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Divergent synthesis of (+)-tanikolide and its analogues employing stereoselective rhodium(II)-catalyzed reaction

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ABSTRACT

In this study, we described the divergent synthesis of (+)-tanikolide and its analogues, such as (4*S*)- and (4*R*)-hydroxytanikolides, and nortanikolide, employing a stereoselective dirhodium(II)-catalyzed reaction to construct the quaternary chiral center of tanokolides. The key steps involve (a) a dirhodium(II)-catalyzed oxonium ylide formation–[2,3]-sigmatropic rearrangement, (b) an *N*-heterocyclic carbene-catalyzed ring-expansion lactonization of tetrahydrofurfural, or (c) an oxidative cleavage of tetrahydrofuran-5-methanol to γ-lactone using a 2-iodobenzamide catalyst. This route would provide high flexibility for analogue synthesis because the long side chain can be introduced at a later stage in the synthesis.

1. Introduction

(+)-Tanikolide (**1**, Fig. 1) and (−)-malyngolide, which are δ-lactones with alkyl long chains and hydroxymethyl groups at C5, were isolated from the marine cyanobacterium *Lyngbya majuscula* collected from Tanikeli Island, Madagascar[1] and the shallow water variety of *Lyngbya Majuscula*,[2] respectively. Interestingly, the stereochemistries of these natural products are opposite in comparison with C5 and alkyl side chains of different lengths. Additionally, malyngolide possesses a methyl group at C2. With respect to their biological activities, tanikolide exhibits strong toxicity against brine shrimp and snails and malyngolide displays an antimicrobial activity against *Mycobacterium smegmatis* and *Streptococcus pyogenes*.[2] Furthermore, tanikolide exhibits antifungal activity against *Candida albicans*,[1] while malyngolide shows no activity against it.[1] Since there is a clear difference in their biological activities in spite of their structural similarities, their analogues, possessing slightly different substituents, may lead to new promising candidates for drug discovery.

In terms of potent biological activities and structural features of (+)-tanikolide and (−)-malyngolide, there have been a large number of reports on the total syntheses of these natural products[3–13] and their analogues.[6n,o] One of the key steps is the stereoselective construction of the quaternary carbon center at C5, which has been accomplished using several different approaches, such as aldol reactions,[3] allylation of ketones such as Keck allylation,[4] addition of Grignard reagents to ketones,[5] epoxidation–epoxide opening,[6] Sharpless asymmetric dihydroxylation,[7] sigmatropic rearrangement,[8] 1,3-dipolar cycloaddition of nitronate and acrolein,[9] asymmetric intramolecular cyclopropanation,[10] bromolactonization,[11] asymmetric allylic alkylation,[12] and others.[13] However, most of these examples are application and demonstration of synthetic methodologies to construct a synthetically challenging quaternary carbon center. To the best of our knowledge, there is only one example of the divergent synthesis of their analogues.[6n,o]

One of the most direct and powerful methods for construction of substituted cyclic ethers is tandem intramolecular oxonium ylide formation from α-diazocarbonyl compounds under catalysis by dirhodium(II) or copper complexes and [2,3]-sigmatropic rearrangement.[14] The synthetic utility of the tandem reaction has been demonstrated through the synthesis of a wide range of natural products.[15] We have reported a stereoselective, copper-catalyzed oxonium ylide formation–rearrangement of α-diazo ketone for the synthesis of the C3–C12 portion of laulimalide.[16] We have also disclosed that a dirhodium(II)-catalyzed tandem reaction of diazoketoesters proceeds with excellent stereoselectivity[17] and is applicable to the synthesis of 2-*epi*-cinatrin C_1 dimethyl ester.[18] As a

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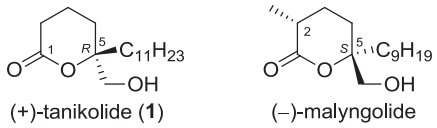


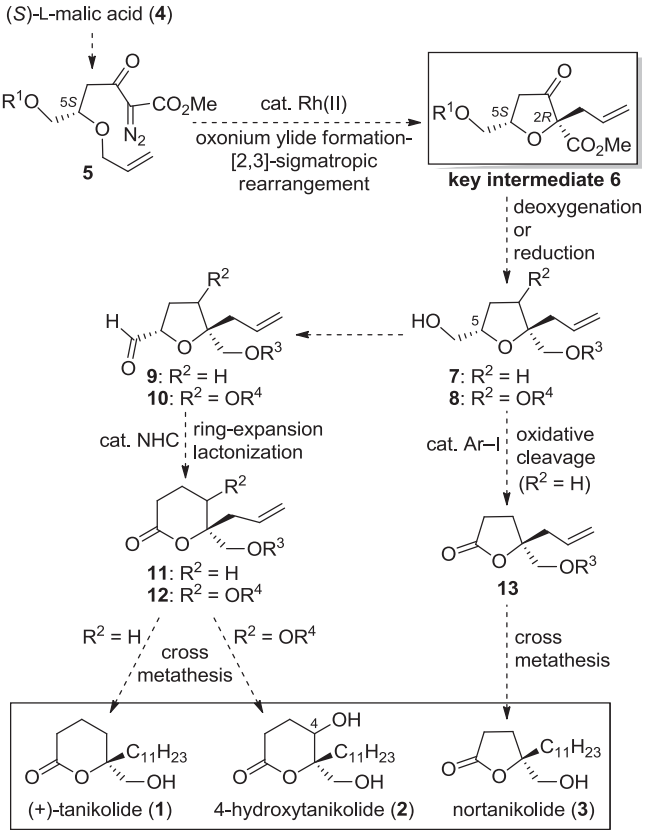
Fig. 1. Structure of (+)-tanikolide (**1**) and (−)-malyngolide.

part of our work in the development of oxonium ylide rearrangement and its application to the synthesis of biologically active compounds, we herein report a divergent synthesis of (+)-tanikolide and its analogues, such as 4-hydroxy- and nortanikolides.[19]

2. Results and discussion

2.1. Synthetic strategy

Our synthetic plan for (+)-tanikolide (**1**) and its analogues, 4-hydroxytanikolides (**2**), and nortanikolide (**3**), is illustrated in Scheme 1. We have already reported the stereoselective dirhodium(II)-catalyzed oxonium ylide formation–[2,3]-sigmatropic rearrangement of 5-allyloxy-2-diazo-3-oxocarboxylate.[17,20] From this observation, we can expect to stereoselectively obtain (2*R*,5*S*)-dihydrofuranone **6**, which has the same configuration at C2 as that of tanikolide, by the dirhodium(II)-catalyzed reaction of (5*S*)-diazoketoester **5**. The diazoester **5** can be prepared from (*S*)-L-malic acid (**4**). The obtained dihydrofuranone **6** could be a key synthetic intermediate for **1**–**3**. In addition, introduction of the alkyl side chain could be conducted at a later stage of the synthesis using cross metathesis to easily synthesize analogues with various side chains. Deoxygenation of the keto group in **6**, followed by the oxidation of the resultant tetrahydrofuran-5-methanol **7** ($R^2 = H$), could provide tetrahydrofurfural **9**. Subsequently, *N*-heterocyclic carbene (NHC)-catalyzed ring-expansion of aldehyde **9**, prepared from the hydroxymethyl group in **7**, to δ-lactone **11**[21] and the following cross metathesis would result in the completion of the total synthesis of **1**. Reduction of ketone **6** could afford the alcohol **8** ($R^2 = OR^4$), which should be converted into **2** in the same manner as that of **7** into **1**. Noranalogue **3** could be synthesized from **7** by an oxidative cleavage reaction[22] and cross metathesis. Consequently, in this synthesis, the C5 hydroxymethyl group plays the following important roles: construction of the C2 chiral center, ring-expansion from γ-lactone to δ-lactone, and oxidative cleavage.

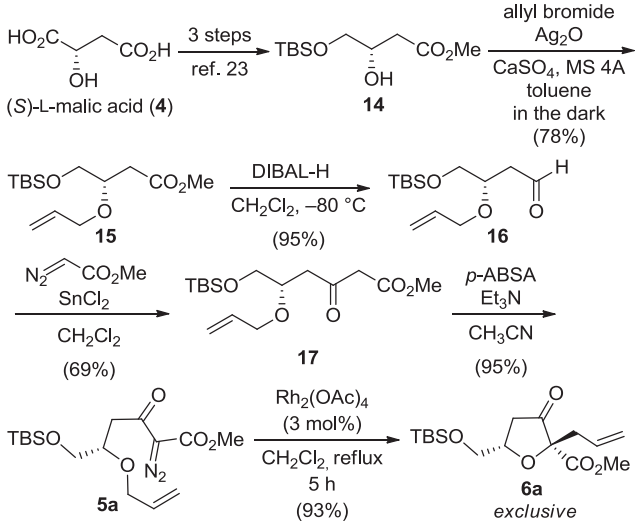


Scheme 1. Synthetic strategy for (+)-tanikolide (**1**) and its analogues **2** and **3**.

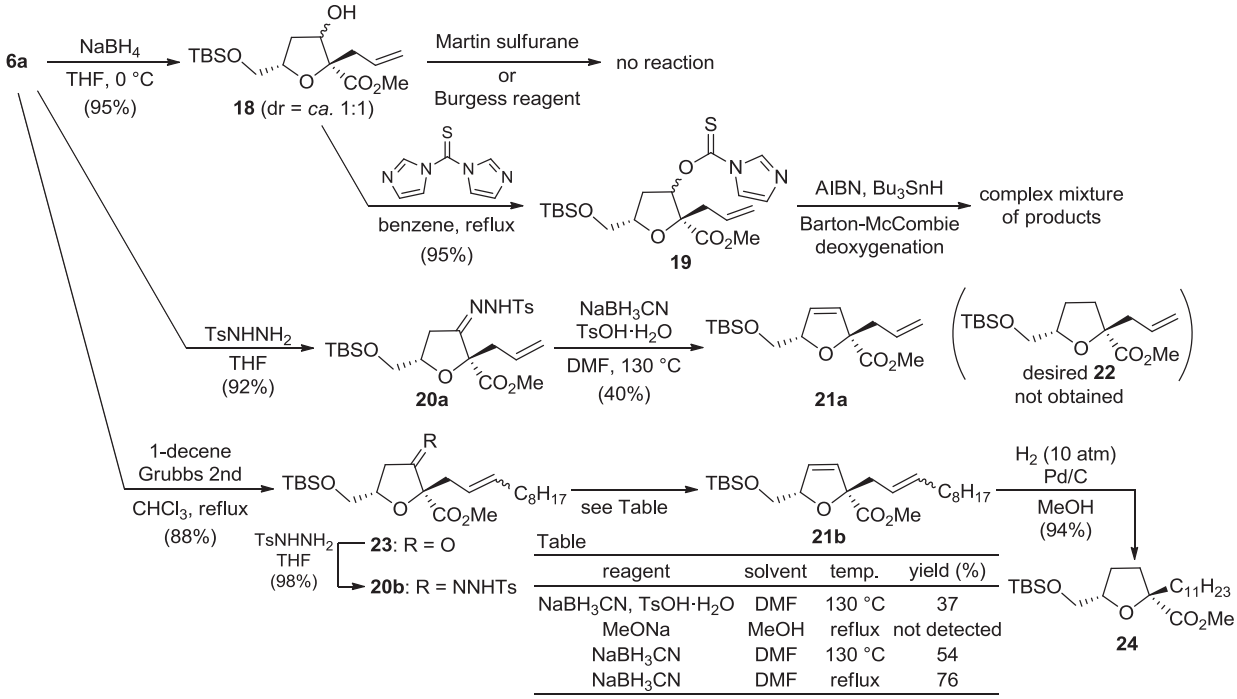
2.2. Total synthesis of (+)-tanikolide

The synthesis of the key intermediate **6a** from (*S*)-L-malic acid (**4**) was investigated as shown in Scheme 2. Conversion of **4** into silyloxyalcohol **14** was conducted in the usual manner.[23] Allylation of the hydroxy group in **14** was accomplished by the treatment with allyl bromide, silver(I) oxide, calcium sulfate, and a molecular sieve (MS) 4 Å for 24 h in the dark, which afforded allyl ether **15** in 78% yield. After the reduction of ester **15** into aldehyde **16** with diisobutylaluminum hydride (DIBAL-H), the resultant **16** was converted to diazoketoester **5a** via β-ketoester **17** by treatment of **16** with methyl diazoacetate with $SnCl_2$ and subsequent diazo transfer from *p*-acetoamidobenzenesulfonyl azide (*p*-ABSA) to **17**. The rhodium(II)-catalyzed oxonium ylide formation–[2,3]-sigmatropic rearrangement of **5a** yielded dihydrofuranone **6a** with perfect stereoselectivity. The reaction of diazoketoester **5a** with 3 mol% of dirhodium(II) tetraacetate in refluxing dichloromethane for 5 h produced the corresponding dihydrofuranone **6a** as the sole product in 93% yield.

With the key synthetic intermediate **6a** in hand, we next examined the deoxygenation of the keto group in dihydrofuranone **6a** (Scheme 3). After conversion of **6a** to alcohol **18** by treatment with sodium borohydride in tetrahydrofuran (THF), the reaction of **18** with Martin sulfurane or Burgess reagents did not proceed at all. Next, we examined the Barton–McCombie deoxygenation of alcohol **18**. Treatment of **18** with 1,1′-thiocarbonyldiimidazole in benzene under reflux provided the corresponding thiocarbamate **19** in 95% yield. The reaction of **19** with tributyltin hydride in the presence of azobisisobutyronitrile (AIBN) gave a complex mixture of products. Since all the attempts to deoxygenate 3-



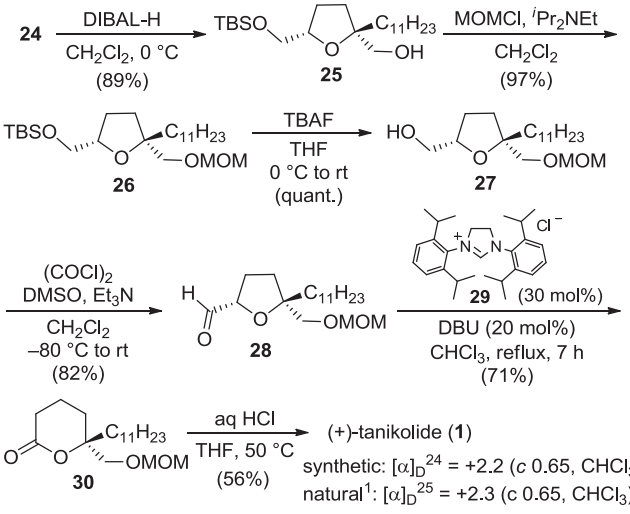
Scheme 2. Stereoselective synthesis of key intermediate **6a**.



Scheme 3. Deoxygenation of dihydrofuranone **6a**.

hydroxytetrahydrofuran **18** were unsuccessful, direct deoxygenation of the ketone in **6a** using Wolff–Kishner-type reduction[24] was then investigated. Treatment of ketone **6a** with tosylhydrazine in THF gave hydrazone **20a** in 92% yield. According to Hutchins' modified conditions,[24b] the reaction of **20a** with sodium cyanoborohydride in the presence of catalytic amounts of *p*-toluenesulfonic acid (TsOH) in *N*,*N*-dimethyformamide (DMF) at 130 °C provided the undesired dihydrofuran **21a** in 40% yield, without any of the desired product **22**. This unexpected result led us to change our synthetic plan. The cross metathesis for extension of the alkyl side chain should be conducted prior to the required hydrogenation of dihydrofuran. The reaction of **6a** with 10 equivalent of 1-decene in the presence of a Grubbs 2nd catalyst proceeded smoothly to afford alkene **23** in 88% yield. After conversion of ketone **23** into tosylhydrazone **20b**, we then examined the reduction of **20b**. The treatment of **20b** with $NaBH_3CN$ and 0.7 equivalent of TsOH in DMF at 130 °C gave dihydrofuran **21b** in only 37% yield. We assumed that the formation of **21b** from **20b** proceeded through a Bamford–Stevens-type reaction. Therefore, we next investigated the reaction under standard Bamford–Stevens conditions. However, treatment of **20b** with sodium methoxide in methanol under reflux did not afford the product **21b**. Thus, we examined the reaction with $NaBH_3CN$ in the absence of TsOH. Gratifyingly, the yield of **21b** was increased (54% yield). Furthermore, we found that the reaction with $NaBH_3CN$ in refluxing DMF afforded **21b** in 76% yield. Catalytic hydrogenation of both cyclic and side alkenes in **21b** provided tetrahydrofuran **24** in 94% yield.

The stage was now set for ring-expansion from γ-lactone to δ-lactone and completion of the synthesis of (+)-tanikolide (**1**, Scheme 4). Conversion of **24** into the precursor for NHC-catalyzed ring expansion was conducted by an uneventful four-step transformation. Hydride reduction of methyl ester **24** with DIBAL-H furnished a primary alcohol **25** in 89% yield. After protection of the hydroxyl group as its methoxymethyl (MOM) ether, it was desilylated with tetrabutylammonium fluoride (TBAF), and subsequent Swern oxidation afforded aldehyde **26**. We then investigate the ring expansion of tetrahydrofuran to δ-lactone **30**.[21] Treatment

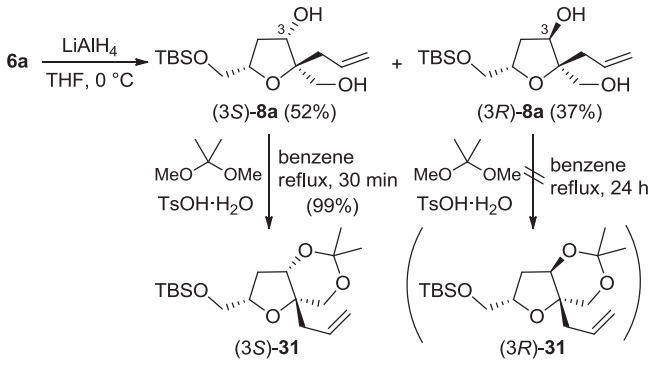


Scheme 4. Synthesis of (+)-tanikolide (**1**).

of **28** with 30 mol% of imidazolium catalyst **29** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in chloroform under reflux for 7 h gave δ-lactone **30** in 71% yield. Finally, the MOM group in **30** was deprotected under acidic conditions to furnish (+)-tanikolide (**1**), mp 39–40 °C (*lit.*[6h] mp 39–41 °C), $[\alpha]_D^{24}$ +2.2 (*c* 0.65, $CHCl_3$) {*lit.*[1] $[\alpha]_D^{25}$ +2.3 (*c* 0.65, $CHCl_3$)}, in 56% yield.

2.3. Synthesis of (4*S*)- and (4*R*)-hydroxytanikolides

Next, we synthesized (4*S*)- and (4*R*)-hydroxytanikolides (**2**) from the key intermediate dihydrofuranone **6a**. Initially, we examined hydride reduction of **6a** (Scheme 5). The reaction of **6a** with lithium aluminum hydride in THF at 0 °C gave a mixture of diols (3*S*)- and (3*R*)-**8a**. These diastereomers could be separated by column chromatography on silica gel, and (3*S*)- and (3*R*)-**8a** were

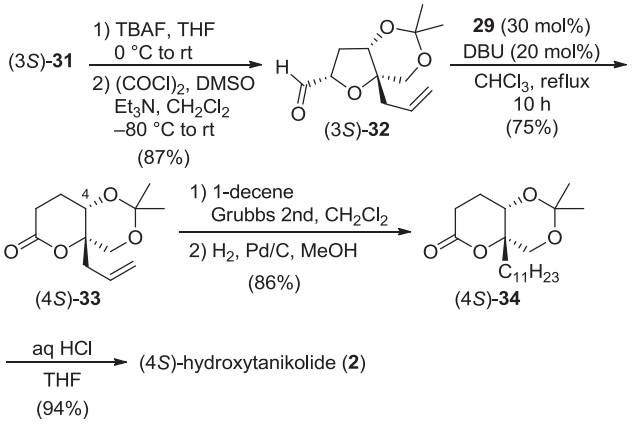


Scheme 5. Reduction of **6a** with $LiAlH_4$.

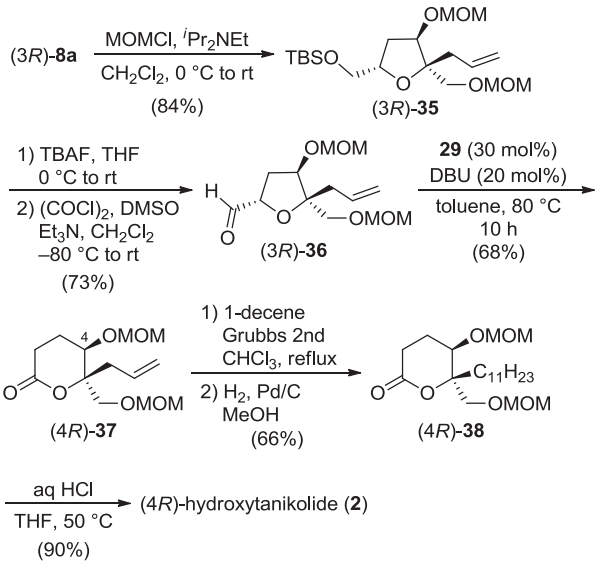
obtained in 52% and 37% yields, respectively. Stereochemical assignments of these diols were obtained from experiments with acetonide formation. The reaction of the major isomer of **8a** with 2,2-dimethoxypropane using a catalytic amount of TsOH in benzene under reflux proceeded smoothly to completion within 30 min, providing acetonide **31** in 99% yield. Conversely, the reaction of the minor isomer of **8a** under the same conditions did not proceed, even after 24 h. Because formation of a *trans*-fused [6.5]-bicyclic system is generally more difficult than that of a *cis*-fused one, the stereochemistries of the major and minor isomers **8a** at C3 were determined to be *S* and *R*, respectively.

With the acetonide (3*S*)-**31** in hand, we then examined the synthesis of (4*S*)-hydroxytanikolide (**2**) employing NHC-catalyzed ring expansion and cross metathesis (Scheme 6). Removal of the *tert*-butyldimethylsilyl (TBS) protecting group in (3*S*)-**31** with TBAF was followed by Swern oxidation to afford aldehyde (3*S*)-**32** in 87% yield. Conversion from (3*S*)-**32** into δ-lactone (4*S*)-**33** was conducted under the same conditions as those for **28**. The product (4*S*)-**33** was obtained in 75% yield. The cross metathesis between alkene (4*S*)-**33** and 1-decene (10 equivalent) followed by hydrogenation provided (4*S*)-**34** in 86% yield. Hydrolysis of acetonide (4*S*)-**34** under acidic conditions furnished (4*S*)-hydroxytanikolide (**2**) in 94% yield.

Following a procedure similar to that for (3*S*)-**8a**, the diol (3*R*)-**8a** was converted into (4*R*)-hydroxytanikolide (**2**, Scheme 7). Protection of the diol as the bis-MOM groups gave (3*R*)-**35** in 84% yield. Desilylation of TBS ether (3*R*)-**35** with TBAF and subsequent Swern oxidation provided aldehyde (3*R*)-**36** in 73% yield. Ring expansion of (3*R*)-**36** using 30 mol% imidazolium catalyst **29** and 20 mol% DBU in toluene at 80 °C proceeded to completion within 10 h, providing



Scheme 6. Synthesis of (4*S*)-hydroxytanikolide (**2**).

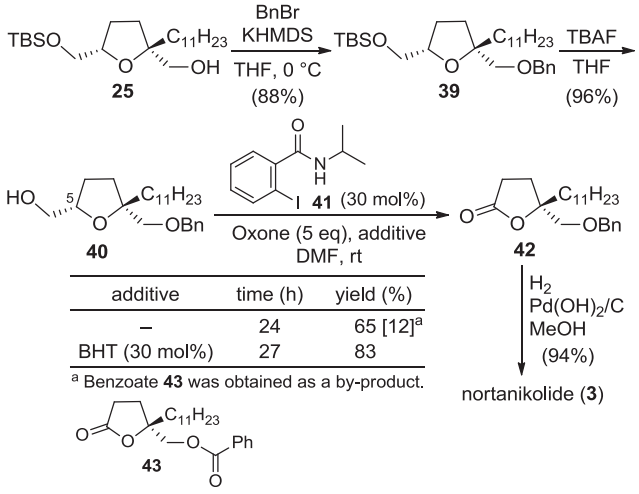


Scheme 7. Synthesis of (4*R*)-hydroxytanikolide (**2**).

δ-lactone (4*R*)-**37** in 68% yield. The cross metathesis for the long side chain extension and following hydrogenation furnished (4*R*)-**38** in 66% yield. The bis-MOM groups in (4*R*)-**38** were deprotected under acidic conditions to afford (4*R*)-hydroxytanikolide (**2**) in 90% yield.

2.4. Synthesis of nortanikolide

Finally, the synthesis of nortanikolide (**3**) from the tetrahydrofuran **25**, which was used as a synthetic intermediate for (+)-tanikolide (**1**), was investigated (Scheme 8). After protection of the hydroxyl group in **25** as its benzyl (Bn) ether, deprotection of the TBS ether with TBAF afforded alcohol **40** in 84% yield. Then, we examined the oxidative cleavage of tetrahydrofuran-5-methanol **40** to γ-lactone. In our previous report on the synthesis of 2-*epi*-cinatrin C_1 dimethyl ester, we employed the oxidative cleavage of tetrahydrofuran-5-methanol to γ-lactone with an excess amount of pyridinium dichromate and acetic anhydride in CH_2Cl_2–DMF under reflux.[18] Although the γ-lactone was obtained in good yield, the reaction was carried out under harsh conditions, such as the use of



additive	time (h)	yield (%)
–	24	65 [12][a]
BHT (30 mol%)	27	83

[a] Benzoate **43** was obtained as a by-product.

Scheme 8. Synthesis of nortanikolide (**3**).

highly toxic hexavalent chromium oxidants and heating at high temperature. To avoid these drawbacks, we recently developed an environmentally benign method for oxidative cleavage using a 2-iodobenzamide catalyst **41**.[22] Therefore, we examined the oxidative cleavage under our original conditions. The reaction of **40** with 30 mol% **41** and 5 equivalent of Oxone in DMF at room temperature provided the corresponding γ-lactone **42** in 65% yield; however, unexpectedly, benzoate **43** was obtained in 12% yield. This result indicates that the oxidation at the benzylic position of **40** proceeded in part to give **43**.[25] To prevent this undesired oxidation, we explored the use of an antioxidant. As expected, the reaction of **40** using 30 mol% 2,6-di-*tert*-butyl-4-hydroxytoluene (BHT) as an antioxidant suppressed the formation of benzoate **43** and afforded **42** in 83% yield. Finally, hydrogenolysis of the benzyl ether in the presence of Pearlman's catalyst ($Pd(OH)_2/C$) in methanol furnished nortanikolide (**3**) in 94% yield.

3. Conclusion

The divergent synthesis of (+)-tanikolide, (4*S*)- and (4*R*)-hydroxytanikolides, and nortanikolide from the key intermediate franone was achieved. The key steps involved a rhodium(II)-catalyzed oxonium ylide formation–[2,3]-sigmatropic rearrangement, an NHC-catalyzed ring expansion of tetrahydrofurfural to δ-lactone, or an oxidative cleavage of tetrahydrofuran-5-methanol to γ-lactone using a 2-iodobenzamide catalyst. As the quaternary chiral center can be easily and stereoselectively constructed, the long side chain can be introduced at a later stage in the synthesis, and δ- and γ-lactone rings can be formed from the common intermediate, the present protocol provides high flexibility for the synthesis of a variety of analogues.

4. Experimental section

4.1. General

Melting points were determined using a Yanaco micro melting point apparatus and are uncorrected. Optical rotations were determined using a JASCO P-2100 polarimeter. Infrared (IR) spectra were recorded on a JASCO FT/IR-460 Plus spectrophotometer and absorbance bands are reported in wavenumber (cm^{-1}). ^1H NMR spectra were recorded on JEOL JNM-ECX400P (400 MHz) spectrometer. Chemical shifts are reported relative to internal standard (tetramethylsilane at δ_H 0.00 or $CDCl_3$ at δ_H 7.26). Data are presented as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, quint = quintet, m = multiplet, br = broad), coupling constant and integration. ^{13}C NMR spectra were recorded on JEOL JNM-ECX400P (100 MHz) spectrometer. The following internal reference was used ($CDCl_3$ at δ 77.0). All ^{13}C NMR spectra were determined with complete proton decoupling. High-resolution mass spectra (HRMS) were determined with JEOL JMS-GCmate II and JEOL JMS-AX505HAD instruments. Column chromatography was performed on Silica Gel 60 PF_{254} (Nacalai Tesque) and Kanto silica gel 60 N (63–210 mesh) under pressure. Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} plates. Visualization was accomplished with UV light and phosphomolybdic acid stain solution followed by heating.

4.2. Synthesis of (+)-tanikolide (*1*)

4.2.1. (*S*)-Methyl 3-allyloxy-4-(tert-butyldimethylsilyloxy) butanoate (*15*)[15j]

Allyl bromide (3.3 mL, 37.7 mmol), Ag_2O (4.36 g, 18.8 mmol), and $CaSO_4$ (3.42 g, 25.1 mmol) were added to a solution of (*S*)-methyl 4-(*tert*-butylsilyloxy)-3-hydroxybutanoate (**14**)[23] (2.34 g, 9.42 mmol) and MS4A (2.34 g) in toluene (38 mL) at room temperature under N_2 in the dark. After stirring for 1 day, Ag_2O (4.36 g, 18.8 mmol) and $CaSO_4$ (3.42 g, 25.1 mmol) were added again to the reaction mixture and the mixture was stirred for 1 day. After further addition of Ag_2O (4.36 g, 18.8 mmol) and $CaSO_4$ (3.42 g, 25.1 mmol), the mixture was stirring for one more day. The reaction mixture was filtered through the pad of Celite. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 4% EtOAc in hexane) to provide **15** (2.13 g, 78%) as a colorless oil: $[\alpha]_D^{24}$ −22.9 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) ν 2954, 2930, 2886, 2858, 1742, 1084, 1006, 838, 778, 669; ^1H NMR (400 MHz, $CDCl_3$) δ 5.88 (ddt, *J* = 17.0, 10.4, 6.0 Hz, 1H), 5.25 (dd, *J* = 17.0, 1.4 Hz, 1H), 5.15 (dd, *J* = 10.4, 1.4 Hz, 1H), 4.15–4.04 (m, 2H), 3.72 (dd, *J* = 10.6, 8.0 Hz, 1H), 3.69 (s, 3H), 3.55 (dd, *J* = 10.6, 5.4 Hz, 1H), 2.61 (dd, *J* = 15.6, 5.4 Hz, 1H), 2.49 (dd, *J* = 15.6, 8.0 Hz, 1H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 135.0, 116.8, 76.4, 71.5, 64.7, 51.6, 37.3, 25.9, 18.3, −5.4.

4.2.2. (*S*)-3-Allyloxy-4-(tert-butyldimethylsilyloxy)butanal (*16*)[26]

DIBAL-H (1.0 M in hexane, 12.7 mL, 12.7 mmol) was added dropwise to a solution of methyl ester **15** (3.05 g, 10.6 mmol) in CH_2Cl_2 (106 mL) at −78 °C under N_2. After stirring at −78 °C for 30 min, the reaction was quenched by the addition of MeOH (25 mL) and saturated aqueous NH_4Cl (12.7 mL) and then allowed to warm to room temperature. The mixture was dried over anhydrous Na_2SO_4 and filtered through a pad of Celite. The filtrate was concentrated in vacuo and the residue was purified by column chromatography (silica gel, 5% EtOAc in hexane) to provide **16** (2.59 g, 95%) as a colorless oil: $[\alpha]_D^{24}$ −25.3 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) ν 2954, 2929, 2857, 1730, 1255, 1094, 838, 778; ^1H NMR (400 MHz, $CDCl_3$) δ 9.81 (t, *J* = 2.4 Hz, 1H), 5.89 (ddt, *J* = 17.0, 10.4, 5.6 Hz, 1H), 5.27 (ddd, *J* = 17.0, 3.2, 1.4 Hz, 1H), 5.17 (ddd, *J* = 10.4, 3.2, 1.4 Hz, 1H), 4.13 (ddt, *J* = 12.7, 5.6, 1.4 Hz, 1H), 4.06 (ddt, *J* = 12.7, 5.6, 1.4 Hz, 1H), 3.93 (quint, *J* = 5.8 Hz, 1H), 3.74 (dd, *J* = 10.4, 5.0 Hz, 1H), 3.59 (dd, *J* = 10.4, 6.2 Hz, 1H), 2.64–2.62 (m, 2H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 134.7, 117.1, 74.9, 71.1, 64.6, 46.3, 25.8, 18.3, −5.5.

4.2.3. (*S*)-Methyl 5-allyloxy-6-tert-butyldimethylsilyloxy-3-oxohexanoate (*17*)

A solution of the methyl diazoacetate (329 mg, 3.29 mmol) in CH_2Cl_2 (9 mL) and a solution of aldehyde **16** (567 mg, 2.19 mmol) in CH_2Cl_2 (15 mL) were added to a suspension of $SnCl_2$ (83 mg, 0.44 mmol) in CH_2Cl_2 (10 mL) over 20 min at room temperature under N_2. After stirring for 5.5 h, the reaction mixture was evaporated and the residue was purified by column chromatography (silica gel, 7% EtOAc in hexane) to provide **17** (501 mg, 69%) as a pale yellow oil: $[\alpha]_D^{25}$ −24.8 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) ν 2954, 2929, 2885, 2858, 1751, 1720, 1322, 1255, 1117, 838, 778; ^1H NMR (400 MHz, $CDCl_3$) δ 5.87 (ddt, *J* = 22.6, 10.6, 5.6 Hz, 1H), 5.24 (dd, *J* = 17.8, 1.4 Hz, 1H), 5.15 (dd, *J* = 10.6, 1.0 Hz, 1H) 4.11 (dd, *J* = 12.6, 5.6 Hz, 1H), 4.03 (dd, *J* = 12.6, 5.6 Hz, 1H), 3.88 (quint, *J* = 6.0 Hz, 1H), 3.74 (s, 3H), 3.68 (dd, *J* = 10.4, 4.8 Hz, 1H), 3.55 (dd, *J* = 10.4, 6.0 Hz, 1H), 3.52 (s, 2H), 2.75 (dd, *J* = 6.0, 1.3 Hz, 2H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 167.5, 134.8, 117.0, 75.8, 71.4, 64.5, 52.3, 50.1, 45.4, 25.9, 18.3, −5.5; HRMS (EI) *m/z* calcd for $C_{16}H_{30}O_5Si$ $(M)^+$ 330.1863, found 330.1854.

4.2.4. (*S*)-Methyl 5-allyloxy-6-tert-butyldimethylsilyloxy-2-diazo-3-oxohexanoate (*5a*)

A solution of *p*-ABSA (1.88 g, 7.84 mmol) in CH_3CN (12 mL) and Et_3N (1.8 mL, 13.1 mmol) was added dropwise to a solution of β-keto ester **17** (2.16 g, 6.53 mmol) in CH_3CN (70 mL) at 0 °C under N_2. After stirring at room temperature for 5.5 h, the reaction mixture was evaporated. The residue was dissolved in ether (80 mL), and

washed with 10% aqueous KOH (2 × 30 mL) water (20 mL) and brine (20 mL), and dried over anhydrous $MgSO_4$. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 7% EtOAc in hexane) to provide **5a** (2.22 g, 95%) as a yellow oil: $[\alpha]_D^{24}$ −13.1 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) *ν* 2955, 2929, 2857, 2135, 1726, 1658, 1438, 1314, 1255, 1200, 1123, 838, 778; ^1H NMR (400 MHz, $CDCl_3$) *δ* 5.89 (ddd, *J* = 22.6, 10.8, 5.6 Hz, 1H), 5.24 (dd, *J* = 17.4, 1.4 Hz, 1H), 5.13 (br d, *J* = 10.8 Hz, 1H), 4.99 (m, 1H), 4.16–4.06 (m, 2H), 3.83 (s, 3H), 3.71 (dd, *J* = 10.4, 5.6 Hz, 1H), 3.17 (dd, *J* = 16.4, 8.0 Hz, 1H), 3.01 (dd, *J* = 16.4, 4.6 Hz, 1H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 190.5, 161.7, 135.2, 116.6, 75.8, 71.5, 65.1, 52.2, 42.6, 25.8, 18.3, −5.4; HRMS (EI) *m/z* calcd for $C_{16}H_{28}N_2O_5Si$ $(M)^+$ 356.1768, found 356.1793.

4.2.5. (2R,5S)-Methyl 2-allyl-5-(tert-butyldimethylsilyloxy)methyl-3-oxotetrahydrofuran-2-carboxylate (**6a**)

A solution of diazoketoester **5a** (1.27 g, 3.56 mmol) in CH_2Cl_2 (17 mL) was added dropwise to a solution of $Rh_2(OAc)_4$ (47 mg, 0.11 mmol, 3 mol%) in CH_2Cl_2 (100 mL) at room temperature under N_2. After refluxing for 5 h, the reaction mixture was evaporated and the residue was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide **6a** (1.08 g, 93%) as a colorless oil: $[\alpha]_D^{24}$ +5.5 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) *ν* 2954, 2929, 2858, 1769, 1748, 1435, 1174, 1109, 838, 779; ^1H NMR (400 MHz, $CDCl_3$) *δ* 5.74 (ddt, *J* = 16.9, 10.1, 7.3 Hz, 1H), 5.20–5.13 (m, 2H), 4.47 (m, 1H), 3.87 (dd, *J* = 10.8, 4.6 Hz, 1H), 3.80 (dd, *J* = 10.8, 3.6 Hz, 1H), 3.75 (s, 3H), 2.71 (ddt, *J* = 13.8, 7.3, 0.9 Hz, 1H), 2.65 (dd, *J* = 18.1, 6.4 Hz, 1H), 2.60 (ddt, *J* = 13.8, 7.3, 0.9 Hz, 1H), 2.56 (dd, *J* = 18.1, 7.3 Hz, 1H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 208.9, 168.2, 130.8, 120.3, 86.4, 76.1, 65.4, 52.8, 39.7, 38.5, 25.8, 18.3, −5.5, −5.6; HRMS (EI) *m/z* calcd for $C_{16}H_{28}O_5Si$ $(M)^+$ 328.1706, found 328.1705.

4.2.6. (2R,5S)-Methyl 5-(tert-butyldimethylsilyloxy)methyl-3-(4-toluenesulfonyl)hydrazinylidene-2-allyltetrahydrofuran-2-carboxylate (**20a**)

Tosylhydrazine (109 mg, 0.58 mmol) was added to a solution of ketone **6a** (174 mg, 0.53 mmol) in THF (0.9 mL) at room temperature under N_2. After stirring at room temperature for 24 h, solvent was removed in vacuo and the residue was purified by column chromatography (silica gel, 20% EtOAc in hexane) to provide **20a** (242 mg, 92%) as a colorless oil: $[\alpha]_D^{19}$ −4.4 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) *ν* 3209, 2953, 2928, 1745, 1435, 1411, 1347, 1254, 1169, 923, 838, 778; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.83 (dt, *J* = 8.7, 1.8 Hz, 2H), 7.33 (s, 2H), 7.31 (s, 1H), 5.57 (ddt, *J* = 17.2, 10.1, 6.9 Hz, 1H), 4.98 (dt, *J* = 10.1, 1.4 Hz, 1H), 4.91 (ddd, *J* = 17.2, 3.2, 1.4 Hz, 1H), 4.30 (ddd, *J* = 6.9, 6.8, 4.6 Hz, 1H), 3.77 (dd, *J* = 10.3, 4.6 Hz, 1H), 3.611 (s, 3H), 3.609 (dd, *J* = 10.3, 6.9 Hz, 1H), 2.75 (dd, *J* = 14.2, 6.9 Hz, 1H), 2.60–2.53 (m, 2H), 2.46 (dd, *J* = 17.4, 6.9 Hz, 1H), 2.43 (s, 3H), 0.84 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 159.7, 144.3, 135.1, 131.4, 129.5, 128.1, 119.7, 86.2, 78.7, 77.2, 64.9, 52.6, 40.6, 30.2, 25.8, 21.6, 18.2, −5.4, −5.5; HRMS (EI) *m/z* calcd for $C_{23}H_{36}N_2O_6SiS$ $(M)^+$ 496.2063, found 496.2083.

4.2.7. (2R,5S)-Methyl 5-(tert-butyldimethylsilyloxy)methyl-2,5-dihydro-2-allylfuran-2-carboxylate (**21a**)

Sodium cyanoborohydride (30 mg, 0.48 mmol) and $TsOH \cdot H_2O$ (7 mg, 0.04 mmol) were added to a solution of tosylhydrazone **20a** (60 mg, 0.12 mmol) in DMF (2.4 mL) at room temperature. After refluxing for 8 h, the reaction mixture was diluted with EtOAc (30 mL) and washed with water (20 mL) and brine (20 mL), and dried over anhydrous $MgSO_4$. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 3% EtOAc in hexane) to provide **21a** (14 mg, 40%) as a colorless oil: $[\alpha]_D^{25}$ −79.9 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) *ν* 2953, 2929, 2857, 1759, 1735, 1256, 1128, 1097, 1074, 917, 838, 778; ^1H NMR (400 MHz, $CDCl_3$) *δ* 6.03 (dd, *J* = 6.0, 1.4 Hz, 1H), 5.88 (dd, *J* = 6.0, 2.3 Hz, 1H), 5.75 (m, 1H), 5.13–5.07 (m, 2H), 4.87 (ddd, *J* = 6.9, 5.0, 2.5 Hz, 1H), 3.83 (dd, *J* = 9.8, 5.0 Hz, 1H), 3.72 (s, 3H), 3.55 (dd, *J* = 9.8, 6.9 Hz, 1H), 2.65 (ddt, *J* = 14.1, 7.3, 1.4 Hz, 1H), 2.54 (ddt, *J* = 14.1, 7.3, 1.4 Hz, 1H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 172.7, 132.0, 130.7, 129.1, 118.8, 93.2, 87.9, 65.9, 52.2, 42.4, 25.8, 18.3, −5.4, −5.5; HRMS (FAB) *m/z* calcd for $C_{16}H_{29}O_4Si$ $(M + H)^+$ 313.1835, found 313.1840.

4.2.8. (2R,5S)-Methyl 5-(tert-butyldimethylsilyloxy)methyl-2-(2-undecen-1-yl)-3-oxotetrahydrofuran-2-carboxylate (**23**)

Grubbs 2nd catalyst (4.7 mg, 0.006 mmol, 1 mol%) was added to the solution of **6a** (181 mg, 0.55 mmol) and 1-decene (1.0 mL, 5.51 mmol) in $CHCl_3$ (5.5 mL) at room temperature under N_2. After refluxing for 3 h, Grubbs 2nd catalyst (4.7 mg, 0.006 mmol, 1 mol%) was added again to the reaction mixture and the mixture was refluxed for 3.5 h. Solvent was removed in vacuo, and the residue was purified by column chromatography (silica gel, 5% EtOAc in hexane) to provide **23** (214 mg, 88%) as a pale yellow oil: $[\alpha]_D^{24}$ +11.3 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) *ν* 2954, 2927, 2856, 1769, 1748, 1254, 1112, 838, 779; ^1H NMR (400 MHz, $CDCl_3$) *δ* 5.56 (dt, *J* = 14.7, 7.1 Hz, 1H), 5.37 (dt, *J* = 15.1, 7.6 Hz, 1H), 4.45 (ddt, *J* = 7.1, 4.8, 4.0 Hz, 1H), 3.86 (dd, *J* = 10.6, 4.8 Hz, 1H), 3.79 (dd, *J* = 10.6, 4.0 Hz, 1H), 3.74 (s, 0.4H), 3.73 (s, 2.6H), 2.72–2.49 (m, 4H), 2.03 (dt, *J* = 15.6 Hz, 7.1 Hz, 0.2H), 1.97 (dt, *J* = 13.6, 6.7 Hz, 0.8H), 1.31 (br s, 2H), 1.29 (br s, 2H) 1.25 (br s, 8H), 0.88 (br s, 12H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 209.1, 168.4, 136.8, 135.3, 121.7, 120.9, 86.7, 86.5, 76.1, 76.0, 65.4, 52.7, 38.9, 38.6, 32.6, 31.9, 29.50, 29.46, 29.4, 29.3, 29.1, 27.4, 25,8, 22.6, 18.3, 14.1, −5.5.; HRMS (EI) *m/z* calcd for $C_{24}H_{44}O_5Si$ $(M)^+$ 440.2958, found 440.2954.

4.2.9. (2R,5S)-Methyl 5-(tert-butyldimethylsilyloxy)methyl-3-(4-toluenesulfonyl)hydrazinylidene-2-(2-undecen-1-yl) tetrahydrofuran-2-carboxylate (**20b**)

Tosylhydrazine (212 mg, 1.14 mmol) was added to a solution of ketone **23** (313 mg, 0.71 mmol) in THF (1.1 mL) at room temperature under N_2. After stirring at room temperature for 24 h, solvent was removed in vacuo and the residue was purified by column chromatography (silica gel, 15% EtOAc in hexane) to provide **20b** (424 mg, 98%) as a colorless oil: $[\alpha]_D^{26}$ +18.2 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) *ν* 3209, 2954, 2926, 2855, 1747, 1599, 1463, 1435, 1409, 1349, 1254, 1170, 1094, 838, 779; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.84 (d, *J* = 8.2 Hz, 1.6H), 7.82 (d, *J* = 8.2 Hz, 0.4H), 7.47 (s, 0.2H), 7.45 (s, 0.8H), 7.31 (d, *J* = 8.2 Hz, 1.6 H), 7.30 (d, *J* = 8.2 Hz, 0.4H), 5.44 (m, 0.2H), 5.28 (dt, *J* = 15.4, 6.4 Hz, 0.8H), 5.13 (dt, *J* = 15.4, 7.1 Hz, 1H), 4.27 (dt, *J* = 11.4, 6.9 Hz, 1H), 3.76 (dd, *J* = 10.5, 4.6 Hz, 1H), 3.60 (s, 3H), 3.59 (m, 1H), 2.77–2.38 (m, 4H), 2.43 (s, 3H), 1.97 (br d, *J* = 6.4 Hz, 0.4H), 1.84 (br d, *J* = 6.4 Hz, 1.6H), 1.26 (br s, 12H), 0.88 (t, *J* = 7.1 Hz, 3H), 0.83 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 170.3, 160.0, 144.2, 136.2, 135.2, 129.5, 128.1, 122.3, 86.6, 78.7, 65.0, 52.5, 39.6, 32.7, 31.9, 29.6, 29.5, 29.32, 29.30, 29.2, 25.8, 22.7, 21.6, 18.2, 14.1, −5.5; HRMS (EI) *m/z* calcd for $C_{31}H_{52}N_2O_6SSi$ $(M)^+$ 608.3315, found 608.3326.

4.2.10. (2R,5S)-Methyl 5-(tert-butyldimethylsilyloxy)methyl-2,5-dihydro-2-(2-undecen-1-yl)furan-2-carboxylate (**21b**)

Sodium cyanoborohydride (270 mg, 4.30 mmol) was added to a solution of tosylhydrazone **20b** (654 mg, 1.07 mmol) in DMF (54 mL) at room temperature. After refluxing for 1 h, the reaction mixture was diluted with EtOAc (150 mL) and washed with water (50 mL) and brine (50 mL), and dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 4% EtOAc in hexane) to provide **21b** (345 mg, 76%) as a colorless oil: $[\alpha]_D^{26}$ −44.0 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) *ν* 2954, 2926, 2856, 1759, 1735, 1255, 1095, 837, 778; ^1H

NMR (400 MHz, $CDCl_3$) δ 6.00 (d, $J=6.0$, 1.2 Hz, 1H), 5.87 (dd, $J=6.0$, 1.6 Hz, 1H), 5.28 (dt, $J=15.6$, 6.8 Hz, 1H), 5.34 (dt, $J=15.6$, 7.2 Hz, 1H), 4.85 (m, 1H), 3.83 (dd, $J=10.0$, 4.4 Hz, 1H), 3.72 (s, 0.1H), 3.70 (s, 2.9H), 3.53 (dd, $J=9.6$, 6.8 Hz, 1H), 2.65 (dd, $J=14.6$, 6.8 Hz, 0.1H), 2.55 (dd, $J=14.0$, 7.2 Hz, 0.9H), 2.47 (dd, $J=14.0$, 7.2 Hz, 0.8H), 2.01 (dd, $J=14.0$, 6.8 Hz, 0.2H), 1.96 (dd, $J=14.0$, 6.8 Hz, 1.8H), 1.25 (br s, 12H), 0.88 (t, $J=7.1$ Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 135.2, 130.6, 130.4, 129.32, 129.26, 122.9, 93.6, 87.8, 65.9, 52.1, 41.4, 32.6, 31.9, 29.5, 29.4, 29.32, 29.28, 29.1, 25.9, 22.7, 18.3, 14.1, −5.4; HRMS (EI) *m/z* calcd for $C_{24}H_{44}O_4Si$ $(M)^+$ 424.3009, found 424.3044.

4.2.11. (2R,5S)-Methyl 5-(tert-butyldimethylsilyloxy)methyl-2-undecanyltetrahydrofuran-2-carboxylate (**24**)

Pd/C (20 mg, 10 wt% of **21b**) was added to the solution of **21b** (204 mg, 0.48 mmol) in MeOH (2.4 mL) at room temperature. The reaction mixture was placed in an autoclave and was vigorously stirred under 10 atm of hydrogen for 2 h. The mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo and the residue was purified by column chromatography (silica gel, 4% EtOAc in hexane) to provide **24** (193 mg, 94%) as a colorless oil: $[\alpha]_D^{24}$ −9.3 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) ν 2926, 2855, 1735, 1463, 1254, 1128, 1090, 838, 778; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.12 (tt, $J=6.4$, 4.6 Hz, 1H), 3.78 (dd, $J=10.1$, 4.6 Hz, 1H), 3.71 (s, 3H), 3.55 (dd, $J=10.1$, 6.8 Hz, 1H), 2.35 (dt, $J=6.8$, 4.1 Hz, 1H), 2.01 (m, 1H), 1.88−1.66 (m, 4H), 1.24 (br s, 12H), 0.88 (br s, 12H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 87.1, 81.0, 65.8, 52.0, 38.6, 35.0, 31.9, 29.8, 29.6, 29.5, 29.4, 29.3, 28.5, 25.9, 24.3, 22.7, 18.3, 14.1, −5.4; HRMS (EI) *m/z* calcd for $C_{24}H_{48}O_4Si$ $(M)^+$ 428.3322, found 428.3362.

4.2.12. (2R,5S)-5-(tert-butyldimethylsilyloxy)methyl-2-undecanyltetrahydrofuran-2-methanol (**25**)

DIBAL-H (1.0 M in hexane, 1.1 mL 1.13 mmol) was added dropwise to a solution of methyl ester **24** (193 mg, 0.45 mmol) in CH_2Cl_2 (4.5 mL) at −78 °C under N_2. After stirring at 0 °C for 15 min, the reaction mixture was quenched by the addition of MeOH (2.2 mL) and saturated aqueous NH_4Cl (1.1 mL) and then allowed to warm to room temperature. The mixture was dried over anhydrous Na_2SO_4 and filtered through a pad of Celite. The filtrate was concentrated in vacuo and the residue was purified by column chromatography (silica gel, 6% EtOAc in hexane) to provide **25** (161 mg, 89%) as a colorless oil: $[\alpha]_D^{24}$ −10.9 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) ν 3471, 2953, 2926, 2855, 1464, 1255, 1090, 837, 777; ^{1}H NMR ($CDCl_3$) δ: 4.11 (br t, $J=7.2$ Hz, 1H), 3.89 (dd, $J=10.8$, 3.2 Hz, 1H), 3.57 (dt, $J=10.8$, 2.8 Hz, 1H), 3.40 (t, $J=10.8$ Hz, 2H), 3.08 (dd, $J=10.8$, 2.8 Hz, 1H), 2.17−2.00 (m, 2H), 1.91−1.75 (m, 2H), 1.47 (br t, $J=4.0$ Hz, 2H), 1.25 (br s, 18H), 0.92 (s, 9H), 0.88 (t, $J=6.8$ Hz, 3H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.5, 79.8, 69.3, 64.8, 37.9, 32.5, 31.9, 30.3, 29.64, 29.59, 29.58, 29.3, 28.0, 25.9, 24.0, 22.7, 18.5, 14.1, −5.5; HRMS (EI) *m/z* calcd for $C_{23}H_{48}O_3Si$ $(M)^+$ 400.3373, found 400.3384.

4.2.13. (2R,5S)-5-(tert-Butyldimethylsilyloxy)methyl-2-(methoxymethyloxy)methyl-2-undecanyltetrahydrofuran (**26**)

^{i}Pr$_2$NEt (0.2 mL, 2.60 mmol) and MOMCl (0.75 mL, 4.33 mmol) was added to the solution of **25** (347 mg, 0.87 mmol) in CH_2Cl_2 (4.3 mL) at 0 °C under N_2. After stirring at 0 °C for 30 min, the reaction mixture was allowed to warm to room temperature and was stirred for 5.5 h. The mixture was quenched by the addition of saturated aqueous $NaHCO_3$ and the mixture was extracted with EtOAc (3 × 10 mL). Combined organic layers were washed with water (10 mL) and brine (10 mL) and dried over anhydrous $MgSO_4$. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 6% EtOAc in hexane) to provide **26** (372 mg, 97%) as a colorless oil: $[\alpha]_D^{24}$ −6.5 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) ν 2926, 2855, 1463, 1254, 1149, 1112, 1053, 837, 776; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63 (s, 2H), 4.03 (dt, $J=10.4$, 6.2 Hz, 1H), 3.65 (dd, $J=10.4$, 4.2 Hz, 1H), 3.53 (dd, $J=10.4$, 6.0 Hz, 1H), 3.41 (d, $J=10.0$ Hz, 1H), 3.37 (d, $J=10.0$ Hz, 1H), 3.36 (s, 3H), 1.99−1.70 (m, 4H), 1.55 (dd, $J=9.4$, 5.6 Hz, 2H), 1.26 (br s, 18H), 0.89 (br s, 12H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.8, 84.8, 79.9, 72.6, 65.9, 55.2, 37.1, 32.5, 31.9, 30.3, 29.7, 29.6, 29.3, 28.4, 25.9, 24.1, 22.7, 18.4, 14.1; HRMS (EI) *m/z* calcd for $C_{25}H_{52}O_4Si$ $(M)^+$ 444.3635, found 444.3658.

4.2.14. (2R,5S)-2-(Methoxymethyloxy)methyl-2-undecanyltetrahydrofuran-5-methanol (**27**)

TBAF (1.0 M in THF, 0.21 mL, 0.21 mmol) was added to a solution of **26** (85 mg, 0.19 mmol) in THF (1.9 mL) at 0 °C under N_2 and then the resulting mixture was stirred at room temperature. After stirring for 2.5 h, the reaction mixture was diluted with EtOAc (20 mL) and washed with water (10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 25% EtOAc in hexane) to provide **27** (63 mg, 100%) as a colorless oil: $[\alpha]_D^{24}$ +0.66 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) ν 3447, 2925, 2854, 1465, 1150, 1112, 1048; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (d, $J=8.4$ Hz, 1H), 4.66 (d, $J=8.4$ Hz, 1H), 4.17 (ddd, $J=9.6$, 6.8, 3.2 Hz, 1H), 3.79 (dt, $J=11.6$, 3.2 Hz, 1H), 3.54 (d, $J=10.0$ Hz, 1H), 3.45 (m, 1H), 3.45 (d, $J=10.0$ Hz, 1H), 3.38 (s, 3H), 2.94 (dd, $J=8.6$, 3.2 Hz, 1H), 2.06−1.93 (m, 3H), 1.76 (m, 1H), 1.56−1.49 (m, 2H), 1.28 (br s, 4H), 1.26 (br s, 14H), 0.88 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.6, 85.2, 80.1, 72.8, 65.1, 55.4, 37.9, 32.6, 31.9, 30.2, 29.64, 29.60, 29.58, 29.5, 29.33, 29.31, 27.6, 24.0, 22.7, 14.1; HRMS (EI) *m/z* calcd for $C_{19}H_{38}O_4$ $(M)^+$ 330.2770, found 330.2779.

4.2.15. (2R,5S)-2-(Methoxymethyloxy)methyl-2-undecanyltetrahydrofuran-5-carboaldehyde (**28**)

A solution of DMSO (0.044 mL, 0.56 mmol) in CH_2Cl_2 (0.24 mL) was dropped to a solution of oxalyl chloride (0.032 mL, 0.38 mmol) in CH_2Cl_2 (0.4 mL) at −78 °C under N_2 over 15 min. A solution of alcohol **27** (62 mg, 0.19 mmol) in CH_2Cl_2 (0.3 mL) was then dropped to the reaction mixture over 15 min. After stirring for 30 min at −78 °C, triethylamine (0.13 mL, 0.94 mmol) was added to the reaction mixture and the mixture was allowed to warm to room temperature over 80 min. After stirred at room temperature for 40 min, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (1 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and combined organic layers were dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 20% EtOAc in hexane to 50% EtOAc in hexane) to provide **28** (51 mg, 82%) as a colorless oil: $[\alpha]_D^{25}$ −22.2 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) ν IR (neat, cm^{-1}) ν 3447, 2925, 2854, 1465, 1150, 1112, 1048; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (d, $J=1.6$ Hz, 1H), 4.64 (s, 2H), 4.30 (t, $J=10.8$ Hz, 1H), 3.51 (d, $J=10.0$ Hz, 1H), 3.46 (d, $J=10.0$ Hz, 1H), 3.36 (s, 3H), 2.18−2.10 (m, 2H), 1.93 (dt, $J=12.0$, 6.8 Hz, 1H), 1.79 (dt, $J=12.0$, 8.0 Hz, 1H), 1.60 (br s, 2H), 1.26 (br s, 18H), 0.88 (t, $J=6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 96.7, 87.1, 83.7, 72.7, 55.4, 37.3, 32.2, 31.9, 30.2, 29.63, 29.60, 29.57, 29.3, 28.0, 24.0, 22.7, 14.1; HRMS (EI) *m/z* calcd for $C_{19}H_{38}O_4$ $(M)^+$ 328.2614, found 328.2616.

4.2.16. (S)-5-(Methoxymethyloxy)methyl-5-undecanyltetrahydropyran-1-one (**30**)

1,3-Bis(2,6-diisopropylphenyl)imidazolinium chloride (**29**) (20 mg, 0.05 mmol, 30 mol%) and DBU (0.005 mL, 0.031 mmol, 20 mol%) was added to the solution of aldehyde **28** (51 mg, 0.16 mmol) in $CHCl_3$ (3.1 mL) at room temperature under N_2. After refluxing for 24 h, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (3 mL) at room temperature. The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and combined

organic layers were dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 20% EtOAc in hexane) to provide **30** (36 mg, 71%) as a colorless oil: $[\alpha]_D^{27}$ −2.8 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) ν 2925, 2854, 1738, 1465, 1330, 1248, 1150, 1114, 1050, 921; ^1H NMR (400 MHz, $CDCl_3$) δ 4.63 (s, 2H), 3.56 (d, J = 10.0 Hz, 1H), 3.51 (d, J = 10.0 Hz, 1H), 3.36 (s, 3H), 2.50 (dt, J = 18.0, 6.8 Hz, 1H), 2.44 (dt, J = 18.0, 6.8 Hz, 1H), 1.98 (dt, J = 12.4, 4.4 Hz, 1H), 1.92 (dt, J = 10.4, 3.6 Hz, 1H), 1.85–1.60 (m, 4H), 1.26 (br s, 18H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 96.7, 84.6, 71.8, 55.4, 38.0, 31.9, 29.9, 29.8, 29.6, 29.59, 29.58, 29.52, 29.46, 29.3, 27.7, 23.0, 22.7, 16.8, 14.1; HRMS (EI) *m/z* calcd for $C_{19}H_{38}O_4$ $(M)^+$ 328.2614, found 328.2648.

4.2.17. (+)-Tanikolide (*1*)

Aqueous HCl (4 M, 1.8 mL) was added dropwise to the solution of MOM ether **30** (120 mg, 0.37 mmol) in THF (1.8 mL) at room temperature. After stirring the reaction mixture at 50 °C for 6 h, the reaction mixture was saturated with NaCl. The mixture was extracted with $CHCl_3$ (3 × 20 mL) and combined organic layers were dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 40% EtOAc in hexane) to provide **1** (59 mg, 56%) as a white solid: mp 39–40 °C (lit.[6h] 39–41 °C); $[\alpha]_D^{24}$ +2.2 (*c* 0.65, $CHCl_3$) (lit.[1] $[\alpha]_D^{25}$ +2.3 (*c* 0.65, $CHCl_3$)); IR (neat, cm^{-1}) ν 3395, 2923, 2851, 1701, 1468, 1265, 1051; ^1H NMR (400 MHz, $CDCl_3$) δ 3.67 (d, J = 12.0 Hz, 1H), 3.54 (d, J = 12.0 Hz, 1H), 2.94 (br s, 1H), 2.47 (t, J = 6.6 Hz, 1H), 1.97–1.80 (m, 3H), 1.75–1.61 (m, 3H), 1.26 (br s, 18H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 86.6, 67.3, 36.7, 31.8, 29.9, 29.7, 29.53, 29.51, 29.47, 29.3, 29.2, 26.6, 23.3, 22.6, 16.6, 14.0.

4.3. Synthesis of (4S)- and (4R)-hydroxytanikolides (*2*)

4.3.1. (2R,3S,5S)- and (2R,3R,5S)-2-allyl-5-(tert-butyldimethylsilyloxy)methyl-3-hydroxytetrahydrofuran-2-methanol {(3S)-*8a*} and {(3R)-*8a*}

$LiAlH_4$ (229 mg, 6.02 mmol) was added to a solution of 3-oxotetrahydrofuran **6a** (989 mg, 3.01 mmol) in THF (15 mL) at 0 °C under N_2. After stirring at 0 °C for 4.5 h, the reaction mixture was diluted by excess amount of Et_2O and quenched by addition of H_2O (1.1 mL) and 15% aqueous NaOH (0.3 mL) and stirred at room temperature for 1 h. The mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo and the residue was purified by column chromatography (silica gel, 25% EtOAc in hexane) to provide (3*S*)-**8a** (471 mg, 52%) as a colorless oil and (3*R*)-**8a** (337 mg, 37%) as a white solid. (3*S*)-**8a**: $[\alpha]_D^{24}$ +17.9 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) ν 3419, 3076, 2954, 2929, 2858, 1640, 1471, 1256, 1091, 837, 778; ^1H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddt, J = 17.6, 9.6, 7.2 Hz, 1H), 5.14 (dd, J = 7.2, 1.2 Hz, 1H), 5.10 (br s, 1H), 4.20–4.13 (m, 2H), 3.92 (dd, J = 11.0, 2.4 Hz, 1H), 3.70 (d, J = 11.6 Hz, 1H), 3.70 (d, J = 6.0 Hz, 1H), 3.62 (d, J = 11.6 Hz, 1H), 3.54 (dd, J = 11.0, 2.4 Hz, 1H), 3.08 (dd, J = 7.6, 6.0 Hz, 1H), 2.43 (dt, J = 13.2, 7.6 Hz, 1H), 2.24 (ddt, J = 13.8, 7.6, 1.2 Hz, 2H), 2.03 (ddd, J = 13.2, 6.0, 5.6 Hz, 1H), 0.93 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.1, 118.4, 86.7, 77.0, 76.4, 65.9, 65.0, 40.0, 36.7, 25.9, 18.5, −5.51; HRMS (EI) *m/z* calcd for $C_{15}H_{30}O_4Si$ $(M)^+$ 302.1913, found 302.1915. (3*R*)-**8a**: mp 43–44 °C, $[\alpha]_D^{25}$ −8.0 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) ν 3323, 3075, 2952, 2931, 2868, 1641, 1464, 1254, 1097, 1033, 996, 836, 777; ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (ddt, J = 17.4, 10.0, 7.2 Hz, 1H), 5.18 (ddd, J = 17.4, 3.6, 1.2 Hz, 1H), 5.13 (ddd, J = 10.0, 1.2, 0.8 Hz, 1H), 4.40 (dd, J = 6.8, 3.6 Hz, 1H), 4.35 (ddt, J = 9.4, 6.8, 2.4 Hz, 1H), 3.93 (dd, J = 11.2, 6.8 Hz, 1H), 3.59 (dd, J = 11.6, 3.6 Hz, 1H), 3.57 (dd, J = 11.2, 1.6 Hz, 1H), 3.48 (dd, J = 11.6, 9.2 Hz, 1H), 2.99 (dd, J = 9.4, 3.6 Hz, 1H), 2.45 (br d, J = 7.2 Hz, 2H), 2.44 (m, 1H), 1.88 (ddd, J = 13.4, 7.2, 3.2 Hz, 1H), 1.82 (br d, J = 3.6 Hz, 1H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.5, 118.1, 87.6, 77.7, 75.3, 67.0, 64.5, 37.1, 36.4, 25.9, 18.5, −5.5; HRMS (EI) *m/z* calcd for $C_{15}H_{30}O_4Si$ $(M)^+$ 302.1913, found 302.1872.

4.3.2. (4aS,6S,7aS)-4a-Allyl-6-(tert-butyldimethylsilyloxy)methyl-2,2-dimethyl-4H-furo[3,2-d][1,3]dioxine {(3S)-*31*}

$TsOH \cdot H_2O$ (22 mg, 0.11 mmol) was added to a solution of diol (3*S*)-**8a** (574 mg, 1.90 mmol) and 2,2-dimethoxypropane (2.3 mL, 19.0 mmol) in benzene (19 mL) at room temperature. After refluxing for 30 min, the reaction mixture was quenched by saturated $NaHCO_3$ at room temperature. After stirring for 15 min at room temperature, the reaction mixture was diluted with EtOAc (20 mL) and washed with water (20 mL) and brine (20 mL), and dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 5% EtOAc in hexane) to provide acetonide (3*S*)-**31** (622 mg, 96%) as a colorless oil: $[\alpha]_D^{24}$ +17.1 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) ν 3077, 2986, 2954, 2929, 2857, 1641, 1472, 1373, 1256, 1227, 1094, 836, 777; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 (m, 1H), 5.13 (s, 1H), 5.10 (d, J = 8.0 Hz, 1H), 4.17 (dddd, J = 11.6, 5.8, 5.2, 1.2 Hz, 1H), 4.07 (d, J = 5.6 Hz, 1H), 3.78 (dd, J = 9.6, 1.6 Hz, 1H), 3.73 (d, J = 12.0 Hz, 1H), 3.65 (dd, J = 9.6, 8.0 Hz, 1H), 3.63 (d, J = 12.0 Hz, 1H), 2.31–2.15 (m, 3H), 1.92 (dd, J = 13.6, 2.8 Hz, 1H), 1.36 (s, 3H), 1.35 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.7, 118.5, 98.3, 82.1, 79.1, 74.5, 66.5, 64.9, 40.2, 34.5, 26.9, 26.0, 21.2, 18.4, −5.2; HRMS (EI) *m/z* calcd for $C_{18}H_{35}O_4Si$ $(M + H)^+$ 343.2305, found 343.2294.

4.3.3. (4aS,6S,7aS)-4a-Allyl-2,2-dimethyl-4H-furo[3,2-d][1,3]dioxine-6-methanol {(3S)-*44*}

TBAF (1.0 M in THF, 1.0 mL, 1.00 mmol) was added to a solution of silyl ether (3*S*)-**31** (312 mg, 0.91 mmol) in THF (9.0 mL) at 0 °C under N_2 and then the resulting mixture was stirred at room temperature. After stirring for 1.5 h, the reaction mixture was diluted with EtOAc (30 mL) and washed with water (15 mL) and brine (15 mL), and dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 45% EtOAc in hexane) to provide alcohol (3*S*)-**44** (206 mg, 99%) as a colorless oil: $[\alpha]_D^{25}$ +53.8 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) ν 3464, 3076, 2988, 2940, 1639, 1438, 1376, 1227, 1201, 1159, 1052, 916, 862; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (m, 1H), 5.15 (d, J = 7.6 Hz, 1H), 5.14 (dd, J = 18.0, 1.6 Hz, 1H), 4.33 (m, 1H), 4.15 (d, J = 5.6 Hz, 1H), 3.79 (d, J = 6.8 Hz, 2H), 3.78 (m, 1H), 3.65 (m, 1H), 2.69 (t, J = 5.0 Hz, 1H), 2.41 (dt, J = 14.4, 5.6 Hz, 1H), 2.23 (dd, J = 14.4, 7.2 Hz, 1H), 2.15 (dd, J = 14.4, 7.6 Hz, 1H), 1.91 (dd, J = 14.4, 3.4 Hz, 1H), 1.40 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.1, 118.9, 98.3, 81.1, 78.1, 73.9, 65.2, 64.4, 39.4, 34.0, 27.4, 20.4; HRMS (EI) *m/z* calcd for $C_{12}H_{20}O_4$ $(M)^+$ 228.1362, found 228.1359.

4.3.4. (4aS,6S,7aS)-4a-Allyl-2,2-dimethyl-4H-furo[3,2-d][1,3]dioxine-6-carboaldehyde {(3S)-*32*}

A solution of DMSO (284 mg, 3.64 mmol) in CH_2Cl_2 (1.3 mL) was dropped to a solution of oxalyl chloride (369 mg, 2.91 mmol) in CH_2Cl_2 (2.0 mL) at −78 °C under N_2 over 15 min. A solution of alcohol (3*S*)-**44** (332 mg, 1.45 mmol) in CH_2Cl_2 (1.5 mL) was then dropped to the reaction mixture over 15 min. After stirring for 30 min at −78 °C, triethylamine (1.0 mL, 7.27 mmol) was added to the reaction mixture and the mixture was allowed to warm to room temperature over 60 min. After stirred at room temperature for 30 min, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL) and combined organic layers were dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 25% EtOAc in hexane) to provide aldehyde (3*S*)-**32** (290 mg, 88%) as a

colorless oil: $[\alpha]_D^{26}$ +37.6 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) ν 2990, 2939, 2817, 1732, 1639, 1449, 1438, 1375, 1227, 1202, 1159, 1096, 1077, 1058, 1024, 921, 857, 821; ^1H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 5.81 (ddt, J = 17.6, 9.6, 7.6 Hz, 1H), 5.17 (d, J = 9.6 Hz, 1H), 5.15 (d, J = 17.6 Hz, 1H), 4.38 (d, J = 10.0 Hz, 1H), 4.16 (d, J = 4.0 Hz, 1H), 3.85 (s, 2H), 2.50 (ddd, J = 13.8, 9.8, 4.0 Hz, 1H), 2.28–2.15 (m, 3H), 1.38 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.1, 131.9, 119.2, 97.9, 82.4, 82.2, 72.8, 64.3, 40.8, 37.3, 27.5, 20.5; HRMS (EI) *m*/*z* calcd for $C_{12}H_{18}O_4$ $(M)^+$ 226.1205, found 226.1211.

4.3.5. (4aS,8aS)-4a-Allyl-2,2-dimethyl-4H-pyrano[3,2-d][1,3] dioxine-6-one {(4S)-**33**}

Catalyst **29** (30 mg, 0.07 mmol, 30 mol%) and DBU (0.007 mL, 0.05 mmol, 20 mol%) was added to the solution of aldehyde (3*S*)-**32** (53 mg, 0.23 mmol) in $CHCl_3$ (7.0 mL) at room temperature under N_2. After refluxing for 10 h, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (3 mL) at room temperature. The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and combined organic layers were dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 30% EtOAc in hexane) to provide lactone (4*S*)-**33** (40 mg, 75%) as a white solid: mp 85–86 °C; $[\alpha]_D^{24}$ +100.3 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) ν 3004, 2986, 2971, 2954, 2909, 1731, 1643, 1456, 1388, 1378, 1350, 1314, 1263, 1209, 1175, 1156, 1119, 1086, 1037, 1007, 986, 941, 863, 732; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (dddd, J = 16.9, 9.6, 7.3, 6.6 Hz, 1H), 5.21 (d, J = 9.6 Hz, 1H), 5.18 (dd, J = 16.9, 1.4 Hz, 1H), 4.03 (t, J = 3.2 Hz, 1H), 3.81 (d, J = 12.6 Hz, 1H), 3.70 (d, J = 12.6 Hz, 1H), 2.76 (ddd, J = 18.2, 12.8, 7.3 Hz, 1H), 2.49–2.43 (m, 2H), 2.31 (dd, J = 14.4, 8.0 Hz, 1H), 2.10 (m 1H), 1.94 (dddd, J = 14.4, 7.4, 3.2, 1.8 Hz, 1H), 1.44 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 130.4, 120.3, 98.7, 79.7, 65.5, 64.9, 40.9, 27.6, 24.3, 22.2, 20.0; HRMS (EI) *m*/*z* calcd for $C_{12}H_{18}O_4$ $(M)^+$ 226.1205, found 226.1243.

4.3.6. (4aS,8aS)-2,2-dimethyl-4a-(2-undecen-1-yl)-4H-pyrano [3,2-d][1,3]dioxine-6-one {(4S)-**45**}

Grubbs 2nd catalyst (3.3 mg, 0.004 mmol) was added to the solution of (4*S*)-**33** (87 mg, 0.38 mmol) and 1-decene (0.36 mL, 1.92 mmol) in CH_2Cl_2 (3.8 mL) at room temperature under N_2. After refluxing for 3 h, 1-decene (0.36 mL, 1.92 mmol) and Grubbs 2nd catalyst (3.3 mg, 0.004 mmol) were added to the reaction mixture and the mixture was refluxed for 3 h. Solvent was removed in vacuo, and the residue was purified by column chromatography (silica gel, 20% EtOAc in hexane) to provide (4*S*)-**45** (119 mg, 92%) as a colorless oil: $[\alpha]_D^{24}$ +59.0 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) ν 2991, 2925, 2854, 1733, 1456, 1377, 1250, 1205, 1162, 1090, 1059, 1003, 989, 938, 864; ^1H NMR (400 MHz, $CDCl_3$) δ 5.56 (dt, J = 15.1, 6.9 Hz, 1H), 5.38 (ddd, J = 15.1, 7.8, 6.9 Hz, 1H), 4.02 (t, J = 3.2 Hz, 1H), 3.80 (d, J = 12.8 Hz, 1H), 3.68 (d, J = 12.8 Hz, 1H), 2.75 (ddd, J = 18.1, 12.5, 7.3 Hz, 1H), 2.45 (ddd, J = 18.1, 6.4, 1.8 Hz, 1H), 2.39 (dd, J = 14.4, 6.4 Hz, 1H), 2.24 (dd, J = 14.4, 7.8 Hz, 1H), 2.15–2.11 (m, 1H), 2.02 (dd, J = 14.0, 6.9 Hz, 2H), 1.92 (dddd, J = 14.5, 7.3, 3.2, 1.8 Hz, 1H), 1.43 (s, 3H), 1.39 (s, 3H), 1.35–1.30 (m, 3H), 1.26 (br s, 9H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 136.7, 121.5, 98.6, 80.0, 65.6, 64.8, 39.7, 32.5, 31.8, 29.4, 29.2, 29.2, 29.1, 27.7, 24.4, 22.6, 22.2, 19.9, 14.1; HRMS (EI) *m*/*z* calcd for $C_{20}H_{34}O_4$ $(M)^+$ 338.2457, found 338.2420.

4.3.7. (4aS,8aS)-2,2-dimethyl-4a-undecyl-4H-pyrano[3,2-d][1,3] dioxine-6-one {(4S)-**34**}

Pd/C {23 mg, 10 wt% of (4*S*)-**45**} was added to the solution of (4*S*)-**45** (231 mg, 0.68 mmol) in MeOH (3.4 mL) at room temperature. The reaction mixture was vigorously stirred under H_2 atmosphere for 1.5 h. The mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo and the residue was purified by column chromatography (silica gel, 25% EtOAc in hexane) to provide (4*S*)-**34** (219 mg, 94%) as a white solid: mp 62–63 °C; $[\alpha]_D^{24}$ +55.1 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) ν 3004, 2945, 2914, 2852, 1725, 1473, 1380, 1262, 1212, 1149, 1092, 1042, 989, 939, 863; ^1H NMR (400 MHz, $CDCl_3$) δ 3.99 (t, J = 2.8 Hz, 1H), 3.81 (d, J = 12.8 Hz, 1H), 3.76 (d, J = 12.8 Hz, 1H), 2.76 (ddd, J = 18.4, 12.4, 7.2 Hz, 1H), 2.45 (ddd, J = 18.4, 5.4, 1.6 Hz, 1H), 2.09 (m, 1H), 1.93 (dddd, J = 14.6, 7.2, 3.6, 1.6 Hz, 1H), 1.66–1.49 (m, 3H), 1.45 (s, 3H), 1.40 (s, 3H), 1.26 (br s, 17H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 98.5, 80.2, 65.5, 65.5, 36.6, 31.9, 30.0, 29.5, 29.5, 29.3, 29.3, 29.3, 27.8, 24.4, 22.7, 22.4, 22.2, 19.9, 14.1; HRMS (EI) *m*/*z* calcd for $C_{20}H_{36}O_4$ $(M)^+$ 340.2614, found 340.2607.

4.3.8. (4S)-hydroxytanikolide (**2**)

1 M HCl (3.2 mL) was added dropwise to the solution of acetonide (4*S*)-**34** (219 mg, 0.64 mmol) in THF (3.2 mL) at room temperature. After stirring the reaction mixture for 24 h, the reaction mixture was quenched by saturated aqueous $NaHCO_3$ (3 mL). The mixture was extracted with Et_2O (3 × 10 mL) and combined organic layers were dried over anhydrous Na_2SO_4. The filtrate concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 50% EtOAc in hexane) to provide (4*S*)-hydroxytanikolide (**2**, 181 mg, 94%) as a white solid: mp 79–80 °C; $[\alpha]_D^{20}$ +13.3 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) ν 3485, 3419, 2954, 2920, 2850, 1764, 1473, 1464, 1402, 1344, 1198, 1112, 1033, 1011, 990, 955, 821; ^1H NMR (400 MHz, $CDCl_3$) δ 4.53 (t, J = 7.2 Hz, 1H), 3.78 (dd, J = 11.6, 4.0 Hz, 1H), 3.61 (dd, J = 11.6, 9.0 Hz, 1H), 2.65–2.47 (m, 3H), 2.37 (ddd, J = 18.0, 12.4, 9.2 Hz, 1H), 2.17 (m, 1H), 2.08 (dd, J = 8.8, 4.0 Hz, 1H), 1.51 (m, 1H), 1.44–1.39 (m, 2H), 1.26 (br s, 17H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 84.3, 73.6, 65.9, 33.3, 31.9, 30.2, 29.60, 29.58, 29.53, 29.45, 29.3, 28.3, 22.8, 22.7, 21.9, 14.1; HRMS (EI) *m*/*z* calcd for $C_{17}H_{32}O_4$ $(M)^+$ 300.2301, found 300.2311.

4.3.9. (2R,3R,5S)-5-(tert-Butyldimethylsilyloxy)methyl-3-methoxymethyloxy-2-(methoxymethyloxy)methyl-2-allyltetrahydrofuran {(3R)-**35**}

^{i}Pr$_2$NEt (0.1 mL, 0.58 mmol) and MOMCl (0.03 mL, 0.41 mmol) was added to the solution of diol (3*R*)-**8a** (35 mg, 0.12 mmol) in CH_2Cl_2 (0.6 mL) at 0 °C under N_2. After stirring at 0 °C for 1 h, the reaction mixture was allowed to warm to room temperature. After stirring the reaction mixture for 3 h, ^{i}Pr$_2$NEt (0.01 mL, 0.06 mmol) and MOMCl (0.004 mL, 0.06 mmol) was added to the solution and the reaction mixture was stirred for 3 h. The mixture was quenched by the addition of saturated aqueous $NaHCO_3$ and the mixture was extracted with EtOAc (3 × 5 mL). Combined organic layers were washed with water (10 mL) and brine (10 mL) and dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide (3*R*)-**35** (38 mg, 84%) as a colorless oil: $[\alpha]_D^{30}$ +6.3 (*c* 0.87, $CHCl_3$); IR (neat, cm^{-1}) ν 3075, 2952, 2929, 2885, 2856, 2823, 2770, 1640, 1471, 1403, 1388, 1362, 1254, 1217, 1149, 1111, 1043, 919, 837, 777; ^1H NMR (400 MHz, $CDCl_3$) δ 5.94 (dddd, J = 17.2, 9.6, 8.4, 6.4 Hz, 1H), 5.10 (d, J = 17.2 Hz, 1H), 5.07 (d, J = 9.6 Hz, 1H), 4.68 (d, J = 9.6 Hz, 1H), 4.66 (d, J = 9.6 Hz, 1H), 4.61 (d, J = 6.8 Hz, 1H), 4.59 (d, J = 6.8 Hz, 1H), 4.22 (dd, J = 6.4, 4.8 Hz, 1H), 4.18 (m, 1H), 3.60 (ddd, J = 14.4, 10.6, 4.0 Hz, 2H), 3.46 (d, J = 10.0 Hz, 1H), 3.38 (s, 3H), 3.35 (s, 3H), 3.34 (d, J = 10.0 Hz, 1H), 2.50 (dd, J = 14.0, 6.4 Hz, 1H), 2.36 (dd, J = 14.0, 8.4 Hz, 1H), 2.13 (dt, J = 13.2, 6.4 Hz, 1H), 2.02 (ddd, J = 13.2, 7.2, 4.8 Hz, 1H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.6, 117.4, 96.8, 96.0, 85.3, 79.7, 77.5, 70.9, 65.6, 55.5, 55.3, 36.2, 34.3, 25.9, 18.3, −5.3, −5.4; HRMS (FAB) *m*/*z* calcd for $C_{19}H_{39}O_6Si$ $(M + H)^+$ 391.2516, found 391.2516.

*4.3.10. (2R,3R,5S)-3-Methoxymethyloxy-2-(methoxymethyloxy) methyl-2-allyltetrahydrofuran-5-methanol {(3R)-**46**}*

TBAF (1.0 M in THF, 1.4 mL, 1.42 mmol) was added to a solution of silyl ether (3*R*)-**35** (503 mg, 1.29 mmol) in THF (13 mL) at 0 °C under N_2 and then the resulting mixture was stirred at room temperature. After stirring for 1.5 h, the reaction mixture was diluted with EtOAc (40 mL) and washed with water (15 mL) and brine (15 mL), and dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 45% EtOAc in hexane) to provide alcohol (3*R*)-**46** (354 mg, 99%) as a colorless oil: $[\alpha]_D^{27}$ +12.4 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) ν 3469, 2933, 2889, 2824, 1639, 1217, 1150, 1110, 1041, 918; ^1H NMR (400 MHz, $CDCl_3$) δ 5.93 (dddd, J = 16.8, 10.0, 8.2, 6.4 Hz, 1H), 5.11 (d, J = 16.8 Hz, 1H), 5.10 (d, J = 10.0 Hz, 1H), 4.69 (d, J = 6.4 Hz, 1H), 4.65 (s, 2H), 4.64 (d, J = 6.4 Hz, 1H), 4.40 (t, J = 6.8 Hz, 1H), 4.27 (ddd, J = 10.9, 5.2, 2.8 Hz, 1H), 3.80 (dt, J = 12.0, 2.8 Hz, 1H), 3.54 (d, J = 13.4 Hz, 1H), 3.52 (d, J = 13.4 Hz, 1H), 3.43 (m, 1H), 3.383 (s, 3H), 3.378 (s, 3H), 2.96 (dd, J = 9.8, 2.8 Hz, 1H), 2.45 (dd, J = 14.0, 6.4 Hz, 1H), 2.32–2.23 (m, 2H), 2.08 (ddd, J = 12.9, 8.0, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.9, 118.0, 96.6, 96.4, 85.1, 78.6, 77.3, 70.5, 65.3, 55.6, 55.5, 36.9, 33.9; HRMS (FAB) *m*/*z* calcd for $C_{13}H_{25}O_6$ $(M + H)^+$ 277.1651, found 277.1652.

*4.3.11. (2R,3R,5S)-3-Methoxymethyloxy-2-(methoxymethyloxy) methyl-2-allyltetrahydrofuran-5-carboaldehyde {(3R)-**36**}*

A solution of DMSO (85 mg, 1.09 mmol) in CH_2Cl_2 (0.4 mL) was dropped to a solution of oxalyl chloride (92 mg, 0.72 mmol) in CH_2Cl_2 (0.8 mL) at −78 °C under N_2 over 15 min. A solution of alcohol (3*R*)-**46** (100 mg, 0.36 mmol) in CH_2Cl_2 (0.6 mL) was then dropped to the reaction mixture over 15 min. After stirring for 30 min at −78 °C, triethylamine (0.25 mL, 1.81 mmol) was added to the reaction mixture and the mixture was allowed to warm to room temperature over 70 min. After stirred at room temperature for 45 min, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL) and combined organic layers were dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 45% EtOAc in hexane) to provide aldehyde (3*R*)-**36** (73 mg, 74%) as a colorless oil: $[\alpha]_D^{25}$ −5.1 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) ν 3445, 2930, 2890, 2824, 1732, 1639, 1217, 1150, 1110, 1040, 918; ^1H NMR (400 MHz, $CDCl_3$) δ 9.68 (d, J = 1.8 Hz, 1H), 5.91 (ddd, J = 17.4, 9.2, 6.9 Hz, 1H), 5.13 (d, J = 17.4 Hz, 1H), 5.11 (d, J = 9.2 Hz, 1H), 4.69 (d, J = 6.9 Hz, 1H), 4.65 (d, J = 6.9 Hz, 1H), 4.61 (d, J = 6.9 Hz, 1H), 4.59 (d, J = 6.9 Hz, 1H), 4.43 (t, J = 7.5 Hz, 1H), 4.24 (dd, J = 5.6, 4.8 Hz, 1H), 3.51 (d, J = 10.1 Hz, 1H), 3.44 (d, J = 10.1 Hz, 1H), 3.39 (s, 3H), 3.35 (s, 3H), 2.54 (dd, J = 14.2, 6.4 Hz, 1H), 2.39 (dd, J = 14.2, 7.1 Hz, 1H), 2.40 (m, 1H), 2.25 (ddd, J = 13.2, 8.0, 4.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 133.7, 118.2, 96.7, 96.1, 87.2, 81.4, 78.7, 70.9, 55.8, 55.4, 36.7, 34.4; HRMS (EI) *m*/*z* calcd for $C_{13}H_{22}O_6$ $(M)^+$ 274.1416, found 274.1396.

*4.3.12. (4R,5S)-4-Methoxymethyloxy-5-(methoxymethyloxy) methyl-5-allyltetrahydropyran-1-one {(4R)-**37**}*

Catalyst **29** (17 mg, 0.040 mmol, 30 mol%) and DBU (0.005 mL, 0.027 mmol, 20 mol%) was added to the solution of aldehyde (3*R*)-**36** (37 mg, 0.14 mmol) in toluene (2.7 mL) at room temperature under N_2. After refluxing for 10 h, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (3 mL) at room temperature. The mixture was extracted with EtOAc (3 × 10 mL) and combined organic layers were dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 40% EtOAc in hexane) to provide lactone (4*R*)-**37** (25 mg, 68%) as a colorless oil: $[\alpha]_D^{24}$ +13.3 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) ν 2932, 2825, 1738, 1342, 1249, 1214, 1149, 1111, 1037, 918; ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (dddd, J = 14.4, 11.6, 8.6, 6.4 Hz, 1H), 5.164 (d, J = 11.6 Hz, 1H), 5.161 (d, J = 14.4 Hz, 1H), 4.76 (d, J = 7.6 Hz, 1H), 4.70 (d, J = 7.6 Hz, 1H), 4.61 (s, 2H), 4.02 (dd, J = 6.4, 3.2 Hz, 1H), 3.60 (d, J = 10.6 Hz, 1H), 3.53 (d, J = 10.6 Hz, 1H), 3.42 (s, 3H), 3.35 (s, 3H), 2.73–2.65 (m, 2H), 2.57–2.49 (m, 2H), 2.21–2.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 131.7, 119.4, 96.8, 96.0, 85.2, 70.9, 69.7, 56.1, 55.6, 37.9, 26.2, 22.1; HRMS (EI) *m*/*z* calcd for $C_{13}H_{22}O_6$ $(M)^+$ 274.1416, found 274.1440.

*4.3.13. (4R,5S)-4-Methoxymethyloxy-5-(methoxymethyloxy) methyl-5-(2-undecen-1-yl)tetrahydropyran-1-one {(4R)-**47**}*

Grubbs 2nd catalyst (4.0 mg, 0.005 mmol) was added to the solution of (4*R*)-**37** (65 mg, 0.23 mmol) and 1-decene (0.45 mL, 2.37 mmol) in $CHCl_3$ (3.3 mL) at room temperature under N_2. After refluxing for 4 h, Grubbs 2nd catalyst (2.0 mg, 0.002 mmol) was added to the reaction mixture and the mixture was refluxed for 2 h. Solvent was removed in vacuo, and the residue was purified by column chromatography (silica gel, 35% EtOAc in hexane) to provide (4*R*)-**47** (66 mg, 72%) as a colorless oil: $[\alpha]_D^{26}$ +13.5 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) ν 2925, 2854, 1741, 1457, 1248, 1212, 1150, 1111, 1038, 975, 919; ^1H NMR (400 MHz, $CDCl_3$) δ 5.58–5.43 (m, 2H), 4.75 (d, J = 6.8 Hz, 1H), 4.69 (d, J = 6.8 Hz, 1H), 4.60 (s, 2H), 4.00 (dd, J = 6.0, 3.2 Hz, 1H), 3.59 (d, J = 10.8 Hz, 1H), 3.52 (d, J = 10.8 Hz, 1H), 3.42 (s, 3H), 3.35 (s, 3H), 2.72–2.43 (m, 4H), 2.20–2.04 (m, 2H), 2.01 (dd, J = 13.0, 6.8 Hz, 2H), 1.26 (br s, 12H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 135.7, 134.0, 122.6, 121.9, 96.8, 96.0, 85.7, 85.4, 71.0, 69.8, 56.1, 55.5, 36.6, 32.6, 31.9, 31.8, 31.1, 29.4, 29.30, 29.26, 29.2, 29.1, 26.33, 26.27, 22.6, 22.2, 14.1; HRMS (EI) *m*/*z* calcd for $C_{21}H_{38}O_6$ $(M)^+$ 386.2668, found 386.2682.

*4.3.14. (4R,5S)-4-Methoxymethyloxy-5-(methoxymethyloxy) methyl-5-undecanyltetrahydropyran-1-one {(4R)-**38**}*

Pd/C {2.2 mg, 10 wt% of (4*R*)-**47**} was added to the solution of (4*R*)-**47** (22 mg, 0.057 mmol) in MeOH (0.3 mL) at room temperature. The reaction mixture was vigorously stirred under H_2 atmosphere for 10 h. The mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo and the residue was purified by column chromatography (silica gel, 35% EtOAc in hexane) to provide (4*R*)-**38** (20 mg, 91%) as a colorless oil: $[\alpha]_D^{26}$ −15.7 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) ν 2925, 2854, 1739, 1466, 1252, 1214, 1150, 1113, 1036, 919; ^1H NMR (400 MHz, $CDCl_3$) δ 4.74 (d, J = 7.3 Hz, 1H), 4.69 (d, J = 7.3 Hz, 1H), 4.62 (s, 2H), 4.03 (dd, J = 6.9, 3.2 Hz, 1H), 3.62 (d, J = 10.8 Hz, 1H), 3.56 (d, J = 10.8 Hz, 1H), 3.41 (s, 3H), 3.36 (s, 3H), 2.67 (dt, J = 18.3, 7.8 Hz, 1H), 2.52 (dt, J = 18.3, 6.4 Hz, 1H), 2.15 (m, 1H), 2.05 (dt, J = 13.9, 6.9 Hz, 1H), 1.85–1.72 (m, 2H), 1.51–1.26 (m, 18H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 96.8, 95.9, 85.8, 71.0, 69.5, 56.0, 55.6, 33.3, 31.9, 30.2, 29.60, 29.59, 29.55, 29.5, 29.3, 26.4, 22.7, 22.5, 22.0, 14.1; HRMS (FAB) *m*/*z* calcd for $C_{21}H_{41}O_6$ $(M + H)^+$ 389.2903, found 389.2921.

*4.3.15. (4R)-hydroxytanikolide (**2**)*

6 M HCl (0.23 mL) was added dropwise to the solution of MOM ether (4*R*)-**38** (54 mg, 0.14 mmol) in THF (0.7 mL) at room temperature. After stirring the reaction mixture at 50 °C for 3 h, the reaction mixture was quenched by saturated aqueous $NaHCO_3$ (2 mL). The mixture was extracted with EtOAc (3 × 10 mL). Combined organic layers were washed with H_2O (10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. The filtrate concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 55% EtOAc in hexane) to provide (4*R*)-hydroxytanikolide (**2**, 38 mg, 90%) as a white solid: mp 50–52 °C; $[\alpha]_D^{26}$ −18.1 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) ν 3399, 3340, 2925, 2920, 2849, 1775, 1466, 1196, 1155, 1035; ^1H NMR (400 MHz, $CDCl_3$) δ 4.55 (t, J = 7.6 Hz, 1H), 3.62 (d, J = 11.2 Hz, 1H), 3.56 (d, J = 11.2 Hz, 1H),

2.64–2.49 (m, 2H), 2.33 (ddd, J = 18.2, 12.7, 9.2 Hz, 1H), 2.20 (m, 1H), 2.15 (s, 1H), 1.87 (br s, 1H), 1.68–1.58 (m, 2H), 1.26 (br s, 18H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 82.5, 74.5, 63.9, 34.2, 31.9, 30.2, 29.61, 29.59, 29.57, 29.5, 29.3, 28.9, 23.3, 22.7, 22.2, 14.1; HRMS (EI) m/z calcd for $C_{17}H_{32}O_4$ $(M)^+$ 300.2301, found 300.2336.

4.4. Synthesis of nortanikolide (**3**)

4.4.1. (2R,5S)-2-Benzyloxymethyl-5-(tert-butyldimethylsilyloxy) methyl-2-undecanyltetrahydrofuran (**39**)

Potassium bis(trimethylsilyl)amide (KHMDS, 0.5 M in toluene, 1.66 mL, 0.83 mmol) was added dropwise to the solution of alcohol **25** (166 mg, 0.41 mmol) in THF (4.1 mL) at −20 °C under N_2. After stirring for 30 min at −20 °C, benzyl bromide (0.10 mL, 0.83 mmol) was added to the reaction mixture and the mixture was allowed to warm to 0 °C. After stirred at 0 °C for 2 h, the reaction mixture was quenched by the addition of saturated aqueous Na_2CO_3 (10 mL). The mixture was extracted with EtOAc (3 × 20 mL) and combined organic layers were dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 3% EtOAc in hexane) to provide benzyl ether **39** (178 mg, 88%) as a colorless oil: $[\alpha]_D^{26}$ −6.4 (c 1.0, $CHCl_3$); IR (neat, cm^{-1}) ν 2953, 2926, 2855, 1463, 1254, 1094, 836, 776; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.28 (m, 5H), 4.53 (dd, J = 16.9, 12.4 Hz, 2H), 4.01 (ddd, J = 12.4, 6.0, 4.6 Hz, 1H), 3.64 (dd, J = 10.5, 4.1 Hz, 1H), 3.51 (dd, J = 10.5, 6.0 Hz, 1H), 3.31 (s, 2H), 1.98–1.87 (m, 2H), 1.83–1.66 (m, 2H), 1.56 (m, 2H), 1.25 (br s, 18H) 0.88 (br s, 12H), 0.032 (s, 3H), 0.027 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 128.2, 127.5, 127.4, 85.1, 79.9, 75.1, 73.4, 65.9, 37.3, 32.6, 31.9, 30.3, 29.68, 29.66, 29.6, 29.4, 29.3, 28.4, 25.9, 24.0, 22.7, 18.4, 14.1, −5.31, −5.33; HRMS (FAB) m/z calcd for $C_{30}H_{55}O_3Si$ $(M + H)^+$ 491.3921, found 491.3885.

4.4.2. (2R,5S)-2-Benzyloxymethyl-2-undecanyltetrahydrofuran-5-methanol (**40**)

TBAF (1.0 M in THF, 0.98 mL, 0.98 mmol) was added to a solution of silyl ether **39** (456 mg, 0.93 mmol) in THF (9.3 mL) at 0 °C under N_2 and then the resulting mixture was stirred at room temperature. After stirring for 2 h, the reaction mixture was diluted with EtOAc (30 mL) and washed with water (15 mL) and brine (15 mL), and dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 17% EtOAc in hexane) to provide alcohol **40** (337 mg, 96%) as a colorless oil: $[\alpha]_D^{26}$ +4.2 (c 1.0, $CHCl_3$); IR (neat, cm^{-1}) ν 3452, 2925, 2853, 1464, 1363, 1206, 1099, 1077, 1030, 735, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.28 (m, 5H), 4.59 (d, J = 11.9 Hz, 1H), 4.52 (d, J = 11.9 Hz, 1H), 4.16 (ddd, J = 10.1, 6.6, 3.2 Hz, 1H), 3.79 (dt, J = 11.4, 3.2 Hz, 1H), 3.47 (d, J = 9.2 Hz, 1H), 3.43 (ddd, J = 11.4, 8.9, 3.2 Hz, 1H), 3.34 (d, J = 9.2 Hz, 1H), 2.92 (dd, J = 8.9, 3.2 Hz, 1H), 2.10 (ddd, J = 11.9, 8.5, 6.4 Hz, 1H), 2.04–1.90 (m, 2H), 1.72 (ddd, J = 11.9, 8.2, 6.9 Hz, 1H), 1.50–1.46 (m, 2H), 1.25 (br s, 18H) 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 128.4, 127.74, 127.73, 85.4, 80.1, 75.3, 73.5, 65.4, 38.1, 32.6, 31.9, 30.2, 29.7, 29.60, 29.59, 29.34, 29.31, 27.7, 23.9, 22.7, 14.1; HRMS (FAB) m/z calcd for $C_{24}H_{41}O_3$ $(M + H)^+$ 377.3056, found 377.3030.

4.4.3. (S)-4-Benzyloxymethyl-4-undecanyltetrahydrofuran-1-one (**42**) and (S)-4-benzoyloxymethyl-4-undecanyltetrahydrofuran-1-one (**43**)

2-Iodobenzamide **41**[27] (17.3 mg, 0.06 mmol), additive (none or BHT, 13.2 mg, 0.06 mmol) and Oxone (612 mg, 1.00 mmol) were added to a solution of tetrahydrofuran-2-methanol **40** (75 mg, 0.20 mmol) in DMF (1.0 mL) at room temperature. After completion of the reaction (checked by TLC), the mixture was diluted with EtOAc (20 mL) and quenched by water (10 mL). The organic layer was washed by saturated aqueous $Na_2S_2O_3$ (10 mL), saturated aqueous $NaHCO_3$ (10 mL), water (10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide lactone **42** (no additive: 47 mg, 65%; with BHT: 60 mg, 83%) as a colorless oil and side product **43** (no additives: 9 mg, 12%; with BHT: trace) as a colorless oil. **42**: $[\alpha]_D^{22}$ +2.7 (c 1.0, EtOH); IR (neat, cm^{-1}) ν 2925, 2854, 1774, 1455, 1203, 1162, 1115, 942, 738, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.27 (m, 5H), 4.58 (d, J = 11.9 Hz, 1H), 4.51 (d, J = 11.9 Hz, 1H), 3.53 (d, J = 10.1 Hz, 1H), 3.47 (d, J = 10.1 Hz, 1H), 2.72 (ddd, J = 18.0, 10.5, 8.7 Hz, 1H), 2.49 (ddd, J = 18.0, 10.5, 4.6 Hz, 1H), 2.26 (ddd, J = 12.8, 10.5, 4.6 Hz, 1H), 1.98 (ddd, J = 12.8, 10.5, 8.7 Hz, 1H), 1.67–1.62 (m, 2H), 1.25 (br s, 18H) 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 137.8, 128.6, 127.8, 127.5, 87.7, 74.8, 73.6, 37.2, 31.9, 29.9, 29.64, 29.58, 29.5, 29.4, 29.32, 29.28, 28.8, 23.1, 22.7, 14.1, −0.02; HRMS (EI) m/z calcd for $C_{23}H_{36}O_3$ $(M)^+$ 360.2665, found 360.2645.**43**: $[\alpha]_D^{26}$ +6.1 (c 1.0, $CHCl_3$); IR (neat, cm^{-1}) ν 2925, 2854, 1778, 1725, 1271, 1114, 943, 712; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, J = 6.9, 1.4 Hz, 2H), 7.59 (dd, J = 7.3, 1.4 Hz, 1H), 7.46 (dd, J = 7.3, 6.9 Hz, 2H), 4.45 (d, J = 11.9 Hz, 1H), 4.35 (d, J = 11.9 Hz, 1H), 2.73 (ddd, J = 18.3, 10.5, 8.2 Hz, 1H), 2.62 (ddd, J = 18.3, 10.5, 5.0 Hz, 1H), 2.26 (ddd, J = 13.3, 10.5, 5.0 Hz, 1H), 2.14 (ddd, J = 13.3, 10.5, 8.2 Hz, 1H), 1.82–1.78 (m, 2H), 1.47–1.39 (m, 2H), 1.38–1.28 (m, 5H), 1.26 (br s, 11H) 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 166.1, 133.4, 129.6, 128.6, 86.3, 68.5, 37.2, 31.9, 29.8, 29.59, 29.57, 29.5, 29.4, 29.31, 29.27, 29.2, 28.5, 23.1, 22.7, 14.1; HRMS (EI) m/z calcd for $C_{23}H_{34}O_4$ $(M)^+$ 374.2457, found 374.2454.

4.4.4. Nortanikolide (**3**)

$Pd(OH)_2/C$ (2.3 mg, 10 wt% of **42**) was added to the solution of **42** (23 mg, 0.06 mmol) in MeOH (0.8 mL) at room temperature. The reaction mixture was vigorously stirred under H_2 for 4 h. The mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo and the residue was purified by column chromatography (silica gel, 45% EtOAc in hexane) to provide nortanikolide (**3**, 16 mg, 94%) as a white solid: mp 43–44 °C; $[\alpha]_D^{22}$ +9.8 (c 1.0, EtOH); IR (KBr, cm^{-1}) ν 3427, 2955, 2917, 2848, 1749, 1469, 1297, 1218, 1078, 1048, 934; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (dd, J = 12.0, 5.2 Hz, 1H), 3.54 (dd, J = 12.0, 3.6 Hz, 1H), 2.70 (ddd, J = 17.9, 10.7, 7.2 Hz, 1H), 2.58 (ddd, J = 17.9, 10.7, 6.4 Hz, 1H), 2.04–1.96 (m, 2H), 1.66 (br t, J = 7.6 Hz, 1H), 1.30 (br s, 5H), 1.25 (br s, 15H) 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 87.8, 67.4, 36.4, 31.9, 29.9, 29.6, 29.54, 29.50, 29.3, 27.4, 23.1, 22.7, 14.1; HRMS (EI) m/z calcd for $C_{16}H_{30}O_3$ $(M)^+$ 270.2195, found 270.2162.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2018.01.035.

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