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Two efficient four-step routes to marine toxin tanikolide

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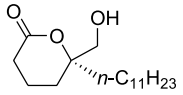
Abstract—We have presented two facile four-step syntheses of (±)-tanikolide from ethyl 2-oxocyclopentanecarboxylate. The overall chemical yields of the two sequences reached as high as 76 and 85%, respectively. The first strategy involved alkylation, Baeyer–Villiger reaction, saponification, and reduction/lactonization. The second approach for synthesizing tanikolide took advantage of the same intermediate, the alkylated ketoester **2**, which was converted to the target molecule in such three steps as deethoxycarbonylation, hydroxymethylation, and Baeyer–Villiger reaction. Our strategies are advantageous because of their high yields and suitability for the preparation of **1** in multigram or larger quantities.

1. Introduction

As a wellspring of drugs and drug leads, natural products have been one of the most rewarding scientific research areas for decades. In particular, marine natural products, perpetually provided by the oceans, have gained increasing popularity owing to their various distinct structures and bioactivities. Gerwick and co-workers[1] reported in 1999, the isolation and structural elucidation of (*R*)-(+)-tanikolide, a brine-shrimp toxic and antifungal metabolite native to the marine cyanobacterium *Lyngbya majuscula* collected from Tanikeli Island. The biological assays of this new toxin demonstrated an LD_{50} of 3.6 μg/mL against brine shrimp and 9.0 μg/mL against the snail. Moreover, a 13-mm diameter inhibition zone (100 μg/disk) was observed when (*R*)-(+)-tanikolide was tested with the fungus *Candida albicans*.[1] Due to the presence of a tertiary carbon center in the δ-lactone framework and the unique bioactivity, the synthesis of tanikolide has aroused considerable interests from the synthetic community.[2] Ogasawara accomplished an enantioselective synthesis of (*R*)-(+)-tanikolide in 12 steps from a known 1,2-enediol bis-silyl ether, where a kinetic resolution based on a ruthenium-promoted catalytic asymmetric hydrogen transfer reaction was utilized as a key step.[2a] It was the remarkable optically active allene strategy that enabled Nelson to realize the asymmetric total synthesis of (*R*)-(+)-tanikolide in six steps from propargyl alcohol.[2b] Afterwards, two different nine-step approaches to the synthesis of tanikolide in the racemic form were achieved by Chen[2c] and Krauss,[2d] respectively; both of the syntheses featured the use of a dihydroxylation and a Grignard addition. The powerful ring closing metathesis (RCM) transformation has found successful applications in forming the δ-lactone framework of tanikolide.[2e,f] More recently, Koumbis and co-workers[2g] accomplished a 10-step enantioselective synthesis of (*R*)-(+)-tanikolide starting from *D*-erythrose, a useful chiron.



(*R*)-(+)-tanikolide

Even nowadays, formulating a highly efficient synthetic strategy for constructing biosignificant natural products remains a tremendous challenge. The chemical community is more willing than ever to show concern for '(reaction) step economy' in organic synthesis. In our case, a suitable cyclopentanone derivative was envisioned as an excellent starting point to develop synthetic avenues to tanikolide with high efficacy. We now wish to provide a full account of our findings regarding the syntheses of this new marine toxin.[3]

Keywords: Tanikolide; Syntheses; Marine natural product.
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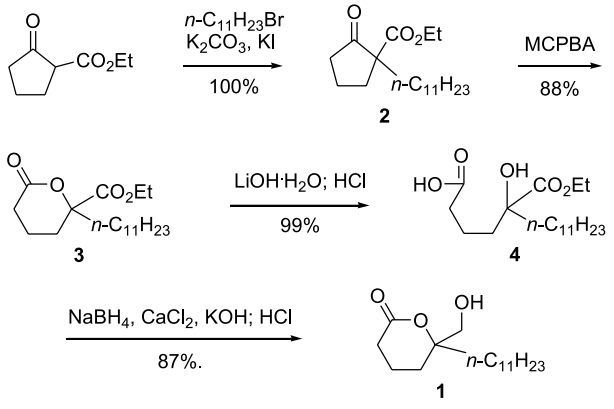
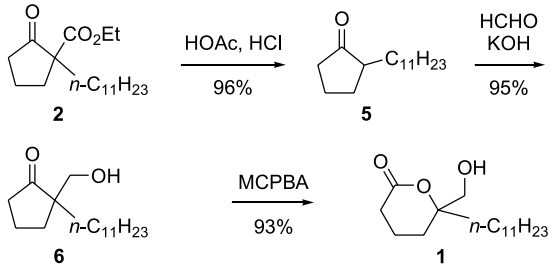
2. Results and discussion

We have developed two shorter and more efficient syntheses of tanikolide (**1**). Our first synthesis,[2h] as outlined in Scheme 1, commenced from the commercially available ethyl 2-oxocyclopentanecarboxylate, which was alkylated[4a–c] with 1-bromoundecane in the presence of K_2CO_3 and KI in refluxing anhydrous acetone for 20 h to furnish the known intermediate[4d] **2** in 100% yield. Baeyer–Villiger oxidation of **2** under typical conditions[5] (MCPBA, $NaHCO_3$, anhydrous $CHCl_3$, rt) led to lactone **3** (88%), in which the monooxygenated tertiary carbon center was in place. With **3** in hand, selective reduction of the ethoxycarbonyl group in the presence of the lactone moiety was attempted. Mild reduction with $NaBH(OAc)_3$ effected no reaction at all. Treatment of **3** with excess $NaBH_4$ in ethanol at rt for 30 min gave a ring-opened dihydroxyester, which indicated that the lactone carbonyl was actually more reactive toward borohydride reduction than the ethoxycarbonyl moiety. If the above reaction mixture was heated at reflux for 1 h, a triol was formed as a result of extensive reduction. After several unfruitful trials, we resorted to a different strategy that involved effecting the reduction at a later stage. Saponification[6] of **3** with $LiOH\cdot H_2O$ in THF/H_2O (1:1) at −2 °C for 4 h followed by acidification with 6 M HCl generated the hydroxydiacid monoester **4** in almost quantitative yield (99%). Under the reaction conditions, the ethoxycarbonyl group was kept intact because of steric hindrance. Finally, monoester **4** was treated with the $NaBH_4/CaCl_2$/KOH reduction system[7] to afford, after lactonization during the acidic workup with 6 M HCl, tanikolide (**1**) in good yield (87%). No reaction took place when $NaBH_4/CaCl_2$ (i.e., in the absence of KOH) or $NaBH_4$ alone was used instead. The spectroscopic data of our synthetic sample of tanikolide (**1**) were in accord with those reported previously.[1,2]



Scheme 1.

Next, an alternative, convenient approach for synthesizing tanikolide emerged that took advantage of the same intermediate **2** but avoided the step of calcium borohydride (generated in situ from $NaBH_4$ and $CaCl_2$) reduction in basic (KOH) media. Deethoxycarbonylative hydrolysis of **2** in refluxing concentrated HCl–HOAc (5:3, v/v) for 2 days cleanly afforded 2-(*n*-undecyl)cyclopentanone[8] (**5**) in 96% yield (Scheme 2). Upon treatment of **5** in methanol with formalin (105 mol%) and KOH (110 mol%) at 0 °C for 2 h,



Scheme 2.

selective hydroxymethylation at C-2 took place to produce aldol **6** with a quaternary carbon center in excellent yield (95%, based on consumed **5**).[9] For this step, longer reaction time proved detrimental to the outcome by allowing the formation of the bis-and tris-hydroxymethylation byproducts. Under the same Baeyer–Villiger oxidation conditions as for **2**, the desired ring expansion was effected to transform **6** into (±)- tanikolide (**1**) in 93% yield.

3. Conclusion

In summary, we have presented two facile four-step syntheses of (±)-tanikolide from ethyl 2-oxocyclopentanecarboxylate. The features of the current work are as follows. (i) The overall chemical yields of the two sequences reached as high as 76 and 85%, respectively. (ii) The first strategy involved alkylation, Baeyer–Villiger reaction, saponification, and reduction/lactonization. Each step proceeds in better than 87% yield. In addition, the net result of the last two steps (i.e., saponification and reduction/lactonization) is an efficient reduction of the ethoxycarbonyl of **3** while keeping the lactone carbonyl intact. The alternative in situ protection (LDA)–reduction ($LiAlH_4$) strategy[10] worked with the analogues of **2** (though the chemical yields were not so impressive, ranging from 53[10c] to 64%[10b]) and should presumably also do with **3**, but no doubt is difficult to scale up. (iii) The second approach for synthesizing tanikolide took advantage of the same intermediate **2** but avoided the step of borohydride reduction in basic media. The alkylated ketoester **2** was converted to the target molecule (**1**) in such three steps as deethoxycarbonylation, hydroxymethylation, and Baeyer–Villiger reaction. (iv) Our strategies are advantageous because of their high yields and suitability for the preparation of **1** in multigram or larger quantities.

4. Experimental

4.1. General

Melting points were determined on an XT-4 apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ (^1H at 300 MHz and ^{13}C at 75.47 MHz) using TMS as the internal standard. Column chromatography was performed on silica gel. Acetone and $CHCl_3$ were distilled over P_2O_5 and CaH_2, respectively, prior to use. IR, MS, and elemental analyses were conducted by the Analytical Laboratory at Shanghai Institute of Organic Chemistry.

4.2. Ethyl 2-oxo-1-(*n*-undecyl)cyclopentanecarboxylate (2)

In a dried 50-mL three-necked round-bottomed flask fitted with a condenser and an addition funnel were placed K_2CO_3 (4.01 g, 29.0 mmol) and KI (0.68 g, 4.1 mmol). A solution of ethyl 2-oxocyclopentanecarboxylate (1.90 mL, 12.8 mmol) in anhydrous acetone (30 mL) was added via the addition funnel. After 10 min, a solution of 1-bromoundecane (2.88 mL, 12.9 mmol) in acetone (8 mL) was added and the mixture was rapidly brought to reflux by heating in an oil bath. After 20 h, the resultant mixture was cooled to rt, diluted with Et_2O (50 mL), and filtered. The filtrate was concentrated at the reduced pressure, diluted with ether, washed in succession with water and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (SiO_2, petroleum ether–EtOAc, gradient, 100:1 to 60:1) to give **2** (3.97 g, 100%) as a pale yellow oil: IR λ_{max} 1725, 1747 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, $J=6.6$ Hz, 3H), 1.20–1.32 (m, 21H), 1.53–1.56 (m, 1H), 1.86–2.00 (m, 4H), 2.22–2.28 (m, 1H), 2.37–2.55 (m, 2H), 4.12–4.20 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.0, 19.6, 22.6, 24.7, 29.3, 29.3, 29.5, 29.6, 29.8, 31.8, 32.6, 33.8, 38.0, 60.5, 61.2, 171.0, 215.1; (only 18 peaks shown in the spectrum); EI-MS: *m/z* (%) 310 (M^+), 157 (61), 156 (100), 110 (100), 97 (64), 67 (58), 55 (93), 43 (85), 41 (80). Anal. Calcd for $C_{19}H_{34}O_3$: C, 73.50; H, 11.04. Found: C, 73.57; H, 11.36.

4.3. 5-Ethoxycarbonyl-5-(*n*-undecyl)-δ-valerolactone (3)

A solution of **2** (3.836 g, 12.36 mmol) in anhydrous $CHCl_3$ (100 mL) was treated with $NaHCO_3$ (1.922 g, 22.88 mmol) and MCPBA (70%, 4.288 g, 17.39 mmol). The mixture was stirred at rt for 20 h, diluted with saturated aqueous $NaHCO_3$ solution (120 mL), vigorously stirred for 15 min, and extracted with CH_2Cl_2. The combined organic layers were washed in succession with water and brine, dried over Na_2SO_4, filtered, and evaporated at the reduced pressure. The yellowish residue was chromatographed (SiO_2, petroleum ether–EtOAc, gradient, 20:1 to 10:1) to give **3** (3.53 g, 88%) as a colorless oil: IR (film) λ_{max} 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, $J=6.6$ Hz, 3H), 1.19–1.34 (m, 19H), 1.61–2.21 (m, 8H), 2.43–2.64 (m, 2H), 4.23–4.31 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.1, 17.0, 22.6, 22.8, 28.6, 29.2, 29.2, 29.4, 29.4, 29.5, 30.4, 31.8, 38.6, 61.8, 86.0, 170.2, 171.9 (only 18 peaks shown in the spectrum); EI-MS: *m/z* (%) 326 (M^+), 253 (100), 225 (44), 97 (22), 71 (22), 57 (35), 55 (76), 43 (57), 41 (46). Anal. Calcd for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50. Found: C, 70.04; H, 10.58.

4.4. 2-Hydroxy-2-(*n*-undecyl)hexanedioic acid 1-ethyl ester (4)

To a cold (−2 °C) mixture of **3** (220 mg, 0.674 mmol) and THF/H_2O (1:1, 8 mL) was added $LiOH\cdot H_2O$ (32.5 mg, 0.774 mmol). The mixture was stirred for 4 h at −2 °C, made acidic (pH=2–3) with 6 M HCl, and extracted with $CHCl_3$. The combined organic layers were dried ($MgSO_4$), and the volatiles were evaporated to give **4** as a solid mass (230 mg, 99%). The crude product was sufficiently pure and used directly in the next reaction. Chromatography (SiO_2, petroleum ether–EtOAc, gradient, 3:1 to 1:1) furnished the analytical sample of **4** as a colorless solid: mp 71–72 °C; ^1H NMR ($CDCl_3$) δ 0.88 (t, $J=6.8$ Hz, 3H), 1.00–1.15 (m, 2H), 1.25–1.33 (m, 19H), 1.44–1.50 (m, 2H), 1.61–1.82 (m, 4H), 2.33–2.39 (m, 2H), 3.28 (br s, 1H), 4.25 (q, $J=7.2$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.2, 18.8, 22.6, 23.3, 29.3, 29.4, 29.4, 29.6 (very strong), 31.8, 33.8, 38.3, 39.2, 61.9, 77.2, 176.6, 179.3 (only 17 peaks shown in the spectrum). Anal. Calcd for $C_{19}H_{36}O_5$: C, 66.24; H, 10.53. Found: C, 66.32; H, 10.51.

4.5. 2-(*n*-Undecyl)cyclopentanone (5)

To a mixture of **2** (1.998 g, 6.44 mmol) in HOAc (15 mL) was added concentrated HCl (25 mL). The mixture was rapidly brought to reflux by heating in an oil bath. After 48 h the volatiles were evaporated at the reduced pressure. The residue was diluted with saturated aqueous $NaHCO_3$ solution and extracted with ether. The combined organic layers were washed in succession with saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated to give **5** (1.47 g, 96%) as a pale yellow oil: IR (film) λ_{max} 1741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, $J=$ 7.2 Hz, 3H), 1.21–1.38 (m, 19H), 1.45–1.58 (m, 1H), 1.69–1.84 (m, 2H), 1.94–2.10 (m, 2H), 2.14 (td, $J=9.8$, 1.2 Hz, 1H), 2.18–2.25 (m, 1H), 2.30 (dt, $J=18$, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.7, 22.6, 27.5, 29.3, 29.5, 29.6, 29.6, 29.6, 29.6, 29.6, 29.6, 31.9, 38.2, 49.2, 220.2; EI-MS: *m/z* (%) 238 (M^+), 238 (15), 156 (25), 97 (21), 84 (100), 83 (16), 55 (16), 43 (12), 41 (17). EI-HRMS: Calcd for $C_{16}H_{30}O$ 238.2297. Found: 238.2282.

4.6. 2-(Hydroxymethyl)-2-(*n*-undecyl)cyclopentanone (6)

To a mixture of **5** (223 mg, 0.935 mmol) and KOH (58 mg, 1.0 mmol) in MeOH (2.5 mL) at 0 °C was slowly added formalin (containing 37% HCHO, 80 mg, 0.98 mmol). The mixture was stirred at 0 °C for 2 h, and the pH was adjusted to 6–7 with 1 M HCl. The volatiles were evaporated under the reduced pressure. The residue was diluted with EtOAc, washed in succession with saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography (SiO_2, petroleum ether–EtOAc, gradient, 10:1 to 6:1) to give recovered **5** (139 mg, 62%) and **6** (90 mg, 36%, or 95% based on consumed **5**). **6**: IR (film) λ_{max} 3435, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, $J=6.6$ Hz, 3H), 1.08–1.35 (m, 18H), 1.35–1.55 (m, 2H), 1.86–1.99 (m, 4H), 2.24–2.40 (m, 2H), 2.72 (br s, 1H, OH), 3.48 (d, $J=11.1$ Hz, 1H), 3.64 (d, $J=11.1$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 19.1, 22.6, 24.0, 29.3, 29.4, 29.5, 29.5, 29.6, 30.2, 30.5, 31.8, 32.4, 38.8, 53.4, 65.6, 224.7; EI-MS: *m/z* (%) 269 (M+1, 96), 114 (100), 96 (38), 95 (26), 68 (27), 55 (31),43 (28), 41 (43). MALDI-HRMS: Calcd for $C_{17}H_{32}NaO_2$ (M+ Na) 291.2300. Found: 291.2295.

4.7. Tanikolide (1)

Method A (*Prepared from* **4**). A mixture of KOH (130 mg, 2.32 mmol), $CaCl_2$ (516 mg, 4.65 mmol) and **4** (200 mg, 0.580 mmol) in anhydrous EtOH (10 mL) was cooled to 0 °C, then $NaBH_4$ (176 mg, 4.65 mmol) was added in one portion. The reaction mixture was stirred for 26 h at rt, cooled to 0 °C, made acidic (pH=ca. 1) with 6 M HCl, evaporated, diluted with water, saturated with solid NaCl,

and extracted with $CHCl_3$. The combined organic layers were dried ($MgSO_4$), set aside for 14 h, and concentrated. The residue was chromatographed (SiO_2, petroleum ether–EtOAc, 1:1) to provide **1** (144 mg, 87%) as a colorless oil.

Method B (*Prepared from* **5**). A solution of **5** (62 mg, 0.23 mmol) in anhydrous $CHCl_3$ (3 mL) was treated with $NaHCO_3$ (29 mg, 0.34 mmol) and MCPBA (70%, 86 mg, 0.35 mmol). The mixture was stirred at rt for 4 h, diluted with saturated aqueous $NaHCO_3$ solution, vigorously stirred for 15 min, and extracted with CH_2Cl_2. The combined organic layers were washed in succession with water and brine, dried over $MgSO_4$, filtered, and concentrated at the reduced pressure. The residue was chromatographed (SiO_2, petroleum ether–EtOAc, 1:1) to provide **1** (61 mg, 93%) as a colorless oil: IR (film) λ_{max} 3424, 1721 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, $J=6.6$ Hz, 3H), 1.21–1.33 (m, 18H), 1.61–1.97 (m, 6H), 2.46–2.51 (m, 2H), 2.78 (br s, 1H, OH), 3.55 (dd, $J=12.0$, 2.1 Hz, 1H), 3.66 (dd, $J=12.0$, 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 16.5, 22.5, 23.2, 26.5, 29.2, 29.3, 29.4, 29.4, 29.5, 29.6, 29.8, 31.7, 36.7, 67.1, 86.5, 172.2; EI-MS: *m*/*z* (%) 253 (M−31, 90), 225 (43), 129 (26), 71 (32), 57 (48), 55 (70), 43 (100), 41 (60). Anal. Calcd for $C_{17}H_{32}O_3$: C, 71.79; H, 11.34. Found: C, 71.64; H, 10.98.

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