

Synthesis of (*R*)-(+)-Tanikolide through Stereospecific C–H Insertion Reaction of Dichlorocarbene with Optically Active Secondary Alcohol Derivatives

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Stereospecific α C–H insertion reaction of protected chiral 1,2-glycols, (*S*)-1,2-isopropylidenedioxytridecane (3) and ethyl (*S*)-4,5-isopropylidenedioxy-pentanoate (4), prepared from (*R*)-glyceraldehyde acetonide (2), with dichlorocarbene generated from CHCl_3 /50% NaOH/cetyltrimethylammonium chloride (as ptc.) took place with complete retention of configuration to provide (*S*)-4-dichloromethyl-2,2-dimethyl-4-undecyl-1,3-dioxolane (5) and ethyl (*S*)-3-(4-dichloromethyl-2,2-dimethyl-1,3-dioxolan-4-yl)-propanoate (8), respectively. The ester (8) was transformed to 5 by elongation of the side chain. The glycol derivative (5) was converted into *O*-TBDPS-protected (*S*)-2-hydroxymethyl-2-undecyloxirane (16). Reaction of 16 with a cuprate reagent containing homoallylic carbon chain followed by oxidative manipulation of the terminal olefin afforded (*R*)-(+)-tanikolide (1).

Key words tanikolide; chiral synthesis; C–H insertion; dichlorocarbene; dichloromethylcarbinol; tertiary alcohol

Optically active tertiary alcohols and the related compounds are widely distributed in biologically active compounds including medicine.¹⁾ Chiral tertiary alcohol derivatives as building blocks for the synthesis of such bioactive compounds have generally been prepared synthetically by biological and chemical methods including kinetic resolution of racemates,^{2–4)} enantioselective oxygenation of 1,1-disubstituted olefins or substituted aromatics,^{5–12)} desymmetrization of prochiral tertiary alcohols,^{13–15)} enantioselective alkylation of ketones,^{16–23)} and asymmetric alkylation of chiral secondary carbinol carbon with memory of chirality.^{24–27)} High levels of chiral induction (>95% ee), however, have been hardly attained by these methods. On the other hand, several excellent practical methods have been developed to obtain optically active secondary alcohols in nearly perfect enantioselectivity.^{28–37)} Devices for introduction of carbon substituents into the α -methine C–H bond of such optically active secondary alcohols with complete stereospecificity in the sense of retention or inversion of configuration would offer facile methods for production of optically active tertiary alcohol derivatives.

We have recently found α C–H insertion reaction of chiral protected alcohol derivatives with dichlorocarbene generated from chloroform and 50% NaOH aqueous solution in the

presence of phase transfer catalyst (ptc.) to provide chiral tertiary alcohol building blocks with complete retention of configuration of the stereogenic center in the starting alcohols (Chart 1).³⁸⁾

(+)-Tanikolide (1) is a δ -lactone metabolite of marine cyanobacterium *Lyngbya majuscul* collected at Tanikeli Island, Madagascar³⁹⁾ and exhibits toxic and antifungal activities. The absolute structure of 1 containing an asymmetric carbon of (*R*) configuration has been determined synthetically by Ogasawara and coworkers.⁴⁰⁾ Several Chemists have achieved syntheses of optically active 1 so far.^{41–44)} This paper reports on a demonstration of the utilities of dichloromethylcarbinol derivatives, prepared by dichlorocarbene C–H insertion reaction of protected chiral secondary alcohols, for synthesis of an optically active tertiary alcohol natural product (*R*)-(+)-tanikolide (1) as shown in Chart 2: Application of the method to chiral glycol acetonides (A) prepared from D-mannitol *via* glyceraldehyde acetonide (2) and utilization of the chiral tertiary alcohol building blocks (B) obtained to the synthesis of 1.

Results and Discussion

The synthesis has been started with glycol derivatives (3)⁴⁵⁾ and (4)⁴⁶⁾ prepared from (*R*)-glyceraldehyde acetonide (2) (Chart 3). Treatment of (*S*)-tridecane-1,2-diol acetonide (3) with chloroform and 50% aqueous NaOH in the presence of cetyltrimethylammonium chloride as a phase transfer catalyst (ptc.)⁴⁷⁾ at 80 °C for 12 h afforded the corresponding dichloromethylated compound (5) in 58% yield with 24% recovery of starting material (3). ¹H-NMR and MS data of 5 supported the structure of 5, and enantiomeric purity of 5

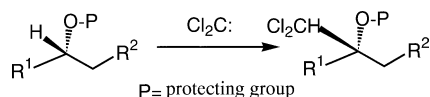


Chart 1. Dichlorocarbene C–H Insertion Reaction of Secondary Alcohol Derivatives

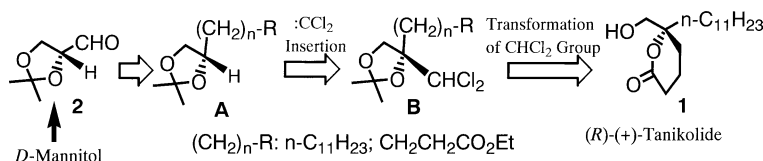
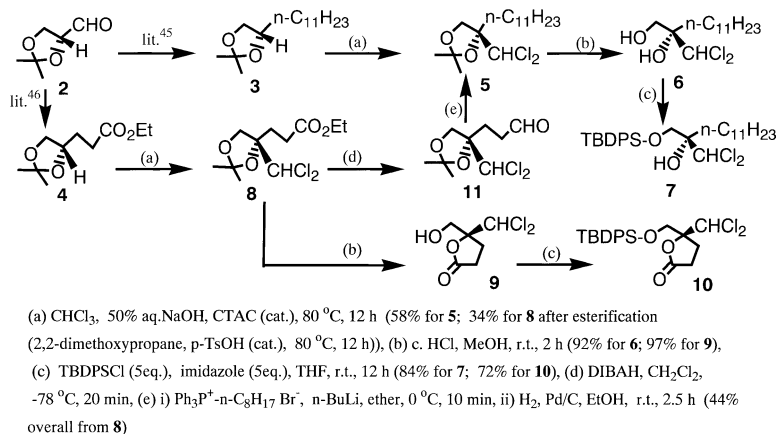
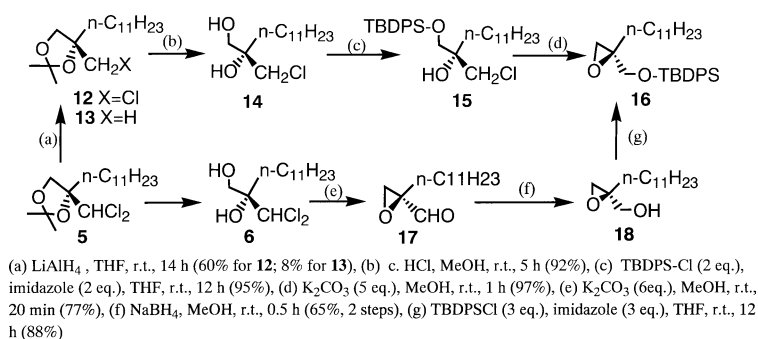


Chart 2. Synthesis of (*R*)-(+)-Tanikolide from D-Mannitol

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Chart 3. Synthesis of Tertiary Dichloromethylcarbinol Derivative (**5**)Chart 4. Synthesis of Epoxy-Alcohol Derivative (**16**), Key Intermediate for **1**

was determined to be over 98% ee by chiral HPLC analysis of the glycol mono-*t*-butyldiphenylsilyl (TBDPS) ether (**7**), which was derived from **5** through acidic hydrolysis providing a glycol (**6**), followed by TBDPS-protection of the primary hydroxyl group as shown in Chart 3. The absolute configuration (*S*) of the quaternary carbon was assigned on the bases of the previous results³⁸⁾ and verified finally by derivation of (*R*)-(+)-tanikolide (**1**) from **5**. On the other hand, the carbene reaction of a glycol-ester derivative (**4**) under the same reaction conditions gave a low yield (21%) of the desired compound (**8**) with a large amount of recovery of the starting material (**4**) after esterification by treatment of the crude product mixture containing carboxylic acids with 2,2-diethoxypropane in the presence of catalytic *p*-TsOH at 80 °C for 12 h. The yield of **8** was improved upto 34% by addition of dichloroethane as a cosolvent, although a large amount (53%) of the starting material (**4**) was recovered after the same treatment of the crude product.⁴⁸⁾ The stereochemical purity of the compound (**8**) was demonstrated by conversion of **8** through acidic treatment affording γ -hydroxymethyl- γ -lactone (**9**) followed by etherification of the alcohol with *t*-butyldiphenylsilyl chloride (TBDPS-Cl) into the TBDPS-derivative (**10**), which showed purity over 98% ee on the chiral HPLC. The ester (**8**) was converted into the compound (**5**) with a long carbon chain by three step sequence of reactions in 44% overall yield through reduction with diisobutylaluminum hydride (DIBAH) giving aldehyde (**11**), Wittig reaction using *n*-octyldienephosphorane, and hydrogenation of the produced olefin (Chart 3).

In extensive trials for reductive mono-dechlorination of **5**

including reduction with *n*-Bu₃SnH,⁴⁹⁾ we found LiAlH_4 as a useful reagent for the transformation. Thus, treatment of **5** with 2 eq of LiAlH_4 in THF for 14 h at room temperature gave a 60% yield of the desired chloromethylcarbinol derivative (**12**) with a small amount of a methyl carbinol (**13**) (8%). The epoxide (**16**), a key intermediate for tanikolide (**1**) was obtained from **12** through a three step sequence of reactions in a high overall yield (85%): acidic deacetonidation providing a diol (**14**), OH-protection of **14** to give a mono-TBDPS ether (**15**), and treatment of **15** with K_2CO_3 . The epoxide (**16**) was provided from **5** through another route by way of the glycol (**6**). Acidic treatment of (**5**) followed by stirring of the intermediate glycol (**6**) with K_2CO_3 in MeOH for 20 min at room temperature afforded successfully an epoxy-aldehyde (**17**) in 71% yield. Reduction of the epoxy-aldehyde (**17**) with NaBH_4 furnished in a high yield an epoxy-alcohol (**18**), which was led to the corresponding TBDPS-ether (**16**) (Chart 4).

The procedure for the three step conversion from (**5**) to (**18**) mentioned above, could be carried out in successive one-pot treatment in MeOH. Homogeneity concerning the stereochemistry and structure of the epoxide (**16**) prepared via the epoxyaldehyde (**17**) were determined by chiral HPLC analysis and identification with the compound (**16**) which was obtained from the chloromethylcarbinol (**12**). The transformation of the glycol (**6**) to the epoxy-aldehyde (**17**) is interpreted to proceed with tandem epoxide migration closely related to the Payne rearrangement^{50–52)} illustrated in Chart 5.

Having the key intermediate (**16**) for the synthesis of (*R*)-

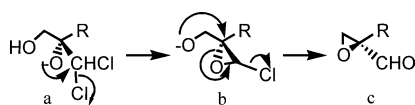
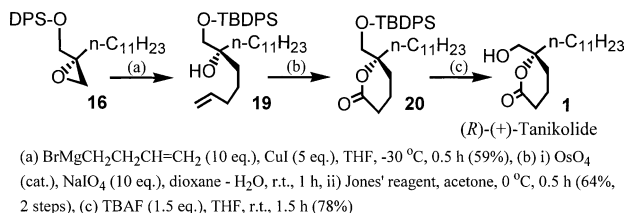


Chart 5. Tandem Epoxide Migration

Chart 6. Synthesis of (*R*)-(+)-Tanikolide (**1**)

(+)-tanikolide (**1**) in hand, construction of the δ -lactone skeleton was performed according to Chart 6. Homoallylation using a 5 eq of a cuprate reagent prepared from 3-butenyl Grignard reagent and CuI in THF at $-30\text{ }^\circ\text{C}$ for 0.5 h gave a tertiary alcohol derivative (**19**) in 59% yield. The terminal olefin was designed as the latent carboxyl group. Thus, Lemieux oxidation of (**19**) with catalytic OsO_4 and an 10 eq of NaIO_4 in aqueous dioxane at room temperature for 1 h provided a crude hemiacetal, which was successfully oxidized with Jones reagent to an optically pure δ -lactone derivative (**20**) in 64% overall yield. The final deprotection of TBDPS-group with tetrabutylammonium fluoride (TBAF) proceeded smoothly to give the target molecule, (*R*)-(+)-tanikolide (**1**), which was identified with the natural one^{39,40} in spectroscopic comparisons including specific optical rotation.

In conclusion, optically active natural (*R*)-(+)-tanikolide (**1**) was synthesized stereospecifically from (*R*)-glyceraldehyde acetonide (**2**) easily prepared from D-mannitol as a chiral source *via* stereospecific insertion reaction of chiral secondary alcohol derivatives with dichlorocarbene. Reduction of dichloromethyl group (**5**) with LiAlH_4 providing chloromethyl group (**12**) and basic treatment of dichloromethylated glycol system (**6**) leading to epoxy-aldehyde (**17**) functionality with complete inversion of configuration of the starting alcohol offer novel methods for transformations of the dichloromethyl carbinol group to synthetically versatile functionalities.^{53,54}

Experimental

Melting points (mp) were measured with a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer. $^1\text{H-NMR}$ spectra was recorded on a JEOL JNM-GX-270 (270 MHz) spectrometer in CDCl_3 with SiMe_4 as an internal standard; J values are given in hertz (Hz). Mass spectra (MS) and high-resolution mass spectra (HR-MS) were recorded on a JEOL JMS-D300 or a JEOL JMS-SX102A spectrometer. High performance liquid chromatography (HPLC) was carried out on Shimadzu LC-6A using solvents and columns ($25\text{ cm} \times 4.6\text{ mm}$) indicated in the text with a flow rate of 1.0 ml/min, and peaks were observed using an UV detector (254 nm). Specific optical rotation $[\alpha]_D$ was measured by JASCO DIP-360 digital polarimeter using a cell ($50\text{ mm} \times 3\text{ mm}$). Products were purified by silica gel chromatography or preparative TLC. Tetrahydrofuran (THF) and diethyl ether (ether) were freshly distilled from sodium benzophenone ketyl prior to use. Dichloromethane and 1,2-dichloroethane were distilled from CaH_2 and stored over molecular sieves. The starting materials, (*S*)-1,2-isopropylidenedioxytridecane (**3**) and ethyl (*S*)-4,5-isopropylidenedioxypentanoate (**4**) were prepared from (*R*)-glyceraldehyde acetonide (**2**) according to the litera-

tures.^{45,46}

(*S*)-4-Dichloromethyl-2,2-dimethyl-4-undecyl-1,3-dioxolane (5**)** To aq. 50% NaOH (50 g) was added a solution of an acetonide **3** (1.90 g, 7.4 mmol) and cetyltrimethylammonium chloride (CTAC) (5 mg) in CHCl_3 (20 ml), and the mixture was warmed at $80\text{ }^\circ\text{C}$ for 12 h under vigorous stirring. After neutralization by addition of dil. H_2SO_4 , the product was extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4 , and evaporated to give a crude mass, which was chromatographed on silica gel (hexane:EtOAc=50:1) to give a dichloromethylcarbinol **5** (1.46 g, 58%) and the starting acetonide **3** (456 mg, 24%). **5**: Colorless oil. $[\alpha]_D^{21} -11.3^\circ$ ($c=0.9$, CHCl_3). $^1\text{H-NMR}$ δ : 0.88 (3H, t, $J=6.6$), 1.27–1.51 (18H, m), 1.41 (3H, s), 1.48 (3H, s), 1.77–1.88 (1H, m), 1.95–2.02 (1H, m), 3.90 (1H, d, $J=9.8$), 4.19 (1H, d, $J=9.3$), 5.78 (1H, s). IR (neat) cm^{-1} : 2989, 2926, 2855, 1466, 1382, 1372, 1253, 1214, 1065, 777. FAB-MS m/z : 339 ($\text{M}+\text{H}^+$); HR-FAB-MS m/z : Calcd for $\text{C}_{17}\text{H}_{33}\text{O}_2\text{Cl}_2$ ($\text{M}+\text{H}^+$): 339.1857, Found: 339.1866.

(*S*)-2-Dichloromethyltridecane-1,2-diol (6**)** To a solution of 4-dichloromethyl-1,3-dioxolane **5** (100 mg, 0.3 mmol) in MeOH (2 ml) was added c. HCl (0.2 ml) and the mixture was stirred for 7 h at room temperature. The whole was concentrated and chromatographed on silica gel (hexane:EtOAc=7:1) to give a 1,2-diol **6** (78 mg, 89%) as an oil. $[\alpha]_D^{20} +2.1^\circ$ ($c=0.46$, CHCl_3). $^1\text{H-NMR}$ δ : 0.86 (3H, t, $J=6.6$), 1.18–1.26 (18H, m), 1.65–1.79 (2H, m), 3.71 (1H, d, $J=11.7$), 3.88 (1H, d, $J=11.7$), 5.96 (1H, s). IR (neat) cm^{-1} : 3418, 2918, 2849, 1473, 1463. EI-MS m/z : 297 ($\text{M}-\text{H}^+$), 269, 267, 215.

(*S*)-2-*t*-Butyldiphenylsilyloxymethyl-1,1-dichlorotridecane-2-ol (7**)** To a solution of the glycol **6** (20 mg, 0.07 mmol) and imidazole (10.0 mg, 0.15 mmol) in THF (1.0 ml) was added *t*-butyldiphenylsilyl chloride (TBDPS-Cl) (39 μl , 0.15 mmol) at $0\text{ }^\circ\text{C}$, and the whole was stirred for 12 h at room temperature. The mixture was concentrated and chromatographed on silica gel (hexane:EtOAc=20:1) to give a TBDPS-ether **7** (26 mg, 72%) as an oil. Chiral HPLC of **7** was performed on CHIRALCEL OD-H using a mixed solvent system of hexane–2-PrOH (500:1), and a peak was observed at the retention time (RT) of 11.17 min, indicating the enantio-excess (ee) to be over 98% by comparison with the racemic one (RT: 8.92, 11.17 min). $^1\text{H-NMR}$ δ : 0.90 (3H, t, $J=6.6$), 1.11 (9H, s), 1.17–1.50 (18H, br), 1.55–1.88 (2H, m), 2.60 (1H, s), 3.70 (1H, d, $J=9.0$), 3.84 (1H, d, $J=9.0$), 6.01 (1H, s), 7.35–7.52 (6H, m), 7.64–7.73 (4H, m).

Ethyl (*S*)-3-(4-Dichloromethyl-2,2-dimethyl-1,3-dioxolan-4-yl)-propanoate (8**)** To 50% aq. NaOH (10 g) was added a solution of an acetonide **4** (100 mg, mmol) and cetyltrimethylammonium chloride (0.2 mg) in CHCl_3 (1.0 ml) and 1,2-dichloroethane (0.5 ml) and the mixture was vigorously stirred at $80\text{ }^\circ\text{C}$ for 5 h, while 6 portions of CHCl_3 (0.5 ml) were added in every 40 min interval. After neutralization of the mixture by addition of 2% H_2SO_4 , the whole was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 , and concentrated to give a crude product, which was heated in 2,2-diethoxypropane (2.0 ml) with *p*-TsOH (5 mg) for 12 h at $80\text{ }^\circ\text{C}$. The whole was concentrated *in vacuo*, and chromatographed on silica gel (hexane:EtOAc=7:1) to give a dichloromethyl derivative **8** (48 mg, 34%) and the starting material **4** (53 mg, 53%). **8**: Colorless oil. $[\alpha]_D^{23} -11.3^\circ$ ($c=0.9$, CHCl_3). $^1\text{H-NMR}$ δ : 1.27 (3H, d, $J=7.1$), 1.41 (3H, s), 1.47 (3H, s), 2.15–2.29 (1H, m), 2.36–2.56 (3H, m), 3.89 (1H, d, $J=9.8$), 4.16 (2H, q, $J=7.2$), 4.20 (1H, d, $J=9.8$), 5.77 (1H, s). IR (neat) cm^{-1} : 2988, 2940, 1736, 1448, 1383, 1374, 1306, 1255, 1215, 1186, 1160, 1082, 1064, 875, 773. FAB-MS m/z : 285 ($\text{M}+\text{H}^+$); HR-FAB-MS m/z : Calcd for $\text{C}_{11}\text{H}_{19}\text{O}_4\text{Cl}_2$ ($\text{M}+\text{H}^+$): 285.0660, Found: 285.0650.

(*S*)-5-Dichloromethyl-5-hydroxymethyl-2,3,4,5-tetrahydrofuran-2-one (9**)** A solution of the acetonide (**8**) (187 mg, 0.68 mmol) in MeOH (5.0 ml) was added c. HCl (0.2 ml), and the mixture was stirred at room temperature for 2 h. The whole was concentrated and the residue was chromatographed on silica gel (hexane:EtOAc=3:1→EtOAc) to give a crystalline lactone **9** (131 mg, 97%). Colorless needle. mp. $75.0\text{--}76.0\text{ }^\circ\text{C}$ (ether–hexane). $[\alpha]_D^{21} +61.3^\circ$ ($c=1.1$, CHCl_3). $^1\text{H-NMR}$ δ : 2.11–2.86 (4H, m), 3.86 (1H, d, $J=12.7$), 3.99 (1H, d, $J=12.2$), 6.05 (1H, s). IR (KBr) cm^{-1} : 3235, 1780, 1220, 1184, 1127, 1065, 941, 785. Anal. Calcd for $\text{C}_6\text{H}_8\text{Cl}_2\text{O}_3$: C, 36.21; H, 4.05. Found: C, 36.39; H, 4.18.

(*S*)-5-Dichloromethyl-5-*t*-butyldiphenylsilyloxymethyl-2,3,4,5-tetrahydrofuran-2-one (10**)** To a solution of the hydroxylactone **9** (20 mg, 0.1 mmol) and imidazole (13.6 mg, 0.2 mmol) in THF (1.0 ml) was added *t*-butyldiphenylsilyl chloride (TBDPS-Cl) (52 μl , 0.2 mmol) at $0\text{ }^\circ\text{C}$, and the whole was stirred for 12 h at room temperature. The mixture was concentrated and chromatographed on silica gel (hexane:EtOAc=30:1) to give a TBDPS-ether **10** (31 mg, 72%) as an oil. Chiral HPLC of **10** was performed on CHIRALCEL OD-H using a mixed solvent system of hexane–2-PrOH (500:1), and a peak was observed at RT of 38.61 min to be over 98% ee by

comparison with the racemic one (RT: 29.81, 38.61). $^1\text{H-NMR}$ δ : 1.05 (9H, s), 1.94—2.05 (1H, m), 2.44—2.79 (3H, m), 3.82 (1H, d, $J=9.0$), 3.90 (1H, d, $J=9.0$), 6.10 (1H, s), 7.32—7.50 (6H, m), 7.62—7.80 (4H, m).

(S)-3-(4-Dichloromethyl-2,2-dimethyl-1,3-dioxolane-4-yl)propanal (11) To a cold solution (-78°C) of the ester **8** (271 mg, 0.95 mmol) in CH_2Cl_2 (10 ml) was added a solution of diisobutylaluminum hydride (DAIBH) (0.95 M/hexane, 1.2 ml, 1.14 mmol), and the mixture was stirred for 20 min at the temperature. After quenching the reaction by addition of MeOH, the whole was extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4 , and concentrated to give a crude aldehyde **11** (188 mg, 86%). $^1\text{H-NMR}$ δ : 1.33 (3H, s), 1.40 (3H, s), 2.08—2.19 (1H, m), 2.32—2.43 (1H, m), 2.54—2.62 (2H, m, 2H), 3.80 (1H, d, $J=9.8$), 4.14 (1H, d), 5.70 (1H, s), 9.75 (1H, s).

Side Chain Elongation of 11 Providing 5 To a cold solution (0°C) of *n*-octyltriphenylphosphonium bromide (0.2 g/ml ether solution, 4.6 ml, 2.0 mmol) in ether (20 ml) was added *n*-BuLi (1.2 ml, 1.50 mol/l in hexane, 1.8 mmol) under nitrogen atmosphere. After stirring the mixture for 5 min, a solution of an aldehyde **11** (188 mg, 0.78 mmol) in ether (20 ml) was added. The mixture was stirred for 10 min at 0°C . The mixture was filtered, and the filtrate was concentrated and chromatographed on silica gel (hexane: $\text{CHCl}_3=20:1$) to give an olefin, (S)-4-dichloromethyl-2,2-dimethyl-4-(3-undecen-1-yl)-1,3-dioxolane (185 mg, 62%) as an oil. A mixture of the olefin (185 mg) in ethanol (2 ml) and 5% Pd/C (10 mg) was vigorously stirred under atmosphere of H_2 for 2.5 h, and the whole was filtered through celite, concentrated, and chromatographed on silica gel to give **5** (155 mg, 83% (44% overall yield from **8**)).

(S)-4-Chloromethyl-2,2-dimethyl-4-undecyl-1,3-dioxolane (12) Under nitrogen atmosphere, a solution of a dichloromethyl-acetonide **5** (1.0 g, 2.95 mmol) in THF (3 ml) was added dropwise into a suspension of LiAlH_4 (140 mg, 3.69 mmol) in THF (8 ml) at 0°C over 10 min. The mixture was stirred for 5 h at room temperature, and then another portion of LiAlH_4 (70 mg, 1.85 mmol) in THF (3 ml) was added and the stirring was continued for 9 h. After careful addition of water to quench the reaction, the whole was filtered through celite. The filtrate was concentrated and chromatographed on silica gel (hexane:EtOAc=50:1) to give a chloromethyl-acetonide **12** (540 mg, 60%) and 2,2,4-trimethyl-4-undecyl-1,3-dioxolane (**13**) (64 mg, 8%). **12**: Colorless oil. $[\alpha]_D^{19} -9.5^\circ$ ($c=1$, CHCl_3). $^1\text{H-NMR}$ δ : 0.88 (3H, t, $J=6.8$), 1.26—1.31 (18H, m), 1.38 (3H, s), 1.43 (3H, s), 1.60—1.79 (2H, m), 3.49 (2H, s), 3.75 (1H, d, $J=9.3$), 4.03 (1H, d, $J=8.8$). IR (neat) cm^{-1} : 2988, 2926, 2855, 1467, 1458, 1381, 1371, 1254, 1210, 1062, 874, 820, 739. FAB-MS m/z : 305 ($\text{M}+\text{H}^+$); HR-FAB-MS m/z Calcd for $\text{C}_{17}\text{H}_{34}\text{O}_2\text{Cl}$ ($\text{M}+\text{H}^+$): 305.2248, Found: 305.2253. **13**: Colorless oil. $^1\text{H-NMR}$ δ : 0.88 (3H, t, $J=6.8$), 1.25—1.65 (20H, m), 1.60 (3H, s), 1.38 (3H, s), 1.40 (3H, s), 3.69 (1H, d), 3.78 (1H, d, $J=8.3$). EI-MS m/z : 270 (M^+), 269, 255.

(S)-2-Chloromethyltridecane-1,2-diol (14) A solution of the acetonide **12** (230 mg, 0.75 mmol) in MeOH (3 ml) was stirred with c. HCl (0.1 ml) at room temperature for 5 h. The mixture was concentrated and chromatographed on silica gel (hexane:EtOAc=1:1) to give a diol (**14**) (184 mg, 92%). Colorless oil. $[\alpha]_D^{20} +2.3^\circ$ ($c=0.9$, CHCl_3). $^1\text{H-NMR}$ δ : 0.88 (3H, t, $J=6.6$), 1.26—1.30 (18H, m), 1.51—1.59 (2H, m), 1.91 (1H, br s), 2.35 (1H, br s), 3.54 (1H, d, $J=4.9$), 3.59 (1H, d, $J=4.9$), 3.62 (1H, d, $J=6.8$), 3.66 (1H, d, $J=6.8$). IR (neat) cm^{-1} : 3391, 2925, 2854, 1466, 1060, 799, 740, 722. EI-MS m/z : 233 ($\text{M}-\text{CH}_2\text{OH}^+$); HR-EI-MS Calcd for $\text{C}_{16}\text{H}_{30}\text{OCl}$ ($\text{M}-\text{CH}_2\text{OH}^+$): 233.1672, Found: 233.1678.

(S)-1-(*t*-Butyldiphenylsilyloxy)-2-chloromethyl-2-tridecanol (15) To a solution of the diol (**14**) (202 mg, 0.76 mmol) and imidazole (104 mg, 1.5 mmol) in THF (3 ml) was added *t*-butyldiphenylsilyl chloride (TBDPS-Cl) (400 μl , 1.53 mmol) at 0°C , and the whole was stirred for 12 h at room temperature. The mixture was concentrated and chromatographed on silica gel (hexane:EtOAc=50:1) to give a mono-TBDPS ether (**15**) (363 mg, 95%). Colorless oil. $[\alpha]_D^{20} +1.7^\circ$ ($c=1.1$, CHCl_3). $^1\text{H-NMR}$ δ : 0.88 (3H, t, $J=6.6$), 1.07 (9H, s), 1.25 (18H, m), 1.51—1.54 (2H, m), 3.49 (1H, d, $J=9.8$), 3.62 (2H, s), 3.68 (1H, d, $J=9.8$), 7.37—7.48 (6H, m), 7.64—7.68 (4H, m). IR (neat) cm^{-1} : 3557, 3072, 3050, 2927, 2856, 1465, 1428, 1114, 824, 740, 701; EI-MS m/z : 445 ($\text{M}-t\text{-Bu}^+$); HR-EI-MS m/z Calcd for $\text{C}_{26}\text{H}_{38}\text{O}_2\text{ClSi}$ ($\text{M}-t\text{-Bu}^+$): 455.2330, Found: 455.2336.

(R)-2-(*t*-Butyldiphenylsilyloxymethyl)-2-undecyloxirane (16) To a solution of the chloromethylcarbinol **15** (364 mg, 0.72 mmol) in MeOH (5 ml) was added K_2CO_3 (0.50 g, 3.60 mmol) at room temperature and the mixture was stirred for 1 h. After dilution with ether (50 ml), the whole was filtered and concentrated. The residue was chromatographed on silica gel (hexane:EtOAc=7:1) to give an epoxide **16** (326 mg, 97%). Colorless oil. $[\alpha]_D^{26} +0.9^\circ$ ($c=0.9$, CHCl_3). $^1\text{H-NMR}$ δ : 0.88 (3H, t, $J=6.3$), 1.06 (9H, s), 1.25 (18H, m), 1.52—1.60 (1H, m), 1.73—1.81 (1H, m), 2.59 (1H, d, $J=4.9$),

2.67 (1H, d, $J=4.9$), 3.69 (2H, s), 7.35—7.46 (6H, m), 7.66—7.69 (4H, m). IR (neat) cm^{-1} : 3071, 3050, 2928, 2856, 1465, 1427, 1113, 824, 740, 702. FAB-MS m/z : 467 ($\text{M}+\text{H}^+$); HR-FAB-MS m/z Calcd for $\text{C}_{30}\text{H}_{47}\text{O}_2\text{Si}$ ($\text{M}+\text{H}^+$): 467.3345, Found: 467.3356.

(R)-2-Undecyloxirane-2-carboxyaldehyde (17) A mixture of the 1,2-diol **6** (470 mg, 1.6 mmol) and K_2CO_3 (1.10 g, 8 mmol) in MeOH (10 ml) was stirred for 20 min at room temperature. After neutralization of the mixture with 2% HCl, the whole was concentrated to give a crude product which was purified by chromatography on silica gel to afford an aldehyde **17** (270 mg, 77%). $[\alpha]_D^{20} +36.1^\circ$ ($c=0.96$, CHCl_3). $^1\text{H-NMR}$ δ : 0.88 (3H, t, $J=6.6$), 1.20—1.45 (18H, m), 1.66—1.73 (1H, m), 1.89—1.94 (1H, m), 3.03 (2H, s), 8.88 (1H, s). IR (neat) cm^{-1} : 2925, 2854, 1735, 1466, 1378. EI-MS m/z : 226 (M^+), 208, 197, 179.

(S)-2-Hydroxymethyl-2-undecyloxirane (18) To a solution of the aldehyde **17** (250 mg, 1.1 mmol) in MeOH (10 ml) was added NaBH_4 (300 mg, 8 mmol), and the whole was stirred for 30 min at the temperature. The reaction was quenched by addition of acetone (2.0 ml), and the whole was diluted with ether and passed through a silica gel column and concentrated to leave a crude oil, which was purified by silica gel chromatography (hexane:EtOAc=7:1) to give an epoxyalcohol **18** (212 mg, 84%) as an oil. $[\alpha]_D^{22} -13.8^\circ$ ($c=0.46$, CHCl_3). $^1\text{H-NMR}$ δ : 0.88 (3H, t, $J=6.5$), 1.18—1.39 (18H, m), 1.45—1.80 (2H, m), 2.66 (1H, d, $J=4.6$), 2.88 (1H, d, $J=4.6$), 3.60—3.68 (1H, dd, $J=12.2$, 8.39), 3.75—3.81 (1H, dd, $J=12.2$, 3.9). IR (neat) cm^{-1} : 3460, 2918, 2849, 1472, 1462. EI-MS m/z : 229 ($\text{M}+\text{H}^+$), 228 (M^+), 197.

One-Pot Transformation of the Dichloromethyl-acetonide (5) to Epoxy-alcohol (18) A solution of the dichloromethyl-acetonide **5** (50 mg, 0.15 mmol) in MeOH (1 ml) was stirred with a HCl/MeOH solution (0.2 ml, 3.3 M/HCl in MeOH) for 15 h at room temperature. To the mixture was added K_2CO_3 (200 mg, 1.50 mmol) and the whole was stirred for 0.5 h. Then, NaBH_4 (28 mg, 0.75 mmol) was added and the whole was stirred for additional 20 min. The reaction was quenched by acetone, and the whole was diluted with ether and passed through a silica gel column. The filtrate was concentrated and chromatographed on silica gel (hexane:EtOAc=7:1) to give the epoxy-alcohol **18** (18 mg, 53%).

Silylation of 18 Providing 16 A mixture of the epoxyalcohol **18** (100 mg, 0.4 mmol), imidazole (90 mg, 1.3 mmol), and *t*-butyldiphenylsilyl chloride (TBDPS-Cl) (340 ml, 1.3 mmol) in THF (5.0 ml) was stirred for 12 h at room temperature. After concentration, the whole was chromatographed on silica gel (hexane:EtOAc=30:1) to give a TBDPS-ether **16** (180 mg, 88%) as an oil. This compound was identical with that obtained from **12** via **15** by spectral comparisons and chiral HPLC, which showed a single peak at the RT of 6.8 min using CHIRALCEL OD-H (hexane:2-PrOH=500:1) indicating over 98% ee by comparison with the racemic one (TR: 5.6, 6.8 min).

(R)-6-(*t*-Butyldiphenylsilyloxymethyl)heptadec-1-en-6-ol (19) Under nitrogen atmosphere, to a cold suspension (-30°C) of CuI (92 mg, 0.48 mmol) in THF (1.0 ml) was added dropwise a solution of 3-butenylmagnesium bromide (0.30 mol/THF, 3.2 ml, 0.96 mmol) over 5 min, and the mixture was stirred for an additional 5 min at -30°C . To the mixture was added a solution of the epoxide **16** (50 mg, 0.11 mmol) in THF (2.0 ml) at the temperature, and the whole was stirred for 30 min. After quenching the reaction by addition of sat. aq. NH_4Cl , the whole was extracted with ether. The organic layer was washed successively with sat. NH_4Cl and brine, dried over Na_2SO_4 , and evaporated to give a crude oil, which was purified by chromatography on silica gel (hexane:EtOAc=50:1) to give an alcohol **19** (33 mg, 59%). Colorless oil. $[\alpha]_D^{23} -0.7^\circ$ ($c=0.8$, CHCl_3). $^1\text{H-NMR}$ δ : 0.88 (3H, t, $J=6.6$), 1.07 (9H, s), 1.25—1.38 (20H, br s), 1.44—1.46 (4H, m), 2.02 (2H, q, $J=6.8$), 3.47 (2H, s), 4.94 (1H, d, $J=8.8$), 4.99 (1H, d, $J=15.6$), 5.73—5.83 (1H, m), 7.35—7.47 (6H, m), 7.64—7.67 (4H, m). IR (neat) cm^{-1} : 3576, 3469, 3072, 3051, 2928, 2856, 1641, 1428, 1113, 910, 823, 740, 702. EI-MS m/z : 465 ($\text{M}-t\text{-Bu}^+$); HR-EI-MS m/z Calcd for $\text{C}_{30}\text{H}_{45}\text{O}_2\text{Si}$ ($\text{M}-t\text{-Bu}^+$): 465.3189, Found: 465.3183.

(R)-6-(*t*-Butyldiphenylsilyloxymethyl)-6-undecyltetrahydropyran-2-one (20) To an aqueous solution of OsO_4 (1.6 mg, 0.006 mmol) and NaIO_4 (135 mg, 0.63 mmol) in water (0.3 ml) was added a solution of the olefin **19** (33 mg, 0.063 mmol) in dioxane (1.0 ml), and the mixture was stirred for 1 h at room temperature. The whole was extracted with ether and the organic layer was washed with brine, dried over Na_2SO_4 , and concentrated. The residue was dissolved in acetone (1.0 ml) and cooled to 0°C . To the mixture was added Jones reagent (0.5 ml) and the whole was stirred for 30 min at 0°C . The whole was extracted with ether, washed with brine, dried over Na_2SO_4 , and concentrated to give a crude product, which was chromatographed on silicagel (hexane:EtOAc=7:1) to give a lactone **20** (21 mg, 64%) as a colorless oil. Chiral HPLC of **20** was performed on CHIRAL-

CEL OD-H using a mixed solvent system of hexane/2-ProOH (100 : 1), and a peak was observed at the RT of 9.2 min, indicating over 98% ee by comparison with the racemic one (RT: 7.8, 9.2 min). $[\alpha]_D^{18}$ -8.7° ($c=0.2$, CHCl_3). $^1\text{H-NMR}$ δ : 0.88 (3H, t, $J=7.1$), 1.06 (9H, s), 1.25 (18H, brs), 1.59—1.70, 1.74—1.83, 1.99—2.04 (6H, m), 2.43 (2H, t, $J=6.6$), 3.58 (2H, dd, $J=14.7$, 10.3), 7.36—7.47 (6H, m), 7.63—7.66 (4H, m). IR (neat) cm^{-1} : 3072, 3050, 2928, 2856, 1738, 1464, 1428, 1248, 1114, 824, 741, 702. FAB-MS m/z : 523 ($\text{M}+\text{H}^+$); HR-FAB-MS m/z Calcd for $\text{C}_{33}\text{H}_{51}\text{O}_3\text{Si}$ ($\text{M}+\text{H}^+$): 523.3607, Found: 523.3600.

(R)-6-Hydroxymethyl-6-undecyltetrahydropyran-2-one (1: Tanikolide)

To a solution of the silyl ether **20** (40 mg, 0.08 mmol) in THF (2.0 ml) was added an aq. solution of $n\text{-Bu}_4\text{NF}\cdot 3\text{H}_2\text{O}$ (120 mg, 0.4 mmol) and the mixture was stirred for 1.5 h at room temperature. The whole was concentrated and the residue was chromatographed on silica gel (hexane:EtOAc=1:1) to give tanikolide **1** (17 mg, 78%). Colorless crystal. mp. 39—41 $^\circ\text{C}$. $[\alpha]_D^{20} +2.5^\circ$ ($c=0.44$, CHCl_3). $^1\text{H-NMR}$ δ : 0.88 (3H, t, $J=6.6$), 1.26 (18H, brs), 1.57—1.91 (6H, m), 2.46—2.52 (2H, m), 3.55 (1H, dd, $J=11.7$, 4.6), 3.66 (1H, dd, $J=11.7$, 4.6); IR (KBr) cm^{-1} : 3393, 2923, 2852, 1705. EI-MS m/z : 253 ($\text{M}-\text{CH}_2\text{OH}^+$); HR-EI-MS m/z Calcd for $\text{C}_{16}\text{H}_{29}\text{O}_2$ ($\text{M}-\text{CH}_2\text{OH}^+$): 253.2168, Found: 253.2162.

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