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# SYNTHESIS OF (*R*)-(+)-TANIKOLIDE, A TOXIC AND ANTIFUNGAL δ–LACTONE FROM THE MARINE CYANOBACTERIUM *LYNGBYA MAJUSCULA*

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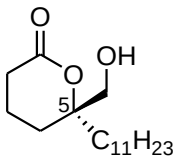
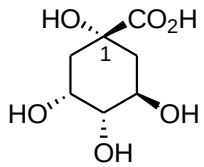
**Abstract** - (*R*)-(+)-Tanikolide, a brine-shrimp toxic and antifungal marine metabolite, isolated from the lipid extract of a blue green algae, cyanobacterium, *Lyngbia mujuscula*, was synthesized starting from (-)-quinic acid.

(*R*)-(+)-Tanikolide (**1**) is a brine-shrimp toxic and antifungal marine metabolite, isolated from the lipid extract of a blue green algae, cyanobacterium, *Lyngbia mujuscula* Gomont (Oscillatoriaceae), from a species collected on the Tanikeli Island, Madagascar.[1] Although more than twenty methods for its synthesis have so far been appeared,[2] in the course of our synthetic studies on biologically active natural products using (-)-quinic acid (**2**) as a chiral source,[3] we planned to synthesize (*R*)-(+)-tanikolide (**1**).

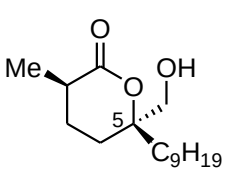
We thought that it might be possible to introduce the stereogenic center at C1 of (-)-**2** into the C5 asymmetric center of (+)-**1** using the same synthetic intermediate lactol (**4**),[3b] which was prepared for our synthesis of (-)-malyngolide (**3**),[4] although **3** possessed the opposite stereochemistry at C5 stereogenic center in (+)-**1**. The lactol (**4**) was derived easily from (-)-quinic acid (**2**).[3b] For the preparation of a chiral lactol such as **4**, an enantioselective enzymatic hydrolysis (e.g. with lipases) of a prochiral meso-diesters may also be a good method.[5]



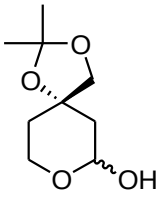
(+)-tanikolide (1)



(-)-quinic acid (2)



(-)-malyngolide (3)



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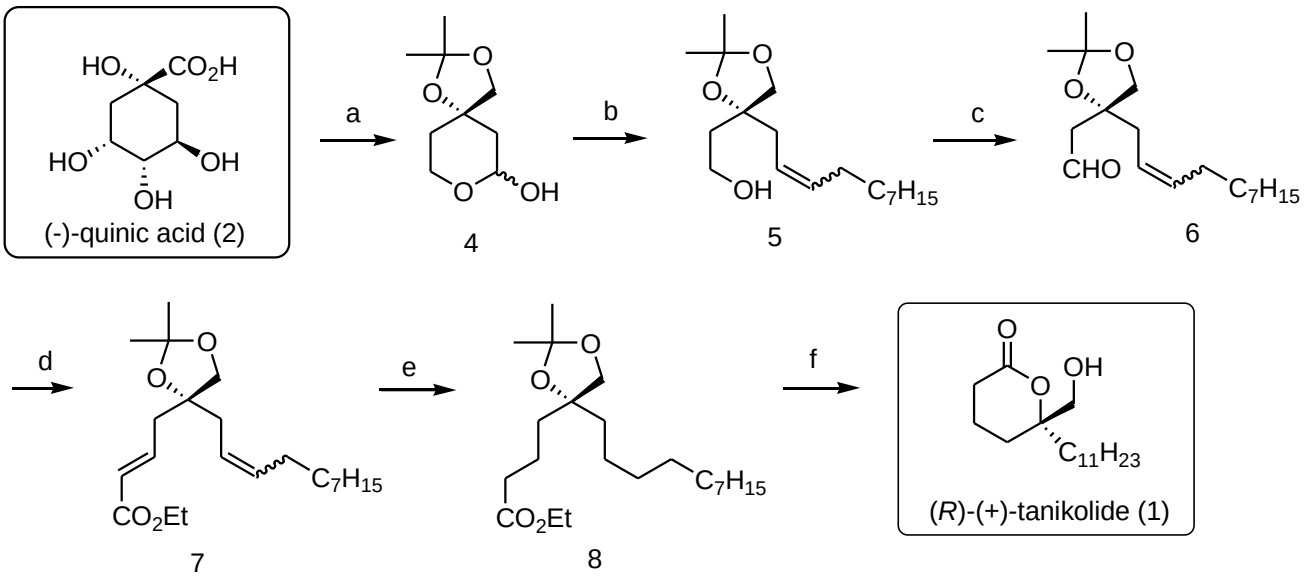
The lactol (**4**) was treated with nonyltriphenylphosphonium bromide in the presence of *n*-BuLi to give an alkene-alcohol (**5**) as a mixture of *E* and *Z*-isomers (25:75) in 90% yield.[6] The alcohol (**5**) was successively oxidized with PDC to an aldehyde (**6**) in 76% yield. Horner-Wadsworth-Emmons reaction of **6** with triethyl phosphonoacetate in the presence of NaH gave an unsaturated ester (**7**) in 90% yield,[7] whose newly formed alkene possessed *E*-form exclusively. The ester (**7**) was successively hydrogenated under $H_2$ atmosphere in the presence of Pd/C catalyst to form a saturated ester (**8**) in 82% yield. Finally, basic hydrolysis of theester group of **8** with NaOH followed by acidic work-up involving deprotection and subsequent lactone formation afforded (*R*)-(+)-tanikolide (**1**);[8] $[\alpha]_D^{22}$ +1.98 (*c* 0.0365, $CHCl_3$) (lit.,[1] $[\alpha]_D^{25}$ +2.3 (*c* 0.65, $CHCl_3$) ) in 76% yield. IR, $^1$H-NMR and $^{13}$C-NMR spectral data of the synthesized (+)-**1** are identical to those of the natural one.[1] Thus, it was demonstrated that the chiral lactol (**4**) was the useful common synthon for the preparation of both (+)-tanikolide (**1**) and (-)-malyngolide (**3**), which have the opposite absolute stereochemistry on their stereogenic centers each other.




**Scheme 1**. *Reagents and conditions*: a) ref. 3b; b) nonyltriphenylphosphonium bromide, *n*-BuLi in THF (90%); c) PDC, MS in $CH_2Cl_2$ (76%); d) triethyl phosphonoacetate, NaH in THF (90%); e) $H_2$, 10% Pd/C in EtOH (82%); f) 1) KOH in EtOH-$H_2O$, 2) 2N HCl, 3) Amberlyst (76%).

## EXPERIMENTAL

Melting points were determined using a Round Science micro-melting point apparatus, model RFS-10, and are uncorrected. IR spectra were measured with a JASCO FT/IR-460 plus infrared spectrophotometer. NMR spectra were recorded on a JEOL AL 400 (400 MHz $^1$H, 100 MHz $^{13}$C) spectrometer using tetramethylsilane as an internal standard. Chemical shifts (δ) are given in ppm. Low- and high-resolution

mass spectra (HRMS) were measured with a JEOL JMS-700TKM instrument at 70 eV. Optical rotation was measured with a JASCO DIP-370 digital polarimeter.

**(*R*)-2-(2,2-Dimethyl-4-(undec-2-enyl)-1,3-dioxolan-4-yl)ethanol (5)**

*n*-Butyllithium (1.6 M in hexane solution, 3.53 mL, 5.64 mmol) was added to a solution of nonyl-triphenylphosphonium bromide (2.70 g, 5.64 mmol) in dry THF (5 mL) under ice cooling and the mixture was stirred at rt under $N_2$ for 1.5 h. A solution of **4** (0.54 g, 2.82 mmol) in dry THF (5 mL) was added to the above reaction mixture under ice cooling and the whole was stirred at rt under $N_2$ for 2 h. The mixture was concentrated under reduced pressure to leave a residue, which was treated with $CHCl_3$. The solution was washed with $H_2O$ and brine, successively, and then dried over anhydrous $Na_2SO_4$. Evaporation of the solvent under reduced pressure gave the residue (3.80 g), which was chromatographed on $SiO_2$ (AcOEt : hexane = 1 : 1) to afford **5** (0.3 g, 90%) as a colorless oil. IR (neat) $cm^{-1}$: 3433, 2925, 2855, 1456, 1369, 1525, 1213, 1158, 1057, 897, 865, 832, 722. $^1H$ NMR ($CDCl_3$) δ: 0.88 (3H, t, *J* = 6.8 Hz, -C(14)-H), 1.27 (12H, br.s, C(8~13)-H), 1.42 (3H, s, $-CH_3$), 1.44 (3H, s, $-CH_3$), 1.85 (2H, m, -C(2)-H), 2.02 (2H, m, -C(7)-H), 2.40 (2H, m, -C(4)-H), 2.72 (1H, br.s, -OH), 3.77 (2H, m, $-CH_2OH$), 3.87 (2H, m, -C(3')-H), 5.28-5.35 (1H, m, -C(6)-H), 5.50-5.56 (1H, m, -C(5)-H). $^{13}C$ NMR ($CDCl_3$) δ: 14.0, 22.6, 26.8, 27.0, 27.5, 29.1, 29.3 (2C), 31.8, 32.6, 35.5, 38.3, 59.2, 72.6, 83.7, 109.5, 123.5, 133.4. MS (*m/z*): 283, 223, 146, 145, 87, 59. HRMS (*m/z*): Calcd for $C_{17}H_{31}O_3$ ($M^+$-$CH_3$): 283.2273. Found: 283.2255. $[\alpha]_D^{22}$ +0.53 (*c* 0.041, $CHCl_3$).

**(*R*)-2-(2,2-Dimethyl-4-(undec-2-enyl)-1,3-dioxolan-4-yl)acetaldehyde (6)**

To a solution of **5** (1.0 g, 3.33 mmol) in dry $CH_2Cl_2$ (50 mL) were added PDC (1.9 g, 5.0 mmol) and dry ground MS (1.9 g) and the whole was stirred at rt overnight. After the mixture was diluted with $Et_2O$, the whole was filtered by the aid of Celite.® The filtrate was concentrated under reduced pressure to give the residue, which was chromatographed on $SiO_2$ (AcOEt : hexane = 1 : 4) to furnish **6** (0.752 g , 76 %) as a colorless oil. IR (neat) $cm^{-1}$: 2986, 2925, 2855, 1724, 1456, 1380, 1370, 1254, 1213, 1158, 1059, 975, 895, 847, 723. $^1H$ NMR ($CDCl_3$) δ: 0.88 (3H, t, *J* = 6.8 Hz, -C(14)-H), 1.26 (12H, br.s, C(8~13)-H), 1.406 (3H, s, $-CH_3$), 1.413 (3H, s, $-CH_3$), 2.00 (2H, m, -C(7)-H), 2.35 (2H, m, -C(4)-H), 2.62 (1H, dd, *J* =15.8, 2.4 Hz, -C(2)-H), 2.72 (1H, dd, *J* = 15.8, 2.4 Hz, -C(2)-H), 3.86 (1H, d, *J* = 9.1 Hz, -C(3')-H), 3.92 (1H, d, *J* = 9.1 Hz, -C(3')-H), 5.35-5.41 (1H, m, -C(6)-H), 5.48-5.61 (1H, m, -C(5)-H), 9.81 (1H, t, *J* = 2.4 Hz, -CHO). $^{13}C$ NMR ($CDCl_3$) δ: 14.1, 22.6, 26.8, 26.9, 27.4, 29.1, 29.2, 29.3, 29.4, 31.8, 36.0, 50.9, 72.4, 81.3, 109.8, 122.9, 123.7, 201.1. MS (*m/z*): 278, 252, 221, 220, 144, 143, 85, 83, 57. HRMS (*m/z*): Calcd for $C_{18}H_{30}O_2$ ($M^+$-$H_2O$): 278.2246. Found: 278.2237. $[\alpha]_D^{23}$ +1.94 (*c* 0.037, $CHCl_3$).

**(*R*)-Ethyl 4-(2,2-dimethyl-4-(undec-2-enyl)-1,3-dioxolan-4-yl)but-2-enoate (7)**

To a suspension of NaH (60% oil dispersion, 0.122 g, 2.95 mmol) in dry THF (20 mL) was added triethyl phosphonoacetate (0.61ml, 2.95 mmol) and the mixture was stirred at 0 °C under $N_2$ for 1 h. A solution of

**6** (0.73 g, 2.46 mmol) in dry THF (20 ml) was added to the reaction mixture and the whole was stirred at rt under $N_2$ for 2 h. After the reaction was quenched by addition of s.$NH_4Cl$ aq. (6 ml), the whole was extracted with AcOEt. The combined organic layer was washed with s.NaCl aq. and dried over anhydrous $Na_2SO_4$. Removal of the solvent under reduced pressure gave the residue (1.30 g), which was chromatographed on $SiO_2$ (AcOEt : hexane = 1 : 9) to yield **7** (0.81 g, 90 %) as a colorless oil. IR (neat) $cm^{-1}$: 2983, 2926, 2855, 1723, 1654, 1456, 1369, 1261, 1212, 1181, 1059, 983, 889, 722. $^1H$ NMR ($CDCl_3$) δ: 0.88 (3H, t, *J* = 6.8 Hz, -C(16)-H), 1.26-1.41 (21H, m, -$CH_3$, -C(10~15)-H), 2.04 (2H, m, -C(9)-H), 2.26-2.42 (2H, m, -C(6)-H), 2.45-2.52 (2H, m, -C(4)-H), 3.80 (2H, m, -C(5')-H), 4.19 (2H, q, *J* = 7.3 Hz, -$CO_2C\underline{H}_2CH_3$), 5.35 (1H, m, -C(8)-H), 5.55 (1H, m, -C(7)-H), 5.87 (1H, d, *J*=15.6 Hz, C(2)-H), 6.96 (1H, m, C(3)-H). $^{13}C$ NMR ($CDCl_3$) δ: 14.0, 14.2, 22.6, 27.0, 27.1, 27.5, 29.2, 29.3, 29.4, 29.5, 31.8, 35.5, 40.1, 60.2, 71.8, 82.6, 109.7, 123.2, 124.5, 133.5, 144.0, 166.1. MS (*m/z*): 351, 253, 213, 195, 155, 127, 85, 83. HRMS (*m/z*): Calcd for $C_{21}H_{35}O_4$ ($M^+$-$CH_3$): 351.2535. Found: 351.2565. $[\alpha]_D^{24}$ +1.51 (*c* 0.0425, $CHCl_3$).

**(*R*)-Ethyl 4-(2,2-dimethyl-4-undecyl-1,3-dioxolan-4-yl)butanoate (8)**

A solution of **7** (0.738 g, 1.93 mmol) in EtOH (28 mL) was stirred under $H_2$ atmosphere in the presence of 10% Pd/C (300 mg) at rt for 3 h. The catalyst was removed by filtration and the filtrate was connected under reduced pressure to give the residue, which was chromatographed on $SiO_2$ (AcOEt : hexane = 1 : 6) to yield **8** (0.606 g, 82 %) as a colorless oil. IR (neat) $cm^{-1}$: 2983, 2926, 2855, 1737, 1456, 1368, 1252, 1212, 1183, 1060, 983, 877, 817. $^1H$ NMR ($CDCl_3$) δ: 0.88 (3H, t, *J* = 6.8 Hz, -C(16)-H), 1.24-1.30 (21H, m, -C(7-15)-H, -$CO_2CH_2C\underline{H}_3$), 1.379 (3H, s, -$CH_3$), 1.384 (3H, s, -$CH_3$), 1.47-1.75 (6H, m, -C(3, 4, 6)-H), 2.32 (2H, t, *J* = 6.8 Hz, -C(2)-H), 3.75 (2H, s, -C(5')-H), 4.13 (2H, q, *J* = 7.2 Hz, -$CO_2C\underline{H}_2CH_3$). $^{13}C$ NMR ($CDCl_3$) δ: 14,1, 14.2, 19.7, 22.6, 24.2, 27.2, 27.4, 29.3, 29.5, 29.6 (3C), 30.1, 31.9, 34.5, 36.6, 37.3, 60.2, 72.9, 83.2, 108.9, 173.4. MS (*m/z*): 355, 325, 295, 255, 215, 157, 85, 83, 57. HRMS (*m/z*): Calcd for $C_{21}H_{39}O_4$ ($M^+$-$CH_3$): 355.2848. Found: 355.2854. $[\alpha]_D^{28}$ +0.68 (*c* 0.025, $CHCl_3$).

**(*R*)-(+)-Tanikolide (1)**

To a solution of **8** (0.54 g, 1.45 mmol) in EtOH (14.3 mL) was added a solution of KOH (3.78 g) in $H_2O$ (14.3 mL) and the whole was stirred at rt for 2 h. After the reaction mixture was adjusted to pH3 by the addition of 2N HCl aq. (50 mL) under ice-cooling, the whole was stirred at rt for 1.5 h. The reaction mixture was salted out and then extracted with AcOEt. The combined organic layer was washed with brine and dried over anhydrous $Na_2SO_4$. Removal of the solvent under reduced pressure leaved the residue (0.532 g), which was dissolved in $CH_3CN$ (20 mL). Amberlyst15 (0.213 g) was added to the solution and the whole was stirred at rt for 3 h. The whole was filtered and the filtrate was concentrated under reduced pressure to give the residue which was dissolved in $Et_2O$. The solution was washed with s.$NaHCO_3$ aq. and then s.NaCl aq. and dried over anhydrous $Na_2SO_4$. Removal of the solvent under reduced pressure furnished the residue (0.457 g) which was chromatographed over $SiO_2$ ($CHCl_3$ : acetone

= 4 : 1) to give **1** (0.312 g, 76 %) as colorless crystals. Mp 40-41 $^{o}$C. IR (Nujol) cm$^{-1}$: 3394, 2922, 2852, 1713, 1466, 1330, 1247, 1196, 1049, 927, 855, 755, 722, 641. $^{1}$H NMR ($CDCl_3$) δ: 0.88 (3H, t, *J* = 6.8 Hz, -C(16)-H), 1.26 (18H, br.s, -C(7-15)-H), 1.58~1.77 (3H, m, -C(6)-H, -C(4)-$H_a$), 1.80-1.94 (3H, m, -C(3)-H, -C(4)-$H_b$ ), 2.42-2.54 (2H, m, -C(2)-H), 3.55 (1H, dd, *J* = 12.0, 6.0 Hz, -$CH_2$OH), 3.66 (1H, dd, *J* = 12.0, 6.0 Hz, -$CH_2$OH). $^{13}$C NMR ($CDCl_3$) δ: 14.0, 16.6, 22.6, 23.3, 26.6, 29.2, 29.4, 29.5 (2C), 29.7 (2C), 29.9, 31.8, 36.8, 67.3, 86.6, 172.1. HRMS (*m/z*): Calcd for $C_{16}H_{29}O_2$ ($M^+$-$CH_2$OH): 253.2167. Found: 253.2192. $[\alpha]_D^{22}$ +1.98 (*c* 0.0365, $CHCl_3$).

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