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Total synthesis of (+)-tanikolide *via* oxidative lactonization

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(+)-Tanikolide has been synthesized in eight linear steps with a 31% overall yield. The key step in the synthesis utilizes a recently developed tandem oxidative cleavage–lactonization of a precursor alkenol to deliver the lactone moiety.

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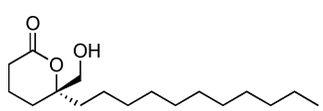
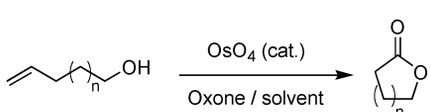
Introduction

(+)-Tanikolide is a natural product isolated from the marine cyanobacteria *Lyngbya majuscula*.[1] It exhibits both brine shrimp toxicity (LD_{50} of 3.6 μg mL^{-1}) and antifungal activities. Recently, several syntheses of both racemic and (+)-tanikolide have appeared in the literature that utilize a variety of approaches including catalytic asymmetric hydrogen transfer, ring-closing metathesis and Baeyer–Villiger oxidation.[2–11] We wish to report our synthesis of **1** using an osmium-mediated lactonization protocol recently developed in our laboratory.[12] The overall synthesis delivers **1** in 31% yield over eight steps.



(+)-tanikolide **1**

Oxidative cleavage of olefins can be cleanly effected by the use of catalytic OsO_4 and Oxone or its soluble form (nBu_4NHSO_5) as the co-oxidant to yield aldehydes and ketones as the immediate products.[13,14] Oxone further oxidizes aldehydes to carboxylic acids; however, if the reaction takes place in the presence of an alcoholic solvent, the corresponding ester is obtained exclusively.[15] This unique feature of Oxone was exploited recently in our laboratories to lactonize alkenols, namely; couple the oxidative cleavage of olefins with the oxidative lactonization of intermediate hydroxy-aldehydes (Scheme 1).[12] This reaction delivers 5 and 6 member lactone rings, even if a hindered tertiary hydroxyl group is present in the cyclization. This oxidative lactonization methodology has now been applied to the synthesis of (+)-tanikolide, which contains a 6-member ring lactone derived from a hindered tertiary alcohol.



Scheme 1

Results and discussion

The synthesis as outlined in Scheme 2 commenced with the alkylation of triethylphosphonoacetate **2** with 1-bromo-4-pentene **3**.[16] Several different conditions were tried for the alkylation. The use of sodium ethoxide in ethanol as the base led to large amounts of by-products. The alkylation proceeded smoothly using NaH as the base in DMF at rt, however, significant amounts of dialkylated products were produced. Finally, the use of 2.0 equiv. of the phosphonoacetate in THF utilizing NaH as the base yielded the desired product **4** in 88% yield after purification by column chromatography. The Wittig olefination was performed using 4.0 equiv. of aqueous formaldehyde and 2.0 equiv. of potassium carbonate in water to yield the corresponding acrylate in 81% yield.[17] The olefination could also be performed without purification of **4**, since the remaining triethylphosphonoacetate from the previous reaction (difficult to separate from **4** due to similar polarities on a large scale) was converted to ethyl acrylate and was easily removed by rotary evaporation. Reduction of the acrylate to the allylic alcohol **5** was achieved using 2.2 equiv. of DIBAL in THF at −20 °C in 93% yield.[18]

Sharpless asymmetric epoxidation using (−)-diethyltartrate as the chiral ligand gave the allylic epoxide **6** in 94% yield and *ca*. 94% ee as judged by ^1H NMR of the diastereomers formed from reaction with (*R*)-(−)-methoxyphenylacetic acid.[19,20] The alcohol was initially protected by installation of a TBDPS group in 82% yield. Epoxide ring-opening was then initiated using catalytic copper iodide and 10 equiv. of decyl magnesium bromide in THF to yield the corresponding tertiary alcohol in 43% yield.[21] The reaction was extremely sluggish at low temperatures and would not proceed to completion. Any attempts to warm the reaction above 0 °C resulted in both deoxygenation to form the alkene **9** and opening of the epoxide by bromide ion to form the bromohydrin **10**. The identity of the impurities was verified by independent synthesis of these compounds and comparison of the resulting NMR spectra. It should be noted that the reaction of **8** with decyl magnesium bromide in the absence of any copper salts led to the isolation of only the bromide **10**, thus suggesting that at the elevated temperatures required for the reaction, the Schlenk equilibrium for the organometallic reagent favors the dialkyl magnesium and $MgBr_2$. Significantly better results were obtained by protecting the epoxy alcohol **6** as the benzyl ether in 89% yield, followed by treatment with 5.0 equiv. decyl magnesium bromide in the presence of 4 mol% of freshly prepared Li_2CuCl_4 at −20 °C to 0 °C.[22] This gave the desired product **8** in 88% yield, which constituted the substrate for the cleavage–lactonization reaction.

9 **10**

The key lactonization step was performed by treating **8** with 4.4 equiv. of soluble Oxone[14] and catalytic OsO_4 in refluxing CH_2Cl_2 to give the benzyl-protected tanikolide in 73% yield. The reaction could also be performed using purified Oxone in DMF with catalytic OsO_4 at room temperature (60% yield), however, the open-chain carboxylic acid was a major by-product. Addition of 4 Å molecular sieves to the reaction did not increase the yield to any appreciable extent. The final deprotection was achieved *via* dehydrogenation using Pearlman's

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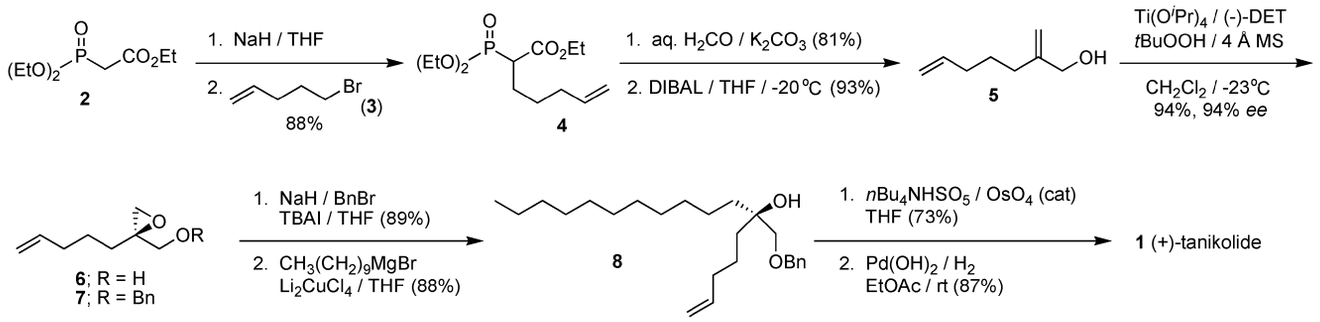
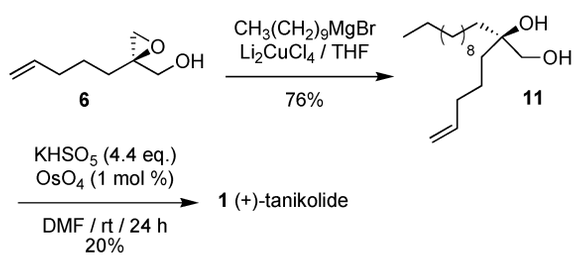


Scheme 2

catalyst in ethyl acetate–chloroform under an atmospheric pressure of hydrogen.

The product was identified as **1** by comparison of the ^{1}H and ^{13}C NMR data with the published data. The optical purity was determined to be 91–93% ee by comparison of the optical rotation with the published value and 90% ee by formation of the (*R*)-(−)-methoxyphenylacetic acid derivative of **1**.[1,11]

Attempts were made to shorten the synthesis by two steps by subjecting the unprotected diol **11** to the oxidative cyclization in the hopes that the six-member ring lactone would be formed preferentially over the seven-member lactone (Scheme 3). Two problems were inherent in this approach. The first was the partial racemization of **6** under the strongly basic ring-opening conditions. Preparation of the (*R*)-(−)-MPA esters of both **6** and **11** showed the ee's to be 93% and 76%, respectively. This is presumably occurring *via* a Payne rearrangement, which could be assisted by Li_2CuCl_4. The alkyl Grignard opening of the Payne rearranged epoxide will lead to the enantiomer of the desired product, thus eroding the stereochemical purity. Secondly, the oxidative cyclization was not clean, yielding the desired **1** in 20% yield, along with three other major impurities.



Scheme 3

Conclusions

In conclusion, we have developed a short and concise route to tanikolide utilizing a unique OsO_4-mediated oxidative cleavage–lactonization protocol as the key step in our synthesis.

Experimental

General experimental procedures

All commercially available starting materials were obtained from Aldrich and used without further purification. Solvents for reactions such as THF and CH_2Cl_2 were dried and freshly distilled prior to use. ^{1}H and ^{13}C NMR spectra were recorded on either a 300 or 500 MHz Varian Inova NMR spectrometer using either $CDCl_3$ or DMSO-d_6 as solvents. Gas chromatographic analyses were performed using an HP 6890 GC system containing an AltechSE-54 capillary column (30m × 320 µm × 0.25 µm). Analytical and preparative TLC were performed using pre-coated silica gel 60 F_{254} plates and visualized using either UV light, *p*-anisaldehyde or potassium permanganate stain. Column chromatography utilized Silicycle 40–60 µm silica gel.

2-(Diethoxyphosphoryl)hept-6-enoic acid ethyl ester (4)

Triethylphosphonoacetate (15.1 g, 67.2 mmol, 2.0 equiv.) in THF (50 mL) was added dropwise to a suspension of NaH (3.0 g of a 60% dispersion in mineral oil washed twice with dry pentane, 73.9 mmol, 2.2 equiv.) in THF (450 mL) at rt. After addition was complete, the mixture was stirred for 1 h at rt after which 1-bromo-4-pentene (5.0 g, 33.6 mmol, 1.0 equiv.) in THF (50 mL) was added dropwise over 15 min. The reaction was heated to reflux and monitored by GC until disappearance of the alkene. The reaction was quenched with water (250 mL) and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over magnesium sulfate and concentrated *via* rotary evaporation. The residue was purified by column chromatography to yield 8.6 g (88% yield) of **4** as a clear liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75 (m, 1H), 5.0 (m, 2H), 4.2 (overlapping signals, 6H), 2.9 (m, 1H), 2.1 (m, 2H), 1.7–2.1 (m, 2H), 1.2–1.5 (overlapping signals, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 137.8, 115.0, 100.3, 62.6, 61.2, 46.5, 44.7, 33.1, 27.5, 26.3, 16.2, 14.0.

2-Methylenehept-6-enoic acid ethyl ester[23]

Compound **4** (1.0 g, 3.4 mmol, 1.0 equiv.) was added to an aqueous solution of potassium carbonate (0.95 g, 6.9 mmol, 2.0 equiv. dissolved in 10 mL of water). Aqueous formaldehyde solution (37%, 1.1 g, 13.6 mmol, 4.0 equiv.) was added to the reaction and the mixture was heated to 80 °C until GC analysis indicated the starting material had been consumed (1–4 h). The reaction was extracted with diethyl ether (4 × 50 mL), the combined organic extracts dried over magnesium sulfate and concentrated *in vacuo* to yield the acrylate ester as a pale yellow liquid. The product was purified *via* column chromatography (9 : 1 hexanes–ethyl acetate) to give the pure product in 81% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.1 (d, 1H), 5.8 (m, 1H), 5.5 (d, 1H), 5.0 (m, 2H), 4.2 (q, 2H), 2.3 (td, 2H), 2.1 (m, 2H), 1.55 (m, 2H), 1.25 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 140.7, 138.4, 124.5, 114.7, 60.5, 33.2, 31.3, 27.6, 14.2.

2-(Hydroxymethyl)-1,6-heptadiene (5)[24]

DIBAL as a 1 M solution in hexanes (59 mL, 59.0 mmol, 2.2 equiv.) was added to a solution of the ethyl ester described in the previous paragraph (4.5 g, 26.8 mmol, 1 equiv.) in dry THF (50 mL) which had been cooled to −20 °C. The reaction was monitored by TLC until the starting material was consumed and then quenched carefully with Rochelle's salt. Glycerol (0.2 mL mmol^{-1} DIBAL) was added slowly and the reaction was allowed to stir vigorously for 6 h. The water layer was saturated with NaCl and then extracted several times with diethyl ether. The combined organics were washed with water and brine, dried over magnesium sulfate, concentrated *in vacuo*, and purified by column chromatography to give **5** in 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.8 (m, 1H), 4.8–5.0 (2 overlapping signals, 4H), 4.0 (s, 2H), 2.5 (br s, 1H), 2.0 (m, 4H), 1.5 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8, 138.5, 114.7, 109.2, 65.8, 33.4, 32.3, 26.9.

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(2-Pent-4-enyloxiranyl)methanol (6)[18]

Powdered 4 Å molecular sieves were dried under vacuum at 130 °C for a minimum of 8 h. The sieves (1.2 g) were weighed into a round bottom flask and further flame-dried and cooled under argon. Freshly distilled methylene chloride (120 mL) dried over calcium hydride was added and the suspension cooled to 0 °C. D-(−)-diethyltartrate (315 μL, 1.8 mmol, 0.08 equiv.) was added, followed by freshly distilled $Ti(OiPr)_4$ (450 μL, 1.5 mmol, 0.07 equiv.). The mixture was stirred at 0 °C for 10 min, then cooled to −23 °C for an additional 50 min. *t*-Butyl hydroperoxide (15.2 mL, 60.8 mmol, 3.0 equiv.) as a 4.0 M solution in toluene was added in one portion and stirring was continued for another 30 min. The alcohol **5** (2.56 g, 20.3 mmol, 1.0 equiv.) in dry methylene chloride (75 mL) was added dropwise over 30 min and stirring was continued for 2 h at −23 °C. The reaction was warmed to −12 °C and stirred for an additional 18 h. Saturated sodium bicarbonate (3 mL) was added and the reaction was warmed to 10 °C while stirring vigorously. Excess magnesium sulfate was added and stirring was continued for another 15 min. The reaction mixture was then filtered through a pad of Celite and washed well with diethyl ether. The filtrate was concentrated and the residue chromatographed by column chromatography to yield the epoxy alcohol **6** in 94% yield. The *ee* was determined to be 94% by ^{1}H NMR after formation of the *R*-(−)-α-methoxyphenyl acetic acid ester. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.8 (m, 1H), 5.0 (m, 2H), 3.8 (d, 1H), 3.6 (d, 1H), 2.9 (d, 1H), 2.6 (d, 1H), 2.2 (br s, 1H), 2.0 (m, 2H), 1.75 (m, 1H), 1.5 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 114.9, 62.8, 59.7, 49.7, 33.6, 31.2, 23.7.

Compound 7

Sodium hydride (340 mg as a 60% dispersion in mineral oil, 8.5 mmol, 1.2 equiv.) was washed twice with dry pentane and then a solution of the epoxy alcohol **6** (1.0 g, 7.0 mmol, 1.0 equiv.) in THF (25 mL) was added dropwise at 0 °C. Stirring was continued for 20 min, at which point a solution of benzyl bromide (1.3 g, 7.7 mmol, 1.1 equiv.) in THF (5 mL) was added. This was followed immediately by the addition of tetrabutylammonium iodide (1.3 g, 3.5 mmol, 0.5 equiv.). The reaction was warmed to rt and stirred for 6 h. After standard workup and purification by column chromatography (3 : 1 hexanes–ethyl acetate), the product was obtained in 89% yield. IR ν_{max}(neat)/cm^{-1} 1642, 1455, 1097; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 (m, 5H), 5.8 (m, 1H), 5.0 (m, 2H), 4.6 (dd, 2H), 3.6 (d, 1H), 3.5 (d, 1H), 2.65 (2 d, 2H), 2.1 (m, 2H), 1.8 (m, 1H), 1.4–1.8 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 137.2, 128.3, 127.6, 114.8, 73.2, 71.9, 58.4, 50.2, 33.6, 31.3, 23.9. HRMS for $C_{15}H_{20}O_2$ [M − H]$^+$: observed 231.1383, calcd. 231.1385.

Compound 8

A solution of Li_2CuCl_4 was prepared by combining rigorously dried $CuCl_2$ (268.9 mg, 2.0 mmol, 1.0 equiv.) with LiCl (169.6 mg, 4.0 mmol, 2.0 equiv.) in dry THF (20 mL). The resulting orange solution was used immediately and prepared fresh for each epoxide ring-opening reaction. Decyl magnesium bromide (10.8 mL of a 1 M solution in diethyl ether, 10.8 mmol, 5.0 equiv.) was added under argon into dry THF (50 mL). The cloudy solution was cooled to −20 °C and then **7** (0.5 g, 2.2 mmol, 1.0 equiv.) dissolved in THF (5 mL) was added dropwise to the solution over 15 min. An aliquot of the Li_2CuCl_4 solution (1.0 mL, 0.1 mmol, 0.05 equiv.) was added and the reaction was allowed to stir for 6 h. The solution gradually darkened from a pale orange to a deep purple as the reaction progressed. Workup followed by column chromatography (9 : 1 hexanes–ethyl acetate) gave **8** in 88% yield. IR ν_{max}(neat)/cm^{-1} 3440, 1640, 1455, 1100, 910; ^{1}H NMR (300 MHz, $CDCl_3$) 7.35 (m, 5H), 5.8 (m, 1H), 5.0 (tt, 2H), 4.6 (s, 2H), 3.3 (s, 2H), 2.2 (s, 1H), 2.0 (m, 2H), 1.1–1.6 (overlapping signals, 24H), 0.9 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 138.8, 137.9, 128.4, 127.7, 127.6, 114.5, 75.6, 73.9, 73.4, 36.6, 36.0, 34.3, 31.9, 30.3, 29.7, 29.6 (2), 29.3, 23.4, 22.8, 22.7, 14.1. HRMS for $C_{25}H_{42}O_2$ [M − H]$^+$: observed 373.3111, calcd. 373.3107.

Benzyl-protected (+)-tanikolide

Alkenol **8** (250.0 mg, 0.65 mmol, 1.0 equiv.) was dissolved in dry methylene chloride (25 mL). Purified Oxone as its tetrabutylammonium salt prepared as previously described[14] (1.38 g, 2.85 mmol, 4.4 equiv.) was added, followed by 1.0 mol% of OsO_4 as a 0.2 M solution in toluene. The solution was heated to reflux for 6 h and cooled back to rt. The methylene chloride was carefully evaporated off using a stream of nitrogen and diethyl ether was added to the residue. The resulting gummy material was stirred until a fine brown powder precipitated. The solid was filtered and the cake was washed well with diethyl ether. The bulk of the ether was evaporated and the remaining material was purified by column chromatography (3 : 1 hexanes–ethyl acetate) to yield 192.0 mg (73% yield) of the desired lactone. IR ν_{max}(neat)/cm^{-1} 1734, 1456, 1100; ^{1}H NMR (300 MHz, $CDCl_3$) 7.35 (m, 5H), 4.6 (s, 2H), 3.45 (s, 2H), 2.45 (m, 2H), 1.4–2.1 (overlapping m, 5H), 1.35 (br m, 19 H), 0.9 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 171.7, 137.9, 128.4, 127.7, 127.6, 84.9, 74.1, 73.5, 45.8, 38.1, 31.9, 29.9, 29.8, 29.6, 29.3, 27.8, 22.9, 22.7, 16.8, 14.1. HRMS for $C_{24}H_{38}O_3$ [M + H]$^+$: observed 375.2898, calcd. 375.2855. The lactonization could also be performed using purified Oxone and OsO_4 in DMF, but a major side product was the open-chain carboxylic acid.

Tanikolide 1

Benzylated (+)-tanikolide (0.1 g, 0.27 mmol) was placed in ethyl acetate (3 mL) and a few drops of chloroform and a catalytic amount of Pearlman's catalyst added. The reaction was placed under an atmosphere of hydrogen gas and allowed to stir at rt for 5 h. The catalyst was filtered off and the filtrate evaporated to yield (+)-tanikolide as a thick oil in 87% yield. IR ν_{max}(neat)/cm^{-1} 3428, 1718, 1252, 1051, 940. ^{1}H NMR (300 MHz, $CDCl_3$) 3.6 (d, 1H, J = 11.9 Hz), 3.5 (d, 1H, 11.9 Hz), 2.5 (m, 2H), 1.6–1.9 (three m, 7H), 1.1–1.4 (m, 18H), 0.9 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 172.3, 86.7, 67.3, 36.7, 31.8, 29.9, 29.7, 29.5, 29.4, 29.2, 26.5, 23.3, 22.6, 16.6, 14.0. The optical rotation was measured using a Perkin-Elmer 341 polarimeter; $[\alpha]_D^{25}$ +2.56 (*c* 0.46, $CHCl_3$). The ester of **1** was formed using (*R*)-(−)-methoxyphenyl acetic acid and the ratio of diastereomers determined to be 100 : 5 by ^{1}H NMR (90% ee).

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