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A concise approach for the synthesis of bitungolides: total syntheses of (–)-bitungolide B & E†

K. Mahender Reddy, J. Shashidhar and Subhash Ghosh*

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The first total synthesis of (–)-bitungolide B and a second-generation total synthesis of (–)-bitungolide E are described. The cornerstone of the approach comprises a convergent and flexible route involving Brown crotylation, highly diastereoselective substrate controlled Paterson *anti*-aldol reaction, hydroxyl-directed 1,3-*syn*/*anti* reduction, Barton–McCombie deoxygenation and RCM reactions. *Via* this route, a common intermediate **13** is readily accessible for the synthesis of the family of bitungolides A–E and franklinolides A–C.

Introduction

Marine organisms have produced a wide range of biologically active and structurally complex secondary metabolites. Bitungolides A–F are new examples of such secondary metabolites isolated from an Indonesian sponge *Theonella* cf. *swinhoei* by Tanaka *et al.* in 2002 (Fig. 1).[1]

Bitungolides comprise a complex structure and a unique family of polyketides that display cytotoxic activity against 3Y1 rat normal fibroblast cells and also inhibit the dual specificity phosphatase VHR. The structure of bitungolides B–F were assigned by inference from the single crystal X-ray analysis of bitungolide A; however, the absolute stereochemistry of bitungolide E and bitungolide F was confirmed through their total synthesis by us and others.[2,3] Recently Zhang *et al.* reported the isolation of three phosphodiester derivatives of bitungolides A, B and D called franklinolides A–C from an Australian sponge sample CMB-01989.[4] Franklinolides displayed cytotoxicity against a human brain cancer cell line. This phosphodiester engenders the potent cytotoxic activity in franklinolides. Bitungolides have attracted considerable attention from both the synthetic and pharmacological communities, due to their intriguing structure and potent cytotoxic activities. So far one total synthesis of (–)-bitungolide E[2b] and three total syntheses of (–)-bitungolide F[2a,3] have been achieved. However to date no total syntheses of bitungolides A–D or the phosphodiester derivatives of bitungolides A, B and D, franklinolides A–C, have been reported. Fascinated by the complex architecture as well as the interesting biological profile of the bitungolides and franklinolides, we wanted to develop a synthetic strategy by which all the congeners of bitungolides A–E and franklinolides A–C could be synthesized. In this article we report the total synthesis of (–)-bitungolides B and E *via* common key intermediate **13**.

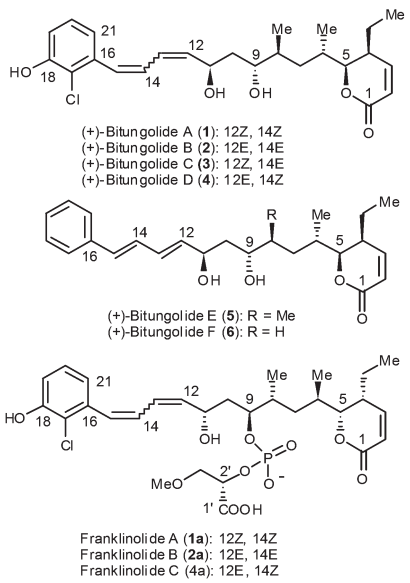

Fig. 1 Structure of (+)-bitungolides, franklinolides.

Results and discussion

Structural inspection of bitungolide B and bitungolide E revealed that they possess similar structural features except for

Fine Chemicals Laboratory, CSIR-Indian Institute of Chemical Technology, Hyderabad-500 007, India. E-mail: subhash@iict.res.in; Fax: +91-40-27191604; Tel: +91-40-27191609

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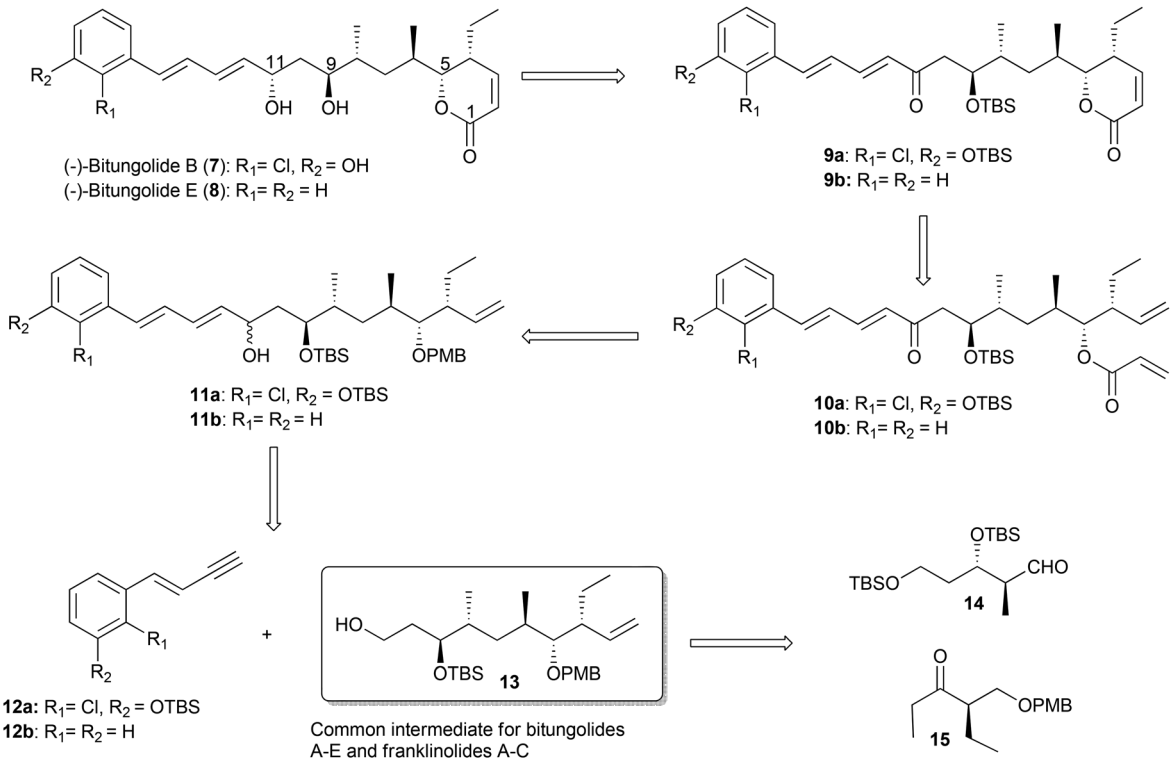
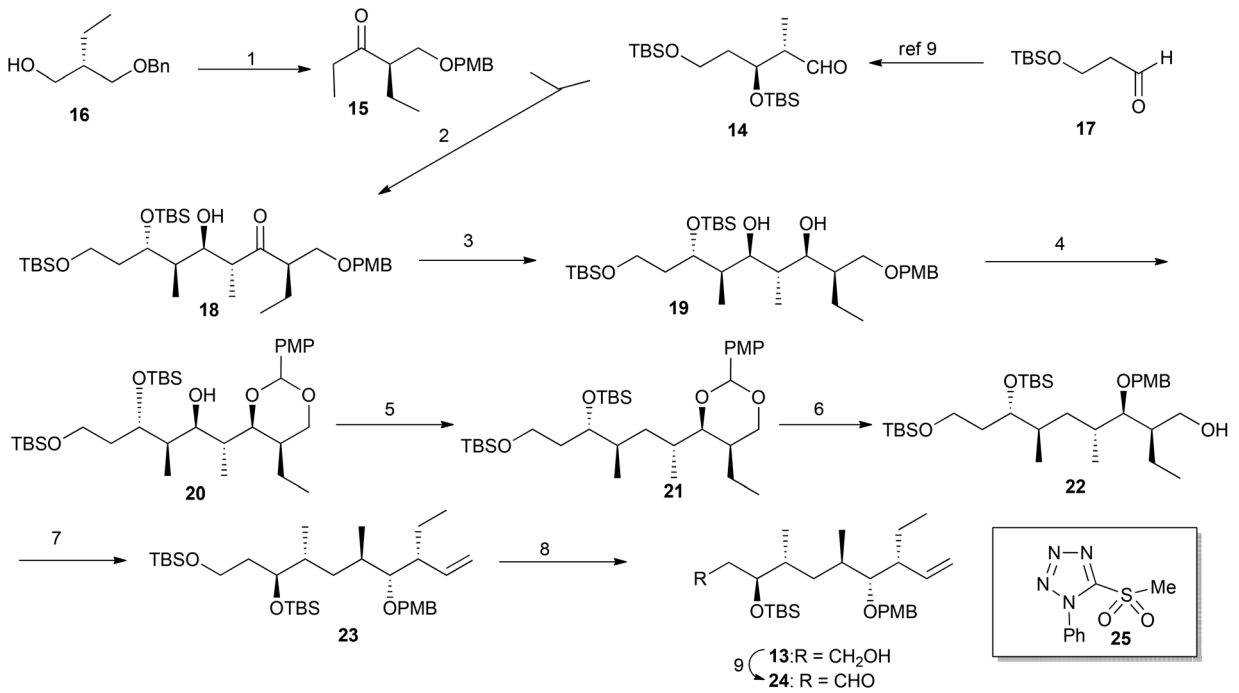


Scheme 1 Retrosynthetic analysis of (–)-bitungolide B and E.

the aromatic ring attached to the *E*,*E*-diene unit. In the case of bitungolide B the phenyl ring contains chlorine and hydroxyl groups whereas in the case of bitungolide E it is a simple phenyl ring. Thus retrosynthetically (–)-bitungolide B and (–)-bitungolide E could be derived from the α,β-unsaturated δ-lactones **9a** and **9b** (Scheme 1) *via* desilylation followed by Evans–Saksena reduction. The α,β-unsaturated δ-lactones **9a** and **9b** would be accessible through ring-closing metathesis of bis-olefinic compounds **10a** and **10b** respectively. The bis-olefinic compounds **10a** and **10b** might be obtained *via* DDQ-mediated allylic alcohol oxidation, concomitant PMB deprotection of **11a** and **11b** followed by acrylation of the resulting hydroxy keto compounds. The *E*,*E*-diene unit in **11a** and **11b** could be introduced through the addition of ene-yne compounds **12a** and **12b** to an aldehyde obtained from alcohol **13** followed by Red-Al reduction of the resulting propargyl alcohols. Common intermediate **13** could be obtained by means of substrate-controlled Paterson *anti*-aldol reaction between aldehyde **14** and ketone **15**.

Synthesis of common intermediate alcohol **13** started from known compound **16** (Scheme 2).[5] Oxidation of alcohol **16** furnished an aldehyde, which on Grignard reaction with EtMgBr followed by hydrogenolysis of the benzyl ether gave a diol. Subsequent selective protection of the primary hydroxyl as the PMB ether[6] followed by Dess–Martin periodinane oxidation[7] of the secondary alcohol afforded ketone **15**. The highly diastereoselective addition of the boron enolate generated from ketone **15** under Paterson conditions[8] to known aldehyde **14**[9] prepared from aldehyde **17** according to the known procedure, provided the desired β-hydroxy ketone **18** in 85% yield, with a diastereomeric ratio of (20 : 1). In order to fix the C5 stereocenter in the final molecule, hydroxyl ketone **18** was subjected to hydroxy-directed 1,3-*syn* reduction (Table 1) with Et_2BOMe[10] and $NaBH_4$ in THF–MeOH (5 : 1), at −78 °C (entry 1). However to our surprise, the reduction of the ketone did not proceed at all. On the other hand reduction with $Zn(BH_4)_2$[11] provided the reduced product but the yield and selectivity were very poor (entry 2). Gratifyingly we found catecholborane,[12] in THF, at −78 °C to −20 °C, reduced hydroxy ketone **18** to 1,3-*syn* diol **19** (entry 3) with good yield (86%) and high selectivity (95% de). The 1,3-*syn* relationship was confirmed *via* the Rychnovsky method.[13a,b] DDQ-mediated rearrangement of the PMB ether[14] afforded secondary alcohol **20**, which on deoxygenation under Barton–McCombie conditions[15] yielded the deoxy compound **21** in 90% yield over two steps. Regioselective opening of the *p*-methoxybenzylidene acetal with DIBAL-H[16] from the less hindered side afforded primary alcohol **22** in 90% yield. Oxidation of the primary alcohol **22** furnished an aldehyde, which on Julia–Kocienski olefination[17] with **25** gave olefinic compound **23**. Selective TBS deprotection of **23** provided common intermediate **13**. The overall sequence proceeded in 14 steps from **16** with an overall yield of 27.8%. Thus, this highly functionalised core **13**, which is a common moiety present in (–)-bitungolides A–E and franklinolides A–C, can be accessed in multi-gram quantities *via* a set of high yielding chemical transformations. Finally Parikh–Doering oxidation[18] of **13** completed the synthesis of aldehyde fragment **24**.



Scheme 2 Synthesis of the common intermediate **13**. *Reagents and conditions*: (1) (a) DMP, CH_2Cl_2, 0 °C, 2 h; (b) EtMgBr, THF, 0 °C, 2 h; (c) H_2, Pd/C, MeOH, rt, 1 h; (d) PMBCl, NaH, DMF 0 °C, 3 h; (e) DMP, CH_2Cl_2, 0 °C, 2 h, 72% over five steps; (2) $(c\text{-}C_6H_{11})_2BCl$, Et_3N, Et_2O, 0 °C, 2 h, then **14**, −78 °C to −20 °C, 14 h, 85%; (3) catecholborane THF, −78 °C to −20 °C, 12 h, 86%; (4) DDQ, 4 Å, MS, CH_2Cl_2, −10 °C, 2 h, 90%; (5) (a) NaHMDS, CS_2 MeI, THF, −78 °C, 2 h; (b) nBu$_3$SnH, AIBN, 120 °C, 1 h, 90% over two steps; (6) DIBAL-H, CH_2Cl_2, −40 °C to −10 °C, 2 h, 90%; (7) (a) SO_3·Py, Et_3N, CH_2Cl_2–DMSO (0.9 : 1.0), 0 °C 1.5 h, (b) **25**, NaHMDS, THF, −78 °C to rt, 18 h, 78% over two steps; (8) HF·Py, THF, 0 °C to rt, 20 h, 93%; (9) SO_3·Py, Et_3N, CH_2Cl_2–DMSO (0.9 : 1.0), 0 °C, 1.5 h, quantitative.

Table 1 Different reagents and conditions screened for the reduction of the C5 ketone

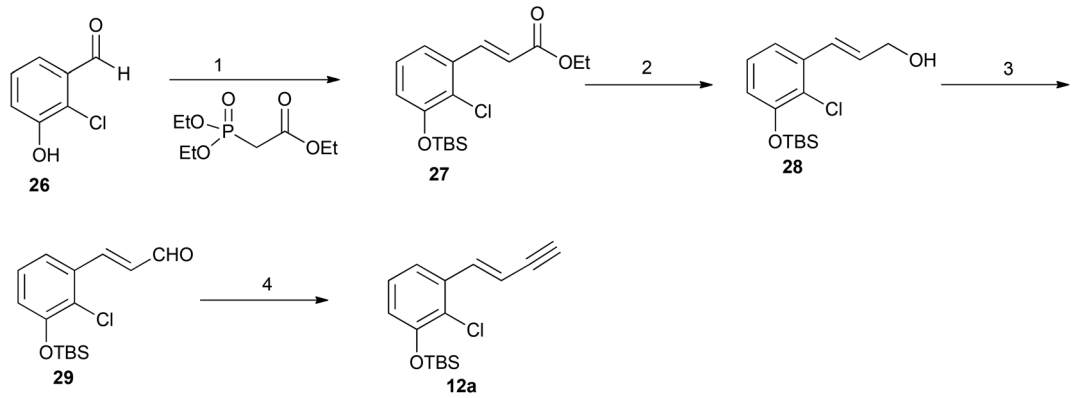
Entry	Conditions	Time	Temperature	Result
1	Et_2B-OMe (1.2 eq.), $NaBH_4$ (1.2 eq.) THF–MeOH (5 : 1)	24 h	−78 °C	No reaction, starting material recovered
2[a]	$Zn(BH_4)_2$ (0.2 M in Et_2O, 10 eq.), CH_2Cl_2	6 h	−40 °C	40% yield based on recovered starting material, 80% de
3	Catecholborane (1 M, 10 eq.), THF	12 h	−78 °C to −20 °C	86% yield, 95% de

[a] In $Zn(BH_4)_2$ reaction a considerable amount of diol was complexed with Zn salts; stirring with silica gel in EtOAc for 5 h led to decomplexation and recovery of the required diol compound.

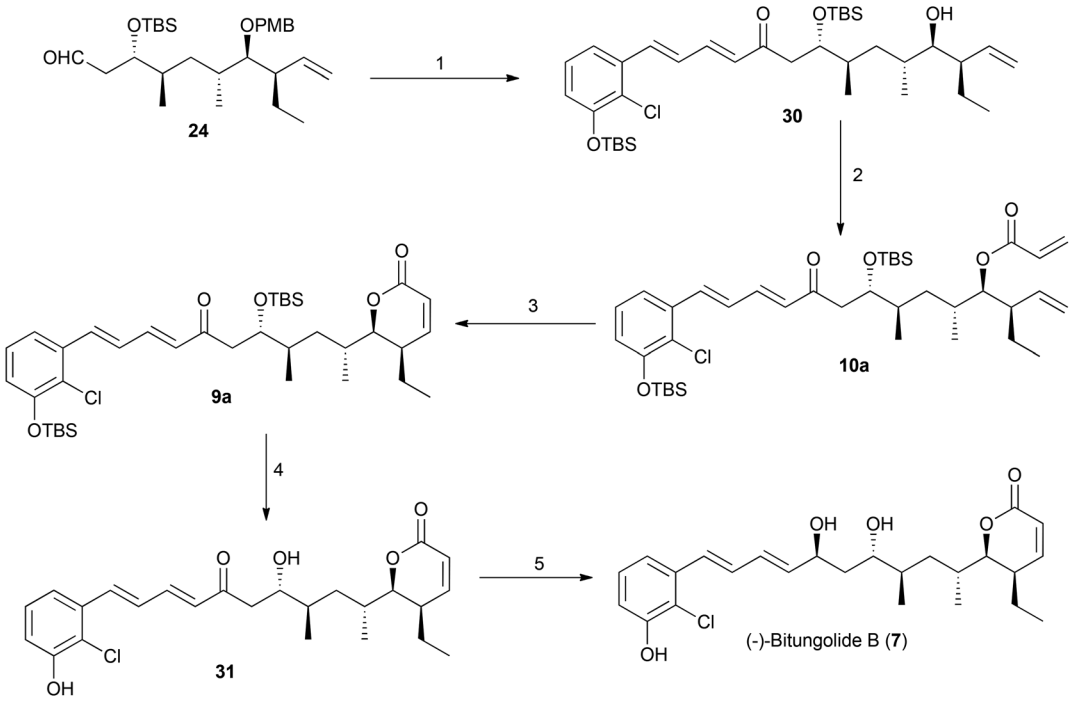
Synthesis of ene-yne fragment **12a** is depicted in Scheme 3. Protection of the commercially available known aldehyde **26** as the TBS ether followed by Horner–Wadsworth–Emmons olefination[19] yielded α,β-unsaturated ester **27**, which on DIBAL-H reduction afforded allylic alcohol **28**. DMP oxidation of allylic alcohol **28** furnished an aldehyde **29**. Initial attempts to make alkyne **12a** from aldehyde **29** by Corey–Fuchs reaction[20] or by Ohira–Bestmann protocol[21] did not yield satisfactory results. On the other hand, aldehyde **29** *via* Colvin rearrangement[22] in the presence of $TMSCHN_2$, LDA in THF at reflux temperature, provided the desired ene-yne **12a** in 75% yield over two steps.

After achieving the fragments aldehyde **24** and ene-yne **12a**, the final synthesis of (−)-bitungolide B was planned by assembling the fragments as depicted in Scheme 4. Addition of the anion generated from compound **12a** to the aldehyde **24** yielded a diastereomeric mixture of propargylic alcohols which on Red-Al reduction[23] followed by DDQ-mediated one pot oxidation of the resulting allylic alcohol[24] and PMB-deprotection afforded the *E*,*E*-diene compound **30** in 60% yield over three steps.

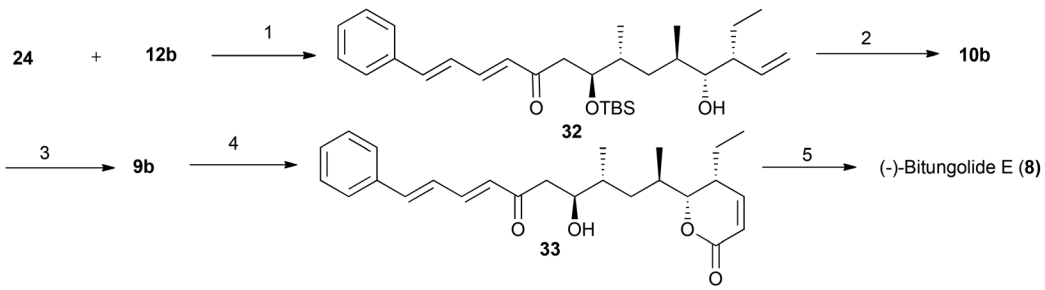
Next, acylation of **30** was carried out with acryloyl chloride to give the bis-olefinic compound **10a** in 85% yield. Ring-closing metathesis[25] of bis-olefinic compound **10a** afforded **9a**. TBS deprotection of **9a** gave β-hydroxy ketone **31**, which on Evans–Saksena reduction[26] furnished (−)-bitungolide B (**7**). Similar to our previous observations, during the syntheses of other bitungolides E and F[2], the spectral data of **7** were identical with those reported for the natural product except for the specific rotation which was comparable in magnitude but opposite in sign {$[\alpha]_D^{25}$ = −44.3 (*c* 0.3, $CHCl_3$); lit.[1] $[\alpha]_D^{27}$ = +42 (*c* 4.2, $CHCl_3$)}. (−)-Bitungolide E (Scheme 5) was synthesized from aldehyde **24** and ene-yne **12b** *via* the same sequence as



Scheme 3 Synthesis of ene-yne fragment **12a**. *Reagents and conditions*: (1) (a) TBSCl, imidazole, THF, 0 °C, 2 h; (b) NaH, THF, –78 °C 1 h 89% over two steps; (2) DIBAL-H, CH_2Cl_2, –78 °C to 0 °C, 1 h, 93%; (3) DMP, CH_2Cl_2, 0 °C, 2 h; (4) $TMSCH_2N_2$, LDA THF, –78 °C, 1 h then reflux for 3 h, 75% over two steps.



Scheme 4 Synthesis of (–)-bitungolide B. *Reagents and conditions*: (1) (a) **12a**, *n*BuLi, THF, –78 °C, 2 h; (b) Red-Al, THF, 0 °C, 1 h; (c) DDQ, $CHCl_3$, buffer, 0 °C, 1 h, 60% over three steps; (2) Acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C, 2 h, 85%; (3) Grubbs 1st generation catalyst, CH_2Cl_2, 40 °C, 20 h, 85%; (4) HF–Py, CH_3CN, rt, 48 h, 80%; (5) $Me_4NHB(OAc)_3$, acetone–AcOH (1 : 1), –25 °C, 3 h, 78%.



Scheme 5 Synthesis of (–)-bitungolide E. *Reagents and conditions*: (1) (a) **12b**, *n*-BuLi, –78 °C, then aldehyde **24**, 45 min; (b) Red-Al, dry THF, 0 °C to rt, 1 h; (c) DDQ, $CHCl_3$ pH 7 buffer (20 : 1), 0 °C, 10 min, 46% over 4 steps; (2) acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h, 79%; (3) G-1 catalyst, CH_2Cl_2, reflux, 20 h, 80%; (4) HF–Py complex, CH_3CN, 0 °C to rt, 15 h, 88%; (5) $Me_4NBH(OAc)_3$, CH_3CN–AcOH (1 : 1), –20 °C, 3 h, 84%.

used for the synthesis of (−)-bitungolide B with an overall yield of 6.0% This entails a longest linear sequence of 21 steps, in comparison with our first generation synthesis[2b] of (−)-bitungolide E which was achieved in 26 steps with an overall yield of 2.5%.

Conclusion

In conclusion we have achieved the first total synthesis of (−)-bitungolide B (22 longest linear sequence from **16**, 7.5%), and the second generation total synthesis of (−)-bitungolide E (22 longest linear sequence, 5.97%). The common intermediate **13** for bitungolides and potent cytotoxic franklinolides was synthesized *via* highly diastereoselective substrate controlled *anti*-aldol reaction as a key step in multigram quantities. This strategy developed here is highly convergent and can be used for the synthesis of other congeners of bitungolides, franklinolides and their analogs for biological studies. Presently we are working in that direction.

Experimental section

General experimental methods

All the reactions were performed under nitrogen or argon atmosphere in oven-dried glass apparatus under magnetic stirring. Anhydrous solvents were dried and distilled by standard methods. Commercially available reagents were used without further purification unless otherwise noted. Column chromatography was carried out using silica gel (60–120 or 100–200 mesh) packed in glass columns. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ solvent on 300 MHz, 400 MHz, 500 MHz and 75 MHz, 100 MHz, 125 MHz spectrometers, respectively, using TMS as an internal standard. Chemical shifts are measured as ppm values relative to internal $CHCl_3$ δ 7.26 or TMS δ 0.0 for ^{1}H NMR and $CHCl_3$ δ 77 for ^{13}C NMR. In ^{1}H NMR the multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; ddd = doublet of double of doublets; dt = doublet of triplets; m = multiplet; brs = broad singlet. Optical rotation values were recorded on a Horiba sepa 300 polarimeter using a 2 mL cell with a 10 mm path length. FTIR spectra were recorded on an Alpha (Bruker) infrared spectrophotometer. High resolution mass spectra (HRMS) [ESI$^+$] were obtained using either a TOF or a double focusing spectrometer.

Synthesis of (*R*)-4-((4-methoxybenzyloxy)methyl)hexan-3-one (15). To a stirred solution of **16** (6 g, 30.93 mmol) in anhydrous CH_2Cl_2 (100 mL) was added Dess–Martin periodinane (13 g, 30.93 mmol) at 0 °C under N_2 atmosphere and the moxture was stirred for 45 min at room temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (15 mL), saturated aqueous $Na_2S_2O_3$ (15 mL) and extracted with EtOAc (2 × 250 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated under vacuum, which gave the aldehyde. The obtained aldehyde was purified by column chromatography, and was used in the next step without further characterization.

To a stirred solution of the above crude aldehyde in THF (120 mL) was added EtMgBr (123 mL, 1 M in THF, 123 mmol) at 0 °C under N_2 atmosphere and the mixture was stirred for 45 min. The reaction was quenched with water (20 mL) and diluted with EtOAc (200 mL). The layers were separated and the aqueous phase was further extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under vacuum to afford a diastereomeric mixture of alcohols which was used directly for the next reaction.

To this crude diastereomeric mixture of alcohols in EtOAc (100 mL) was added Pd/C (1 g) and it was subjected to hydrogenation under atmospheric pressure using a H_2-filled balloon. After 2 h, the reaction mixture was filtered through a short pad of celite and the filter cake was washed with EtOAc. The filtrate and washings were combined and concentrated under vacuum to afford the crude 1,3-diols, which were used directly in the next reaction.

To a stirred solution of the above crude diol in DMF (200 mL) was added NaH (1.4 g, 33.99 mmol) at rt under N_2 atmosphere. After 75 min of stirring at rt, PMBCl (4.6 mL, 33.99 mmol) was added very slowly to the reaction mixture and stirred for another 30 min. Then the reaction mixture was quenched with saturated NH_4Cl (5 mL) and extracted with EtOAc (200 mL). The organic extract was washed with brine (15 mL), dried over Na_2SO_4, and concentrated under vacuum to afford a diastereomeric mixture of secondary alcohols, which was used directly in the next step.

To a stirred solution of the above crude secondary alcohol in anhydrous CH_2Cl_2 (85 mL) was added Dess–Martin periodinane (13 g, 30.93 mmol) at 0 °C under N_2 atmosphere and the mixture was stirred for 45 min at rt. Then the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (15 mL) and saturated $Na_2S_2O_3$ (15 mL) and extracted with EtOAc (2 × 250 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (SiO_2, 5% EtOAc–hexane) to afford **15** (5.5 g, 72% over five steps) as a colourless oil. R_f 0.6 (10% EtOAc in hexanes); $[\alpha]_D^{25}$ = −16.42 (*c* 2.1 in $CHCl_3$); IR (neat): ν_{max} 2965, 2868, 1710, 1512, 1460, 1246, 1174, 1088, 1033, 819 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.2 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.39 (ABq, *J* = 12.6 Hz, 2H), 3.79 (s, 3H), 3.57 (dd, *J* = 8.9, 8.7 Hz, 1H), 3.46 (dd, *J* = 9.0, 5.2 Hz, 1H), 2.76 (m, 1H), 2.56–2.40 (m, 2H), 1.60 (dq, *J* = 15.2, 7.6 Hz, 1H), 1.44 (dq, *J* = 14.9, 7.4 Hz, 1H), 1.03 (t, *J* = 7.3 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.9, 159.1, 130.2, 129.1 (2C), 113.7 (2C), 72.8, 70.9, 55.2, 53.5, 36.6, 21.8, 11.7, 7.4. HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{22}O_3Na$ 273.1461, found 273.1459.

Synthesis of (3*R*,5*R*,6*R*,7*R*,8*S*)-8,10-bis(*tert*-butyldimethylsilyloxy)-6-hydroxy-3-((4-methoxybenzyloxy)methyl)-5,7-dimethyldecan-4-one (18). To a solution of chlorodicyclohexylborane (13.9 mL, 13.9 mmol) in anhydrous ether (30 mL) at −78 °C

were added dropwise triethylamine (2.4 mL, 16.75 mmol) followed by ketone **15** (2.4 g, 9.31 mmol) in ether (15 mL) *via* cannula. The milky mixture was stirred at 0 °C for 2.5 h. Then the solution was again cooled to −78 °C before slow addition of aldehyde **14** (5 g, 13.97 mmol) in anhydrous ether (15 mL) *via* cannula and the resulting solution was stirred for 2 h at the same temperature. Then the reaction mixture was kept at −25 °C overnight and after that it was stirred at 0 °C for 30 min and monitored by TLC. After completion of the reaction, it was quenched successively with MeOH (26 mL), pH = 7 buffer (26 mL), H_2O_2 (50%) (26 mL) and it was stirred for another 30 min at room temperature and extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed sequentially with water (20 mL), brine (20 mL) and dried over Na_2SO_4. The organic extracts were concentrated under vacuum and the residue was purified by column chromatography (SiO_2, 60–120 mesh, 7% EtOAc–hexane) to afford **18** (4.76 g, 85%) as a colorless oil. R_f 0.5 (10% EtOAc in hexanes); $[\alpha]_D^{25}$ = –4.6 (*c* 3.0 in $CHCl_3$); IR (neat): ν_{max} 3481 (br), 2930, 2858, 1711, 1513, 1463, 1251, 1092, 1035, 1007, 836, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.21 (d, *J* = 8.9 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 4.41 (ABq, *J* = 10.8 Hz, 2H), 4.16 (d, *J* = 9.8 Hz, 1H), 3.99 (m, 1H), 3.80 (s, 3H), 3.51–3.68 (m, 4H), 3.41 (brs, OH), 2.88 (m, 1H), 2.82 (m, 1H), 1.94–1.80 (m, 2H), 1.75–1.63 (m, 2H), 1.43 (m, 1H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.92–0.86 (m, 24H), 0.09 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.7, 159.1, 130.3, 129.1 (2C), 113.7 (2C), 75.3, 72.9, 72.8, 70.3, 59.6, 55.2, 54.2, 49.3, 37.5, 35.7, 25.9 (6C), 21.1, 18.2, 17.9, 12.8, 11.8, 10.6, −4.4, −4.8, −5.4, −5.5. HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{62}NaO_6Si_2$ 633.3977, found 633.3985.

Synthesis of (3*R*,4*S*,5*S*,6*S*,7*R*,8*S*)-8,10-bis(*tert*-butyldimethylsilyloxy)-3-((4-methoxybenzyloxy)methyl)-5,7-dimethyldecane-4,6-diol (19). A stirred solution of compound **18** (4 g, 6.55 mmol) in THF (50 mL) at −40 °C was treated with catecholborane (65 mL, 1 M in THF, 65.0 mmol). After stirring for 12 h at −40 °C the reaction mixture was quenched with MeOH and extracted with EtOAc (2 × 100 mL). The organic extract was washed with 3 N NaOH (2 × 50 mL), followed by water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (SiO_2, 10% EtOAc–hexanes) to afford **19** (3.4 g, 86%) as a colorless oil. R_f 0.4 (10% EtOAc in hexanes); $[\alpha]_D^{25}$ = –9.3 (*c* 1.7 in $CHCl_3$); IR (neat): ν_{max} 3619 (br), 3422 (br), 2954, 2932, 2859, 1513, 1464, 1250, 1089, 1037, 1006, 834, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.28 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 4.47 (ABq, *J* = 11.3 Hz, 2H), 4.04–3.95 (m, 2H), 3.85 (dd, *J* = 9.0, 1.5 Hz, 1H), 3.80 (s, 3H), 3.69–3.48 (m, 4H), 1.92–1.65 (m, 5H), 1.50 (m, 1H), 1.32 (m, 1H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.93 (t, *J* = 6.8 Hz, 3H), 0.89 (s, 18H), 0.68 (d, *J* = 6.8 Hz, 3H), 0.1 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 130.9, 129.1 (2C), 113.6 (2C), 77.3, 76.9, 75.9, 72.9, 71.5, 59.5, 55.2, 42.7, 37.8, 37.7, 36.1, 25.86 (3C), 25.80 (3C), 18.2, 17.9, 17.6, 12.8, 12.7, 11.1, −4.5, −4.9, −5.4, −5.5. HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{33}H_{65}O_6Si_2$ 613.4314, found 613.4315.

(2*R*,3*S*,4*R*,5*S*)-5,7-Bis(*tert*-butyldimethylsilyloxy)-2-((4*S*,5*R*)-5-ethyl-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)-4-methylheptan-3-ol (20). To a solution of **19** (2.5 g, 4.08 mmol) in CH_2Cl_2 containing 4 Å MS (3.2 g) was treated with DDQ (1.4 g, 6.12 mmol) at −10 °C. After stirring for 2 h at the same temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with EtOAc (2 × 100 mL). The organic extract was washed with water (2 × 10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 5–6% EtOAc–hexane) to afford **20** (2.2 g, 90%) as a colourless liquid. R_f 0.6 (10% EtOAc–hexanes); $[\alpha]_D^{25}$ = +35.5 (*c* 0.45 in $CHCl_3$); IR (neat): ν_{max} 3522, 2955, 2930, 2855, 1741, 1517, 1464, 1250, 1086, 834, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.31 (d, *J* = 8.9 Hz, 2H), 6.83 (d, *J* = 7.9 Hz, 2H), 5.44 (s, 1H), 4.28 (d, *J* = 10.8 Hz, 1H), 3.90 (m, 1H), 3.85–3.81 (m, 3H), 3.80 (s, 3H), 3.71–3.59 (m, 2H), 3.56 (brs, OH), 1.97– 1.85 (m, 2H), 1.75 (m, 1H), 1.70–1.64 (m, 2H), 1.57 (m, 1H), 1.39 (m, 1H), 1.04 (t, *J* = 6.9 Hz, 3H), 0.9 (s, 9H), 0.88 (s, 9H), 0.83 (d, *J* = 6.9 Hz, 3H), 0.75 (d, *J* = 6.9 Hz, 3H), 0.05 (s, 6H), 0.03 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160, 130.8, 127.3 (2C), 113.7 (2C), 102.1, 86.9, 73.8, 72.3, 69.6, 59.5, 55.3, 39.4, 37.4, 37.12, 37.05, 25.99 (3C), 25.96 (3C), 18.3, 18.1, 16.6, 12.0, 11.4, 9.4, −4.4, −4.8, −5.3 (2C). HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{62}NaO_6Si_2$ 633.3977, found 633.3979.

(5*S*)-5-((2*R*,4*R*)-4-((4*R*,5*R*)-5-Ethyl-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)pentan-2-yl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane (21). To a stirred solution of **20** (2 g, 3.28 mmol) in anhydrous THF (15 mL) at −78 °C was added 1 M NaHMDS (32.8 mL, 32.8 mmol) and the reaction mixture was stirred at the same temperature for 30 min. CS_2 (4 mL, 65.6 mmol) was added to that solution and stirred for 30 min at −78 °C. Then MeI (6.2 mL, 98.4 mmol) was added to that reaction mixture and stirred for 15 min at the same temperature. It was quenched by addition of H_2O (5 mL) and extracted with EtOAc (2 × 50 mL). The organic extract was washed with water (10 mL), brine (10 mL), dried over (Na_2SO_4), filtered and concentrated under vacuum to afford the methyl xanthate derivative, which was used immediately in the next step without further purification.

The crude methyl xanthate derivative, Bu_3SnH (5 mL) and a catalytic amount of AIBN (0.4 g, 0.32 mmol) were taken in a round bottomed flask and the mixture was heated at 120 °C for 1 h. It was then quenched with H_2O (5 mL). The reaction mixture was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with water (5 mL), brine (5 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO_2 3% EtOAc–hexane) to afford **21** (1.7 g, 90% over two steps) as a colorless liquid. R_f 0.5 (5% EtOAc in hexanes); $[\alpha]_D^{25}$ = +26.3 (*c* 1.1 in $CHCl_3$); IR (neat): ν_{max} 2956, 2933, 2856, 1516, 1464, 1250, 1093, 833, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.39 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.43 (s, 1H), 4.28 (m, 1H), 3.88 (m, 1H), 3.80 (s, 3H), 3.73–3.57 (m, 3H), 3.41 (m, 1H), 1.75–1.44 (m, 3H), 1.38–1.15 (m, 6H), 0.98 (t, *J* = 7.5 Hz, 3H), 0.94–0.81 (m, 21H), 0.78 (d, *J* = 6.8 Hz, 3H), 0.03 (s, 12H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 131.8, 127.1 (2C), 113.4 (2C), 101.5, 85.6, 73.7, 69.3, 60.5, 55.2, 37.2, 35.95, 35.89, 35.6, 31.6, 25.95 (3C), 25.91 (3C), 18.3, 18.1, 16.3, 14.1, 14, 12, −4.4, −4.5, −5.25, −5.29. HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{33}H_{62}NaO_5Si_2$ 617.4028, found 617.4032.

(2*R*,3*R*,4*R*,6*R*,7*S*)-7,9-Bis(*tert*-Butyldimethylsilyloxy)-2-ethyl-3-(4-methoxybenzyloxy)-4,6-dimethylnonan-1-ol (22). To a solution of **21** (1 g, 1.68 mmol) in anhydrous CH_2Cl_2 (10 mL) at −40 °C, DIBAL-H (6.8 mL, 1.0 M in toluene, 6.72 mmol) was added dropwise and stirred at that temperature for 2 h. The reaction was then quenched by slow addition of anhydrous MeOH (0.5 mL), followed by saturated sodium potassium tartrate solution. The reaction mixture was stirred (~2 h) until two clear layers separated. The organic layer was separated out and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed sequentially with water (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO_2 12% EtOAc–hexane) to afford **22** (0.9 g, 90%) as a colorless liquid. R_f 0.3 (15% EtOAc in hexanes); $[\alpha]_D^{25}$ = −4.35 (c 0.85 in $CHCl_3$); IR (neat): ν_{max} 3442, 2928, 2857, 1514, 1464, 1384, 1250, 1090, 1040, 943, 835, 775 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.25 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 4.52 (ABq, J = 10.7 Hz, 2H), 3.80 (s, 3H), 3.74–3.58 (m, 5H), 3.37 (dd, J = 6.4, 3.5 Hz, 1H), 2.02 (brs, 1H), 1.85 (m, 1H), 1.75–1.47 (m, 5H), 1.37–1.19 (m, 3H), 0.97–0.81 (m, 27H), 0.04 (brs, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 130.8, 129.3 (2C), 113.7 (2C), 85.8, 73.8, 73.5, 63.6, 60.3, 55.2, 44.0, 36.0, 35.4, 35.3, 32.7, 25.94 (3C), 25.89 (3C), 18.8, 18.3, 18.1, 16.7, 13.7, 12.5, −4.4, −4.5, −5.3, −5.4. HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{33}H_{64}NaO_5Si_2$ 619.4184, found 619.4186.

(*S*)-5-((2*R*,4*R*,5*R*,6*R*)-6-Ethyl-5-(4-Methoxybenzyloxy)-4-methyloct-7-en-2-yl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane (23). To a stirred solution of the alcohol **22** (0.7 g, 1.17 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0 °C, anhydrous DMSO (4 mL), Et_3N (0.9 mL, 5.85 mmol) and SO_3–py complex (0.93 g, 5.85 mmol) were added sequentially under N_2 atmosphere and was stirred for 1 h. Saturated aqueous NH_4Cl (5 mL) was added and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with water (5 mL), brine (5 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent furnished the crude aldehyde, which was passed through a short pad of silica gel and used as such for the next reaction.

To the stirred solution of sulfone (0.78 g, 3.51 mmol) in THF (12 mL) at −78 °C was added NaHMDS (2.3 mL, 1 M in THF, 2.34 mmol) under an argon atmosphere. After 30 minutes the crude aldehyde in THF (6 mL) was added at −78 °C to the reaction mixture. The reaction mixture was gradually warmed to room temperature and stirred for 18 h. Then the reaction was quenched with water (5 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extract was washed with brine (10 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography (SiO_2, 3% EtOAc–hexanes) to afford **23** (0.54 g, 78% over two steps) as yellow oil. R_f 0.3 (5% EtOAc in hexanes); $[\alpha]_D^{22}$ = −12.64 (c 1.15, $CHCl_3$). IR (neat): ν_{max} 2960, 2921, 2823, 1564, 1411, 1248 and 1034 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.27 (d, J = 7.8 Hz, 2H), 6.86 (d, J = 8 Hz, 2H), 5.54 (dt, J = 17.0, 10.1 Hz, 1H), 5.04 (dd, J = 10.0, 2.0 Hz, 1H), 4.99 (dd, J = 17.0, 2.0 Hz, 1H), 4.51 (ABq, J = 11.0 Hz, 2H), 3.80 (s, 3H), 3.68 (m, 1H), 3.65–3.58 (m, 2H), 3.09 (dd, J = 7.0, 4.0 Hz, 1H), 2.17 (m, 1H), 1.82–1.74 (m, 2H), 1.64–1.54 (m, 2H), 1.31–1.18 (m, 3H), 1.12 (m, 1H), 0.94 (d, J = 7 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.83 (t, J = 8 Hz, 3H), 0.78 (d, J = 7 Hz, 3H), 0.04 (s, 6H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 140.2, 131.3, 129.0 (2C), 115.9, 113.6 (2C), 87.7, 74.9, 73.7, 60.6, 55.2, 49.6, 36.0, 35.2, 33.3, 33.2, 25.96 (3C), 25.9(3C), 22.9, 18.3, 18.1, 17.3, 13.5, 11.8, −4.4, −4.6, −5.3(2C). HRMS(ESIMS) m/z [M + Na]$^+$: calcd for $C_{34}H_{64}O_4NaSi_2$ 615.4240, found: 615.4238.

(3*S*,4*R*,6*R*,7*R*,8*R*)-3-(*tert*-Butyldimethylsilyloxy)-8-ethyl-7-(4-methoxybenzyloxy)-4,6-dimethyldec-9-en-1-ol (13). To the solution of **23** (0.3 g, 0.50 mmol) in anhydrous THF (3.5 mL) in a polypropylene vial, was added HF–py complex (40%, 0.06 mL) at 0 °C. The reaction mixture was slowly warmed to rt and stirred for 20 h. Then it was cautiously poured into saturated $NaHCO_3$ solution and stirred for 30 min. Then both the layers were separated and the aqueous layer was further extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with saturated $CuSO_4$ (20 mL), water (10 mL), brine (10 mL) and dried over Na_2SO_4. The solvent was evaporated under vacuum. The residue was purified by column chromatography (SiO_2, 18% EtOAc–hexanes) to afford **13** (220 mg, 93% yield) as a colourless viscous liquid. R_f 0.2 (10% EtOAc in hexanes); $[\alpha]_D^{22}$ = +6.21 (c 1.00, $CHCl_3$). IR (neat): ν_{max} 3542 (br), 2938, 2867, 1524, 1474, 1364, 1270, 1090, 953, 845, 775 cm^{-1} ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 5.54 (dt, J = 17.0, 10.0 Hz, 1H), 5.06 (dd, J = 10.0, 1.7 Hz, 1H), 5.0 (dd, J = 17.2, 1.7 Hz, 1H), 4.51 (ABq, J = 11.0 Hz, 2H), 3.80 (s, 3H), 3.75–3.65 (m, 3H), 3.10 (dd, J = 7.7, 3.4 Hz, 1H), 2.17 (m, 1H), 1.85–1.73 (m, 2H), 1.71–1.57 (m, 3H), 1.29–1.18 (m, 2H), 1.12 (m, 1H), 0.95 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.84 (t, J = 7.7 Hz, 3H), 0.78 (d, J = 6.8 Hz, 3H), 0.08 (s, 3H), 0.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0, 140.0, 131.1, 129.1 (2C), 116.0, 113.6 (2C), 87.6, 76.3, 75.1, 61.0, 55.2, 49.7, 35.9, 33.6, 33.4, 33.2, 25.8 (3C), 22.8, 17.9, 17.4, 12.8, 11.7, −4.3, −4.7. HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{28}H_{50}O_4NaSi$ 501.3376, found: 501.3373.

(*E*)-Ethyl 3-(3-(*tert*-butyldimethylsilyloxy)-2-chlorophenyl)-acrylate (27). To a stirred solution of commercially available **26** (2 g, 12.7 mmol) in anhydrous THF (80 mL) at 0 °C were added imidazole (2 g, 29.2 mmol) and TBSCl (2.5 g, 16.99 mmol) sequentially under N_2 atmosphere. After 2 h of stirring at rt, the reaction mixture was quenched with saturated NH_4Cl (15 mL) and extracted with EtOAc (2 × 100 mL). The combined organic extract was washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was used immediately in the next reaction without further purification.

To a stirred solution of NaH (0.76 g, 19.5 mmol) in THF (60 mL) was added ethyl 2-(diethoxyphosphoryl)acetate (4.3 g, 19.5 mmol) at 0 °C under N_2 atmosphere and stirred for 45 min. Then the reaction mixture was cooled to −78 °C and to that was added the above crude 3-(*tert*-butyldimethylsilyloxy)-2-chlorobenzaldehyde in THF (20 mL) *via* cannula. After 30 min, the reaction mixture was quenched with saturated NH_4Cl (10 mL) solution and allowed to attain room temperature. The reaction mixture was extracted with EtOAc (2 × 100 mL). The combined organic extract was washed with brine (15 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (SiO_2, 4% EtOAc–hexanes) to afford **27** (3.8 g, 89% yield) as a yellow viscous liquid. R_f 0.5 (10% EtOAc in hexanes); IR (neat): ν_{max} 2955, 2859, 1737, 1695, 1573, 1464, 1291, 1237, 1045, 990, 831, 780 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 8.11 (d, J = 16 Hz, 1H), 7.23 (dd, J = 7.7, 1.0 Hz, 1H), 7.12 (t, J = 8.0 Hz, 1H), 6.91 (dd, J = 7.7, 1.0 Hz, 1H), 6.40 (d, J = 16 Hz, 1H), 4.28 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H), 1.04 (s, 9H), 0.23 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 152.1, 141, 134.3, 126.9, 121.5, 120.8, 120, 126.6, 60.6, 25.6 (3C), 19.3, 14.3, −4.4 (2C). HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{26}O_3ClSi$ 341.1334, found 341.1313.

(*E*)-3-(3-(*tert*-Butyldimethylsilyloxy)-2-chlorophenyl)prop-2-en-1-ol (28). To a solution of **27** (1.5 g, 4.41 mmol) in anhydrous CH_2Cl_2 (35 mL) at −78 °C was added DIBAL-H (1.0 M in toluene, 11 mL, 11.0 mmol) and the mixture was stirred at that temperature for 15 min. Then the reaction mixture was slowly warmed to 0 °C and stirred for 1 h. The reaction was then quenched by slow addition of a few drops MeOH followed by saturated aqueous sodium potassium tartrate solution. The reaction mixture was stirred (~2 h) until two clear layers separated and was then extracted with EtOAc (2 × 50 mL). The combined organic extract was washed with water (5 mL), brine (5 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO_2, 10% EtOAc–hexanes) to afford **28** (1.17 g, 93% yield) as a colorless liquid. R_f 0.2 (10% EtOAc in hexanes); IR (neat): ν_{max} 3338, 2930, 2858, 1570, 1466, 1288, 1254, 1020, 841, 782, 680 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.13 (dd, J = 7.7, 1.0 Hz, 1H), 7.05 (t, J = 7.9 Hz, 1H), 7.0 (td, J = 16.2, 1.0 Hz, 1H), 6.79 (dd, J = 7.9, 1.3 Hz, 1H), 6.3 (td, J = 15.8, 5.6 Hz, 1H), 4.33 (dd, J = 5.6, 1.5 Hz, 2H), 1.04 (s, 9H), 0.23 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.7, 136.5, 131.4, 127.5, 126.6, 124.8, 119.4, 119.2, 63.4, 25.6 (3C), 18.3, −4.4 (2C). HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{15}H_{23}O_2ClNaSi$ 321.1048, found 321.1044.

(*E*)-(3-(But-1-en-3-ynyl)-2-chlorophenoxy)(*tert*-butyl)dimethylsilane (12a). To a solution of the alcohol **28** (0.7 g, 2.35 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C was added Dess–Martin periodinane (1.5 g, 3.45 mmol) under N_2 atmosphere and the mixture was stirred for 45 min at rt. Saturated $NaHCO_3$ (10 mL) and saturated $Na_2S_2O_3$ (10 mL) were added to the reaction mixture and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column gave an aldehyde which was used directly for the next reaction.

To a solution of diisopropylamine (0.4 mL, 2.82 mmol) in anhydrous THF (8 mL) was added *n*-butyllithium (1.6 M in hexane, 1.8 mL 2.82 mmol) at −78 °C and the mixture was stirred for 30 min. $TMSCHN_2$ (2 M in hexanes, 1.4 mL, 2.82 mmol) was added to the reaction mixture and stirred for another 30 min. A solution of crude aldehyde prepared above in THF (15 mL) was then added to the reaction mixture and stirred for 1 h at −78° C and 3 h at reflux temperature. Cold water (10 mL) was added and extracted with ether (2 × 50 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (SiO_2, 1% EtOAc–hexanes) to afford **12a** (0.514 g, 75% yield over two steps) as a clear yellow oil. R_f 0.5 (5% EtOAc in hexanes); IR (neat): ν_{max} 2930, 2857, 1570, 1466, 1288, 1253, 998, 838, 781, 681 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.47 (d, J = 16.1 Hz, 1H), 7.14 (dd, J = 7.9, 1.5 Hz, 1H), 7.09 (t, J = 7.9 Hz, 1H), 6.84 (dd, J = 7.9, 1.5 Hz, 1H), 6.1 (dd, J = 16.3, 2.3 Hz, 1H), 3.1 (d, J = 2.3 Hz, 1H), 1.04 (s, 9H), 0.23 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152, 139.6, 135.6, 126.8, 125.1, 120.4, 118.7, 109.5, 82.6, 79.8, 25.6 (3C), 18.3, −4.4 (2C); MS (EI) m/z 292 (M^+). Anal. Calcd for $C_{16}H_{21}ClOSi$: C, 65.62; H, 7.23; found: C, 64.97; H, 7.39.

(1*E*,3*E*,7*S*,8*R*,10*R*,11*R*,12*R*)-7-(*tert*-Butyldimethylsilyloxy)-1-(3-(*tert*-butyldimethylsilyloxy)-2-chlorophenyl)-12-ethyl-11-hydroxy-8,10-dimethyltetradeca-1,3,13-trien-5-one (30). To a stirred solution of the alcohol **13** (0.170 g, 0.35 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0 °C, anhydrous DMSO (4 mL), Et_3N (0.25 mL, 1.78 mmol) and SO_3–Py complex (0.283 g, 1.78 mmol) were added sequentially under N_2 atmosphere and the mixture was stirred for 45 min. Saturated aqueous NH_4Cl (5 mL) was added and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with water (5 mL), brine (5 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent furnished the crude aldehyde, which was passed through a short pad of silica gel and used as such for the next reaction.

A solution of **12a** (91.0 mg, 0.71 mmol) in anhydrous THF (3 mL) at −78 °C was treated with *n*-BuLi (1.6 M in hexane, 0.44 mL, 0.71 mmol) and stirred for 40 min. A solution of the aldehyde prepared above in anhydrous THF (3 mL) was added to the reaction mixture and stirred for 1 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl (5 mL) solution at 0 °C and extracted with EtOAc (2 × 40 mL). The combined organic extracts were washed with water (5 mL) brine (5 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure and purification of the residue *via* column chromatography (SiO_2, 7% EtOAc–hexanes) afforded a mixture of diastereomeric alcohols (0.23 g, 88% yield), which were used directly for the next reaction.

To a solution of the above diastereomeric mixture of alcohols (0.23 g, 0.308 mmol) in anhydrous THF (5 mL) at 0 °C was added Red-Al (3.46 M in toluene, 0.24 mL, 0.83 mmol)

and the mixture was stirred at rt for 1 h. The reaction mixture was then quenched with MeOH (2 mL) and saturated aqueous potassium sodium tartrate solution (5 mL) at 0 °C. The reaction mixture was allowed to stir at rt until two layers separated and it was extracted with EtOAc (2 × 40 mL). The combined organic extracts were washed with water (5 mL), brine (5 mL), dried over Na_2SO_4, and concentrated under vacuum. Purification of the residue by column chromatography (SiO_2, 6% EtOAc–hexanes) afforded the diene compound as a mixture of diastereomers (0.195 g, 85% yield).

To a stirred solution of the mixture of dienes (40.0 mg, 0.066 mmol) in $CHCl_3$ and pH = 7 phosphate buffer (20 : 1, 4 mL) at 0 °C, DDQ (30 mg, 0.13 mmol) was added and stirred for 1 h at 0 °C. The reaction was then quenched with saturated aqueous $NaHCO_3$ (5 mL) solution and extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with water (5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (SiO_2, 12% EtOAc–hexanes) to afford **30** (135 mg, 60% yield over four steps) as a clear oil. R_f 0.4 (10% EtOAc in hexanes); $[\alpha]_D^{25}$ = –5.3 (*c* 0.8 in $CHCl_3$); IR (neat): ν_{max} 3412 (br), 2970, 2860, 2361, 1676, 1526, 1463, 1190, 845, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.41 (d, *J* = 15.3 Hz, 1H), 7.36–7.23 (m, 2H), 7.12 (t, *J* = 8 Hz, 1H), 6.87–6.80 (m, 2H), 6.30 (d, *J* = 15.3 Hz, 1H), 5.52 (dt, *J* = 17.7, 10.5 Hz, 1H), 5.09 (dd, *J* = 10.2, 1.6 Hz, 1H), 5.02 (dd, *J* = 17.7, 1.6 Hz, 1H), 4.15 (m, 1H), 3.29 (m, 1H), 2.83 (m, 1H), 2.48 (dd, *J* = 14.5, 4.0 Hz, 1H), 2.06 (m, 1H), 1.81–1.61 (m, 3H), 1.36–1.08 (m, 3H), 1.04 (s, 9H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.89–0.84 (m, 15H), 0.24 (s, 6H), 0.05 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200, 152.1, 142.7, 140.9, 139.2, 137.4, 135.7, 131.6, 129.1, 126.8, 120.5, 119.3, 116.4, 79.0, 74.1, 49.6, 43.6, 36.4, 32.7, 31.3, 25.8(3C), 25.6(3C), 22.6, 18.3, 18.0, 16.9, 13.9, 11.5, −4.4, −4.6, −4.7(2C). HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{36}H_{61}O_4ClNaSi_2$ 671.3694, found 671.3697.

(3*R*,4*R*,5*R*,7*R*,8*S*,11*E*,13*E*)-8-(*tert*-Butyldimethylsilyloxy)-14-(3-(*tert*-butyldimethylsilyloxy)-2-chlorophenyl)-3-ethyl-5,7-dimethyl-10-oxotetradeca-1,11,13-trien-4-yl acrylate (10a). To a stirred solution of **30** (80 mg, 0.123 mmol) in anhydrous CH_2Cl_2 (3 mL) at 0 °C, Et_3N (0.05 mL, 0.369 mmol) and acryloyl chloride (0.01 mL, 0.246 mmol) were added sequentially under nitrogen atmosphere and the mixture was stirred at the same temperature for 2 h. Then it was quenched with water (2 mL) and extracted with EtOAc (2 × 30 mL). The organic extract was washed with saturated $NaHCO_3$ (5 mL), brine (5 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO_2, 7% EtOAc–hexanes) provided **10a** (73 mg, 85% yield) as a colorless oil. R_f 0.6 (10% EtOAc in hexanes); $[\alpha]_D^{25}$ = –11.2 (*c* 0.7 in $CHCl_3$); IR (neat): ν_{max} 2970, 2890, 2361, 1646, 1516, 1463, 1190, 840, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.44–7.23 (m, 2H), 7.12 (m, 1H), 6.89–6.80 (m, 2H), 6.41 (dd, *J* = 17.3, 1.6 Hz, 1H), 6.31 (d, *J* = 15.8 Hz, 1H), 6.15 (dd, *J* = 17.3, 10.5 Hz, 1H), 5.83 (dd, *J* = 9.8, 1.5 Hz, 1H), 5.46 (m, 1H), 5.14–5.0 (m, 2H), 4.91 (dd, *J* = 9.0, 3.0 Hz, 1H), 4.16–4.07 (m, 2H), 2.83 (dd, *J* = 15.1, 8.3 Hz, 1H), 2.47 (dd, *J* = 15.1, 3.7 Hz, 1H), 2.27 (m, 1H), 1.94–1.73 (m, 2H), 1.06–0.98 (m, 13H), 0.91–0.76 (m, 18H), 0.23 (s, 6H), 0.04 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 166.3, 152.2, 142.7, 138.0, 137.5, 135.6, 131.7, 130.7, 129.1, 128.6, 126.8, 125.8, 120.6, 119.3, 117.2, 80.0, 74.0, 48.1, 43.8, 36.4, 32.1, 31.6, 25.9 (3C), 25.6 (3C), 23.0, 18.3, 18.0, 16.7, 13.7, 11.4, −4.3, −4.5, −4.7. HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{39}H_{64}O_5ClSi_2$ 703.3975, found 703.3980.

(5*R*,6*R*)-6-((2*R*,4*R*,5*S*,8*E*,10*E*)-5-(*tert*-Butyldimethylsilyloxy)-11-(3-(*tert*-butyldimethylsilyloxy)-2-chlorophenyl)-4-methyl-7-oxoundeca-8,10-dien-2-yl)-5-ethyl-5,6-dihydro-2*H*-pyran-2-one (9a). A solution of **10a** (50 mg, 0.071 mmol) in anhydrous CH_2Cl_2 (26 mL) was degassed and Grubbs' first generation catalyst (10 mg, 0.0071 mmol) was added under nitrogen atmosphere. The resulting pale purple solution was heated to reflux (50 °C) for 20 h. The solvent was evaporated under vacuum and the crude residue was purified by column chromatography (SiO_2, 15% EtOAc–hexanes) to give **9a** (40 mg, 85% yield) as a clear oil. R_f 0.4 (10% EtOAc in hexanes); $[\alpha]_D^{25}$ = –45.4 (*c* 0.5 in $CHCl_3$); IR (neat): ν_{max} 3100, 2917, 2750, 1186, 1013, and 1094, 835, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.41 (d, *J* = 16.0 Hz, 1H), 7.35 (dd, *J* = 16.0, 11.0 Hz, 1H), 7.24 (m, 1H), 7.14–7.04 (m, 2H), 6.88–6.81 (m, 2H), 6.31 (d, *J* = 15 Hz, 1H), 6.04 (d, *J* = 10 Hz, 1H), 4.14 (m, 1H), 3.94 (dd, *J* = 11.0, 3.0 Hz, 1H), 2.86 (dd, *J* = 15.0, 8.0 Hz, 1H), 2.46 (dd, *J* = 15.0, 3.0 Hz, 1H), 2.35 (m, 1H), 1.9 (m, 1H), 1.78–1.46 (m, 5H), 1.04 (s, 9H), 0.97 (t, *J* = 8.0 Hz, 3H), 0.9–0.82 (m, 15H), 0.24 (s, 6H), 0.06 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200, 164.8, 150.9, 142.7, 138.4, 137.4, 131.7, 130.8, 129.1, 128.7, 126.7, 120.9, 120.5, 119.3, 84.7, 73.7, 42.9, 36.7, 36.4, 35.7, 31.5, 25.8(3C), 25.6(3C), 23.7, 18.0, 14.7, 14.0, 13.3, 11.0, −4.3 (2C), −4.7 (2C). HRMS (ESI) *m*/*z* $[M + H]^+$ calcd $C_{37}H_{60}O_5ClSi_2$ 674.3589, found 674.3586.

(5*R*,6*R*)-6-((2*R*,4*R*,5*S*,8*E*,10*E*)-11-(2-Chloro-3-hydroxyphenyl)-5-hydroxy-4-methyl-7-oxoundeca-8,10-dien-2-yl)-5-ethyl-5,6-dihydro-2*H*-pyran-2-one (31). To a solution of **9a** (20 mg, 0.0296 mmol) in anhydrous CH_3CN (3 mL) in a polypropylene vial was added HF–Py complex (70%, 2.20 μl) at 0 °C. The reaction was slowly warmed to rt and stirred for 48 h. After completion of the reaction, it was cautiously poured into aqueous $NaHCO_3$ (5 mL) solution and stirred for 30 min and extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with saturated $CuSO_4$ (5 mL) solution, water (5 mL), brine (5 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO_2, 24% EtOAc in hexanes) to afford **31** (10.5 mg, 80% yield) as colourless oil. R_f 0.5 (40% EtOAc in hexanes); $[\alpha]_D^{25}$ = –91.3 (*c* 0.3 in $CHCl_3$); IR (neat): ν_{max} 3403 (br), 3300 (br), 2917, 2850, 1246, 1093, 1034, 835, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.41 (dd, *J* = 15.2, 11.0 Hz, 1H), 7.35 (d, *J* = 15.2 Hz, 1H), 7.25–7.16 (m, 2H), 7.11–6.96 (m, 2H), 6.88 (dd, *J* = 15.9, 11.0 Hz, 1H), 6.32 (d, *J* = 15.9 Hz, 1H), 6.05 (d, *J* = 9.8 Hz, 1H), 3.98 (dd, *J* = 9.6, 2.0 Hz, 1H), 3.94 (m, 1H), 2.87–2.67 (m, 2H), 2.40–2.28 (m, 2H), 1.95 (m, 1H), 1.62 (m, 4H), 0.93 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 165.0, 151.2, 143.0, 138.8, 137.2, 136.0, 130.7, 129.3, 127.7, 127.6, 120.8, 118.6, 116.4, 84.9, 72.1, 42.4, 36.6, 35.4, 35.0, 31.1, 20.1,

14.3, 13.9, 11.0. HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{32}O_5Cl$ 447.1938, found 447.1935.

(5*R*,6*R*)-6-((2*R*,4*R*,5*S*,7*S*,8*E*,10*E*)-11-(2-Chloro-3-hydroxyphenyl)-5,7-dihydroxy-4-methylundeca-8,10-dien-2-yl)-5-ethyl-5,6-dihydro-2*H*-pyran-2-one, {(−)-bitungolide B} (7). To a solution of **31** (8 mg, 0.018 mmol) in anhydrous CH_3CN (1.5 mL) at −30 °C were added $Me_4NBH(OAc)_3$ (19.7 mg, 0.075 mmol) and glacial AcOH (1.5 mL) sequentially. The temperature of the reaction was slowly raised to −20 °C, and stirring was continued at this temperature for 3 h. Then the reaction mixture was quenched with saturated potassium sodium tartrate (2 mL) at 0 °C and stirred at rt for 1 h. The reaction mixture was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 mL), water (2 mL), brine (2 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO_2, 40% EtOAc–hexanes) to afford 7 (6 mg, 78% yield) as a white amorphous solid. R_f 0.5 (60% EtOAc in hexanes); $[\alpha]_D^{25}$ = − 44.3 (*c* 0.3 in $CHCl_3$); IR (neat): ν_{max} 3403 (br), 3380 (br), 2917, 2850, 1701, 1246, 1093, 1034, 830 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.16 (m, 1H), 7.14 (m, 1H), 7.07 (dd, *J* = 9.8, 6.7 Hz, 1H), 6.90 (m, 1H), 6.88 (d, *J* = 15.3 Hz, 1H), 6.78 (dd, *J* = 14.8, 9.8 Hz, 1H), 6.52 (ddd, *J* = 15.8, 9.9, 1.9 Hz, 1H), 6.05 (d, *J* = 9.8 Hz, 1H), 5.96 (dd, *J* = 15.3, 5.9 Hz, 1H), 5.66 (brs, OH), 4.61 (m, 1H), 3.97 (dd, *J* = 10.8, 2.9 Hz, 1H), 3.79 (m, 1H), 2.68 (brs, OH), 2.43 (brs, OH), 2.36 (m, 1H), 1.95 (m, 1H), 1.84–1.66 (m, 5H), 1.5 (m, 1H), 1.20 (ddd, *J* = 12.8, 10.8, 1.9 Hz, 1H), 0.96 (t, *J* = 7.9 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 151.6, 151.1, 137.8, 135.8, 131.3, 129.9, 128.0, 127.5, 120.9, 119.1, 118.1, 114.7, 85.0, 73.4, 70.3, 38.8, 36.7, 36.1, 35.2, 31.0, 20.1, 14.7, 14.6, 11.0. HRMS (ESI) *m*/*z* $[M + Na]^+$: calcd for $C_{25}H_{33}O_5ClNa$ 471.1908, found 471.1912.

(1*E*,3*E*,7*S*,8*R*,10*R*,11*R*,12*R*)-7-(*tert*-Butyldimethylsilyloxy)-12-ethyl-11-hydroxy-8,10-dimethyl-1-phenyltetradeca-1,3,13-trien-5-one (32). Compound **32** (50 mg, 45% over four steps) was synthesized as a clear oil from **12b** (91.0 mg, 0.71 mmol) and aldehyde **24** (150 mg, 0.30 mmol) by following the same procedure as described for the synthesis of compound **30**. R_f 0.27 (SiO_2, 10% EtOAc–hexanes); $[\alpha]_D^{25}$ = +42.61 (*c* 0.21, $CHCl_3$); IR (neat): ν_{max} 3400 (br), 2925, 2855, 1515, 1587, 1461, 1252, and 1066 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.25–7.43 (m, 2H), 7.41–7.27 (m, 4H), 7.01–6.82 (m, 2H), 6.30 (d, *J* = 15.5 Hz, 1H), 5.51 (ddd, *J* = 17.1, 10.4, 9.2 Hz, 1H), 5.09 (dd, *J* = 10.4, 2.0 Hz, 1H), 5.03 (dd, *J* = 10.4, 2.0 Hz, 1H) 4.14 (dt, *J* = 8.3, 3.7 Hz, 1H), 3.28 (dd, *J* = 7.9, 3.7 Hz, 1H), 2.81 (dd, *J* = 14.5, 8.3 Hz, 1H), 2.46 (dd, *J* = 14.5, 3.7 Hz, 1H), 2.06 (m, 1H), 1.85–1.58 (m, 6H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.89–0.84 (m, 15H), 0.04 (s, 3H), −0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.0, 142.9, 141.3, 139.2, 136.0, 130.8, 129.1, 128.8, 127.2, 126.7, 116.4, 79.0, 74.1, 49.7, 43.8, 36.4, 32.7, 31.3, 25.8, 22.6, 18.0, 17.0, 13.8, 11.6, −4.6, −4.7; HRMS (ESI) *m*/*z* calcd for $C_{30}H_{48}O_3NaSi$ [M + Na]+: 507.3270, found: 507.3272.

(3*R*,4*R*,5*R*,7*R*,8*S*,11*E*,13*E*)-8-(*tert*-Butyldimethylsilyloxy)-3-ethyl-5,7-dimethyl-10-oxo-14-phenyltetradeca-1,11,13-trien-4-yl acrylate (10b). Compound **10b** (34 mg, 79% yield) was synthesized as a clear oil from **32** (40 mg, 0.082 mmol) *via* the same procedure as described for the synthesis of **10a**. R_f = 0.50 (SiO_2, 8% EtOAc–hexanes); $[\alpha]_D^{25}$ = +93.84 (*c* 0.18, $CHCl_3$); IR (neat): ν_{max} 2928, 2855, 1720, 1648, 1616, 1580, 1460, 1260, 1192, and 1066 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.53–7.44 (m, 2H), 7.43–7.30 (m, 4H), 7.04–6.78 (m, 2H), 6.44 (dd, *J* = 17.2, 1.6 Hz, 1H), 6.30 (d, *J* = 15.6 Hz, 1H), 6.14 (dd, *J* = 17.2, 9.9 Hz, 1H), 5.84 (dd, *J* = 9.9, 1.6 Hz, 2H), 5.46 (ddd, *J* = 17.2, 9.8, 9.0 Hz, 1H), 5.11 (dd, *J* = 10.7, 2.5 Hz, 1H), 4.96 (m, 1H), 4.12 (m, 1H), 2.82 (dd, *J* = 14.8, 8.2 Hz, 1H), 2.46 (dd, *J* = 14.8, 4.1 Hz, 1H), 2.25 (m, 1H), 1.80 (m, 1H), 1.66–1.35 (m, 5H), 0.91–0.75 (m, 18H), 0.04 (s, 3H), −0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 200.0, 166.3, 142.9, 141.4, 137.9, 136.0, 130.8, 130.7, 129.1, 128.8, 128.5, 127.2, 126.7, 117.2, 80.0, 74.0, 48.0, 43.9, 36.3, 32.0, 31.6, 25.8, 23.0, 18.0, 16.6, 13.6, 11.4, −4.7, −4.6; HRMS (ESI) *m*/*z* calcd for $C_{33}H_{50}O_4NaSi$ $[M + Na]^+$: 561.3376, found: 561.3369.

(5*R*,6*R*)-6-((2*R*,4*R*,5*S*,8*E*,10*E*)-5-(*tert*-Butyldimethylsilyloxy)-4-methyl-7-oxo-11-phenylundeca-8,10-dien-2-yl)-5-ethyl-5,6-dihydro-2*H*-pyran-2-one (9b). Compound **9b** (18 mg, 80% yield) was synthesized as a clear oil from **10b** (25 mg, 0.046 mmol) *via* the same procedure as described for the synthesis of compound **9a**. R_f = 0.43 (SiO_2, 15% EtOAc–hexanes); $[\alpha]_D^{25}$ = −112.20 (*c* 0.14, $CHCl_3$); IR (neat): ν_{max} 2926, 2855, 1722, 1616, 1589, 1461, 1382, 1250, and 1062 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.53–7.42 (m, 2H), 7.42–7.27 (m, 4H), 7.08 (dd, *J* = 9.8, 6.0 Hz, 1H), 7.02–6.82 (m, 2H), 6.29 (d, *J* = 15.1 Hz, 1H), 6.05 (d, *J* = 9.8 Hz, 1H), 4.14 (m, 1H), 3.94 (dd, *J* = 9.8, 3.0 Hz, 1H), 2.85 (dd, *J* = 14.3, 8.3 Hz, 1H), 2.44 (dd, *J* = 14.3, 3.0 Hz, 1H), 2.34 (m, 1H), 1.97–1.43 (m, 6H), 0.97 (t, *J* = 7.3 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.84 (s, 9H), 0.05 (s, 3H), −0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 200.0, 164.8, 150.9, 142.9, 141.2, 136.1, 130.9, 129.0, 128.7, 127.2, 126.8, 120.9, 84.7, 73.7, 42.9, 36.7, 36.4, 35.7, 31.4, 25.8, 22.6, 17.9, 14.6, 13.3, 10.9, −4.7; HRMS (ESI) *m*/*z* calcd for $C_{31}H_{46}O_4NaSi$ $[M + Na]^+$: 533.3630, found: 533.3638.

(5*R*,6*R*)-5-Ethyl-6-((2*R*,4*R*,5*S*,8*E*,10*E*)-5-hydroxy-4-methyl-7-oxo-11-phenylundeca-8,10-dien-2-yl)-5,6-dihydro-2*H*-pyran-2-one (33). Compound **33** (9.5 mg, 88% yield) was synthesized as a clear oil from **9b** (14 mg, 0.027 mmol) by following the same procedure as described for compound **31**. R_f = 0.32 (SiO_2, 20% EtOAc–hexanes); $[\alpha]_D^{25}$ = −180 (*c* 0.14, $CHCl_3$); IR (neat): ν_{max} 3474(br), 2924, 2868, 1715, 1615, 1585, 1458, 1382, 1252 and 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.51–7.43 (m, 2H), 7.42–7.28 (m, 4H), 7.05 (dd, *J* = 9.8, 6.8 Hz, 1H), 7.01 (d, *J* = 15.7 Hz, 1H), 6.87 (dd, *J* = 14.7, 10.8 Hz, 1H), 6.27 (d, *J* = 15.7 Hz, 1H), 6.04 (d, *J* = 9.8 Hz, 1H), 3.96 (dd, *J* = 10.8, 2.9 Hz, 1H), 3.92 (m, 1H), 2.82 (dd, *J* = 16.7, 2.0 Hz, 1H), 2.66 (dd, *J* = 16.7, 9.8 Hz, 1H), 2.34 (m, 1H), 1.95 (m, 1H), 1.84–1.66 (m, 3H), 1.65–1.47 (m, 2H), 1.00 (t, *J* = 7.8 Hz, 3H), 0.95 (d, *J* = 5.9 Hz, 0.95 (d, *J* = 5.9 Hz, 3H), 0.91 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 201.7, 165.1, 151.3, 143.8, 142.3, 135.8, 129.6, 129.4, 128.9, 127.4, 126.4, 121.0, 85.0, 72.3, 42.3, 36.7, 35.0, 31.2, 20.2, 14.5, 14.1, 13.7, 10.8; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{32}O_4Na$ $[M + Na]^+$: 419.2198, found: 419.2197.

(5*R*,6*R*)-6-((2*R*,4*R*,5*S*,7*S*,8*E*,10*E*)-5,7-Dihydroxy-4-methyl-11-phenylundeca-8,10-dien-2-yl)-5-ethyl-5,6-dihydro-2*H*-pyran-2-one, {(−)-bitungolide E} (8). Compound **8** (5 mg, 84% yield) was synthesized as a clear oil from **33** (7 mg, 0.0176) *via* the same procedure as described for the synthesis of **7**. R_f = 0.46 (SiO_2, 40% EtOAc–hexanes); $[\alpha]_D^{25}$ = −104.82 (*c* 0.2, $CHCl_3$); IR (neat): ν_{max} 3404 (br), 2960, 2924, 2855, 1713, 1459, 1384, 1258, and 1059 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.39 (br d, *J* = 7.3 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 2H), 7.22 (br t, *J* = 7.3 Hz, 1H), 7.08 (dd, *J* = 9.5, 6.6 Hz, 1H), 6.78 (dd, *J* = 15.4, 10.3 Hz, 1H), 6.56 (br d, *J* = 15.4 Hz, 1H), 6.46 (dd, *J* = 15.4, 10.3 Hz, 1H), 6.04 (d, *J* = 9.6 Hz, 1H), 5.90 (dd, *J* = 15.4, 5.9 Hz, 1H), 4.61 (m, 1H), 3.97 (dd, *J* = 10.3, 2.9 Hz, 1H), 3.80 (m, 1H), 2.36 (m, 1H), 1.95 (m, 1H), 1.84–1.76 (m, 2H), 1.72–1.68 (m, 3H), 1.49 (m, 1H), 1.20 (m, 1H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.9, 151.2, 137.2, 136.1, 132.6, 130.3, 128.6, 128.2, 127.5, 126.3, 120.9, 85.0, 73.3, 70.4, 38.8, 36.7, 36.1, 35.2, 31.0, 20.1, 14.7, 14.6, 11.0; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{34}O_4Na$ $[M + Na]^+$: 421.2354, found: 421.2349.

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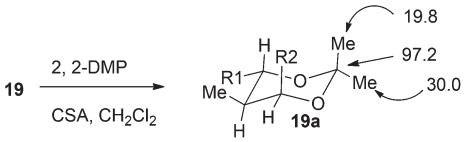

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