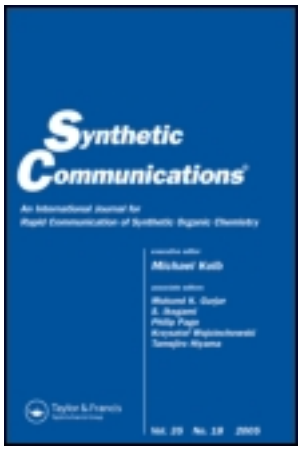

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TOTAL SYNTHESIS OF (±)TANIKOLIDE

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TOTAL SYNTHESIS OF (±)TANIKOLIDE

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ABSTRACT

A total synthesis of (±)tanikolide **1** is described. The six-membered lactone moiety of the title compound was completed through oxidation of α,δ-dihydroxyl compound by PDC.

Key Words: Tanikolide; Lactonization; Synthesis

INTRODUCTION

The Cyanobacteria (blue–green algae) are an exciting source of novel bioactive natural products, many structurally diverse metabolites exhibit a rich variety of biological activity.[1] Recently, a new

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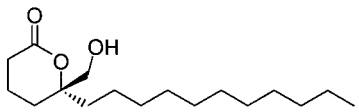


tanikolide **1**

Figure 1. The structure of (R)-tanikolide.

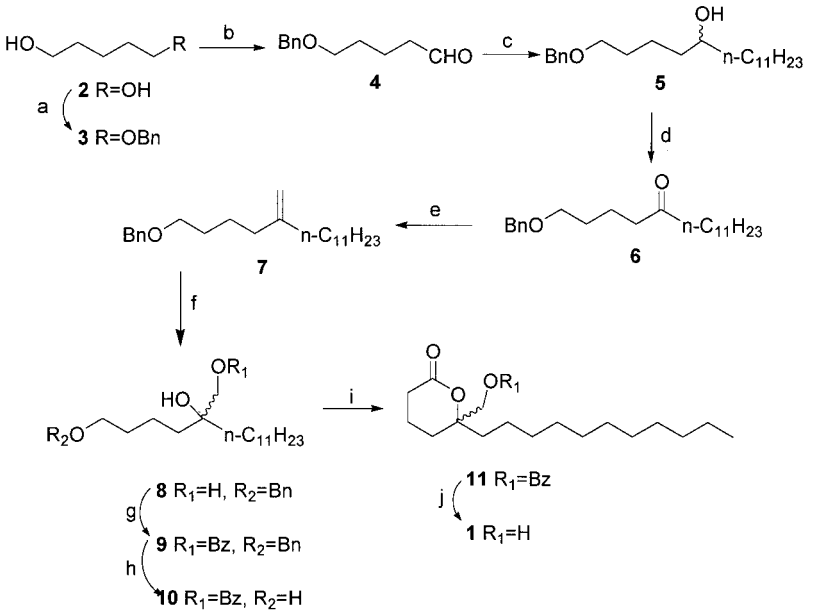
brine-shrimp toxic and antifungal compound, (+)tanikolide **1** has been isolated from the lipid extract of a Madagascan collection of the marine cyanobacterium *Lyngbya majuscula* by Gerwick et al.[2] (Figure 1). The structure of tanikolide and its absolute configuration at C-5 was determined as R by ^{1}H NMR analysis of its derivatives. Quickly, Ogasawara et al.[3] reported the total synthesis of (+)tanikolide by employing a catalytic asymmetric hydrogen transfer reaction as the key step. Trost finished the total synthesis of (−)malyngolide by using the deracemization of 3-nonyl-3,4-epoxybut-1-ene with Pd(0) in the presence of chiral N, P-ligand as key step.[4] Herein, we report a new route to (±)tanikolide.[5]

RESULTS AND DISCUSSION

The synthesis began with monobenzylation of 1,5-pentanediol **2**, followed by oxidation of the primary alcohol **3** to give 5-benzyloxypentanal **4** in 73%, then treated with undecyl magnesium bromide to afford 1-benzyloxy-5-hexadecanol **5** in 66% (Scheme 1), After oxidation of **5** with PDC, the transformation of 1-benzyloxy-5-hexadecanone **6** to the corresponding compound **7** was achieved by reacting with triphenylmethylphosphonium iodide in the presence of potassium *tert*-butoxide in THF (99% yield).[6]

Asymmetric dihydroxylation with AD-mix-α or AD-mix-β of **7** afforded diol **8** in excellent yield, but the ee. of the products is very low. Maybe the substrate don't match with catalyst,[7] so we decide to finish the total synthesis of (±)tanikolide, firstly.

Dihydroxylation of **7** with OsO_4/NMO gave diol **8** in 79%, then monobenzoylation of the primary alcohol of **8** afforded 2-(*n*-undecy)-6-benzyloxy-l-benzoyloxy-2-hexanol **9** in 97%. Alcohol **9** was converted to 2-(*n*-undecy)-1-benzoyloxy-2,6-hexanediol **10** by hydrogenation. In selective oxidation and lactonization of the α,δ-diol of **10**, conventional Fetizon reagents (Ag_2CO_3/Celite)[8] treatment resulted in unsatisfactory yields of the 6-(*n*-undecyl)-6-benzoyloxymethyl-2-pyraone **11**. Upon treatment with PDC in methylene dichloride, however, **11** was obtained in high yield (80%). Removal of the benzoyl group furnished (±)tanikolide **1**. It's spectroscopic



Scheme 1. Reagents and conditions: a. BnCl/NaOH, rt, 50%; b. PCC,73%; c. n-$C_{11}H_{23}MgBr$, 66%; d. PDC,71%; e. $CH_3P^+PhI^-/^tBuOK$, 99%; f. OsO_4/NMO, 79%; g. BzCl/Py, $-60^\circ C$ to rt, 97%; h. 10% Pd/C, H_2, 1 atm., 86%; i. PDC, 80%; j. NaCN(cat.)/MeOH, 93%.

data (IR, ^1H NMR, ^{13}C NMR and Mass) were virtually identical with those reported.

In summary, (±)tanikolide **1** was synthesized in an efficient way. The asymmetric synthesis of (+)tanikolide **1** is in progress.

EXPERIMENTAL

^1H NMR spectra were recorded on a Varian AM-90 and a Brucker AM-300-spectrometer using $CDCl_3$ or CCl_4. ^{13}C NMR was reported at 75 MHz (Brucker AM-300). All chemical shifts (δ) were reported relative to TMS. Mass spectra were recorded on an HP5989 A mass spectrometer. IR spectra and EA was recorded on a Perkin-Elmer 983 and Italian Carlo-Erba 1106, respectively. TLC was performed on precoated plates of silica gel HF_{254} (0.5 mm, Yantai, China). Flash column chromatography was carried out on silica gel (300–400 mesh, Yantai, China).

5-Benzyloxy-1-pentanol (3)

To a stirred solution of **2** (10 g, 96 mmol) and NaOH (4.8 g, 120 mmol) in DMSO (30 mL) was added benzyl chloride (12.2 g, 96 mmol) slowly. The resulting mixture was stirred at rt for additional 6 h and then poured into ice-water (300 mL), extracted with EtOAc (3×50 mL). The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography to give a colorless oil **3** (9.3 g, 50%). δ_H (90 MHz, CCl_4): 7.50–7.10 (m, 5H), 4.48 (s, 2H), 3.70–3.30 (m, 4H), 1.80–1.30 (m, 6H).

5-Benzyloxy-pentanal (4)

A solution of **3** (4.0 g, 20.6 mmol) in CH_2Cl_2 (15 mL) was added to a solution of PCC (13 g, 3 equiv.) in CH_2Cl_2 (100 mL). The reaction mixture was stirred at rt for 1 h. The upper phase was separated and the precipitate was washed with CH_2Cl_2. The combined organic phase was concentrated in vacuo and purified by flash chromatography to afford **4** (2.9 g, 73%). δ_H (90 MHz, CCl_4): 9.83 (s, 1H, -CHO), 7.50–7.0 (m, 5H), 4.50 (s, 2H, $PhCH_2$-), 3.48 (t, $J = 6.0$ Hz, 2H, BnO-CH_2-), 2.60–2.20 (m, 2H, -$\underline{CH_2}$CHO), 2.0–1.45 (m, 4H).

1-Benzyloxy-5-hexadecanol (5)

A solution of **4** (1.35 g, 7.0 mmol) in Et_2O (20 mL) was added dropwise to a solution of *n*-undecyl magnesium bromide [9.6 mmol in Et_2O (15 mL)] at 0°C under stirring. After being stirred for 30 min at this temperature, the resulting mixture was stirred at rt for additional 1 h and quenched by saturated aqueous NH_4Cl solution. The organic phase was separated and the aqueous phase was extracted with EtOAc (100 mL). The combined organic phase was washed with brine, dried over anhy. Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography to provide a colorless oil **5** (1.6 g, 66%). ν_{max}: 3402 (w, OH), 2928 (s), 2855 (s), 1455 (s), 1363 (m), 1102 (s), 967 (m), 734 (s), 697 (s). δ_H: 7.47–7.20 (m, 5H, Ar-H), 4.51 (s, 2H, $PhCH_2$-), 3.58 (m, IH, $\underline{CH}$OH), 3.48 (t, $J = 6.2$ Hz, 2H, $BnOCH_2$-), 2.12–1.88 (m, 2H), 1.75–1.57 (m, 2H), 1.57–1.15 (m, 22H), 0.89 (t, $J = 6.5$ Hz, 3H, -CH_3). *m/z* (%): 349 (M^++1, 0.36), 313 (3.5), 239 (10), 107 (23), 91 (100). Anal. $C_{23}H_{40}O_2$. Calcd: C, 79.25; H, 11.57. Found: C, 79.33; H, 11.32.

1-Benzyloxy-5-hexadecanone (6)

PDC (623 mg, 2 equiv.) was added in one portion to a solution of **5** (277 mg, 079 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 24 h at rt. and filtered on Celite. The solvent was evaporated under reduced pressure. The residue was purified by flash chromatography to provide **6** (195 mg, 71%). ν_{max}: 2918 (s), 2850 (s), 1700 (s), 1469 (s), 1455 (m), 1126 (s), 730 (s), 694 (s). δ_H: 7.41–7.25 (m, 5H, Ar-H), 4.49 (s, 2H, $PhCH_2$-), 3.47 (t, $J = 6.1$ Hz, 2H, $BnOCH_2$-), 2.42 (t, $J = 6.8$ Hz, 2H, -CH_2CO-), 2.37 (t, $J = 7.5$ Hz, 2H, -$COCH_2$-), 1.75–1.49 (m, 6H,), 1.40–1.19 (m, 16H), 0.88 (t, $J = 6.2$ Hz, 3H, -CH_3). m/z (%): 347 ($M^+ + 1$, 4.35), 255 (4.8), 239 (50), 107 (8), 91 (100). Anal. $C_{23}H_{38}O_2$. Calcd: C, 79.71; H, 11.05. Found: C, 79.68; H, 10.97.

Compound 7

Triphenylmethylphosphonium iodide (1.1 g, 4 equiv.) was suspensioned in THF (10 mL) and cooled to 0°C. Solid ^{t}BuOK (273 mg, 4 equiv.) was added and the resulting mixture was stirred for 30 min before ketone **6** (240 mg, 0.61 mmol) in THF (3 mL) was added at same temperature. Stirring was continued for another 30 min at this temperature, and then, the reaction mixture was quenched with saturated aqueous NH_4Cl solution. The biphase layer was separated and the aqueous phase was extracted with EtOAc (50 mL). The combined organic phase was washed in sequence with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography to afford **7** (236 mg, 99%). ν_{max}: 2927 (s), 2855 (s), 1455 (br), 1362 (m), 1105 (w), 887 (m), 733 (m), 697 (m). δ_H: 7.40–7.23 (m, 5H, Ar-H), 4.70 (s, 2H, =CH_2-), 4.50 (s, 2H, $PhCH_2$-), 3.48 (t, $J = 6.4$ Hz, 2H, OCH_2-), 2.10–1.93 (m, 4H, -CH_2-), 1.71–1.47 (m, 4H, -CH_2-), 1.47–1.19 (m, 18H), 0.88 (t, $J = 6.2$ Hz, 3H, -CH_3). m/z (%): 344 (M^+, 3.10), 263 (29), 253 (16), 235 (20), 145 (8), 109 (21), 95 (33), 91 (100). Anal. $C_{24}H_{40}O$. Calcd: C, 83.66; H, 11.70. Found: C, 83.69; H, 11.32.

Diol (8)

To a cooled (0°C) stirred solution of NMO (22 mg, 1.1 equiv.) in acetone (2 mL) was added a solution of O_SO_4 [2 mg, 0.2 mL solution of ^{t}BuOH/H_2O (1/1)]. Stirring was continued for additional 15 min at 0°C.

Olefin **7** (38 mg, 0.11 mmol) in acetone (1 mL) was added to the above mentioned solution and the resulting mixture was stirred at rt. for 9 h and then quenched with Na_2SO_3 (100 mg) under stirring for 30 min. The mixture was extracted with EtOAc. The organic phase was washed with water, brine, dried over anhy. Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography to give alcohol **8** (33 mg, 79%). ν_{max}: 3404 (w), 2926 (s), 2854 (s), 1455 (s), 1103 (br), 733 (m), 697 (m). δ_H: 7.45–7.21 (m, 5H, Ar-H), 4.50 (s, 2H, $PhCH_2$-), 3.49 (t, $J = 6.2$ Hz, 2H, $BnOCH_2$-), 3.42 (s, 2H, -$\underline{CH_2}OH$), 2.20 (s, 1H, OH), 2.0 (s, 1H, OH), 1.78–1.57 (m, 2H), 1.57–1.10 (m, 24H), 0.88 (t, $J = 5.9$ Hz, 3H, -CH_3). *m/z* (%): 347 (M^+ -CH_2OH, 0.95), 239 (16), 205 (3), 107 (5), 91 (100). Anal. $C_{24}H_{42}O_3$. Calcd: C, 76.14; H, 11.18. Found: C, 76.14; H, 11.00.

2-(*n*-Undecyl)-6-benzoyloxy-1-benzoyloxy-2-hexanol (9)

Pyridine (0.13 mL, 5 equiv.) and PhCOCl (38 ul, 1 equiv.) in CH_2Cl_2 (2 mL) was added successively to a stirred solution of **8** (126 mg, 0.33 mmol) in CH_2Cl_2 (8 mL) at -60°C. The resulting mixture was allowed to warm to rt. and stirred for 4 h at this temperature. After quenching with saturated aqueous NH_4Cl, this mixture was diluted with EtOAc. The organic phase was separated and the aqueous phase was extracted with EtOAc. The combined organic phase was washed with water, brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (PE : acetone = 5 : 1) to afford **9** (155 mg, 97%). ν_{max}: 3480 (w), 2927 (s), 2855 (s), 1723 (s), 1453 (m), 1274 (s), 1114 (s), 1027 (m), 711 (s). δ_H: 8.10–7.97 (m, 2H, Ar-H), 7.63–7.53 (m, 1H, Ar-H), 7.53–7.37 (m, 2H, Ar-H), 7.37–7.23 (m, 5H, OAr-H), 4.50 (s, 2H, $PhCH_2$-), 4.25 (s, 2H, $BzO\text{-}CH_2$-), 3.50 (t, $J = 6.2$ Hz, 2H, $BnOCH_2$-), 1.92 (s, 1H, -OH), 1.73–1.43 (m, 4H), 1.43–1.10 (m, 22H), 0.88 (t, $J = 6.2$ Hz, 3H, -CH_3). *m/z* (%): 465 (1.61), 343 (23.45), 239 (34), 219 (19), 105 (69), 91 (100). Anal. $C_{31}H_{46}O_4$. Calcd: C, 77.14; H, 9.60. Found: C, 76.82; H, 9.41.

2-(*n*-Undecyl)-1-benzoyloxy-2,6-hexanediol (10)

9 (155 mg, 0.32 mmol) and Pd/C (10%, 15 mg) was added to EtOAc (10 mL) and the solution was reduced with hydrogen for 4h at room temperature under a hydrogen pressure of 1 atm. The resulting mixture was filtered, concentrated and the residue was purified by flash chromatography to give diol **10** (108 mg, 86%). ν_{max}: 3378 (w), 2926 (s), 2855 (s), 1724 (s), 1452 (m), 1274 (s), 1116 (m), 1028 (m), 711(s). δ_H: 8.10–7.95 (m, 2H, Ar-H),

7.60–7.50 (m, 1H, Ar-H), 7.50–7.30 (m, 2H; Ar-H), 4.25 (s, 2H, BzO-CH_2-), 3.66 (t, $J = 6.0$ Hz, 2H, HO$\underline{CH_2}$-), 2.13 (brs, 2H, -OH), 1.70–1.37 (m, 8H), 1.37–1.13 (m, 18H), 0.86 (t, $J = 6.3$ Hz, 3H, -CH_3); δ_c: 166.65, 133.16, 129.61, 128.46, 73.73, 69.79, 62.46, 36.90, 36.30, 33.0, 31.89, 30.18, 29.63, 29.60, 29.58, 29.53, 29.32, 23.36, 22.66, 19.42, 14.09. *m/z* (%): 393 ($M^+ + 1$, 0.14), 375 (M^+-H_2O, 16), 253 (18), 239 (100), 219 (15), 105 (88), 97 (27); Anal. $C_{24}H_{40}O_4$: Calcd: C, 73.42; H, 10.72. Found: C, 73.17; H, 10.23.

6-(*n*-Undecyl)-6-benzoyloxymethyl-2-pyranone (11)

A solution of diol **10** (56 mg, 0.14 mmol) and PDC (268 mg, 5 equiv.) in CH_2Cl_2 (5 mL) was stirred overnight at room temperature, filtered on Celite and concentration in vacuo. The residue was purified by flash chromatography to provide **11** (44 mg, 80%). ν_{max}: 2926 (s), 2855 (s), 1726 (s), 1452 (m), 1270 (s), 1116 (s), 711 (s); δ_H: 8.13–7.97 (m, 2H, Ar-H), 7.69–7.52 (m, 1H, Ar-H), 7.52–7.39 (m, 2H, Ar-H), 4.38 (dd, $J = 11.6$ Hz, 2H, -CH_2OBz), 2.53 (t, $J = 6.7$ Hz, 2H, -CH_2COO-), 2.01–1.53 (m, 6H), 1.53–1.35 (m, 2H), 1.35–1.20 (m, 16H), 0.88 (t, $J = 6.4$ Hz, 3H, -CH_3); δ_c: 170.74, 166.05, 133.35, 129.68, 128.56, 83.96, 67.91, 37.90, 31.91, 29.89, 29.78, 29.62, 29.59, 29.52, 29.42, 29.33, 27.77, 23.15, 22.69, 16.70, 14.12. *m/z* (%): 389 ($M^+ + 1$, 12.51), 267 (3), 253 (89), 225 (63), 105 (100), 97 (10). Anal. $C_{24}H_{36}O_4$: Calcd: C, 74.19; H, 9.34. Found: C, 74.54; H, 9.46.

(±)Tanikolide (1)

A solution of **11** (80 mg, 0.2 mmol) and NaCN (33 mg, 0.07 mmol) in MeOH (3 mL) was stirred for 5 h at room temperature and diluted with EtOAc (20 mL). The resulting mixture washed with diluted $FeCl_3$, water, brine, dried over anhyd. Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash chromatography to give (±)tanikolide **1** (53 mg, 93%). ν_{max}: 3395 (w), 2921 (s), 2851 (s), 1700 (s, C=O), 1469 (m), 1264 (m), 1046 (m), 931 (m), 721 (m), 643 (m); δ_H: 3.66 (d, $J = 11.9$ Hz, 1H), 3.54 (d, $J = 11.9$ Hz, 1H), 2.50–2.45 (m, 2H, OCOCH_2-), 1.93–1.85 (m, 3H, -CH_2-), 1.75–1.67 (m, 3H), 1.37–1.17 (m, 18H), 0.88 (t, $J = 6.3$ Hz, 3H, -CH_3); ^{13}C: 171.9 (-COO-), 86.5, 67.5, 36.73, 31.9, 29.97, 29.78, 29.59, 29.57, 29.52, 29.44, 29.30, 26.65, 23.41, 22.65, 16.68, 14.07. *m/z* (%): 253 (100), 225 (51.8), 129 (27); Anal. $C_{17}H_{32}O_3$: Calcd: C, 71.79; H, 11.34. Found: C, 71.93, H, 10.88.

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