{25}$ = −1.9 (*c* = 0.54, $CHCl_3$). IR (neat): 3404, 2926, 2854, 1457, 1368, 1097, 735, 697. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.84 – 0.90 (*m*, 3 H); 0.91 – 0.98 (*m*, 3 H); 1.20 – 1.61 (*m*, 20 H); 1.67 – 1.87 (*m*, 1 H); 3.16 – 3.41 (*m*, 2 H); 3.46 – 3.70 (*m*, 2 H); 4.50 (*s*, 2 H); 7.23 – 7.40 (*m*, 5 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.0; 17.0; 17.2; 22.6; 25.6; 25.6; 25.7; 29.2; 29.3; 29.4; 29.5; 29.6; 29.6; 31.8; 32.7; 33.3; 33.5; 34.6; 34.6; 37.3,37.4; 62.9; 72.0; 72.2; 72.9; 72.9; 75.6; 75.8; 127.4; 127.4; 127.5; 127.5; 128.2; 138.6; 138.6. ESI-MS: 357 ([*M* + Na]$^+$). HR-ESI-MS: 335.29507 ([*M* + H]$^+$, $C_{22}H_{39}O_3^+$; calc. 335.29446).

(2*R*)-1-(Benzyloxy)-2-methyltetradecan-5-one (**7**). To a stirred soln. of oxalyl chloride (1.5 ml, 20.9 mmol) in dry CH_2Cl_2 (30 ml) at −78 °C was added DMSO (2.7 ml, 41.9 mmol). After 30 min, a soln. of the secondary alcohol **6** (3.5 g, 10 mmol) in 15 ml of CH_2Cl_2 was added over 12 min. After 0.3 h, Et_3N (10.5 ml) was added, and the mixture was allowed to stir at room temperature for 1 h. The mixture was poured into H_2O (150 ml) and extracted thrice with Et_2O (200 ml). The combined org. extracts were washed with brine (100 ml), dried ($MgSO_4$), concentrated *in vacuo* and purified by CC to give **7** as a liquid (2.7 g, 77% yield from **6**). R_f (10% AcOEt/PE) 0.50. $[\alpha]_D^{25}$ = +2.8 (*c* = 0.33, $CHCl_3$). IR (neat): 2954, 2926, 2855, 1714, 1456, 1369, 1098, 772. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.84 – 0.90 (*m*, 3 H); 0.92 (*d*, *J* = 6.5, 3 H); 1.22 – 1.33 (*m*, 12 H); 1.37 – 1.48 (*m*, 2 H); 1.50 – 1.63 (*m*, 2 H); 1.67 – 1.87 (*m*, 2 H); 2.33 – 2.49 (*m*, 3 H); 3.22 – 3.34 (*m*, 2 H); 4.49 (*s*, 2 H); 7.27 – 7.39 (*m*, 5 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.0; 16.9; 22.6; 23.8; 27.6; 29.2; 29.3; 31.5; 31.8; 33.0; 40.3; 42.7; 72.9; 75.5; 127.4; 127.4; 128.2; 138.5; 211.4. ESI-MS: 355 ([*M* + Na]$^+$). HR-ESI-MS: 355.26068 ([*M* + Na]$^+$, $C_{22}H_{36}NaO_2^+$; calc. 355.26075).

({[(2*R*)-2-Methyl-5-methylidenetetradecyl]oxy}methyl)-benzene (**8**). To a soln. of (methyl)triphenylphosphonium bromide, (7.0 g, 19.8 mmol) in dry THF was added LiHMDS (1M in THF, 19.8 ml) at 0 °C, and the mixture was stirred for 45 min, and then compound **7** (2.2 g, 6.6 mmol) was added. The resulting mixture was allowed to stir at 25 °C for 4 h. After completion, the mixture was quenched with a sat. aq. NH_4Cl soln. (50 ml) and extracted with AcOEt (2 × 100 ml). The org. extracts were washed with brine (2 × 50 ml) and dried (Na_2SO_4). Removal of the solvent followed by flash chromatography over SiO_2 afforded the product **8** as a colorless liquid (1.4 g, 70% yield). R_f (10% AcOEt/PE) 0.80. $[\alpha]_D^{25}$ = +5.7 (*c* = 0.1, $CHCl_3$). IR (neat): 3423, 3070, 2961, 2933, 2894, 2859, 1721, 1468, 1427,

1294, 1269, 1108, 703. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.83 – 0.92 (*m*, 3 H); 0.95 (*d*, *J* = 6.6, 3 H); 1.18 – 1.47 (*m*, 14 H); 1.47 – 1.63 (*m*, 2 H); 1.68 – 1.88 (*m*, 1 H); 1.90 – 2.15 (*m*, 4 H); 3.20 – 3.40 (*m*, 2 H); 4.50 (*s*, 2 H); 4.69 (*s*, 2 H); 7.26 – 7.42 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.1; 17.0; 22.6; 27.8; 29.3; 29.4; 29.5; 29.5; 31.7; 31.8; 33.2; 33.3; 36.0; 72.9; 75.8; 108.4; 127.3; 127.4; 128.2; 138.7; 150.2. ESI-MS: 353 ([*M* + Na]$^+$).

(2*RS*)-2-[(3*R*)-4-(Benzyloxy)-3-methylbutyl]undecane-1,2-diol (**9**). To a stirred soln. of olefin **8** (1.0 g, 3.03 mmol) in a 1:1 mixture of ^{t}BuOH (15.1 ml) and H_2O (15.1 ml) were added sequentially $K_3[Fe(CN)_6]$ (2.9 g, 9.09 mmol), K_2CO_3 (1.25 gm, 9.09 mmol), $(DHQ)_2PHAL$ (118 mg, 0.15 mmol, 5 mol %), $MeSO_2NH_2$ (0.287 g, 3.03 mmol, 1.0 equiv.), and OsO_4 (0.15 ml of a 0.1M soln. in H_2O, 0.5 mol %) at 0 °C. The resulting soln. was stirred at the same temperature for 12 h, and then the reaction was quenched with an aq. Na_2SO_3 soln. (50 ml). The aq. layer was extracted with AcOEt (50 ml × 2). The combined org. layers were washed with a sat. aq. NaCl soln. (40 ml), dried ($MgSO_4$), concentrated *in vacuo*, and purified by flash chromatography over SiO_2 to afford the unseparable diastereoisomers, (2*RS*)-2-[(3*R*)-4-(benzyloxy)-3-methylbutyl]undecane-1,2-diol (**9**; 0.84 g, 80% yield) [14]. R_f (30% AcOEt/PE) 0.25. Liquid. $[\alpha]_D^{25}$ = +4.8 (*c* = 0.17, $CHCl_3$). IR (neat): 3421, 2925, 2854, 1720, 1458, 1379, 1273, 1097, 735, 697. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.84 – 0.91 (*m*, 6 H); 0.93 (*d*, *J* = 1.5, 3 H); 0.95 (*d*, *J* = 1.5, 3 H); 1.23 – 1.31 (*m*, 16 H); 1.37 – 1.54 (*m*, 4 H); 1.67 – 1.88 (*m*, 1 H); 3.31 (*d*, *J* = 6.0, 2 H); 3.45 (*s*, 2 H); 4.50 (*s*, 2 H); 7.21 – 7.42 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.0; 17.0; 17.1; 22.6; 23.2; 23.3; 26.9; 27.1; 29.2; 29.5; 29.6; 30.1; 31.8; 32.6; 32.6; 33.7; 35.5; 35.6; 67.9; 72.9; 74.6; 75.5; 76.5; 76.9; 77.4; 127.4; 127.5; 128.2; 138.4. ESI-MS: 387 ([*M* + Na]$^+$). HR-ESI-MS: 387.28827 ([*M* + Na]$^+$, $C_{23}H_{40}NaO_3^+$; calc. 387.28697).

(2*R*,5*RS*)-1-(Benzyloxy)-5-({[*tert*-butyl(diphenyl)silyl]-oxy}methyl)-2-methyltetradecan-5-ol (**10**). To a stirred soln. of **9** (0.50 g, 1.37 mmol) in dry CH_2Cl_2 (20 ml) were added TBDPSCl (0.30 ml, 1.37 mmol) and imidazole (0.14 g, 2.0 mmol) at 0 °C, and the mixture was stirred at room temperature for 45 min. The reaction was quenched with H_2O (2 × 10 ml), the mixture was extracted with CH_2Cl_2 (2 × 50 ml), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography over SiO_2 gave the unseparable TBDPS ethers **10** as a colorless liquid (0.85 g, 82% yield). R_f (10% AcOEt/PE) 0.35. Liquid. $[\alpha]_D^{25}$ = +3.4 (*c* = 0.16, $CHCl_3$). IR (neat): 3389, 3069, 2929, 2856, 1718, 1588, 1466, 1426, 1388, 1360, 1111, 820, 701. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.84 – 0.95 (*m*, 6 H); 1.05 – 1.10 (*m*, 24 H); 1.21 – 1.30 (*m*, 4 H); 1.38 – 1.50 (*m*, 1 H); 1.54 – 1.65 (*m*, 1 H); 2.16 – 2.28 (*m*, 1 H); 3.15 – 3.37 (*m*, 2 H); 3.46 (*s*, 2 H); 4.48 (*s*, 2 H); 7.29 – 7.48 (*m*, 10 H); 7.61 – 7.77 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.0; 17.1; 19.2; 22.6; 23.3; 24.7; 26.5; 26.6; 26.8; 27.0; 27.6; 27.8; 27.9; 27.9; 29.2; 29.5; 29.6; 30.2; 31.8; 33.0; 33.9; 35.8; 68.8; 72.9; 74.4; 75.6; 127.3; 127.4; 127.4; 127.6; 128.2; 129.0; 129.5; 129.7; 133.0; 134.1; 134.7; 135.5. ESI-MS: 625 ([*M* + Na]$^+$). HR-ESI-MS: 625.40649 ([*M* + Na]$^+$, $C_{39}H_{58}NaO_3Si^+$; calc. 625.40474).

(2*R*,5*RS*)-5-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-2-methyltetradecane-1,5-diol (**11**). To a stirred soln. of **10** (0.75 g, 1.24 mmol) in AcOEt (15 ml) was added 10% Pd/C (75 mg) and kept for 5 h at room temperature under H_2 pressure. The mixture was filtered over *Celite*, concentrated under reduced pressure, and then purified by flash chromatography over SiO_2 afforded the diol as a colorless liquid **11** (0.50 g, 84% yield). R_f (20% AcOEt/PE) 0.20. Liquid. $[\alpha]_D^{25}$ = −1.4 (*c* = 0.33, $CHCl_3$). IR (neat): 3419, 2930, 2856, 1721, 1454, 1369, 1272, 1108, 1076, 1016, 753, 703. ^{1}H-NMR (600 MHz, $CDCl_3$): 0.86 – 0.92 (*m*, 6 H); 1.07 (*s*, 9 H); 1.21 – 1.33 (*m*, 18 H); 1.37 – 1.61 (*m*, 3 H); 3.39 – 3.51 (*m*, 4 H); 7.36 – 7.46 (*m*, 6 H); 7.65 (*d*, *J* = 7.5, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.1; 16.5; 16.5; 19.2; 22.6; 23.4; 23.4; 26.3; 26.8; 29.2; 29.5; 29.6; 30.2; 31.8; 32.8; 32.8; 35.9; 36.0; 36.1; 36.1; 67.8; 68.6; 68.7; 74.4; 127.7; 129.7; 133.0; 135.5. ESI-MS: 535 ([*M* + Na]$^+$). HR-ESI-MS: 535.35661 ([*M* + Na]$^+$, $C_{32}H_{52}NaO_3Si^+$; calc. 535.35779).

(3*R*,6*RS*)-6-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)tetrahydro-3-methyl-6-nonyl-2*H*-pyran-2-one (**12**). To a stirred soln. of diol **11** (400 mg, 0.78 mmol) in a mixture of CH_2Cl_2 (6 ml) and H_2O (3 ml), TEMPO (24 mg, 0.15 mmol) and BAIB (628 mg, 1.95 mmol) were added at 0 °C and then stirred at room temperature for 1.0 h. After completion, the mixture was extracted with CH_2Cl_2 (2 × 20 ml), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography over SiO_2 afforded the lactone **12** as unseperable diastereoisomers (250 mg, 65% yield). R_f (10% AcOEt/PE) 0.55. Liquid. $[\alpha]_D^{25}$ = −8.2 (*c* = 0.33, $CHCl_3$). IR (neat): 3448, 2952, 2855, 1734, 1636, 1461, 1382, 1109, 765, 702, 613. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.80 – 0.94 (*m*, 6 H); 1.06 (*d*, *J* = 3.9, 9 H); 1.21 – 1.32 (*m*, 14 H); 1.54 – 1.67 (*m*, 3 H); 1.68 – 1.94 (*m*, 1 H); 1.98 – 2.19 (*m*, 1 H); 2.27 – 2.49 (*m*, 2 H); 3.51 – 3.63 (*m*, 2 H); 7.36 – 7.48 (*m*, 6 H); 7.61 – 7.77 (*m*, 4 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 13.7; 16.7; 16.9; 18.8; 22.3; 22.3; 22.7; 24.8; 25.0; 26.4; 26.5; 26.8; 27.3; 28.9; 28.9; 29.1; 29.1; 29.3; 29.5; 29.6; 29.8; 31.0; 31.4; 31.5; 35.1; 35.1 37.1; 37.9; 66.8; 68.1; 85.4; 85.4; 127.4; 129.4; 129.5; 129.8; 132.3; 132.4; 132.5; 132.6; 135.2; 135.2; 135.2; 135.3; 137.1; 174.2; 174.6. ESI-MS: 531 ([*M* + Na]$^+$). HR-ESI-MS: 531.32470 ([*M* + Na]$^+$, $C_{32}H_{48}NaO_3Si^+$; calc. 531.32649).

(–)-Malyngolide (**1a**) and **(–)-5-epi-Malyngolide** (**1b**). To a stirred soln. of lactone **12** (150 mg, 0.29 mmol) in dry THF was added 1.0M TBAF in THF (0.5 ml, 1.5 equiv.) at 0 °C. The resulting mixture was allowed to stir for 20 min at room temperature. After completion, the reaction was quenched with a sat. $NaHCO_3$ soln. (20 ml) and extracted with AcOEt (2 × 10 ml). The org. extracts were washed with brine (2 × 50 ml) and dried (Na_2SO_4). Removal of the solvent followed by purification on CC over SiO_2 afforded the pure **1a** and **1b** [5e][15].

(–)-Malyngolide (= **(3*R*,6*S*)-Tetrahydro-6-(Hydroxymethyl)-3-methyl-6-nonyl-2*H*-pyran-2-one**; **1a**). Colorless liquid. Yield: 55% (55 mg). R_f (20% AcOEt/PE) 0.20. $[\alpha]_D^{25}$ = −12.5 (*c* = 1, $CHCl_3$), −12.8 (*c* = 1.8, $CHCl_3$). IR (neat): 3415, 2925, 2854, 1725, 1461, 1377, 1212, 1109, 741. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.88 (*t*, *J* = 6.9, 3 H); 1.20 – 1.39 (*m*, 19 H); 1.48 – 1.84 (*m*, 3 H); 1.85 – 2.19 (*m*, 2 H); 2.34 – 2.58 (*m*, 1 H); 3.48 (*d*, *J* = 12.0, 1 H); 3.66 (*d*, *J* = 12.0, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.0; 17.1; 22.6; 23.6; 25.1; 26.2; 29.2; 29.4; 29.6; 29.9; 31.8; 35.5; 36.4; 67.7; 86.8; 175.0. ESI-MS: 293 ([*M* + Na]$^+$). HR-ESI-MS: 293.20756 ([*M* + Na]$^+$, $C_{16}H_{30}NaO_3^+$; calc. 293.20872).

(–)-5-*epi*-Malyngolide (= **(3*R*,6*R*)-Tetrahydro-6-(Hydroxymethyl)-3-methyl-6-nonyl-2*H*-pyran-2-one**; **1b**). Colorless liquid. Yield: 33% (35 mg). R_f (20% AcOEt/PE) 0.25. $[\alpha]_D^{25}$ = −19.0 (*c* = 1, $CHCl_3$), −18.4 (*c* = 0.7, $CHCl_3$). IR (neat): 3445, 2925, 2854, 1727, 1462, 1377, 1331, 1256, 1211, 1083, 800, 723. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.87 (*t*, *J* = 6.9, 3 H); 1.23 – 1.33 (*m*, 19 H); 1.55 – 1.71 (*m*, 2 H); 1.72 – 1.84 (*m*, 1 H); 1.86 – 2.02 (*m*, 2 H); 2.35 – 2.54 (*m*, 1 H); 3.60 (*s*, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.0; 17.2; 22.6; 23.1; 25.4; 27.0; 29.2; 29.4; 29.6; 29.9; 31.8; 35.1; 37.4; 67.6; 86.2; 175.2. HR-ESI-MS: 293.20915 ([*M* + Na]$^+$, $C_{16}H_{30}NaO_3^+$; calc. 293.20872).

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