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Protection-Group-Free Semisyntheses of Parthenolide and Its Cyclopropyl Analogue

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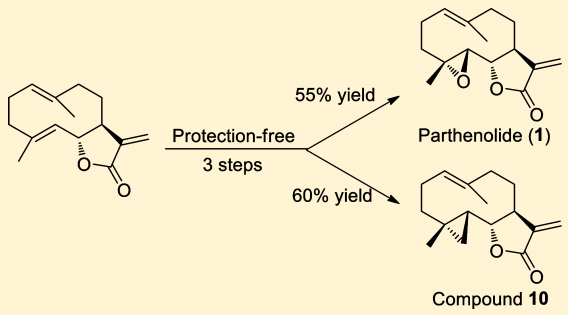
Supporting Information

ABSTRACT: Parthenolide showed extensive bioactivities including selective eradication of AML stem cells. Herein we report protection-free semisyntheses of parthenolide and its cyclopropyl analogue (compound **10**) from the abundant natural product costunolide with an overall yield of 55 and 60%, respectively. Compound **10** was more stable than parthenolide, and it maintained comparable activities against AML cell lines and AML stem cells. Therefore, compound **10** might be a superior small molecule than parthenolide as a tool for investigation of cancer stem cell biology.



Parthenolide (**1**, Figure 1), a prominent naturally occurring germacrane sesquiterpene lactone originally isolated from the shoots of feverfew (*Tanacetum parthenium*), has been extensively studied for its biological activities.[1−3] The search term "parthenolide" yielded approximately 700 articles between 1950 and 2013 by searching ISI web of knowledge. Parthenolide was demonstrated as the first small molecule that selectively kills acute myelogenous leukemia stem cells (LSCs) while sparing normal stem cells.[4] Furthermore, the finding has been reproduced in several leukemia and/or lymphoma models and solid tumors including bone tumor, breast cancer, melanoma, mesenchymal tumor, and prostate cancer.[1] However, parthenolide (**1**) has relatively poor pharmacologic properties that limit its potential clinical application. Dimethylaminoparthenolide (DMAPT, Figure 1), the water-soluble dimethylamino Michael adduct of parthenolide **1**, showed improved solubility and bioavailability.[5] Therefore, the ability of DMAPT to selectively eradicate LSCs[6] led to clinical trials for the treatment of AML, acute lymphoblastic leukemia (ALL), and chronic lymphocytic leukemia (CLL) in the United Kingdom.[7] However, parthenolide **1** is unstable under both acidic and basic conditions[8] and in media containing 0.5% serum.[9] The half-life of **1** in mouse plasma is only 0.34 h.[10]

To our knowledge, parthenolide **1** has not been synthesized to date. We proposed that the epoxide moiety in **1** might be responsible for its instability and short half-life in mouse plasma. Therefore, replacement of the epoxide moiety with the potentially bioisosteric cyclopropyl moiety might provide a novel stable cyclopropyl analogue. Moreover, the cyclopropane motif is found in many natural products and has attracted special attention for its pharmacological activities.[11] In addition, the cyclopropyl scaffold is a useful tool for the design of constrained bioactive molecules that project pharmacophore into the appropriate protein binding pockets.[12,13] Thus, we report the synthesis of parthenolide and its hitherto unreported cyclopropyl analogue (compound **10**).

Costunolide (**2**, Figure 1), a germacranolide available from the roots of *Saussurea lappa*,[14] which seemed to be a suitable substrate to be transformed into parthenolide **1** and its cyclopropyl analogue **10**. Following the presumed biosynthetic pathway of parthenolide (Figure 2), we attempted to synthesize parthenolide from costunolide **2** by direct epoxidation (Scheme 1).[15] However, direct epoxidation of costunolide **2** using the literature method afforded 1,10-epoxycostunolide,[16] and no parthenolide **1** was isolated (Scheme 1). Alternatively, hydrolyzation of costunolide gave compound **3**, which converts back to costunolide rapidly in neutral or acidic conditions. Moreover, treatment of compound **3** with *tert*-butyl hydroperoxide (TBHP) and $VO(acac)_2$ afforded a complicated mixture. Furthermore, direct treatment of costunolide **2** with Et_2Zn/CH_2I_2 also provided a complicated mixture.

Our first generation synthetic sequence commenced with reduction of the lactone in compound **2** (Scheme 2). It has been reported that direct reduction with lithium aluminum hydride leads to a complex mixture.[17] According to the literature, a two-step reduction using 1.1 equiv of DIBAL in CH_2Cl_2 at 0 °C followed by sodium borohydride treatment afforded compound **4** in 62% yield over two steps.[17] In our modified procedure, compound **2** was treated with 4 equiv of DIBAL in toluene at room temperature (RT), and then

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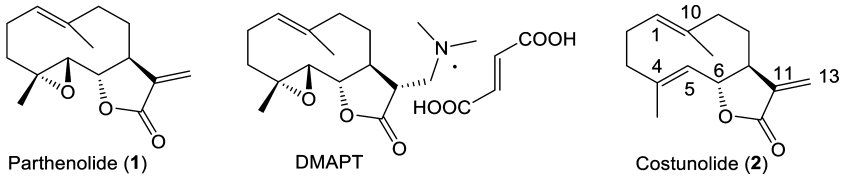


Figure 1. Structures of parthenolide **1**, DMAPT, and costunolide **2**.

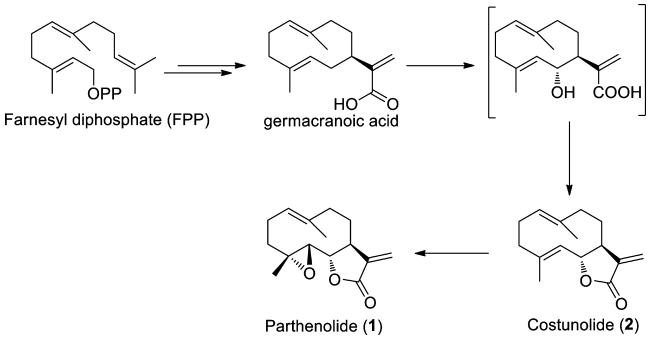
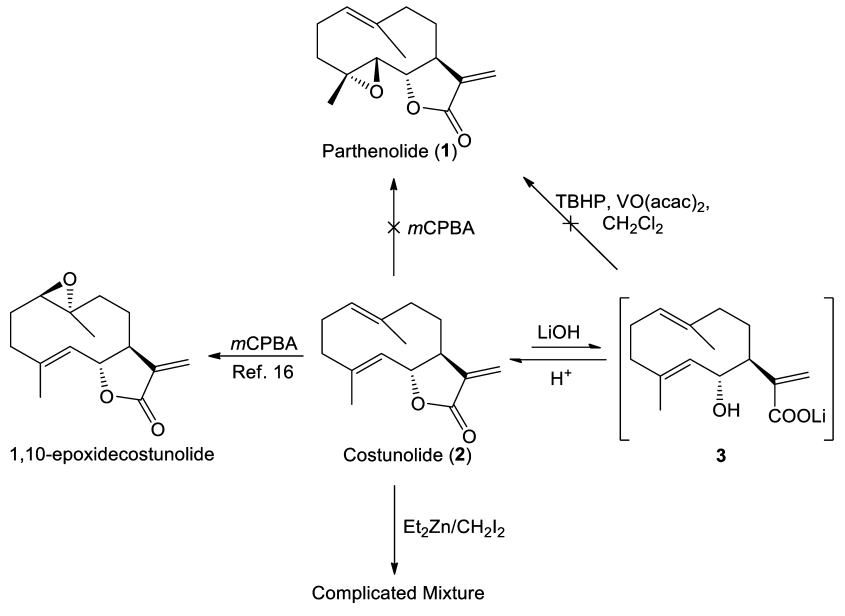


Figure 2. Presumed biosynthetic pathway of parthenolide.

compound **4** was obtained in one step (79% yield). Selective protection of the primary alcohol as a *tert*-butyldimethylsilyl ether by treatment of compound **4** with TBSCl gave compound **5** in 93% yield.[17] The following aim was to achieve selective epoxidation of the C4−C5 double bond of compound **5** in the presence of the C1−C10 and C11−C13 double bonds. We initially tried the epoxidation of compound **5** using *m*-chloroperoxybenzoic acid (*m*-CPBA) (Table 1, entries 1 and 2). Unfortunately, these conditions failed to provide compound **6**. The epoxidation employing TBHP and $VO(acac)_2$ afforded compound **6** in a yield of 67% (Table 1, entry 3). Treatment of compound **5** with $Ti(O\text{-}i\text{-}Pr)_4$, D-(−)-DIPT, and TBHP in CH_2Cl_2[18] at RT gave compound **6** in a good yield of 71% (Table 1, entry 4). Deprotection of compound **6** followed by oxidation with TEMPO and $PhI(OAc)_2$ in CH_2Cl_2 at RT afforded **1** in 80% yield (two steps).[19] Spectral data as well as optical rotation of the synthetic parthenolide are similar to that reported.[20,21] Its structure was further confirmed by X-ray analysis (X-ray data available in the S13 of Supporting Information). Next, treatment of compound **5** with Et_2Zn/CH_2I_2 led to the cyclopropanation product **8**.[22] Notably, a single diastereomer was observed. The following deprotection and oxidation yielded the cyclopropyl analogue of parthenolide (i.e., compound **10**). X-ray analysis (X-ray data available in the S27 of Supporting Information) revealed that the conformations of synthesized parthenolide and its cyclopropyl analogue **10** were very similar (Scheme 2). Total yields of parthenolide **1** and compound **10** from costunolide in five steps were 42 and 48%, respectively.

The second generation synthesis of parthenolide and compound **10** featured a regioselective and stereoselective epoxidation or cyclopropanation of compound **4** without employing a protecting group (Scheme 3). The attempts to achieve selective epoxidation of compound **4** for synthesis of compound **7** are shown in Table 2. Treatment of compound **4** with *m*-CPBA failed to give compound **7** (Table 2, entries 1 and 2). Epoxidation of compound **4** with TBHP, $VO(acac)_2$ (Table 2, entry 3), and $Ti(O\text{-}i\text{-}Pr)_4$, D-(−)-DIPT, and TBHP (Table 2, entry 4) afforded compound **7** in yields of 77 and 78%, respectively. After oxidation of compound **7**, parthenolide was obtained in a high yield of 89%. Therefore, we developed a protection-group-free semisynthesis of parthenolide **1** from the abundant starting material costunolide **2**. The convenient and efficient semisynthesis of parthenolide was achieved in three steps from costunolide with an overall yield of 55%. Similarly, compound **4** was treated with Et_2Zn/CH_2I_2 to provide

Scheme 1. Direct Epoxidation or Cyclopropanation of Costunolide



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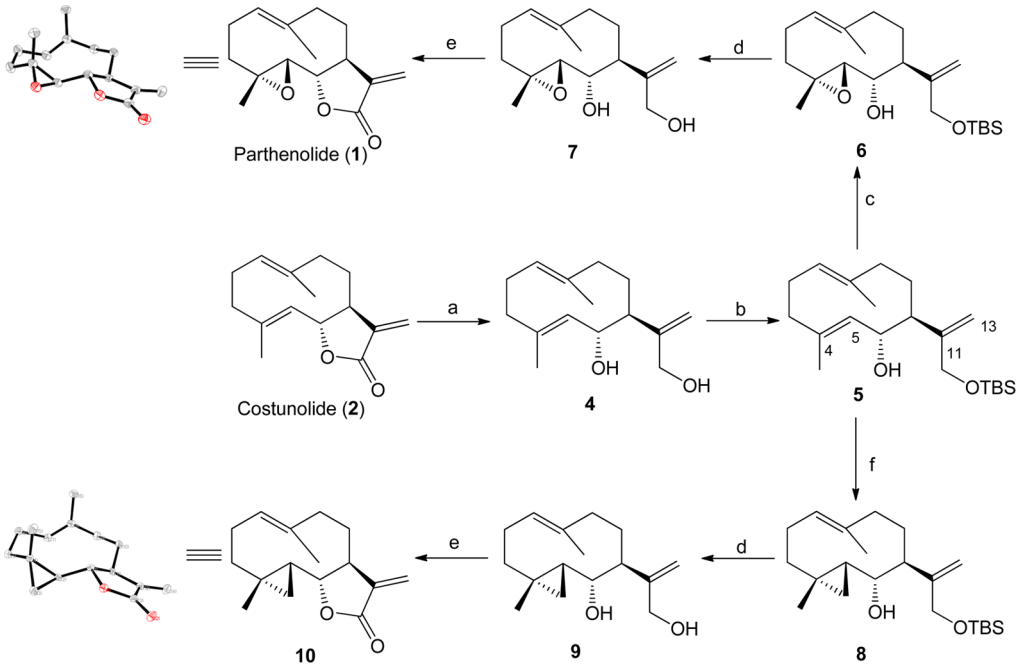
Scheme 2[a]



[a]Reagents and conditions: (a) DIBAL, toluene, RT, 4 h, 79%; (b) TBSCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 4 h, 93%; (c) $Ti(O\text{-}i\text{-}Pr)_4$, D-(−)-DIPT, TBHP, CH_2Cl_2, −20 °C, 20 h, 71%; (d) TBAF, THF, 0 °C, 1 h, 90% for compound **7**, 88% for compound **9**; (e) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, RT, 10 h, 89% for parthenolide **1**, 90% for compound **10**; (f) Et_2Zn, CH_2I_2, CH_2Cl_2, −10 °C, 1 h, 82%.

Table 1. Epoxidation of Compound 5 for Synthesis of Compound 6

entry	conditions	yield (%)
1	*m*-CPBA, CH_2Cl_2, RT	0
2	*m*-CPBA, NaOAc, CH_2Cl_2, RT	0
3	TBHP, $VO(acac)_2$, CH_2Cl_2, 0 °C, 0.5 h	67
4	$Ti(O\text{-}i\text{-}Pr)_4$, D-(−)-DIPT, TBHP, CH_2Cl_2, −20 °C, 20 h	71

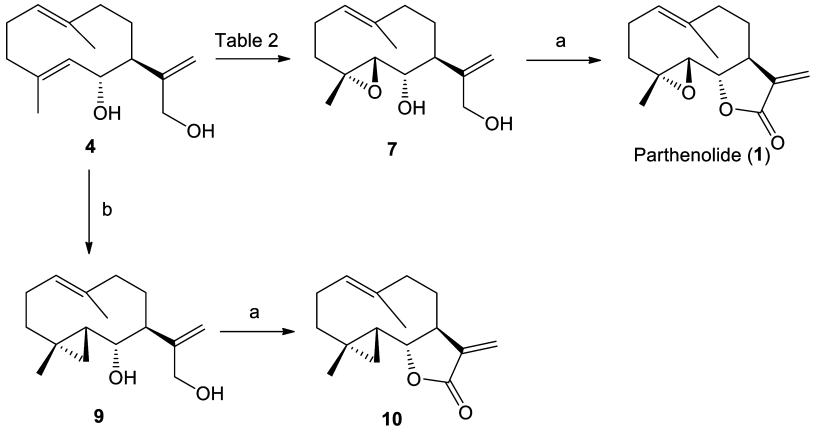
Table 2. Epoxidation of Compound 4 for Synthesis of Compound 7

entry	conditions	yield (%)
1	*m*-CPBA, CH_2Cl_2, RT	0
2	*m*-CPBA, NaOAc, CH_2Cl_2, RT	0
3	TBHP, $VO(acac)_2$, CH_2Cl_2, 0 °C, 0.5 h	77
4	$Ti(O\text{-}i\text{-}Pr)_4$, D-(−)-DIPT, TBHP, CH_2Cl_2, −20 °C, 20 h	78

compound **9**. The following oxidation afforded compound **10**. The overall yield of the protection-free synthesis of compound **10** from costunolide was 60%. The regioselectivity in the epoxidation or cyclopropanation of compound **4** might be due to the higher electron density of the trisubstituted C4−C5 double bond than the disubstituted C11−C13 double bond, and the stereoselectivity might be derived from the inducing effect of 6-OH.

With compound **10** in hand, we first checked its chemical stability compared with parthenolide **1**. Under acidic

Scheme 3[a]



[a]Reagents and conditions: (a) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, RT, 10 h, 89% for parthenolide **1**, 90% for compound **10**; (b) Et_2Zn, CH_2I_2, CH_2Cl_2, −10 °C, 1 h, 84%.

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conditions, parthenolide **1** was converted to micheliolide in 8 h through a reported transannular cyclization initiated by opening up the epoxy moiety.[23] In contrast, compound **10** stayed nearly intact over 72 h under the same conditions. The half-life of parthenolide **1** in mouse plasma was only 1.6 h, whereas that of compound **10** was 13.9 h (Table 3). These studies suggested that structure optimization from parthenolide **1** to compound **10** improved the physiological stability by 8.7-fold.

Table 3. Half-Life of Parthenolide 1 and Compound 10 in Mouse Plasma

parameters	parthenolide (**1**)	compound **10**
$t_{1/2}$	1.6 h	13.9 h

Parthenolide **1** and compound **10** were assayed against the cultured AML cell line HL-60, the doxorubicin (DOX)-resistant cell line HL-60/A, and the multi-drug-resistant AML progenitor cell line KG-1a. DOX, a clinically popular anti-AML agent, was used as a positive control. The results are summarized in Table 4. Overall, the activities exhibited by compound **10** against HL-60, HL-60/A, and KG-1a cells were comparable to those of parthenolide **1**. For compound **10**, the activities against the drug-resistant cell line HL-60/A and multi-drug-resistant AML progenitor cell line KG-1a were comparable to that against the sensitive cell line HL-60 (IC_{50} = 3.8 ± 0.3, 6.2 ± 0.6, and 8.6 ± 1.1 μM for HL-60, HL-60/A, and KG-1a cells, respectively). DOX is 74-fold less potent against HL-60/A cells than against HL-60 cells (IC_{50} = 5.9 vs 0.08 μM) and 20-fold less potent against KG-1a cells.

Table 4. Inhibitory Effects of Parthenolide 1 and Compound 10 on HL-60, HL-60/A, and KG-1a Cell Lines[a]

	IC_{50}[b] (μM)		
compounds	HL-60[c]	HL-60/A[d]	KG-1a[e]
DOX[f]	0.08 ± 0.02	5.9 ± 1.2	1.6 ± 0.1
parthenolide **1**	2.1 ± 0.5	3.6 ± 0.9	5.8 ± 0.2
10	3.8 ± 0.3	6.2 ± 0.6	8.6 ± 1.1

[a]All values are the mean of three independent experiments. [b]IC_{50}: 50% cytotoxic concentration. [c]HL-60: cultured AML cell line. [d]HL-60/A: doxorubicin-resistant cell line. [e]KG-1a: AML progenitor cell line. [f]DOX: doxorubicin, a clinically popular anti-AML agent used as a positive control.

Parthenolide **1** and compound **10** were further tested in an assay against primary total leukemia cells, leukemia stem/progenitor cells ($CD34^+$), and leukemia stem cells ($CD34^+CD38^-$) isolated from AML patient blood samples (Table 5). The cell viability was determined by annexin labeling after 18 h of treatment. At 5 μM, compound **10** showed significant activities against $CD34^+CD38^-$ labeled cells and $CD34^+CD38^-$ labeled cells, and the cell viabilities of total leukemia cells, stem/progenitor cells, and leukemia stem cells after treatment with compound **10** were 15.3, 9.2, and 6.0%, respectively. These data indicated that the survival rates of AML stem/progenitor cells and AML stem cells were less than those of total leukemia cells upon treatment with compound **10**. This finding further proved that compound **10** can selectively eradicate AML progenitor/stem cells and stem cells.

In summary, parthenolide has been studied intensively for its extensive biological activities,[1−9,24−26] but it is unstable and has a short half-life in mouse plasma.[8,10] Herein we report a protection-free and highly stereoselective semisynthesis of parthenolide from costunolide in three steps. To overcome the instability of parthenolide, a novel cyclopropyl analogue (compound **10**) of parthenolide was synthesized efficiently in three steps from costunolide via a similar sequence with an overall yield of 60%. Compound **10** demonstrated significantly higher stability than parthenolide both under acidic conditions and in plasma, and it maintained comparable activities against regular cancer cell lines (HL-60 and HL-60/A), the AML progenitor cell line KG-1a, and primary AML stem and progenitor cells from AML patient blood samples. Notably, the results suggest that the oxygen atom of the parthenolide epoxide might not be essential for its activity. Thus, replacement of the epoxide moiety of parthenolide with the bioisosteric cyclopropyl moiety not only showed pharmacological activity but also resulted in the discovery of the more promising anticancer compound **10** for further investigation. Therefore, analogue **10** might be a superior small molecule than parthenolide **1** as a tool for further investigation of cancer stem cell biology.

EXPERIMENTAL SECTION

Material. The UPLC-MS/MS system consisted of an ultra performance liquid chromatograph (UPLC) and a mass spectrometer. All solvents and chemicals were of HPLC grade. Male Kunming mice (20 ± 2 g) were supplied by the lab animal center of Academy of Military Medical Science (Beijing, China). The experimental protocol was approved by the Nankai University Ethics Committee for the use of experimental animals and conformed to the Guide for Care and Use of Laboratory Animals. Mice were housed at 22 ± 2 °C and 55 ± 5% relative humidity under a 12 h light−dark cycle. The blood samples were collected from the orbital veins at setting time.

Stability tests of Parthenolide 1 and Compound 10 in Mouse Plasma. Solutions of 10 μL of parthenolide **1** and compound **10** (2 mg/mL in acetonitrile) separately were placed in 100 μL mouse blank plasma solution. The tubes were then incubated in a bath incubator at 37 °C. Samples were removed at predetermined time intervals. The concentration of parthenolide **1** and compound **10** was analyzed by HPLC.

Cell Isolation and Culture. Primary human AML samples were obtained from volunteer donors from Institute of Hematology & Blood Diseases Hospital (Tianjin, China). Umbilical cord blood samples were obtained from volunteer donor in Maternity Hospital (Tianjin, China). Mononuclear cells were isolated from the samples using Ficoll-Plaque density gradient separation and cryopreserved in

Table 5. Survival Rates of Total AML Cells, $CD34^+$ AML Cells, $CD34^+CD38^-$ AML Cells from AML Patient'S Blood Sample in Response to Parthenolide 1 and Compound 10[a]

	2.5 μM			5 μM		
compounds	total	$CD34^+$	$CD34^+CD38^-$	total	$CD34^+$	$CD34^+CD38^-$
parthenolide **1**	21.0 ± 1.3	17.2 ± 0.9	12.2 ± 1.6	4.1 ± 0.1	3.0 ± 0.4	2.1 ± 0.4
10	29.7 ± 0.4	27.8 ± 0.7	20.5 ± 0.8	15.3 ± 0.7	9.2 ± 0.9	6.0 ± 1.0

[a]Percents of cell viability normalized to untreated controls of total leukemia cells, $CD34^+$ cells, and $CD34^+CD38^-$ cells.

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freezing medium of 90% FBS and 10% dimethylsulfoxide (DMSO) until use. Cells were cultured in serum-free IMDM (Iscove's modified Dulbecco's media) for 1 h before treating with compounds. All the drug treatments were performed in triplicate. The cell viability assay was carried out using the well-documented 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) assay.[27] All the tested cells were cultured with drugs for 72 h before adding the MTT reagent. Each experiment was repeated three times.

Flow Cytometry. Apoptosis assays were performed as follows. After 18 h of treatment, with the compounds in IMDM, normal and AML samples were isolated and stained by the antibodies CD34-allophycocyanin (APC), CD38-PECy7, for 30 min. Cells were washed in cold PBS and resuspended in 100 μL of Annexin-V buffer; Annexin-V−fluorescein isothiocyanate (FITC) and propidium iodide (PI) were added, and the tubes were vortexed gently. After incubation at 25 °C for 15 min, the samples were analyzed on a BD LSRII flow cytometer (BD Biosciences), and the data were analyzed using a Prism 5 software.

Chemistry. Parthenolide **1** and the starting material costunolide **2** were obtained from Accendatech Co., Ltd. (Tianjin, China). The used solvents were purified and dried according to common procedures. 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. High-resolution mass spectra were conducted using Q-TOF LC/MS by ESI-FTICR technique.

*Synthesis of (1R,2E,6E,10S)-10-(3-Hydroxyprop-1-en-2-yl)-3,7-dimethylcyclodeca-2,6-dienol (Compound **4**).* To a solution of costunolide (1.39 g, 6 mmol) in toluene (40 mL) was added a solution of DIBAL (1.0 M solution in toluene, 24 mL, 24 mmol) at 0 °C, and the mixture was stirred at RT for 4 h. To the mixture was added 10% aqueous solution of potassium sodium tartrate (10 mL) at 0 °C. The aqueous layers were extracted with Et_2O (3 × 20 mL). The combined organic layers was washed with saturated NaCl aqueous solution, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc = 3/1) to give compound **4** (1.11 g, 79%) as a colorless oil. Compound **4**:[17] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16 (s, 1H), 5.01 (s, 1H), 4.79 (br d, J = 10.4 Hz, 1H), 4.68 (d, J = 9.7 Hz, 1H), 4.24−4.09 (m, 3H), 2.52 (br s, 1H), 2.43−2.32 (m, 1H), 2.29−2.19 (m, 3H), 2.15−2.06 (m, 2H), 2.00−1.88 (m, 2H), 1.80−1.69 (m, 2H), 1.67 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 137.9, 134.6, 132.9, 126.7, 111.9, 71.5, 64.8, 55.0, 41.6, 39.5, 32.1, 25.8, 17.0, 16.3; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{15}H_{25}O_2$ 237.1855, found 237.1847.

*Synthesis of (1R,2E,6E,10S)-10-(3-((tert-Butyldimethylsilyl)oxy)-prop-1-en-2-yl)-3,7-dimethylcyclodeca-2,6-dienol (Compound **5**).* To a solution of compound **4** (115 mg, 0.49 mmol), DMAP (6 mg, 0.049 mmol), Et_3N (0.12 mL, 0.82 mmol), and CH_2Cl_2 (2.3 mL) was added TBSCl (0.54 M in CH_2Cl_2, 1 mL, 0.54 mmol) at 0 °C. The resulting mixture was stirred for 4 h. The reaction was quenched by adding saturated brine (2.4 mL). The mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude residue. The residue was purified by column chromatography (hexane/EtOAc = 30/1) to afford compound **5** as a colorless oil (159 mg, 93%). Compound **5**:[17] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16 (s, 1H), 5.00 (s, 1H), 4.80 (br d, J = 10.0 Hz, 1H), 4.64 (br d, J = 9.6 Hz, 1H), 4.21−4.06 (m, 3H), 2.66 (s, 1H), 2.40−2.30 (m, 1H), 2.29−2.16 (m, 2H), 2.16−2.01 (m, 3H), 2.01−1.92 (m, 1H), 1.71−1.62 (m, 5H), 1.41 (s, 3H), 0.93 (s, 9H), 0.11 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 137.3, 133.8, 132.9, 126.7, 112.1, 70.3, 65.1, 55.6, 41.5, 39.3, 31.7, 25.7, 25.6, 18.1, 16.7, 16.2, −5.6; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{21}H_{39}O_2Si$ 351.2719, found 351.2710.

*Synthesis of (1S,2S,3S,10R,E)-3-(3-((tert-Butyldimethylsilyl)oxy)-prop-1-en-2-yl)-6,10-dimethyl-11-oxabicyclo[8.1.0]undec-6-en-2-ol (Compound **6**). Method A.* In a 100 mL round-bottomed flask, 4 Å molecular sieves (723 mg) were dispersed in anhydrous CH_2Cl_2 (19 mL). Then D-(−)-diisopropyl tartrate (60 μL, 0.28 mmol) was added to the reaction flask, and the mixture was cooled to −40 °C. After 10 min, Ti(O-*i*-Pr)$_4$ (70 μL, 0.24 mmol) was added, and the mixture was stirred at −40 °C for 15 min. After that time, TBHP (3.3 M in toluene, 1.1 mL, 3.63 mmol) was introduced, and the mixture was stirred at −40 °C for 30 min; then compound **5** (817 mg, 2.35 mmol) was added as a solution in dichloromethane (4 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 (20 mL), warmed to RT, and stirred for 3 h. After filtering through Celite, the solution was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography [petroleum ether (PE)/EtOAc = 97/3] to provide compound **6** (607 mg, 71%) as a colorless oil. Compound **6**: IR (KBr, cm^{-1}) 3441, 3079, 1254, 1011, 842, 780; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (br d, J = 8.4 Hz, 1H), 5.12 (s, 1H), 4.92 (s, 1H), 4.20 (d, J = 13.2 Hz, 1H), 4.15 (d, J = 13.2 Hz, 1H), 3.40−3.30 (m, 1H), 2.69 (d, J = 8 Hz, 1H), 2.50 (s, 1H), 2.39−2.07 (m, 5H), 2.04−1.93 (m, 1H), 1.81 (dd, J = 14.8, 7.6 Hz, 1H), 1.69 (s, 3H), 1.64−1.52 (m, 1H), 1.29 (s, 3H), 1.27−1.18 (m, 1H), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 135.7, 124.4, 110.8, 71.5, 70.2, 65.1, 63.2, 52.8, 40.5, 37.4, 33.2, 25.9, 23.6, 18.3, 17.8, 17.4, −5.4; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{21}H_{39}O_3Si$ 367.2668, found 367.2663.

Method B. TBHP (3.3 M in toluene, 0.22 mL, 0.75 mmol) was added to a solution of compound **5** (220 mg, 0.63 mmol) and VO(acac)$_2$ (33 mg, 0.13 mmol) in CH_2Cl_2 (15 mL) at 0 °C. After stirring for 0.5 h, aqueous saturated Na_2SO_3 (20 mL) was added, and the aqueous layers were extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (PE/EtOAc = 97/3) to provide compound **6** (154 mg, 67%) as a colorless oil.

*Synthesis of (1S,2S,3S,10R,E)-3-(3-Hydroxyprop-1-en-2-yl)-6,10-dimethyl-11-oxabicyclo[8.1.0]undec-6-en-2-ol (Compound **7**).* A solution of compound **6** (366 mg, 1.0 mmol) in THF (40 mL) was treated with TBAF (1 M in THF, 1.9 mL, 1.9 mmol). After stirring for 1 h, aqueous saturated NH_4Cl (10 mL) was added. The aqueous layers were extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford a crude residue. The residue was purified by column chromatography (PE/EtOAc = 7/3) to yield compound **7** as a colorless oil (227 mg, 90%). Compound **7**: $[\alpha]_D^{25}$ = −9.2 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) 3430, 3077, 1262, 1023, 803; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19 (br d, J = 8.8 Hz, 1H), 5.09 (s, 1H), 4.95 (s, 1H), 4.17 (d, J = 12.4 Hz, 1H), 4.09 (d, J = 12.4 Hz, 1H), 3.41 (t, J = 8.8 Hz, 1H), 2.92 (s, 1H), 2.79 (d, J = 8.0 Hz, 1H), 2.54−2.38 (m, 2H), 2.37−2.25 (m, 2H), 2.24−2.00 (m, 3H), 1.85−1.71 (m, 2H), 1.68 (s, 3H), 1.30 (s, 3H), 1.28−1.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 135.6, 124.7, 112.6, 71.8, 70.4, 65.0, 64.4, 52.7, 40.7, 37.3, 33.2, 23.8, 17.5, 17.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{15}H_{24}O_3Na$ 275.1623, found 275.1622.

*Direct Epoxidation of Compound **4** To Give Compound **7**. Method 1.* In a 20 mL round-bottom flask, 4 Å molecular sieves (700 mg) were dispersed in anhydrous CH_2Cl_2 (10 mL). D-(−)-Diisopropyl tartrate (20 μL, 0.093 mmol) was added to the reaction flask, and the mixture was cooled to −40 °C. After 10 min, Ti(O-*i*-Pr)$_4$ (24 μL, 0.82 mmol) was added and stirred at −40 °C for 15 min. After that time, TBHP (3.3 M in toluene, 0.50 mL, 1.65 mmol) was introduced, and the mixture was stirred at −40 °C for 30 min; then compound **4** (190 mg, 0.81 mmol) was added as a solution in dry CH_2Cl_2 (2 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 (7 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 (PE/EtOAc = 7/3) to provide compound **7** (158 mg, 78%) as a colorless oil.

Method 2. TBHP (3.3 M in toluene, 0.1 mL, 0.33 mmol) was added to a solution of compound **4** (63 mg, 0.27 mmol) and

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$VO(acac)_2$ (14 mg, 0.054 mmol) in CH_2Cl_2 (6 mL) at 0 °C. After stirring for 0.5 h, aqueous saturated Na_2SO_3 (7 mL) was added, and the aqueous layers were extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent and purification by column chromatography (PE/EtOAc = 7/3) provided compound **7** (52 mg, 77%) as a colorless oil.

*Synthesis of Parthenolide (**1**).* To a solution of compound **7** (227 mg, 0.9 mmol) in CH_2Cl_2 (4.5 mL) were added $PhI(OAc)_2$ (942.5 mg, 2.9 mmol) and TEMPO (45 mg, 0.3 mmol). Resulting mixture was stirred at RT for 10 h. The mixture was poured into cold 0.5 M aqueous solution of Na_2SO_3 (40 mL) and extracted with Et_2O (2 × 20 mL). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE/EtOAc = 9/1) to provide parthenolide (**1**) (198 mg, 89%) as a colorless crystal solid. Parthenolide (**1**): mp 116−117 °C [lit. 114−115 °C[20]]; $[\alpha]_D^{25}$ = −80.2 (*c* = 1, $CHCl_3$), lit. $[\alpha]_D^{25}$ = −79.0 (*c* = 1, $CHCl_3$);[21] ^{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, 139.2, 134.7, 125.1, 121.3, 82.5, 66.2, 61.6, 47.5, 41.1, 36.3, 30.5, 24.1, 17.2, 16.9.

*Synthesis of (1R,2R,3S,10S,E)-3-(3-((tert-Butyldimethylsilyl)oxy)-prop-1-en-2-yl)-6,10-dimethylbicyclo[8.1.0]undec-6-en-2-ol (Compound **8**).* To a stirred solution of the compound **5** (175 mg, 0.5 mmol) in CH_2Cl_2 (4 mL) was added diethylzinc (1.0 M in hexane, 25 mL, 25.00 mL) at −10 °C, and the reaction mixture was stirred at the same temperature for 15 min. CH_2I_2 (0.16 mL, 2 mmol) was added to the reaction mixture at −10 °C, and the resulting mixture was stirred for 1.5 h. The reaction was quenched by addition of aqueous NH_4Cl solution (1 mL). The organic layers were separated; the aqueous layers were extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude residue. The residue was purified by column chromatography (hexane/EtOAc = 50/1) to give compound **8** (150 mg, 82%) as a colorless oil. Compound **8**: IR (KBr, cm^{-1}) 3422, 1259, 1085, 842, 781; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (dd, *J* = 11.3, 3.2 Hz, 1H), 5.13 (s, 1H), 4.93 (s, 1H), 4.21 (d, *J* = 13.0 Hz, 1H), 4.05 (d, *J* = 13.0 Hz, 1H), 3.27 (s, 1H), 2.70−2.31 (m, 3H), 2.26−2.12 (m, 1H), 2.10−2.03 (m, 2H), 2.01−1.95 (m, 1H), 1.94−1.80 (m, 1H), 1.77−1.64 (m, 4H), 0.96 (s, 3H), 0.91 (s, 9H), 0.85−0.74 (m, 2H), 0.38−0.33 (m, 2H), 0.093 (s, 3H), 0.091 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 133.8, 126.7, 112.0, 71.0, 65.6, 39.4, 32.7, 25.8, 25.1, 19.4, 18.2, 18.1, 17.8, 16.5, −5.49, −5.52; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{40}O_2NaSi$ 387.2695, found 387.2685.

*Synthesis of (1R,2R,3S,10S,E)-3-(3-Hydroxyprop-1-en-2-yl)-6,10-dimethylbicyclo[8.1.0]undec-6-en-2-ol (Compound **9**).* To a solution of compound **8** (3.27 g, 9.0 mmol) in THF (60 mL) was added TBAF (1 M in THF, 18 mL, 18 mmol) at 0 °C. After stirring for 1 h, aqueous saturated NH_4Cl (10 mL) was added. The aqueous layers were extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography (PE/EtOAc = 7/3) to afford compound **9** as a white solid (1.98 g, 88%). Compound **9**: mp 100−101 °C, $[\alpha]_D^{25}$ = +27.6 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) 3327, 3065, 1445, 1027, 900; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25−5.15 (m, 1H), 5.08 (s, 1H), 4.90 (s, 1H), 4.15 (d, *J* = 12.8 Hz, 1H), 4.04 (d, *J* = 12.8 Hz, 1H), 3.32−3.19 (m, 1H), 2.50−2.41 (m, 1H), 2.40−2.31 (m, 1H), 2.25−2.10 (m, 2H), 2.13−1.92 (m, 4H), 1.90−1.81 (m, 1H), 1.80−1.74 (m, 1H), 1.70 (s, 3H), 0.97 (s, 3H), 0.90−0.72 (m, 2H), 0.36 (dd, *J* = 9.1, 4.3 Hz, 1H), 0.26−0.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 133.9, 126.4, 112.2, 72.5, 65.1, 56.4, 41.5, 39.2, 35.1, 32.8, 25.0, 20.3, 18.0, 17.9, 16.4; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{26}O_2Na$ 273.1830, found 273.1837.

*Direct Cyclopropanation of Compound **4** To Afford Compound **9**.* To a stirred solution of compound **4** (118 mg, 0.5 mmol) in CH_2Cl_2 (4 mL) was added diethylzinc (1.0 M in hexane, 1 mL, 1 mmol) at −10 °C, and the reaction mixture was stirred at the same temperature for 15 min. Diiodomethane (0.16 mL, 2 mmol) was added to the reaction mixture at −10 °C, and the resulting mixture was stirred for 2 h. After aqueous NH_4Cl solution (1 mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc = 4/1) to give compound **9** as a white solid (105 mg, 84%).

*Synthesis of (3aS,9aS,10aR,10bR,E)-6,9a-Dimethyl-3-methylene-3,3a,4,5,8,9,9a,10,10a,10b-decahydro-2H-cyclopropa[9,10]cyclodeca[1,2-b]furan-2-one (Compound **10**).* Compound **9** (1.98 g, 7.9 mmol) was dissolved in CH_2Cl_2 (45 mL) and treated with $PhI(OAc)_2$ (8.3 g, 25.7 mmol) and TEMPO (396 mg, 2.53 mmol). The resulting mixture was stirred for 10 h. The mixture was poured into 0.5 M aqueous solution of Na_2SO_3 (200 mL) and extracted with Et_2O (2 × 100 mL). The organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (PE/EtOAc = 99/1) to afford compound **10** (1.76 g, 90%) as a white crystal solid. Compound **10**: $[\alpha]_D^{25}$ = −57.6 (*c* = 1, $CHCl_3$); mp 100−101 °C; IR (KBr, cm^{-1}) 2918, 1758, 1443, 1252, 1147; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.27 (d, *J* = 3.5 Hz, 1H), 5.57 (d, *J* = 3.0 Hz, 1H), 5.20 (br d, *J* = 11.5 Hz, 1H), 3.83 (t, *J* = 7.0 Hz, 1H), 2.80 (t, *J* = 7.6 Hz, 1H), 2.50−2.31 (m, 2H), 2.24 (td, *J* = 13.0, 1.7 Hz, 1H), 2.13−1.98 (m, 3H), 1.90−1.79 (m, 1H), 1.71 (s, 3H), 1.00 (s, 3H), 0.90−0.77 (m, 2H), 0.61−0.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 141.1, 133.0, 127.7, 120.7, 84.7, 50.3, 41.1, 38.2, 33.5, 31.7, 25.2, 19.9, 18.0, 17.6, 16.4.; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{23}O_2$ 247.1698, found 247.1694.

■ ASSOCIATED CONTENT

Supporting Information

Copies of the NMR spectra of compounds **1**−**10** and X-ray data of parthenolide (**1**) and compound **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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