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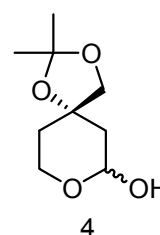
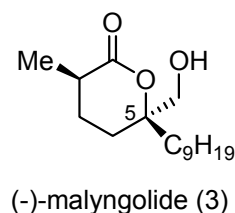
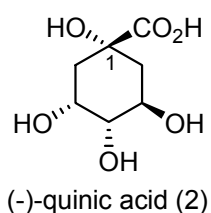
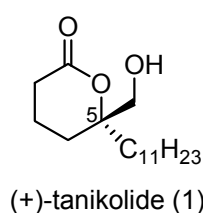
SYNTHESIS OF (*R*)-(+)-TANIKOLIDE, A TOXIC AND ANTIFUNGAL δ -LACTONE FROM THE MARINE CYANOBACTERIUM *LYNGBYA MAJUSCULA*

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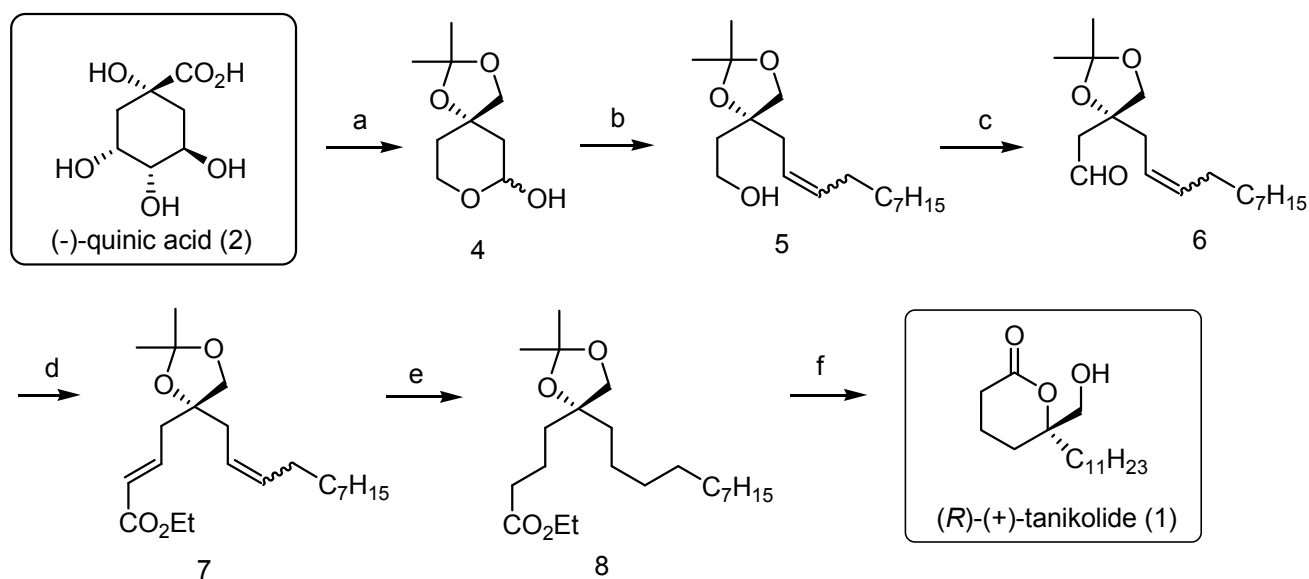
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Abstract - (*R*)-(+)-Tanikolide, a brine-shrimp toxic and antifungal marine metabolite, isolated from the lipid extract of a blue green algae, cyanobacterium, *Lyngbia mujuscula*, was synthesized starting from (-)-quinic acid.

(*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-diester may also be a good method.⁵



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 H₂ atmosphere in the presence of Pd/C catalyst to form a saturated ester (**8**) in 82% yield. Finally, basic hydrolysis of the ester 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, CHCl₃) (lit.,¹ $[\alpha]_D^{25} +2.3$ (*c* 0.65, CHCl₃)) in 76% yield. IR, ¹H-NMR and ¹³C-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 CH₂Cl₂ (76%); d) triethyl phosphonoacetate, NaH in THF (90%); e) H₂, 10% Pd/C in EtOH (82%); f) 1) KOH in EtOH-H₂O, 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 ¹H, 100 MHz ¹³C) 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 nonyltriphenylphosphonium bromide (2.70 g, 5.64 mmol) in dry THF (5 mL) under ice cooling and the mixture was stirred at rt under N₂ 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 N₂ for 2 h. The mixture was concentrated under reduced pressure to leave a residue, which was treated with CHCl₃. The solution was washed with H₂O and brine, successively, and then dried over anhydrous Na₂SO₄. Evaporation of the solvent under reduced pressure gave the residue (3.80 g), which was chromatographed on SiO₂ (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 (CDCl₃) 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, -CH₃), 1.44 (3H, s, -CH₃), 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, -CH₂OH), 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). ¹³C NMR (CDCl₃) 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 C₁₇H₃₁O₃ (M⁺-CH₃): 283.2273. Found: 283.2255. [α]_D²² +0.53 (*c* 0.041, CHCl₃).

(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 CH₂Cl₂ (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 Et₂O, the whole was filtered by the aid of Celite.[®] The filtrate was concentrated under reduced pressure to give the residue, which was chromatographed on SiO₂ (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 (CDCl₃) 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, -CH₃), 1.413 (3H, s, -CH₃), 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). ¹³C NMR (CDCl₃) 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 C₁₈H₃₀O₂ (M⁺-H₂O): 278.2246. Found: 278.2237. [α]_D²³ +1.94 (*c* 0.037, CHCl₃).

(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 (0.61 ml, 2.95 mmol) and the mixture was stirred at 0 °C under N₂ 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 N₂ for 2 h. After the reaction was quenched by addition of s.NH₄Cl aq. (6 ml), the whole was extracted with AcOEt. The combined organic layer was washed with s.NaCl aq. and dried over anhydrous Na₂SO₄. Removal of the solvent under reduced pressure gave the residue (1.30 g), which was chromatographed on SiO₂ (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 (CDCl₃) δ: 0.88 (3H, t, *J* = 6.8 Hz, -C(16)-H), 1.26-1.41 (21H, m, -CH₃, -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, -CO₂CH₂CH₃), 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). ¹³C NMR (CDCl₃) 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 C₂₁H₃₅O₄ (M⁺-CH₃): 351.2535. Found: 351.2565. [α]_D²⁴ +1.51 (*c* 0.0425, CHCl₃).

(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 H₂ 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 SiO₂ (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 (CDCl₃) δ: 0.88 (3H, t, *J* = 6.8 Hz, -C(16)-H), 1.24-1.30 (21H, m, -C(7-15)-H, -CO₂CH₂CH₃), 1.379 (3H, s, -CH₃), 1.384 (3H, s, -CH₃), 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, -CO₂CH₂CH₃). ¹³C NMR (CDCl₃) 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 C₂₁H₃₉O₄ (M⁺-CH₃): 355.2848. Found: 355.2854. [α]_D²⁸ +0.68 (*c* 0.025, CHCl₃).

(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 H₂O (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 Na₂SO₄. Removal of the solvent under reduced pressure leaved the residue (0.532 g), which was dissolved in CH₃CN (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 Et₂O. The solution was washed with s.NaHCO₃ aq. and then s.NaCl aq. and dried over anhydrous Na₂SO₄. Removal of the solvent under reduced pressure furnished the residue (0.457 g) which was chromatographed over SiO₂ (CHCl₃ : acetone

= 4 : 1) to give **1** (0.312 g, 76 %) as colorless crystals. Mp 40-41 °C. IR (Nujol) cm^{-1} : 3394, 2922, 2852, 1713, 1466, 1330, 1247, 1196, 1049, 927, 855, 755, 722, 641. ^1H 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, -CH₂OH), 3.66 (1H, dd, $J = 12.0, 6.0$ Hz, -CH₂OH). ^{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 $\text{C}_{16}\text{H}_{29}\text{O}_2$ (M^+ -CH₂OH): 253.2167. Found: 253.2192. $[\alpha]_{\text{D}}^{22} +1.98$ (c 0.0365, CHCl_3).

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REFERENCES

1. I. P. Singh, K. E. Milligan, and W. H. Gerwick, *J. Nat. Prod.*, 1995, **62**, 1333.
2. B. Gourdet and H. W. Lam, *Angew. Chem. Int. Ed.*, 2010, **49**, 8733; and the previous total syntheses of tanikolide are cited therein.
3. a) K. Matsuo, M. Morita, and K. Kawashima, *Chem. Pharm. Bull.*, 1997, **45**, 1734; b) K. Matsuo, T. Matsumoto, and K. Nishiwaki, *Heterocycles*, 1998, **48**, 1213; c) K. Matsuo, W. Sugimura, Y. Shimizu, K. Nishiwaki, and H. Kuwajima, *Heterocycles*, 2000, **53**, 1505.
4. R. E. Moore, J. H. Cardellina II, E. V. Arnold, and J. Clardy, *J. Org. Chem.*, 1979, **44**, 4039.
5. A. L. Gutman, K. Zoubi, and T. Bravdo, *J. Org. Chem.*, 1990, **55**, 3546.
6. F. Bohlmann and H. G. Viehe, *Chem. Ber.*, 1955, **88**, 1347.
7. K. Matsuo, T. Arase, S. Ishida, and Y. Sakaguchi, *Heterocycles*, 1996, **43**, 1287.
8. K. Matsuo, Y. Hasuike, and H. Kado, *Chem. Pharm. Bull.*, 1990, **38**, 2847.