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Total Synthesis of (−)-Bitungolide F and Determination of Its Absolute Stereochemistry

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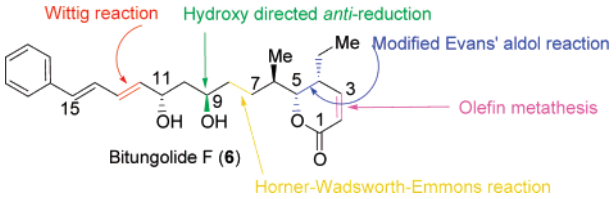

A highly convergent total synthesis of bitungolide F leading to the assignment of its absolute stereochemistry is described. The key steps include a Horner−Wadsworth−Emmons olefination to construct the C7−C8 bond, a Wittig reaction to introduce the conjugate *E*,*E*-olefinic moiety in the molecule, and finally a ring-closing metathesis reaction to construct the six-membered α,*β*-unsaturated *δ*-lactone of the molecule. Modified Evans's *syn*-aldol reaction, using Crimmins's protocol, was used to install the stereochemistries at the C4 and C5 centers. The stereochemistry at C9 was introduced by means of hydroxy-directed reduction of the C9 keto using Evans's protocol.

Among the marine organisms, marine sponges are considered to be one of the most important sources of pharmacologically active compounds.[1] *Theonella swinhoei* is one such marine sponge which produced a wide range of interesting biologically active compounds having fascinating structures.[2] As a result, sponges of the *T. swinhoei* family have attracted considerable attention of natural product chemists, synthetic organic chemists, as well as biologists over the years. In 2002, Tanaka et al. isolated a series of unique polyketides, bitungolide A−F (**1**−**6**),[3] from the Indonesian sponge *Theonella* cf. *swinhoei* (Figure 1). The structure of bitungolide A (**1**) was established by X-ray and the rest of the family by spectroscopic correlation. These compounds showed cytotoxic effects against 3Y1 rat normal fibroblast cells and inhibit dual-specificity phosphatase VHR. Due to their interesting biological activities and unique structural features, we became interested in the total synthesis of bitungolides. In this paper, we report the first asymmetric total synthesis of bitungolide F along with its absolute stereochemistry.

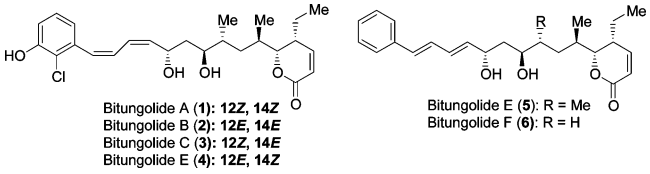

FIGURE 1. Structures of bitungolides.

Upon inspection of the structure of bitungolide F, we suggested (Scheme 1) that a Wittig reaction between aldehyde **8** and the carbanion obtained from **7** could install the conjugated (*E*,*E*)-diene in the molecule. Aldehyde **8** could be obtained by means of ring-closing metathesis of the diene **9**, which in turn could be obtained from **11** via **10** using stereoselective hydroxy-directed reduction of the C9 keto of **11** using Evans's protocol. We expected that compound **11** could be obtained through Horner−Wadsworth−Emmons reaction between the ketophosphonate **12** and the aldehyde **13**, which in turn could be synthesized from the known aldehyde **14** using a modified Evans's *syn*-aldol reaction.

Thus our synthesis commenced (Scheme 2) with the addition of (*Z*)-enolate, generated from **16**, using Crimmins's protocol[4] to the known aldehyde **14**[5] to give **17** with excellent diastereoselectivity (98:2 dr). Separation of the diastereomers by standard silica gel column chromatography gave the required **17** in 96% yield. Reductive removal of the chiral auxiliary from **17** with $LiBH_4$[6] in ether furnished the 1,3-diol compound **18** in 90% yield, which was protected as a *p*-methoxybenzylidine acetal **19** in 94% yield using the dimethyl acetal of *p*-methoxybenzaldehyde and a catalytic amount of CSA in CH_2Cl_2.[7] Compound **19** was converted to the aldehyde **13** in two steps. TBDPS deprotection of **19** with TBAF gave primary alcohol **20**, which was oxidized with Dess−Martin periodinane[8] to give the required aldehyde **13**.[9]

Synthesis of the ketophosphonate **12** (Scheme 3) started from the known diol compound **22**, which was prepared easily from (−)-malic acid (**21**) according to reported procedures.[10a,b] Selective protection of the primary hydroxy group as TBDPS ether and secondary hydroxy group as TES ether gave the compound **24**,[10c] which on treatment with lithiated methyldimethyl phosphonate afforded ketophosphonate **12** in 81% yield.

Having both the fragments **12** and **13** in hand, the stage was set for their crucial coupling via Horner−Wadsworth−Emmons reaction.[11] Thus the reaction between the aldehyde **13** and the

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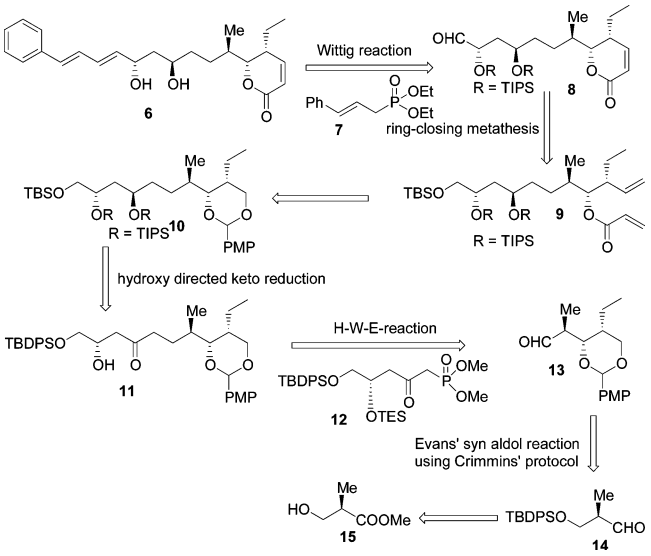
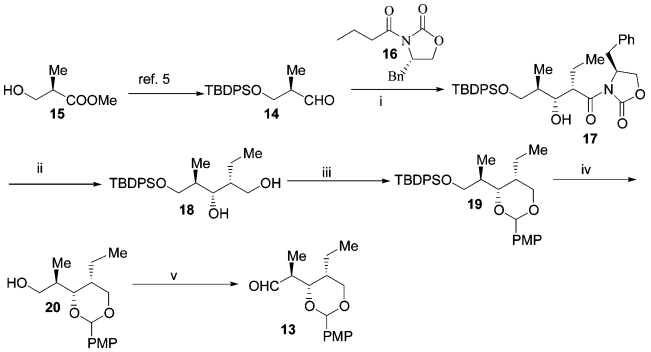
SCHEME 1. Retrosynthetic Analysis of Bitungolide F (6)

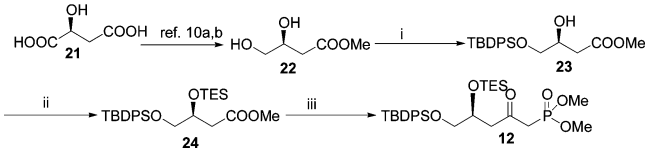


SCHEME 2. Synthesis of Aldehyde 13[a]



[a] Reagents and conditions: (i) **16**, $TiCl_4$, (−)-sparteine, 0 °C, CH_2Cl_2, 20 min then **14**, 0 °C, 10 min, 96%; (ii) $LiBH_4$, Et_2O, cat. H_2O, 0 °C, 90%; (iii) PMP-acetal, CSA (cat.), CH_2Cl_2, 0 °C to rt, 12 h, 94%; (iv) TBAF, THF, 0 °C, 12 h, 91%; (v) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 1 h, 90%.

SCHEME 3. Synthesis of Ketophosphonate 12[a]



[a] Reagents and conditions: (i) TBDPSCl, Et_3N, cat. DMAP CH_2Cl_2, 0 °C to rt, 2 h, 98%; (ii) TESCl, Et_3N, DMAP (cat.), CH_2Cl_2, 0 °C to rt, 2 h, 81%; (iii) *n*-BuLi, $MePO(OMe)_2$, THF, −78 °C to rt, 81%.

ketophosphonate **12** (Scheme 4) using LiCl and DIPEA in acetonitrile afforded compound **25** in 98% yield. Reduction of the double bond under hydrogenation conditions using Pd−C as a catalyst in the presence of a catalytic amount of ammonium acetate in EtOAc at room temperature afforded keto compound **26**.[12] For the hydroxy-directed stereoselective reduction of the C9 keto functionality, it was necessary to remove the TES protection group, and its selective deprotection in the presence of primary TBDPS was achieved using a catalytic amount of CSA in CH_2Cl_2−MeOH (4:1) at 0 °C to give **11** in 87% yield.

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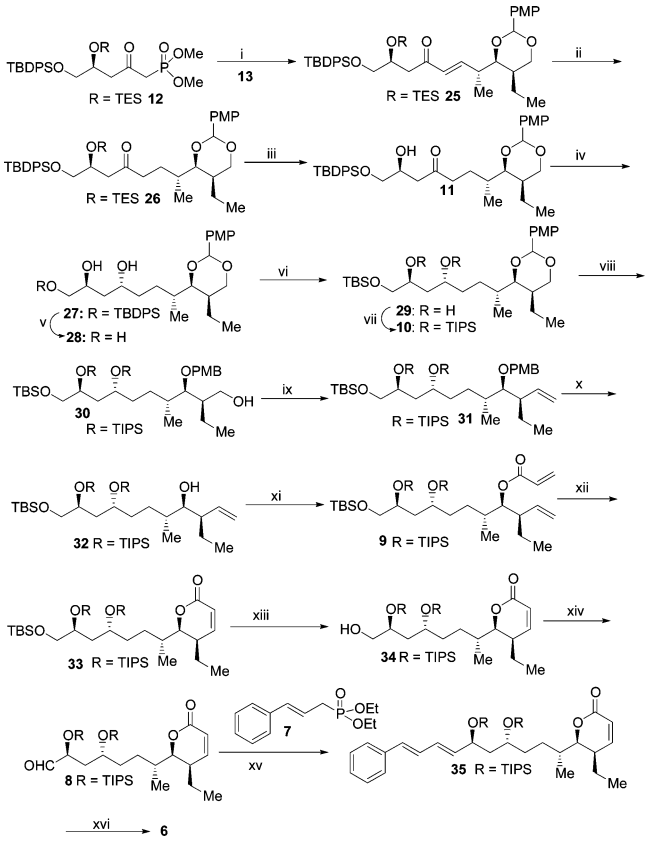
SCHEME 4. Coupling of Aldehyde 13 with the Ketophosphonate 12 and Completion of the Synthesis[a]



[a] Reagents and conditions: (i) LiCl, DIPEA, rt, 30 min, then **13**, 12 h, 98%; (ii) Pd/C, EtOAc, NH_4OAc (cat.), rt, 2 h, 95%; (iii) CSA (cat.), CH_2Cl_2/MeOH (4:1), 0 °C, 10 min, 87%; (iv) $Me_4NBH(OAc)_3$, AcOH/acetone (1:1), −20 °C, 10 h, 92%; (v) TBAF, THF, 0 °C to rt, 12 h, 95%; (vi) TBSCl, Et_3N, DMAP (cat.), CH_2Cl_2, 0 °C to rt, 2 h, 87%; (vii) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 0.5 h, 95%; (viii) DIBAL-H, CH_2Cl_2, −40 to 0 °C, 2 h, 92%; (ix) (a) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 30 min, (b) PPh_3=CH_2, ether, 0 °C, 10 min, 96% over two steps; (x) DDQ, $CHCl_3$/pH 7 buffer (20:1), 0 °C to rt, 30 min, 91%; (xi) acryloyl chloride, Et_3N, 0 °C to rt, 30 min, 65%; (xii) 10 mol % of Grubbs's first-generation catalyst, CH_2Cl_2, 50 °C, 24 h, 85% (based on recovered SM); (xiii) CSA (cat.), CH_2Cl_2/MeOH (4:1), 0 °C, 24 h, 80%; (xiv) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 2 h, 91%; (xv) **7**, NaHMDS, THF, 0 °C, 20 min, then **8**, rt, 2 h, 52%; (xvi) HF/Py, THF, rt, 24 h, 71%.

Stereoselective hydroxy-directed 1,3-*anti*-reduction of the keto group following Evans's protocol[13] using $[Me_4NBH(OAc)_3]$ in AcOH/acetone (1:1) at −20 °C for 10 h afforded 1,3-*anti*-diol compound **27** in 97% yield with excellent diastereoselectivity (>20:1 in favor of *anti*). Separation of the minor isomer by standard silica gel chromatography afforded pure **27** (92% yield), which on routine protecting group manipulations furnished compound **10**. Reductive opening of the PMP-acetal of **10** with DIBAL- H[14] in CH_2Cl_2 at 0 °C from the less hindered side gave the primary alcohol **30**, which on oxidation followed by Wittig reaction with Ph_3P=CH_2 in ether at 0 °C afforded compound **31** in 88% yield over three steps. PMB deprotection with DDQ[15] under buffer conditions furnished secondary alcohol **32** in 91% yield, which on acylation with acryloyl chloride gave the

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bisolefinic compound **9**. Ring-closing metathesis reaction[16] of **9** with Grubbs's first-generation catalyst furnished six-membered α,β-unsaturated δ-lactone **33** in 85% yield (based on recovered starting material). Selective deprotection of the TBS group using catalytic CSA in CH_2Cl_2/MeOH (4:1) at 0 °C for 24 h afforded the primary alcohol **34**, which on oxidation with DMP gave aldehyde **8**. Crucial Wittig olefination between the aldehyde **8** and the carbanion obtained from **7**[17] smoothly afforded the desired (*E*,*E*)-diene **35** ($^3J_{12-13}$ = 15.5 Hz) as the only isolable product in 52% yield. Finally, deprotection of the TIPS protecting groups using HF·Py in THF furnished bitungolide F in 71% yield, whose spectral data (^{1}H and ^{13}C) were in good agreement with the literature value. The specific rotation of synthetic bitungolide F ($[\alpha]^{25}_D = -42.8$, $c = 0.035$, $CHCl_3$) is comparable in magnitude to that of natural bitungolide F ($[\alpha]^{25}_D = +43.0$, $c = 0.85$, $CHCl_3$) but of opposite sign. Therefore, the absolute stereochemistry of the natural bitungolide F is the enantiomer of **6**, and the absolute configuration of the stereocenters is (4*S*,5*S*,6*S*,9*S*,11*R*).

In conclusion, we have achieved the first asymmetric total synthesis of (−)-bitungolide F in a convergent fashion and established the absolute stereochemistry of the natural product. Currently, we are working on the total synthesis of other bitungolides, which will be reported in due course.

Experimental Section

(2*S*,5*E*,7*S*)-1-[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy-7-[(4*S*,5*S*)-5-ethyl-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]-2-[(1,1,1-triethylsilyl)oxy]-5-octen-4-one (25). To a solution of compound **20** (3.26 g, 10.5 mmol) in CH_2Cl_2 (35 mL) were added $NaHCO_3$ (2.98 g, 21.0 mmol) and Dess−Martin periodinane (DMP) (6.68 g, 15.75 mmol). The reaction mixture was stirred for 1 h at room temperature under nitrogen atmosphere. Saturated $Na_2S_2O_3$ (25 mL) and $NaHCO_3$ (25 mL) were then added, and the biphasic mixture was stirred for 15 min and extracted with 50% EtOAc in petroleum ether (2 × 100 mL). The combined organic phase was washed with water (75 mL) and brine (75 mL), dried (Na_2SO_4), and concentrated in vacuo. The aldehyde **13** (R_f = 0.64, 10% EtOAc in petroleum ether), thus obtained, was directly used after flash chromatography (3.2 g, 99%) for the next reaction without further characterization.

To a stirred solution of **12** (8.98 g, 15.75 mmol) in dry CH_3CN were added LiCl (668 mg, 15.75 mmol) and DIPEA (28.0 mL, 157.5 mmol) sequentially at room temperature. After 30 min, aldehyde **13** (3.2 g, 10.3 mmol in CH_3CN) was added to the reaction mixture under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 12 h. CH_3CN was evaporated on a rotary evaporator, and the residue was diluted with EtOAc (200 mL) and washed with a saturated aqueous solution of NH_4Cl (50 mL), water (50 mL), and brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 12−15% EtOAc in petroleum ether) afforded pure compound **25** (7.79 g, 98%) as colorless oil: $[\alpha]^{22}_D = +28.33$ (*c* 3.65, $CHCl_3$); IR (neat) ν_{max} 2956, 2877, 1670, 1462, 1247, 1113, 741, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.66−7.54 (m, 4H), 7.40−7.25 (m, 6H), 7.02−6.72 (m, 4H), 6.12 (dd, *J* = 7.8, 16.4 Hz, 1H), 5.36 (m, 2H), 4.32−4.20 (m, 1H), 3.91−3.81 (m, 1H), 3.75 (s, 3H), 3.58 (dd, *J* = 4.7, 10.1 Hz, 1H), 3.51−3.36 (m, 3H), 2.92−2.55 (m, 3H), 1.95−1.73 (m, 1H), 1.53−1.20 (m, 2H), 1.01 (s, 9H), 0.99−0.95 (m, 3H), 0.85−0.73 (m, 12H), 0.43 (q, *J* = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.1, 159.8, 150.1, 135.5, 133.4, 131.2, 130.7, 129.6, 127.6 127.2, 113.5, 101.6, 83.6, 69.5, 69.1, 67.7, 55.2, 45.1, 37.5, 36.9, 26.8, 19.2, 16.2, 14.2, 11.9, 6.7, 4.7; HRMS (ESIMS) calcd for $C_{43}H_{62}O_6NaSi_2$ $[M + Na]^+$ 753.3982, found 753.4005.

(2*S*,4*S*,6*S*)-1-[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy-6-[(4*S*,5*S*)-5-ethyl-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]heptane-2,4-diol (27). A solution of compound **11** (515 mg, 0.83 mmol) in acetone/AcOH (1:1, 4 mL) was cooled to −20 °C, and then $Me_4NBH(OAc)_3$ was added (548 mg, 2.08 mmol) to it and stirred at the same temperature for 10 h. The reaction was monitored by TLC. After disappearance of the starting material, the reaction mixture was quenched with a saturated aqueous solution of sodium potassium tartarate and stirred at room temperature for 0.5 h, then diluted with EtOAc (30 mL). The organic layer was washed with $NaHCO_3$ (2 × 10 mL), water (15 mL), and brine (15 mL), dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (SiO_2, 20−25% EtOAc in petroleum ether eluant) gave pure compound **27** (502 mg, 97%) as colorless syrup: $[\alpha]^{27}_D = +11.38$ (*c* 1.2, $CHCl_3$); IR (neat) ν_{max} 3750, 2930, 2361, 1516, 1462, 1248, 826, 772 cm^{-1}; ^{1}H NMR ($CDCl_3$,3 00 MHz) δ 7.69−7.63 (m, 4H), 7.44−7.36 (m, 8H), 6.87 (d, *J* = 9.0 Hz, 2H), 5.44 (s, 1H), 4.28 (m, 1H), 4.06−3.96 (m, 1H), 3.91−3.83 (m, 2H), 3.77 (s, 3H), 3.64 (dd, *J* = 4.5, 9.8 Hz, 1H), 3.58−3.46 (m, 2H), 1.87−1.72 (m, 4H), 1.65−1.30 (m, 6H), 1.07 (s, 9H), 1.00 (t, *J* = 7.6 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.8, 135.4, 133.1, 131.5, 129.7, 127.8, 127.2, 113.5, 101.8, 84.9, 69.3, 68.9, 67.8, 55.1, 38.9, 37.1, 34.5, 33.5, 29.7, 28.9, 26.7, 19.1, 16.2, 14.4, 11.9; HRMS (ESIMS) calcd for $C_{37}H_{52}O_6NaSi$ $[M + Na]^+$ 643.3430, found 643.3429.

(5*S*,6*S*)-6-(1*S*,3*S*,5*S*)-6-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-1-methyl-3,5-di[(1,1,1-triisopropylsilyl)oxy]hexyl-5-ethyl-5,6-dihydro-2*H*-2-pyranone (33). A solution of compound **9** (172 mg, 0.233 mmol) in dry degassed CH_2Cl_2 was treated with Grubbs's first generation catalyst (18.9 mg, 0.023 mmol) at room temperature under nitrogen atmosphere. The resulting pale purple color solution was heated to reflux (ca. 50 °C) for 24 h. The solvent was evaporated in vacuo. Purification of the crude residue by column chromatography (SiO_2, 7−9% EtOAc in petroleum ether eluant) gave pure compound **33** (113 mg, 85% based on recovered starting material) as clear oil: $[\alpha]^{27}_D = -68.7$ (*c* 2.25, $CHCl_3$); IR (neat) ν_{max} 2927, 2864, 2337, 1724, 1462, 1252, 1217, 1058, 761, 675 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.01 (dd, *J* = 6.4, 9.7 Hz, 1H), 6.01 (d, *J* = 9.7 Hz, 1H), 3.95 (dd, *J* = 3.1, 7.3 Hz, 1H), 3.90−3.78 (m, 2H), 3.59 (dd, *J* = 4.4, 9.9 Hz, 1H), 3.48 (dd, *J* = 6.0, 9.9 Hz, 1H), 2.28 (m, 1H), 1.99−1.78 (m, 3H), 1.74−1.59 (m, 3H), 1.58−1.44 (m, 3H), 1.08−1.01 (m, 42H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.90−0.85 (m, 12H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.7, 150.7, 121.1, 84.3, 71.4, 70.3, 68.1, 43.7, 36.7, 34.6, 33.9, 27.7, 25.9, 20.1, 18.3, 18.2, 14.8, 12.8, 12.7, 11.0, −5.5; HRMS (ESIMS) calcd for $C_{39}H_{80}O_5NaSi_3$ $[M + Na]^+$ 735.5211, found 735.5201.

(5*S*,6*S*)-5-Ethyl-6-(1*S*,3*S*,5*S*,6*E*,8*E*)-1-methyl-9-phenyl-3,5-di[(1,1,1-triisopropylsilyl)oxy]-6,8-nonadienyl-5,6-dihydro-2*H*-2-pyranone (35). To a solution of compound **34** (7 mg, 0.012 mmol) in CH_2Cl_2 (1 mL) were added $NaHCO_3$ (3.3 mg, 0.023 mmol) and Dess−Martin periodinane (DMP) (7.5 mg, 0.017 mmol). The reaction mixture was stirred for 1 h at room temperature under nitrogen atmosphere. Saturated $Na_2S_2O_3$ (1 mL) and $NaHCO_3$ (0.2 mL) were then added, and the biphasic mixture was stirred for 15 min and extracted with 40% EtOAc in petroleum ether (2 × 10 mL). The combined organic phase was washed with water (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo to yield the aldehyde **8** (6 mg, 91%) which was directly carried to the next step without further purification or characterization. To a solution of compound **7** (30 mg, 0.12 mmol) in dry THF (3 mL)

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was added NaHMDS (1.0 M solution in THF, 0.1 mL, 0.1 mmol) at 0 °C. After stirring for 20 min at 0 °C, the reaction mixture turned into a dark red color, then aldehyde **8** (6 mg, 0.011 mmol) in THF (1 mL) was added at the same temperature. The reaction was continued for 0.5 h at the same temperature, then warmed to room temperature and stirred for 1 h. The reaction was quenched with a saturated aqueous NH_4Cl solution (3 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with brine (2 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2, 7% EtOAc in petroleum ether) provided compound **35** (4 mg, 52%) as a colorless oil: $[\alpha]^{27}_D = -32.9$ (*c* 0.33, $CHCl_3$); IR (neat) ν_{max} 2920, 2848, 1710, 1465, 972, 771 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.43−7.36 (m, 2H), 7.33−7.28 (m, 2H,), 7.21 (m, 1H), 7.04 (dd, J = 6.7, 9.6 Hz, 1H), 6.75 (dd, J = 10.4, 15.5 Hz, 1H), 6.53 (d, J = 15.5 Hz, 1H), 6.29 (dd, J = 10.4, 15.5 Hz, 1H), 6.03 (d, J = 9.6 Hz, 1H), 5.79 (dd, J = 8.1, 15.5 Hz, 1H), 4.33 (m, 1H), 3.98 (dd, J = 3.0, 10.4 Hz, 1H), 3.86 (m, 1H), 2.31 (m, 1H), 2.01−1.90 (m, 3H), 1.86−1.73 (m, 3H), 1.70−1.42 (m, 3H), 1.08−1.04 (m, 42H), 0.93 (t, J = 7.4 Hz, 3H), 0.89 (d, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.6, 150.7, 137.5, 137.3, 132.1, 130.2, 128.5, 128.5, 127.5, 127.4, 126.4, 126.3, 121.0, 84.3, 71.3, 69.8, 46.7, 36.7, 34.0, 33.8, 29.7, 29.3, 27.6, 22.7, 20.1, 18.3, 18.2, 18.1, 14.9, 12.8, 12.8, 12.6, 12.5, 11.0; HRMS (ESIMS) calcd for $C_{42}H_{72}O_4NaSi_2$ $[M + Na]^+$ 719.4866, found 719.4875.

Bitungolide-F (6). To a solution of compound **35** (4 mg, 0.005 mmol) in dry THF (1 mL) was added HF·py complex (40%, 0.1 mL) at 0 °C, and the mixture was stirred at room temperature for 18 h. The reaction mixture was cautiously poured into an aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined extracts were washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 45−50% EtOAc in petroleum ether) afforded compound **6** (1.5 mg, 71%) as a hygroscopic yellow solid: $[\alpha]^{25}_D = -42.8$ (*c* 0.035, $CHCl_3$); IR (neat) ν_{max} 3506, 2920, 1706, 1460, 965, 771, 637 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40 (d, J = 7.6 Hz, 2H), 7.31 (t, J = 7.6 Hz, 2H), 7.22 (t, J = 7.6 Hz, 1H), 7.07 (dd, J = 6.1, 9.8 Hz), 6.78 (dd, J = 10.4, 15.3 Hz), 6.56 (d, J = 15.3 Hz, 1H), 6.46 (dd, J = 10.4, 15.3 Hz, 1H), 6.04 (d, J = 9.8 Hz, 1H), 5.90 (dd, J = 6.1, 15.3 Hz, 1H), 4.59 (m, 1H), 4.00 (dd, J = 3.1, 10.5 Hz, 1H), 3.98 (m, 1H), 2.33 (m, 1H), 1.96−1.84 (m, 2H), 1.81−1.74 (m, 2H), 1.69−1.61 (m, 2H), 1.50−1.42 (m, 2H), 1.30 (m, 1H), 0.95 (t, J = 7.6 Hz, 3H), 0.91 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.8, 151.1, 137.2, 136.0, 132.7, 130.4, 128.2(2), 127.5, 126.4(2), 120.9, 84.4, 70.3, 69.4, 42.6, 36.6, 34.5, 33.6, 28.6, 20.1, 14.9, 11.0; HRMS (ESIMS) calcd for $C_{24}H_{32}O_4Na$ $[M + Na]^+$ 407.2198, found 407.2194.

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Supporting Information Available: Experimental procedures, spectral data for compounds **17**−**20**, **12**, **26**, **11**, **28**, **29**, **10**, **30**−**32**, **9**, and **34**, and the copies of ^1H and ^{13}C NMR spectra for compounds **17**−**20**, **12**, **25**, **26**, **11**, **27**−**29**, **10**, **30**−**32**, **9**, **33**−**35**, and **6** and natural bitungolide F. This material is available free of charge via the Internet at http://pubs.acs.org.

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