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Total Syntheses and Structure-Acitvity Relaltionship Study of Parthenolide Analogues

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Abstract: Two new parthenolide analogues were obtained by total synthesis and assayed for their *in vitro* anticancer activities to study their structure–activity relationship. Based on the structure and anticancer activity results, two new SAR can be drawn: (1) replacement of the lactone moiety with lactam moiety greatly decreased the anticancer activity; (2) the C-14 methyl group of parthenolide might be important for its high anticancer activity.

Keywords: Parthenolide; Total synthesis; Anticancer activity; Analogue

Accumulating evidence has demonstrated that cancer stem cells (CSCs) are responsible for tumor initiation and progression. CSCs contribute to therapeutic resistance and are considered to be the most likely cause of cancer relapse.[1–3] Consequently, much effort has been made to design molecules that can target CSCs specifically and sensitize them to therapy.[4]

Sesquiterpene lactones (SLs), which usually contain a γ-lactone ring, are a large group of natural products with a wide range of biological activities such as anticancer, anti-inflammatory, antiviral, antibacterial and antifungal activities. SLs are primarily classified on the basis of their carbocyclic skeletons into pseudoguainolides, guaianalides, germanocranolides, eudesmanolides, heliangolides and hyptocretenolides *etc*.[5,6] Parthenolide (PTL, **1**, Figure 1), a prominent member of germanocranolides,[7,8] is the major SL responsible for bioactivity of feverfew (*Tanacetum parthenium*), an herbal medicine that has been used to treat migraine and rheumatoid arthritis for centuries.[9] Recent studies have demonstrated that PTL can induce death of leukemia stem cells (LSC)[10,11] and breast cancer stem cells (BCSC)[12] while sparing normal hematopoietic cells. However, PTL was unstable and demonstrated low water solubility[13,14], which led to poor oral bioavailability. A PTL analogue, 11,13-dehydro-13-dimethylamino-parthenolide (DMAPT), presented improved oral bioavailability and retained comparable anticancer activity to PTL.[11] Notably, DMAPT has entered clinical trial for the treatment of acute myelocytic leukemia (AML), acute lymphoblastic leukemia (ALL), and chronic lymphocytic leukemia (CLL) in the United Kingdom.[15]

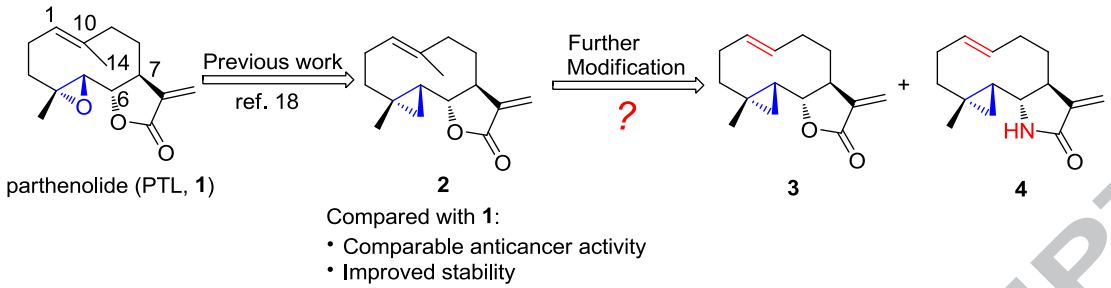
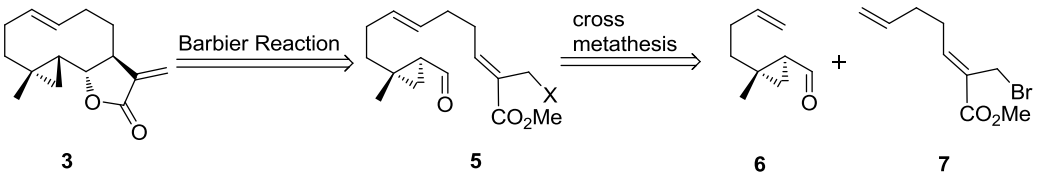


Figure 1. Design of compounds **3** and **4**.

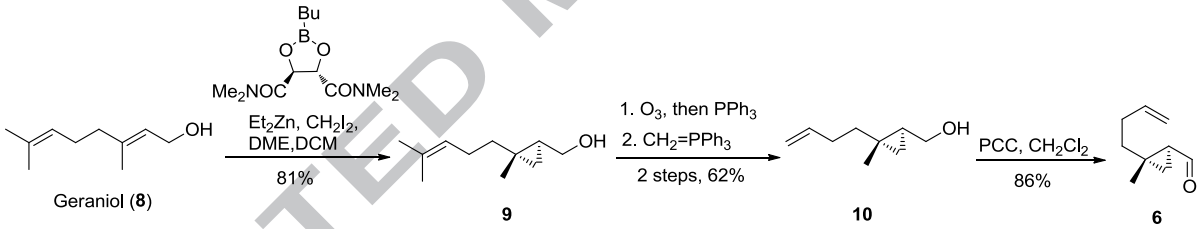
In view of the intensive biological activities of PTL, and in particular its ability to selectively kill cancer stem cells, we reported the first total synthesis of PTL and a series of PTL analogues and established their preliminary SAR.[16–18] Recently, we reported a protecting group-free semisynthesis of parthenolide and its cyclopropyl analogue (**2**) from the abundant natural product costunolide.[18] Cyclopropyl analogue was significantly more stable than parthenolide under acidic condition and in plasma, and it maintained comparable activities against acute myeloid leukemia (AML) cell lines and AML stem cells. Our ongoing efforts are to elaborate this natural product scaffold for further study of structure activity relationship (SAR) and obtain PTL analogues with enhanced potency and improved drug-like properties. Herein, we report the asymmetric total synthesis and further SAR study of parthenolide analogues (Figure 1).

It was reported that the C-14 methyl group is liable to undergo hydroxylation reaction by cytochrome P450 enzymes, and the P450-catalyzed oxidation led to a complete loss of activity.[19] Therefore, we designed the compound **3** with removal of the C-14 methyl group. Based on strategy of the total synthesis of PTL and its analogues,[17] we envisioned that compound **3** could be generated from **5** through Barbier reaction (Scheme 1). The C1-C10 double bond was supposed to be furnished by cross metathesis reaction between aldehyde **6** and known compound **7**.



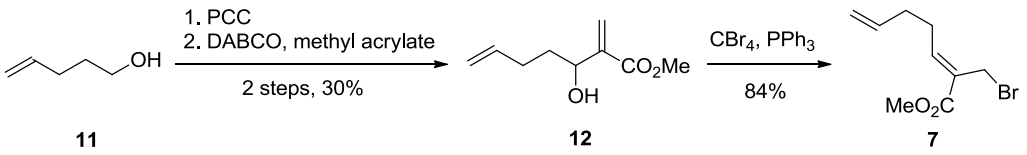
Scheme 1. Retrosynthesis of compound **3**.

Our investigation started with synthesis of aldehyde **6**, which was obtained from commerical available geraniol (**8**) in three steps (Scheme 2). Asymmetric cyclopropanation of geraniol[20] provided alcohol **9**. The formed primary alcohol **9** was subjected to ozonation and wittig reaction in one pot to afford compound **10** in yield of 62% for two steps, which was treated with pyridinium chlorochromate (PCC) to furnish the corresponding aldehyde **6** in yield of 86%.



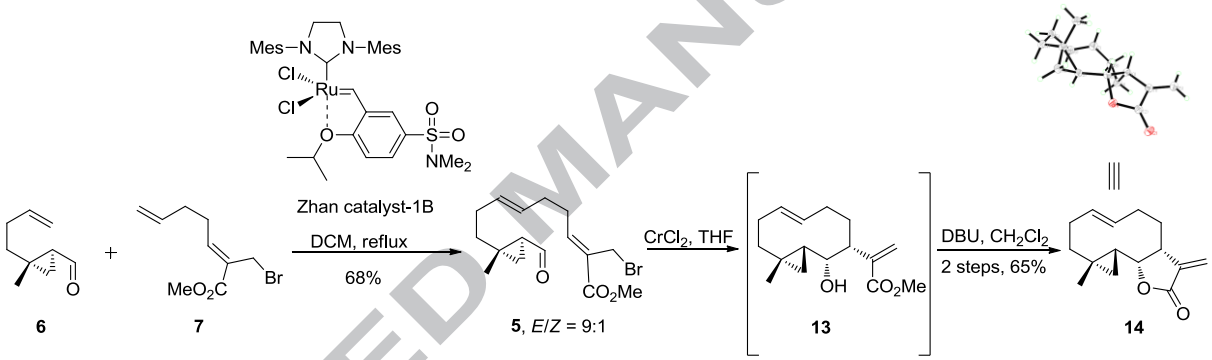
Scheme 2. Synthesis of aldehyde **6**.

Primary alcohol **11** underwent oxidation with PCC, followed by Baylis-Hillman reaction with methylacrylate to yield ester **12** in yield of 30% for two steps (Scheme 3). Bromization of **12** with CBr_4 and PPh_3 furnished compound **7**.



Scheme 3. Synthesis of compound **7**.

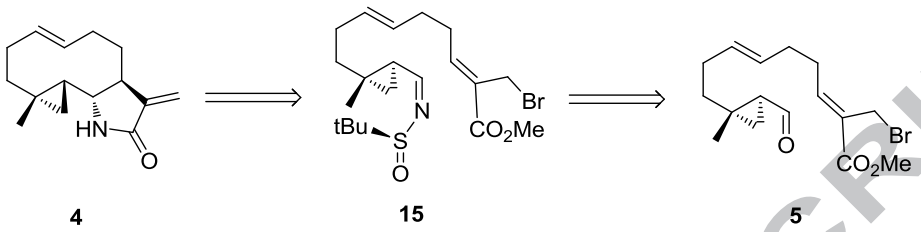
With aldehyde **6** and compound **7** in hand, we implemented the cross metathesis reaction between **6** and **7**. Fortunately, acceptable selectivity (1,10 double bond *E*/*Z* up to 9:1) and moderate yield (68%) were achieved by using the Zhan Catylyst 1B as the catalyst in refluxing CH_2Cl_2 (Scheme 4). The cyclization precursor (*E*)-**5** was subjected to intramolecular Barbier reaction to obtained intermediate **13**, without further purification, which was transformed to lactone 6,7-*cis*-**14** in 65% yield without the desired 6,7-*trans*-**3**. The structure of lactone **14** was further confirmed by X-ray assay.



Scheme 4. Synthesis of compound **14**.

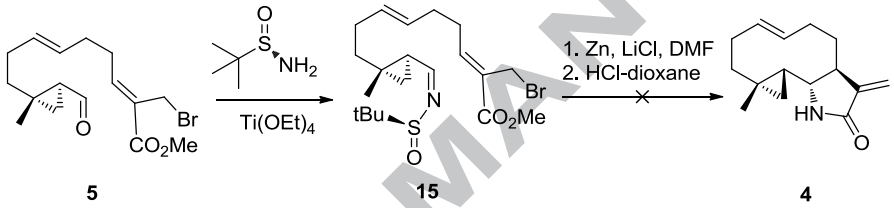
There is a lactone in the structure of PTL. Normally, lactone moiety is prone to be hydrolyzed in base condition, acid condition or hydrolase. PTL is highly lipophilic and the lactone moiety is prone to metabolic cleavage *in vivo*.[21] Therefore, we designed compound **4** with replacement of the lactone with a lactam moiety to improve the stability and hydrophilic character.[6,21,22] Lin et al. have developed an efficient and facile one-pot approach for the asymmetric synthesis of highly substituted γ-lactam containing a α-methylene moiety through Zn-promoted intermolecular aza-Barbier reaction.[23] According to the strategy, we envisioned that the Zn-promoted intramolecular aza-Barbier reaction of **15** could constructed the ten-membered ring of lactam **4**. Cyclization precursor **15** could be obtained from intermediate **5** by condensation with *tert*-butyl

sulfonamide (Scheme 5). Unfortunately, treatment of **15** with the common Zn-promoted aza-Barbier reaction condition did not provide any of the desired lactam **4** (Scheme 6).



4 **15** **5**

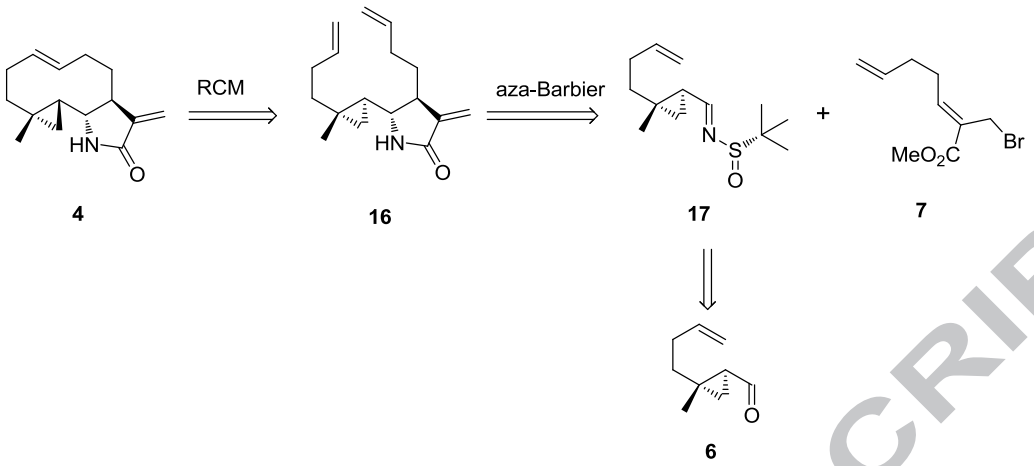
Scheme 5. First retrosynthesis of compound **4**.



5 **15** **4**

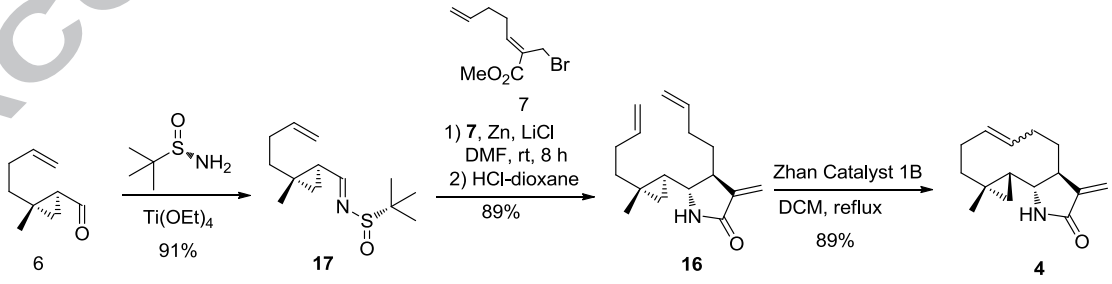
Scheme 6. Attempt for synthesis of compound **4**.

Therefore, we changed our synthesis route. We expected to obtain compound **4** from cyclization precursor **16** by ring cross metathesis (RCM) reaction. Cyclization precursor **16** was supposed to be synthesized by coupling of **17** and **7** according to Lin et al developed strategy. Compound **17** could be obtained from **6** (Scheme 7).



Scheme 7. Second retrosynthesis of compound **4**

Condensation of **6** with (*S*)-*N*-*tert*-butanesulfinylimine catalyzed by $Ti(OEt)_4$ produced **17** in 91% yield (Scheme 8).[24] Compound **17** went through the one pot coupling with **7** to get the cyclization intermediate which was then treated with HCl-dioxane to afford **16** with removal of the auxiliary. The final step was the ring close by cross metathesis reaction. However, there are few reports of construction of ten-membered carbocycle by RCM reaction.[25] Fortunately, compound **4** (ratio of geometric isomers = 70:30) was smoothly obtained by using Zhan Catalyst 1B in CH_2Cl_2 in yield of 89%.

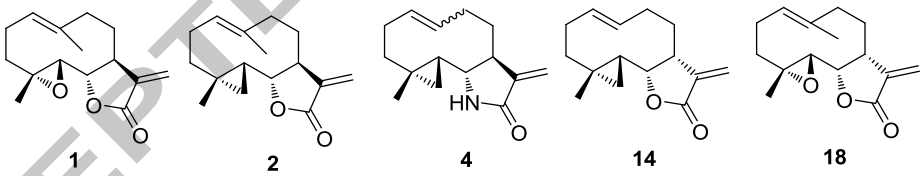


Scheme 8. Synthesis of compound **4**.

With the compounds **4** and **14** in hand, we evaluated their anticancer activities against a series of cancer cell lines, i.e. lung cancer cell line A549, AML progenitor cell line KG-1a, acute

myeloid leukemia (AML) cell line HL-60, doxorubicin-resistant cell line HL-60/A, chronic myeloid leukemia (CML) cell line K562, and doxorubicin-resistant cell line K562/A. As shown in Table 1, compound **2** showed comparable anticancer activity to that of parthenolide (**1**). The result demonstrated that replacement of the epoxide moiety of parthenolide with the bioisosteric cyclopropyl moiety maintained its anticancer activity.[18] Compound **14** exhibited moderate potency against the tested cancer cell lines with IC_{50} values ranging from 9.2 μM to 20.2 μM. For AML cell line HL60, compound **14** (IC_{50} = 12.0 μM) was less potent than compound **18** (IC_{50} = 2.9 μM). The result suggests that the C-14 methyl group of parthenolide might be important for its high anticancer activity. However, Lactam **4** exhibited diminished cytotoxicity against the six cancer cell lines (IC_{50} > 50 μM), which demonstrated that replacement of the lactone moiety with lactam moiety greatly decreased the anticancer activity.

Table 1. Anticancer activity of compounds **1, 2, 4, 14** and **18** [a]



Compounds	IC_{50} (μM) [b]					
	A549 [c]	KG-1a [d]	HL-60 [e]	HL-60/A [f]	K562 [g]	K562/A [h]
1	4.4±0.8	5.0±0.4	2.1±0.5 [i]	3.6±0.9 [i]	2.7±0.9	4.6±0.3
2	5.8±1.4	8.3±1.2	3.8±0.3 [i]	6.2±0.6 [i]	6.3±0.8	5.9±1.4
4	>50	>50	>50	>50	>50	>50
14	9.2±1.8	18.5±2.3	12.0±1.7	15.1±0.9	14.4±1.5	20.2±3.1
18	-	-	2.9 ± 0.8 [j]	-	-	-

[a] All values are the mean of three independent experiments, [b] IC_{50}: 50% cytotoxic concentration, [c] A549: lung cancer cell line. [d] KG-1a: AML progenitor cell line, [e]HL-60: AML cell line, [f] HL-60/A: doxorubicin-resistant cell line, [g] K562: CML cell line, [h] K562/A: doxorubicin-resistant cell line, [i] Data from reference 18, [j] Data from reference 17.

In summary, two new parthenolide analogues were synthesized and evaluated for their *in vitro* anticancer activities. Based on the above structure and anticancer activity results, the following SAR can be drawn: (1) replacement of the lactone moiety with lactam moiety greatly decreased the anticancer activity; (2) the C-14 methyl group might be important for high anticancer activity. However, more investigations are necessary for extensive SAR study and ultimate design and synthesis of parthenolide-derived anticancer agents.

Acknowledgements

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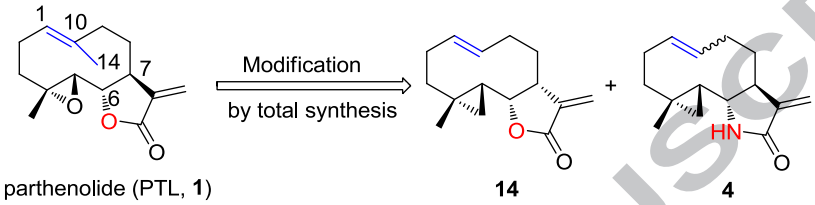

parthenolide (PTL, **1**) **14** **4**

- **the C-14 methyl group of parthenolide might be important for its high anticancer activity**
- **replacement of the lactone moiety with lactam moiety greatly decreased the anticancer activity**

Two new parthenolide analogues were obtained by total synthesis and assayed for their *in vitro* anticancer activities to study their structure–activity relationship. Based on the structure and anticancer activity results, two new SAR can be drawn: (1) replacement of the lactone moiety with lactam moiety greatly decreased the anticancer activity; (2) the C-14 methyl group of parthenolide might be important for its high anticancer activity.