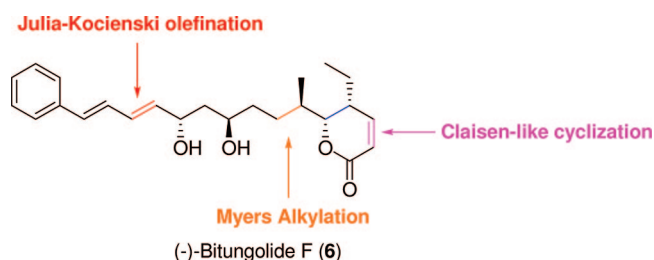


Total Synthesis of (–)-Bitungolide F

Yingpeng Su,[†] Yanfen Xu,[†] Junjie Han,[†] Jiyue Zheng,[†] Jing Qi,[†] Tuo Jiang,[†] Xinfu Pan,[†]
and Xuegong She^{*,†,‡}Department of Chemistry, State Key Laboratory of Applied Organic Chemistry, Lanzhou University,
Lanzhou 730000, P. R. China, and State Key Laboratory for Oxo Synthesis and Selective Oxidation,
Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, P. R. China

shexg@lzu.edu.cn

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An efficient total synthesis of (–)-bitungolide F (6) in 17 steps and 20.1% yield is described herein. Key steps involve a Myers asymmetric alkylation to introduce the C6 methyl with proper stereochemistry, a Claisen-like cyclization to construct the α,β -unsaturated δ -lactone and a Julia–Kocienski olefination to assemble the conjugated diene moiety.

Introduction

Natural products possessing α,β -unsaturated δ -lactone moieties often exhibit useful pharmacological properties, which include antitumor, antibacterial, and antiproliferative effects.^{1–4} Bitungolides A–F (1–6) (Figure 1) were isolated by Tanaka and co-workers from the Indonesian sponge *Theonella* of *swinhoei* in 2002.⁵ Structurally, these compounds incorporate a 5'-ethyl substituent on the α,β -unsaturated δ -lactone moiety

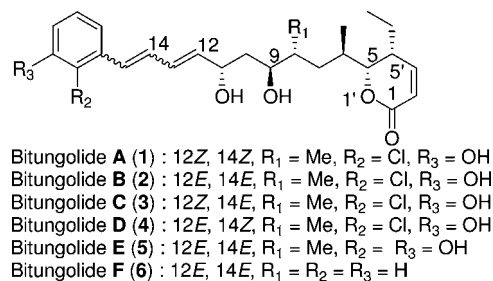


FIGURE 1. Structures of the bitungolides.

as well as an *anti* 1,3-diol unit and two conjugated double bonds attached to a substituted arene. The absolute stereochemistry of bitungolide A (1) was determined unambiguously by X-ray diffraction. The structures of analogues 2–6 were assigned by spectral correlations to 1.

These compounds constitute a new class of *Theonella* metabolites that exhibit cytotoxic effects against 3Y1 rat normal fibroblast cells and inhibition toward dual-specificity phosphatase VHR. In 2008, Ghosh and co-workers reported the first asymmetric total synthesis of (–)-bitungolide F (6), which confirmed its absolute stereochemistry.⁶ Shortly afterward, we published an enantioselective synthetic approach toward the

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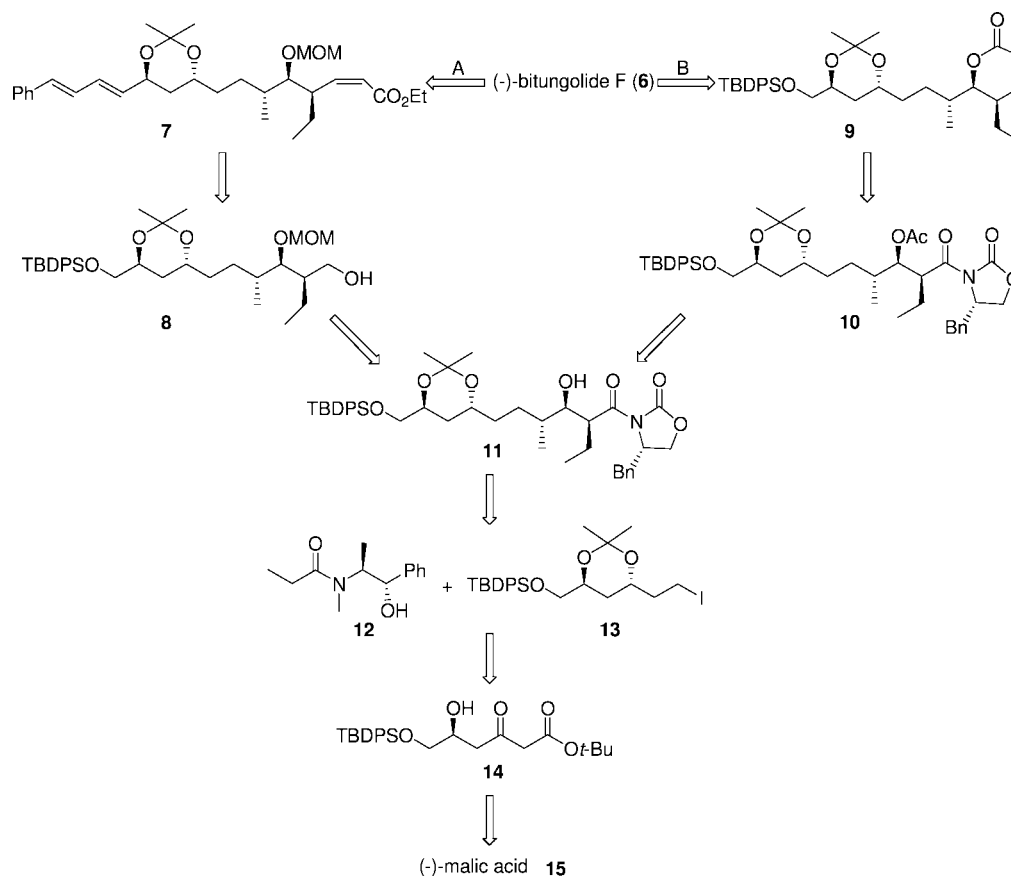
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SCHEME 1. Retrosynthetic Analysis



C1–C12 fragment of bitungolides A–E (**1–5**).⁷ As a continuation of our previous synthesis efforts, herein we report a detailed description of our asymmetric synthesis of (–)-bitungolide F (**6**). Our route involves an uncommon Claisen-like cyclization and a Julia–Kocienski olefination as key features.

Synthetic Strategy. Bitungolide F (**6**) bears a 5'-ethyl substituted α,β -unsaturated δ -lactone moiety and a carbon chain embodying three stereocenters. Construction of closely spaced stereogenic centers was a challenging problem, especially for the δ -lactone ring. Though ring-closing metathesis⁸ offered wonderful advantages in forming *cis*-olefins in six-membered rings, we intended to utilize other easily accessed methods for construction of the α,β -unsaturated δ -lactone moiety.

According to our earlier synthetic experience with the C1–C12 fragment of bitungolides A–E (**1–5**),⁷ two different routes of ring closure including an acid-promoted cyclization of *cis*- α,β -unsaturated ester **7** and an uncommon Claisen-like cyclization⁹ of imide acetate **10** were proposed (Scheme 1). On the basis of the postulation above, we targeted functionalized imide alcohol **11** as the common precursor of **7** and **10**. Intermediate **11** could be produced from (–)-malic acid **15** via

a sequence of chirality-induced manipulations involving hydroxyl-directed reduction,¹⁰ a Myers asymmetric alkylation,¹¹ and an Evans asymmetric aldol reaction.¹²

Results and Discussion

Synthesis of Acetonide Iodide 13. The synthesis of acetonide iodide **13** began with known diol **16**, which was obtained from commercially available (–)-malic acid **15** via a known two-step operation (Scheme 2).¹³ The resulting primary hydroxyl group was selectively protected as β -hydroxyl silyl ether **17** in 90% yield. Claisen condensation of silyl ether **17** with 4 equiv of the corresponding enolate of $\text{CH}_3\text{COO}t\text{-Bu}$ afforded δ -hydroxyl- β -keto ester **14** in 85% yield.¹⁴ Hydroxyl-directed 1,3-*anti* reduction of the carbonyl group with $\text{Me}_4\text{NBH}(\text{OAc})_3$ in AcOH and CH_3CN (1:1) at -20°C for 10 h furnished dihydroxyl ester **18** in 95% yield¹⁰ in a 96:4 diastereoselectivity. Next, diol **18** was converted into acetonide **19** with 2,2-

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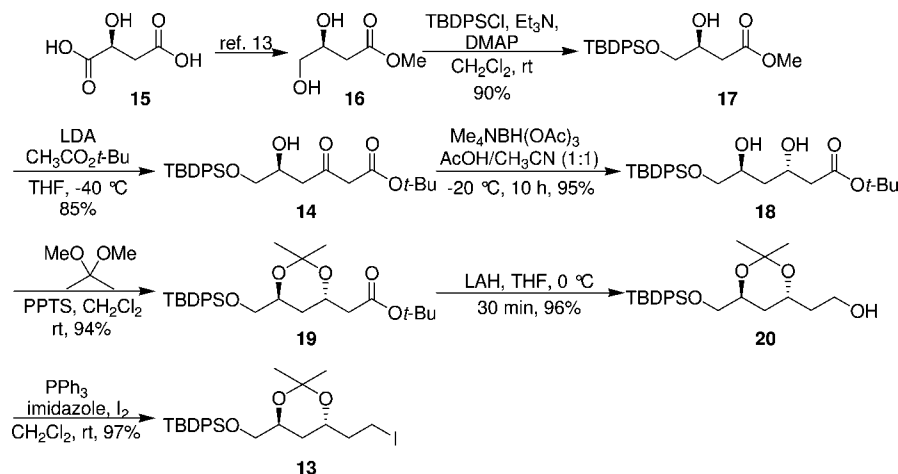
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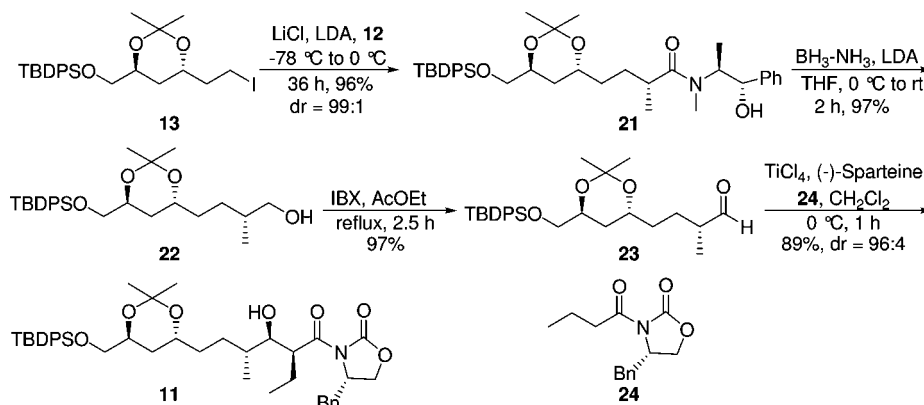
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SCHEME 2. Synthesis of Iodide 13



SCHEME 3. Synthesis of Alcohol 11



dimethoxypropane in 94% yield. In the reduction of ester **19** to alcohol **20**, the desired alcohol was obtained in low yield (30%) accompanied by desilylated byproduct when 1.5 equiv of LiAlH_4 was used. After many trials, 4 equiv of LiAlH_4 at 0 °C for 30 min was optimal, minimizing desilylation and generating alcohol **20** in 96% yield. Iodination of alcohol **20** using Appel's conditions¹⁵ gave iodide **13** in 97% yield. Iodide **13** was found to be very sensitive and decomposition often occurred at room temperature, and thus it was used immediately upon formation or stored at –20 °C in the absence of light.

Synthesis of Key Intermediate 11. Our route to imide alcohol **11** from iodide **13** is outlined in Scheme 3. Introduction of the new chiral center in amide **21** was achieved via a standard Myers asymmetric alkylation¹¹ in which pseudoephedrine propionate **12** was coupled to iodide **13** to generate amide **21** in both excellent yield (96%) and diastereoselectivity (99:1). Cleavage of the auxiliary group of **21** by LDA and borane–ammonia complex successfully led to the formation of alcohol **22**. Alcohol **22** was oxidized to aldehyde **23** using IBX/ EtOAc ¹⁶ instead of IBX/ DMSO ¹⁷ due to easier laboratory operation and a more reliable yield. The crude aldehyde **23** from the IBX/ EtOAc oxidation could be utilized directly for further reaction without column purification or distillation. Subjection of aldehyde **23** to the Evans asymmetric aldol reaction¹² under Crimmins

conditions¹⁸ efficiently constructed the *syn* configuration of the neighboring stereocenters in imide alcohol **11** in 89% yield.

Initial Synthesis Efforts toward Bitungolide F: Acid-Promoted Cyclization (Route A, Scheme 4). MOM-protection of the free hydroxyl group of imide alcohol **11** generated MOM ether **25** in 92% yield. Treatment of **25** with NaBH_4 in $\text{THF}/\text{H}_2\text{O}$ resulted in cleavage of the Evans template and furnished alcohol **8** (90% yield).¹⁹ Oxidation of **8** with IBX/ EtOAc provided aldehyde **26**, which was subjected to Horner–Wadsworth–Emmons olefination using ethyl (di-*o*-tolylphosphono)acetate²⁰ to give *Z*-enoate **27**. Desilylation of ester **27** produced primary alcohol **28**. DMP oxidation²¹ followed by a Horner–Emmons reaction (Takacs modified procedure²²) with **29** was supposed to result in the desired precursor **7**. However, to our surprise, an unexpected epimerization at C11 occurred. The chemical shift of the acetal carbon was δ 98.5 ppm in its ¹³C NMR spectrum, indicating the product should be assigned as *syn*-1,3-diol **30** according to literature precedent.²³ We had hoped to obtain *epi*-bitungolide **F** **31** for subsequent study of bioactivity versus structure. Unfortunately, treatment of **30** with

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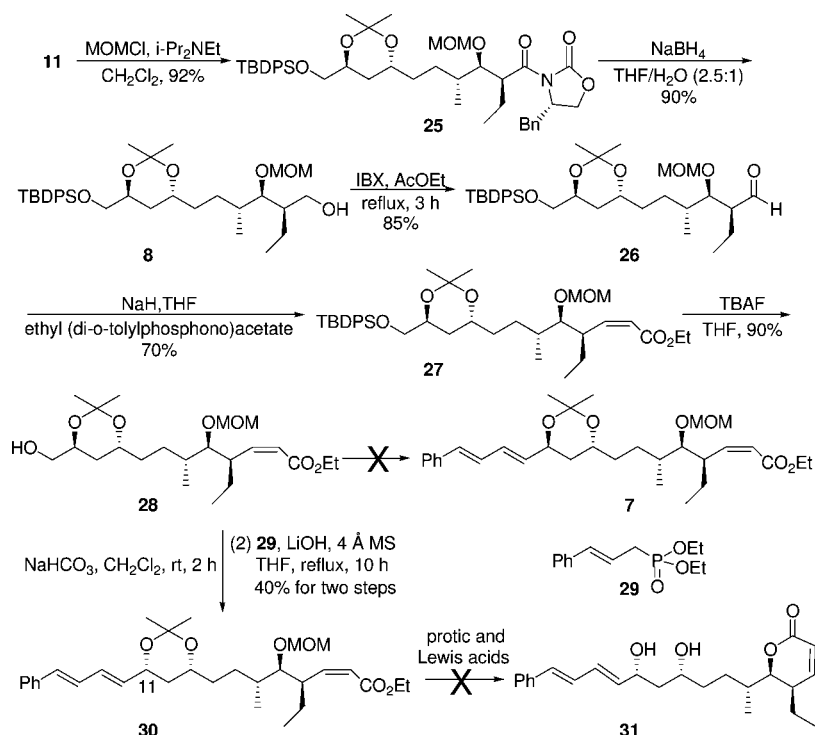
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SCHEME 4. Unsuccessful Route towards Bitungolide F



various protic and Lewis acids (e.g., aq HCl,²⁴ PPTS,²⁵ Dowex-500W (H⁺),²⁶ TMSBr, TMSI,²⁷ AlCl₃/NaI,²⁸ and AcCl/EtOH²⁹) failed to effect the desired cyclization to **31**. Therefore, an alternative route to finish bitungolide F was undertaken.

Completed Synthesis of (–)-Bitungolide F (6): Uncommon Claisen-Like Cyclization (Route B, Scheme 5). In order to prepare potential substrate **10** for the uncommon Claisen-like cyclization, the free hydroxyl group in Evans adduct **11** was acetylated to afford imide acetate **10**. Gratifyingly, treatment of **10** with 4 equiv of potassium hexamethyldisilazide at –78 °C led to rapid expulsion of the oxazolidinone, giving β -keto lactone **32** in 97% yield.⁹ It is noteworthy to mention that an excellent yield could only be obtained by appropriate laboratory work-ups: extracts must be maintained under neutral conditions (pH 6–7). The keto lactone **32** was easily converted into the enol triflate **33** in 93% yield with Tf₂O and Et₃N. Three equivalents of Et₃N was necessary to prevent possible deaceta-

lation. Reductive removal of the enol triflate with Pd(PPh₃)₄, Et₃N, and Et₃SiH³⁰ produced α,β -unsaturated δ -lactone **9** in 96% yield. In this process, the addition of Et₃N was indispensable; otherwise, a desilylation took place.

With lactone **9** in hand, we intended to construct the *trans* C12–C13 double bond via a Julia–Kocienski olefination. Deprotection of silyl ether **9** was explored using a suitable fluoride source. However, treatment of **9** with TBAF generated the desired alcohol **34** in 39% yield along with an unidentified byproduct. Other reagents such as NH₄F or NH₄F/Et₃N also failed. Finally, we found that utilization of 20 equiv of Et₃N·3HF³¹ and 30 equiv of Et₃N for TBDPS deprotection gave alcohol **34** in 97% yield. Then IBX/EtOAc oxidation of alcohol **34** led to the corresponding aldehyde, which was subjected to Julia–Kocienski olefination coupling³² with BT-sulfone **35**. In the formation of olefin **36**, several bases (e.g., LiHMDS, LiHMDS/HMPA, KHMDS, or LDA) were tested at –78 °C to rt in THF (Table 1). We found that utility of LiHMDS gave the most favorable *E/Z* (1.9/1) ratio. To our delight, mixtures with unfavorable *E/Z* ratios could be converted into the desired compound **36** in toluene at 110 °C (*E/Z* = 5:1 by ¹H NMR), while other regular methods (e.g., PhSH/AIBN, *h* ν or I₂/hexane reflux) for converting the configuration of olefins resulted in complex products.

Treatment of compound **36** with 50% aqueous TFA removed the acetone protecting group,³³ producing bitungolide F (**6**).

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SCHEME 5. Synthesis of Bitungolide F

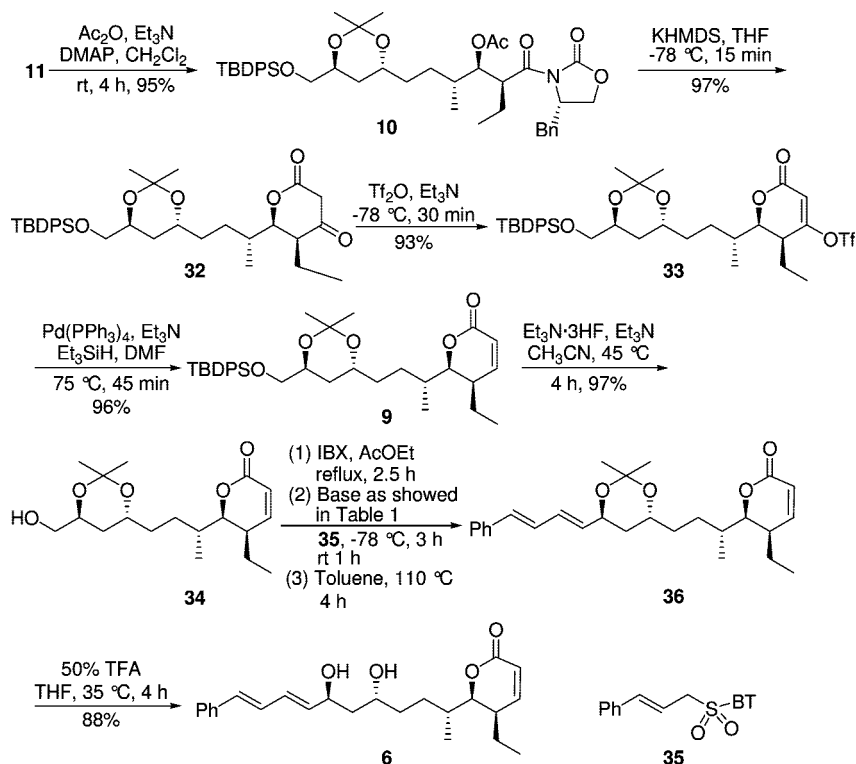


TABLE 1. Condition Optimization of Julia–Kocienski Olefination

base	LiHMDS	LiHMDS/HMPA	KHMDS	LDA
<i>E/Z</i>	1.9/1	1/2.4	1/5	1.6/1

Our synthetic bitungolide F (**6**) was identical in all respects (^1H and ^{13}C NMR, MS, IR) to the natural product reported by Tanaka's group,⁵ except for its optical rotation, which had the opposite sign but a similar absolute value ($[\alpha]_{\text{D}}^{20} = -49$, c 0.50, CHCl_3 ; lit. $[\alpha]_{\text{D}} = +43.0$, c 0.85, CHCl_3) to the natural product. Our work further confirms the absolute stereochemistry of bitungolide F as reported by Ghosh and co-workers.⁶

Conclusion

The total synthesis of (–)-bitungolide F (**6**) was completed in 17 steps and 20.1% overall yield from commercially available diol **16**. The required stereochemical configuration at C9, C6, C5, and C4 in (–)-bitungolide F (**6**) were secured, respectively, via hydroxyl-directed 1,3-*anti* reduction, a Myers alkylation, and an Evans *syn*-aldol reaction. A significant feature in this synthetic venture concerned efficient construction of the α,β -unsaturated δ -lactone moiety by an uncommon Claisen-like cyclization, while the *trans* C12–C13 double bond was assembled by Julia–Kocienski olefination. This work presents a highly efficient method for the preparation of bitungolides. The synthesis of bitungolides A–E is under investigation in our laboratory.

Experimental Section

Synthesis of Dihydroxyl Ester 18 from β -Hydroxy Keto Ester 14. To a stirred suspension of tetramethylammonium triacetoxyborohydride (2.630 g, 10 mmol) in acetonitrile (5 mL) was added glacial acetic acid (5 mL). The mixture was stirred at rt for 30 min. After cooling to $-20\text{ }^\circ\text{C}$, the β -hydroxy keto ester **14** (912

mg, 2 mmol) in a mixture of acetic acid and acetonitrile (v/v 1:1, 4 mL) was added dropwise. The mixture was stirred at $-20\text{ }^\circ\text{C}$ for over 10 h. A saturated solution of sodium potassium tartrate (20 mL) and EtOAc (20 mL) was added followed by vigorous stir at rt for 30 min. The mixture was extracted with EtOAc ($3 \times 15\text{ mL}$). The combined organic layers was washed with water (20 mL), NaHCO_3 ($2 \times 10\text{ mL}$), and brine, dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc, 6:1) to afford diol **18** (870 mg, 95%, $\text{dr} = 96:4$) as a colorless oil: $[\alpha]_{\text{D}}^{20} = -1$ (c 2.20, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 1.06 (s, 9 H), 1.45 (s, 9 H), 1.55 (t, $J = 6.0\text{ Hz}$, 2 H), 2.40 (m, 2 H), 2.88 (d, $J = 2.8\text{ Hz}$, 1 H), 3.48 (d, $J = 3.6\text{ Hz}$, 1 H), 3.56 (dd, $J = 10.0\text{ Hz}$, $J = 7.2\text{ Hz}$, 1 H), 3.66 (dd, $J = 10.0\text{ Hz}$, $J = 4.0\text{ Hz}$, 1 H), 4.04 (m, 1 H), 4.27 (m, 1 H), 7.40 (m, 6 H), 7.66 (m, 4 H); ^{13}C NMR (100 MHz, CDCl_3) δ 19.2, 26.8, 28.1, 38.5, 42.5, 65.4, 67.9, 81.2, 127.7, 129.8, 133.1 (2), 135.5, 172.2; IR (KBr) ν_{max} 3438, 3071, 2932, 1725, 1152, 1111, 704 cm^{-1} ; HRMS (ESIMS) calcd for $\text{C}_{26}\text{H}_{38}\text{O}_5\text{SiNa}$ $[\text{M} + \text{Na}]^+$ 481.2381, found 481.2373.

Synthesis of Amide 21 from Iodide 13. To a suspension of lithium chloride (3.113 g, 74.1 mmol) and diisopropylamine (3.5 mL, 25.1 mmol) in THF (17 mL) was added *n*-butyllithium (1.92 M in hexanes, 12.2 mL, 23.3 mmol) via a syringe at $-78\text{ }^\circ\text{C}$. The resulting suspension was warmed to $0\text{ }^\circ\text{C}$ within 30 min and then recooled to $-78\text{ }^\circ\text{C}$. A solution of amide **12** (2.709 g, 12.3 mmol) in THF (33 mL, followed by a 2 mL rinse) at $0\text{ }^\circ\text{C}$ was added via a syringe. The mixture was stirred at $-78\text{ }^\circ\text{C}$ for 1 h, at $0\text{ }^\circ\text{C}$ for 15 min, and at $23\text{ }^\circ\text{C}$ for 5 min. The mixture was cooled to $0\text{ }^\circ\text{C}$, and the iodide **13** (3.14 g, 5.8 mmol) in THF (7 mL, followed by a 4 mL rinse) was added to the reaction via a syringe. After stirring for 36 h at $0\text{ }^\circ\text{C}$, the reaction mixture was treated with saturated NH_4Cl (aq) (50 mL), and the resulting mixture was extracted with EtOAc ($3 \times 50\text{ mL}$). The combined organic extract was dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes/EtOAc, 3:1) to afford amide **21** (3.50 g, 96%, $\text{dr} = 99:1$) as a viscous yellow oil: $[\alpha]_{\text{D}}^{20} = +23$ (c 3.3, CH_2Cl_2); ^1H NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 300 MHz,

CDCl_3) δ 0.88* (d, J = 6.6 Hz, 3 H), 1.05 (d, J = 6.9 Hz, 3 H), 1.08 (s, 9 H), 1.13 (d, J = 6.6 Hz, 3 H), 1.34 (s, 6 H), 1.37–1.59 (m, 3 H), 1.61–1.65 (m, 3 H), 2.61 (m, 1 H), 2.84 (s, 3 H), 2.90* (s, 3 H), 3.62 (dd, J = 10.5 Hz, J = 5.4 Hz, 1 H), 3.72 (m, 2 H), 3.94 (m, 1 H), 4.05* (m, 1 H), 4.53 (m, 1 H), 4.70* (m, 1 H), 4.61 (d, J = 8.1 Hz, 1 H), 4.55* (d, J = 8.1 Hz, 1 H), 7.23* (m, 5 H), 7.34 (m, 11 H), 7.70 (m, 4 H); ^{13}C NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 75 MHz, CDCl_3) δ 14.3, 17.4, 19.1, 24.7, 26.7, 29.9, 33.5, 34.5, 36.4, 66.5, 66.6, 67.5, 76.1, 99.9, 126.1, 126.7*, 127.3, 127.4, 127.5, 128.1, 128.5*, 129.4, 133.5, 133.6, 135.5, 142.4, 177.1*, 178.5; IR (KBr) ν_{max} 2931, 2858, 1781, 1696, 1381, 1217, 1108, 1033, 703 cm^{-1} ; HRMS (ESIMS) calcd for $\text{C}_{38}\text{H}_{53}\text{NO}_5\text{SiNa}$ [$\text{M} + \text{Na}$] $^+$ 654.3585, found 654.3582.

Reduction of Amide 21 to Alcohol 22. To diisopropylamine (3.2 mL, 22.7 mmol) in THF (16 mL) at -78°C was added a solution of *n*-butyllithium (1.92 M in hexanes, 11.6 mL, 22.2 mmol). After the mixture stirred at -78°C for 10 min and at 0°C for 10 min, $\text{BH}_3\text{-NH}_3$ (705 mg, 22.7 mmol) was added in one portion. The mixture was stirred at 0°C for 15 min and at rt for 15 min. A solution of amide **21** (3.5 g, 5.5 mmol) in THF (15 mL) was added via a syringe at 0°C , and the mixture was stirred at rt for 2 h. The reaction was quenched by slow addition of brine (20 mL) at 0°C . The organic layer was separated, and the aqueous phase was extracted with EtOAc (4 \times 30 mL). The combined organic layers were washed with brine (25 mL) and dried over Na_2SO_4 . After concentration in vacuo, purification by flash column chromatography (hexane/EtOAc, 4:1) provided alcohol **22** (2.518 g, 97%) as a viscous colorless liquid: $[\alpha]_D^{20} = -11$ (c 1.0, CH_2Cl_2); ^1H NMR (300 MHz, CDCl_3) δ 0.91 (d, J = 6.6 Hz, 3 H), 1.06 (s, 9 H), 1.28 (m, 1 H), 1.34 (s, 3 H), 1.36 (s, 3 H), 1.43 (m, 1 H), 1.45–1.62 (m, 5 H), 3.45 (m, 2 H), 3.61 (dd, J = 10.5 Hz, J = 5.4 Hz, 1 H), 3.71 (dd, J = 10.5 Hz, J = 6.0 Hz, 1 H), 3.73 (m, 1 H), 3.95 (m, 1 H), 7.39 (m, 6 H), 7.69 (m, 4 H); ^{13}C NMR (75 MHz, CDCl_3) δ 16.6, 19.3, 24.8, 24.9, 26.8, 28.7, 32.9, 34.7, 35.5, 66.7, 67.0, 67.7, 68.0, 100.2, 127.6, 129.6, 133.8, 135.6, 135.7; IR (KBr) ν_{max} 3410, 2933, 2859, 1378, 1224, 1111, 704 cm^{-1} ; HRMS (ESIMS) calcd for $\text{C}_{28}\text{H}_{42}\text{O}_4\text{SiNa}$ [$\text{M} + \text{Na}$] $^+$ 493.2745, found 493.2740.

Synthesis of Aldehyde 23 from Alcohol 22. To a solution of alcohol **22** (712 mg, 1.5 mmol) in EtOAc (25 mL) was added IBX (1.273 g, 4.5 mmol). The resulting suspension was refluxed for 2.5 h in ambient atmosphere. The reaction was cooled to rt and filtered through a glass frit. The filter cake was washed with Et_2O (3 \times 15 mL), and the combined filtrate was concentrated to dryness. The residue was purified by flash column chromatography (hexane/EtOAc, 15:1) to give aldehyde **23** (691 mg, 97%) as a colorless liquid: $[\alpha]_D^{20} = -24$ (c 3.0, CH_2Cl_2); ^1H NMR (300 MHz, CDCl_3) δ 1.07 (s, 9 H), 1.11 (d, J = 6.9 Hz, 3 H), 1.35 (s, 3 H), 1.36 (s, 3 H), 1.51 (m, 4 H), 1.66 (m, 2 H), 2.35 (m, 1 H), 3.63 (dd, J = 10.5 Hz, J = 4.5 Hz, 1 H), 3.72 (dd, J = 10.8 Hz, J = 6.6 Hz, 1 H), 3.75 (m, 1 H), 3.95 (m, 1 H), 7.40 (m, 6 H), 7.71 (m, 4 H), 9.63 (d, J = 4.2 Hz, 1 H); ^{13}C NMR (75 MHz, CDCl_3) δ 13.4, 19.2, 24.8 (2), 26.4, 26.8, 33.1, 34.5, 46.1, 66.5, 66.6, 67.6, 100.1, 127.6, 129.6, 133.6, 133.7, 135.6 (2), 204.9; IR (KBr) ν_{max} 2933, 2858, 1726, 1377, 1224, 1111, 704 cm^{-1} ; HRMS (ESIMS) calcd for $\text{C}_{28}\text{H}_{40}\text{O}_4\text{SiNa}$ [$\text{M} + \text{Na}$] $^+$ 491.2588, found 491.2591.

Synthesis of Imide Alcohol 11 via Evans Asymmetric Aldol Reaction. To a solution of oxazolidinone **24** (446 mg, 1.8 mmol) in CH_2Cl_2 (12 mL) at 0°C was added dropwise TiCl_4 (0.21 mL, 1.9 mmol), and the mixture was stirred for 5 min. Subsequently, (–)-sparteine (1.057 g, 4.5 mmol) in CH_2Cl_2 (5 mL) was added to the yellow slurry. The dark red enolate solution was stirred for 30 min at 0°C followed by addition of aldehyde **23** (930 mg, 2.0 mmol) in CH_2Cl_2 (9 mL). The mixture was stirred for 1 h at 0°C and quenched with half-saturated NH_4Cl (aq) (10 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 \times 20 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc, 6:1) to give imide alcohol **11** (1.156 g, 89%, dr = 96:4) as

a viscous yellow liquid: $[\alpha]_D^{20} = +19$ (c 1.48, CH_2Cl_2); ^1H NMR (300 MHz, CDCl_3) δ 0.93 (d, J = 6.9 Hz, 3 H), 1.00 (t, J = 7.5 Hz, 3 H), 1.06 (s, 9 H), 1.30 (m, 3 H), 1.34 (s, 3 H), 1.36 (s, 3 H), 1.53 (m, 1 H), 1.67 (m, 4 H), 1.94 (m, 1 H), 2.72 (dd, J = 12.9 Hz, J = 9.9 Hz, 2 H), 3.38 (dd, J = 12.9 Hz, J = 3.0 Hz, 1 H), 3.57 (m, 1 H), 3.60 (dd, J = 10.5 Hz, J = 4.8 Hz, 1 H), 3.70 (dd, J = 10.5 Hz, J = 5.7 Hz, 1 H), 3.72 (m, 1 H), 3.93 (m, 1 H), 4.13 (m, 1 H), 4.16 (m, 2 H), 4.71 (m, 1 H), 7.25 (m, 2 H), 7.35 (m, 9 H), 7.68 (m, 4 H); ^{13}C NMR (75 MHz, CDCl_3) δ 11.9, 15.7, 18.4, 19.2, 24.8, 24.9, 26.7, 28.5, 33.0, 34.6, 36.2, 37.9, 46.1, 55.5, 65.9, 66.7, 67.0, 67.6, 75.7, 100.1, 127.3, 127.5 (2), 128.9, 129.3, 129.5, 133.6, 133.7, 135.1, 135.6 (2), 153.0, 176.7; IR (KBr) ν_{max} 3419, 3070, 2933, 2858, 1468, 1427, 1380, 1225, 1111, 705 cm^{-1} ; HRMS (ESIMS) calcd for $\text{C}_{42}\text{H}_{57}\text{NO}_7\text{SiNa}$ [$\text{M} + \text{Na}$] $^+$ 738.3797, found 738.3804.

Synthesis of β -Keto Lactone 32 from Imide Acetate 10. The imide acetate **10** (1.07 g, 1.41 mmol) was dissolved in THF (56 mL) and cooled to -78°C . KHMDS (6.21 mL of a 0.91 M solution in THF, 5.64 mmol) was added via a syringe within 2 min. After stirring for 15 min, the reaction was quenched by the rapid addition of saturated NH_4Cl (30 mL). The mixture was allowed to warm to rt. Addition of glacial acetic acid into the mixture gave the neutral condition (pH 6–7). The mixture was extracted with EtOAc (4 \times 30 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes/EtOAc, 3:1) to provide β -keto lactone **32** (793 mg, 97%) as a viscous colorless oil: $[\alpha]_D^{20} = -29$ (c 0.8, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 0.91 (d, J = 7.2 Hz, 3 H), 0.96 (t, J = 7.5 Hz, 3 H), 1.06 (s, 9 H), 1.30 (m, 1 H), 1.35 (s, 6 H), 1.44 (m, 1 H), 1.52 (m, 2 H), 1.80 (m, 5H), 2.51 (dm, J = 8.4 Hz, 1 H), 3.37 (d, J = 19.2 Hz, 1 H), 3.54 (d, J = 19.2 Hz, 1 H), 3.63 (dd, J = 10.5 Hz, J = 4.8 Hz, 1 H), 3.72 (dd, J = 10.5 Hz, J = 6.0 Hz, 1 H), 3.73 (m, 1 H), 3.94 (m, 1 H), 4.20 (dm, J = 9.6 Hz, 1 H), 7.40 (m, 6 H), 7.70 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 11.5, 14.6, 16.9, 19.2, 24.8, 24.9, 26.7, 28.6, 32.8, 33.5, 34.7, 45.2, 49.9, 66.6, 67.6, 82.2, 100.2, 127.5 (2), 129.5, 133.6, 133.7, 135.6 (2), 167.5, 203.0; IR (KBr) ν_{max} 2932, 2859, 1665, 1610, 1380, 1222, 1110, 703 cm^{-1} ; HRMS (ESIMS) calcd for $\text{C}_{34}\text{H}_{48}\text{O}_6\text{SiNa}$ [$\text{M} + \text{Na}$] $^+$ 603.3112, found 603.3123.

Synthesis of δ -Lactone 9 from Triflate 33. To a solution of triflate **33** (1.039 g, 1.459 mmol) in DMF (15 mL) were added $\text{Pd}(\text{PPh}_3)_4$ (169 mg, 0.146 mmol), Et_3N (0.81 mL, 5.836 mmol), and triethylsilane (0.47 mL, 2.918 mmol). The resulting mixture was heated at 75°C for 45 min. The solution turned black, and reaction was monitored by TLC. The reaction mixture was quenched with saturated NaHCO_3 (30 mL) and diluted with Et_2O (150 mL) and water (30 mL). The aqueous was separated, and the organic layer was washed with water (3 \times 60 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes/EtOAc, 8:1) to provide δ -lactone **9** (790 mg, 96%) as a colorless oil: $[\alpha]_D^{20} = -78$ (c 3.00, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 0.90 (d, J = 6.6 Hz, 3 H), 0.96 (t, J = 7.5 Hz, 3 H), 1.06 (s, 9 H), 1.27 (m, 1 H), 1.34 (s, 3 H), 1.35 (s, 3 H), 1.41 (m, 1 H), 1.50 (m, 2 H), 1.65 (m, 3 H), 1.85 (m, 2 H), 2.32 (m, 1 H), 3.61 (dd, J = 10.5 Hz, J = 4.5 Hz, 1 H), 3.71 (dd, J = 10.5 Hz, J = 6.0 Hz, 1 H), 3.73 (m, 1 H), 3.94 (m, 1 H), 3.99 (dd, J = 10.5 Hz, J = 3.0 Hz, 1 H), 6.04 (d, J = 9.3 Hz, 1 H), 7.07 (dd, J = 9.9 Hz, J = 6.6 Hz, 1 H), 7.38 (m, 6 H), 7.69 (m, 4 H); ^{13}C NMR (75 MHz, CDCl_3) δ 11.0, 14.7, 19.2, 20.1, 24.9, 26.8, 28.2, 33.0, 33.6, 34.7, 36.6, 66.7, 66.9, 67.7, 84.3, 100.1, 120.9, 127.5, 129.5, 133.7, 133.8, 135.6, 135.7, 151.0, 164.8; IR (KBr) ν_{max} 2959, 2932, 2858, 1726, 1654, 1465, 1427, 1380, 1248, 1225, 1110, 1061, 1023, 704 cm^{-1} ; HRMS (ESIMS) calcd for $\text{C}_{34}\text{H}_{48}\text{O}_5\text{SiNa}$ [$\text{M} + \text{Na}$] $^+$ 587.3163, found 587.3170.

Typical Procedure for Julia–Kocienski Olefination: Synthesis of Olefin 36 from Alcohol 34. To a solution of alcohol **34** (33 mg, 0.101 mmol) in EtOAc (5 mL) was added IBX (85 mg, 0.303 mmol). The resulting suspension was refluxed in ambient

atmosphere. After 2.5 h, the reaction was cooled to rt and filtered through a glass frit. The filter cake was washed with Et₂O (3 × 10 mL), and the combined filtrate was concentrated to yield the desired aldehyde, which was directly used for further transformation without purification. To a solution of the sulfone **35** (34 mg, 0.106 mmol) in THF (3 mL) at –78 °C was added dropwise LiHMDS (1.0 M in THF, 0.11 mL, 1.06 mmol). After the mixture was stirred for 30 min, a solution of the crude aldehyde in THF (1 mL) was added dropwise. The reaction was stirred at –78 °C for 3 h, warmed to rt, and stirred for 1 h. Saturated NH₄Cl (aq) was added. The mixture was then extracted with EtOAc (3 × 10 mL). The combined organic layers was washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc, 8:1) to afford a mixture of two geometrical isomerides (*E/Z* = 1.9/1 based on ¹H NMR). A solution of the mixture of two geometrical isomerides (7 mg, 0.014 mmol) in toluene (3 mL) was heated at 110 °C for 4 h. After cooling to rt, the solvent was concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc, 8:1) to afford desired olefin **36** (5 mg, 56% for three steps, *E/Z* = 5/1) as a colorless liquid: $[\alpha]^{20}_{\text{D}} = -88$ (*c* 0.40, CHCl₃); ¹H NMR (400 MHz, (CD₃)₂CO) δ 0.94 (d, *J* = 6.8 Hz, 3 H), 0.94 (t, *J* = 7.2 Hz, 3 H), 1.29 (m, 2 H), 1.32 (s, 3 H), 1.38 (s, 3 H), 1.45 (m, 2 H), 1.71 (m, 3 H), 1.86 (m, 2 H), 2.47 (m, 1 H), 3.87 (m, 1 H), 4.04 (dd, *J* = 10.0 Hz, *J* = 2.8 Hz, 1 H), 4.47 (dm, *J* = 15.2 Hz, 1H), 5.90 (dd, *J* = 15.6 Hz, *J* = 6.0 Hz, 1 H), 5.97 (d, *J* = 9.6 Hz, 1 H), 6.42 (dd, *J* = 15.2 Hz, *J* = 10.4 Hz, 1 H), 6.61 (d, *J* = 16.0 Hz, 1 H), 6.90 (dd, *J* = 15.6 Hz, *J* = 10.4 Hz, 1 H), 7.21 (dd, *J* = 9.6 Hz, *J* = 6.8 Hz, 1 H), 7.22 (t, *J* = 6.8 Hz, 1 H), 7.32 (t, *J* = 7.2 Hz, 2 H), 7.46 (d, *J* = 7.2 Hz, 2 H); ¹³C NMR (100 MHz, (CD₃)₂CO) δ 11.2, 15.0, 20.9, 25.2, 25.9, 29.0, 33.7, 34.4, 37.2, 39.1, 67.3, 68.0, 84.9, 100.7, 121.4, 127.2, 128.4, 129.5, 129.7, 130.8, 133.0, 136.0, 138.4, 152.3, 164.6; IR(KBr) ν_{max} 2962, 2928, 2873, 1724, 1596, 1462, 1379, 1249, 1223, 989, 693 cm^{–1}; HRMS (ESIMS) calcd for C₂₇H₃₆O₄Na [M + Na]⁺ 447.2506, found 447.2500.

Synthesis of (–)-Bitungolide F (6) from Olefin 36. To a solution of olefin **36** (5 mg, 0.012 mmol) in THF (1 mL) was added 50% aqueous trifluoroacetic acid (60 μ L), and the mixture was stirred at 35 °C for 4 h. The reaction was quenched with four drops of Et₃N. The mixture was concentrated to dryness under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc, 1:1) to afford compound **6** (4 mg, 88%) as a gray solid: $[\alpha]^{20}_{\text{D}} = -49$ (*c* 0.38, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.91 (d, *J* = 6.8 Hz, 3 H), 0.96 (t, *J* = 7.6 Hz, 3 H), 1.29 (m, 2 H), 1.48 (m, 1 H), 1.67 (m, 2 H), 1.76 (m, 2 H), 1.91 (m, 2 H), 2.33 (m, 1 H), 3.97 (m, 1 H), 4.00 (dd, *J* = 10.8 Hz, *J* = 3.2 Hz, 1 H), 4.59 (m, 1 H), 5.90 (dd, *J* = 15.2 Hz, *J* = 6.0 Hz, 1 H), 6.04 (d, *J* = 9.6 Hz, 1 H), 6.46 (dd, *J* = 15.2 Hz, *J* = 10.8 Hz, 1 H), 6.56 (d, *J* = 16.0 Hz, 1 H), 6.78 (dd, *J* = 15.6 Hz, *J* = 10.4 Hz, 1 H), 7.08 (dd, *J* = 9.6 Hz, *J* = 6.4 Hz, 1 H), 7.22 (t, *J* = 7.2 Hz, 1 H), 7.31 (t, *J* = 7.6 Hz, 2 H), 7.40 (d, *J* = 7.6 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 11.0, 14.9, 20.1, 28.6, 33.6, 34.6, 36.6, 42.6, 69.4, 70.3, 84.5, 120.9, 126.4, 127.5, 128.6, 128.2, 130.4, 132.7, 136.1, 137.2, 151.1, 164.8; IR(KBr) ν_{max} 3397, 2962, 2926, 2873, 1713, 1656, 1593, 1452, 1383, 1257, 1062, 1025, 991, 693 cm^{–1}; HRMS (ESIMS) calcd for C₂₄H₃₂O₄Na [M + Na]⁺ 407.2193, found 407.2184.

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Supporting Information Available: Experimental procedures, spectral data, and copies of ¹H and ¹³C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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