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The first total synthesis of (−)-bitungolide E

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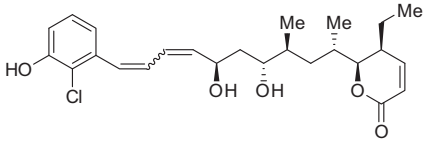
ABSTRACT

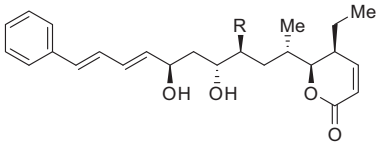
The first total synthesis of (−)-bitungolide E is described. The key steps include a Myers' alkylation, modified Evans' syn aldol-reaction, using Crimmins protocol, Sharpless asymmetric epoxidation and ring-closing metathesis reaction.

Secondary metabolites produced by marine sponges are considered to be one of the most important sources of pharmacologically active compounds.[1] Bitungolides A-F (1–6) form a new class of secondary metabolites isolated by Tanaka et al. from the Indonesian sponge *Theonella* cf. *swinhoei* (Fig. 1).[2]

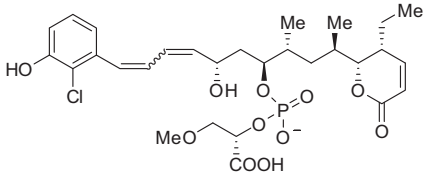
These compounds showed potent cytotoxic activity against 3Y1 rat normal fibroblast cells and inhibit dual-specificity phosphatase VHR. The structure of bitungolide A (**1**) was established by X-ray and the rest of the family by spectroscopic correlation. Very recently, Zhang et al. have isolated three novel polyketide phospho-



(+)–Bitungolide A (**1**): 12*Z*, 14*Z*
(+)–Bitungolide B (**2**): 12*E*, 14*E*
(+)–Bitungolide C (**3**): 12*Z*, 14*E*
(+)–Bitungolide D (**4**): 12*E*, 14*Z*



(+)–Bitungolide E (**5**): R = Me
(+)–Bitungolide F (**6**): R = H



(-)-Franklinolide A (**1a**): 12*Z*, 14*Z*
(-)-Franklinolide B (**2a**): 12*E*, 14*E*
(-)-Franklinolide *C* (**4a**): 12*E*, 14*Z*

Figure 1. Structures of natural (+)-bitungolides and (−)-franklinolides.

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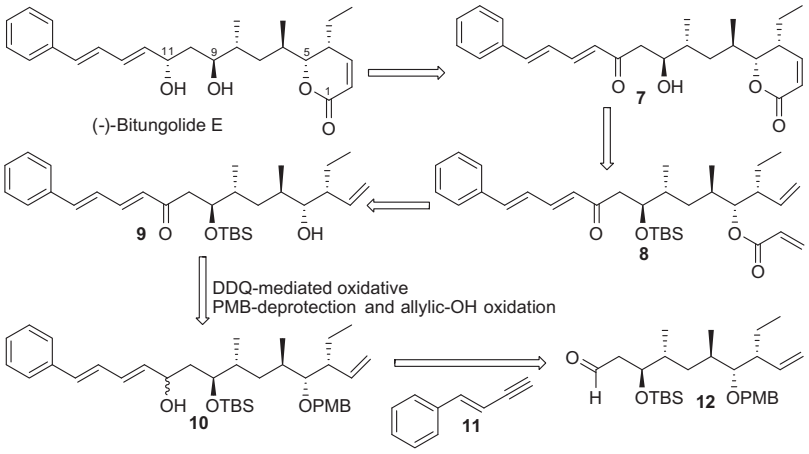
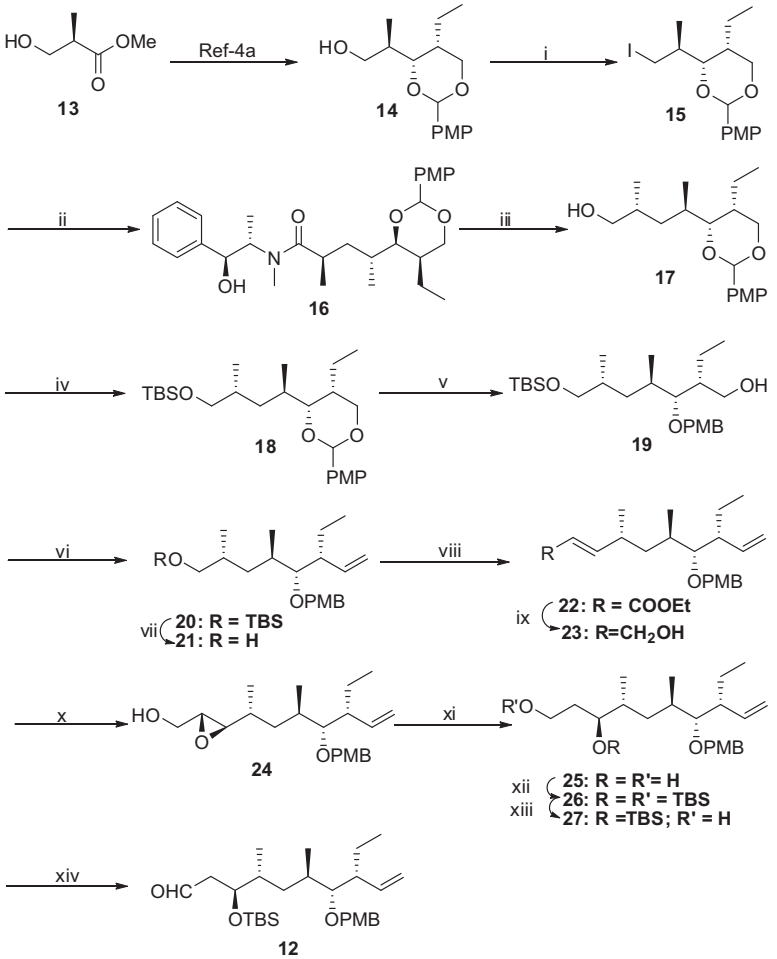
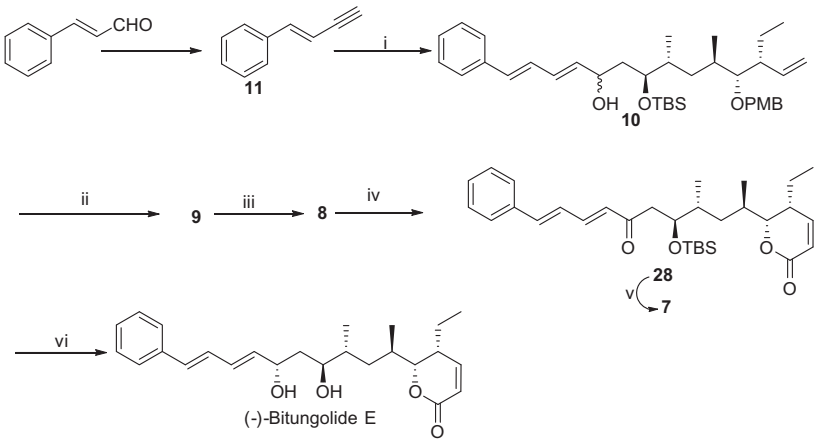
diesters, franklinolides A–C[3], which are nothing but the 3-O-methyl-2-phosphoglyceric acid phosphodiester adduct of (−)-bitungolides (A–B and D).[3] Initial biological studies revealed that these compounds are much more cytotoxic than bitungolides. Therefore, it is very important to develop a synthetic strategy by which not only (−)-bitungolides (A–E) but also their phosphodiester derivatives franklinolides A–C can be synthesized. In 2008, we achieved the first total synthesis of (−)-bitungolide F and deter-



Scheme 1. Retrosynthetic analysis of (−) bitungolide E.



Scheme 2. Reagents and condition: (i) TPP, I_2, imidazole, THF, 50 °C, 20 min, 97%; (ii) (1*S*,2*S*)-pseudo ephedrine propionamide, LDA, LiCl, THF, −78 °C to rt, 14 h, 88%; (iii) LDA, $BH_3{\cdot}NH_3$, THF, −78 °C to rt, 4 h, 95%; (iv) TBS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C–rt, 1 h, 98%; (v) DIBAL-H, CH_2Cl_2, −40 °C to −10 °C, 2 h, 89%; (vi) (a) SO_3–Py complex, DMSO:CH_2Cl_2 (1:1), 0 °C–rt, 90 min; (b) $PPh_3{=}CH_2$, NaHMDS, THF, −78 °C to rt, 18 h, 91% over two steps; (vii) TBAF, THF, 0 °C–rt, 10 h, 86%; (viii) (a) SO_3–Py complex, DMSO:CH_2Cl_2 (1:0.9), 0 °C–rt, 1.5 h; (b) $Ph_3P{=}CHCOOEt$, benzoic acid (cat.), toluene, 90 °C, 15 min, 98% over two steps; (ix) DIBAL-H, CH_2Cl_2, −78 °C to 0 °C, 1 h, 87%; (x) $Ti(O^iPr)_4$, (−)-DIPT, TBHP, CH_2Cl_2, -20 °C, 6 h, 79%; (xi) Red-Al, THF, 0 °C to rt, 4 h, 71%; (xii) TBS–OTf, 2,6-lutidine, CH_2Cl_2, 0 °C–rt, 3 h, 96%; (xiii) HF–py complex, THF, 0 °C–rt, 20 h, 89%; (xiv) SO_3–Py complex, DMSO:CH_2Cl_2 (1:1), 0 °C–rt, 45 min.



Scheme 3. Reagents and conditions: (i) (a) **11**, *n*-BuLi, −78 °C, then aldehyde **12**, 45 min; (b) Red-Al, dry THF, 0 °C–rt, 1 h; (ii) DDQ, $CHCl_3$/pH 7 buffer(20:1), 0 °C, 10 min, 46% over 4 steps; (iii) acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C–rt, 1 h, 79%; (iv) G-1 catalyst, CH_2Cl_2, reflux, 20 h, 80%; (v) HF–Py complex, CH_3CN, 0 °C–rt, 15 h, 88%; (vi) $Me_4NBH(OAc)_3$, CH_3CN/AcOH (1:1), −20 °C, 3 h, 84%.

mined its absolute stereochemistry.[4a] Subsequently, two more total syntheses have appeared in the literature.[4b,c] Although three total syntheses of (−)-bitungolide F have been reported in the literature, so far no total synthesis of other bitungolides (A–E) is reported.[5] In this Letter, we wish to report the first total synthesis of (−)-bitungolide E.

The retrosynthetic analysis of (−)-bitungolide E is outlined in Scheme 1. We planned to introduce the C11OH with the required stereochemistry at the final stage via hydroxyl directed 1,3-*anti* reduction of the β-hydroxy carbonyl compound (**7**), which we thought of synthesizing through ring closing metathesis reaction of the *bis*-olefinic compound **8**. Compound **8** could be obtained via acrylylation of **9**. We envisaged that the oxidation of the C11OH and the PMB deprotection of **10** could be performed in a single step by using DDQ to give **9**. The allylic alcohol **10** would be obtained via the addition of the acetylinic compound **11** to the aldehyde **12**, a common (C2–C11) fragment of bitungolides A–E, followed by *E*-selective reduction of the triple bond.

Thus, our synthesis commenced from-the known alcohol **14** which was prepared from (-)-*R*-Roche ester as per the reported chemistry reported by us (Scheme 2).[4a] Reaction of the primary alcohol **14** with triphenylphosphine (TPP) and iodine furnished the iodo compound **15**, in 97% yield.[6] Then, Myers alkylation[7] of (1*S*,2*S*)-pseudo ephedrine propionamide with **15** gave the alkylated product **16** in 88% yield. Removal of the chiral auxiliary from **16** with $BH_3{\cdot}NH_3$[7] yielded the primary alcohol **17**, which on TBS protection gave the compound **18** in 93% yield over two steps. Next, the PMB-acetal was opened with DIBAL-H[8] from the less hindered side to give the primary alcohol **19**, which on oxidation, followed by Wittig reaction with $Ph_3P{=}CH_2$ in THF, furnished the olefin **20** in 81% yield over three steps. TBS-deprotection of **20** with TBAF gave a primary alcohol **21**, which on oxidation followed by Wittig reaction with the stable ylide $Ph_3P{=}CHCOOEt$ in the presence of a catalytic amount of benzoic acid in toluene at 90 °C gave the α,β-unsaturated ester **22** with exclusive *E*-geometry.[9] DIBAL-H reduction of the α,β-unsaturated ester in CH_2Cl_2 afforded the corresponding allylic alcohol, which on Sharpless asymmetric epoxidation[10] with (−)-DIPT gave the epoxy alcohol **24** in 68% yield over two steps. Opening of the epoxy alcohol with red-Al[11] gave 1,3-diol **25**, which on protecting group manipulations followed by oxidation furnished the aldehyde **12**, a common (C2–C11) fragment of bitungolides A–E.

The remaining part of the synthesis is shown in Scheme 3. Addition of the anion generated from the ene-yne compound **11** to the aldehyde **12** gave a mixture of diastereomeric alcohol (1:1). Although they were separable via simple silica gel chromatography, we preferred to proceed with the mixture as it was oxidized in the later stage of the synthesis. Accordingly, reduction of the mixture of diastereomeric alcohol with red-Al[12] afforded the required *E,E*-diene system in good yield, which on treatment with DDQ, underwent allylic oxidation[13] of the C11-*OH* as well as PMB deprotection[8] of compound **10** and afforded the keto alcohol **9** in good yield. Acylation of the secondary alcohol of **9** with acryloyl chloride gave the *bis*-olefinic compound **8**, which on ring-closing metathesis reaction[14] with Grubbs' 1st generation catalyst furnished six membered α,β-unsaturated δ-lactone **28** in 80% yield. TBS- deprotection of **28** gave β-hydroxy keto compound **7**, which on hydroxyl directed reduction following the Evans' protocol[15] furnished (−)-bitungolide E in 84% yield, whose spectral data,[16] (^1H and ^{13}C) were in good agreement with the literature value. As expected, the specific rotation of synthetic (−)-bitungolide E ($[\alpha]_D^{25}$ = −104.8, *c* −0.2, $CHCl_3$) is comparable in magnitude to that of natural (+)-bitungolide E[2] ($[\alpha]_D^{25}$ = +107.0, *c* −1.26, $CHCl_3$) but of opposite sign.

In conclusion, we have developed a strategy for the synthesis of (−)-bitungolides E. By varying the configuration of the double bond geometry of compound **11** and by changing the reduction protocol for the partial reduction of triple bond, total synthesis of other (−)-bitungolides (A–D) as well as (−)-franklinolides (A–C) can be achieved. Total synthesis of biologically active naturally occurring (+)-bitungolides can also be achieved using the above strategy by changing the chiral starting material and auxiliaries. We are currently working in that direction, which will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.04.008.

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16. *Analytical and spectral data of compound* **28**: R_f = 0.43 (SiO_2, 15% EtOAc in petroleum ether); $([\alpha]_D^{22} = -112.20$ (*c* 0.14, $CHCl_3$); IR (neat): υ_{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, 20.1, 17.9, 14.6, 13.3, 10.9, −4.7; HRMS (ESIMS): Calcd for $C_{31}H_{46}O_4NaSi$ $[M+Na]^+$: 533.3063. Found: 533.3048; Analytical and spectral data of compound **7**: R_f = 0.32 (SiO_2, 20% EtOAc in petroleum ether); $([\alpha]_D^{22} = -180.66$ (*c* 0.14, $CHCl_3$); IR (neat): υ_{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, 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, 22.6, 20.2, 14.5, 14.1, 10.8; HRMS (ESIMS): Calcd for $C_{25}H_{32}O_4Na$ $[M+Na]^+$: 419.2198. Found: 419.2197; Analytical and spectral data of compound **(−)-**Bitungolide E: R_f = 0.46 (SiO_2, 40% EtOAc in petroleum ether); $([\alpha]_D^{22} = -104.82$ (*c* 0.2, $CHCl_3$); IR (neat): υ_{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* = 6.6, 9.5 Hz, 1H), 6.78 (dd, *J* = 10.3, 15.4 Hz, 1H), 6.56 (br d, *J* = 15.4 Hz, 1H), 6.46 (dd, *J* = 10.3, 15.4 Hz, 1H), 6.04 (d, *J* = 9.6 Hz, 1H), 5.90 (dd, *J* = 5.9, 15.4 Hz, 1H), 4.63–4.57 (m, 1H), 3.97 (dd, *J* = 2.9, 10.3 Hz, 1H), 3.80 (m, 1H), 2.36 (m, 1H), 1.95 (m, 1H), 1.80 (m, 2H), 1.70 (m, 1H), 1.60–1.40 (m, 2H), 1.40–1.39 (m,1H), 1.25–1.17 (m, 1H), 0.96 (d, *J* = 7.3 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.89 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.9, 151.2, 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 (ESIMS): calcd for $C_{25}H_{34}O_4Na$ $[M+Na]^+$: 421.2354. Found: 421.2347.