

## Studies toward Synthesis of Arteminolides: Intramolecular [5+2] Oxidopyrylium Ion Cycloaddition Reactions with Silicon Tether

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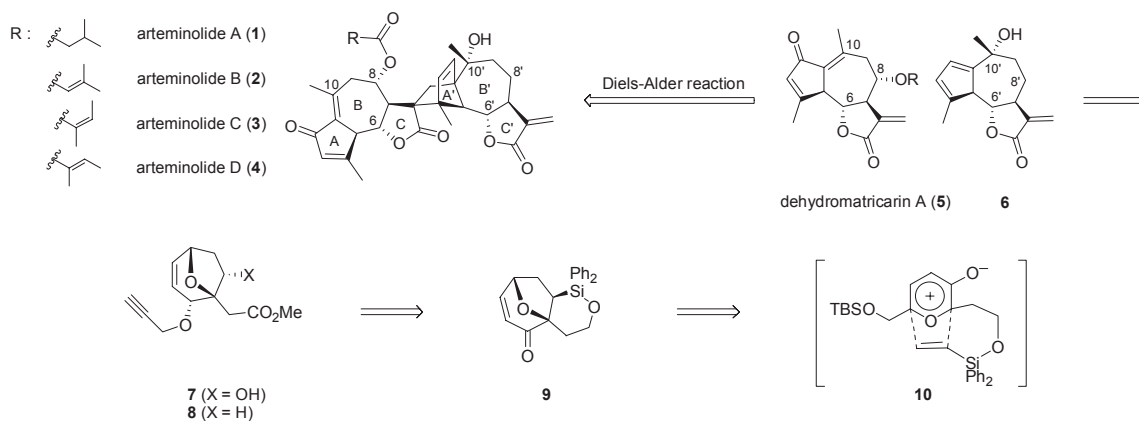
**Key Words:** Oxidopyrylium ion, [5+2] Cycloaddition reaction, Vinylsilane, Arteminolide

Arteminolides A-D (**1-4**) are sesquiterpene lactones isolated from the leaves of *Artemisia sylvatica* Maxim and have been reported to be the strongest inhibitors of farnesyltransferase (FTase)<sup>1</sup> with good selectivity from natural sources.<sup>2</sup> While the biological profile and structural complexity of these natural products are intriguing, there has been no report on the synthesis of these natural products since their first isolation in 1998.<sup>3</sup>

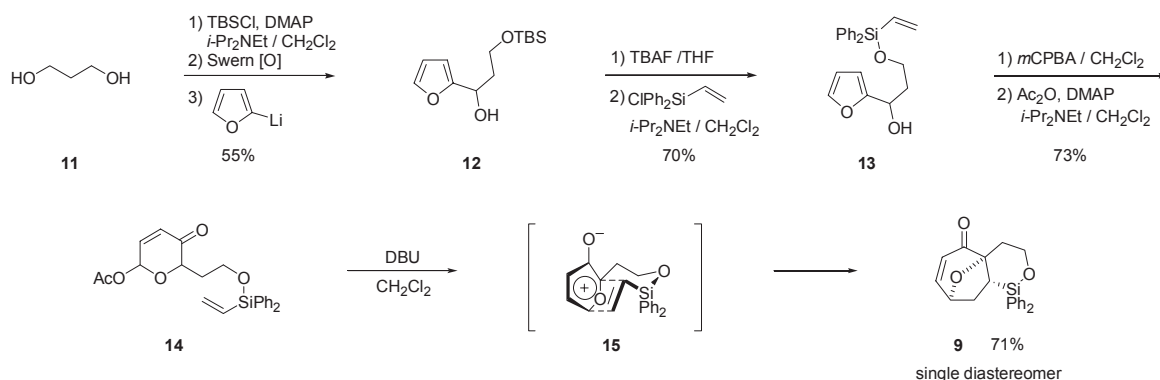
The most logical precursors for the total synthesis of arteminolides are dehydromatricarin (**5**) and **6**, since they are believed to be the biogenic precursors of arteminolides through Diels-Alder reaction<sup>4</sup> (Scheme 1). Identification of enone **5** and diene **6** along with studies on the related natural products strongly support this route.<sup>4b</sup> We envisioned that the two precursors, **5** and **6**, could be obtained from the intermediates **7** and **8**, respectively, through a sequence including Pauson-Khand reaction.

The intermediates **7** and **8** could be prepared from a common precursor **9**, in which the silicon was incorporated to serve as surrogates for both hydroxyl group and hydrogen corresponding to C8-OH of **5** and C8'-H of **6**, respectively.<sup>5</sup> The ether bridge of **9** would allow selective induction of stereochemistry at C6 and C8, and C6' in turn could be obtained through an intramolecular [5+2] cycloaddition reaction of oxidopyrylium ion<sup>6</sup> with vinylsilane **10** as the key step since we observed that the cycloaddition reaction with silylated olefin proceeded well.<sup>3b</sup>

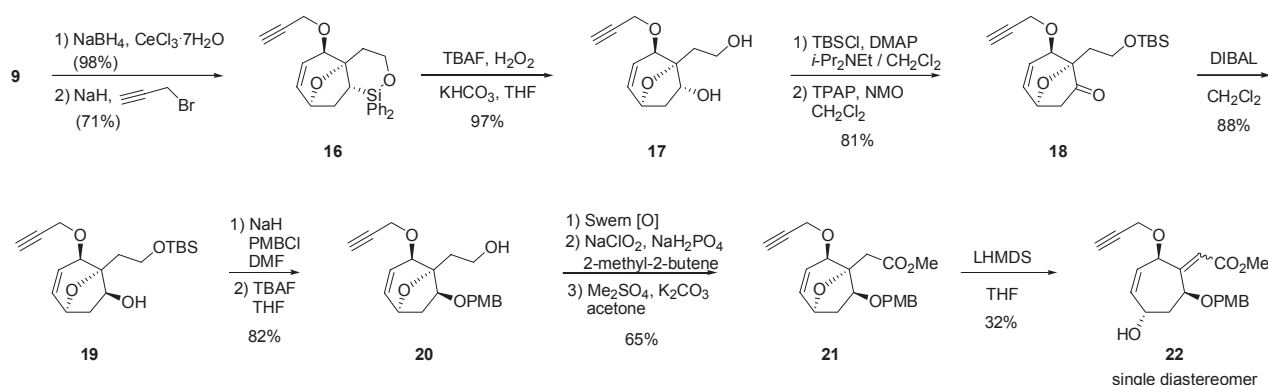
The synthesis of the common intermediate **9** commenced with selective mono-silylation of 1,3-propanediol (**11**), followed by Swern oxidation, resulting in corresponding aldehyde which was then coupled with lithiated furan to afford furanyl alcohol **12** in 55% yield for three steps (Scheme 2). The TBS group was replaced by vinylsilyl group *via* removal of TBS using TBAF



**Scheme 1.** Structure of arteminolides A-D (**1-4**) and their retrosynthetic analysis



**Scheme 2.** Synthesis of the common intermediate **9**



Scheme 3. Transformation of 9 to 21

generating corresponding diol, followed by selective coupling of the primary hydroxyl group with the vinylsilyl chloride in the presence of *i*-Pr<sub>2</sub>NEt to produce vinylsilyl ether **13** in 70% yield. As a precursor to the oxidopyrylium ion, pyran **14** was prepared in two-steps including oxidation-rearrangement of **13** using *m*CPBA in CH<sub>2</sub>Cl<sub>2</sub>,<sup>7</sup> followed by acetylation of the resulting secondary hydroxyl group using Ac<sub>2</sub>O and DMAP in the presence of *i*-Pr<sub>2</sub>NEt. Treatment of pyran **14** in methylene chloride with DBU generated the oxidopyrylium ion, and *in situ* cycloaddition reaction proceeded well to give the desired product **9** as a single diastereomer<sup>8</sup> in 71% yield *via* a transition state **15**, in which the cycloaddition occurs with favorable chair form of six-membered ring. Through this route, we could synthesize the desired common skeleton of the B- and B'-rings of arteminolides in eight-steps and 20% overall yield from the propanediol **11**.

Since the C8-OR in B-ring determined the identity of the activity of arteminolides<sup>1</sup> and the replacement of the silicon in **9** with hydrogen was easily done under the conventional conditions for removal of silyl, we focused on the transformation of **9** into functionalized B-ring. The ether bridge of **9** allowed stereoselective reduction of the carbonyl, which resulted in the corresponding alcohol in high yield as a single diastereomer with the hydroxyl group *trans* to the silyl group.<sup>8</sup> The generated hydroxyl group was converted to propargyl ether **16** for the construction of A-ring through Pauson-Khand reaction as well as protection of the hydroxyl group. Treatment of **16** with Tamao oxidation conditions using KF, H<sub>2</sub>O<sub>2</sub> and KHCO<sub>3</sub> in THF-MeOH<sup>5a</sup> gave diol **17** in only 20% yield but, instead, the modified conditions using TBAF, H<sub>2</sub>O<sub>2</sub> and KHCO<sub>3</sub> in THF increased the yield to 97%. After protection of the primary hydroxyl group in **17** as TBS ether the remaining secondary hydroxyl group was epimerized through oxidation using TPAP-NMO, followed by reduction using DIBAL to afford alcohol **19**, in which the hydroxyl group and the propargyl ether are at desired *cis* conformation. Protection of the hydroxyl group as PMB ether was followed by removal of TBS to give primary alcohol **20**. Treatment of **20** with Swern oxidation conditions afforded the resulting aldehyde, which was then oxidized using NaClO<sub>2</sub> and NaH<sub>2</sub>PO<sub>4</sub>, and methylated using Me<sub>2</sub>SO<sub>4</sub> to afford ester **21** in 65% yield. The ether bridge had to be removed for the form-

ation of the five-membered A-ring stereoselectively through Pauson-Khand reaction since the direct Pauson-Khand reaction of **21** would produce the opposite stereo-isomer to **6** at the ring junction. Base-mediated cleavage of the ether bridge with LHMDS successfully cleaved the ether bridge to afford **22** as a single diastereomer (Scheme 3).

In summary, we prepared compound **9** which has the common ring skeleton of the B- and B'-rings of arteminolides in eight-steps and 20% overall yield from the 1,3-propanediol, through a route that featured an unprecedented intramolecular [5+2] oxidopyrylium cycloaddition reaction with vinylsilyl ether tether as the key step. Studies directed toward the completion of the synthesis of arteminolides through the stereoselective Pauson-Khand reaction are currently underway.

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