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Concise asymmetric synthesis of (*R*)-(+)-tanikolide

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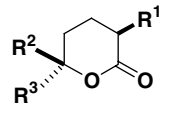
Abstract—A highly stereoselective total synthesis of (*R*)-(+)-tanikolide, a δ-lactonic marine natural product, was accomplished in seven steps from easily available starting materials with a 51% overall yield. An asymmetric synthesis of an α-hydroxy aldehyde having a stereogenic quaternary center, by the use of (*S*)-2-(anilinomethyl)pyrrolidine as a chiral auxiliary, was employed in a key step.

1. Introduction

(+)-Tanikolide **1** is a δ-lactonic natural product, isolated from the lipid extract of a blue-green algae, cyanobacterium *Lyngbya majuscula* collected at Tanikeli Island, Madagascar, by Gerwick et al. in 1999 (Fig. 1).[1] A characteristic feature of the structure of (+)-tanikolide **1** is the chiral quaternary carbon center with a hydroxymethyl group and a long-alkyl side-chain. The structure of (+)-tanikolide **1** was determined by the spectroscopic analysis and its absolute configuration was determined to be (*R*) by the ^{1}H NMR analysis of its amide derivative[1] and also by enantioselective total synthesis.[2–11]



(*R*)-(+)-tanikolide **1**; R^1=H, R^2=*n*-$C_{11}H_{23}$, R^3=CH_2OH

(*2R,5S*)-(−)-malyngolide **2**; R^1=CH_3, R^2=CH_2OH, R^3=*n*-C_9H_{19}

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

Although (+)-tanikolide **1** was isolated from the same marine source, cyanobacterium *Lyngbya majuscula* Gomont, as (−)-malyngolide **2**[12] and their structures have a similarity with each other, the absolute configuration of the stereogenic quaternary center is opposite, the length of the aliphatic side-chain is different, and a methyl substituent at the C-2 position of the δ-lactone **2** is lacking in **1** (Fig. 1). Furthermore, they show different biological activities, that is, **1** exhibits antifungal activity against *Candida albicans* and strong toxicity against brine shrimp (LD_{50} of 3.6 μg mL^{-1}) and snail (LD_{50} of 9.0 μg mL^{-1}), whereas (−)-malyngolide **2** shows antimicrobial activity against *Streptococcus pyogenes*, *Staphylococcus*, *Pseudomonas*, and *Mycobacterium smegmatis*, but no activity to *C. albicans*.

Several enantioselective syntheses of (+)-tanikolide **1** have already been reported.[2–11] Baeyer–Villiger oxidation of chiral cyclopentanone derivatives,[2,3,11] ring-closing metathesis of open-chain compounds,[4,6] or oxidative cleavage of a carbon–carbon double bond to form a lactone[7] or lactol[8] have been employed for the construction of δ-lactone framework. Only one group has reported a more direct method, namely, the preparation and lactonization of chiral δ-hydroxy carboxylic acid,[5] although the overall yield was not so high due to a rather long sequence. Herein we report a versatile method for a highly stereoselective synthesis of δ-hydroxy carboxylic acid having chiral tertiary alcohol moiety and the synthesis of (+)-tanikolide **1**, applying the asymmetric synthesis of an α-hydroxy aldehyde using a chiral aminal (Scheme 1).[13]

2. Results and discussion

As (+)-tanikolide **1** has an (*R*)-configuration, (*R*)-4-hydroxy-4-hydroxymethylhexadecanoic acid **7** is an appropriate precursor for the lactonization. Considering the

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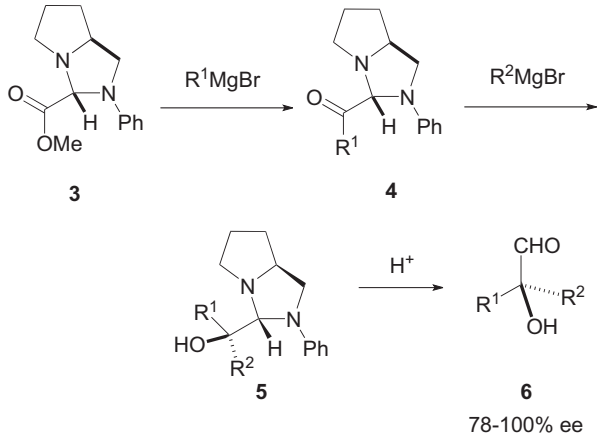
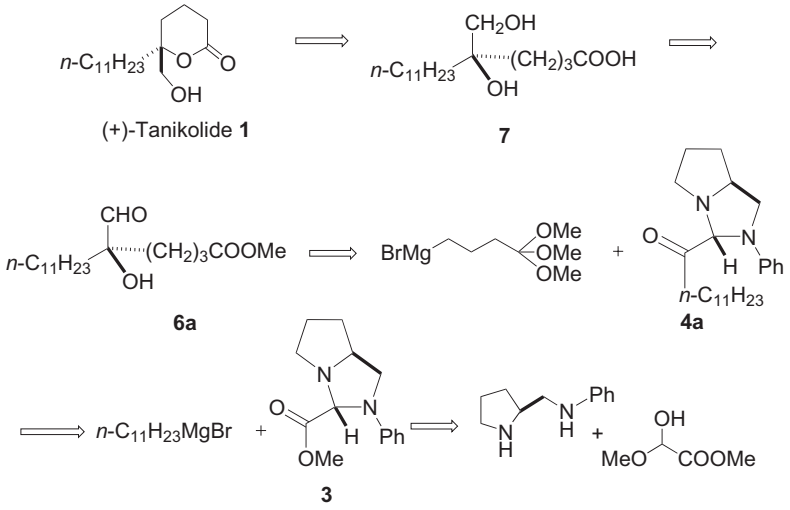


Scheme 1. Asymmetric synthesis of α-hydroxy aldehyde.

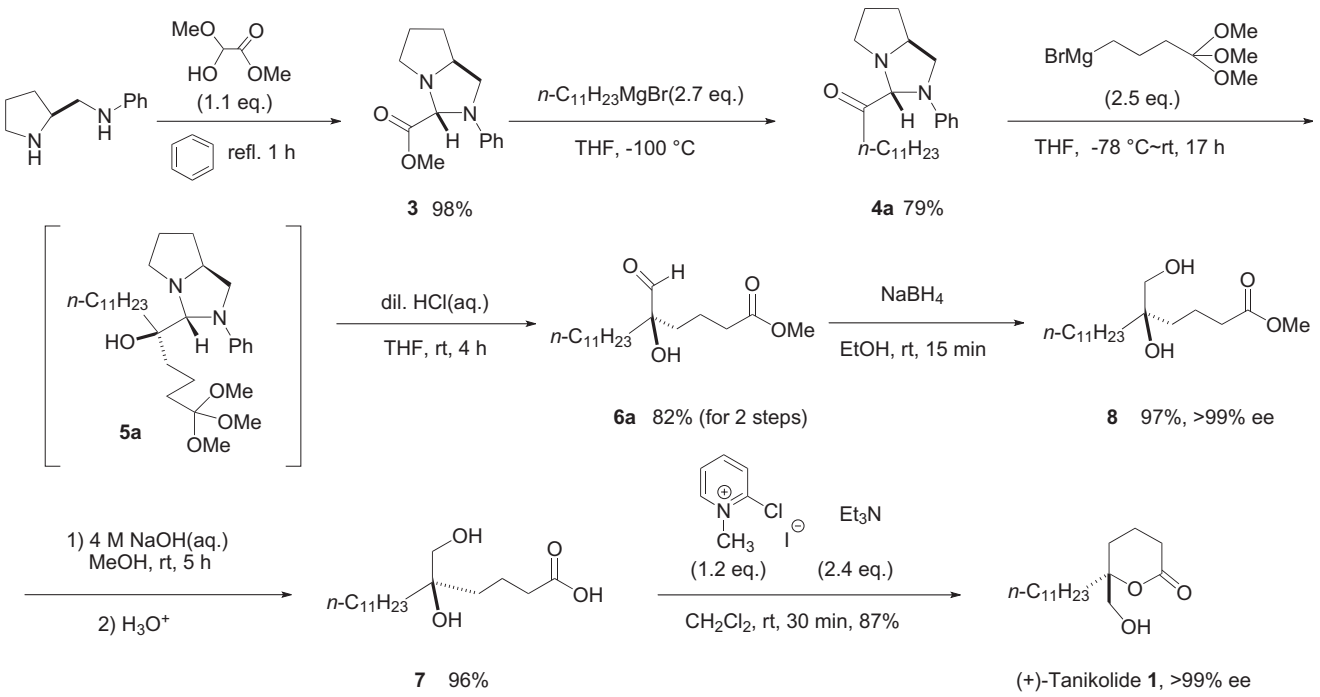
stereochemical course of the reaction of keto aminal **4** and the Grignard reagent,[13] the desired α-hydroxy aldehyde **6a** is obtained by the reaction of keto aminal **4a** and 4,4,4-trimethoxybutylmagnesium bromide whose alkyl group can be easily converted into the 3-methoxycarbonylpropyl group (Scheme 2).

2-Methoxycarbonylaminal **3** was prepared by mixing (*S*)-2-(anilinomethyl)pyrrolidine and methyl 2-hydroxy-2-methoxyacetate in refluxing benzene with removal of water azeotropically for 1 h. Although aminal **3** was used without purification in the previous reports,[13] **3** was isolated in 98% yield after removal of the solvent from the reaction mixture followed by silica-gel column chromatography. The reaction of **3** with undecylmagnesium bromide was then examined in THF at −78 °C in the presence of magnesium chloride to give keto aminal **4a** in 57%. The yield was increased to 79% by carrying out the reaction using 2.7 equiv of undecylmagnesium bromide at −100 °C in the absence of magnesium chloride with little formation of the corresponding tertiary alcohol, although the formation of tertiary alcohol sometimes decreased the yield of keto aminal in the reaction of small alkyl Grignard reagents with **3** without magnesium chloride.[13b] Next, 4,4,4-trimethoxybutylmagnesium bromide (2.5 equiv) was added to a THF solution of **4a** at −78 °C and the reaction mixture was gradually warmed up to room temperature. Simultaneous mild acidic hydrolysis of the aminal moiety and orthoester moiety of the resulting crude hydroxyl aminal **5a** afforded chiral α-hydroxy aldehyde **6a**, methyl (*R*)-4-formyl-4-hydroxyhexadecanoate, in 82% yield from **4a** after purification by silica-gel column chromatography. Chiral diol ester **8**, methyl (*R*)-4-hydroxy-4-hydroxymethylhexadecanoate, was then obtained in 97% yield by reduction of **6a** with sodium borohydride in ethanol at room temperature. The enantiomeric excess (ee) of **8** was determined to be more than 99% by chiral HPLC analysis of the corresponding *tert*-butyldiphenylsilyl (TBDPS) ether (*R*)-**9**, methyl (*R*)-5-*t*-butyldiphenylsiloxymethyl-5-hydroxyhexadecanoate.

As chiral diol ester **8** was obtained, intramolecular transesterification was examined under various reaction conditions. However, starting material **8** was recovered when the reaction was carried out in refluxing toluene. A side reaction, probably dehydration, took place in the reaction using TsOH in refluxing toluene, or in CH_2Cl_2 at room temperature, and (+)-tanikolide **1** was not obtained. Under basic conditions (6 equiv NaH in THF, rt, 1 h), the starting materials was recovered. Chiral diol ester **8** was then hydrolyzed to examine the lactonization reaction. (*R*)-4-Hydroxy-4-hydroxymethylhexadecanoic acid **7** was obtained in 96% yield by treatment of chiral diol ester **8** with NaOH in MeOH–H_2O at room temperature for 5 h. The lactonization reaction using Mukaiyama reagent,[14] 2-chloro-1-methylpyridinium iodide, as a dehydrating reagent afforded (+)-tanikolide **1**, $[\alpha]_D^{23} = +2.85$ (c 0.65, $CHCl_3$) (natural:[1] $[\alpha]_D^{25} = +2.3$ (c 0.65, $CHCl_3$); synthetic:[2] $[\alpha]_D^{25} = +2.9$ (c 0.65, $CHCl_3$)); mp 47.5–48.5 °C (synthetic:[2] mp 38–40 °C), in high yield (87%) under milder reaction conditions compared with the reported method.[5] The corresponding ε-lactone was not obtained without the protection of the primary hydroxy group. The synthetic route is summarized in Scheme 3. The enantiomeric excess



Scheme 2. Retrosynthetic analysis of (+)-tanikolide **1**.



Scheme 3. Synthesis of (+)-tanikolide **1**.

of the resulting (+)-tanikolide **1** was confirmed to be more than 99% by chiral HPLC analysis of the corresponding TBDPS ether (*R*)-**10**, (*R*)-6-*tert*-butyldiphenylsiloxymethyl-6-undecyltetrahydropyran-2-one.[8] $[\alpha]_D^{29} = -7.9$ (*c* 0.81, $CHCl_3$). (Daicel Chiralcel OD–H (25 cm × 0.46 cm i.d.); 254 nm UV detector; eluent, hexane/2-PrOH = 100/1; flow rate, 0.5 mL/min; t_S, 14.9 min, t_R, 18.1 min).[15]

3. Conclusion

In conclusion, we achieved a concise asymmetric synthesis of (*R*)-(+)-tanikolide **1**, a δ-lactonic marine natural product, in high enantiomeric excess (>99% ee) with 51% overall yield. This method will be useful for the synthesis of related compounds as all reagents are commercially available; all experiments can be carried out using easy operations, and the chiral auxiliary is recyclable.

4. Experimental

4.1. General

All air-sensitive experiments were carried out under an atmosphere of argon. Melting points were determined on a SANWA TSUSHO SMP3 melting point apparatus and are uncorrected. IR spectra were recorded on a HORIBA FT-730 spectrometer. ^1H and ^{13}C NMR spectra were recorded on JEOL JNM-EX-270 spectrometer or JEOL JNM-AL-400 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. Optical rotations were measured on a JASCO P-1000 automatic polarimeter. HPLC analyses were carried out on JASCO instruments (pump, PU-2080 plus; detector, UV-2075). Elemental analyses were carried out on a Vario EL Elemental analyzer. TLC analyses were done on silica-gel 60 F_{254}-precoated aluminum backed sheets (E. Merck). Preparative TLC was performed on silica-gel-coated plates (Wakogel B-5F, 20 cm × 20 cm). Wakogel C-200 and Silica gel 60 N (spherical, neutral, 63–210 μm) were used for column chromatography.

4.2. (2*R*,5*S*)-2-Dodecanoyl-3-phenyl-1,3-diazabicyclo-[3,3,0]-octane 4a

An Et_2O solution of undecylmagnesium bromide, prepared from 1-bromoundecane (1.412 g, 6.0 mmol) and Mg turnings (0.160 g, 6.6 mmol) in Et_2O (12 mL) in the presence of a small amount of iodine, was added dropwise through a syringe to a stirred THF (10 mL) solution of **3** (0.246 g, 1.0 mmol) at −100 °C. The reaction was monitored carefully by TLC and saturated aqueous NH_4Cl was added to the reaction mixture quickly after the disappearance of **3** by TLC (about 20 min after the end of the addition of the Grignard reagent). The reaction mixture was then warmed to room temperature and extracted with Et_2O 4 times. The combined organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by silica-gel (spherical, neutral) column chromatography (CH_2Cl_2/Et_2O = 30/1) to give **4a** (0.293 g, 79%) as a pale yellow oil. $[\alpha]_D^{23} = -29.3$ (*c* 1.0, $CHCl_3$); IR (neat): γ 2953, 2925, 2853, 1716 (CO), 1600, 1505, 1367 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.6 Hz, 3H), 1.08–1.62 (m, 18H), 1.64–2.20 (m, 4H), 2.30–2.62 (m, 2H), 2.82 (dt, *J* = 13.0, 4.9 Hz, 1H), 3.12 (dd, *J* = 7.9, 6.6 Hz, 1H), 3.21 (ddd, *J* = 11.1, 6.1, 4.1 Hz, 1H), 3.77 (t, *J* = 7.9 Hz, 1H), 3.85–3.97 (m, 1H), 4.43 (s, 1H), 6.46 (d, *J* = 8.6 Hz, 2H), 6.73

(t, $J = 7.3$ Hz, 1H), 7.20 (t, $J = 8.2$ Hz, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$): 14.2, 22.8, 23.4, 25.1, 29.2, 29.3, 29.4, 29.5, 29.7 (×2), 30.4, 32.0, 36.6, 53.2, 55.0, 62.8, 86.2, 112.4 (×2), 117.3, 129.2 (×2), 145.6, 209.7. Anal. Calcd for $C_{24}H_{38}N_2O$: C, 77.79; H, 10.34; N, 7.56. Found: C, 77.81; H, 10.50; N, 7.17.

4.3. Methyl (*R*)-4-formyl-4-hydroxyhexadecanoate 6a

A THF solution of 4,4,4-trimethoxybutylmagnesium bromide (6.4 mL, 3.0 mmol), prepared from 4,4,4-trimethoxybutylbromide (1.363 g, 6.0 mmol), and Mg turnings (0.160 g, 6.6 mmol) in THF (12 mL) in the presence of a small amount of iodine, was added dropwise through a syringe to a stirred THF (4.8 mL) solution of **4a** (0.445 g, 1.2 mmol) at −78 °C and the reaction mixture was gradually warmed to room temperature over 17 h. The saturated aqueous NH_4Cl and water were added to the reaction mixture. The aqueous layer was extracted with Et_2O (3 times). The combined organic layer was washed with water and brine, and then dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, crude **5a** was obtained as a yellow oil and was hydrolyzed without purification.

Dilute hydrochloric acid (0.7%, 4.8 mL) was added to a THF (8 mL) solution of the resulting crude hydroxyl aminal **5a**. The reaction mixture was stirred at room temperature for 4 h, and extracted with Et_2O 4 times. The combined organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by silica-gel column chromatography (hexane/Et_2O = 3/1) to afford α-hydroxy aldehyde **6a** (0.309 g) in 82% overall yield from **4a** as a yellow oil. $[\alpha]_D^{24} = +5.9$ (c 1.0, $CHCl_3$); IR (neat): γ 3500 (OH), 2924, 2854, 1734 (COOR), 1718 (CHO), 1457, 1437, 1174 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.88 (t, $J = 6.6$ Hz, 3H), 1.02–1.54 (m, 19H), 1.61–1.78 (m, 5H), 2.27–2.38 (m, 2H), 3.28 (s, 1H), 3.66 (s, 3H), 9.50 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$): 14.2, 18.6, 22.7, 23.0, 29.3, 29.4, 29.5, 29.6 (×2), 29.9, 31.9, 33.9, 35.3, 36.2, 51.6, 80.3, 173.4, 204.1; Anal. Calcd for $C_{18}H_{34}O_4$: C, 68.75; H, 10.90. Found: C, 68.91; H, 10.87.

4.4. Methyl (*R*)-4-hydroxy-4-hydroxymethylhexadecanoate 8

A small amount of sodium borohydride (ca. 0.011 g) was added to a stirred solution of α-hydroxy aldehyde **6a** (0.278 g, 0.884 mmol) in ethanol (5 ml) at room temperature. The reaction mixture was stirred for 15 min at the same temperature. Water was added to stop the reaction, and the mixture was extracted with Et_2O 4 times. The combined organic layer was washed with dilute hydrochloric acid (about 0.7%), water and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by silica-gel column chromatography (hexane/Et_2O = 1/10) to afford diol ester **8** (0.270 g, 97%) as a pale yellow oil. $[\alpha]_D^{24} = -1.1$ (c 1.0, $CHCl_3$); IR (neat): γ 3369 (OH), 2924, 2853, 1741 (CO), 1465, 1438, 1171, 1051 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.88 (t, $J = 6.6$ Hz, 3H), 1.17–1.38 (m, 18H), 1.40–1.72 (m, 6H), 1.95 (br s, 1H), 2.08 (br s, 1H), 2.35 (t, $J = 6.9$ Hz, 2H), 3.40–3.54 (m, 2H), 3.68 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$): 14.2, 18.9, 22.7, 23.4, 29.4, 29.7 (×4), 30.3, 32.0, 34.2, 35.1, 35.9, 51.6, 67.9, 74.5, 174.1; Anal. Calcd for $C_{18}H_{36}O_4$: C, 68.31; H, 11.47. Found: C, 68.05; H, 11.54.

4.5. Methyl (*R*)-5-*tert*-butyldiphenylsiloxymethyl-5-hydroxyhexadecanoate 9

To a solution of diol ester **8** (8.9 mg, 0.028 mmol) and imidazole (9.5 mg, 0.140 mmol) in DMF (0.1 mL) was added a solution of *t*-butyldiphenylsilyl chloride (TBDPSCl) (38.5 mg, 0.140 mmol) in DMF (0.4 mL) at 0 °C. After the reaction mixture was stirred at room temperature for 41 h, water was added to the mixture. The mixture was extracted with Et_2O (4 times). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by preparative TLC (hexane/AcOEt = 7/1) to afford methyl (*R*)-5-*tert*-butyldiphenylsiloxymethyl-5-hydroxyhexadecanoate **9** (5.1 mg, 33%) as a colorless oil. $[\alpha]_D^{28} = -2.7$ (c 0.25, $CHCl_3$); IR (neat): γ 3452 (OH), 2927, 2855, 1742 (COOR), 1464, 1428, 1113 cm^{-1};^{1}H NMR (270 MHz, $CDCl_3$): δ 0.88 (t, $J = 6.6$ Hz, 3H), 1.07 (s, 9H), 1.12–1.72 (m, 24H), 2.23–2.38 (m, 3H), 3.42–3.52 (m, 2H), 3.65 (s, 3H), 7.33–7.52 (m, 6H), 7.59–7.72 (m, 4H); ^{13}C NMR (67.8 MHz, $CDCl_3$): 14.2, 19.1, 19.4, 22.8, 23.6, 27.0 (×3), 29.4, 29.7 (×4), 30.4, 32.0, 34.6, 35.5, 36.1, 51.5, 68.8, 74.2, 127.7 (×4), 129.7 (×2), 133.0 (×2), 135.5 (×4), 173.8.

The ee of (*R*)-**9** was more than 99% by HPLC analysis using a chiral column (Daicel Chiralcel OD–H 25 cm × 0.46 cm i.d.; 254 nm UV detector; eluent, hexane/2-PrOH = 99.75/0.25; flow rate, 1.0 mL/min; t_S, 20.0 min, t_R, 24.6 min).[16]

4.6. (*R*)-4-Hydroxy-4-hydroxymethylhexadecanoic acid 7

NaOH (4 M solution in H_2O, 1 mL) was added to a stirred solution of diol ester **8** (0.236 g, 0.75 mmol) in methanol (4 mL). The reaction mixture was stirred for 5 h at room temperature. Dilute hydrochloric acid (about 0.7%) was added to the reaction mixture until the solution became pH 2. The mixture was then extracted with Et_2O (4 times). The combined organic layer was washed with water and brine, and dried over anhydrous $MgSO_4$. After removal of the solvent under reduced pressure, (*R*)-4-hydroxy-4-hydroxymethylhexadecanoic acid **7** (0.217 g, 96%) was obtained in an almost pure form as a white solid. mp 76.1–76.4 °C; $[\alpha]_D^{27} = -0.8$ (c 1.0, $CHCl_3$); IR (KBr): γ 3474 (OH), 3180, 2953, 2918, 2849, 1731 (CO), 1466, 1212, 1200, 1170, 1046 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.88 (t, $J = 6.4$ Hz, 3H), 0.98–1.79 (m, 24H), 2.38 (t, $J = 6.6$ Hz, 2H), 3.37–3.60 (m, 2H), 4.43 (br s, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$): 14.2, 18.7, 22.8, 23.4, 29.4, 29.7 (×4), 30.3, 32.0, 34.0, 34.8, 35.8, 67.8, 74.9, 177.9; Anal. Calcd for $C_{17}H_{34}O_4$: C, 67.51; H, 11.33. Found: C, 67.34; H, 11.10.

4.7. (+)-Tanikolide 1

A solution of (*R*)-4-hydroxy-4-hydroxymethylhexadecanoic acid **7** (151.6 mg, 0.5 mmol) and triethylamine (122.4 mg, 1.2 mmol) in CH_2Cl_2 (9 mL) was added dropwise to a solution of 2-chloro-1-methylpyridinium iodide (153.2 mg, 0.6 mmol) in CH_2Cl_2 (3 mL). After the reaction mixture was stirred at room temperature for 30 min, water was added to the mixture. The mixture was extracted with CH_2Cl_2 (4 times). The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by silica-gel column chromatography with Et_2O as the eluent to yield (+)-tanikolide **1** (123.3 mg, 87%) as a pale yellow solid. mp 47.5–48.5 °C (synthetic:[2] mp 38–40 °C); $[\alpha]_D^{23} = +2.85$ (c 0.65, $CHCl_3$) (natural:[1] $[\alpha]_D^{25} = +2.3$ (c 0.65, $CHCl_3$); synthetic:[2] $[\alpha]_D^{25} = +2.9$ (c 0.65, $CHCl_3$)); IR (KBr): γ 3360 (OH), 2953, 2921, 2850, 1731(CO), 1469, 1270, 1082 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, $J = 6.8$ Hz, 3H), 1.18–1.39 (m, 18H), 1.56–2.00 (m, 6H), 2.40–2.55 (m, 2H), 2.64 (br s, 1H), 3.55 (dd, $J = 12.0$, 6.0 Hz, 1H), 3.67 (dd, $J = 12.0$, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.2, 16.7, 22.7, 23.5, 26.6, 29.3, 29.5, 29.6 (×3), 29.8, 30.0, 31.9, 36.7, 67.4, 86.6, 171.8; Anal. Calcd for $C_{17}H_{32}O_3$: C, 71.79; H, 11.34. Found: C, 71.90; H, 11.33.

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