Total Synthesis of (+)-Tanikolide, Using Regioselective Elimination of a Vicinal Dibromoalkane

Tadaaki Ohgiya, Kensuke Nakamura,[1] and Shigeru Nishiyama*

Department of Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi 3-14-1, Kohoku-ku, Yokohama 223-8522

[1]Quantum Bioinformatics Group, Center for Promotion of Computational Science and Engineering, Japan Atomic Energy Research Institute, 8-1 Umemidai, Soraku-gun, Kyoto 619-0215

Received February 28, 2005; E-mail: nisiyama@chem.keio.ac.jp

Total synthesis of (+)-tanikolide, a bioactive δ-lactone of marine origin, was successfully accomplished by utilizing a bromoalkene derivative conveniently synthesized from the corresponding 1-acyloxy-2,3-dibromoalkane by the regioselective and mild HBr-elimination reaction, along with the Pd-mediated C–C coupling reaction and the Sharpless asymmetric epoxidation as key steps.

We recently reported an efficient synthesis of 2-bromo-1-alkenes by the regioselective HBr-elimination reaction from the corresponding 1-*O*-substituted-2,3-dibromoalkanes under mild basic conditions using DBU or sodium acylates (NaOAc, NaOPiv).[1] The synthesis of biologically active natural products was demonstrated by employing our own synthetic protocol of 2-bromo-1-alkenes, as convenient substrates of transition metal-mediated coupling reactions (Fig. 1).[1a,1b] In the case of the elimination reaction of 1-*O*-substituted-2,3-dibromoalkanes, the *syn*-(1*R**,2*R**) and *anti*-orientated (1*R**,2*S**) derivatives will be expected to undergo the *trans*-elimination leading to the corresponding bromoalkenes (**I**, **II**), which would be converted into tri-substituted olefinic structures (**III**, **IV**). We have demonstrated an availability of the substituted bromoalkenes towards natural products synthesis. As part of such investigations, (+)-tanikolide **1**,[2] a biologically active δ-lactone natural product, was synthesized by introducing of chiral centers into the alkenes (Fig. 2).[1c]

(+)-Tanikolide **1**, possessing a structure closely related to that of (−)-malyngolide **2**,[3] was isolated from the marine Cyanobacterium, *Lyngbia majuscula*, collected in Tanikeli Island, Madagascar. A peculiar feature of **1** is the chiral quaternary carbon center with a hydroxymethyl group and a multicarbon chain. Upon comparison with **2**, obtained from the same source collected in Hawaii, **1** has the opposite absolute stereochemistry, different lengths of the alkyl chain, and various biologically activities as follows. Whereas **1** exhibited antifungal activity against *Candida albicans*, toxicity against brine shrimp (LD_{50} of 3.6 μg/mL) and snail (LD_{50} of 9.0 μg/mL), **2** showed antimicrobial activity against *Streptococcus pyogenes* and *Myco-*

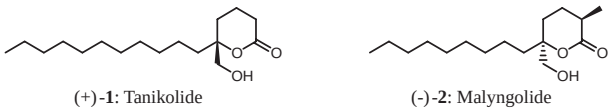


Fig. 2. Structure of tanikolide and malyngolide.

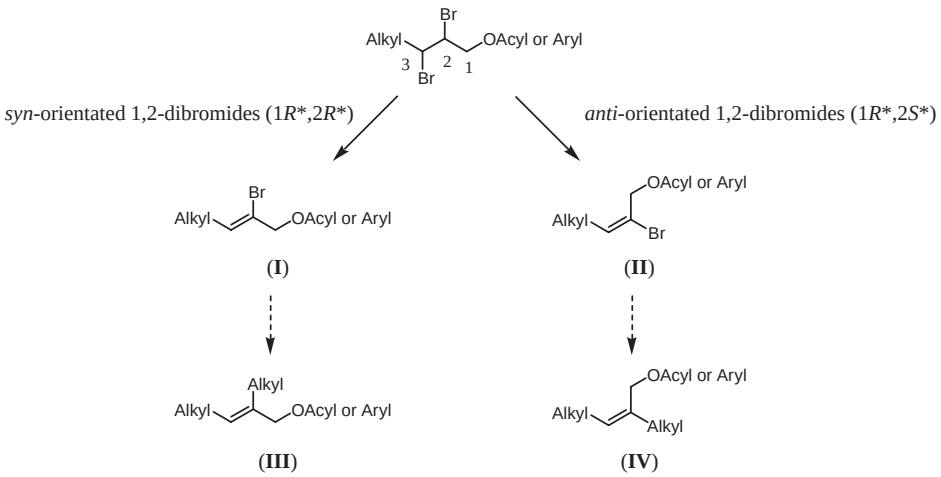


Fig. 1. Regioselective *trans*-elimination reaction of 1-*O*-substituted-2,3-dibromoalkanes and their derivatization into appropriately functionalized units.

Published on the web August 4, 2005; DOI 10.1246/bcsj.78.1549

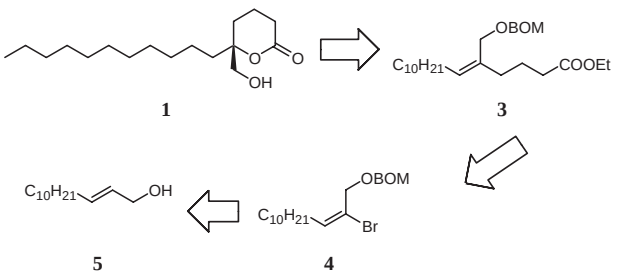
bacterium smegmatis, and no activity against *C. albicans*.[2,3] To contribute information about the structure-activity relationship of these bioactive lactones, several synthetic studies of **1** have already been reported.[4] The first total synthesis of (+)-**1** was achieved by the asymmetric hydrogen transfer reaction of a tricyclic alcohol.[4a] The ring-closing metathesis (RCM) approach for the construction of the δ-lactone moiety as a key step was reported by two groups.[4c,4d]

We describe herein a synthesis of **1** by our bromoalkene approach, which involved the Pd-mediated coupling reaction[5] and the Sharpless asymmetric epoxidation.[6] How to direct the elimination reaction leading to the corresponding alkenes was also evaluated by theoretical calculations.

Results and Discussion

According to the retrosynthetic analysis (Scheme 1), the targeted natural product **1** would be synthesized from **3** by utilizing the Sharpless asymmetric dihydroxylation,[7] or the Sharpless asymmetric epoxidation[6] to construct the tertiary alcohol moiety, and the following assembly of the lactone framework. The tri-substituted alkene **3** may be afforded by the Pd-mediated coupling reaction[5] from key intermediate **4**, which can be produced from allyl alcohol **5** by the regioselective HBr-elimination reaction.[1]

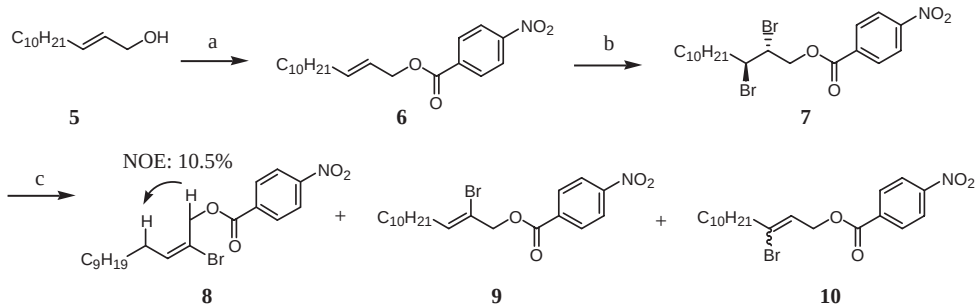
According to this plan, synthesis of **1** was started from protection of **5** with a *p*-nitrobenzoyl group (Scheme 2), the electron-withdrawing effect of which would improve the yield and regioselectivity of the HBr-elimination reaction of the vicinal dibromide **7**.[1] Ester **6**, obtained in quantitative yield, was submitted to bromination with Pyr.-HBr_3 to yield the racemic **7** in 95% yield. Regioselective *trans*-elimination of the vicinal dibromide carrying the *p*-nitrobenzoyloxy group at the adjacent position with DBU[1] provided the bromoalkene derivatives **8**, **9**, and **10** in 94% yield (**8**:**9**:**10** = 60:1:1). Their stereochemistry was determined by the ^{1}H NMR techniques involving the NOE experiments.



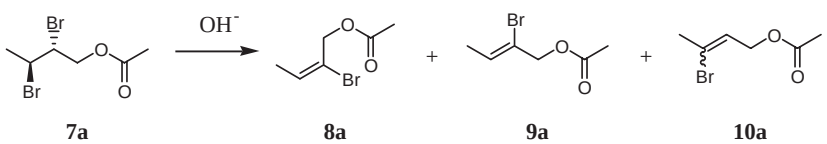
Scheme 1. Retrosynthesis of tanikolide.

To explain the preferential production of **8** from **7**, we carried out theoretical calculations. For the ab initio DFT calculations at B3LYP/6-31+G* level, **7a** and a hydroxyl anion were used as a model system (Scheme 3, Fig. 3). The first transition state (**TS1**) leads to the product **8a**, and the second transition state (**TS2**) leads to **10a**. **TS1** is calculated to be ca. 1.0 kcal/mol more stable than **TS2**. The gas phase calculation indicates that the elimination reaction of a hydrogen atom at the C-2 position and a bromine atom at the C-3 atom to produce **8a** is more feasible than the elimination at the opposite side to produce **10a**. This is probably due to a high acidity of the hydrogen at C-2 position by an electron-withdrawing effect of a *O*-functional group at C-1 position, as compared with that at C-3 position. The computational result is in good agreement with the experimental regioselectivity between **8a** and **10a**. The selectivity between **8a** and **9a** can be explained in the following manner. Three conformations of **7a** are shown in Fig. 4. The *anti*-conformation (**7aa**) is ready for the *trans* β-elimination to form product **8a**. To form **9a**, it has to undergo *cis* β-elimination from **7ab** or **7ac**, which is less feasible compared with *trans* β-elimination.

The *p*-nitrobenzoyloxy group should be converted into other *O*-functional groups to prevent formation of a π-allyl complex[8] under Pd-mediated coupling conditions. Thus, hydrolysis of a mixture of bromoalkene derivatives **8**, **9**, and **10** under basic conditions, followed by chromatographic separation, afforded **11** in 94% yield, which was etherified to give the BOM ether **4** in 98% yield (Scheme 4).



Scheme 2. Reagents and conditions: a) 4-$O_2NC_6H_4COCl$, Pyr., CH_2Cl_2, rt (100%). b) Pyr.-HBr_3, AcOH, rt (95%). c) DBU, DMF, 50 °C (94%; **8**:**9**:**10** = 60:1:1).



Scheme 3. Model system of regioselective elimination reaction with hydroxyl anion.

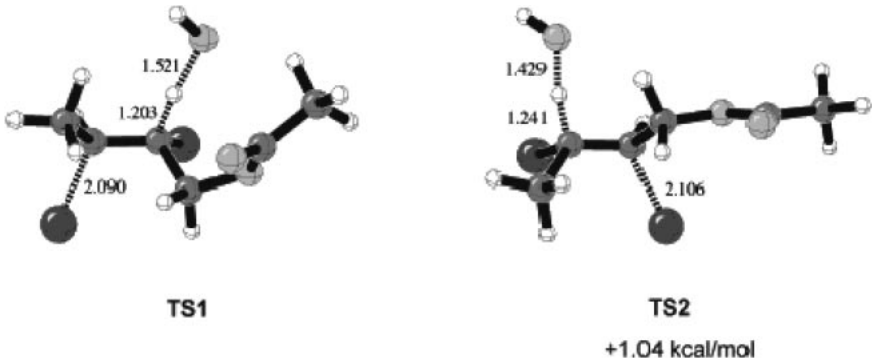


Fig. 3. Transition states of proton abstraction from dibromoalkane by hydroxyl anion optimized at B3LYP/6-31+G* (distances are in angstrom).

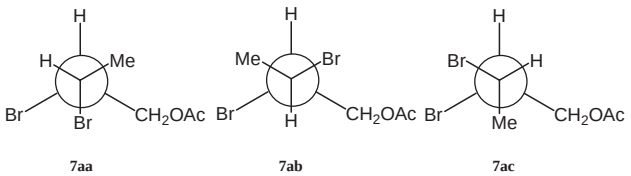
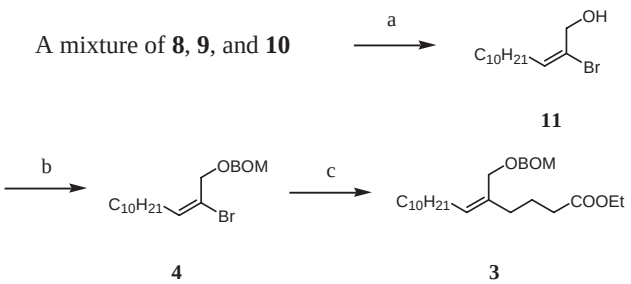


Fig. 4. Three conformations of model compound **7a**.

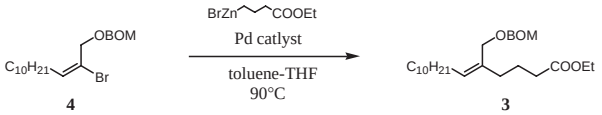


Scheme 4. Reagents and conditions: a) LiOH, dioxane, 0 °C, followed by chromatographic separation (94%). b) BOMCl, iPr$_2$NEt, CH_2Cl_2, rt (98%). c) 5 mol% Pd(dppf)Cl_2, BrZn$(CH_2)_3$COOEt, THF–PhMe, 90 °C (73%).

The following Pd-mediated coupling reaction[5] of the bromo-alkene system was a crucial step. After inspection of several reaction conditions, the desired Pd-mediated coupling reaction[5] with BrZn$(CH_2)_3$COOEt was achieved upon employing 5 mol% of Pd(dppf)Cl_2 in THF–PhMe at 90 °C to give the tri-substituted olefin **3** in 73% yield (Table 1). Upon utilizing other Pd-catalysts, such as Pd$(Et_3P)_4$ and $Pd_2(dba)_3$, a considerable amount of byproducts was produced, contrary to the decrease of yield of **3**. Upon employing 15 mol% of Pd(dppf)Cl_2, **3** was obtained in lower yield than the case of 5 mol% of the catalyst, probably owing to promotion of the degradation reaction.

In the next stage, we selected the Sharpless asymmetric epoxidation[6] for construction of a chiral quaternary carbon center (Scheme 5), while the Sharpless asymmetric dihydroxylation[7] of **3** did not proceed at low temperature, and the enantioselectivity of the oxidation product was less than 50% ee[9] at ambient temperature. The BOM group of **3** cleaved under acidic conditions to give the allyl alcohol **12** in 80% yield, to which a chiral center was successfully introduced by the Sharpless asymmetric epoxidation[6] to give **13** in 99% yield with 94% ee.[9] The siloxy ether **14**, obtained from **13** in quantitative yield, was submitted to reductive-opening reaction of the epoxy ring with $LiEt_3BH$ to give a 1:1 mixture of diol **15** and the silyl-migrated isomer **16** in 94% yield, which without separation was oxidized with PCC to give a 6:1 mixture of the six-membered ring lactone **17** and the seven-membered ring lactone **18** in 60% yield. Finally, exposure of the mixture to TBAF provided (+)-**1** in 87% yield, $[\alpha]_D^{22}$ +1.9 (*c* 1.0, $CHCl_3$) {lit., $[\alpha]_D^{25}$ +2.3 (*c* 0.65, $CHCl_3$)}.[2] The synthetic (+)-**1** was identical to the natural product under the full range of spectroscopic data.[2]

Table 1. Pd-Mediated Coupling Reactions of **4** with BrZn$(CH_2)_3$COOEt

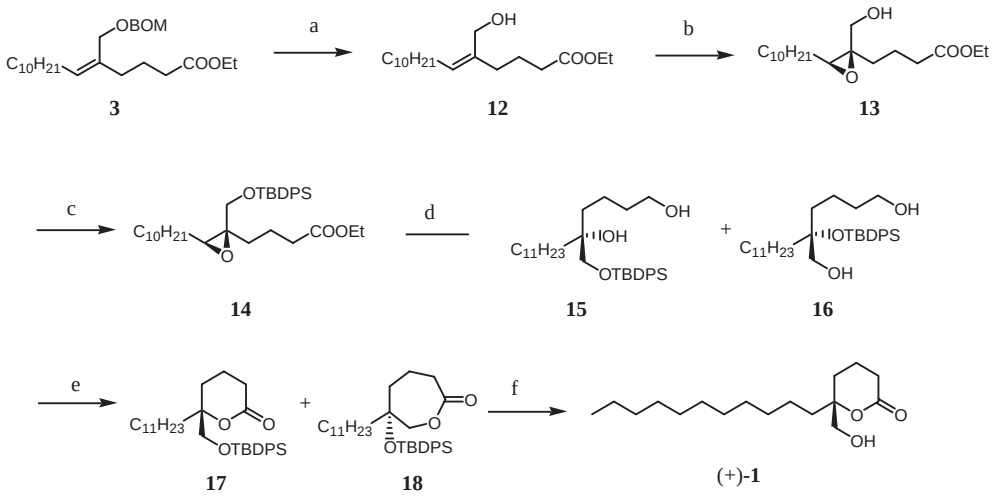


Entry	Pd catalyst (equiv mol)		BrZn$(CH_2)_3CO_2$Et (equiv mol)	Yields/%
1	Pd$(Ph_3P)_4$	0.05	2	38
2	Pd(dppf)Cl_2	0.05	3	73
3		0.15	3	46
4	$Pd_2(dba)_2$	0.05	3	24
5	Pd$(Ph_3P)_2Cl_2$	0.05	3	28
6	Pd$(Et_3P)_2Cl_2$	0.05	3	11

In conclusion, upon employing our efficient and simple bromoalkene synthesis by the regioselective HBr-elimination reaction, the stereoselective total synthesis of (+)-**1** was conveniently achieved. Our strategy will be applicable to several related natural and artificial compounds for investigation of their structure–activity relationships.

Experimental

General. All reactions were carried out under an argon atmosphere unless otherwise noted. Optical rotations were measured on a JASCO DIP-360 digital polarimeter with a sodium (D line) lamp. IR spectra were recorded on a JASCO FT/IR-410 spectrophotometer. ^{1}H NMR spectra and ^{13}C NMR spectra were obtained on JEOL JNM-GX400 spectrometers in $CDCl_3$ using tetramethylsilane as an internal standard. High-resolution mass spectra were obtained on a Hitachi M-80B GC-MS spectrometer operating at



Scheme 5. Reagents and conditions: a) conc. HCl, EtOH, 50 °C (80%). b) D-(−)-DET, TBHP, Ti(O*i*Pr)$_4$, MS4A, CH_2Cl_2, −30 °C (99%). c) TBDPSCl, Imd, DMF, rt (100%). d) $LiEt_3BH$, THF, 60 °C (94%; **15**:**16** = 1:1). e) PCC, MS4A, CH_2Cl_2, 0 °C (60%; **17**:**18** = 6:1). f) TBAF, THF, rt (87%).

the ionization energy of 70 eV. Preparative and analytical TLC were carried out on silica-gel plates (Kieselgel 60 PF_{254}, E. Merck AG., Germany) using UV light and/or 5% molybdophosphoric acid in ethanol for detection. Kanto Chemical silica 60N (spherical, neutral, 63–210 μm) was used for column chromatography.

Synthesis of (*E*)-2-Tridecenyl 4-Nitrobenzoate (6). To a solution of (*E*)-2-tridecen-1-ol (**5**) (1.00 g, 5.0 mmol) in $CHCl_3$ (20 mL) were successively added Pyr. (3.58 g, 45 mmol) and 4-nitrobenzoyl chloride (1.23 g, 6.6 mmol) at 0 °C; the mixture was stirred at ambient temperature for 2.5 h. The mixture was diluted with $CHCl_3$, and washed with 1 mol/L aq HCl, H_2O, and brine. The organic layer was dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane:EtOAc = 100:1) to yield **6** (1.75 g, quantitative yield) as a colorless oil: IR (film) 2925, 2854, 1728, 1608, 1531, 1464 cm^{-1}. ^{1}H NMR δ 0.88 (3H, t, J = 6.8 Hz), 1.18–1.35 (14H, m), 1.41 (2H, m), 2.09 (2H, q, J = 6.8 Hz), 4.81 (2H, d, J = 6.8 Hz), 5.68 (1H, td, J = 6.8, 15.6 Hz), 5.89 (1H, td, J = 6.8, 15.6 Hz), 8.22 (2H, d, J = 8.8 Hz), 8.29 (2H, d, J = 8.8 Hz). ^{13}C NMR δ 14.1, 22.7, 28.9, 29.2, 29.4, 29.5, 29.7 (×2), 32.0, 32.3, 66.7, 123.0, 123.4 (×2), 130.6 (×2), 135.7, 137.8, 150.4, 164.4. Calcd for $C_{20}H_{29}O_4N$: C, 69.14; H, 8.41; N, 4.03%. Found: C, 69.19; H, 8.53; N, 3.88%.

Synthesis of (2*R,3*S**)-2,3-Dibromotridecyl 4-Nitrobenzoate (7).** To a solution of **6** (129 mg, 0.37 mmol) in AcOH (2 mL) was added Pyr.-HBr_3 (131 mg, 0.41 mmol) at ambient temperature; the mixture was stirred at the same temperature for 3 h. The mixture was diluted with $CHCl_3$, and washed with 1 mol/L aq HCl, H_2O, sat. aq $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane:EtOAc = 100:1) to yield **7** (179 mg, 95%) as a colorless oil: IR (film) 2925, 2854, 1731, 1608, 1531, 1456 cm^{-1}. ^{1}H NMR δ 0.88 (3H, t, J = 6.8 Hz), 1.18–1.45 (14H, m), 1.49 (2H, m), 1.94–2.05 (2H, m), 2.17–2.27 (2H, m), 4.30 (1H, dt, J = 3.2, 8.8 Hz), 4.54 (1H, m), 4.84 (1H, dd, J = 6.4, 12.4 Hz), 4.95 (1H, dd, J = 3.2, 12.4 Hz), 8.25 (2H, d, J = 8.8 Hz), 8.33 (2H, d, J = 8.8 Hz). ^{13}C NMR δ 14.2, 22.7, 26.6, 28.9, 29.35, 29.42, 29.55, 29.60, 31.9, 36.9, 53.1, 54.9, 68.2, 123.6 (×2), 130.8 (×2), 134.8, 150.7, 163.9. Calcd for $C_{20}H_{29}O_4NBr_2$: C, 47.36; H, 5.76; N, 2.76%. Found: C, 47.52; H, 5.83; N, 2.66%.

Synthesis of a Mixture of 8, 9, and 10. To a solution of **7** (2.25 g, 4.4 mmol) in DMF (22.5 mL) was added DBU (713 mg, 4.7 mmol) at 0 °C; the mixture was stirred at 60 °C for 1.5 h. The mixture was diluted with Et_2O and washed with H_2O and brine. The organic layer was dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane:EtOAc = 100:1) to yield a 60:1:1 mixture of **8**, **9**, and **10** (1.77 g, 94%) as a colorless oil. Selected spectroscopic data of (*E*)-2-bromo-2-tridecenyl 4-nitrobenzoate **8** in the mixture: IR (film) 2925, 2854, 1731, 1645, 1608, 1531, 1466 cm^{-1}. ^{1}H NMR δ 0.88 (3H, t, J = 6.8 Hz), 1.18–1.42 (14H, m), 1.44 (2H, m), 2.23 (2H, q, J = 8.0 Hz), 5.10 (2H, s), 6.23 (2H, t, J = 8.0 Hz), 8.26 (2H, d, J = 8.8 Hz), 8.31 (2H, d, J = 8.8 Hz). ^{13}C NMR δ 14.1, 22.7, 29.0, 29.1, 29.3, 29.4, 29.57, 29.59, 30.0, 31.9, 64.7, 116.5, 123.5 (×2), 130.8 (×2), 135.1, 139.4, 150.6, 164.0. HRMS calcd for $C_{20}H_{28}O_4N$ (M^+ − Br) 346.2018, found m/z 346.2002.

Synthesis of (*E*)-2-Bromo-2-tridecen-1-ol (11). To a solution of a 60:1:1 mixture of **8**, **9**, and **10** (589 mg, 1.4 mmol) in dioxane (20 mL) was added H_2O (5.4 mL) solution of LiOH–H_2O (72 mg, 1.7 mmol) at ambient temperature; the mixture was stirred at the same temperature for 30 min. The mixture was then diluted with $CHCl_3$ and washed with H_2O and brine. The organic layer was dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane:EtOAc = 50:1) to yield **11** (361 mg, 94%) as a colorless oil: IR (film) 3336, 2924, 2854, 1643, 1466 cm^{-1}. ^{1}H NMR δ 0.88 (3H, t, J = 6.8 Hz), 1.18–1.36 (14H, m), 1.39 (2H, m), 1.91 (1H, t, J = 6.3 Hz), 2.11 (2H, q, J = 7.8 Hz), 4.30 (2H, d, J = 6.3 Hz), 6.02 (1H, t, J = 7.8 Hz). ^{13}C NMR δ 14.2, 22.7, 29.1, 29.2, 29.35, 29.40, 29.57, 29.62, 29.7, 31.9, 62.6, 124.1, 135.4. Calcd for $C_{13}H_{25}OBr$: C, 56.32; H, 9.09%. Found: C, 56.23; H, 8.93%.

Synthesis of (*E*)-1-(Benzyloxymethyl)oxy-2-bromo-2-tridecene (4). To a solution of **11** (950 mg, 3.4 mmol) in CH_2Cl_2 (25 mL) were successively added *i*Pr_2NEt (4.45 g, 34 mmol) and BOMCl (2.68 g, 17 mmol) at 0 °C; the mixture was stirred at the same temperature for 20 h. The mixture was diluted with $CHCl_3$, and then washed with 1 mol/L aq HCl, H_2O, and brine. The organic layer was dried (Na_2SO_4), and concentrated in vacuo.

The residue was purified by silica-gel column chromatography (hexane:EtOAc = 50:1) to yield **4** (1.34 g, 98%) as a colorless oil: IR (film) 2924, 2854, 1643, 1496, 1456 cm^{-1}. ^1H NMR δ 0.88 (3H, t, $J = 6.4$ Hz), 1.18–1.36 (14H, m), 1.37 (2H, m), 2.01 (2H, q, $J = 7.8$ Hz), 4.34 (2H, s), 4.66 (2H, s), 4.80 (2H, s), 6.14 (1H, t, $J = 7.8$ Hz), 7.27–7.37 (5H, m). ^{13}C NMR δ 14.2, 22.7, 29.1, 29.2, 29.38, 29.43, 29.60, 29.63, 29.8, 31.9, 66.4, 69.6, 93.1, 119.9, 127.7, 127.9 (×2), 128.4 (×2), 137.6, 137.9. Calcd for $C_{21}H_{33}O_2Br$: C, 63.47; H, 8.37%. Found: C, 63.55; H, 8.36%.

Synthesis of Ethyl (*Z*)-5-[(Benzyloxymethyl)oxy]methyl-5-hexadecenoate (3). To a solution of **4** (790 mg, 2.0 mmol) in toluene (24 mL) were successively added $Pd(dppf)Cl_2$ (80 mg, 0.098 mmol) and $BrZn(CH_2)_3COOEt$ (0.5 mol/L solution in THF, 12 mL, 6.0 mmol) at 0 °C; the mixture was stirred at 90 °C for 1 h. The mixture was diluted with $CHCl_3$, and washed with 1 mol/L aq HCl, H_2O, and then brine. The organic layer was dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane:EtOAc = 50:1) to yield **3** (627 mg, 73%) as a colorless oil: IR (film) 2925, 2854, 1736, 1496, 1456 cm^{-1}. ^1H NMR δ 0.88 (3H, t, $J = 6.4$ Hz), 1.18–1.45 (19H, m), 1.77 (2H, quintet, $J = 7.2$ Hz), 2.07 (2H, q, $J = 7.2$ Hz), 2.13 (2H, t, $J = 7.2$ Hz), 2.29 (2H, t, $J = 7.2$ Hz), 4.11 (2H, s), 4.12 (2H, q, $J = 7.6$ Hz), 4.62 (2H, s), 4.74 (2H, s), 5.41 (1H, t, $J = 7.2$ Hz), 7.27–7.37 (5H, m). ^{13}C NMR δ 14.2, 14.3, 22.7, 23.4, 27.8, 29.35, 29.38, 29.6, 29.66, 29.67, 30.0, 31.9, 33.9, 34.7, 60.2, 64.4, 69.3, 93.7, 127.6, 127.7 (×2), 128.3 (×2), 131.0, 134.0, 137.9, 173.6. Calcd for $C_{27}H_{44}O_4$: C, 74.96; H, 10.25%. Found: C, 74.88; H, 10.07%.

Synthesis of Ethyl (*Z*)-5-Hydroxymethyl-5-hexadecenoate (12). To a solution of **3** (746 mg, 1.7 mmol) in EtOH (25 mL) were added conc. HCl (1.25 mL, 15 mmol) at 0 °C; the mixture was stirred at 50 °C for 7 h. The mixture was then diluted with $CHCl_3$, and washed with H_2O and brine. The organic layer was dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane:EtOAc = 6:1) to yield **12** (431 mg, 80%) as a colorless oil: IR (film) 3437, 2924, 2854, 1738, 1463 cm^{-1}. ^1H NMR δ 0.88 (3H, t, $J = 6.8$ Hz), 1.20–1.38 (19H, m), 1.78 (2H, quintet, $J = 7.6$ Hz), 2.05 (2H, q, $J = 7.6$ Hz), 2.15 (2H, t, $J = 7.6$ Hz), 2.30 (2H, t, $J = 7.6$ Hz), 4.12 (2H, q, $J = 6.8$ Hz), 4.14 (2H, s), 5.32 (1H, t, $J = 7.2$ Hz). ^{13}C NMR δ 14.2, 14.3, 22.7, 23.5, 27.6, 29.34, 29.38, 29.6, 29.7 (×2), 30.1, 32.0, 33.8, 34.5, 60.2, 60.3, 129.7, 137.1, 173.8. Calcd for $C_{19}H_{36}O_3$: C, 73.03; H, 11.61%. Found: C, 72.94; H, 11.55%.

Synthesis of Ethyl (5*R*,6*S*)-5,6-Epoxy-5-hydroxymethylhexadecanoate (13). To a solution of D-(−)-DET (83 mg, 0.40 mmol) in dry CH_2Cl_2 (1 mL) were successively added $Ti(OiPr)_4$ (116 mg, 0.41 mmol) and MS4A powder (100 mg) at −30 °C; the mixture was stirred at the same temperature for 20 min. To the reaction mixture were successively added **12** (90 mg, 0.29 mmol) in dry CH_2Cl_2 (3 mL) and TBHP (5.1 mol/L in isooctane, 130 μL, 0.66 mmol) at −30 °C; the mixture was stirred at −30 °C for 10 h. To the reaction mixture was added 10% H_2O solution of L-(+)-tartaric acid (3 mL) at −20 °C; the mixture was stirred at the same temperature for 30 min. After the mixture was stirred at ambient temperature for 1 h, the mixture was filtered, the filtrate was diluted with $CHCl_3$, then washed with H_2O and brine. The organic layer was dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane:EtOAc = 6:1) to yield **13** (94 mg, 99%, 94% ee[9]) as a colorless oil: $[\alpha]_D^{22}$ −5.7 (*c* 1.0, $CHCl_3$); IR (film) 3454, 2925, 2854, 1738, 1464 cm^{-1}. ^1H NMR δ 0.88 (3H, t, $J = 6.4$ Hz), 1.18–1.63 (21H, m), 1.68–1.81 (2H, m), 1.89 (2H, ddd, $J = 5.2$, 10.8, 14.0 Hz), 2.33 (2H, t, $J = 6.8$ Hz), 2.86 (1H, t, $J = 6.0$ Hz), 3.68 (1H, d, $J = 11.6$ Hz), 3.76 (1H, d, $J = 11.6$ Hz), 4.13 (2H, q, $J = 7.2$ Hz). ^{13}C NMR δ 14.2, 14.3, 20.2, 22.7, 26.7, 28.1, 29.4, 29.5, 29.56, 29.57, 29.6, 31.9, 33.1, 34.1, 60.4, 61.9, 62.8, 63.7, 173.3. Calcd for $C_{19}H_{36}O_4$: C, 69.47; H, 11.07%. Found: C, 69.31; H, 10.91%.

Synthesis of Ethyl (5*S*,6*S*)-5,6-Epoxy-5-[(*tert*-butyldimethylsilyl)oxy]methylhexadecanoate (14). To a solution of **13** (48 mg, 0.15 mmol) in DMF (1 mL) were successively added Imd (90 mg, 1.3 mmol) and TBDPSCl (106 mg, 0.39 mmol) at 0 °C; the mixture was stirred at ambient temperature for 13 h. The mixture was diluted with Et_2O, and washed with H_2O and brine. The organic layer was dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane:EtOAc = 2:1) to yield **14** (83 mg, quantitative yield) as a colorless oil: $[\alpha]_D^{22}$ +1.1 (*c* 1.0, $CHCl_3$); IR (film) 2927, 2856, 1736, 1589, 1464 cm^{-1}. ^1H NMR δ 0.88 (3H, t, $J = 6.8$ Hz), 1.07 (9H, s), 1.16–1.48 (21H, m), 1.63–1.78 (3H, m), 1.83 (1H, m), 2.30 (2H, t, $J = 7.2$ Hz), 2.77 (1H, t, $J = 6.0$ Hz), 3.63 (1H, d, $J = 11.6$ Hz), 3.72 (1H, d, $J = 11.6$ Hz), 4.12 (2H, q, $J = 7.2$ Hz), 6.35–7.46 (6H, m), 7.66 (2H, t, $J = 8.0$ Hz), 7.67 (2H, t, $J = 8.0$ Hz). ^{13}C NMR δ 14.2, 14.3, 19.3, 20.3, 22.7, 26.8, 26.9 (×3), 28.1, 29.4, 29.52, 29.56, 29.60, 29.64, 32.0, 33.0, 34.5, 60.3, 62.6, 63.1, 63.4, 127.6 (×2), 129.7 (×2), 132.7 (×2), 133.2 (×2), 135.5 (×2), 135.6 (×2), 173.2. Calcd for $C_{35}H_{54}O_4Si$: C, 74.15; H, 9.60%. Found: C, 74.07; H, 9.47%.

Synthesis of (5*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]methyl-5-undecyl-δ-hexadecylolactone (17) and (5*R*)-5-(*tert*-Butyldimethylsilyl)oxy-5-undecyl-ε-hexylolactone (18). To a solution of **14** (83 mg, 0.15 mmol) in dry THF (0.5 mL) was added $LiEt_3BH$ (1.0 mol/L solution in THF, 1.5 mL, 1.5 mmol) at 0 °C; the mixture was stirred at 60 °C for 15 min. The mixture was diluted with $CHCl_3$, and then washed with H_2O and brine. The organic layer was dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane:EtOAc = 3:2) to yield a 1:1 mixture of **15** and **16** (72.5 mg, 94%) as a colorless oil: IR (film) 3365, 2927, 2854, 1589, 1464 cm^{-1}. ^1H NMR δ 0.88 (3H, t, $J = 6.8$ Hz), 0.90 (4.5H, s), 1.04 (4.5H, s), 1.16–1.64 (27H, m), 3.40 (1H, s), 3.48 (1H, s), 3.53 (1H, t, $J = 6.4$ Hz), 3.62 (1H, t, $J = 6.4$ Hz), 6.35–7.52 (6H, m), 7.63 (2H, d, $J = 6.4$ Hz), 7.72 (2H, d, $J = 6.4$ Hz). Calcd for $C_{33}H_{54}O_5Si \cdot 0.2H_2O$: C, 74.72; H, 10.34%. Found: C, 74.61; H, 10.17%.

To a solution of 1:1 mixture of **15** and **16** (72 mg, 0.14 mmol) in dry CH_2Cl_2 (3 mL) were successively added MS4A powder (100 mg) and PCC (155 mg, 0.72 mmol) at 0 °C; the mixture was stirred at the same temperature for 1 h. The mixture was filtered and concentrated in vacuo. The residue was purified by preparative TLC (hexane:acetone = 6:1) to yield a 6:1 mixture of **17** and **18** (43 mg, 60%) as a colorless oil: IR (film) 2927, 2854, 1741, 1589, 1464 cm^{-1}. ^1H NMR δ 0.88 (3H, t, $J = 6.8$ Hz), 1.02 (1.26H, s), 1.06 (7.74H, s), 1.16–1.45 (18H, m), 1.60–1.90 (5.14H, m), 2.04 (0.86H, m), 2.45 (1.72H, t, $J = 6.8$ Hz), 2.47 (0.28H, t, $J = 6.8$ Hz), 3.56 (0.86H, d, $J = 10.4$ Hz), 3.60 (0.86H, d, $J = 10.4$ Hz), 3.82 (0.14H, d, $J = 12.8$ Hz), 3.98 (0.14H, d, $J = 12.8$ Hz), 6.35–7.47 (6H, m), 7.65 (3.44H, dd, $J = 1.2$, 8.0 Hz), 7.70–7.73 (0.56H, m). HRMS calcd for $C_{29}H_{41}O_3Si$ ($M^+ - {}^tBu$) 465.2825, found m/z 465.2832. This mixture was submitted to the next reaction without further purification.

Synthesis of (+)-Tanikolide (1). To a solution of the 6:1 mixture of **17** and **18** (43 mg, 0.082 mmol) in THF (1 mL) was added TBAF (1 mol/L in THF, 150 μL, 0.15 mmol) at 0 °C; the mixture was stirred at ambient temperature for 1 h. The mixture was concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane:EtOAc = 1:1) to yield **1** (20.4 mg, 87%) as a colorless oil: $[\alpha]_D^{22}$ +1.9 (*c* 1.0, $CHCl_3$); IR (film) 3417, 2924, 2854, 1730, 1710, 1466 cm^{-1}. ^1H NMR δ 0.88 (3H, t, J = 6.4 Hz), 1.23–1.40 (18H, m), 1.55–1.78 (4H, m), 1.82–1.95 (2H, m), 2.12 (1H, br), 2.42–2.55 (2H, m), 3.55 (1H, d, J = 12.0 Hz), 3.66 (1H, d, J = 12.0 Hz). ^{13}C NMR δ 14.2, 16.7, 22.7, 23.5, 26.6, 29.4, 29.5, 29.58, 29.63, 29.7, 29.8, 30.0, 31.9, 36.6, 67.5, 86.5, 171.5. Calcd for $C_{17}H_{32}O_3 \cdot 0.2H_2O$: C, 70.89; H, 11.34%. Found: C, 70.73; H, 11.24%.

This work was supported by a Grant-in-Aid for the 21st Century COE program "KEIO Life Conjugate Chemistry", as well as Scientific Research C from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References

1 a) T. Ohgiya and S. Nishiyama, *Chem. Lett.*, **33**, 1084 (2004). b) T. Ohgiya and S. Nishiyama, *Heterocycles*, **63**, 2349 (2004). c) T. Ohgiya and S. Nishiyama, *Tetrahedron Lett.*, **45**, 8273 (2004).

2 I. P. Singh, K. E. Milligan, and W. H. Gerwick, *J. Nat. Prod.*, **62**, 1333 (1999).

3 J. H. Cardllina, II, R. E. Moore, E. V. Arnold, and J. Clardy, *J. Org. Chem.*, **44**, 4039 (1979).

4 a) R. M. Kanada, T. Taniguchi, and K. Ogasawara, *Synlett*, **2000**, 1019. b) H. Tanaka, Y. Kozuki, and K. Ogasawara, *Tetrahedron Lett.*, **43**, 4175 (2002). c) H. Mizutani, M. Watanabe, and T. Honda, *Tetrahedron*, **58**, 8929 (2002). d) M. Carda, S. Rodriguez, E. Castillo, A. Bellido, S. Diaz-Oltra, and J. A. Marco, *Tetrahedron*, **59**, 857 (2003). e) A. E. Koumbis, K. M. Dieti, M. G. Vikentiou, and J. K. Gallos, *Tetrahedron Lett.*, **44**, 2513 (2003). f) J. M. Schomaker and B. Borhan, *Org. Biomol. Chem.*, **2**, 621 (2004).

5 E. Negishi, L. F. Valente, and M. Kobayashi, *J. Am. Chem. Soc.*, **102**, 3298 (1980).

6 a) M. G. Finn and K. B. Sharpless, "On the Mechanism of Asymmetric Epoxidation with Titanium-Tartrate Catalysts. Asymmetric Synthesis," ed by J. D. Morrison, Academic, Tokyo (1985), Vol. 5, pp. 247–308. b) T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, **102**, 5974 (1980).

7 a) K. B. Sharpless, W. Amberg, M. Beller, H. Chen J. Hartung, Y. Kawanami, D. Lubben, E. Manoury, Y. Ogino, T. Shibata, and T. Ukita, *J. Org. Chem.*, **56**, 4585 (1991). b) K. B. Sharpless, W. Amberg, Y. L. Bennai, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu, and X.-L. Zhang, *J. Org. Chem.*, **57**, 2768 (1992).

8 a) B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, **102**, 4730 (1980). b) B. M. Trost and N. Asakawa, *Synthesis*, **1999**, 1491.

9 The optical purity was determined by the 400 MHz ^1H NMR spectra of the corresponding MTPA esters.