Pergamon

Tetrahedron 58 (2002) 8929–8936

TETRAHEDRON

Enantioselective total synthesis of δ-lactonic marine natural products, (+)-tanikolide and (−)-malyngolide, via RCM reaction

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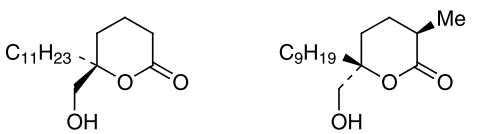
Received 20 August 2002; revised 9 September 2002; accepted 17 September 2002

Abstract—Enantioselective total synthesis of δ-lactonic marine natural products, (+)-tanikolide and (−)-malyngolide isolated from *Lyngbya majuscula*, was achieved by using the Sharpless asymmetric epoxidation and a ring-closing metathesis, as key reactions.

1. Introduction

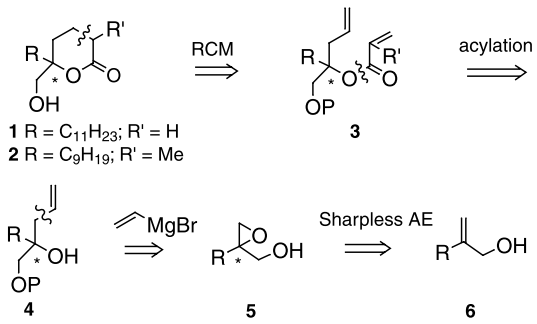
(+)-Tanikolide[1] and (−)-malyngolide,[2] both isolated from the lipid extract of the marine cyanobacterium *Lymgbia majuscula*, are naturally occurring δ-lactonic bioactive compounds, which contain a chiral quaternary carbon center with a hydroxymethyl group as a common structural feature. The structures of these compounds including the absolute stereochemistries were determined by spectroscopic methods and also by the total synthesis.[3,4] (+)-Tanikolide exhibited antifungal activity against *Candida albicans*, and also showed an LD_{50} of 3.6 μg/ml against brine shrimp and 9.0 μg/ml against the snail.[1] It is also known that (+)-tanikolide has an opposite configuration at the C-5 position to that of (−)-malyngolide showing antimicrobial activity against *Streptococcus pyogenes* but no activity to *C. albicans* (Fig. 1).[1]

In 1990, we reported[5] the enantioselective synthesis of (−)-malyngolide, where the oxidative ring transformation of a furylcarbinol derivative to the corresponding pyranone was employed as the key reaction. As an extension of our work on the synthesis of biologically active lactonic natural compounds, we are interested in the synthesis of both (+)-tanikolide **1** and (−)-malyngolide **2** by using a common synthetic strategy.



1 (+)-tanikolide **2** (-)-malyngolide

Figure 1. Structures (+)-tanikolide and (−)-malyngolide.



Scheme 1. Retrosynthetic analysis for (+)-tanikolide and (−)-malyngolide.

Our retrosynthetic analysis for (+)-tanikolide and (−)-malyngolide is shown in Scheme 1, where introduction of a chiral quaternary carbon center should readily be achieved by the Sharpless asymmetric epoxidation of allyl alcohol **6**,[6] followed by regioselective epoxy-ring opening of chiral epoxide **5** with a vinyl group. Moreover, we decided to utilize a ring-closing metathesis (RCM) of diene **3**, easily derived from *tert*-alcohol **4**, for the construction of a δ-lactone moiety, since this reaction seems to be one of the most promising methods for the construction of both carbacyclic and heterocyclic ring systems.[7]

Thus, the starting materials were prepared as follows.

2. Results and discussion

Treatment of tridecanal **7** with the Eschenmoser salt[8] gave α-methylene aldehyde **9**, which, on reduction with sodium

Keywords: ring-closing metathesis; (+)-tanikolide; (−)-malyngolide; marine natural product; lactonic compound.

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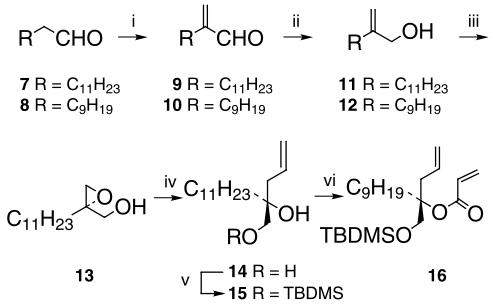


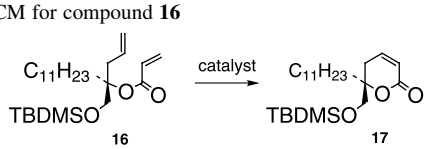
Scheme 2. Preparation of starting materials. *Reagents and conditions*: (i) methylene-*N*,*N*-dimethylammonium iodide, Et_3N, CH_2Cl_2, room temperature (72% for **9**, 81% for **10**); (ii) $NaBH_4$, $CeCl_3$, MeOH, 0°C to room temperature (98% for **11**, 90% for **12**); (iii) L-(+)-DIPT, $Ti(O^iPr)_4$, TBHP, CaH_2, MS 3A, CH_2Cl_2, −20°C (82%); (iv) CuI, vinylmagnesium bromide, THF, −20°C (69%); (v) TBSOTf, $^iPr_2NEt$, CH_2Cl_2, 0°C (100%); (vi) EtMgBr, acryloyl chloride, THF, room temperature (74%).

borohydride in the presence of cerium chloride[9] in MeOH furnished allyl alcohol **11** (Scheme 2).

The Sharpless asymmetric epoxidation of **11** with *tert*-butyl hydroperoxide, titanium tetra-isopropoxide and L-(+)-diisopropyl tartrate gave epoxide **13** in 82% yield, whose optical purity was determined as 96% ee based on the HPLC analysis of its benzoate using the chiral stationary phase (CHIRALCEL OB, Daicel Chemical Industries). Regioselective ring-opening of epoxide **13** was achieved by treatment with vinylmagnesium bromide in the presence of copper(I) iodide to provide the desired *tert*-alcohol **14**. After protection of the primary hydroxy group of **14** as a silyl ether, acylation of **15** was achieved by treatment with ethylmagnesium bromide as the base and acryloyl chloride to yield diene **16**. Since we were able to establish a convenient procedure for the preparation of a key precursor in optically active form, our attention was focused on searching for the best reaction conditions for RCM.

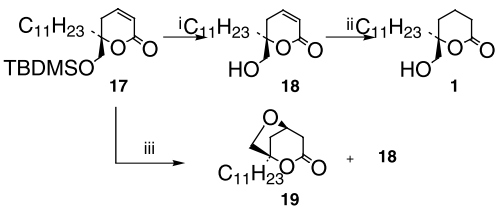
First, diene **16** was subjected to RCM by using 5 mol% of Grubbs' reagent (**A**)[10] as the catalyst in benzene at 70°C for 15 h, where the desired α,β-unsaturated δ-lactone **17** was isolated in 86% yield (Table 1). When this reaction was carried out in the presence of 5 mol% of Hoveyda-recyclable ruthenium catalyst (**B**), which is known to be a highly reactive catalyst for RCM,[11] the yield was increased to 96% as expected. It is noteworthy that this reaction was

Table 1. RCM for compound **16**



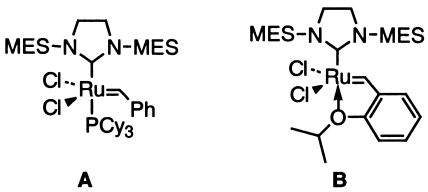
Catalyst	Mol%	Time (h)	Temperature (°C)	Yield[a] (%)
A	5	15	70	86
B	5	3	70	96
C	1	3	70	>99

All reactions were carried out in benzene.
[a] Isolated yield.



Scheme 3. Synthesis of (+)-tanikolide. *Reagents and conditions*: (i) TsOH, EtOH/H_2O (4:1), 80°C (98%); (ii) H_2, 5% Pd–C, hexane, room temperature (85%); (iii) TBAF, THF, 0°C (50% for **19**, 43% for **18**).

found to be effective even with the use of 1 mol% of the catalyst (**B**).

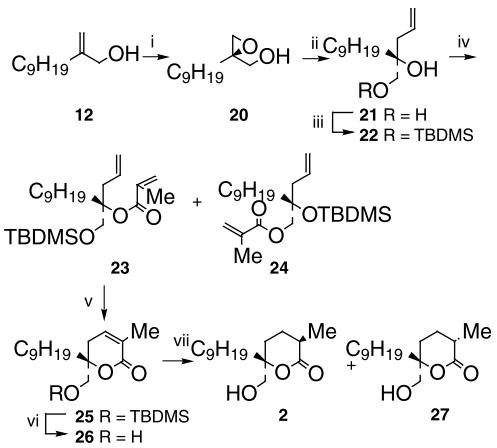


Desilylation of δ-lactone **17** with TBAF in THF gave the desired primary alcohol **18** in 43% yield together with the intramolecular 1,4-addition product **19** in 50% yield (Scheme 3).

However, treatment of **17** with *p*-toluenesulfonic acid in aqueous ethanol afforded **18** as the sole product in 98% yield. Finally, catalytic hydrogenation of α,β-unsaturated δ-lactone **18** over 5% palladium on carbon under an atmospheric pressure of hydrogen in hexane furnished (+)-tanikolide **1**, mp 44–46°C; $[\alpha]_D$=+1.93 (c=0.6, $CHCl_3$) {lit.,[4b] mp 38–40°C, $[\alpha]_D$=+2.3 (c=0.7, $CHCl_3$)}, whose spectroscopic data including specific optical rotation value were identical with those reported.[4b]

Since we succeeded in the enantioselective synthesis of (+)-tanikolide in relatively short reaction sequences as above, we decided to apply this strategy to the synthesis of (−)-malyngolide **2**. Recently, Marco et al. reported a similar synthetic approach to (−)-malyngolide,[4c] in which they observed that the RCM of the diene derived from *tert*-alcohol with methacryloyl chloride afforded none of the desired product, unfortunately. We, however, thought that this type of cyclization would be a reasonable approach to (−)-malyngolide based on the above results, and worth attempting by using our own substrate. Thus, allyl alcohol **12** was prepared from undecanal **8** by two steps, via **10**, in 73% overall yield. As the configuration at the quaternary chiral center of (−)-malyngolide was opposite to that of tanikolide, D-(−)-diisopropyl tartrate was employed in the Sharpless asymmetric epoxidation to produce chiral epoxide **20** with 95% ee (Scheme 4).[12]

After ring-opening of epoxide **20** with vinylmagnesium bromide, the resulting diol **21** was converted into mono-silyl ether **22** as above, and then the remaining *tert*-hydroxy group of **22** was acylated with methacryloyl chloride in the presence of ethylmagnesium bromide as the base to give ester **23** accompanied with the acyl rearranged product **24** in 48 and 43% yields, respectively. Attempted RCM of **23** with 5 mol% of Grubbs' catalyst (**A**) for 15 h produced the



Scheme 4. Synthesis of (−)-malyngolide. *Reagents and conditions*: (i) D-(−)-DIPT, $Ti(O^iPr)_4$, TBHP, CaH_2, MS 3A, CH_2Cl_2, −20°C (83%); (ii) CuI, vinylmagnesium bromide, THF, −20°C (77%); (iii) TBSOTf, $^iPr_2NEt$, CH_2Cl_2, 0°C (95%); (iv) EtMgBr, methacryloyl chloride, THF, −20°C (48% for **23**, 43% for **24**); (v) catalyst **B** (5 mol%), benzene, 70°C (88%); (vi) TsOH, EtOH/H2O (4:1), 80°C (96%); (vii) H_2, 5% Pd–C, hexane, room temperature (80% for **2**, 12% for **27**).

desired product **25** in 34% yield, fortunately. When 1 mol% of the Hoveyda-recyclable ruthenium catalyst (**B**) was used in the reaction, yield was increased to 68%. Finally, the best yield (88%) was obtained by the use of 5 mol% of the catalyst in benzene at 70°C for 7 h. In order to accomplish the total synthesis, deprotection of the silyl group of **25** with *p*-toluenesulfonic acid in aqueous ethanol was carried out to give the primary alcohol **26**, which, on catalytic reduction over 5% palladium on carbon under an atmosphere of hydrogen, afforded (−)-malyngolide **2**, $[\alpha]_D=-13.8$ (c=0.7, $CHCl_3$) {lit.,[4d] $[\alpha]_D=-13$ (c=2, $CHCl_3$)}, and *epi*-malyngolide **27**, in 80 and 12% yields, respectively. Again, the spectroscopic data of these compounds were identical with those reported.[5]

3. Conclusion

Thus, we have succeeded in the synthesis of (+)-tanikolide and (−)-malyngolide in relatively short steps by using a common synthetic strategy, where RCM played an important role for the construction of heterocyclic ring systems. Further applications of this methodology to the synthesis of biologically active compounds including natural products are in progress in this laboratory.

4. Experimental

4.1. General experimental procedures

Melting points were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were obtained using a JASCO FT/IR-200 spectrophotometer as thin films. ^1H NMR and ^{13}C NMR spectra were obtained on JEOL LAMBDA-270 (^1H NMR: 270 MHz, ^{13}C NMR: 76.8 MHz) instrument for solutions in $CDCl_3$, and chemical shifts are reported on the δ-scale from internal TMS. MS spectra were measured with a JEOL JMS-D 300 spectrometer. Elemental analyses were performed on a Yanaco-MT5.

4.1.1. 2-Methylidenetridecanal (9). To a stirred solution of tridecanal (5.0 g, 25.2 mmol) and triethylamine (10.5 ml, 75.6 mmol) in CH_2Cl_2 was added Eschenmoser's salt (9.3 g, 50.4 mmol) at ambient temperature, and the resulting mixture was stirred for further 15 h. After addition of saturated aqueous $NaHCO_3$ solution, the mixture was extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography (hexane/AcOEt, 7:1) to afford compound **9** (3.8 g, 72%) as a colorless oil. ^1H NMR: δ 0.88 (3H, t, J=6.7 Hz, 13-CH_3), 1.20–1.35 (16H, br s, 5-, 6-, 7-, 8-, 9-, 10-, 11- and 12-CH_2), 1.35–1.51 (2H, m, 4-CH_2), 2.23 (2H, t, J=7.4 Hz, 3-CH_2), 5.98 (1H, d, J=0.7 Hz, 14-C*H*H), 6.24 (1H, d, J=0.7 Hz, 14-CH*H*), 9.54 (1H, s, CHO); ^{13}C NMR: δ 14.1, 22.7, 27.8, 29.2, 29.3, 29.4, 29.5, 29.6, 31.9, 133.8, 150.4, 194.8; IR (thin film): 1697, 1628, 1466, 940, 770, 725. Anal. calcd for $C_{14}H_{26}O$: C, 79.94; H, 12.46. Found: C, 79.84; H, 12.20; HRMS calcd for $C_{14}H_{26}O$ (M^+): 210.1984, found 210.2008.

4.1.2. 2-Methylidenetridecan-1-ol (11). To a solution of $CeCl_3{\cdot}7H_2O$ (5.0 g, 13.3 mmol) in MeOH (35.0 ml) were added successively $NaBH_4$ (0.75 g, 20.0 mmol) and a solution of aldehyde **9** (1.6 g, 6.67 mmol) in MeOH (5.0 ml) at 0°C. After being stirred for 2 h at room temperature, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution and the organic solvent was evaporated to leave a residue. The residue was filtered through the Celite pad, and the filtrate was extracted with AcOEt. The organic layers were dried over Na_2SO_4, and concentrated under reduced pressure to leave a residue, which was purified by column chromatography on silica gel (hexane/AcOEt, 7:1) to give allyl alcohol **11** (1.8 g, 96%) as a colorless oil. ^1H NMR: δ 0.88 (3H, t, J=6.6 Hz, 13-CH_3), 1.26–1.36 (18H, m, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 11- and 12-CH_2), 1.44 (1H, t, J=7.6 Hz, OH), 2.06 (2H, dd, J=7.3, 7.9 Hz, 3-CH_2), 4.08 (2H, d, J=6.1 Hz, 1-CH_2), 4.87 (1H, dd, J=1.2, 2.5 Hz, 14-C*H*H), 5.00 (1H, dd, J=0.7, 1.5 Hz, 14-CH*H*); ^{13}C NMR: δ 14.1, 22.7, 27.8, 29.3, 29.4, 29.4, 29.5, 29.6, 31.9, 33.0, 65.9, 108.9, 149.3; IR (thin film): 3310, 1660, 1465, 1027 890; HRMS calcd for $C_{14}H_{28}O$ (M^+): 212.2140, found 212.2148.

4.1.3. (2*S*)-2,3-Epoxy-2-undecanylpropan-1-ol (13). To a stirred suspension of activated MS 3A (0.30 g) and CaH_2 (40 mg, 0.94 mmol) in CH_2Cl_2 (2.5 ml) was added $Ti(O^iPr)_4$ (0.35 ml, 1.18 mmol) at room temperature. The stirred mixture was cooled to −20°C, and treated with L-(+)-DIPT (0.33 g, 1.42 mmol) in CH_2Cl_2 (2.0 ml). After being stirred for 30 min at the same temperature, a solution of allyl alcohol **11** (1.0 g, 4.72 mmol) in CH_2Cl_2 (12.0 ml) was added dropwise to the solution, and the mixture was stirred for further 1 h. TBHP (1.3 ml, 7.08 mmol) was then added to this mixture over a period of 30 min. After being stirred for 48 h at −20°C, Me_2S (0.42 ml, 5.64 mmol) was slowly added and the mixture was stirred for further 30 min at the same temperature. To this mixture were added 10% aqueous of tartaric acid (2.8 ml, 1.88 mmol), NaF (1.2 g, 29.2 mmol) and Et_2O (7.9 ml), and the resulting mixture was vigorously stirred for 2 h at room temperature. The precipitate was filtered off through a Celite pad. The filtrate was washed successively with saturated aqueous $NaHCO_3$ solution and brine, and dried over Na_2SO_4. Evaporation of

the solvent gave a residue, which was purified by column chromatography on silica gel (hexanes/AcOEt, 1:1) to give epoxy alcohol **13** (0.88 g, 82%) as a colorless oil. $[\alpha]_D^{25}=-12.6$ (c=1.05, $CHCl_3$); ^{1}H NMR: δ 0.88 (3H, t, J=6.7 Hz, 11′-CH_3), 1.24–1.41 (18H, br s, 2′-, 3′-, 4′-, 5′-, 6′-, 7′-, 8′-, 9′- and 10′-CH_2), 1.44–1.84 (2H, m, 1′-H_2), 2.67 and 2.88 (each 1H, each d, J=4.6 Hz, 3-CH_2), 3.64 (1H, dd, J=8.3, 12.2 Hz, 1-CH*H*), 3.78 (1H, dd, J=3.6, 12.2 Hz, 1-C*H*H); ^{13}C NMR: δ 14.0, 22.6, 24.6, 29.3, 29.4, 29.6, 29.7, 31.8, 31.9, 49.8, 60.0, 62.7; IR (thin film): 3440, 3050, 1470, 1050, 895, 810, 720. Anal. calcd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36. Found: C, 73.42; H, 12.35; HRMS calcd for $C_{14}H_{28}O_2$ (M^+): 228.2089, found 228.2070. The ee of the benzoate of **13** was determined to be 96% by HPLC analysis on a Chiralcel OB (Daicel Chemical Industries) using hexane–^{i}PrOH (99.5:0.5, v/v).

4.1.4. (2*R*)-1-Benzoyloxy-2,3-epoxy-2-undecanylpropane. To a stirred solution of epoxy alcohol **13** (100 mg, 0.44 mmol) in CH_2Cl_2 (4.4 ml) was added Et_3N (0.18 ml, 1.32 mmol) at 0°C under argon atmosphere, and benzoyl chloride (76.0 μl, 0.66 mmol) was added dropwise to the mixture. After being stirred for 2 h at room temperature, the reaction was quenched by addition of saturated aqueous NH_4Cl solution, and extracted with CH_2Cl_2. The organic layers were washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel (hexanes/AcOEt, 1:1) to give benzoate of **13** (142 mg, 98%) as a colorless oil. $[\alpha]_D^{23}=-2.44$ (c=1.00, $CHCl_3$); ^{1}H NMR: δ 0.88 (3H, t, J=6.6 Hz, 11′-CH_3), 1.19–1.52 (18H, br s, 2′-, 3′-, 4′-, 5′-, 6′-, 7′-, 8′-, 9′- and 10′-CH_2), 1.44–1.84 (2H, m, 1′-H_2), 2.74 and 2.84 (each 1H, each d, J=4.6 Hz, 3-CH_2), 4.26 and 5.52 (each 1H, each d, J=12.0 Hz, 1-H_2), 7.46 (2H, m, *m*-PhH), 7.58 (1H, tt, J=1.3, 7.4 Hz, *p*-PhH), 8.04–8.07 (2H, m, *o*-PhH); ^{13}C NMR: δ 14.1, 22.7, 24.6, 29.3, 29.4, 29.5, 29.6, 31.9, 32.1, 50.7, 57.5, 66.2, 128.4, 129.7, 129.8, 133.1, 166.1; IR (thin film): 3000, 1726, 1466, 1452, 1270, 1110, 710. Anal. calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.97; H, 9.84; HRMS calcd for $C_{21}H_{32}O_3$ (M^+): 332.2351, found 332.2346.

4.1.5. (4*R*)-4-Hydroxymethylpentadec-1-en-4-ol (14). To a stirred suspension of CuI (280 mg, 1.50 mmol) in THF (20.0 ml) was added dropwise 1.0 M solution of vinylmagnesium bromide in THF (20.0 ml, 20.0 mmol) at −20°C under argon atmosphere, and the mixture was stirred for 30 min. A solution of epoxy alcohol **13** (1.14 g, 5.00 mmol) in THF (5.0 ml) was added to the mixture at same temperature, and the resulting mixture was stirred for further 48 h. After addition of saturated aqueous NH_4Cl solution, the reaction mixture was filtered through the Celite pad, and the filtrate was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4 and concentrated under the reduced pressure to leave a residue, which was purified column chromatography on silica gel (hexanes/AcOEt, 1:1) to give diol **14** (880 mg, 69%) as a colorless oil. $[\alpha]_D^{24}=+0.57$ (c=1.01, $CHCl_3$); ^{1}H NMR: δ 0.88 (3H, t, J=6.6 Hz, 11′-CH_3), 1.22–1.33 (18H, m, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13- and 14-CH_2), 1.41–1.54 (2H, m, 5-CH_2), 1.88 (2H, br, 2xOH), 2.28 (2H, dt, J=1.2, 7.6 Hz, 3-CH_2), 3.47 (2H, br d, J=2.6 Hz, CH_2OH), 5.10–5.19 (2H, m, 1-CH_2), 5.84 (1H, dddd, J=7.4, 9.2, 11.9, 15.0 Hz, 2-CH); ^{13}C NMR: δ 14.1, 22.7, 23.3, 29.3, 29.6, 30.2, 31.9, 36.3, 40.6, 67.9, 74.2, 118.8, 133.4; IR (thin film): 3390, 1640, 1470, 1060, 998, 912, 720. Anal. calcd for $C_{16}H_{32}O_2$: C, 74.94; H, 12.58. Found: C, 75.15; H, 12.60; HRMS calcd for $C_{16}H_{32}O_2$ (M^+-H_2O): 239.2375, found 239.2389.

4.1.6. (4*R*)-4-(*tert*-Butyldimethylsilyloxymethyl)pentadec-1-en-4-ol (15). Diol **14** (810 mg, 3.16 mmol) and ^{i}Pr$_2$NEt (1.30 ml, 7.59 mmol) were dissolved in CH_2Cl_2 (16.0 ml) under argon atmosphere. After being cooled to 0°C, TBSOTf (0.90 ml, 3.80 mmol) was added dropwise to the solution, and the mixture was stirred for further 30 min at the same temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4, and removed volatiles under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes/AcOEt, 1:1) to afford alcohol **15** (1.17 g, 100%) as a colorless oil. $[\alpha]_D^{22}=+5.81$ (c=1.07, $CHCl_3$); ^{1}H NMR: δ 0.07 (6H, s, 2×SiMe), 0.86–0.93 (12H, m, 15-CH_3 and *tert*-BuSi), 1.21–1.47 (20H, br s, 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13- and 14-CH_2), 2.14–2.23 (2H, m, 3-CH_2), 2.25 (1H, s, OH), 3.32 (1H, d, J=9.6 Hz, TBSOC*H*H), 3.38 (1H, d, J=9.6 Hz, TBSOCH*H*), 4.96–5.06 (2H, m, 1-CH_2), 5.83 (1H, m, 2-CH); ^{13}C NMR: δ −5.5, 14.1, 18.2, 22.7, 23.1, 25.8, 29.3, 29.6, 30.3, 32.0, 36.2, 40.9, 68.0, 73.7, 117.8, 134.1; IR (thin film): 3560, 3480, 1465, 1255, 1100, 1005, 910, 840, 775. Anal. calcd for $C_{22}H_{46}O_2Si$: C, 71.28; H, 12.51. Found: C, 71.46; H, 12.22; HRMS calcd for $C_{16}H_{32}O_2$ (M^+-TBS+H): 256.2402, found 256.2402.

4.1.7. (4*R*)-4-Acryloyloxy-4-(*tert*-butyldimethylsilyloxymethyl)pentadec-1-ene (16). To a stirred solution of alcohol **15** (1.28 g, 3.46 mmol) in THF (17.3 ml) was added dropwise 1.0 M solution of ethylmagnesium bromide in THF (3.81 ml, 3.81 mmol) at room temperature under argon atmosphere. After being stirred for 20 min, acryloyl chloride (0.56 ml, 6.92 mmol) was added slowly to the solution, and the whole mixture was stirred for further 5 h at room temperature. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution and the mixture was extracted with AcOEt. The extract was washed with brine and concentrated under reduced pressure to leave a residue, which was purified by column chromatography on silica gel (hexanes/AcOEt, 4:1) to give acrylate **16** (1.04 g, 74%) as a colorless oil. $[\alpha]_D^{25}=-4.21$ (c=1.00, $CHCl_3$); ^{1}H NMR: δ 0.02 (6H, s, 2×MeSi), 0.87 (12H, m, 15-CH_3 and *tert*-BuSi), 1.20–1.34 (18H, br s, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13- and 14-CH_2), 1.85 (2H, m, 5-CH_2), 2.56 (1H, dd, J=7.5, 14.0 Hz, 3-C*H*H), 2.61 (1H, dd, J=7.3, 14.0 Hz, 3-CH*H*), 3.70 and 3.80 (each 1H, each d, J=10.1 Hz, CH_2OTBS), 5.06 (1H, br d, J=10.2 Hz, 1-C*H*H), 5.08 (1H, br d, J=17.1 Hz, 1-CH*H*), 5.65–5.81 (2H, m, 2-CH and COCHC*H*H), 6.02 (1H, dd, J=10.4, 17.3 Hz, COCH), 6.29 (1H, dd, J=1.7, 17.3 Hz, COCHCH*H*); ^{13}C NMR: δ −5.5, 14.1, 18.1, 22.7, 22.8, 25.8, 29.3, 29.5, 29.6, 29.6, 29.8, 31.9, 32.9, 37.9, 63.4, 86.3, 118.3, 129.6, 129.8, 133.0, 165.1; IR (thin film): 1724, 1640, 1620, 1400, 1200, 1120, 980, 920, 840, 780. Anal. calcd for $C_{25}H_{48}O_3Si$: C, 70.70; H, 11.39. Found: C, 70.58; H, 11.54.

4.1.8. (5*R*)-5-(*tert*-Butyldimethylsilyloxy)methylhexadec-2-en-5-olide (17). To a solution of acrylate **16** (50 mg,

0.12 mmol) in benzene (24 ml) was added Ru catalyst (**B**) (0.74 mg, 1.20 μmol), and the mixture was stirred for 3.5 h at 70°C. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexanes/AcOEt, 20:1) to give compound **17** (46.6 mg, 100%) as a colorless oil. $[\alpha]_D^{23}=-11.0$ (c=1.04, $CHCl_3$); ^{1}H NMR: δ 0.02 and 0.04 (each 3H, each s, 2×MeSi), 0.84–0.88 (12H, m, 16-CH_3 and *tert*-BuSi), 1.18–1.48 (18H, br s, 7-, 8-, 9-, 10-, 11-, 12-, 13-, 14- and 15-CH_2), 1.61–1.75 (2H, m, 6-CH_2), 2.34 (1H, ddd, J=2.3, 3.8, 19.0 Hz, 4-C*H*H), 2.62 (1H, ddd, J=1.9, 4.8, 19.0 Hz, 4-CH*H*), 3.53 and 3.67 (each 1H, each d, J=10.1 Hz, $TBSOCH_2$), 5.97 (1H, ddd, J=2.0, 2.1, 9.9 Hz, 2-CH), 6.73 (1H, ddd, J=4.0, 4.6, 9.9 Hz, 3-CH); ^{13}C NMR: δ −5.6, −5.6, 14.1, 18.1, 22.6, 23.0, 25.7, 28.9, 29.3, 29.4, 29.5, 29.6, 29.9, 31.9, 36.7, 65.8, 83.8, 120.5, 143.6, 163.5; IR (thin film): 1728, 1468, 1464, 1383, 1254, 1114, 840, 810, 780. Anal. calcd for $C_{23}H_{44}O_3Si$: C, 69.64; H, 11.18. Found: C, 69.86; H, 11.27; HRMS calcd for $C_{23}H_{44}O_3Si$ (M^+): 396.3060, found 396.3062.

4.1.9. (5*R*)-5-Hydroxymethylhexadec-2-en-5-olide (18). To a mixed solution of compound **17** (427 mg, 1.08 mmol) in EtOH (14.4 ml) and H_2O (3.6 ml) was added $TsOH\cdot H_2O$ (20.5 mg, 0.11 mmol), and the mixture was stirred for 17 h at 80°C. After being cooled to room temperature, the reaction was quenched by addition of brine, and the mixture was extracted with Et_2O. The extract was dried over Na_2SO_4 and concentrated under reduced pressure to leave a residue, which was purified by column chromatography on silica gel (hexanes/AcOEt, 1:1) to give alcohol **18** (297 mg, 98%) as a colorless oil. $[\alpha]_D^{25}=+12.5$ (c=0.61, $CHCl_3$); ^{1}H NMR: δ 0.88 (3H, t, J=6.7 Hz, 16-CH_3), 1.22–1.35 (18H, br s, 7-, 8-, 9-, 10-, 11-, 12-, 13-, 14- and 15-CH_2), 1.63–1.84 (2H, m, 6-CH_2), 1.91 (1H, dd, J=5.9, 7.8 Hz, OH), 2.31 (1H, ddd, J=1.6, 5.3, 19.0 Hz, 4-C*H*H), 2.78 (1H, ddd, J=2.6, 3.3, 19.0 Hz, 4-CH*H*), 3.56 (1H, dd, J=7.8, 11.9 Hz, C*H*HOH), 3.75 (1H, dd, J=5.9, 11.9 Hz, CH*H*OH), 6.02 (1H, ddd, J=1.7, 2.6, 9.9 Hz, 2-CH), 6.81 (1H, ddd, J=3.4, 5.3, 9.9 Hz, 3-CH); ^{13}C NMR: δ 14.1, 22.7, 23.7, 28.1, 29.3, 29.4, 29.5, 29.6, 29.9, 31.9, 35.7, 66.4, 84.8, 120.4, 144.0; IR (thin film): 3430, 1740, 1466, 1380, 1250, 1060, 1030, 960, 810; HRMS calcd for $C_{17}H_{29}O_3$ (M^+-1): 281.2117, found 281.2127.

4.1.10. (+)-Tanikolide (1). A mixture of alcohol **18** (297 mg, 1.05 mmol) and 5% palladium on carbon (59.4 mg) in hexane (30.0 ml) was stirred for 1 h at room temperature under an atmospheric pressure of hydrogen. After filtration of the catalyst, the filtrate was concentrated to leave a residue, which was purified by column chromatography on silica gel (hexanes/AcOEt, 1:3) to afford tanikolide **1** (254 mg, 85%) as a white solid. Mp 44–46°C $[\alpha]_D^{25}=+1.93$ (c=0.59, $CHCl_3$); ^{1}H NMR: δ 0.88 (3H, t, J=6.7 Hz, 16-CH_3), 1.23–1.35 (18H, br, 7-, 8-, 9-, 10-, 11-, 12-, 13-, 14- and 15-CH_2), 1.62–1.94 (6H, m, 3-, 4-CH_2 and 6-CH_2), 2.46–2.50 (2H, m, 2-CH_2), 3.55 and 3.66 (each 1H, each dd, J=6.8, 11.9 Hz, CH_2OH); ^{13}C NMR: δ 14.0, 16.6, 22.6, 23.3, 26.6, 29.2, 29.4, 29.5, 29.5, 29.7, 29.9, 31.8, 36.7, 67.3, 86.6; IR (thin film): 3420, 1734, 1714, 1466, 1332, 1250, 1040; HRMS calcd for $C_{17}H_{32}O_3$ (M^+): 284.2351, found 284.2325.

4.1.11. 2-Methylideneundecanal (10). To a stirred solution of undecanal (1.0 g, 5.87 mmol) and triethylamine (2.5 ml, 17.6 mmol) in CH_2Cl_2 was added Eschenmoser's salt (1.6 g, 8.81 mmol) at ambient temperature, and the resulting mixture was stirred for further 14 h. After addition of saturated aqueous $NaHCO_3$ solution, the mixture was extracted with CH_2Cl_2. The extract was dried over $NaSO_4$ and concentrated under reduced pressure to leave a residue, which was purified by silica gel column chromatography (hexane/AcOEt, 7:1) to give the compound **10** (0.86 g, 81%) as a colorless oil. ^{1}H NMR: δ 0.88 (3H, t, J=6.6 Hz, 11-CH_3), 1.21–1.35 (12H, br s, 5-, 6-, 7-, 8-, 9- and 10-CH_2), 1.36–1.52 (2H, m, 4-CH_2), 2.44 (2H, t, J=7.3 Hz, 3-CH_2), 5.99 (1H, s, 14-C*H*H), 6.24 (1H, d, J=1.0 Hz, 14-CH*H*), 9.54 (1H, s, CHO); ^{13}C NMR: δ 14.1, 22.6, 27.7, 29.3, 29.4, 29.5, 31.9, 133.9, 150.4, 194.8; IR (thin film): 1697, 1628, 1466, 1380, 1330, 940. Anal. calcd for $C_{12}H_{22}O$: C, 79.07; H, 12.27. Found: C, 79.06; H, 12.16; HRMS calcd for $C_{12}H_{22}O$ (M^+): 182.1671, found 182.1661.

4.1.12. 2-Methylideneundecan-1-ol (12). To a solution of $CeCl_3\cdot 7H_2O$ (7.40 g, 19.8 mmol) in MeOH (45.0 ml) were added successively $NaBH_4$ (0.56 g, 14.8 mmol) and a solution of aldehyde **10** (1.80 g, 9.89 mmol) in MeOH (5.0 ml) at 0°C. After being stirred for 30 min at room temperature, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution and the organic solvent was evaporated to leave a residue. The residue was filtered through the Celite pad, and the filtrate was extracted with AcOEt. The extract was dried over Na_2SO_4 and concentrated under reduced pressure to leave a residue, which was purified by column chromatography on silica gel (hexane/AcOEt, 7:1) to give allyl alcohol **12** (1.62 g, 90%) as a colorless oil. ^{1}H NMR: δ 0.88 (3H, t, J=6.6 Hz, 13-CH_3), 1.23–1.35 (12H, m, 5-, 6-, 7-, 8-, 9- and 10-CH_2), 1.37–1.52 (2H, m, 4-CH_2), 2.06 (2H, dd, J=7.3, 7.7 Hz, 3-CH_2), 4.08 (2H, d, J=4.5 Hz, 1-CH_2), 4.87 (1H, dd, J=1.2, 2.5 Hz, 1′-C*H*H), 5.01 (1H, d, J=1.2 Hz, 1′-CH*H*); ^{13}C NMR: δ 14.1, 22.6, 27.7, 29.3, 29.4, 29.5, 29.5, 31.9, 33.0, 65.8, 108.9, 149.3; IR (thin film): 3324, 1650, 1466, 1458, 1028, 896; HRMS calcd for $C_{12}H_{24}O$ (M^+): 184.1827, found 184.1813.

4.1.13. (2*R*)-2,3-Epoxy-2-nonanylpropan-1-ol (20). To a stirred suspension of activated MS 3A (0.30 g) and CaH_2 (46 mg, 1.09 mmol) in CH_2Cl_2 (2.7 ml) was added $Ti(O^iPr)_4$ (0.4 ml, 1.36 mmol) at room temperature. The stirred mixture was cooled to −20°C, and treated with D-(−)-DIPT (0.38 g, 1.63 mmol) in CH_2Cl_2 (4.0 ml). After being stirred for 30 min at the same temperature, a solution of allyl alcohol **12** (1.0 g, 5.44 mmol) in CH_2Cl_2 (13.6 ml) was added dropwise to the solution, and the mixture was stirred for further 1 h. TBHP (1.5 ml, 8.15 mmol) was added to this mixture over a period of 30 min. After being stirred for 48 h at −20°C, Me_2S (0.48 ml, 6.52 mmol) was slowly added and the mixture was stirred for 30 min at the same temperature. To this mixture were added 10% aqueous of tartaric acid (3.3 ml, 2.17 mmol), NaF (1.4 g, 33.7 mmol) and Et_2O (9.0 ml), and the resulting mixture was vigorously stirred for 2 h at room temperature. The precipitate was filtered off through a Celite pad. The filtrate was washed successively with saturated aqueous $NaHCO_3$ solution and brine, and dried over Na_2SO_4. Evaporation of the solvent

gave a residue, which was purified by column chromatography on silica gel (hexanes/AcOEt, 1:1) to give epoxy alcohol **20** (0.9 g, 83%) as a colorless oil. $[\alpha]_D^{25}=+13.6$ (c=0.99, $CHCl_3$); ^1H NMR: δ 0.88 (3H, t, J=6.7 Hz, 9′-CH_3), 1.26–1.56 (14H, br s, 2′-, 3′-, 4′-, 5′-, 6′-, 7′- and 8′-CH_2), 1.68–1.83 (2H, m, 1′-H_2), 2.67 and 2.89 (each 1H, each d, J=4.6 Hz, 3-CH_2), 3.64 (1H, dd, J=8.2, 12.2 Hz, 1-CH*H*), 3.78 (1H, dd, J=3.5, 12.2 Hz, 1-C*H*H); ^{13}C NMR: δ 14.1, 22.6, 24.6, 29.3, 29.5, 29.7, 31.8, 31.9, 49.8, 62.7; IR (thin film): 3428, 1465, 1050. Anal. calcd for $C_{12}H_{24}O_2$: C, 71.71; H, 12.16. Found: C, 71.95; H, 12.08; HRMS calcd for $C_{12}H_{24}O_2$ (M^+): 200.1776, found 200.1756. The ee of the benzoate of **20** was determined to be 95% by HPLC analysis on a Chiralcel OB (Daicel Chemical Industries) using hexane–^{i}PrOH (99.5:0.5, v/v).

4.1.14. (2*S*)-1-Benzoyloxy-2,3-epoxy-2-nonanylpropane. To a stirred solution of epoxy alcohol **20** (77 mg, 0.39 mmol) in CH_2Cl_2 (3.9 ml) was added Et_3N (0.16 ml, 1.16 mmol) at 0°C under argon atmosphere, and then benzoyl chloride (67.0 μl, 0.58 mmol) was added dropwise to the mixture. After being stirred for 30 min at room temperature, the reaction was quenched by addition of saturated aqueous of NH_4Cl, and extracted with CH_2Cl_2. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel (hexanes/AcOEt, 1:1) to give benzoate of **20** (106 mg, 91%) as a colorless oil. $[\alpha]_D^{25}=+2.65$ (c=0.99, $CHCl_3$); ^1H NMR: δ 0.86 (3H, t, J=6.9 Hz, 9′-CH_3), 1.25–1.44 (14H, br s, 2′-, 3′-, 4′-, 5′-, 6′-, 7′- and 8′-CH_2), 1.56–1.69 (1H, m, 1′-*H*H), 1.81–1.92 (1H, m, 1′-H*H*), 2.74 and 2.83 (each 1H, each d, J=4.6 Hz, 3-CH_2), 4.26 and 5.52 (each 1H, each d, J=12.0 Hz, 1-H_2), 7.42–7.61 (3H, m, *m*- and *p*-PhH), 8.04 (2H, m, *o*-PhH); ^{13}C NMR: δ 14.0, 22.6, 24.5, 29.2, 29.4, 29.6, 31.8, 32.0, 50.7, 57.5, 66.2, 128.4, 129.6, 129.7, 133.1, 166.1; IR (thin film): 1724, 1452, 1315, 1270, 1180, 1120, 1070, 1025, 710. Anal. calcd for $C_{19}H_{28}O_3$: C, 75.21; H, 9.29. Found: C, 74.96; H, 9.27; HRMS calcd for $C_{19}H_{28}O_3$ (M^+): 304.2038, found 304.2011.

4.1.15. (4*R*)-4-Hydroxymethyltridec-1-en-4-ol (21). To a stirred suspension of CuI (103 mg, 0.54 mmol) in THF (7.0 ml) was added dropwise 1.0 M solution of vinyl magnesium bromide in THF (5.4 ml, 5.4 mmol) at −20°C under argon atmosphere, and the mixture was stirred for 30 min. A solution of epoxy alcohol **20** (360 mg, 1.8 mmol) in THF (3.0 ml) was added to the mixture at the same temperature, and the resulting mixture was stirred for further 48 h. After addition of saturated aqueous NH_4Cl solution, the reaction mixture was filtered through the Celite pad. The filtrate was extracted with AcOEt, and the extract was washed with brine, dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified column chromatography on silica gel (hexanes/AcOEt, 1:1) to afford diol **21** (317 mg, 77%) as a colorless oil. $[\alpha]_D^{24}=-0.93$ (c=1.00, $CHCl_3$); ^1H NMR: δ 0.88 (3H, t, J=6.7 Hz, 13-CH_3), 1.21–1.38 (12H, m, 7-, 8-, 9-, 10-, 11- and 12-CH_2), 1.41–1.49 (1H, m, 6-C*H*H), 1.56–1.60 (1H, m, 6-CH*H*), 1.89–1.90 (2H, m, 5-CH_2), 2.28 (2H, d, J=7.6 Hz, 3-CH_2), 3.48 (2H, d, J=5.9 Hz, CH_2OH), 5.10–5.19 (2H, m, 1-CH_2), 5.84 (1H, dddd, J=7.6, 9.2, 11.9, 15.0 Hz, 2-CH); ^{13}C NMR: δ 14.1, 22.7, 23.3, 29.3, 29.5, 30.2, 31.9, 40.7, 67.9, 74.1, 118.9, 133.4; IR (thin film): 3390, 1640, 1465, 1055, 915; HRMS calcd for $C_{14}H_{27}O_2$ (M^+-1): 227.2011, found 227.2028.

4.1.16. (4*R*)-4-(*tert*-Butyldimethylsilyloxymethyl)tridec-1-en-4-ol (22). Diol **21** (450 mg, 1.97 mmol) and ^{i}Pr$_2$NEt (0.83 ml, 4.74 mmol) were dissolved in CH_2Cl_2 (10.0 ml) under argon atmosphere. After being cooled to 0°C, TBSOTf (0.54 ml, 2.37 mmol) was added dropwise to the solution, and the resulting mixture was stirred for 30 min at the same temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to leave a residue, which was purified by column chromatography on silica gel (hexanes/AcOEt, 3:1) to afford alcohol **22** (640 mg, 95%) as a colorless oil. $[\alpha]_D^{23}=-6.68$ (c=1.00, $CHCl_3$); ^1H NMR: δ 0.05 (6H, s, 2×MeSi), 0.84–0.90 (12H, m, 13-CH_3 and *tert*-BuSi), 1.12–1.39 (16H, m, 5-, 6-, 7-, 8-, 9-, 10-, 11- and 12-CH_2), 2.15–2.30 (2H, m, 3-CH_2), 2.31 (1H, s, OH), 3.37 and 3.42 (each 1H, each d, J=9.6 Hz, 1′-CH_2), 5.01–5.12 (2H, m, 1-CH_2), 5.73–5.12 (1H, m, 2-CH); ^{13}C NMR: δ −5.5, 14.1, 18.2, 22.7, 23.1, 25.8, 29.3, 29.6, 30.3, 31.9, 36.2, 40.9, 68.0, 73.7, 117.8, 134.1; IR (thin film): 3572, 3472, 1640, 1465, 1255, 1095, 915, 840, 775. Anal. calcd for $C_{20}H_{42}O_2Si$: C, 69.95; H, 12.55. Found: C, 70.11; H, 12.35; HRMS calcd for $C_{20}H_{42}O_2Si$ (M^++1): 343.3032, found 343.3060.

4.1.17. (4*S*)-4-Acryloyloxy-4-(*tert*-butyldimethylsilyloxymethyl)tridec-1-ene (23) and (4*S*)-4-acryloyloxy- methyl-4-(*tert*-butyldimethylsilyloxy)tridec-1-ene (24). To a stirred solution of alcohol **22** (272 mg, 0.80 mmol) in THF (8.0 ml) was added dropwise 1.0 M solution of ethylmagnesium bromide in THF (1.59 ml, 1.59 mmol) at room temperature under argon atmosphere. After being stirred for 30 min, methacryloyl chloride (0.23 ml, 2.39 mmol) was added slowly to the solution, and the resulting mixture was stirred for further 14 h at room temperature. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution and the mixture was extracted with AcOEt. The extract was washed with brine and concentrated under reduced pressure to give a residue, which was purified by column chromatography on silica gel (hexanes/AcOEt, 20:1). The first fraction gave methacrylate **23** (157 mg, 48%) as a colorless oil. $[\alpha]_D^{22}=+3.25$ (c=0.99, $CHCl_3$); ^1H NMR: δ 0.02 (6H, s, 2×MeSi), 0.84–0.89 (12H, m, 13-CH_3 and *tert*-BuSi), 1.21–1.30 (14H, br s, 6-, 7-, 8-, 9-, 10-, 11- and 12-CH_2), 1.87–1.88 (5H, m, 5-CH_2 and CCH_3), 2.59 and 2.70 (each 1H, each dd, J=7.4, 14.0 Hz, 3-CH_2), 3.72 and 3.81 (each 1H, each d, J=10.1 Hz, CH_2OTBS), 5.02–5.13 (2H, m, 1-CH_2), 5.46 (1H, m, CC*H*H), 5.65–5.82 (1H, m, 2-CH), 5.99 (1H, dd, J=0.9, 1.7 Hz, CCH*H*); ^{13}C NMR: δ −5.6, 14.1, 18.1, 18.4, 22.7, 22.9, 25.7, 29.3, 29.5, 29.9, 31.9, 33.0, 37.9, 63.4, 86.0, 118.2, 124.5, 133.1, 137.5, 166.4; IR (thin firm): 1716, 1639, 1180, 1120, 840. Anal. calcd for $C_{24}H_{46}O_3Si$: C, 70.01; H, 11.26. Found: C, 70.19; H, 11.29; HRMS calcd for $C_{24}H_{47}O_3Si$ (M^++1): 411.3294, found 411.3302. The second fraction gave isomer **24** (139 mg, 43%) as a colorless oil. ^1H NMR: δ 0.02 (6H, s, 2×MeSi), 0.83–0.90 (12H, m, 13-CH_3 and *tert*-BuSi), 1.22–1.35 (14H, br, 6-, 7-, 8-, 9-, 10-, 11- and 12-CH_2), 1.69–1.97 (5H, m, 5-CH_2 and $COCCH_3$), 2.48–2.61 (2H,

m, 3-CH_2), 3.63–3.80 (2H, m, CH_2OCO), 5.00–5.05 (2H, m, 1-CH_2), 5.57–5.72 (2H, m, 2-CH and COCC*H*H), 5.79 (1H, s, COCCH*H*); IR (thin film): 1730, 1678, 1640, 1466, 1376, 1252, 1116, 920, 840, 780; HRMS calcd for $C_{24}H_{46}O_3Si$ (M^+): 410.3216, found 410.3228.

4.1.18. (5*S*)-2-Methyl-5-(*tert*-butyldimethylsilyloxy)-methyl-tetradec-2-en-5-olide (25). To a solution of methacrylate **23** (250 mg, 0.61 mmol) in benzene (122 ml) was added Ru catalyst (**B**) (19 mg, 0.03 mmol), and the mixture was stirred for 7 h at 70°C. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexanes/AcOEt, 20:1) to give compound **25** (205 mg, 88%) as a colorless oil. $[\alpha]_D^{26}=+10.6$ ($c=1.00$, $CHCl_3$); ^1H NMR: δ 0.02 and 0.04 (each 3H, each s, 2×MeSi), 0.84–0.89 (12H, m, 14-CH_3 and *tert*-BuSi), 1.20–1.45 (14H, br s, 7-, 8-, 9-, 10-, 11-, 12- and 13-CH_2), 1.62–1.69 (2H, m, 6-CH_2), 1.89 (3H, dd, $J=1.9$, 3.6 Hz, 2-CH_3), 2.26–2.39 (1H, m, 4-C*H*H), 2.49–2.62 (1H, m, 4-CH*H*), 3.51 and 3.64 (each 1H, each d, $J=9.9$ Hz, $TBSOCH_2$), 6.39–6.43 (1H, m, 3-CH); ^{13}C NMR: δ −5.6, −5.6, 14.1, 17.0, 18.1, 22.6, 23.0, 25.7, 29.2, 29.4, 29.9, 31.8, 36.6, 66.0, 83.7, 127.2, 137.5, 165.0; IR (thin film): 1720, 1470, 1463, 1360, 1246, 1110, 840. Anal. calcd for $C_{22}H_{42}O_3Si$: C, 69.20; H, 11.14. Found: C, 69.05; H, 11.06; HRMS calcd for $C_{22}H_{42}O_3Si$ (M^+): 382.2903, found 382.2900.

4.1.19. (5*S*)-2-Methyl-5-hydroxymethyltetradec-2-en-5-olide (26). To a mixed solution of compound **25** (170 mg, 0.45 mmol) in EtOH (6.0 ml) and H_2O (1.5 ml) was added $TsOH{\cdot}H_2O$ (8.5 mg, 0.04 mmol), and the mixture was stirred for 15 h at 80°C. After being cooled to room temperature, the reaction was quenched by addition of brine and the mixture was extracted with Et_2O. The extract was dried over Na_2SO_4 and concentrated to leave a residue, which was purified by column chromatography on silica gel (hexanes/AcOEt, 1:1) to give alcohol **26** (115 mg, 96%) as a colorless oil. $[\alpha]_D^{25}=-12.4$ ($c=1.01$, $CHCl_3$); ^1H NMR: δ 0.88 (3H, t, $J=6.7$ Hz, 14-CH_3), 1.20–1.35 (14H, br s, 7-, 8-, 9-, 10-, 11-, 12- and 13-CH_2), 1.60–1.78 (2H, m, 6-CH_2), 1.84–1.94 (4H, m, 2-CH_3 and OH), 2.20–2.33 (1H, m, 4-C*H*H), 2.66–2.79 (1H, m, 4-CH*H*), 3.54 (1H, d, $J=7.7$, 12.0 Hz, C*H*HOH), 3.72 (1H, dd, $J=5.9$, 12.0 Hz, CH*H*OH), 6.47–6.50 (1H, m, 3-CH); ^{13}C NMR: δ 14.1, 16.9, 22.6, 23.8, 28.3, 29.2, 29.4, 29.4, 29.9, 31.8, 35.6, 66.4, 84.7, 127.3, 137.8; IR (thin film): 3424, 1714, 1366, 1128, 1060; HRMS calcd for $C_{16}H_{28}O_3$ (M^+): 268.2038, found 268.2022.

4.1.20. Malyngolide (2) and *epi*-malyngolide (27). A mixture of alcohol **26** (20 mg, 0.07 mmol) and 5% palladium on carbon (10 mg) in hexane (2.0 ml) was stirred for 12 h at room temperature under an atmospheric pressure of hydrogen. After filtration of the catalyst, the filtrate was concentrated to leave a residue, which was purified by column chromatography on silica gel (hexanes/AcOEt, 1:3). The first fraction gave malyngolide **2** (16.1 mg, 80%) as a colorless oil. $[\alpha]_D^{25}=-13.8$ ($c=0.71$, $CHCl_3$); ^1H NMR: δ 0.88 (3H, t, $J=6.7$ Hz, 14-CH_3), 1.21–1.34 (16H, br, 6-, 7-, 8-, 9-, 10-, 11-, 12- and 13-CH_2), 1.50–1.82 (5H, m, 4-CH_2 and 2-Me), 1.89–2.20 (3H, m, 3-CH_2 and OH), 2.36–2.52 (1H, m, 2-CH), 3.48 (1H, dd, $J=4.9$, 12.1 Hz, C*H*HOH), 3.66 (1H, m, CH*H*OH); ^{13}C NMR: δ 14.1, 17.1, 22.6, 23.6, 25.2, 26.2, 29.2, 29.4, 29.5, 30.0, 31.8, 35.5, 36.6, 67.7, 86.9, 175.4; IR (thin film): 3422, 1728, 1710, 1460, 1378, 1328, 1252, 1218, 1102, 1068; HRMS calcd for $C_{16}H_{30}O_3$ (M^+): 270.2195, found 270.2191. The second fraction gave *epi*-malyngolide **27** (2.4 mg, 12%) as a colorless oil. ^1H NMR: δ 0.88 (3H, t, $J=6.7$ Hz, 14-CH_3), 1.26–1.34 (16H, br, 6-, 7-, 8-, 9-, 10-, 11-, 12- and 13-CH_2), 1.64–2.27 (7H, m, 3-CH_2, 4-CH_2 and 2-Me), 1.89–2.23 (1H, br, OH), 2.36–2.52 (1H, m, 2-CH), 3.61 (2H, S, CH_2OH); ^{13}C NMR: δ 14.1, 17.2, 22.6, 23.1, 25.4, 27.1, 29.2, 29.5, 29.5, 29.9, 31.8, 35.2, 37.5, 61.0, 61.8, 67.7, 86.3, 175.3; IR (thin film): 3422, 1728, 1710, 1460, 1378, 1332, 1210, 1110, 1086; HRMS calcd for $C_{16}H_{30}O_3$ (M^+): 270.2195, found 270.2176.

Acknowledgements

This work was supported by the Ministry of Education, Culture, Sports, Science and Technology of Japan. We are grateful to Professor A. H. Hoveyda, J. S. Kingsbury and S. B. Garber (Boston College) for a most generous gift of the ruthenium catalyst.

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12. The ee was determined by HPLC analysis of the benzoate of **20** using a chiral stationary phase (CHIRALCEL OB, Daicel Chemical Industries).