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Syntheses of 5-Hexadecanolide, 6-Acetoxy-5-hexadecanolide and Tanikolide

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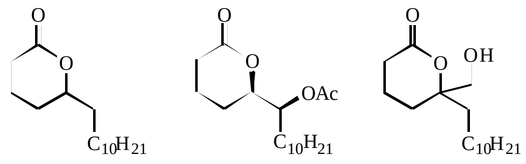
Total syntheses of 5-hexadecanolide (**1**), 6-acetoxy-5-hexadecanolide (**2**) and tanikolide (**3**) are described. 1-Bromoundecane (**4**) and 5-benzyl-1-pentanal (**5**) were chosen as starting materials. Wittig olefination and Grignard addition **4** and **5** afforded the 16-carbon skeleton, which underwent a series of functional group transformations to give δ-lactone derivatives **1**, **2** and **3**.

INTRODUCTION

In this report, we describe the total syntheses of δ-lactone **1**, **2** and **3** (see Fig. 1). 5-Hexadecanolide, **1**, a pheromone isolated from the mandibular glands of the oriental hornet *Vespa orientalis* in 1969,[1] has been proposed as a pheromone playing the role of a queen substance. Its biological properties have induced many attempts to synthesize the compound.[2]

6-Acetoxy-5-hexadecanolide, **2**, is the major component of the apical droplets that form on the eggs of the mosquito *Culex pipens fatigans*.[3] The substance acts as an oviposition pheromone attracting gravid females of the same and same related mosquito species inducing them to oviposit in the same spot where the original eggs are found. These behaviors can be used to lure the mosquito away from populated areas to a place where they can be readily. Despite the presence of inactive isomers, the biological activity of the natural isomer is unaffected. In other words, optical purity is not necessary as the biological activity of the synthetic racemic mixture is similar to that of the natural product.[4] More than thirty synthetic reports have been published[5] and they provide an inexpensive method to prepare the pheromone for use in benefit resource-poor nations that suffer from several diseases conveyed by mosquito.

Tanikolide, **3**, is a new brine-shrimp toxic and antifungal metabolite and isolated from the marine cyanobacteria (blue-green algae) *Lyngbya majuscula* Gomont collected from Tanikeli Island, Madagascar.[6] This structure of **3** has been determined by many spectroscopic methods and tested for toxicity and showed an LD_{50} of 3.6 μg/mL against brine shrimp and 9.0 μg/mL against the snail.[6] Quite recently, Ogasawara and coworkers have reported the synthetic approach by catalytic asymmetric hydrogen transfer reaction as the key step.[7]



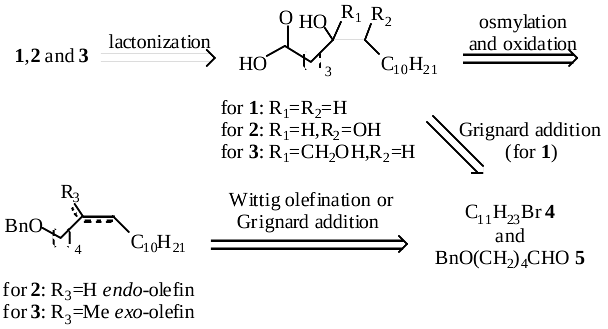
1 **2** **3**

Fig. 1.

RESULTS AND DISCUSSION

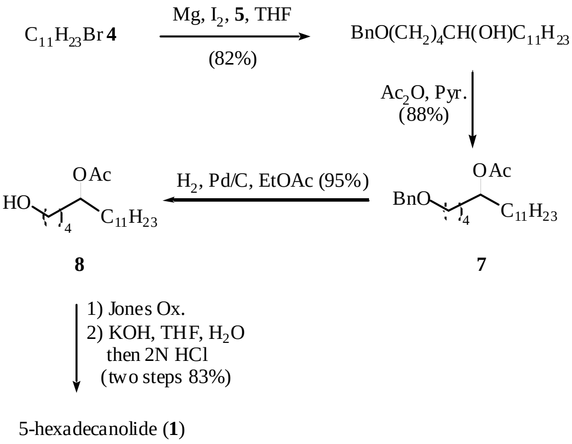
Scrutiny of the three molecules shows they share 11-carbon normal long chain and δ-substituted lactone. The 5-hexadecanolide (**1**) is the basic skeleton of compounds **2** and **3**. Our synthetic plan for **1**, **2** and **3** represented a different strategy for constructing the δ-lactone derivatives (as outlined in Scheme I).

Scheme I

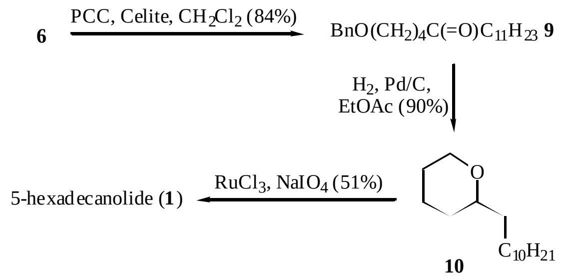


Our approach to the synthesis of 5-hexadecanolide (**1**) involved Grignard addition. Grignard reagent of 1-bromoundecane (**4**) was added to 5-benzyl-1-pentanal (**5**) and afforded *O*-benzyl alcohol **6** (see Scheme II). The hydroxy group of **6** was acetylated by acetic anhydride (Ac_2O) and pyridine to give acetate **7**. Debenzylation of **7** by catalytic hydrogenolysis (10% Pd/C) gave primary alcohol **8**, which on treatment with Jones reagent afforded an acid. This acid was deprotected by potassium hydroxide (KOH) and lactonized in 2N hydrogen chloride (HCl) to furnish 5-hexadecanolide (**1**). A second approach for the construction of the δ-lactone ring of **1** is shown in Scheme III. Alcohol **6** was oxidized with pyridinium chlorochromate (PCC) and Celite to give ketone **9**. Debezylation of ketone **9** afforded the unexpected tetrahydropyranyl ether ring **10** in 90% yield. Oxidation of cyclic ether ring **10** by ruthenium (III) chloride ($RuCl_3$) and sodium periodate ($NaIO_4$) furnished the compound **1**. Two convenient and straightforward synthetic pathways towards 5-hexadecanolide (**1**) are presented. By these methods, lactone **1** was either obtained in an overall yield of 56% (5 step procedure) or 31% (4 step procedure) from compound **4**.

Scheme II

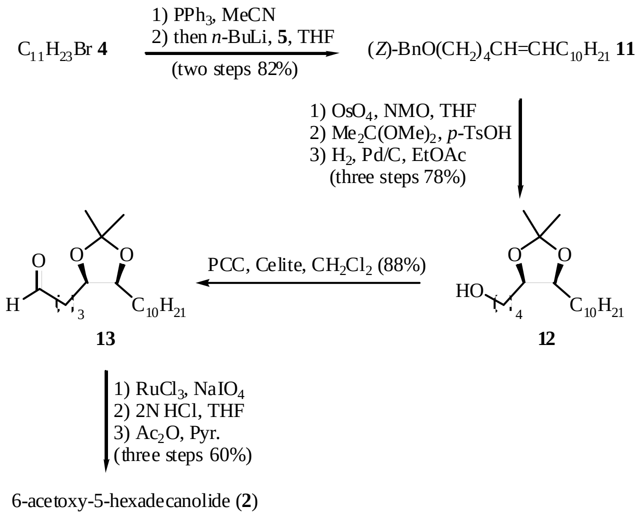


Scheme III



The synthetic approach of 6-acetoxy-5-hexadecanolide (**2**) utilized Wittig olefination protocol. The *O*-benzyl *endo*-olefin **11** was obtained by Wittig reaction of **4** and **5** in 82% yield (see Scheme IV). Osmylation of **11** with osmium tetraoxide (OsO_4) as catalyst and *N*-methylmorphorline-*N*-oxide (NMO) gave diol. Without purification, the diol was protected as the acetonide using 2,2-dimethyoxypropane in acidic condition and debenzylated with 10% palladium on activated carbon as catalyst in ethyl acetate afforded product **12**. With alcohol **12** in hand, the alcohol was oxidized with PCC and Celite to give the corresponding aldehyde **13**. Oxidation of aldehyde **13** furnished the carboxylic acid with $RuCl_3$ and $NaIO_4$ and subsequent lactonization with 2N HCl gave the δ-lactone. Finally, acetylation of hydroxy δ-lactone yielded the target molecular **2**. The overall yield of 33% of **2** was obtained (9 step procedure) from compound **4**.

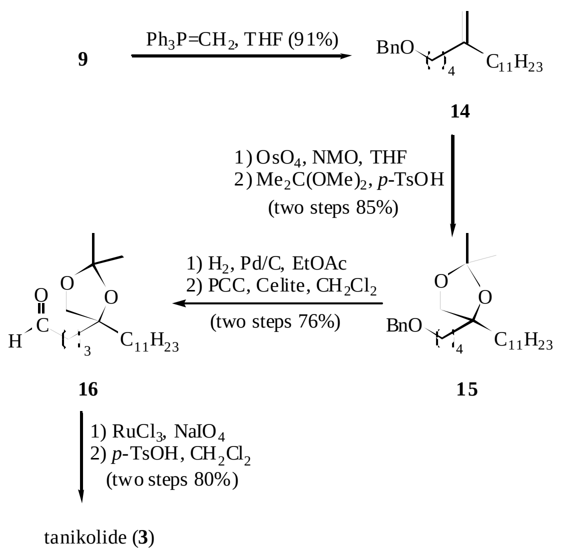
Scheme IV



The synthetic approach to tanikolide (**3**) utilized Grignard addition and Wittig olefination protocol. Olefination of ketone **9** with methyltriphenylphosphonium iodide in basic condition afforded *exo*-olefin **14**. Osmylation of **14** with OsO_4 as catalyst and NMO gave diol. Without purification, the diol was protected as the acetonide **15** using 2,2-dimethyoxypropane in 78% yield. Debenzylation of **15** with 10% palladium on activated carbon as catalyst in ethyl acetate afforded alcohol. The alcohol was oxidized with PCC and Celite to give aldehyde **16**. This aldehyde was slowly converted to acetal compound[8] in $CDCl_3$ solution for one week. Oxidation of aldehyde **16** furnished the carboxylic acid with $RuCl_3$ and $NaIO_4$ and subsequent lactonization with *p*-toluenesulfonic acid (*p*-TsOH) gave tanikolide (**3**). The overall yield of 32% of **3** was obtained (9 step procedure) from compound **4**.

In summary, we have developed these routes to δ-

Scheme V



lactone derivatives based on Grignard addition and Wittig olefination protocol.

EXPERIMENTAL SECTION

General

Tetrahydrofuran was distilled prior to use from a deep-blue solution of sodium-benzophenone ketyl. All other reagents and solvents were obtained from commerical sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Solution of products in organic solvents were dried with anhydrous magnesium sulfate before concentration *in vacuo*. Crude products were purified by preparative TLC or column chromatography on silica gel. All reported temperatures are uncorrected.

1-Benzyl-hexadecan-5-ol (6)

In a three-necked flask with a dropping funnel, stirrer, and reflux condenser, magnesium turnings (0.24 g, 10.0 mmol) were covered with dry tetrahydrofuran (20 mL) and treated with about 1/20 of a total of 1-bromoundecane (**4**) (0.5 g, 2.1 mmol) in tetrahydrofuran (20 mL) with stirring. After the reaction had started, the remaining **4** was added dropwise with further stirring in such a way that the ether boiled gently. When the Grignard reagent was prepared, the reagent was added dropwise *via* a syringe to a solution of 5-benzyl-1-pentanal (**5**) (0.4 g, 2.1 mmol). After the addition was complete, the mixture was heated on the water bath (60 °C) with stirring for 30 min, and it was then cooled, hydrolysed by the addition of water (1 mL), and subsequently treated with 5N HCl (2 × 20 mL) to dissolve the precipitate that had been formed. The mixture was filtered and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (2 × 20 mL), dried by magnesium sulfate, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate = 6/1) afforded 0.6 g (82%) of **6**: IR (film) 3410 cm^{-1}; Electrospray-MS: $C_{23}H_{40}O_2$ *m/z* (%) = 349 (M^++1, 100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 6.8 Hz, 3H), 1.20-1.70 (m, 27H and 1.24 br s), 3.46 (t, *J* = 6.5 Hz, 2H), 3.55-3.61 (m, 1H), 4.49 (s, 2H), 7.23-7.34 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.57, 128.35 (2x), 127.65 (2x), 127.51, 72.91, 71.88, 70.30, 37.49, 37.18, 31.92, 29.72, 29.70, 29.66, 29.64 (3x), 29.35, 25.66, 22.69, 22.3, 14.10.

Acetic acid 1-(benzylbutyl) undecanyl ester (7)

To a stirred solution of **6** (100 mg, 0.29 mmol) in pyridine (2 mL) was added acetic anhydride (1 mL) and the mixture was stirred for 20 h at room temperature. The resulting mixture was poured into 2N hydrogen chloride (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried by magnesium sulfate, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate = 20/1) afforded 100 mg (88%) of **7** as a colorless oil: IR (film) 1735 cm^{-1}; Electrospray-MS: $C_{25}H_{42}O_3$ *m/z* (%) = 391 (M^++1, 100), 331 (43); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 6.6 Hz, 3H), 1.20-1.65 (m, 26H and 1.23 br s), 2.01 (s, 3H), 3.44 (t, *J* = 6.5 Hz, 2H), 4.48 (s, 2H), 4.80-4.90 (m, 1H), 7.24-7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.94, 138.59, 128.34 (2x), 127.62 (2x), 127.49, 74.30, 72.88, 70.14, 34.08, 33.89, 31.91, 29.64 (2x), 29.62, 29.58, 29.53 (2x), 29.34, 25.31, 22.68, 22.02, 21.28, 14.12.

Acetic acid 1-(hydroxylbutyl) undecanyl ester (8)

Compound **7** (100 mg, 3.0 mmol) was dissolved in ethyl acetate (10 mL) and to which was added 10% palladium on activated carbon as catalyst. Then hydrogen was bubbled into the mixture for 10 min, and stirring occurred at room temperature for 3 h. Filtration through a short plug of Celite and washing with ethyl acetate (3× 10 mL) resulted in the desired alcohol **8**. Purification on silica gel (hexane/ethyl acetate = 4/1) afforded 73 mg (95%) of **8** as a colorless oil: IR (film) 3421, 1738 cm^{-1}; Electrospray-MS: $C_{18}H_{36}O_3$ *m/z* (%) = 301 (M^++1, 100), 241 (85); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, *J* = 6.6 Hz, 3H), 1.20-1.80 (m, 27H and 1.22 br s), 2.01 (s, 3H), 3.60 (t, *J* = 6.5 Hz, 2H), 4.80-4.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.05, 74.23, 62.70, 34.11, 33.89, 32.52, 31.90, 29.63, 29.60, 29.56, 29.52 (2x), 29.33, 25.31, 22.67, 21.56, 21.27, 14.10.

5-Hexadecanolide (1)

Method 1: To a solution of **3** (60 mg, 0.2 mmol) in acetone (10 mL) at room temperature was added excess Jones reagent. The mixture was stirred for 10 min and treated with 2-propanol (0.5 mL) to destroy the unreacted oxidation reagent. After the solvent was removed, the residue was diluted with water and extracted with ethyl acetate (4× 10 mL). The combined organic layers were dried by magnesium sulfate, filtered and evaporated. Without purification, to the crude acid (62 mg) was added tetrahydrofuran (2 mL), water (2 mL) and potassium hydroxide (10 mg). The reaction mixture was heated at reflux for 5 h. Then it was cooled to room temperature and the aqueous layer was collected. The aqueous layer was acidified with 2N HCl and extracted with ether (3 × 10 mL) and the combined organic layers were dried by magnesium sulfate, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate = 3/1) afforded 42 mg (83%) of **1**: IR (film) 1742 cm^{-1}; Electrospray-MS: $C_{16}H_{30}O_2$ *m/z* (%) = 255 (M^++1, 100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.4 Hz, 3H), 1.27-1.90 (m, 24H and 1.27 br s), 2.40-2.65 (m, 2H), 4.20-4.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.02, 80.62, 35.83, 31.89, 29.62, 29.59, 29.54, 29.48, 29.46, 29.41, 29.32, 27.78, 24.92, 22.67, 18.49, 14.11.

1-Benzyl-hexadecan-5-one (9)

To the alcohol **6** (100 mg, 0.29 mmol) in methylene chloride (10 mL) was added to a mixture of pyridinium chlorochromate (100 mg, 0.46 mmol) and Celite (1.0 g) in methylene chloride (10 mL). After being stirred at room temperature for 2 h, the mixture was diluted with ethyl acetate (20 mL) and filtered through a short silica gel column. The filtrate was dried by magnesium sulfate, filtered and concentrated to produce crude **9**. Purification on silica gel (hexane/ethyl acetate = 20/1) afforded **9** 83 mg (84%) as a colorless oil: IR (film) 1713 cm^{-1}; Electrospray-MS: $C_{23}H_{38}O_2$ *m/z* (%) = 347 (M^++1, 100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 6.8 Hz, 3H), 1.23 (br s, 16H), 1.50-1.65 (m, 8H), 2.35 (t, *J* = 6.7 Hz, 2H), 2.40 (t, *J* = 7.0 Hz, 2H), 3.45 (t, *J* = 5.5 Hz, 2H), 4.47 (dd, *J* = 5.5, 5.5 Hz, 2H), 7.23-7.34 (m, 5H).

1-Undecanyl tetrahydro-pyran (10)

Compound **9** (80 mg, 0.23 mmol) was dissolved in ethyl acetate (10 mL) and to which was added 10% palladium on activated carbon as catalyst. Then hydrogen was bubbled into the mixture for 10 min, and stirring occurred at room temperature for 3 h. Filtration through a short plug of Celite and washing with ethyl acetate (3× 10 mL) resulted in the desired alcohol **10**. Purification on silica gel (hexane/ethyl acetate = 50/1) afforded 50 mg (90%) of **10** as a colorless oil: IR (film) 2925 cm^{-1}; Electrospray-MS: $C_{16}H_{32}O$ *m/z* (%) = 241 (M^++1, 100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J* = 6.6 Hz, 3H), 1.18-1.80 (m, 26H and 1.23 br s), 3.603.16-3.22 (m, 1H), 3.35-3.42 (m, 1H), 3.92-3.97 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 77.94, 68.49, 36.68, 31.94, 31.91, 29.75, 29.66, 29.62 (3x), 29.35, 26.25, 25.53, 23.62, 22.68, 14.11.

5-Hexadecanolide (1)

Method 2: The ether **10** (50 mg, 0.21 mmol) was dissolved in carbon tetrachloride (2 mL), acetonitrle (2 mL) and water (3 mL) with vigorous stirring. Then sodium periodate (210 mg, 1.0 mmol) and ruthenium (III) chloride hydrate (5 mg) were added. The reaction was stopped after 6 h, diluting with methylene chloride (20 mL) and the organic layer was separated. The aqueous layer was then extracted with methylene chloride (2× 10 mL) and the organic layers were filtered on a Celite pad, collected and concentrated. Purification on silica gel (hexane/ethyl acetate = 3/1) afforded 27 mg (51%) of **1**.

1-Benzyl-hexadecan-5-ene (11)

To a stirred solution of undecyl triphenyl phosphonium bromide (5.0 g, 9.25 mmol) in tetrahydrofuran (50 mL) was added *n*-butyllitium (5.3 mL, 1.6 M, 8.5 mmol) and hexamethylphosphoric triamide (HMPA, 1.5 mL) at -78 °C. The orange red colored mixture was stirred at -78 °C for 1 h. 5-Benzyl-1-pentanal (**5**) (1.5 g, 7.8 mmol) was added to the reaction mixture at -78 °C *via* a syringe and further stirred at -78 °C for 2 h. The reaction was quenched with aqueous saturated ammonium chloride (10 mL) and the mixture was extracted with diethyl ether (3 × 50 mL) and the combined organic layers were washed with brine (2 × 20 mL), dried by magnesium sulfate, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate = 50/1) afforded 2.1 g (82%) of **11** as a colorless oil: Electrospray-MS: $C_{23}H_{38}O$ *m/z* (%) = 331 (M^++1, 100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.6 Hz, 3H), 1.21-1.64 (m, 20H and 1.23 br s), 1.95-2.23 (m, 4H), 3.46 (t, *J* = 6.6 Hz, 2H), 4.49 (s, 2H), 5.29-5.39 (m, 2H), 7.23-7.34 (m, 5H).

4-(2,2-Dimethyl-[1,3]dioxolane-4-yl-5-undecanyl)butan-1-ol (12)

To a solution of *endo*-olefin **11** (1.0 g, 3.0 mmol) in tetrahydrofuran (20 mL) and *t*-butanol (10 mL) was added

N-methylmorphorline-*N*-oxide (1.0 g, 4.3 mmol) in water (50%). The mixture was allowed to stir at room temperature for 10 min and then treated with the solution of 2% osmium tetraoxide in tetrahydrofuran (5 mL). After 3 h, to the mixture was added dilute sodium bisulfite solution (10%, 10 mL) and extracted with ethyl acetate (3 × 50 mL). The organic phase was washed with brine, dried by magnesium sulfate, filtered and evaporated. Without purification, the crude diol (1.1 g, 3.0 mmol) and *p*-toluenesulfonic acid (20 mg) were dissolved in 2,2-dimethyoxypropane (10 mL) at room temperature for 30 min. The mixture was filtered on basic alumina and the filtrate concentrated under reduced pressure. The residue acetonide (1.2 g, 3.0 mmol) was dissolved in ethyl acetate (30 mL) and to which was added 10% palladium on activated carbon (50 mg) as catalyst. Then hydrogen was bubbled into the mixture for 10 min, and stirring occurred at room temperature for 3 h. Filtration through a short plug of Celite and washing with ethyl acetate (20 mL) resulted in the desired alcohol **12**. Purification on silica gel (hexane/ethyl acetate = 3/1) afforded 0.74 g (three steps 78%) of **12** as a colorless oil: IR (film) 3416 cm^{-1}; Electrospray-MS: $C_{19}H_{38}O_3$ *m/z* (%) = 315 (M^++1, 36), 257 (100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, *J* = 6.5 Hz, 3H), 1.10-1.62 (m, 31H and 1.24, 1.28, 1.41 br s), 3.57 (t, *J* = 6.2 Hz, 2H), 3.90-4.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 78.01, 77.89, 62.37, 32.40, 31.69, 29.49, 29.38, 29.22, 29.1, 28.39, 26.02, 25.76, 22.43, 22.30, 13.82.

4-(2,2-Dimethyl-[1,3]dioxolane-4-yl-5-undecanyl)-butyraldehyde (13)

To the alcohol **12** (0.7 g, 2.2 mmol) in methylene chloride (10 mL) was added to a mixture of pyridinium chlorochromate (0.6 g, 2.8 mmol) and Celite (1.0 g) in methylene chloride (20 mL). After being stirred at room temperature for 2 h, the mixture was diluted with ethyl acetate (20 mL) and filtered through a short silica gel column. The filtrate was washed with water (2 × 10 mL), dried by magnesium sulfate, filtered and concentrated to produce crude aldehyde **13**. Purification on silica gel (hexane/ethyl acetate = 3/1) afforded **13** 0.61g (88%) as a colorless oil: IR (film) 2857, 2716, cm^{-1}; Electrospray-MS: $C_{19}H_{36}O_3$ *m/z* (%) = 313 (M^++1, 9), 255 (100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.0 Hz, 3H), 1.12-1.67 (m, 24H and 1.23, 1.34, 1.43 br s), 1.82-1.88 (m, 4H), 2.51 (t, *J* = 7.0 Hz, 2H), 3.90-4.05 (m, 2H), 9.75 (s, 1H).

6-Acetoxy-5-hexadecanolide (2)

Aldehyde **13** (0.5 g, 1.6 mmol) was dissolved in carbon tetrachloride (4 mL), acetonitrle (4 mL) and water (6 mL) with vigorous stirring. Then sodium periodate (0.5 g, 2.3 mmol) and ruthenium (III) chloride hydrate (5 mg) were added. The reaction was stopped after 6 h, diluted with methylene chloride (20 mL) and the organic layer was separated. The aqueous layer was then extracted with methylene chloride (2 × 10 mL) and the organic layers were filtered on a Celite pad, collected and concentrated. Then a mixture of crude acid in tetrahydrofuran (10 mL) and 2N hydrogen chloride (5 mL) was heated for 16 h. After removing the solvents, the residue was extracted with ethyl acetate (3 × 20 mL) and water (10 mL) and the combined organic layers were washed with brine (2 × 20 mL), dried by magnesium sulfate, filtered and evaporated. To a stirred solution of the crude hydroxy δ-lactone in pyridine (2 mL) was added acetic anhydride (1 mL) and the mixture was stirred for 20 h at room temperature. The resulting mixture was poured into 2N hydrogen chloride (5 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried by magnesium sulfate, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate = 2/1) afforded 0.3 g (three steps 60%) of **2** as a colorless oil: IR (film) 1744 cm^{-1}; Electrospray-MS: $C_{18}H_{32}O_4$ *m/z* (%) = 313 (M^++1, 100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 6.7 Hz, 3H), 1.07-1.99 (m, 22H and 1.23 br s), 2.06 (s, 3H), 2.27-2.67 (m, 2H), 4.27-4.37 (m, 1H), 4.90-5.01 (m, 1H).

2-(4-Benzylbutyl)-undecan-1-ene (14)

To a stirred solution of methyltriphenylphosphonium iodide (5.0 g, 2.0 mmol) in dry tetrahydrofuran (20 mL) was added *n*-butyllitium (1.0 mL, 1.6 M, 1.6 mmol) at -78 °C. The orange red colored mixture was stirred at -78 °C for 1 h. Ketone **9** (0.5 g, 1.44 mmol) was added to the reaction mixture at -78 °C *via* a syringe and further stirred at -78 °C for 2 h. The reaction was quenched with aqueous saturated ammonium chloride (10 mL) and the mixture was extracted with diethyl ether (3 × 50 mL) and the combined organic layers were washed with brine (2 × 20 mL), dried by magnesium sulfate, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate = 20/1) afforded 450 mg (91%) of **14** as a colorless oil: IR (film) 2920 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 6.5 Hz, 3H), 1.24-1.70 (m, 22H and 1.24 br s), 1.90-2.10 (m, 4H), 3.46 (t, *J* = 6.4 Hz, 2H), 4.49 (s, 2H), 4.68 (s, 2H), 7.23-7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.96, 138.66, 128.34 (2x), 127.65 (2x), 127.48, 108.67, 72.87, 70.35, 36.05, 35.80, 31.93, 29.69, 29.65 (2x), 29.58, 29.48, 29.46, 29.36, 27.85, 24.35, 22.70, 14.13.

4-Benzylbutyl-4-undecanyl-2,2-dimethyl-[1,3]dioxolane (15)

To a solution of *exo*-olefin **14** (450 mg, 1.31 mmol) in tetrahydrofuran (10 mL) and *t*-butanol (3 mL) was added *N*-methylmorphorline-*N*-oxide (0.5 g, 2.2 mmol) in water (50%). The mixture was allowed to stir at room temperature for 10 min and then treated with the solution of 2% osmium tetraoxide in tetrahydrofuran (5 mL). After 3 h, to the mixture was added dilute sodium bisulfite solution (10%, 10 mL) and extracted with ethyl acetate (3× 20 mL). The organic phase was washed with brine, dried by magnesium sulfate, filtered and evaporated. Without purification, the crude diol (470 mg) and *p*-toluenesulfonic acid (20 mg) were dissolved in 2,2-dimethyoxypropane (10 mL) at room temperature for 30 min. The mixture was filtered on basic alumina and the filtrate concentrated under reduced pressure. Purification on silica gel (hexane/ethyl acetate = 10/1) afforded 465 mg (85%) of **15** as a colorless oil: Electrospray-MS: $C_{27}H_{46}O_3$ *m/z* (%) = 419 (M^++1, 6), 361 (100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 6.7 Hz, 3H), 1.20-1.70 (m, 32H and 1.24, 1.36 br s), 3.46 (t, *J* = 6.4 Hz, 2H), 3.71 (s, 2H), 4.48 (s, 2H), 7.23-7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.57, 128.35 (2x), 127.64 (2x), 127.50, 108.79, 83.57, 72.93, 72.91, 70.18, 37.33, 37.10, 31.91, 30.22, 30.18, 29.65 (2x), 29.63, 29.57, 29.35, 27.19, 27.16, 24.18, 22.69, 20.86, 14.13.

4-(2,2-Dimethyl-[1,3]dioxolane-4-yl-4-undecanyl)-butyraldehyde (16)

Compound **15** (450 mg, 1.07 mmol) was dissolved in ethyl acetate (30 mL) and to which was added 10% palladium on activated carbon (50 mg) as catalyst. Then hydrogen was bubbled into the mixture for 10 min, and stirring occurred at room temperature for 3 h. Filtration through a short plug of Celite and washing with ethyl acetate (20 mL) resulted in the desired alcohol. Purification on silica gel (hexane/ethyl acetate = 3/1) afforded 320 mg (92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J* = 6.6 Hz, 3H), 1.11-1.75 (m, 31H and 1.23, 1.35 brs), 3.63 (t, *J* = 6.5 Hz, 2H), 3.69 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.84, 83.55, 72.85, 62.71, 37.34, 36.99, 33.13, 31.89, 30.16, 29.64, 29.61, 29.59, 29.55, 29.33, 27.18, 27.11, 24.21, 22.67, 20.35, 14.11. Alcohol (300 mg, 0.91 mmol) in methylene chloride (10 mL) was added to a mixture of pyridinium chlorochromate (320 mg, 1.48 mmol) and Celite (1.0 g) in methylene chloride (10 mL). After being stirred at room temperature for 2 h, the mixture was diluted with ethyl acetate (20 mL) and filtered through a short silica gel column. The filtrate was washed with water (2× 10 mL), dried by magnesium sulfate, filtered and concentrated to produce crude aldehyde **16**. Purification on silica gel (hexane/ethyl acetate = 3/1) afforded **16** 247 mg (83%) as a colorless oil: IR (film) 2854, 2718 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J* = 6.6 Hz, 3H), 1.18-1.75 (m, 30H and 1.23, 1.35, 1.36 br s), 2.46-2.42 (m, 2H), 3.70 (d, *J* = 8.0 Hz, 2H), 3.73 (d, *J* = 8.0 Hz, 2H), 9.75 (t, *J* = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.26, 108.98, 83.25, 72.81, 44.11, 37.34, 36.57, 31.89, 30.13, 29.62, 29.60, 29.58, 29.53, 29.32, 27.19, 27.03, 24.27, 22.67, 16.78, 14.10.

Tanikolide (3)

Aldehyde **16** (238 mg, 0.73 mmol) was dissolved in carbon tetrachloride (4 mL), acetonitrle (4 mL) and water (6 mL) with vigorous stirring. Then sodium periodate (257 mg, 1.2 mmol) and ruthenium (III) chloride hydrate (5 mg) were added. The reaction was stopped after 6 h, diluted with methylene chloride (10 mL) and the organic layer was separated. The aqueous layer was then extracted with methylene chloride (2 × 10 mL) and the organic layers were filtered on a Celite pad, collected and concentrated. Then a mixture of crude acid in dichloromethane (10 mL) and *p*-toluenesufonic acid (10 mg) was stirred for 1 h. After removing the solvents, the residue was extracted with ethyl acetate (3 × 20 mL) and water (10 mL) and the combined organic layers were washed with brine (2 × 20 mL), dried by magnesium sulfate, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate = 1/1) afforded **3** 165 mg (80%) as a colorless oil: IR (film) 3424, 1723 cm^{-1}; Electrospray-MS: $C_{17}H_{32}O_3$ *m/z* (%) = 285 (M^++1, 100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J* = 6.3 Hz, 3H), 1.23 (br s, 18H), 1.51-1.95 (m, 6H), 2.46-2.50 (m, 2H), 2.53 (br s, 1H), 3.50 (d, *J* = 11.9 Hz, 1H), 3.62 (d, *J* = 11.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.99, 86.60, 67.43, 36.70, 31.88, 29.97, 29.76, 29.59, 29.58, 29.53, 29.45, 29.31, 26.58, 23.41, 22.66, 16.64, 14.10.

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Key Words

5-Hexadecanolide; 6-Acetoxy-5-hexadecanolide; Tanikolide; δ-Lactone; Pheromone; LD_{50}; Undecanal; 1-Bromoundecane; Wittig olefination;

Grignard addition.

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8. **1-Undecanyl-6,8-dioxa-bicyclo[3.2.1]octane** Electrospray-MS: $C_{17}H_{32}O_2$ *m/z* (%) = 285 (M^++17, 100), 267 (M^+-1, 20); ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.85 (t, *J* = 6.7 Hz, 3H), 1.15-1.95 (m, 26H and 1.23 br s), 3.40 (d, *J* = 6.8 Hz, 1H), 3.89 (d, *J* = 6.8 Hz, 1H), 5.49 (br s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) 102.65, 81.25, 72.36, 36.97, 32.36, 31.90, 30.87, 30.11, 29.62, 29.59, 29.52, 29.47, 29.33, 24.05, 22.67, 16.57, 14.10.