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A new synthesis of tanikolide

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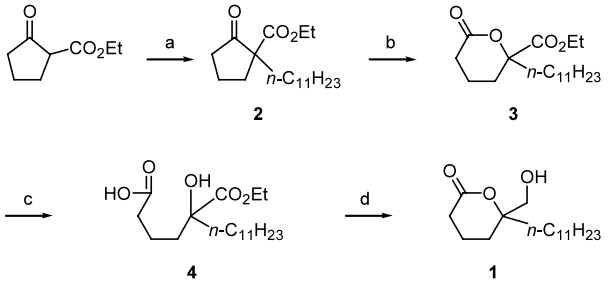
Abstract—We report a concise synthesis of tanikolide **1**, which was obtained from ethyl 2-oxocyclopentanecarboxylate in four steps: alkylation, Baeyer–Villiger reaction, saponification, and reduction/lactonization, in 70% overall yield. Our strategy should be suitable for the preparation of **1** in multigram or larger quantities. 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 oceans perpetually provide us with marine natural products possessing various structures and bioactivities. Gerwick and co-workers[1] reported in 1999 the discovery of (*R*)-(+)-tanikolide, a new brine-shrimp toxic and antifungal metabolite isolated from the marine cyanobacterium *Lyngbya majuscula* collected from Tanikeli Island. When tested for toxicity, this compound displayed an LD_{50} of 3.6 μg/mL against brine shrimps and 9.0 μg/mL against the snail.[1] Due to the presence of a tertiary carbon center in the δ-lactone framework and the unique bioactivity, tanikolide has been a particularly attractive target for synthetic organic chemists. 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.[2] 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.[3] More recently, two different nine-step approaches to the synthesis of tanikolide **1** (Scheme 1) in the racemic form were achieved by Chen and Krauss, respectively; both of the syntheses featured the use of a dihydroxylation and a Grignard addition.[4]

We have developed a shorter and more efficient synthesis of tanikolide **1**, as outlined in Scheme 1. Our synthesis commenced from the commercially available ethyl 2-oxocyclopentanecarboxylate, which was alkylated[5a–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[5d] **2** in 93% yield. Baeyer–Villiger oxidation of **2** under typical conditions[6] (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



Scheme 1. Synthesis of tanikolide. (a) *n*-$C_{11}H_{23}Br$ (101 mol%), K_2CO_3 (227 mol%), KI (32 mol%), acetone (anh.), reflux, 20 h, 93%; (b) MCPBA (141 mol%), $NaHCO_3$ (185 mol%), $CHCl_3$ (anh.), rt, 20 h, 88%; (c) $LiOH{\cdot}H_2O$ (115 mol%), THF/H_2O (1:1), −2°C; 6 M HCl (to pH 2–3), rt, 99%; (d) $NaBH_4$ (800 mol%), $CaCl_2$ (800 mol%), KOH (400 mol%), EtOH, 0°C; rt, 26 h; 6 M HCl (to pH ca. 1), 0°C, 87%.

Keywords: tanikolide; synthesis; marine natural products.

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lactone carbonyl was actually more reactive towards 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[7] 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 remained intact because of steric hindrance. Finally, monoester **4** was treated with the $NaBH_4/CaCl_2/KOH$ reduction system[8] to afford, after lactonization during the acidic workup with 6 M HCl, tanikolide **1**[9] 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.[1–4]

In summary, we present a facile synthesis of tanikolide **1**, which was obtained from ethyl 2-oxocyclopentanecarboxylate in four steps: alkylation, Baeyer–Villiger reaction, saponification, and reduction/lactonization, in 70% overall yield. Each step proceeds in better than 85% yield. Although the total synthesis reported herein is that of racemic **1**, it would be straightforward to generate either antipode by starting with an appropriate chiral enolate precursor instead of ethyl 2-oxocyclopentanecarboxylate. In addition, the net result of the last two steps (i.e. saponification and reduction/lactonization) is an efficient reduction of the ethoxycarbonyl group of **3** while keeping the lactone carbonyl intact. The alternative in situ protection (LDA)-reduction ($LiAlH_4$) strategy[10] worked with analogues of **2** (though the chemical yields were not so impressive, ranging from 53%[10c] to 64%[10b]) and should presumably also work with **3**, but will no doubt be difficult to scale-up. Our strategy is advantageous because of its high yield and suitability for the preparation of **1** in multigram or larger quantities.

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9. Tanikolide **1**: a colorless oil. IR (film) ν_{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 (bs, 1H), 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 13.96, 16.50, 22.52, 23.22, 26.46, 29.17, 29.33, 29.40, 29.44, 29.46, 29.60, 29.85, 31.74, 36.71, 67.10, 86.54, 172.20; 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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