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Total Syntheses of Parthenolide and its Analogs with Macrocyclic Stereocontrol

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ABBREVIATIONS USED

DMAPT, dimethylaminoparthenolide; SAR, structure–activity relationship; SAE, Sharpless asymmetric epoxidation; TBDPS, *tert*-butyldiphenylsilyl; TBAF, tetrabutylammonium fluoride; TFA, trifluoroacetic acid; DABCO, 1,4-diazabicyclo[2.2.2]octane; THF, tetrahydrofuran; MS, molecular sieves; DIPT, diisopropyl tartrate; TBHP, *tert*-butyl hydroperoxide; DMF, dimethylformamide; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; NaHMDS, sodium hexamethyldisilazide; DIBALH, diisobutylaluminum hydride; TBAI, tetrabutylammonium iodide.

ABSTRACT

The first total synthesis of parthenolide (**1**) is described. The key feature of this synthesis is the formation of a 10-membered carbocylic ring by a macrocyclic stereocontrolled Barbier reaction, followed by a photo-induced *Z/E* isomerization. The biological evaluation of a small library of parthenolide analogs (**19**, **33** and **34**) disclosed a preliminary structure–activity relationship (SAR). The results revealed that the C1, C10 double bond configuration of parthenolide has little or no effect on the activity; and the C6 and C7 configurations of the lactone ring have a moderate impact on the activities against some cancer cell lines.

INTRODUCTION

Germacranolides, a type of germacrane sesquiterpene lactone, have a unique 10-membered carbocyclic skeleton and a *trans*- or *cis*-fused γ-lactone containing an α-methylene group in many cases. Among them, the incorporation of an epoxide ring, hydroxyl groups, or esterified hydroxyl groups are common (Figure 1).[1] Germacranolides are known to possess a wide variety of biological and pharmacological activities.[2] In particular, germacranolides can be processed into a variety of polycyclic sesquiterpene frameworks[3] (Scheme 1). Therefore, it was envisaged that germacranolides would provide a platform for the total synthesis of other types of sesquiterpene lactones. However, the total syntheses of germacranolides have remained challenging as the germacrene carbocycle core is unstable to acidic, basic, and thermal conditions (leading to cyclized and/or rearranged, fragmented products), and germacranolides can often exist as conformers at ambient temperature, thus making the purification and product analysis more difficult.[4] To date, there are only a few reports on the total syntheses of germacranolides.[5] The construction of the 10-membered ring system with stereochemical control is of paramount importance in these endeavors. Yamakawa *et al.* attempted to furnish the 10-membered ring system by a Barbier-type reaction. However, they obtained dilactones fused to a 20-membered

ring unit.[6] Recently, Baran *et al.* successfully furnished the 10-membered germacrane ring system with a *cis*-fused γ-lactone through a unique Pd-catalyzed macrocyclization.[5d]

Parthenolide (**1**, Figure 1), a prominent germacranolide originally purified from the shoots of feverfew (*Tanacetum parthenium*), which was used by the Europeans for a variety of ornamental and medicinal purposes for centuries, has attracted particular attention owing to its extensive biological activities.[7] Most importantly, parthenolide has been demonstrated as a small molecule that can selectively kill cancer stem cells.[8] Cancer stem cells have been postulated to be responsible for the failure of cancer treatment.[9] Moreover, parthenolide has been shown to inhibit solid tumor stem cells.[8a] However, parthenolide is unstable under both acidic and basic conditions[10] as well as in media containing 0.5% serum.[11] An amino-adduct of parthenolide, DMAPT, has advanced into clinical studies in humans.[12] Despite this great progress, to the best of our knowledge, the total synthesis of parthenolide has not yet been carried out, posing a barrier to an extensive structure–activity relationship (SAR) analysis for developing more effective and selective parthenolide-based drugs.

Recently, we reported a protecting group-free semisynthesis of parthenolide from the abundant natural product costunolide.[13] Herein, we report the first asymmetric total synthesis of parthenolide, 7-*epi*-parthenolide, and their 1(10)-*Z*-isomers. The biological evaluation of these analogs establishing the preliminary SAR within this class of compounds is also described

RESULTS AND DISCUSSION

Compounds syntheses

Our initial retro-synthetic analysis of parthenolide is shown in Scheme 2. We envisioned that parthenolide could be generated by lactonization from **A**, α-methylene-γ-hydroxyl ester or α-methylene-γ-hydroxyl nitrile, which could be prepared by an intramolecular Barbier-type reaction of **B**. The Barbier-type reaction has been used in the total synthesis of guaianolides.[14] The absolute stereochemistry could be controlled by the 4(5)-epoxy moiety obtained from **C** by a standard Sharpless asymmetric epoxidation (SAE). Furthermore, **C** could be elaborated from known compound **13**.

Our investigation commenced with known compound **13** (Scheme 3), which was obtained from farnesol in three steps.[15] Treatment of **13** with methyl acrylate and 1,4-diazabicyclo[2.2.2]octane (DABCO) gave substituted acrylate **14**, which then was chlorinated with simultaneous double bond isomerization to afford (*Z*)-**15** exclusively. However, cleavage of the TBDPS protecting group of **15** was unexpectedly difficult. Under standard TBAF or TFA conditions, no desired alcohol **16** was detected, and the starting material decomposed to a complex mixture. Fortunately, TBDPS deprotection of **15** was achieved using HF-pyridine in 91% yield.[16] The formed primary alcohol **16** was subjected to the standard SAE reaction[17] to produce compound **17**, which underwent oxidation to yield the corresponding aldehyde **18**. At this juncture, we poised to investigate the cyclization of **18** to construct the desired 10-membered ring. Under a variety of reductive Barbier-type coupling conditions, Zn^0,[18] In^0,[19] SmI_2,[20] or $CrCl_2$[21] in THF, no desired product was detected. Interestingly, this cyclization proceeded well with $CrCl_2$ in degassed dry DMF. Without purification, the initially formed α-methylene-γ-hydroxyl ester intermediate was treated with DBU to generate lactone **19**. However, an X-ray crystal structure of the product revealed that lactone **19** was the C-7 epimer of parthenolide (Scheme 3).

It was hypothesized that the *Z*-allylmetal reagent led to the *syn* product in accordance with the Felkin-Anh transition state; the relative stereochemistry of the lactone ring could be predicted from the precedent cyclic transition state for the addition of an allylmetal reagent to aldehydes, in which the (*E*)/(*Z*) stereochemistry of the double bond correlates to the *anti*/*syn* stereochemistry of the adduct.[22] Since the *Z*-double bond of our allymetal substrate led to the *cis* adduct, we presumed that the *E*-double bond of our allymetal substrate might result in the formation of the desired *trans* adduct; therefore, we designed the *E*-allylmetal substrate from the same intermediate **13**. Similar to the above steps, the Baylis-Hillman reaction of **13** with acrylonitrile, followed by chlorination delivered compounds **21a** and **21b** in a ratio of 3:1; the major product **21a** was the *E*-allylic chloride (Scheme 4). Compounds **21a** and **21b** were subjected to deprotection, SAE, and oxidation to afford aldehydes **22a** and **22b**, respectively. To our surprise, the separated aldehyde **22a** or **22b** went through the Barbier reaction to afford 6,7-*cis*-γ-hydroxyl nitrile **23** exclusively, and no desired 6,7-*trans* product was observed. In the transformation of **23** to lactone **19**, various procedures were tested, including the treatment of **23** with NaHMDS to remove the hydroxyl proton and lactonization,[23] DIBALH reduction to the hemiacetal and reoxidation,[24] base-catalyzed hydrolysis followed by acidic workup,[25] as well as strong acid-catalyzed hydrolysis with heating.[26] However, all of these methods led to decomposition of the starting material. The fragile epoxy moiety in **23** might be responsible for the failure of the transformation under these conditions. Fortunately, lactone **19** was successfully synthesized by first transforming **23** to hydroxyl amide **24** by H_2O_2-promoted hydrolysis,[27] followed by refluxing with DBU in benzene.[28]

Both the *E*- and *Z*-allylmetal substrates afforded the *cis* adduct. Thus, the geometry of the allylic chloride double bond was not the main factor that controlled the stereochemistry of the

lactone ring. The failure of this approach necessitated exploration of an alternative route to produce the desired *trans*-fused lactone. The conformation or geometrical preference of the large ring could direct the outcome of the reaction, with remote stereogenic elements providing enough conformational influence to direct formation of the desired product.[29] We speculated that the 1,10-double bond geometric configuration might affect the configuration of the two new stereogenic centers.

First, 1(10)-*Z*-cyclization precursors **28a** and **28b** were designed and synthesized (Scheme 5). We commenced with the known compound **25**, which was prepared from nerol in five steps.[30] Alcohol **25** was protected with TBDPS, and then selective cleavage of the C10-C11 double bond afforded aldehyde **26**. Next, aldehyde **26** underwent the Baylis-Hillman reaction with acrylonitrile, followed by chlorination to generate **27a** and **27b** (**27a**:**27b** = 3:1). The cyclization precursors **28a** and **28b** were obtained from **27a** and **27b** via three steps in 81% and 76% yields, respectively.

With **28a** in hand, various cyclization conditions were explored to furnish the desired 6,7-*trans* **30** (Table 1). Similar to our previous attempts, treatment of **28a** with the common Barbier-type coupling conditions of $CrCl_2$ in THF (entry 1, Table 1) did not provide any of the desired cyclized product. Gratifyingly, in the polar aprotic solvent DMF, compound **28a** was converted to 6,7-*cis* **29** and the desired 6,7-*trans* **30** in a ratio of 1.3:1 and 35% yield (entry 2, Table 1). Encouraged by this preliminary result, we further investigated a variety of reaction temperatures, additives, and solvents for the cyclization induced by $CrCl_2$ (entries 3–8, Table 1). However, in these experiments, the desired 6,7-*trans* **30** was obtained only as the minor product. Recently, Baran and coworkers successfully synthesized the medium-sized germacrane ring system through an umpolung allylation.[5d] Using their optimized conditions (entry 9, Table 1),[5d] compound **28a**

was smoothly transformed to **29** and **30** in a ratio of 2.8:1 in 16% yield (entry 9, Table 1). Switching the catalyst from $[Pd(PPh_3)_2Cl_2]$ to $[Pd(PPh_3)_4]$ further reduced the amount of 6,7-*trans* **30** (*cis:trans* = 3.7:1, entry 10, Table 1). Despite extensively investigating various reaction conditions, the Barbier reaction was met with limited success; none of the reactions proceeded with acceptable yield or selectivity. Considering the relatively low reactivity of allylic chloride, we added tetrabutylammonium Iodide (TBAI) to the reaction mixture, which enhanced the ratio of 6,7-*trans* **30** (entry 11, Table 1). Inspired by this result, we first converted the allylic chloride into allylic iodide and then the crude product was submitted to the Barbier reaction using $CrCl_2$ in THF, the two-steps procedure resulted in an increased ratio of 6,7-*trans* **30** (1:1) and a moderate yield (52%) (entry 12, Table 1). However, the mixed solvent of DMF/THF (1:2) reduced the yield and ratio of 6,7-*trans* **30** (entry 13, Table 1).

Following the previously optimized reaction conditions, cyclization of compound **28b** afforded a mixture of compounds **29** and **30** in a ratio of 1.9:1. This result further illustrated that the geometry of the allylic chloride double bond was not the only important factor that controlled the stereochemistry of the lactone ring and that the 1,10-double bond geometric configuration also affected the outcome of the two new stereogenic centers.

The mixture of **29** and **30** was hydrolyzed using basic hydrogen peroxide to produce compounds **31**, **32**, and **33** (Scheme 6). Compound **31** was converted to lactone **34** by refluxing in benzene with DBU. Compound **32** was unstable, and purification by silica gel column chromatography resulted in its partial transformation into compound **33**. Upon stirring with DBU in CH_2Cl_2, complete conversion of **32** into **33** was achieved.

With **33** in hand, completion of the synthesis entailed conversion of the 1(10)-*Z*-double bond of **33** into the requisite *E* configuration (Scheme 6). Irradiation of **33** with UV light (254 nm) afforded **1** in 58% conversion and 77% yield based on the recovery of starting material. All spectroscopic data of this product corresponded with the reported data for the natural product.[31–33] Meanwhile, 1(10)-*E*-**19** was irradiated to provide the corresponding product 1(10)-*Z*-**34** in 59% yield based on the recovery of starting material.

Compound **35**, the 1(10)-*Z* isomer of **17**, which was prepared from **26** in five steps, was also subjected to Barbier reaction conditions (Scheme 7). Surprisingly, exposure of **35** to $CrCl_2$ in DMF followed by lactonization with DBU in CH_2Cl_2 cleanly provided only *cis* **34**.

Activities against cultured cancer cell lines

Next, parthenolide (**1**) and the synthesized analogs (**19**, **33**, and **34**) were subjected to biological assays against the cultured acute myeloid leukemia cell line HL-60, rat glioma cell line C6, and human breast cancer cell lines MCF-7 and SUM159. As indicated in Table 2, compounds **1**, **19**, **33**, and **34** showed similar activities against HL-60 cells with IC_{50} values of 2.5 μM, 2.9 μM, 1.2 μM, and 4.2 μM, respectively. Melampomagnolide B, the allylic alcohol analogue of compound **33** showed high activities against primary leukemia cells.[34] For the C6 cell line, **33** was slightly more potent than parthenolide (IC_{50} = 3.9 μM vs. 6.6 μM); and compounds **19** (IC_{50} = 24.0 μM) and **34** (IC_{50} = 41.8 μM) showed reduced inhibitory activities compared to that of parthenolide. The activity against MCF-7 cells exhibited by compound **33** (IC_{50} = 5.9 μM) was comparable to that of parthenolide (IC_{50} = 6.9 μM), while compounds **19** (IC_{50} = 17.6 μM) and **34** (IC_{50} = 13.0 μM) showed less potency than parthenolide and compound **33**. Surprisingly, compounds **33** and **34** showed high activity against the human breast cancer cell

line SUM159, which has a high percentage of breast cancer stem/progenitor cells,[35] with IC_{50} values of 7.7 μM and 3.5 μM, respectively.

Based on the above activity results, the preliminary SAR was determined to be as follows: (1) the C1, C10 double bond configuration of parthenolide has little or no effect on the activity; and (2) the C6 and C7 configurations of the lactone ring have a moderate impact on the activities against some cancer cell lines.

CONCLUSIONS

In summary, the intramolecular Barbier reaction with compounds **18**, **22**, **35** readily afforded 6,7-*cis* diastereoisomer **19** as the only cyclic product. This indicate that both *E* and *Z* double bond geometry in the allylmetal moieties correlates to the *anti* stereochemistry of the adduct, and the commonly used cyclic Felkin-Anh transition state is not able to explain this phenomena.[22] Based upon the concept of macrocyclic stereocontrol proposed by Still,[36] several designs and attempts were applied to furnish the *trans*-fused 10-membered germacrane ring system. The successful final fusion started with compound **28a**, and the Barbier reaction with macrocyclic stereocontrol generated *trans* isomer **30** in low selectivity, followed by formation of lactone ring to obtain compound **33**, and the final photo-induced *Z*/*E* double bond isomerization provided parthenolide. Moreover, the synthetic sequences outlined in this study also enabled the formation of some parthenolide analogs. Therefore, the synthetic route may be useful to design and synthesize other backbone-modified parthenolide analogs, so that more effective and selective parthenolide-based drugs can be developed. Finally, the syntheses to parthenolide and its analogs illustrated here may provide a general strategy to obtain some *trans*-germacroanolide of medical interest.

EXPERIMENTAL SECTION

Chemistry. General. Unless otherwise mentioned, all reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions. The used solvents were purified and dried according to common procedures (Purification of laboratory chemicals (Six edition), Wilfred L. F. Armarego and Christina L. L. Chai). Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm Tsingdao silica gel plates (60F-254). Visualization was achieved using UV light, phosphomolybdic acid in ethanol or potassium permanganate in water, each followed by heating. Tsingdao silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. FTIR spectra were obtained with a Bruker Tensor 27 instrument. All IR samples were prepared as thin film and reported in wave numbers (cm^{-1}). NMR spectra were recorded with a 400 MHz (^{1}H: 400 MHz, ^{13}C: 100 MHz) spectrometer and referenced to the solvent peak for $CDCl_3$. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br. = broad, m = multiplet), coupling constants and integration. The purity of the final compounds was determined to be $\geqslant$ 95% by means of analytical high pressure liquid chromatography (HPLC) on a Shimadzu LD-20A system with an ODS-C18 column (4.6 × 150 mm, 5 μm) eluted at 1 mL/min with Milli-Q water and CH_3CN.

*tert-Butyl(((2E,6E)-9-(3,3-dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl)oxy)diphenylsilane (**S1**).* TBDPSCl (29.1 mL, 0.124 mol) was added to a mixture of farnesol (25.4 g, 0.115 mol), anhydrous dichloromethane (200 mL) and imidazole (9.3 g, 0.136 mol) at 0 ^{o}C. The resulting mixture was stirred for 1 h, and then it was diluted with dichloromethane,

poured over water, and extracted with more dichloromethane. The combined organic layer was dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The crude residue was dissolved in a 1.2 L solvent system of THF/H_2O = 3/1, was added *N*-bromosuccinimide (20.6 g, 0.116 mol) in small portions over a period of 1 h at 0 ^oC. After another 1 h stirring, 2.5 L of ether were added and the organic layer was washed with brine. The organic layer was dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure to afford the crude bromohydrin. The crude bromohydrin was dissolved in a slurry containing K_2CO_3 (27.0 g, 0.207 mol) in 610 mL of methanol. After 1 h, most of the methanol was removed under reduced pressure and the residue was extracted with diethyl ether to afford the crude epoxides. Purification by flash column chromatography (0–1% ethyl acetate/hexane) to provide **S1** (26.3 g, 0.055 mol, 48%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.75–7.67 (m, 4H), 7.45–7.35 (m, 6H), 5.39 (t, *J* = 6.1 Hz, 1H), 5.17 (t, *J* = 6.4 Hz, 1H), 4.23 (d, *J* = 6.2 Hz, 2H), 2.71 (t, *J*= 6.2 Hz, 1H), 2.21–2.04 (m, 4H), 2.04–1.96 (m, 2H), 1.63 (s, 3H), 1.69–1.56 (m, 2H), 1.45 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 135.7, 134.4, 134.2, 129.6, 127.7, 124.8, 124.3, 64.3, 61.3, 58.4, 39.6, 36.5, 27.6, 27.0, 26.5, 25.0, 19.3, 18.9, 16.5, 16.2.

*(4E,8E)-10-((tert-Butyldiphenylsilyl)oxy)-4,8-dimethyldeca-4,8-dienal (**13**)*. A solution of **S1** (26.1 g, 0.055 mol) in THF:H_2O (82:18, 365 mL) was treated with $NaIO_4$ (6.68 g, 0.031 mol, 0.6 equiv) and HIO_4•$2H_2O$ (13.75 g, 0.060 mol, 1.1 equiv) at 0 ^oC. The resulting mixture was stirred at 0 ^oC for 10 min and then warmed to room temperature. After 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (250 mL), and aqueous layer was extracted with EtOAc (3×500 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column

chromatography (0–1% ethyl acetate/hexane) to give the desired aldehyde **13** (22.5 g, 0.052 mol, 94%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (t, *J* = 1.2 Hz, 1H), 7.69–7.71 (m, 4H), 7.36–7.44 (m, 6H), 5.38 (t, *J* = 6 Hz, 1H), 5.14 (t, *J* = 6.4 Hz, 1H), 4.22 (d, *J* = 6 Hz, 2H), 2.50 (td, *J* = 6, 1.2 Hz, 2H), 2.31 (t, *J* = 7.6 Hz, 2H), 2.05–2.11 (m, 2H), 1.96–2.00 (m, 2H), 1.62 (s, 3H), 1.44 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.7, 136.9, 135.8, 134.2, 133.3, 129.7, 127.7, 125.2, 124.4, 61.3, 42.3, 39.4, 31.9, 27.0, 26.3, 19.3, 16.5, 16.3; HRMS (ESI-TOF) calcd for $C_{28}H_{38}NaO_2Si$ [M+Na^+] 457.2533, found 457.2533.

*(6E,10E)-Methyl 12-((tert-butyldiphenylsilyl)oxy)-3-hydroxy-6,10-dimethyl-2-methylenedodeca-6,10-dienoate (**14**)*. A solution of aldehyde **13** (650 mg, 1.49 mmol) and DABCO (33 mg, 0.298 mmol) in methyl acrylate (1.34 mL, 14.9 mmol) was stirred at room temperature for 2 days, then additional DABCO (33 mg, 0.298 mmol) was added and the mixture was stirred at room temperature for another 30 days. Evaporation in vacuum and column chromatography (0–10% ethyl acetate/hexane) gave the hydroxyl ester **14** as a colorless oil (598 mg, 1.150 mmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 7.0 Hz, 4H), 7.47–7.32 (m, 6H), 6.23 (s, 1H), 5.81 (s, 1H), 5.38 (t, *J* = 6.0 Hz, 1H), 5.17 (t, *J* = 6.4 Hz, 1H), 4.44–4.34 (m, 1H), 4.22 (d, *J* = 6.4 Hz, 2H), 3.78 (s, 3H), 2.62–2.56 (m, 1H), 2.15–2.04 (m, 3H), 2.03–1.94 (m, 2H), 1.82–1.63 (m, 3H), 1.62 (s, 3H), 1.44 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 142.9, 137.0, 135.7, 134.6, 134.1, 129.5, 127.6, 124.8, 124.7, 124.2, 70.8 , 61.2, 51.8, 39.5, 35.9, 34.5, 26.9, 26.3, 19.2, 16.3, 16.0; IR (KBr, cm^{-1}): 3440, 3051, 2937, 1714, 1630, 1435, 1195, 1108, 1061, 703; HRMS (ESI-TOF) calcd for $C_{32}H_{48}NO_4Si$ [M+NH_4^+] 538.3347, found 538.3342.

*(2Z,6E,10E)-Methyl 12-((tert-butyldiphenylsilyl)oxy)-2-(chloromethyl)-6,10-dimethyldodeca-2,6,10-trienoate (**15**)*. To a solution of **14** (520 mg, 1.00 mmol) in dry CCl_4 (10 mL) was added

n-Bu_3P (300 mg, 1.48 mmol) at room temperature under Ar. The resulting mixture was stirred for 2 h, concentrated under reduced pressure and purified by column chromatography (0–1% ethyl acetate/hexane) to afford **15** as a colorless oil (447 mg, 0.831mmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76–7.64 (m, 4H), 7.45–7.33 (m, 6H), 6.99 (t, *J* = 7.6 Hz, 1H), 5.39 (t, *J* = 6.0 Hz, 1H), 5.17 (t, *J* = 6.2 Hz, 1H), 4.32 (s, 2H), 4.23 (d, *J* = 6.0 Hz, 2H), 3.79 (s, 3H), 2.42 (q, *J* = 7.6 Hz, 2H), 2.16 (t, *J* = 7.6 Hz, 2H), 2.15–2.04 (m, 2H), 1.99 (t, *J* = 7.6 Hz, 2H), 1.63 (s, 3H), 1.45 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 148.6, 137.0, 135.8, 134.3, 133.6, 129.7, 129.2, 127.8, 125.7, 124.4, 61.3, 52.3, 39.5, 38.2, 37.4, 27.6, 27.0, 26.5, 19.4, 16.5, 16.2; IR (KBr, cm^{-1}): 3047, 2936, 1961, 1823, 1720, 1435, 1282, 1109, 1058, 703; HRMS (ESI-TOF) calcd for $C_{32}H_{47}ClNO_3Si$ [M+NH_4^+] 556.3008, found 556.3012.

*(2Z,6E,10E)-Methyl 2-(chloromethyl)-12-hydroxy-6,10-dimethyldodeca-2,6,10-trienoate (**16**).* To a solution of **15** (33 mg, 0.06 mmol) in THF (1 mL) was added pyridine hydrofluoride (70%, 0.14 mL, 1.0 mmol). The reaction mixture was stirred for 2.5 h, and then diluted with dichloromethane (10 mL). The resulting solution was washed with saturated aqueous sodium bicarbonate solution (5 mL), and then the organic phase was dried over magnesium sulfate and concentrated under reduced pressure and purified by column chromatography (0–30% ethyl acetate/hexane) to provide product **16** as colorless oil. (15 mg, 0.050 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 (t, *J* = 7.6 Hz, 1H), 5.36 (t, *J* = 6.4 Hz, 1H), 5.13 (t, *J* = 6.5 Hz, 1H), 4.29 (s, 2H), 4.11 (d, *J* = 6.8 Hz, 2H), 3.76 (s, 3H), 2.39 (q, *J* = 7.2 Hz, 2H), 2.16–2.05 (m, 4H), 2.05–1.96 (m, 2H), 1.71 (br s , 1H), 1.63 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 148.6, 139.0, 133.6, 129.0, 125.4, 123.8, 59.4, 52.2, 39.4, 38.0, 37.3, 27.3, 26.2, 16.3, 16.0; IR (KBr, cm^{-1}): 3354, 2926, 2858, 1718, 1646, 1440, 1286, 1197, 779; HRMS (ESI-TOF) calcd for $C_{16}H_{25}ClNaO_3$ [M+Na^+] 323.1384, found 323.1385.

*(2Z,6E)-Methyl 2-(chloromethyl)-9-((2R,3R)-3-(hydroxymethyl)-2-methyloxiran-2-yl)-6-methylnona-2,6-dienoate (**17**).* In a 10 mL round-bottom flask, 4 Å molecular sieves (100 mg) were dispersed in anhydrous CH_2Cl_2 (2.8 mL). D-(–)-diisopropyl tartrate (8.6 μL, 0.04 mmol) was added to the reaction flask and the mixture was cooled to –40 ^oC. After 10 min, Ti(O-*i*-Pr)$_4$ (10 μL, 0.03 mmol) was added and stirred at –40 ^oC for 15 min. After that time, TBHP (3.3 M in toluene, 0.15 mL,0.49 mmol) was introduced and the mixture was stirred at –40 ^oC for 30 min, then compound **16** (100 mg, 0.33 mmol) was added as a solution in anhydrous CH_2Cl_2 (1 mL). The reaction mixture was warmed to –18 ^oC and kept at this temperature overnight. The reaction was quenched by addition of acetone containing 2% water (3 mL), warmed to room temperature and stirred for 3 h. After filtering through Celite, the solvent was dried over $MgSO_4$, concentrated under reduced pressure. The crude mixture was purified by column chromatography (0–35% ethyl acetate/hexane) to provide compound **17** as a colorless oil (98 mg, 0.310 mmol, 93%, *ee* = 92%). $[\alpha]_D^{20}$ = 4.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 (t, *J* = 7.6 Hz, 1H), 5.14 (t, *J* = 6.7 Hz, 1H), 4.30 (s, 2H), 3.79 (dd, *J* = 12.0, 4.4 Hz, 1H), 3.77 (s, 3H), 3.66 (dd, *J* = 12.0, 6.6 Hz, 1H), 2.94 (dd, *J* = 6.6, 4.4 Hz, 1H), 2.40 (q, *J* = 7.6 Hz, 2H), 2.14 (t, *J* = 7.6 Hz, 2H), 2.13–2.03 (m, 2H), 1.70–1.63 (m, 1H), 1.61 (s, 3H), 1.52–1.42 (m, 1H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 148.5, 134.1, 129.2, 124.9, 63.1, 61.5, 61.1, 52.3, 38.4, 38.0, 37.4, 27.3, 23.6, 16.9, 16.0; IR (KBr, cm^{-1}): 3427, 3055, 2938, 2865, 1718, 1490, 1440, 1221, 954; HRMS (ESI-TOF) calcd for $C_{16}H_{25}ClNaO_4$ [M+Na^+] 339.1334, found 339.1330.

*(2Z,6E)-Methyl 2-(chloromethyl)-9-((2R,3S)-3-formyl-2-methyloxiran-2-yl)-6-methylnona-2,6-dienoate (**18**)*. To a solution of alcohol **17** (150 mg, 0.475 mmol) in CH_2Cl_2 (6.4 mL) was added $NaHCO_3$ (395 mg, 4.702 mmol) and Dess–Martin periodinane (403 mg, 0.950 mmol) at room temperature. After 1 h, sat. aq. $NaHCO_3$ (10 mL) was added and the reaction mixture was stirred

at room temperature for 10 min. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The CH_2Cl_2 layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (0–15% ethyl acetate/hexane) gave aldehyde **18** (136 mg, 0.433 mmol, 91%) as a clear colorless oil. $[\alpha]_D^{20}$ = –42.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (d, *J* = 5.0 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 5.13 (td, *J* = 7.2, 0.8 Hz,1H), 4.31 (s, 2H), 3.77 (s, 3H), 3.16 (d, *J* = 5.0 Hz, 1H), 2.41 (q, *J* = 7.5 Hz, 2H), 2.23–2.05 (m, 4H), 1.76–1.66 (m, 1H), 1.62 (s, 3H), 1.61–1.52 (m, 1H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5, 166.1, 148.1, 134.7, 129.1, 123.9, 64.0, 63.5, 52.1, 38.1, 37.9, 37.2, 27.2, 23.3, 17.2, 16.0; IR (KBr, cm^{-1}): 2922, 2852, 2729, 1719, 1645, 1441, 1282, 781; HRMS (ESI-TOF) calcd for $C_{16}H_{24}ClO_4$ [M+H$^+$] 315.1358, found 315.1360.

*7-epi-Parthenolide (**19**)*. Under Ar, to a solution of $CrCl_2$ (86 mg, 0.699 mmol) in dry DMF (10 mL) was added a solution of the aldehyde **18** (34 mg, 0.108 mmol) in 2 mL dry DMF over 2 h at room temperature. When the addition was completed, the reaction was allowed to stir for another 2 h and quenched with water (6.0 mL). The reaction mixture was extracted with Et_2O, the combined organic layers were combined and washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was dissolved in 4 mL of CH_2Cl_2 to which DBU (2.1 mg, 0.014 mmol) was added. After stirring for 48 h, the reaction mixture was concentrated, purified by flash chromatography (0–10% ethyl acetate/hexane) to yield compound **19** as a white solid (11 mg, 0.044 mmol, 41% over 2 steps). mp 125–126 ^{o}C; $[\alpha]_D^{20}$ = 26.4 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.18 (s, 1H), 5.65 (s, 1H), 5.31 (s, 1H), 4.07 (dd, *J* = 9.2, 5.6 Hz, 1H), 2.98–2.89 (m, 1H), 2.81 (d, *J* = 9.2 Hz, 1H), 2.47–2.16 (m, 4H), 2.15–2.03 (m, 2H), 1.71 (s, 3H), 1.62–1.51 (m, 1H), 1.30 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 143.2, 121.4, 80.0, 62.4, 60.8, 16.9; IR (KBr, cm^{-1}): 3056, 2930, 2867, 1753,

1599, 1491, 1440, 1226, 950; HRMS (ESI-TOF) calcd for $C_{15}H_{21}O_3$ [M+H$^+$] 249.1485, found 249.1489.

*(6E,10E)-12-((tert-Butyldiphenylsilyl)oxy)-3-hydroxy-6,10-dimethyl-2-methylenedodeca-6,10-dienenitrile (**20**)*. A solution of aldehyde **13** (18.9 g, 43.548 mmol) and DABCO (970 mg, 8.661 mmol) in acrylonitrile (86 mL, 1.313 mol) was stirred at room temperature for 2 days, then additional DABCO (970 mg, 8.661 mmol) was added and the mixture was stirred at room temperature for another 20 days. The mixture was concentrated and the residue was purified by silica gel column chromatography (0–10% ethyl acetate/hexane) to give compound **20** (17.2 g, 35.318 mmol, 81%) as an colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.67 (m, 4H), 7.48–7.34 (m, 6H), 5.97 (d, *J* = 0.8 Hz, 1H), 5.95 (s, 1H), 5.39 (t, *J* = 6.0 Hz, 1H), 5.20 (t, *J* = 6.4 Hz, 1H), 4.28–4.16 (m, 3H), 2.26 (dd, *J* = 9.6, 4.9 Hz, 1H), 2.16–2.07 (m, 4H), 2.02 (t, *J* = 7.2 Hz, 2H), 1.91–1.81 (m, 1H), 1.78–1.70 (m, 1H), 1.65 (s, 3H), 1.46 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 135.8, 134.1, 134.0, 129.8, 129.7, 127.8, 127.1, 125.8, 124.4, 117.2, 71.9, 61.4, 39.4, 35.4, 33.7, 27.0, 26.2, 19.3, 16.4, 15.9; IR (KBr, cm^{-1}): 3471, 3064, 2933, 2858, 2227, 1667, 1431, 1108, 1059, 703; HRMS (ESI-TOF) calcd for $C_{31}H_{42}NO_2Si$ [M+H$^+$] 488.2979, found 488.2981.

*(2E,6E,10E)-12-((tert-Butyldiphenylsilyl)oxy)-2-(chloromethyl)-6,10-dimethyldodeca-2,6,10-trienenitrile (**21a**)* and *(2Z,6E,10E)-12-((tert-butyldiphenylsilyl)oxy)-2-(chloromethyl)-6,10-dimethyldodeca-2,6,10-trienenitrile (**21b**)*. To a solution of **20** (1.21 g, 2.485 mmol) in dry CCl_4 (24.8 mL) was added *n*-Bu_3P (0.92 mL, 3.677 mmol) at room temperature under Ar. After 2 h, the reaction mixture was concentrated and purified by column chromatography (0–1% ethyl acetate/hexane) to provide **21a** (748 mg, 1.481 mmol, 60%) and **21b** (250 mg, 0.495 mmol, 20%).

21a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78–7.64 (m, 4H), 7.49–7.33 (m, 6H), 6.46 (t, *J* = 7.6 Hz, 1H), 5.40 (t, *J* = 5.8 Hz, 1H), 5.15 (t, *J* = 6.4 Hz, 1H), 4.25 (d, *J* = 6.2 Hz, 2H), 4.09 (s, 2H), 2.53 (q, *J* = 7.4 Hz, 2H), 2.15 (t, *J* = 7.2 Hz, 2H), 2.12–2.06 (m, 2H),2.07–1.96 (m, 2H), 1.65 (s, 3H), 1.46 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 136.9, 135.8, 134.2, 132.9, 129.7, 127.7, 126.3, 124.4, 115.7, 112.5, 61.3, 44.1, 39.4, 37.9, 29.9, 27.0, 26.4, 19.3, 16.5, 16.0; IR (KBr, cm^{-1}): 3062, 2933, 2858, 2223, 1639, 1433, 1266, 1108, 1057, 705; HRMS (ESI-TOF) calcd for $C_{31}H_{40}ClNNaOSi$ [M+Na^+] 528.2460, found 528.2457.

21b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.66 (m, 4H), 7.46–7.34 (m, 6H), 6.52 (t, *J* = 7.6 Hz, 1H), 5.39 (t, *J* = 6.2 Hz, 1H), 5.16 (t, *J* = 6.6 Hz, 1H), 4.24 (d, *J* = 6.2 Hz, 2H), 4.11 (s, 2H), 2.38 (q, *J* = 7.5 Hz, 2H), 2.18–2.04 (m, 4H), 2.05–1.96 (m, 2H), 1.62 (s, 3H), 1.46 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 136.9, 135.8, 135.0, 134.3, 129.8, 127.8, 126.5, 124.5, 118.2, 112.4, 61.3, 39.4, 38.3, 37.8, 27.4, 27.0, 26.8, 19.4, 16.5, 16.1; IR (KBr, cm^{-1}): 3048, 2932, 2857, 2224, 1963, 1667, 1634, 1590, 1427, 1109, 1058; HRMS (ESI-TOF) calcd for $C_{31}H_{44}ClN_2OSi$ [M+NH_4^+] 523.2906, found 523.2903.

(2E,6E,10E)-2-(Chloromethyl)-12-hydroxy-6,10-dimethyldodeca-2,6,10-trienenitrile ***(S2)***. To a solution of **21a** (140 mg, 0.277 mmol) in THF (5 mL) was added pyridine hydrofluoride (70%, 0.26 mL, 1.857 mmol). The reaction mixture was stirred for 2.5 h, and then diluted with dichloromethane (40 mL). The resulting solution was washed with saturated aqueous sodium bicarbonate solution (10 mL), then the organic phase was dried over magnesium sulfate and the solvent was removed under reduced pressure. Resulting residue was purified by column chromatography (0–30% ethyl acetate/hexane) to give the alcohol **S2** as a colorless oil. (57 mg, 0.213 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (t, *J* = 7.6 Hz, 1H), 5.36 (t, *J* = 6.8 Hz, 1H), 5.10 (t, *J* = 6.4 Hz, 1H), 4.11 (d, *J* = 6.7 Hz, 2H), 4.08 (s, 2H), 2.49 (q, *J* = 7.4 Hz, 2H),

2.15–2.04 (m, 4H), 2.04–1.96 (m, 2H), 1.71 (br s, 1H), 1.63 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 139.0, 133.0, 125.9, 123.8, 115.6, 112.5, 59.3, 44.0, 39.3, 37.8, 29.9, 26.2, 16.3, 15.9; IR (KBr, cm^{-1}): 3351, 2921, 2860, 2224, 1666, 1638, 1441, 1270, 1000, 715; HRMS (ESI-TOF) calcd for $C_{15}H_{22}ClNNaO$ [M+Na^+] 290.1282, found 290.1285.

*(2E,6E)-2-(Chloromethyl)-9-((2R,3R)-3-(hydroxymethyl)-2-methyloxiran-2-yl)-6-methylnona-2,6-dienenitrile (**S3**)*. In a 10 mL round-bottom flask, 4 Å molecular sieves (200 mg) were dispersed in anhydrous CH_2Cl_2 (6 mL). D-(–)-diisopropyl tartrate (18 μL, 0.087 mmol) was added to the reaction flask and the mixture was cooled to –40 ^{o}C. After 10 min, Ti(O-*i*-Pr)$_4$ (20 μL, 0.072 mmol) was added and stirred at –40 ^{o}C for 15 min. After that time, TBHP (3.3 M in toluene, 0.33 mL, 1.089 mmol) was introduced and the mixture was stirred at –40 ^{o}C for 30 min, then a solution of **S2** (193 mg, 0.723 mmol) in dry CH_2Cl_2 (1.5 mL) was added. The reaction mixture was warmed to –18 ^{o}C and kept at this temperature overnight. The reaction was quenched by addition of acetone containing 2% water (6 mL), warmed to room temperature and stirred for 3 h. After filtering through Celite, the solvent was dried over $MgSO_4$, concentrated under reduced pressure. The crude mixture was purified by column chromatography (0–35% ethyl acetate/hexane) to provide **S3** as a colorless oil (186 mg, 0.658 mmol, 91%, *ee* = 88%). $[\alpha]_D^{20}$ = 8.6 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (t, *J* = 7.6 Hz, 1H), 5.12 (t, *J* = 7.0 Hz, 1H), 4.09 (s, 2H), 3.84–3.74 (m, 1H), 3.70–3.59 (m, 1H), 2.93 (dd, *J* = 6.6, 4.4 Hz, 1H), 2.50 (q, *J* = 7.4 Hz, 2H), 2.32 (br s, 1H), 2.17–2.02 (m, 4H), 1.69–1.62 (m, 1H), 1.61 (s, 3H), 1.49 (ddd, *J* = 13.7, 9.0, 7.1 Hz, 1H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 133.4, 125.4, 115.6, 112.5, 63.0, 61.4, 61.0, 44.0, 38.2, 37.7, 29.8, 23.5, 16.7, 15.9; IR (KBr, cm^{-1}): 3428, 3055, 2934, 2863, 2224, 1637, 1441, 1222, 1031, 717; HRMS (ESI-TOF) calcd for $C_{15}H_{23}ClNO_2$ [M+H^+] 284.1412, found 284.1417.

*(2E,6E)-2-(Chloromethyl)-9-((2R,3S)-3-formyl-2-methyloxiran-2-yl)-6-methylnona-2,6-dienenitrile (**22a**)*. To a solution of **S3** (49 mg, 0.173 mmol) in CH_2Cl_2 (2.5 mL) was added $NaHCO_3$ (145 mg, 1.726 mmol) and Dess–Martin periodinane (146 mg, 0.344 mmol) at room temperature. After 1 h, sat. aq. $NaHCO_3$ (5 mL) was added. The resulting mixture was stirred at room temperature for 10 min. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The CH_2Cl_2 layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (0–15% ethyl acetate/hexane) to give **22a** (44 mg, 0.157 mmol, 91%) as a clear colorless oil. $[\alpha]_D^{20}$ = –59.4 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (d, *J* = 5.0 Hz, 1H), 6.48 (t, *J* = 7.6 Hz, 1H), 5.11 (t, *J* = 6.9 Hz, 1H), 4.10 (s, 2H), 3.16 (d, *J* = 4.9 Hz, 1H), 2.52 (q, *J* = 7.4 Hz, 2H), 2.24–2.05 (m, 4H), 1.71 (dt, *J* = 15.1, 7.6 Hz, 1H), 1.62 (s, 3H),1.65–1.55 (m, 1H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 151.6, 134.1, 124.7, 115.6, 112.7, 64.1, 63.5, 44.0, 38.1, 37.8, 29.7, 23.4, 17.3, 16.0; IR (KBr, cm^{-1}): 2929, 2731, 2223, 1720, 1637, 1445, 715; HRMS (ESI-TOF) calcd for $C_{15}H_{21}ClNO_2$ [M+H$^+$] 282.1255, found 282.1260.

*(2Z,6E,10E)-2-(Chloromethyl)-12-hydroxy-6,10-dimethyldodeca-2,6,10-trienenitrile (**S4**)*. To a solution of **21b** (380 mg, 0.752 mmol) in THF (11 mL) was added Ppyridine hydrofluoride (70%, 0.67 mL, 4.785 mmol). The reaction mixture was stirred for 2.5 h, and diluted with dichloromethane (80 mL). The resulting solution was washed with saturated aqueous sodium bicarbonate solution (30 mL), and then the organic phase was dried over magnesium sulfate. The solvent was removed under reduced pressure. The crude residue was purified by column chromatography (0–30% ethyl acetate/hexane) to afford **S4** (178 mg, 0.669 mmol, 89%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (t, *J* = 7.6 Hz, 1H), 5.43–5.36 (m, 1H), 5.14 (t, *J* = 6.4 Hz, 1H), 4.15 (d, *J* = 6.7 Hz, 2H), 4.12 (s, 2H), 2.39 (q, *J* = 7.4 Hz, 2H), 2.17–2.09 (m,

4H), 2.08–2.01 (m, 2H), 1.67 (s, 3H), 1.60 (s, 3H), 1.38 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 139.1, 132.8, 126.3, 123.9, 118.2, 112.3, 59.5, 39.4, 38.3, 37.8, 27.2, 26.3, 16.4, 16.0; IR (KBr, cm^{-1}): 3350, 2922, 2858, 2224, 1667, 1634, 1445, 1265, 1005, 727; HRMS (ESI-TOF) calcd for $C_{15}H_{26}ClN_2O$ [M+NH_4^+] 285.1728, found 285.1726.

*(2Z,6E)-2-(Chloromethyl)-9-((2R,3R)-3-(hydroxymethyl)-2-methyloxiran-2-yl)-6-methylnona-2,6-dienenitrile (**S5**).* In a 10 mL round-bottom flask, 4 Å molecular sieves (115 mg) was dispersed in anhydrous CH_2Cl_2 (5.4 mL). D-(–)-diisopropyl tartrate (11 μL, 0.050 mmol) was added to the reaction flask and the mixture was cooled to –40 °C. After 10 min, Ti(O-*i*-Pr)$_4$ (14 μL, 0.047 mmol) was added and stirred at –40 °C for 15 min. After that time, TBHP (3.3 M in toluene, 0.20 mL, 0.660 mmol) was introduced and the mixture was stirred at –40 °C for 30 min, then a solution of **S4** (115 mg, 0.431 mmol) in dry CH_2Cl_2 (1 mL) was added. The reaction mixture was warmed to –18 °C and kept at this temperature overnight. The reaction was quenched by addition of acetone containing 2% water (5 mL), warmed to room temperature and stirred for 3 h. After filtering through Celite, the solvent was dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by column chromatography (0–35% ethyl acetate/hexane) to provide **S5** as a colorless oil (107 mg, 0.378 mmol, 88%, *ee* = 87%). $[\alpha]_D^{20}$ = 12.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (t, *J* = 7.6 Hz, 1H), 5.14 (t, *J* = 6.7 Hz, 1H), 4.11 (s,2H), 3.83–3.75 (m, 1H), 3.70–3.63 (m, 1H), 2.94 (dd, *J* = 6.5, 4.4 Hz, 1H), 2.38 (q, *J* = 7.4 Hz, 2H), 2.23 (br s, 1H), 2.17–2.03 (m, 4H), 1.60 (s, 3H), 1.68–1.49 (m, 2H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 133.1, 125.8, 118.2, 112.3, 63.0, 61.5, 61.0, 38.3, 38.2, 37.7, 27.1, 23.6, 16.8, 15.9; IR (KBr, cm^{-1}): 3445, 2927, 2859, 2224, 1634, 1448, 1388, 1263, 1031, 726; HRMS (ESI-TOF) calcd for $C_{15}H_{26}ClN_2O_2$ [M+NH_4^+] 301.1677, found 301.1679.

*(2Z,6E)-2-(Chloromethyl)-9-((2R,3S)-3-formyl-2-methyloxiran-2-yl)-6-methylnona-2,6-dienenitrile (**22b**)*. To a solution of **S5** (71 mg, 0.251 mmol) in CH_2Cl_2 (3.6 mL) was added $NaHCO_3$ (210 mg, 2.500 mmol) and Dess–Martin periodinane (212 mg, 0.499 mmol) at room temperature. After 1 h, sat. aq. $NaHCO_3$ (5 mL) was added, and reaction was stirred at room temperature for 10 min. The CH_2Cl_2 layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The CH_2Cl_2 layer was combined, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (0–15% ethyl acetate/hexane) to yield **22b** (64 mg, 0.228 mmol, 91%) as a clear colorless oil. $[\alpha]_D^{20}$ = –54.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (d, *J* = 5.0 Hz, 1H), 6.52 (t, *J* = 7.6 Hz, 1H), 5.16–5.10 (m, 1H), 4.14 (s, 2H), 3.16 (d, *J* = 5.0 Hz, 1H), 2.40 (q, *J* = 7.5 Hz, 2H), 2.18–2.09 (m, 4H), 1.77–1.68 (m, 1H), 1.64–1.55 (m, 1H), 1.61 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 152.3 134.0, 124.8, 118.1, 112.5, 64.0, 63.6, 38.3, 38.1, 37.7, 27.1, 23.5, 17.3, 16.0; IR (KBr, cm^{-1}): 2923, 2853, 2223, 1721, 1634, 1449, 1405, 1264, 1240, 799; HRMS (ESI-TOF) calcd for $C_{15}H_{24}ClN_2O_2$ [M+NH_4^+] 299.1521, found 299.1523.

*2-((1S,2S,3R,10R,E)-2-Hydroxy-6,10-dimethyl-11-oxabicyclo[8.1.0]undec-6-en-3-yl)acrylonitrile (**23**)*. Under Ar, to a solution of $CrCl_2$ (532 mg, 4.329 mmol) in dry DMF (60 mL) was added a solution of **22a** (120 mg, 0.427 mmol) in 10 mL dry DMF over 2 h at room temperature. The reaction mixture was allowed to stir for another 8 h and quenched with 30 mL of water. The reaction mixture was extracted with Et_2O. The combined extracts were washed with water, then brine, dried over $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, the crude product was purified by flash chromatography (0–20% ethyl acetate/hexane) to provide **23** as a colorless oil (38 mg, 0.154 mmol, 36%); Under Ar, to a stirring solution of $CrCl_2$ (123 mg, 1.001 mmol) in dry DMF (16 mL) was added a solution of the

22b (33 mg, 0.117 mmol) in 2 mL dry DMF over 2 h at room temperature. The reaction mixture was allowed to stir for another 4 h at the same temperature and quenched with 8 mL of water. The reaction mixture was extracted with Et_2O. The combined extracts were washed with water and brine, dried over $MgSO_4$, and filtered. After removal of the solvent under reduced pressure, the crude residue was purified by flash chromatography (0–20% ethyl acetate/hexane) to give **23** (11.4 mg, 0.046 mmol, 39%). $[\alpha]_D^{20}$ = –77.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (s, 1H), 5.89 (d, *J* = 1.1 Hz, 1H), 5.36–5.24 (m, 1H), 3.64 (d, *J* = 7.7 Hz, 1H), 2.62 (br s, 1H), 2.43–2.20 (m, 4H), 2.19–2.00 (m, 3H), 1.90–1.73 (m, 2H), 1.68 (s, 3H), 1.34–1.26 (m, 1H), 1.25 (s, 3H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 130.5, 119.1, 73.4, 67.7, 60.7, 16.5; IR (KBr, cm^{-1}): 3452, 3107, 2925, 2222, 1884, 1714, 1445, 869; HRMS (ESI-TOF) calcd for $C_{15}H_{25}N_2O_2$ $[M+NH_4^+]$ 265.1911, found 265.1912.

*2-((1S,2S,3R,10R,E)-2-Hydroxy-6,10-dimethyl-11-oxabicyclo[8.1.0]undec-6-en-3-yl)acrylamide (**24**)*. Nitrile **23** (188 mg, 0.761 mmol) was dissolved in a DMSO/THF mixture (2:1, 2.3 mL) containing K_2CO_3 (33 mg, 0.253 mmol). A solution of 30% aqueous H_2O_2 (0.94 mL, 8.067 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at 30 °C for 1.5 h, then quenched by the addition of brine and extracted several times with Et_2O. The organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated. The crude product was purified by chromatography on silica gel (50–100% ethyl acetate/hexane) to give product **24** (178 mg, 0.672 mmol, 88%) as a white solid. mp 160–162 °C; $[\alpha]_D^{20}$ = –88.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (s, 1H), 6.31 (s, 1H), 5.68 (s, 1H), 5.38 (s, 1H), 5.35–5.20 (m, 1H), 3.46 (d, *J* = 7.7 Hz, 1H), 2.68–2.45 (m, 2H), 2.43–2.27 (m, 1H), 2.25–1.92 (m, 4H), 1.85–1.70 (m, 1H), 1.64 (s, 3H), 1.56–1.45 (m, 1H), 1.33–1.20 (m, 1H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 148.5, 137.2, 123.7, 120.8, 74.9, 68.2, 60.1, 46.3, 37.3, 24.8, 23.1, 16.6;

IR (KBr, cm^{-1}): 3372, 3187, 2480, 1668, 1437, 826; HRMS (ESI-TOF) calcd for $C_{15}H_{24}NO_3$ $[M+H^+]$ 266.1751, found 266.1749.

*7-epi-Parthenolide (**19**)*. Compound **24** (38.0 mg, 0.143 mmol) and DBU (43.6 mg, 0.287 mmol) was dissolved in 8.3 mL of benzene. The reaction mixture was refluxed for 12 h and concentrated under vacuum. The residue was submitted to silica gel chromatography (0–10% ethyl acetate/hexane) to provide **19** as a white solid (33.1 mg, 0.133 mmol, 93%).

*tert-Butyldiphenyl(((2E,6Z)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)oxy)silane (**S6**)*. TBDPSCl (17.3 mL, 66.249 mmol) was added to a solution of **25** (13.0 g, 58.463 mmol) and imidazole (4.9 g, 71.974 mmol) in anhydrous dichloromethane (130 mL) at 0 ^oC. The reaction mixture was stirred for 1 h, and then it was diluted with dichloromethane, poured over water, and extracted with more dichloromethane. The combination of organic layer was dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (0–2% ethyl acetate/hexane) to afford **S6** as a colorless oil (26.9 g, 58.478 mmol, 99%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.74–7.70 (m, 4H), 7.48–7.36 (m, 6H), 5.42 (t, J = 5.8 Hz, 1H), 5.19–5.12 (m, 2H), 4.26 (d, J = 6.3 Hz, 2H), 2.14–2.04 (m, 6H), 2.03–1.97 (m, 2H), 1.72 (s, 6H), 1.64 (s, 3H), 1.47 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 135.8, 135.5, 134.3, 131.7, 129.7, 127.8, 125.0, 124.6, 124.3, 61.4, 40.0, 32.2, 27.0, 26.8, 26.4, 25.9, 23.6, 19.4, 17.8, 16.5; IR (KBr, cm^{-1}): 3070, 3048, 2929, 2858, 1666, 1587, 1427, 1108, 1059, 702; HRMS (ESI-TOF) calcd for $C_{31}H_{48}NOSi$ $[M+NH_4^+]$ 478.3500, found 478.3493.

*tert-Butyl(((2E,6Z)-9-(3,3-dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl)oxy)diphenylsilane (**S7**)*. To a solution of **S6** (3.26 g, 7.087 mmol) in 76 mL THF/H_2O = 3/1 (6

mL) was added *N*-bromosuccinimide (1.4 g, 7.865 mmol) in small portions over a period of 1 h at 0 ^{o}C. After 1 h, 250 mL of ether were added and the organic layer was washed with brine. The organic layer was dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure to afford the crude bromohydrin. The crude bromohydrin was dissolved in a slurry of K_2CO_3 (1.75 g, 12.655 mmol) in methanol (30 mL). After 1 h, most of the methanol was removed under reduced pressure and the residue was extracted with diethyl ether to afford crude product. The crude product was purified by flash silica gel chromatography (0–1% ethyl acetate/hexane) to yield the **S7** (2.26 g, 4.748 mmol, 67%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.65(m, 4H), 7.47–7.32 (m, 6H), 5.39 (t, *J* = 6.3Hz, 1H), 5.17 (t, *J* = 6.6 Hz, 1H), 4.23 (d, *J* = 6.2 Hz, 2H), 2.72 (t, *J* = 6.4 Hz, 1H), 2.22–2.14 (m, 2H), 2.13–2.05 (m, 2H), 2.03–1.95 (m, 2H), 1.71 (d, *J* = 1.0 Hz, 3H), 1.68–1.53 (m, 2H), 1.45 (s, 3H), 1.31 (s, 3H), 1.28 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 135.8, 134.5, 134.3 129.7, 127.7, 125.6, 124.4, 64.3, 61.3, 58.5, 39.8, 28.7, 27.6, 27.0, 26.3, 25.1, 23.5, 19.4, 18.9, 16.5; IR (KBr, cm^{-1}): 2931, 2859, 1462, 1427, 1109, 1058, 703; HRMS (ESI-TOF) calcd for $C_{31}H_{48}NO_2Si$ [M+NH_4^+] 494.3449, found 494.3452.

*(4Z,8E)-10-((tert-Butyldiphenylsilyl)oxy)-4,8-dimethyldeca-4,8-dienal (**26**)*. A solution of **S7** (2.51 g, 5.273 mmol, 1 eq.) in THF:H_2O (82:18, 39 mL) was treated with $NaIO_4$ (641 mg, 2.997 mmol, 0.6 equiv) and HIO_4•$2H_2O$ (1.32 g, 5.792 mmol, 1.1 equiv) at 0 ^{o}C. The mixture was stirred at 0 ^{o}C for 10 min and then warmed to room temperature. After 1 h, the reaction mixture were quenched with saturated aqueous $NaHCO_3$ (25 mL), and aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuum. The crude product was purified by silica gel chromatography (0–1% ethyl acetate/hexane) to give the desired aldehyde **26** (2.21 g, 5.092 mmol, 96%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (t, *J* = 1.7 Hz, 1H), 7.72–7.66 (m, 4H), 7.45–7.35 (m,

6H), 5.38 (t, *J* = 6.4 Hz, 1H), 5.18 (t, *J* = 6.7 Hz, 1H), 4.23 (d, *J* = 6.2 Hz, 2H), 2.53–2.44 (m, 2H), 2.35 (t, *J* = 7.6 Hz, 2H), 2.13–2.05 (m, 2H), 1.99 (t, *J* = 6.8 Hz, 2H), 1.69 (s, 3H), 1.45 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.4, 136.8, 135.8, 134.3, 133.2, 129.7, 127.8, 126.4, 124.5, 61.3, 42.5, 39.7, 27.0, 26.2, 24.5, 23.2, 19.4, 16.5; IR (KBr, cm^{-1}): 3070, 2857, 2717, 1725, 1384, 1108, 703; HRMS (ESI-TOF) calcd for $C_{28}H_{42}NO_2Si$ [M+NH_4^+] 452.2979, found 452.2976.

*(6Z,10E)-12-((tert-Butyldiphenylsilyl)oxy)-3-hydroxy-6,10-dimethyl-2-methylenedodeca-6,10-dienenitrile (**S8**)*. A solution of aldehyde **26** (1.89 g, 4.354 mmol) and DABCO (97 mg, 0.866 mmol) in acrylonitrile (8.6 mL, 131.285 mmol) was stirred at room temperature for 2 days, then additional DABCO (97 mg, 0.866 mmol) was added and the mixture was stirred at room temperature for another 20 days. The mixture was concentrated and the residue was purified by silica gel chromatography (0–10% ethyl acetate/hexane) to give the **S8** (1.73 g, 3.550 mmol, 82 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.66 (m, 4H), 7.46–7.34 (m, 6H), 6.00 (s, 1H), 5.97 (s, 1H), 5.38 (t, *J* = 5.6 Hz, 1H), 5.19 (t, *J* = 6.8 Hz, 1H), 4.26–4.17 (m, 3H), 2.21–2.05 (m, 4H), 2.03–1.96 (m, 3H), 1.90–1.80 (m, 1H), 1.71 (d, *J* = 0.9 Hz, 3H), 1.45 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 135.8, 134.3, 134.0, 129.9, 129.7, 127.8, 127.1, 126.5, 124.5, 117.1, 72.3, 61.3, 39.7, 33.9, 27.6, 27.1, 26.3, 23.3, 19.4, 16.6; IR (KBr, cm^{-1}): 3478, 2926, 2856, 2227, 1432, 1108, 704; HRMS (ESI-TOF) calcd for $C_{31}H_{45}N_2O_2Si$ [M+NH_4^+] 505.3245, found 505.3238.

*(2E,6Z,10E)-12-((tert-Butyldiphenylsilyl)oxy)-2-(chloromethyl)-6,10-dimethyldodeca-2,6,10-trienenitrile (**27a**) and (2Z,6Z,10E)-12-((tert-butyldiphenylsilyl)oxy)-2-(chloromethyl)-6,10-dimethyldodeca-2,6,10-trienenitrile (**27b**)*. To a solution of **S8** (427 mg, 0.877 mmol) in dry CCl_4 (9 mL) was added *n*-Bu_3P (0.32 mL, 1.30 mmol) at room temperature under Ar. The

reaction mixture was stirred for 2 h, concentrated under reduced pressure. The crude residue was purified by column chromatography (0–1% ethyl acetate/hexane) to afford **27a** (296 mg, 0.586 mmol, 67%) and **27b** (99 mg, 0.196 mmol, 22%).

27a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.64 (m, 4H), 7.46–7.35 (m, 6H), 6.48 (t, *J* = 7.7 Hz, 1H), 5.38 (t, *J* = 5.8 Hz, 1H), 5.21 (t, *J* = 6.7 Hz, 1H), 4.23 (d, *J* = 6.2 Hz, 2H), 4.09 (s, 2H), 2.52 (q, *J* = 7.5 Hz, 2H), 2.21 (t, *J* = 7.4 Hz, 2H), 2.10–2.03 (m, 2H), 2.02–1.95 (m, 2H), 1.71 (s, 3H), 1.45 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 136.8, 135.8, 134.3, 132.8, 129.7, 127.8, 127.0, 124.6, 115.5, 112.6, 61.3, 44.0, 39.7, 30.3,29.9, 27.0, 26.4, 23.3, 19.4, 16.5; IR (KBr, cm^{-1}): 3070, 3046, 2932, 2858, 2223, 1589, 1427, 1108, 1058, 705; HRMS (ESI-TOF) calcd for $C_{31}H_{44}ClN_2OSi$ [$M+NH_4^+$] 523.2906, found 523.2900.

27b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.66 (m, 4H), 7.48–7.31 (m, 6H), 6.54 (t, *J* = 7.7 Hz, 1H), 5.43–5.33 (m, 1H), 5.23 (t, *J* = 6.5 Hz, 1H), 4.23 (d, *J* = 6.2 Hz, 2H), 4.11 (s, 2H), 2.38 (q, *J* = 7.6 Hz, 2H), 2.19 (t, *J* = 7.5 Hz, 2H), 2.09–2.04 (m, 2H), 2.03–1.95 (m, 2H), 1.69 (d, *J*= 1.0 Hz, 3H), 1.45 (s, 3H), 1.05 (s,9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 136.6, 135.8, 134.3, 132.6, 129.7, 127.8, 127.3, 124.7, 118.1, 112.6, 61.3, 39.7, 38.2, 30.3, 27.3, 27.0, 26.4, 23.2, 19.4, 16.5; IR (KBr, cm^{-1}): 3070, 3046, 2931, 2858, 2223, 1591, 1427, 1108, 1058, 704; HRMS (ESI-TOF) calcd for $C_{31}H_{44}ClN_2OSi$ [$M+NH_4^+$] 523.2906, found 523.2896.

*(2E,6Z,10E)-2-(Chloromethyl)-12-hydroxy-6,10-dimethyldodeca-2,6,10-trienenitrile (**S9**)*. To a solution of **27a** (140 mg, 0.277mmol) in THF (4.2 mL) was added pyridine hydrofluoride (70%, 0.24 mL, 1.714 mmol). The reaction mixture was stirred for 2.5 h, and then diluted with dichloromethane (40 mL). The resulting solution was then washed with saturated aqueous sodium bicarbonate solution (10 mL), and then the organic phase was dried over magnesium

sulfate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (0–30% ethyl acetate/hexane) to afford **S9** (59 mg, 91%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (t, *J* = 7.7 Hz, 1H), 5.41 (t, *J* = 6.3 Hz, 1H), 5.20 (t, *J* = 6.5 Hz, 1H), 4.15 (d, *J* = 6.8 Hz, 2H), 4.10 (s, 2H), 2.51 (q, *J* = 7.5 Hz, 2H), 2.19 (t, *J* = 7.5 Hz, 2H), 2.14–1.98 (m, 4H), 1.71 (d, *J*= 0.7 Hz, 3H), 1.67 (s, 3H), 1.30 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 139.3, 133.0, 126.8, 123.8, 115.6, 112.7, 59.5, 44.0, 39.7, 30.4, 30.0, 26.4, 23.3, 16.5; IR (KBr, cm^{-1}): 3345, 2925, 2864, 2224, 1636, 1444, 1000, 715; HRMS (ESI-TOF) calcd for $C_{15}H_{26}ClN_2O$ [M+NH_4^+] 285.1728, found 285.1730.

*(2E,6Z)-2-(Chloromethyl)-9-((2R,3R)-3-(hydroxymethyl)-2-methyloxiran-2-yl)-6-methylnona-2,6-dienenitrile (**S10**)*. In a 10 mL round-bottom flask, 4 Å molecular sieves (250 mg) were dispersed in anhydrous CH_2Cl_2 (8.6 mL). D-(–)-diisopropyl tartrate (24 μL, 0.112 mmol) was added to the reaction flask and the mixture was cooled to –40 °C. After 10 min, Ti(O-*i*-Pr)$_4$ (28 μL, 0.093 mmol) was added and stirred at –40 °C for 15 min. After that time, TBHP (3.3 M in toluene, 0.42 mL,1.386 mmol) was introduced and the mixture was stirred at –40 °C for 30 min, then **S9** (250 mg, 0.936 mmol) in dry CH_2Cl_2 (3 mL) was added. The reaction mixture was warmed to –18 °C and kept at this temperature overnight. The reaction was quenched by addition of acetone containing 2% water (9 mL), warmed to room temperature and stirred for 3 h. After filtering through Celite, the solvent was dried over $MgSO_4$, concentrated under reduced pressure. The crude mixture was purified by column chromatography (0–35% ethyl acetate/hexane) to provide compound **S10** as a colorless oil (246 mg, 0.871 mmol, 93%, *ee* = 97%). $[\alpha]_D^{20}$ = 1.6 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (t, *J* = 7.8 Hz, 1H), 5.18 (t, *J* = 7.0 Hz, 1H), 4.10 (s, 2H), 3.83–3.74 (m, 1H), 3.72–3.62 (m, 1H), 2.96 (dd, *J* = 6.4, 4.6 Hz, 1H), 2.49 (q, 7.6 Hz, 2H), 2.19 (t, *J*= 7.5 Hz, 2H), 2.13–2.02 (m, 3H), 1.70 (d, *J* = 0.9 Hz, 3H), 1.63 (dt, *J* = 13.5,

7.6 Hz, 1H), 1.51 (ddd, *J* = 21.1, 10.6, 5.9 Hz, 1H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 133.4, 126.2, 115.6, 112.8, 62.9, 61.5, 61.1, 44.0, 38.6, 30.3, 29.9, 23.6, 23.3, 17.0; IR (KBr, cm^{-1}): 3434, 2933, 2224, 1447, 1207, 1031, 714; HRMS (ESI-TOF) calcd for $C_{15}H_{23}ClNO_2$ [M+H$^+$] 284.1412, found 284.1412.

*(2E,6Z)-2-(Chloromethyl)-9-((2R,3S)-3-formyl-2-methyloxiran-2-yl)-6-methylnona-2,6-dienenitrile (**28a**)*. To a solution of **S10** (195 mg, 0.689 mmol) in CH_2Cl_2 (10 mL) was added $NaHCO_3$ (579 mg, 6,893 mmol) and Dess–Martin periodinane (585 mg, 1,379 mmol) at room temperature. After 1 h, sat. aq. $NaHCO_3$ (10 mL) were added and the reaction was stirred at room temperature for 10 min. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The CH_2Cl_2 layers were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash chromatography (0–15% ethyl acetate/hexane) to afford **28a** (186 mg, 0.662 mmol, 96%) as a clear colorless oil. $[\alpha]_D^{20}$ = –52.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (d, *J* = 4.9 Hz, 1H), 6.49 (t, *J* = 7.7 Hz, 1H), 5.17 (t, *J* = 7.1 Hz, 1H), 4.10 (s, 2H), 3.19 (d, *J* = 4.9 Hz, 1H), 2.50 (q, *J* = 7.6 Hz, 2H), 2.19 (t, *J* = 7.5 Hz, 2H), 2.13–2.04 (m, 2H), 1.72 (d, *J* = 1.0 Hz, 3H), 1.69–1.58 (m, 2H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 151.1, 134.1, 125.5, 115.5, 112.9, 64.1, 63.6, 44.0, 38.3, 30.3, 29.9, 23.34, 23.27, 17.4; IR (KBr, cm^{-1}): 2962, 2936, 2860, 2223, 1720, 1447, 1270, 714; HRMS (ESI-TOF) calcd for $C_{15}H_{21}ClNO_2$ [M+H$^+$] 282.1255, found 282.1254.

*(2Z,6Z,10E)-2-(Chloromethyl)-12-hydroxy-6,10-dimethyldodeca-2,6,10-trienenitrile (**S11**)*. To a solution of **27b** (110 mg, 0.218 mmol) in THF (3.3 mL) was added pyridine hydrofluoride (70%, 0.19 mL, 1.357 mmol). The reaction mixture was stirred for 2.5 h, and then diluted with dichloromethane (30 mL). The resulting solution was then washed with saturated aqueous sodium bicarbonate solution (10 mL), and then the organic phase was dried over magnesium

sulfate and the solvent was removed under reduced pressure and purified by column chromatography (0–30% ethyl acetate/hexane) to afford **S11** (52 mg, 0.196 mmol, 90%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (t, *J* = 7.8 Hz, 1H), 5.41 (td, *J* = 6.9, 1.1 Hz, 1H), 5.22 (t, *J* = 6.6 Hz, 1H), 4.16 (d, *J* = 6.8 Hz, 2H), 4.13 (s, 2H), 2.38 (q, *J* = 7.5 Hz, 2H), 2.20 (t, *J* = 7.4 Hz, 2H), 2.15–2.00 (m, 4H), 1.69 (d, *J* = 1.0 Hz, 3H), 1.68 (s, 3H), 1.25 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 139.2, 132.7, 127.1, 123.9, 118.1, 112.6, 59.5, 39.7, 38.2, 30.2, 27.2, 26.4, 23.2, 16.5; IR (KBr, cm^{-1}): 3345, 2958, 2735, 2224, 1634, 1446; HRMS (ESI-TOF) calcd for $C_{15}H_{26}ClN_2O$ [M+NH_4^+] 285.1728, found 285.1733.

*(2Z,6Z)-2-(Chloromethyl)-9-((2R,3R)-3-(hydroxymethyl)-2-methyloxiran-2-yl)-6-methylnona-2,6-dienenitrile (**S12**)*. In a 10 mL round-bottom flask, 4 Å molecular sieves (80 mg) were dispersed in anhydrous CH_2Cl_2 (2.5 mL). D-(–)-diisopropyl tartrate (7.7 μL, 0.036 mmol) was added to the reaction flask and the mixture was cooled to –40 °C. After 10 min, Ti(O-*i*-Pr)$_4$ (0.90 μL, 0.030 mmol) was added and stirred at –40 °C for 15 min. After that time, TBHP (3.3 M in toluene, 0.13 mL,0.429 mmol) was introduced and the mixture was stirred at –40 °C for 30 min, then **S11** obtained above (79 mg, 0.296 mmol) was added as a solution in dry CH_2Cl_2 (1 mL). The reaction mixture was warmed to –18 °C and kept at this temperature overnight. The reaction was quenched by addition of acetone containing 2% water (3 mL), warmed to room temperature and stirred for 3 h. After filtering through Celite, the solvent was dried over $MgSO_4$, concentrated under reduced pressure. The crude mixture was purified by column chromatography (0–35% ethyl acetate/hexane) to provide compound **S12** as a colorless oil (76 mg, 0.269 mmol, 91%, *ee* = 95%). $[\alpha]_D^{20}$ = 6.6 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (t, *J* = 7.8 Hz, 1H), 5.21 (t, *J* = 7.1 Hz, 1H), 4.13 (s, 2H), 3.86–3.78 (m, 1H), 3.74–3.64 (m, 1H), 2.97 (dd, *J* = 6.5, 4.4 Hz, 1H), 2.38 (q, *J* = 7.5 Hz, 2H), 2.23–1.16 (m, 2H), 2.07 (q, *J* = 7.5 Hz, 2H), 1.87 (br s,

1H), 1.69 (d, *J*= 0.9 Hz, 3H), 1.64–1.50 (m, 2H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 133.1, 126.6, 118.1, 112.7, 63.0, 61.5, 61.0, 38.6, 38.2, 30.2, 27.2, 23.6, 23.2, 17.0; IR (KBr, cm^{-1}): 3430, 2929, 2860, 2224, 1452, 1031, 727; HRMS (ESI-TOF) calcd for $C_{15}H_{26}ClN_2O_2$ [M+NH_4^+] 301.1677, found 301.1673.

*(2Z,6Z)-2-(Chloromethyl)-9-((2R,3S)-3-formyl-2-methyloxiran-2-yl)-6-methylnona-2,6-dienenitrile (**28b**)*. To a solution of **S12** (63 mg, 0.223 mmol) in CH_2Cl_2 (3.2 mL) was added $NaHCO_3$ (187 mg, 2.226 mmol) and Dess–Martin periodinane (189 mg, 0.445 mmol) at room temperature. After 1 h, sat. aq. $NaHCO_3$ (5 mL) was added and the mixture was stirred at room temperature for 10 min. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The CH_2Cl_2 layers were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (0–15% ethyl acetate/hexane) to yield aldehyde **28b** (58 mg, 0.206 mmol, 93%) as a clear colorless oil. $[\alpha]_D^{20}$ = –44.6 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (d, *J* = 4.9 Hz, 1H), 6.53 (t, *J* = 7.8 Hz, 1H), 5.19 (t, *J* = 7.1 Hz, 1H), 4.13 (s, 2H), 3.19 (d, *J* = 4.9 Hz, 1H), 2.38 (q, *J* = 7.6 Hz, 2H), 2.20 (t, *J* = 7.4 Hz, 2H), 2.09 (q, *J* = 7.6 Hz, 2H), 1.70 (s, 3H), 1.68–1.58 (m, 2H), 1.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.6, 152.0, 133.8, 125.8, 118.1, 112.8, 64.0, 63.6, 38.4, 38.2, 30.2, 27.1, 23.4, 23.2, 17.5; IR (KBr, cm^{-1}): 3029, 2223, 1721, 1634, 1452, 888; HRMS (ESI-TOF) calcd for $C_{15}H_{24}ClN_2O_2$ [M+NH_4^+] 299.1521, found 299.1521.

*Compounds **29** and **30** from **28a**.* To a solution of **28a** (410 mg, 1.459 mmol) in acetone (7.3 mL) was added NaI (1.09 g, 7.272 mmol). The mixture was stirred overnight at room temperature under N_2 and then partitioned between CH_2Cl_2 (20 mL) and H_2O (6 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL), and the combined organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuum to yield crude iodide.

Under Ar, to a solution of $CrCl_2$ (1.1 g, 8.950 mmol) in dry THF (150 mL) was added a solution of the iodide in 17 mL dry THF over 2 h at room temperature. When the addition was completed, the reaction was allowed to stir for another 2 h at the same temperature. The reaction mixture was quenched with water and extracted with Et_2O, the combined extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (0–30% ethyl acetate/hexanes) yielded unseparable **29** and **30 (**1:1, 189 mg, 0.765 mmol, 52%).

*Compounds **29** and **30** from **28b***. Following the same procedure as **28a**, **29** and **30** were obtained from **28b** in a 1.9:1 mixture (66% yield).

*2-((1S,2S,3R,10R,Z)-2-Hydroxy-6,10-dimethyl-11-oxabicyclo[8.1.0]undec-6-en-3-yl)acrylamide (**31**)*. Mixture of nitrile **29**/**30** (90 mg, 0.364 mmol, about 1:1) was dissolved in a solution of K_2CO_3 (16 mg, 0.123 mmol) in DMSO/THF (2:1, 1.2 mL). After cooling of the solution to 0 ^oC, 30% aqueous H_2O_2 solution (0.45 mL, 3.870 mmol) was added dropwise. The reaction mixture was stirred at 30 ^oC for 1 h, then quenched by the addition of brine and extracted several times with Et_2O. The organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified and the two isomers separated by chromatography on silica gel (50–100% ethyl acetate/hexanes) to give **31** (42 mg, 0.158 mmol) as a white solid and **32** (31 mg, 0.117 mmol, which cyclized partly to **33** during purification) and **33** (10 mg, 0.040 mmol, colorless solid) in 86% overall yield.

31: mp 192–194 ^oC; $[\alpha]_D^{20}$ = –72.7 (*c* = 1.0, EtOH); ^1H NMR (400 MHz, CD_3OD) δ 5.69 (s, 1H), 5.43 (s, 1H), 5.36 (br d, *J* = 9.0 Hz, 1H), 3.50 (d, *J* = 6.8 Hz, 1H), 3.24 (d, *J* = 5.9 Hz, 1H), 2.87–2.75 (m, 1H), 2.73 (d, *J* = 11.9 Hz, 1H), 2.52–2.37 (m, 1H), 2.26–2.16 (m, 1H), 1.99–1.79 (m, 3H), 1.69 (s, 3H), 1.64–1.57 (m, 2H), 1.30 (s, 3H), 1.30–1.26 (m, 1H); ^{13}C NMR (100 MHz,

CD_3OD) δ 174.5, 149.8, 136.4, 126.4, 119.7, 75.8, 66.4, 61.8, 42.6, 37.6, 29.7, 25.5, 24.4, 22.6, 22.4; IR (KBr, cm^{-1}): 3365, 3190, 2959, 2921, 2861, 1673, 1592, 1441, 1041, 815; HRMS (ESI-TOF) calcd for $C_{15}H_{24}NO_3$ $[M+H^+]$ 266.1751, found 266.1753.

*(1aR,7aS,10aS,10bS,Z)-1a,5-Dimethyl-8-methylene-2,3,6,7,7a,8,10a,10b-octahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-9(1aH)-one (**33**)*. Compound **32** (31 mg, 0.117 mmol, mixed with **33**) and DBU (19.7 mg, 0.130 mmol) was dissolved in CH_2Cl_2 (3.8 mL) and stirred for 24 h at room temperature. The organic solvent was evaporated to dryness under vacuum and the residue submitted to silica gel chromatography (0–10% ethyl acetate/hexane) to afford **33** as a white solid (26.8 mg, 0.107 mmol, 92%). mp 124–125 °C; $[\alpha]_D^{25}$ = –26.7 (*c* = 0.5, EtOH), lit. $[\alpha]^{25}_D$ = –31° (*c* = 0.87, EtOH)[31a]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (d, *J* = 3.5 Hz, 1H), 5.53 (d, *J* = 3.2 Hz, 1H), 5.33 (br t, *J* = 8.1 Hz, 1H), 3.83 (t, *J* = 9.3 Hz, 1H), 2.90 (d, *J* = 9.4 Hz, 1H), 2.81–2.71 (m, 1H), 2.50–2.33 (m, 2H), 2.33–2.18 (m, 1H), 2.16–2.04 (m, 3H), 1.71 (s, 3H), 1.64 (ddt, *J* = 7.0, 4.8, 3.0 Hz, 1H), 1.53 (s, 3H), 1.14–1.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 139.1, 135.7, 125.8, 119.9, 81.3, 63.5, 60.1, 42.4, 37.2, 26.9, 25.8, 23.9, 21.5, 18.0; IR (KBr, cm^{-1}) 3099, 2963, 2926, 1764, 1446, 1417, 1305, 1259, 1138, 1027, 996, 811; HRMS (ESI-TOF) calcd. for $C_{15}H_{24}NO_3$ $[M+NH_4^+]$ 266.1751, found 266.1753.

*(1aR,7aR,10aS,10bS,Z)-1a,5-Dimethyl-8-methylene-2,3,6,7,7a,8,10a,10b-octahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-9(1aH)-one (**34**)*. Compound **31** (21.5 mg, 0.081 mmol) and DBU (24mg, 0.158 mmol) was dissolved in 4.7 mL of benzene and refluxed for 40 h. The organic solvent was evaporated to dryness under vacuum and the residue submitted to silica gel chromatography (0–10% ethyl acetate/hexane) to afford **34** as a white solid (18.1mg, 0.073 mmol, 91%). mp 142–144 °C; $[\alpha]_D^{20}$ = 82.1 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (d, *J* = 1.7 Hz, 1H), 5.67 (d, *J* = 1.4 Hz, 1H), 5.29 (t, *J* = 8.1 Hz, 1H), 4.21 (dd, *J* = 8.6, 6.6

Hz, 1H), 3.17–3.10 (m, 1H), 3.08 (d, *J* = 8.7 Hz, 1H), 2.35–2.14 (m, 3H), 2.13–2.01 (m, 2H), 1.81–1.71 (m, 2H), 1.65 (s, 3H), 1.47 (s, 3H), 1.16–1.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 140.3, 136.8, 124.0, 122.7, 80.9, 60.0, 59.6, 43.5, 38.9, 30.3, 29.3, 22.7, 22.1, 17.7; IR (KBr, cm^{-1}): 2958, 2924, 1749, 1457, 1261, 1093, 1025, 804; HRMS (ESI-TOF) calcd. for $C_{15}H_{24}NO_3$ [M+NH_4^+] 266.1751, found 266.1746.

*(1aR,7aR,10aS,10bS,Z)-1a,5-Dimethyl-8-methylene-2,3,6,7,7a,8,10a,10b-octahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-9(1aH)-one (**34**) (from **19**)*. A solution of **19** (12.0 mg, 0.048mmol) in 5 mL of benzene was degassed for 30 min by bubbling with N_2, The solution was irradiated with UV-light (254 nm, 48 w) for 48 h. The solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel column (0–5% ethyl acetate/hexanes) to provide unreacted **19** (3.4 mg, 0.014 mmol) and **34** (5.1 mg, 0.021 mmol, 59% based on the recovered **19**).

*Parthenolide (**1**)*. A solution of **33** (21.1mg, 0.085mmol) in 10 mL of benzene was degassed for 30 min by bubbling with N_2. The solution was irradiated with UV-light (254 nm, 48 w) for 48 h. The solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel column (0–5% ethyl acetate/hexane) to provide starting material **33** (9.7 mg, 0.039 mmol) and parthenolide (**1**) (8.8 mg, 0.035 mmol, 77% based on the recovered **33**). Parthenolide (**1**): mp 114–116 °C; $[\alpha]^{25}_D$ = –80.2° (*c* = 1, $CHCl_3$), lit. $[\alpha]^{25}_D$ = –80° (*c* = 0.66, $CHCl_3$)[33]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (d, *J* = 3.6 Hz, 1H), 5.62 (d, *J* = 2.8 Hz, 1H), 5.21 (br d, *J* = 10 Hz, 1H), 3.86 (t, *J* = 8.4 Hz, 1H), 2.84–2.73 (m, 2H), 2.46–2.33 (m, 2H), 2.24–2.10 (m, 4H), 1.71 (s, 3H), 1.78–1.68 (m, 1H), 1.30 (s, 3H), 1.29–1.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 139.4, 134.7, 125.4, 121.4, 82.6, 66.5, 61.7, 47.8, 41.3, 36.5, 30.8, 24.3, 17.4, 17.2; IR (KBr, cm^{-1}): 3098, 2973, 2935, 2860, 1757, 1659, 1445, 1254, 1144, 1075, 946.

*(6Z,10E)-methyl 12-((tert-butyldiphenylsilyl)oxy)-3-hydroxy-6,10-dimethyl-2-methylenedodeca-6,10-dienoate (**S13**)*. A solution of aldehyde **26** (278 mg, 0.641 mmol) and DABCO (14 mg, 0.125 mmol) in methyl acrylate(1.7 mL, 18.759 mmol) was stirred at room temperature for 2 days, then additional DABCO (14 mg, 0.125 mmol) was added and the mixture was stirred at room temperature for another 20 days. The mixture was concentrated and the residue was purified by silica gel column chromatography (0–10% ethyl acetate/hexane) to give the product **S13** (238 mg, 0.458 mmol, 71 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.65 (m, 4H), 7.45–7.33 (m, 6H), 6.24 (s, 1H), 5.82 (s, 1H), 5.39 (t, *J* = 6.2 Hz, 1H), 5.15 (t, *J* = 6.7 Hz, 1H), 4.42–4.35 (m, 1H), 4.22 (d, *J* = 6.2 Hz, 2H), 3.77 (s, 3H), 2.55–2.50 (m, 1H), 2.15 (t, *J* = 7.9 Hz, 2H), 2.12–2.06 (m, 2H), 2.03–1.95 (m, 2H), 1.79–1.64 (m, 2H), 1.70 (s, 3H), 1.44 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 143.1, 137.4, 136.2, 135.2, 134.7, 130.1, 128.2, 126.1, 125.5, 124.8, 72.1, 61.7, 52.4, 40.3, 35.0, 28.7, 27.4, 26.7, 23.8, 19.8, 16.9; IR (KBr, cm^{-1}): 3442, 3050, 2933, 2859, 1715, 1595, 1434, 1109, 1059, 703; HRMS (ESI-TOF) calcd for $C_{32}H_{44}NaO_4Si$ [M+Na^+] 543.2901, found 543.2901.

*(2Z,6Z,10E)-methyl 12-((tert-butyldiphenylsilyl)oxy)-2-(chloromethyl)-6,10-dimethyldodeca-2,6,10-trienoate (**S14**)*. To a solution of **S13** (1.2 g, 2.308 mmol) in dry CCl_4 (23 mL) was added *n*-Bu_3P (700 mg, 3.460 mmol) at room temperature under Ar. The reaction mixture was stirred for 1.5 h, concentrated and purified by column chromatography (0–1% ethyl acetate/hexane) to yield **S14** as a colorless oil (1.02 g, 1.896 mmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.66 (m, 4H), 7.45–7.34 (m, 6H), 7.01 (t, *J* = 7.7 Hz, 1H), 5.39 (t, *J* = 6.2 Hz, 1H), 5.20 (t, *J* = 6.8 Hz, 1H), 4.34 (s, 2H), 4.23 (d, *J* = 6.3 Hz, 2H), 3.79 (s, 3H), 2.41 (q, *J* = 7.6 Hz, 2H), 2.22 (t, *J* = 7.6 Hz, 2H), 2.08 (q, *J* = 7.2 Hz, 2H), 2.03–1.96 (m, 2H), 1.71 (s, 3H), 1.45 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 148.3, 136.8, 135.8, 134.3, 133.4, 129.7, 129.4, 127.8, 126.6,

124.5, 61.3, 52.3, 39.7, 37.3, 30.6, 27.5, 27.0, 26.4, 23.3, 19.4, 16.5; IR (KBr, cm^{-1}): 2931, 2858, 1723, 1427, 1109, 704; HRMS (ESI-TOF) calcd for $C_{32}H_{47}ClNO_3Si$ $[M+NH_4^+]$ 556.3008, found 556.3006.

*(2Z,6Z,10E)-methyl 2-(chloromethyl)-12-hydroxy-6,10-dimethyldodeca-2,6,10-trienoate (**S15**).* To a solution of **S14** (101 mg, 0.188 mmol) in THF (3.1 mL) was added pyridine hydrofluoride (70%, 0.18 mL, 1.286 mmol). The reaction mixture was stirred for 2.5 h, and then diluted with dichloromethane (20 mL). The resulting solution was then washed with saturated aqueous sodium bicarbonate solution (10 mL), and then the organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by column chromatography (0–30% ethyl acetate/hexane) to give product **S15** as a colorless oil (49 mg, 0.163 mmol, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (t, J = 7.7 Hz, 1H), 5.43–5.37 (m, 1H), 5.19 (t, J = 6.8 Hz, 1H), 4.32 (s, 2H), 4.14 (br d, J = 4.9 Hz, 2H), 3.78 (s, 3H), 2.40 (q, J = 7.6 Hz, 2H), 2.21 (t, J = 7.6 Hz, 2H), 2.1–2.07 (m, 2H), 2.06–1.98 (m, 2H), 1.70 (d, J = 0.6 Hz, 3H), 1.66 (s, 3H), 1.30 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 148.3, 139.4, 133.6, 129.4, 126.4, 123.8, 59.5, 52.3, 39.7, 37.3, 30.6, 27.4, 26.4, 23.3, 16.4; IR (KBr, cm^{-1}): 3411, 2951, 1718, 1645, 1441, 1285, 780; HRMS (ESI-TOF) calcd for $C_{16}H_{25}ClNaO_3$ $[M+Na^+]$ 323.1384, found 323.1388.

*(2Z,6Z)-methyl 2-(chloromethyl)-9-((2R,3R)-3-(hydroxymethyl)-2-methyloxiran-2-yl)-6-methylnona-2,6-dienoate (**S16**).* In a 10 mL round-bottom flask, 4 Å molecular sieves (30 mg) were dispersed in anhydrous CH_2Cl_2 (2.0 mL). D-(–)-diisopropyl tartrate (3.0 μL, 0.012 mmol) was added to the reaction flask and the mixture was cooled to –40 ^{o}C. After 10 min, Ti(O-*i*-Pr)$_4$ (3.0 μL, 0.010 mmol) was added and stirred at –40 ^{o}C for 15 min. After that time, TBHP (3.3 M in toluene, 0.045 mL, 0.149 mmol) was introduced and the mixture was stirred at –40 ^{o}C for 30

min, then the alcohol **S15** (30 mg, 0.100 mmol) was added as a solution in dry CH_2Cl_2 (1 mL). The reaction mixture was warmed to –18 ^oC and kept at this temperature overnight. The reaction was quenched by addition of acetone containing 2% water (3 mL), warmed to room temperature and stirred for 3 h. After filtering through Celite, the solvent was dried over $MgSO_4$, concentrated under reduced pressure. The crude mixture was purified by column chromatography (0–35% ethyl acetate/hexane) to provide the epoxy alcohol **S16** (29 mg, 0.092 mmol, 92%, *ee* = 85%) as a colorless oil. $[\alpha]_D^{20}$ = 8.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (t, *J* = 7.7 Hz, 1H), 5.18 (t, *J* = 6.9 Hz, 1H), 4.33 (s, 2H), 3.85–3.80 (m, 1H), 3.79 (s, 3H), 3.69 (dd, *J* = 12.0, 6.6 Hz, 1H), 2.96 (dd, *J* = 6.5, 4.5 Hz, 1H), 2.40 (q, *J* = 7.6 Hz, 2H), 2.22 (t, *J* = 7.6 Hz, 2H), 2.14–2.04 (m, 2H), 1.79 (br s, 1H), 1.71 (d, *J*= 1.1 Hz, 3H), 1.68–1.61 (m, 1H), 1.49 (ddd, *J*= 13.8, 9.2, 7.3 Hz, 1H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 148.2, 134.0, 129.5, 125.9, 62.9, 61.6, 61.1, 52.4, 38.7, 37.3, 30.5, 27.4, 23.7, 23.3, 17.0; IR (KBr, cm^{-1}): 3431, 2931, 2859, 1724, 1646, 1464, 1246, 1213, 1093, 836, 780; HRMS (ESI-TOF) calcd for $C_{16}H_{25}ClNaO_3$ [M+NH_4^+] 334.1780, found 334.1780.

*(2Z,6Z)-methyl 2-(chloromethyl)-9-((2R,3S)-3-formyl-2-methyloxiran-2-yl)-6-methylnona-2,6-dienoate (**S17**)*. To a solution of epoxy alcohol **S16** (25 mg, 0.079 mmol) in CH_2Cl_2 (1.1 mL) was added $NaHCO_3$ (67 mg, 0.798 mmol) and Dess–Martin periodinane (67 mg, 0.158 mmol) at room temperature. After 1 h, sat. aq. $NaHCO_3$ (2 mL) was added and the reaction mixture was stirred at room temperature for 10 min. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 2 mL). The CH_2Cl_2 layers were combined, dried using Na_2SO_4 and evaporated, purified by flash chromatography (0–15% ethyl acetate/hexane) gave epoxy aldehyde **S17** (22 mg, 0.070 mmol, 89%) as a clear colorless oil. $[\alpha]_D^{20}$ = –39.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (d, *J* = 4.9 Hz, 1H), 6.97 (t, *J* = 7.7 Hz, 1H), 5.16 (t, *J* = 7.1

Hz, 1H), 4.33 (s, 2H), 3.79 (s, 3H), 3.18 (d, J = 4.9 Hz, 1H), 2.40 (q, J =7.6 Hz, 2H), 2.22 (t, J = 7.6 Hz, 2H), 2.11 (q, J = 7.5 Hz, 2H), 1.72(s, 3H), 1.71–1.65 (m, 1H), 1.63–1.54 (m, 1H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 166.3, 148.0, 134.7, 129.6, 125.2, 64.1, 63.6, 52.4, 38.5, 37.3, 30.5, 27.3, 23.4, 23.3, 17.4; IR (KBr, cm^{-1}): 2953, 2853, 2730, 1720, 1646, 1443, 1283, 1197, 1061, 783; HRMS (ESI-TOF) calcd for $C_{16}H_{27}ClNO_4$ [M+NH_4^+] 332.1623, found 332.1622.

*(1aR,7aR,10aS,10bS,Z)-1a,5-Dimethyl-8-methylene-2,3,6,7,7a,8,10a,10b-octahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-9(1aH)-one (**34**)*. Under Ar, to a solution of $CrCl_2$ (29.0 mg, 0.236 mmol) in dry DMF (4 mL) was added a solution of **S17** (12.0 mg, 0.038 mmol) in 1 mL dry DMF over 2 h at room temperature. When the addition was completed, the reaction was allowed to stir for another 2 h and quenched with 3.0 mL of water. The reaction mixture was extracted with Et_2O, the combined extracts were washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was dissolved in 1.2 mL of CH_2Cl_2 to which DBU (0.7 mg, 0.005 mmol) was added. After stirring for 48 h, the reaction mixture was concentrated, purified by flash chromatography (0–10% ethyl acetate/hexane) to get yield the lactone **34** (3.8 mg, 0.015 mmol, 39% over 2 steps).

Experimental procedure for biological assay

Cell lines and reagents Human promyelocytic leukemia cell line HL-60, rat glioma cell line C6, human breast cancer cell lines MCF7 and SUM159 were obtained from State Key Laboratory of Experimental Hematology, Institute of Hematology, Chinese Academy of Medical Sciences (Tianjin, China). HL-60, SUM159 and MCF7 was maintained in RPMI 1640 (Hyclone) supplemented with 10% fetal bovine erum (Hyclone) and 1% antibiotic-antimycotic (Hyclone).

C6 was maintained in F12K (Boster Biological Technology Co., Ltd) supplemented with 15% HI horse serum (Gibco), 2.5% fetal bovine serum (Hyclone) and 1% antibiotic-antimycotic (Hyclone). Cell counting kit was purchased from Solarbio Science &Technology Co., Ltd (Beijing, China). Aldehyde dehydrogenase based cell detection kit was purchased from StemCell Technologies (Vancouver, Canada).

CCK cell proliferation assay C6, HL-60, MCF7 and SUM159 were seeded in 96-well plates at a density of 3,000 to 5,000 cells per well. Then 24 h later, the cells were treated with increasing concentrations of **19**, **33**, **34**, and parthenolide. After 72 h of incubation, 20 μL cell counting kit was added to each well. The plates were maintained in incubator for 1 to 4 h. Viable cells were detected by measuring OD value at 450 nm using Multiscan FC (Thermo). The inhibition rate (IR) was calculated as follows: IR = (1-OD value of treated row/OD value of control row) × 100%. All the experiments were carried out as triplicated and we tested every compound for three times.

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SUPPORTING INFORMATION

Experimental procedure for synthesis of compound **25**, copies of the NMR spectra of all new compounds, and X-ray data of compounds **19** and **31**. This material is available free of charge via the Internet at http://pubs.acs.org/.

REFERENCES

(1) (a) Sorm, F. Sesquiterpenes with ten-membered carbon rings. Review. *J. Agric. Food Chem.* **1971**, *19*, 1081–1087. (b) Fraga, B. M. Natural sesquiterpenoids. *Nat. Prod. Rep.* **1988**, *5*, 497–521. (c) Fraga, B. M. Natural sesquiterpenoids. *Nat. Prod. Rep*. **2013**, *30*, 1226–1264.

(2) (a) Sattar, E. A.; Galal, A. M.; Mossa, G. S. Antitumor germacranolides from *Anvillea garcinii*. *J. Nat. Prod.* **1996**, *59*, 403–405. (b) Mittra, S.; Datta, A. P.; Singh, S. K.; Singh, A. 5-Hydroxytryptamine-inhibiting property of Feverfew: role of parthenolide content. *Acta Pharmacol. Sin*. **2000**, *21*, 1106–1114. (c) Beekman, C.; Woerdenbag, H. J.; van Uden, W.; Pras, N.; Konings, A. W. T. H.; Wikstroem, V. T.; Schmidt, J. Structure-cytotoxicity relationships of some helenanolide-type sesquiterpene lactones. *J. Nat. Prod.* **1997**, *60*, 252–257. (d) Wedge, D. E.; Galindo, J. C. G.; Macías, F. A. Fungicidal activity of natural and synthetic sesquiterpene lactone analogs. *Phytochemistry* **2000**, *53*, 747–757. (e) François, G.; Passreiter, C. M.; Woerdenbag, H. J.; Van Looveren, M. Antiplasmodial activities and cytotoxic effects of aqueous extracts and sesquiterpene lactones from *Neurolaena lobata*. *Planta Med*. **1996**, *62*, 126–129. (f) Macías, F. A.; Oliva, R.; Varela, R. M.; Torres, A.; Molinillo, J. M. G. Allelochemicals from sunflower leaves cv. Peredovick. *Phytochemistry* **1999**, *52*, 613–621.

(3) (a) Zhai, J. D.; Li, D.; Long, J.; Zhang, H. L.; Lin, J. P.; Qiu, C. J.; Zhang, Q.; Chen, Y. Biomimetic semisynthesis of arglabin from parthenolide. *J. Org. Chem.* **2012**, *77*, 7103–7107. (b) Wilton, J. H.; Doskotch, R. W. Acid cyclization and other products of the germacranolide epoxide lipiferolide. *J. Org. Chem.* **1983**, *48*, 4251–4256. (c) Hernández, A. S.; Afonso, M. M.; González, A. G.; Galindo, A. Partial synthesis of germacranolides with pyran and furan-type rings. *Tetrahedron Lett.* **1992**, *33*, 4747–4750. (d) Parodi, F. J.; Fischer, N. H. The first

biomimetic conversion of a germacrolide-4-epoxide into a xanthanolide. *J. Chem. Soc., Chem. Commun.* **1986**, *18*, 1405–1405.

(4) (a) Minnaard, A. J.; Wijnberg, J. B. P. A.; de Groot, A. The synthesis of germacrane sesquiterpenes and related compounds. *Tetrahedron* **1999**, *55*, 2115–2146. (b) Azarken, R.; Guerra, F. M.; Moreno-Dorado, F. J.; Jorge, Z. D.; Massanet, G. M. Substituent effects in the transannular cyclizations of germacranes. Synthesis of 6-epi-costunolide and five natural steiractinolides. *Tetrahedron* **2008**, *64*, 10896–10905.

(5) (a) Still, W. C.; Murata, S.; Revial, G.; Yoshihara, K. Synthesis of the cytotoxic germacranolide eucannabinolide. *J. Am. Chem. Soc.* **1983**, *105*, 625–627. (b) Takahashi, T.; Nemoto, H.; Kanda, Y.; Tsuji, J.; Fujise, Y. [2,3]-Wittig rearrangement of a 13-membered diallylic ether. Six-step synthesis of costunolide. *J. Org. Chem*. **1986**, *51*, 4315–4316. (c) Takahashi, T.; Nemoto, H.; Kanda, Y.; Tsuji, J.; Fujise, Y. Macroring contraction methodology : 3. Total syntheses of costunolide and haageanolide using transannular [2,3]-wittig rearrangement of 13-membered diallylic ethers as key reaction. *Tetrahedron* **1987**, *43*, 5499–5520. (d) Foo, K.; Usui, I.; Götz, D. C. G.; Werner, E. W.; Holte, D.; Baran, P. S. Scalable, enantioselective synthesis of germacrenes and related sesquiterpenes inspired by terpene cyclase phase logic. *Angew. Chem. Int. Ed.* **2012**, *51*, 1–6.

(6) Nishitani, K.; Isozaki, M.; Yamakawa, K. A synthesis of α-methylene-γ-lactones fused to medium and large rings by intramolecular cyclization of formylated allyl halides. *Chem. Pharm. Bull.* **1990**, *38*, 28–35.

(7) (a) Kwoka, B. H.; Koha, B.; Ndubuisia, M. I.; Elofssona, M.; Crews, C. M. The anti-inflammatory natural product parthenolide from the medicinal herb Feverfew directly binds

to and inhibits IκB kinase. *Chem. Biol.* **2001**, *8*, 759–766. (b) Tiuman, T. S.; Ueda-Nakamura, T.; Cortez, D. A. G.; Dias Filho, B. P.; Morgado-Díaz, J. A.; De Souza, W.; Nakamura, C. V. Antileishmanial activity of parthenolide, a sesquiterpene lactone isolated from tanacetum parthenium. *Antimicrob. Agents Chemother.* **2005**, *49*, 176–182. (c) Miglietta, A.; Bozzo, F.; Gabriel, L.; Bocca, C. Microtubule-interfering activity of parthenolide. *Chem. Biol. Interact.* **2004**, *149*, 165–173. (d) Parada-Turska, J.; Paduch, R.; Majdan, M.; Kandefer-Szerszen, M.; Rzeski, W. Antiproliferative activity of parthenolide against three human cancer cell lines and human umbilical vein endothelial cells. *Pharmacol. Rep.* **2007**, *59*, 233–237.

(8) (a) Ghantous, A.; Sinjab, A.; Herceg, Z.; Darwiche, N. Parthenolide: from plant shoots to cancer roots. *Drug. Discov. Today* **2013**, *18*, 894–905. (b) Guzman, M. L.; Rossi, R. M.; Karnischky, L.; Li, X.; Peterson, D. R.; Howard, D. S.; Jordan, C. T. The sesquiterpene lactone parthenolide induces apoptosis of human acute myelogenous leukemia stem and progenitor cells. *Blood* **2005**, *105*, 4163–4169.

(9) Abbott, A. Cancer: the root of the problem. *Nature* **2006**, *442*, 742–743.

(10) Jin, P.; Madieh, S.; Augsburger, L. L. The solution and solid state stability and excipient compatibility of parthenolide in feverfew. *AAPS PharmSciTech* **2007**, *8*, 200–205.

(11) Lesiak, K.; Koprowska, K.; Zalesna, I.; Nejc, D.; Duẗchler, M.; Czyz, M. Parthenolide, a sesquiterpene lactone from the medical herb feverfew, shows anticancer activity against human melanoma cells in vitro. *Melanoma Res.* **2010**, *20*, 21–34.

(12) Kevin, P. New agents for the treatment of leukemia: discovery of DMAPT (LC-1). *Drug Discov. Today* **2010**, *15*, 322.

(13) Long, J.; Ding, Y. H.; Wang, P. P.; Zhang, Q.; Chen, Y. Protection-group-free semisyntheses of parthenolide and its cyclopropyl analogue. *J. Org. Chem*. **2013**, *78*, 10512–10518.

(14) Yang, H. S.; Gao, Y. Z.; Qiao, X. X.; Xie, L. G.; Xu, X. H. Concise total synthesis of (–)-8-epigrosheimin. *Org. Lett.* **2011**, *13*, 3670–3673.

(15) Sen, S. E.; Garvin, G. M. Syntheis of (2*E*,6*E*)-[10-^{3}H]farnesol and (2*E*,6*E*)-[10-^{3}H]farnesal for insect dehydrogenase studies. *J. Labelled Compd. Radiopharm*. **1995**, *36*, 1063–1069.

(16) Keaton, K. A.; Phillips, A. J. Titanium (II)-mediated cyclizations of (silyloxy) enynes: a total synthesis of (–)-7-demethylpiericidin A1. *J. Am. Chem. Soc.* **2006**, *128*, 408–409.

(17) (a) Katsuki, T.; Sharpless, K. B. The first practical method for asymmetric epoxidation. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976. (b) Bravo, F.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. Alkene substituents for selective activation of endo-regioselective polyepoxide oxacyclizations. *Org. Lett.* **2004**, *6*, 4487–4489. (c) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. Catalytic asymmetric epoxidation and kinetic resolution: modified procedures including in situ derivatization. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.

(18) (a) Semmelhack, M. F.; Tomesch, J. C.; Czarny, M.; Boettger, S. Preparation of 2-(alkylthiomethyl)acrylates. *J. Org. Chem*. **1978**, *43*, 1259–1262. (b) Semmelhack, M. F.; Wu, E. S. C. Synthetic methods for sesquiterpene .alpha.-methylene-.gamma.-lactones. *J. Am. Chem. Soc.* **1976**, *98*, 3384–3386. (c) Wang, Z.; Warder, S. E.; Perier, H.; Grimm, E. L.; Bernstein, M. A. A straightforward approach to the synthesis of the tricyclic core of taxol. *J. Org. Chem.* **1993**, *58*, 2931–2932.

(19) (a) Bryan, V. J.; Chan, T. H. Indium mediated intramolecular carbocyclization in aqueous media. A facile and stereoselective synthesis of fused α-methylene-γ-butyrolactones. *Tetrahedron Lett.* **1996**, *37*, 5341–5342. (b) Paquette, L. A.; Rothhaar, R. R. Competitive intramolecular/intermolecular chelation options operative during indium-promoted additions to pyridyl aldehydes and to glyoxylic acid under aqueous conditions. *J. Org. Chem*. **1999**, *64*, 217–224.

(20) (a) Matsuda, F.; Sakai, T.; Okada, N.; Miyashita, M. Extremely convenient cyclization of medium rings using SmI_2. *Tetrahedron Lett.* **1998**, *39*, 863–864. (b) Tamiya, H.; Goto, K.; Matsuda, F. Efficient medium-ring cyclization under non-high-dilution conditions using SmI_2. *Org. Lett.* **2004**, *6*, 545–547.

(21) (a) Still, W. C.; Mobilio, D. Synthesis of asperdiol. *J. Org. Chem*. **1983**, *48*, 4785–4786. (b) Rayner, C. M.; Astles, P. C.; Paquette, L. A. Total synthesis of furanocembranolides. 2. Macrocyclization studies culminating in the synthesis of a dihydropseudopterolide and gorgiacerone. Related furanocembranolide interconversions. *J. Am. Chem. Soc.* **1992**, *114*, 3926–3936. (c) Wender, P. A.; McKinney, J. A.; Mukai, C. General methodology for the synthesis of neocarzinostatin chromophore analogs: intramolecular chromium-mediated closures for strained ring synthesis. *J. Am. Chem. Soc.* **1990**, *112*, 5369–5370. (d) Joyasawal, S.; Lotesta, S. D.; Akhmedov, N. G.; Williams, L. J. Spirodiepoxide strategy to the C ring of pectenotoxin 4: Synthesis of the C1–C19 sector. *Org. Lett.* **2010**, *12*, 988–991.

(22) Denmark, S. E.; Almstead, N. G. *Allylation of Carbonyls: Methodology and Stereochemistry. In Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, **2000**; pp 369–370, 376, 386–388.

(23) Mycka, R. J.; Steward, O. W.; Fleming, F. F. γ-Hydroxynitrile alkylations electrophile-dependent stereoselectivity. *Org. Lett.* **2010**, *12*, 3030–3033.

(24) Fürstner, A.; Aïssa, C.; Riveiros, R.; Ragot, J. Total synthesis of amphidinolide T4. *Angew. Chem. Int. Ed.* **2002**, *41*, 4763–4766.

(25) Wang, X. B.; Erickson, S. D.; Iimori, T.; Still, W. C. Enantioselective complexation of organic ammonium ions by simple tetracyclic podand ionophores. *J. Am. Chem. Soc.* **1992**, *114*, 4128–4137.

(26) Ghosh, A. K.; Liu, C. Enantioselective total synthesis of (+)-amphidinolide T1. *J. Am. Chem. Soc.* **2003**, *125*, 2374–2375.

(27) (a) Bernardi, L.; Bonini, B. F.; Capitò, E.; Comes-Franchini, M.; Dessole, G.; Fini, F.; Fochi, M.; Herrera, R. P.; Ricci, A. Towards the synthesis of highly functionalized chiral α-Amino nitriles by aminative cyanation and their synthetic applications. *Eur. J. Org. Chem.* **2006**, *1*, 207–217. (b) Benedetti, F.; Magnan, M.; Miertus, S.; Norbedo, S.; Parat, D.; Tossi, A. Stereoselective synthesis of non symmetric dihydroxyethylene dipeptide isosteres via epoxyalcohols derived from α-amino acids. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3027–3030.

(28) (a) Arcelli, A.; Balducci, D.; Grandi, A.; Porzi, G.; Sandri, M.; Sandri, S. Chiral 1,4-morpholin-2,5-dione derivatives as α-glucosidase inhibitors: Part 2. *Tetrahedron: Asymmetry* **2005**, *16*, 1495–1501. (b) Benedetti, F.; Magnan, M.; Miertus, S.; Norbedo, S.; Parat, D.; Tossi, A. Stereoselective synthesis of non symmetric dihydroxyethylene dipeptide isosteres via epoxyalcohols derived from α-amino acids. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3027–3030.

(29) (a) Still, W. C.; Novack, V. J. Total synthesis of (.+–.)-3-deoxyrosaranolide. *J. Am. Chem. Soc.* **1984**, *106*, 1148–1149. (b) Still, W. C.; Galynker, I. Chemical consequences of conformation in macrocyclic compounds: An effective approach to remote asymmetric induction. *Tetrahedron* **1981**, *37*, 3981–3996. (c) Afonso, M. M.; Mansilla, H.; Palenzuela, J. A.; Galindo, A. Acid cyclization of 5-ketogermacren-6,12-olides. A reactivity and conformational study. *Tetrahedron* **1996**, *52*, 11827–11840.

(30) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. Simple reagents for direct halonium-induced polyene cyclizations. *J. Am. Chem. Soc.* **2010**, *132*, 14303–14314.

(31) (a) Neukirch, H.; Kaneider, N. C.; Wiedermann, C. J.; Guerrieroa, A.; D'Ambrosio, M. Parthenolide and its photochemically synthesized 1(10)*Z* isomer: chemical reactivity and structure–activity relationship studies in human leucocyte chemotaxis. *Bioorg. Med. Chem.* **2003**, *11*, 1503–1510. (b) Arai, T.; Tokumaru, K. Photochemical one-way adiabatic isomerization of aromatic olefins. *Chem. Rev.* **1993**, *93*, 23–39. (c) Bach, T.; Hehn, J. P. Photochemical reactions as key steps in natural product synthesis. *Angew. Chem. Int. Ed.* **2011**, *50*, 1000–1045.

(32) Jacobsson, U.; Kumar, V.; Saminathan, S. Sesquiterpene lactones from *Michelia champaca*. *Phytochemistry* **1995**, *39*, 839–843.

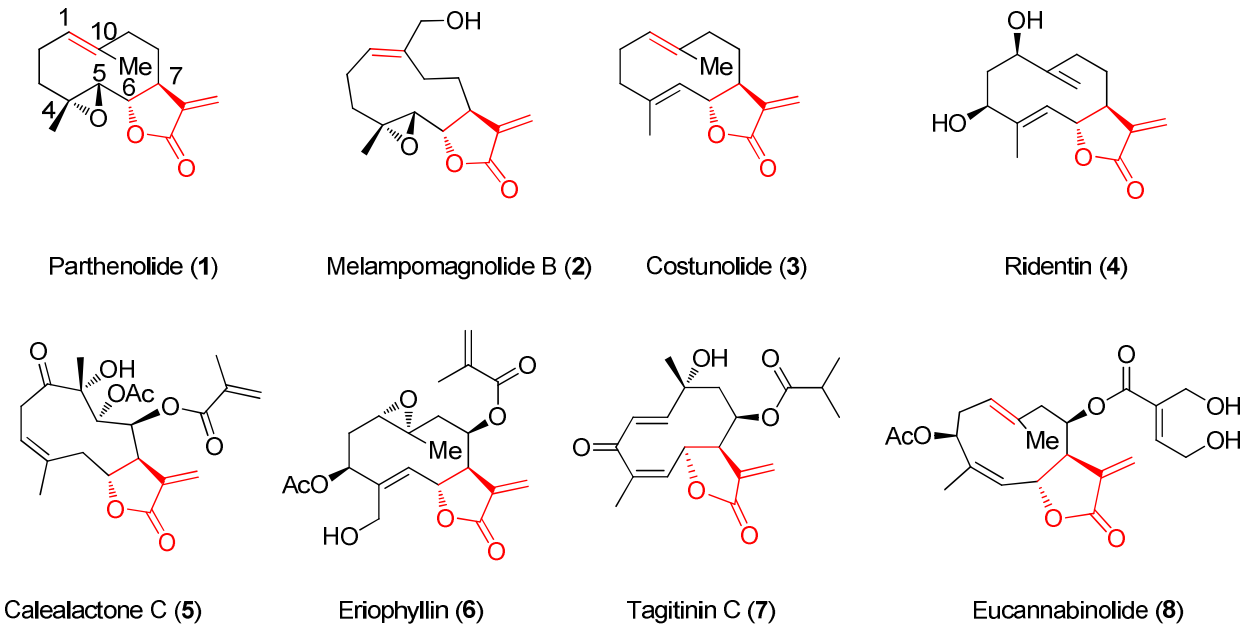
(33) Kotsos, M. P.; Aligiannis, N.; Myrianthopoulos, V.; Mitaku, S.; Skaltsounis, L. Sesquiterpene lactones from *Staehelina fruticosa*. *J. Nat. Prod.* **2008**, *71*, 847–851.

(34) Nasim, S.; Pei, S.; Hagen, F. K.; Jordan, C. T.; Crooks, P. A. Melampomagnolide B: A new antileukemic sesquiterpene. *Bioorg. Med. Chem.* **2011**, *19*, 1515–1519.

(35) Li, Y.; Zhang, T.; Korkaya, H.; Liu, S.; Lee, H. F.; Newman, B.; Yu, Y.; Clouthier, S. G.; Schwartz, S. J.; Wicha, M. S.; Sun, D. Intrinsic resistance of tumorigenic breast cancer cells to chemotherapy. *Clin. Cancer Res.* **2010**, *16*, 2580–2590.

(36) Still, W. C.; Galynker, I. Chemical consequences of conformation in macrocyclic compounds: An effective approach to remote asymmetric induction. *Tetrahedron* **1981**, *37*, 3981–3996.

A. Selected germacranolides containing a *trans*-fused γ-lactone.



B. Selected germacranolides containing a *cis*-fused γ-lactone.

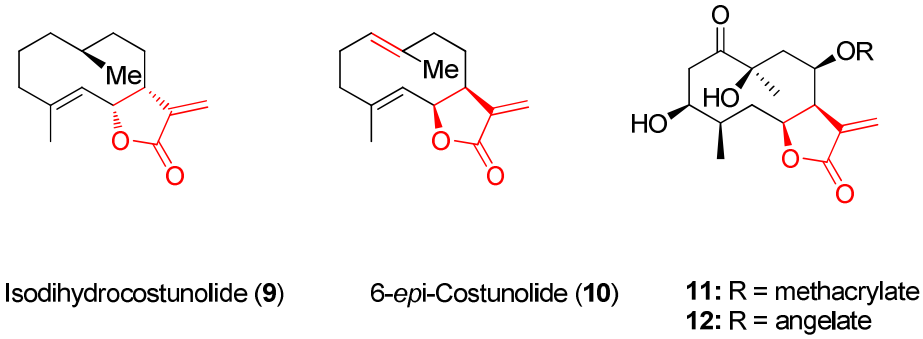
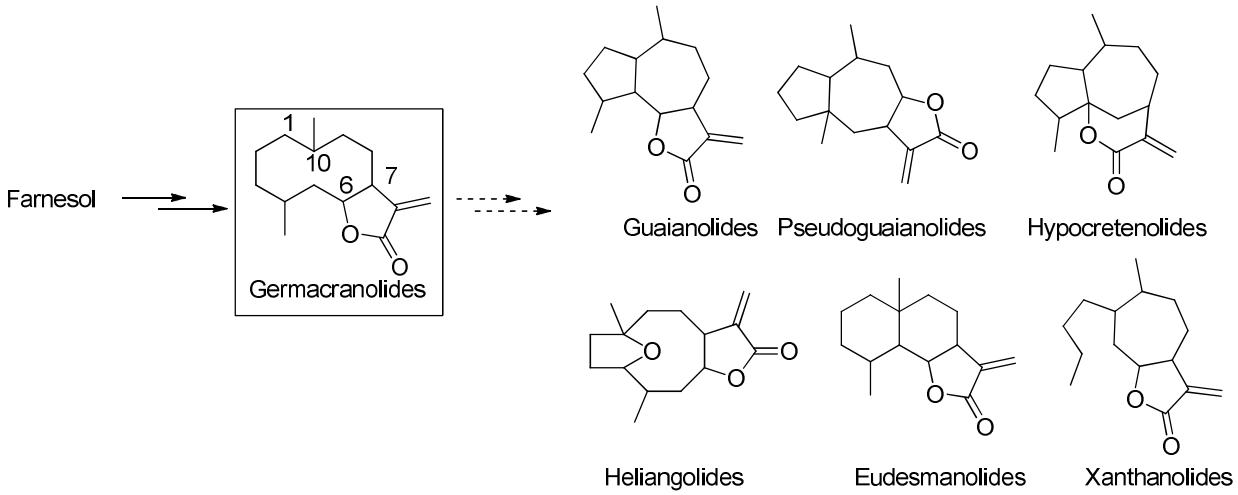
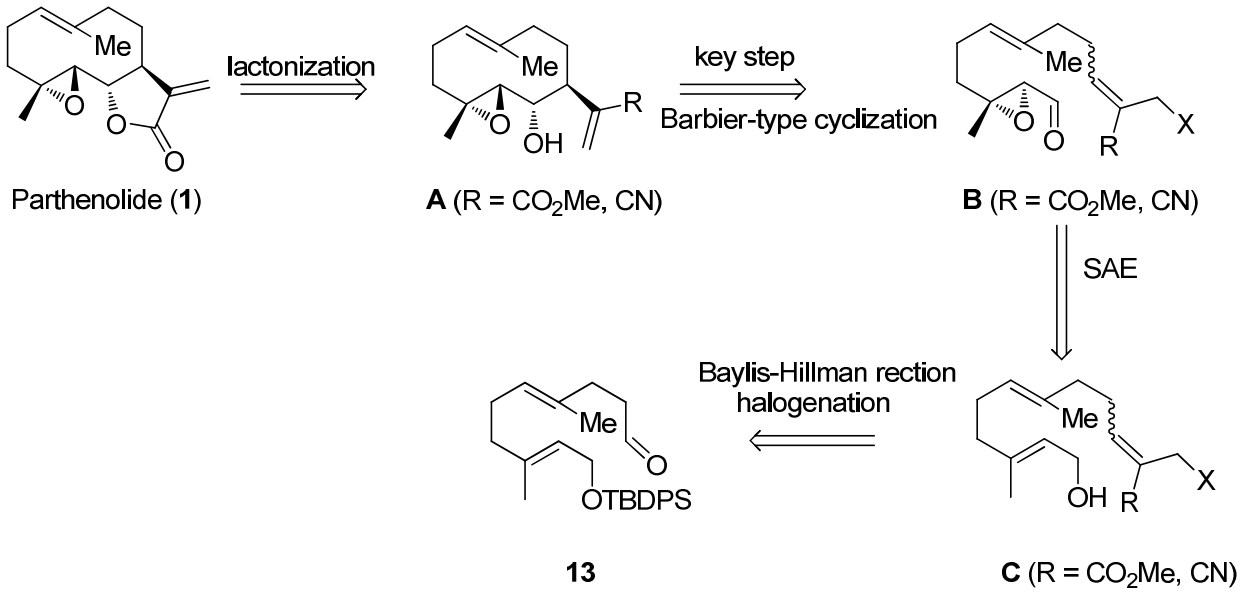


Figure 1. Selected naturally occurring germacranolides.

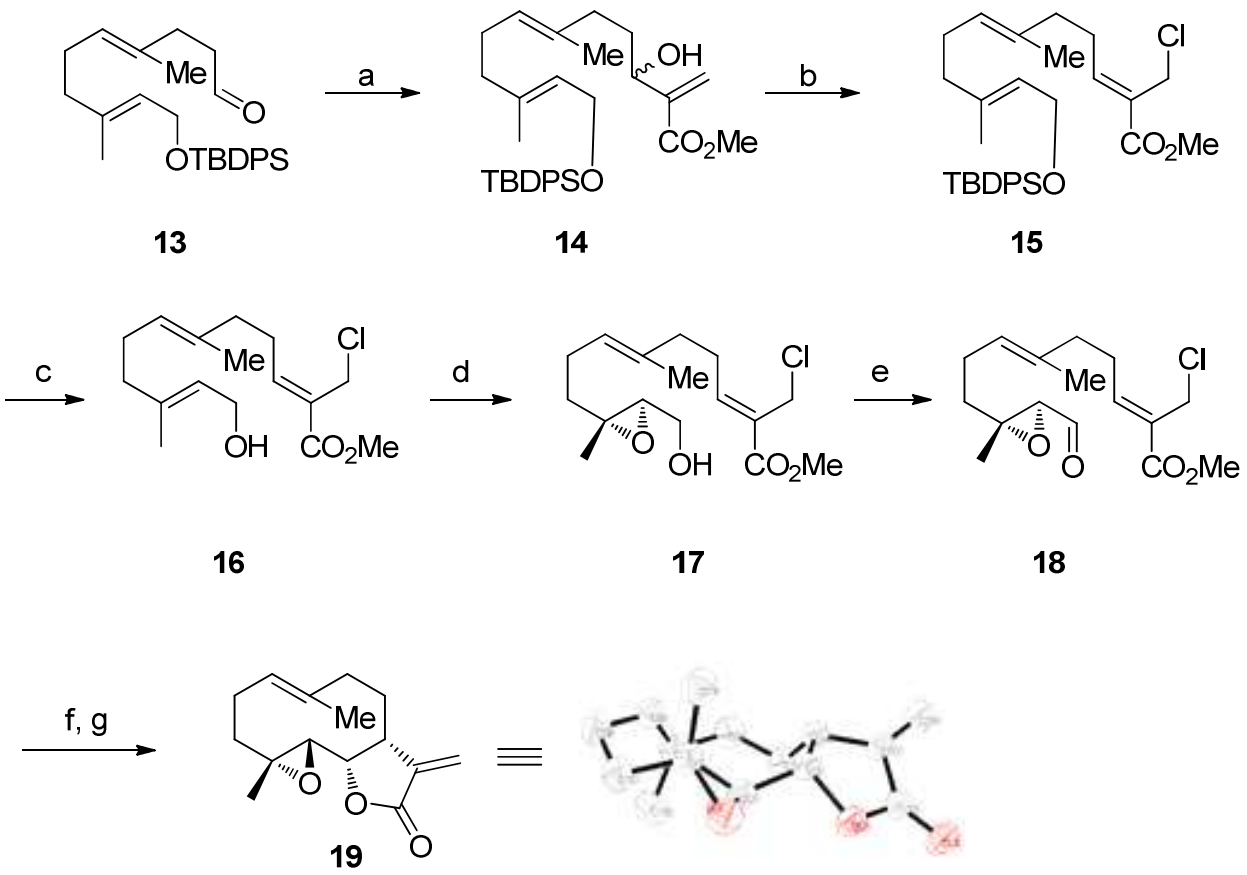
Scheme 1. Germacranolides and their synthetic relationship with other sesquiterpene lactones.



Scheme 2. Initial retrosynthetic analysis of parthenolide.

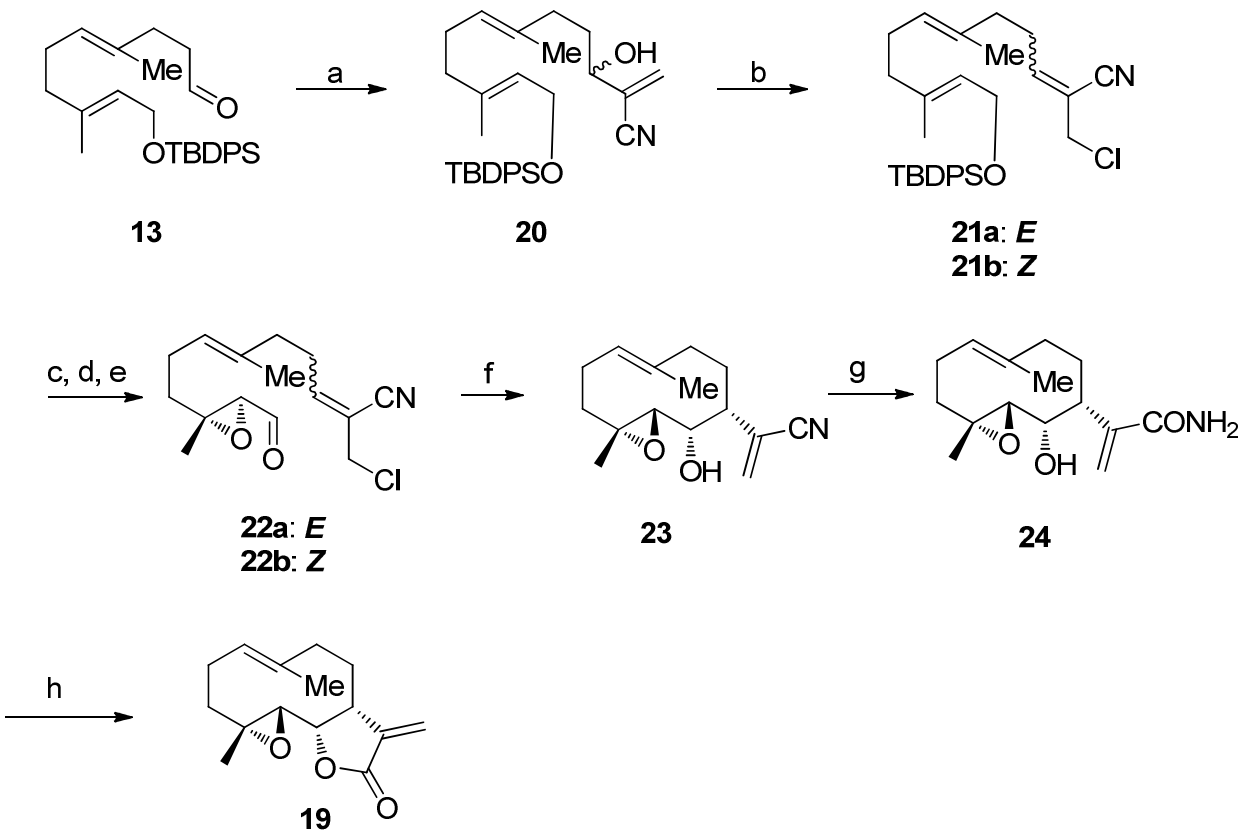


Scheme 3. Synthesis of 7-*epi*-parthenolide 19[a]



[a]Reagents and conditions: a) methyl acrylate, DABCO, RT, 77%; b) CCl_4, *n*-Bu_3P, 83%; c) HF-pyridine, THF, 91%; d) 4 Å MS, Ti(O*i*Pr)$_4$ (0.1 equiv), (–)-DIPT (0.12 equiv), TBHP (1.5 equiv), CH_2Cl_2, –40 °C to –18 °C, 93%, *ee* = 92%; e) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 92%; f) $CrCl_2$, DMF; g) DBU, CH_2Cl_2, 41% over 2 steps.

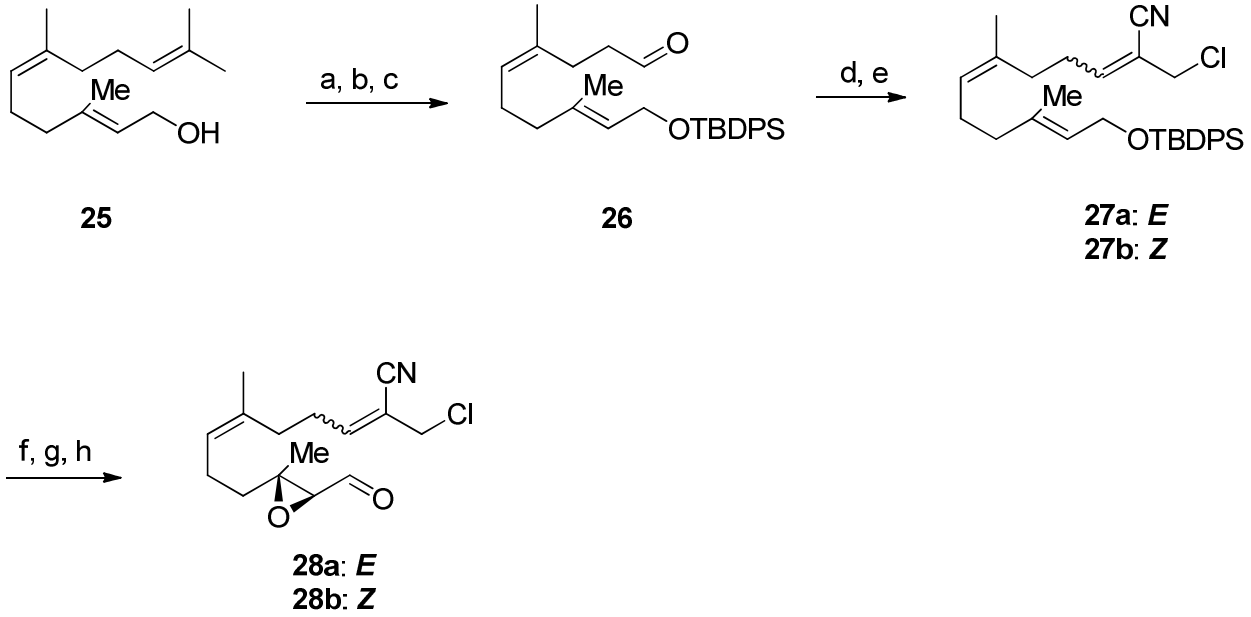
Scheme 4. Synthesis of 7-*epi*-parthenolide 19 by another route[a]



13 **20** **21a**: ***E*** **21b**: ***Z*** **22a**: ***E*** **22b**: ***Z*** **23** **24** **19**

[a]Reagents and conditions: a) acrylonitrile, DABCO, RT, 81%; b) CCl_4, *n*-Bu_3P, 80%, **21a**/**21b** = 3:1; c) HF-Pyridine, THF; d) 4 Å MS, Ti(O*i*Pr)$_4$ (0.1 equiv), (–)-DIPT (0.12 equiv), TBHP (1.5 equiv), CH_2Cl_2, –40 °C to –18 °C; e) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2. for **22a** 3 steps, 73%, *ee* = 88%; for **22b** 3 steps, 71%, *ee* = 87%; f) $CrCl_2$, DMF, 36% from **22a**; 39% from **22b**; g) K_2CO_3, H_2O_2, DMSO/THF, 88%; h) DBU, benzene, reflux, 93%.

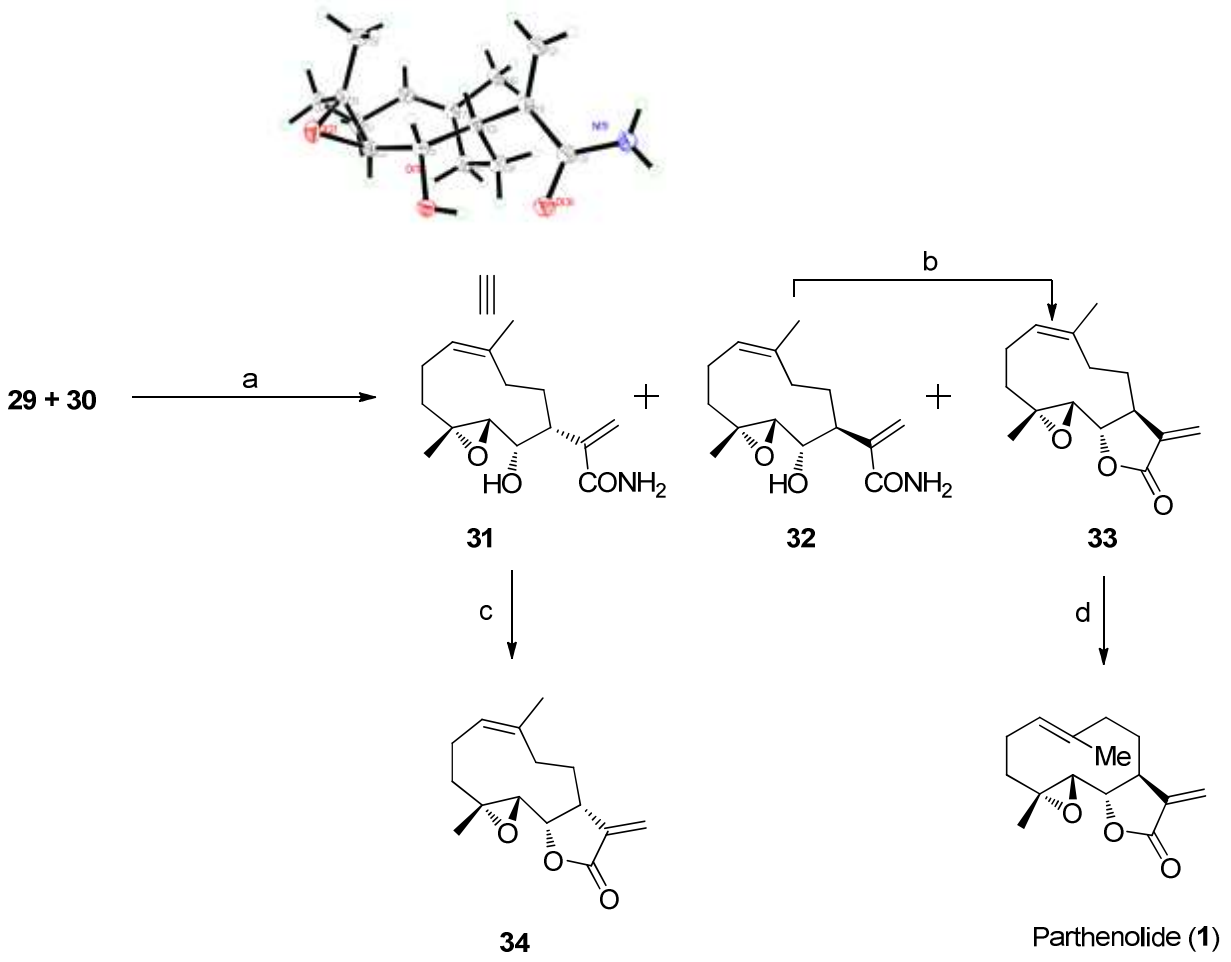
Scheme 5. Synthesis of cyclization precursors 28a and 28b[a]



25 **26** **27a**: ***E*** **27b**: ***Z*** **28a**: ***E*** **28b**: ***Z***

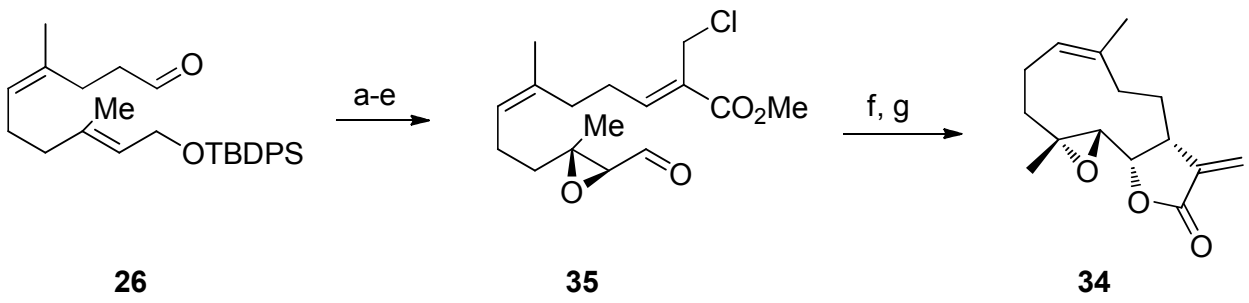
[a]Reagents and conditions: a) TBDPSCl, imidazole; b) NBS, THF/H_2O, then K_2CO_3, MeOH; c) H_5IO_6, $NaIO_4$, 63% over 3 steps; d) acrylonitrile, DABCO, RT; e) CCl_4, *n*-Bu_3P, 73% over 2 steps, 27a/b= 3:1; f) HF-Pyridine, THF; g) 4 Å MS, Ti(O*i*Pr)$_4$ (0.1 equiv), (–)-DIPT (0.12 equiv), TBHP (1.5 equiv), CH_2Cl_2, –40 ^oC to –18 ^oC; h) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, for 28a 3 steps, 81%, *ee* = 97%, for 28b 3 steps, 76%, *ee* = 95%.

Scheme 6. Synthesis of parthenolide (1), 33 and 34[a]



[a]Reagents and conditions: a) K_2CO_3, H_2O_2, DMSO/THF, 86%; b) DBU,CH_2Cl_2, RT, 92%; c) DBU, benzene, reflux, 91%; d) *hv* (254 nm), benzene, conversion: 58%, yield: 77% based on recovered starting material.

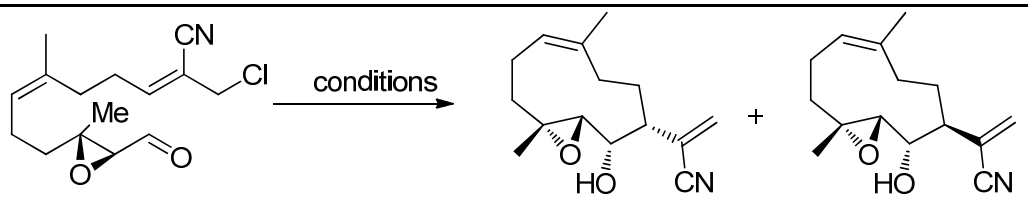
Scheme 7. Synthesis of 34 by another way[a]



26 **35** **34**

[a]Reagents and conditions: a) methyl acrylate, DABCO, RT; b) CCl_4, *n*-Bu_3P; c) HF-Pyridine, THF; d) 4 Å MS, Ti(O*i*Pr)$_4$ (0.1 equiv), (–)-DIPT (0.12 equiv), TBHP (1.5 equiv), CH_2Cl_2, –40 ^oC to –18 ^oC; e) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 5 steps, 41%, *ee* = 85%; f) $CrCl_2$, DMF; g) DBU, CH_2Cl_2, 2 steps, 39%.

Table 1. Cyclization of compound **28a**.



28a **29** **30**

Entry	Reaction conditions	Ratio of **29**:**30**[a] (yield[b])
1	$CrCl_2$, THF, RT	0
2	$CrCl_2$, DMF, RT	1.3:1 (35%)
3	$CrCl_2$, DMF, 50 ^oC	1.8:1 (38%)
4	$CrCl_2$, DMF, 0 ^oC	1.1:1 (17%)
5	$CrCl_2$, LiBr, DMF, RT	1.2:1 (34%)
6	$CrCl_2$, $MgBr_2 \cdot Et_2O$, DMF, RT	1.2:1 (34%)
7	$CrCl_2$, DMF/DMSO=1/2, RT	1.7:1 (41%)
8	$CrCl_2$, DMF/THF=1/2, RT	1.1:1 (20%)
9	$Pd_2Cl_2(PPh_3)_2$, Et_2Zn, K_2CO_3, DMA, RT	2.8:1 (16%)
10	$Pd(PPh_3)_4$, Et_2Zn, THF, RT	3.7:1 (19%)
11	$CrCl_2$, TBAI, DMF, RT	1.1:1 (36%)

12	**a) NaI, acetone b) $CrCl_2$, THF, RT**	**1:1 (52%)**
13	a) NaI, acetone b) $CrCl_2$, DMF/THF=1:2, RT	1.3:1 (49%)

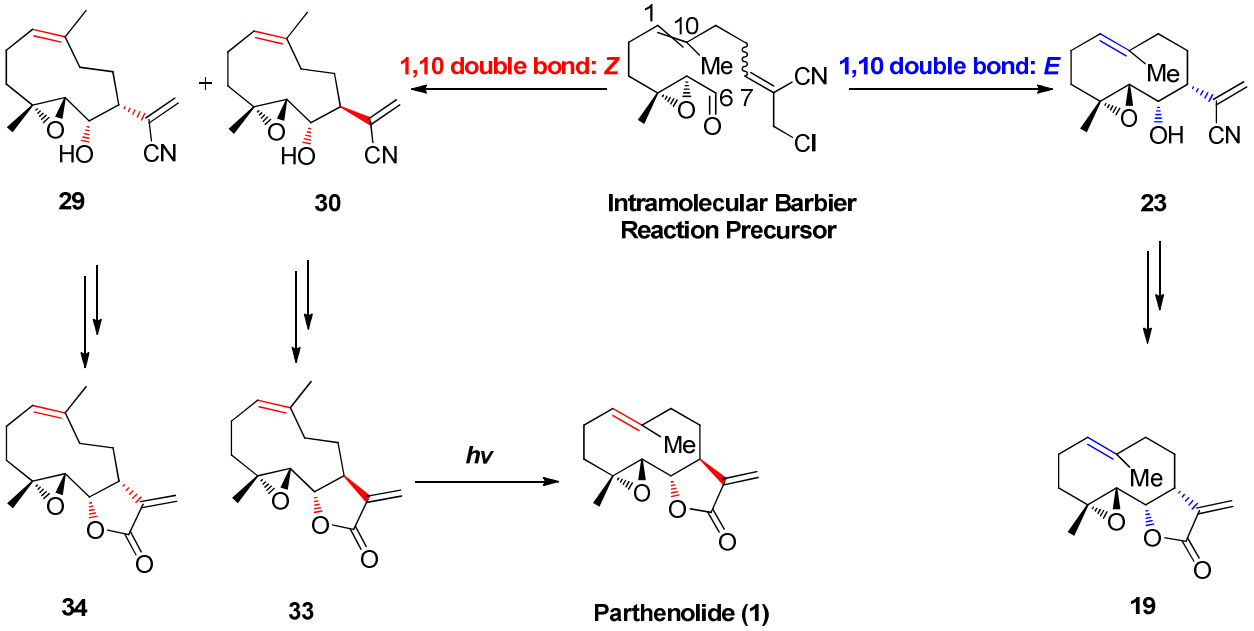
[a] Ratio determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Isolated yield.

Table 2. Inhibitory effects of parthenolide (**1**) and compounds **19**, **33**, **34** on HL-60, C6, MCF-7, and SUM159.[a]

Compounds	IC_{50}[b] (μM)			
	HL-60[c]	C6[d]	MCF-7[e]	SUM159[e]
Parthenolide	2.5±0.4	6.6±0.8	6.9±0.7	10.3±1.3
19	2.9±0.5	24.0±1.7	17.6±3.5	12.3±1.1
33	1.2±0.3	3.9±0.3	5.9±1.0	7.7±0.3
34	4.2±2.3	41.8±7.1	13.0±0.6	3.5±0.5

[a]All values are the mean of three independent experiments. [b]IC_{50}: 50% cytotoxic concentration. [c] HL-60: cultured acute myeloid leukemia cell line. [d]C6: rat glioma cell line. [e]MCF-7 and SUM159: human breast cancer cell lines.

Table of Contents graphic


1,10 double bond: Z
1,10 double bond: E
Intramolecular Barbier Reaction Precursor
29
30
23
34
33
Parthenolide (1)
19
hv