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Silicon-Tethered Intramolecular [5+2] Oxidopyrylium-Based Cycloaddition and Reductive Cleavage of Ether Bridge: Synthetic Studies Toward Arteminolides

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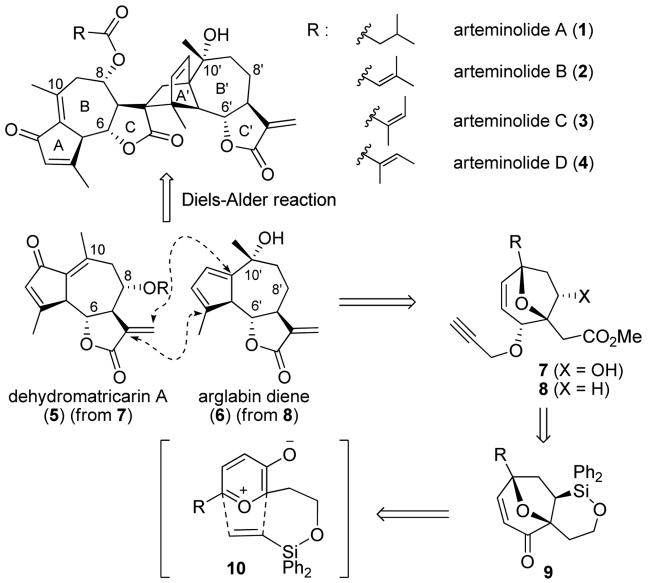
Arteminolides A-D (**1**-**4**), natural triterpene lactones, were isolated from the leaves of *Artemisia sylvatica* Maxim and have been reported to be strong inhibitiors of farnesyltrnasferase (FTase) targeting members of the Ras superfamily of small GTP-binding proteins critical to cell cycle progression.[1,2] Thus, arteminolides have displayed the tumor cell growth inhibition in a dose-dependent manner.[1] In addition, arteminolide A (**1**) exhibited selective inhibition of recombinant rat FTase with no significant inhibition of rat squalene synthase or geranylgeranyltransferase (GGTase),[1a] and arteminolide C (**3**) blocked in vivo growth of human colon and lung tumor xenograft without the loss of body weight in nude mice.[1b] As well as the biological profile their structural complexity with the rigid ring skeleton could facilitate the study on the structure-activity relationships (SARs) with three dimensional information, which can direct new FTase inhibitor with high therapeutic value. Despite their favorable biological profile and intriguing structural complexity the success in the synthesis of arteminolides has not been reported since their first isolation in 1998.[3]

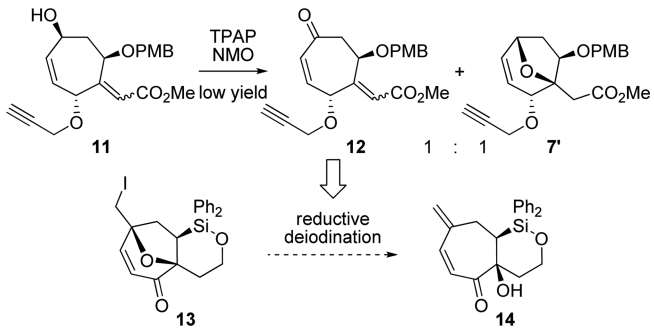
Due to identification of dehydromatricarin A (**5**) and arglabin diene (**6**), the biogenic synthesis of arteminolides are believed to be accomplished *via* Diels-Alder reaction between the two precursors[4] (Scheme 1). Since the most logical precursors for the total synthesis of these natural products are the two biogenic precursors, we envisioned a common intermediate **9** which could offer the two precursors, **5** and **6**, *via* Pauson-Khand reactions of **7** and **8**, respectively. The intermediate **9** contains the silicon which could serve as surrogates for both hydroxyl group and hydrogen corresponding to C8-OH of **5** and C8'-H of **6**, respectively,[5] and was expected to be obtained through intramolecular [5+2] dipolar cycloaddition reaction of oxidopyrylium ylide.[6] The silyl group would be stable under various reaction conditions and readily converted to the hydroxyl with the retention of the configuration.[5]



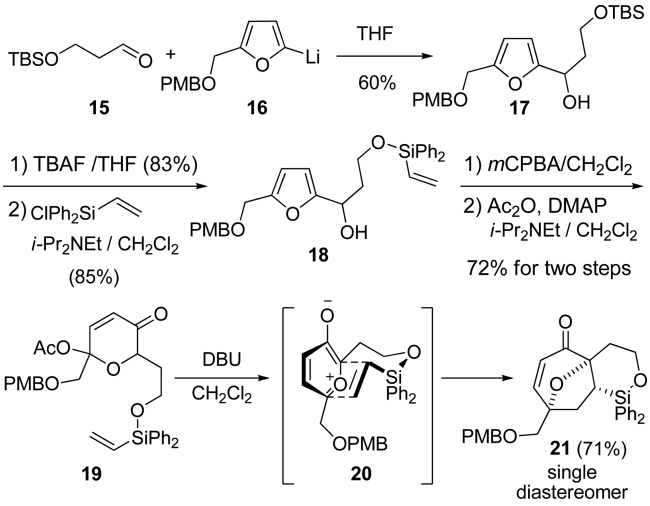
Scheme 1. Arteminolides A-D (**1**-**4**) and retrosynthesis.

We previously found that base-mediated cleavage of the ether bridge in **7'** (R = H, R' = PMB) afforded **11** in low yield (32%).[3c] In addition, attempts to oxidize alcohol **11** into ketone **12** under various reaction conditions for introduction of the exo methylene and methyl group at C10 and C10', respectively, resulted in ketone **12** with unacceptable low yields and, unexpectedly, TPAP oxidation produced a 1:1 mixture of ketone **12** and initial ether bridged **7'**. These unfavorable results directed our efforts to prepare intermediate **13** possessing iodomethyl group which could allow to cleave the ether bridge using reductive deiodination,[7] resulting in exo methylene (Scheme 2).

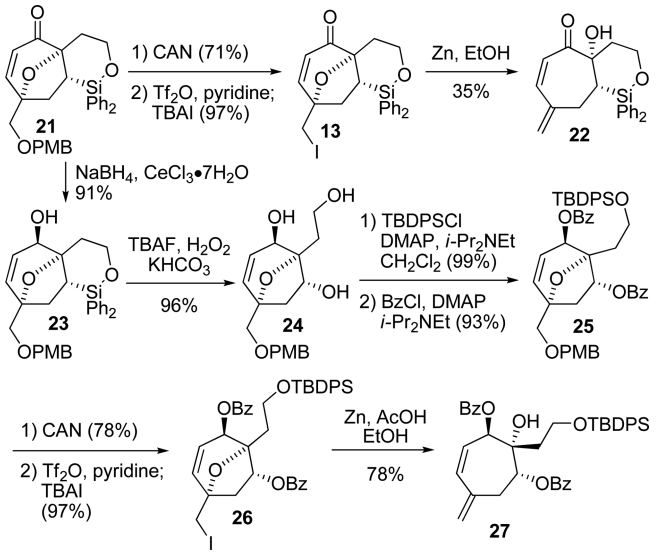
The synthesis of **13** commenced with aldehyde **15** which was prepared by selective mono-silylation of 1,3-propanediol, followed by Swern oxidation. Coupling of **15** with lithiated furan **16** produced furanyl alcohol **17** in 60% yield, which was then converted to vinylsilyl ether **18** having necess-



Scheme 2. Unexpected products of oxidation of **11** and reductive deiodination for cleavage of ether bridge.



Scheme 3. Preparation of compound **21** *via* [5+2] oxidopyrylium ion cycloaddition reaction.



Scheme 4. Ether bridge cleavage by reductive deiodination.

ary carbon framework for the intermediate **13** by replacement of the TBS group with vinylsilyl group in two step operation. Oxidation-rearrangement of **18** using *m*CPBA,[8] followed by acetylation of the resulting tertiary hydroxyl group produced pyran **19** as a precursor to the oxidopyrylium ion. Oxidopyrylium ion was generated by treatment of pyran **14** with DBU in CH_2Cl_2 and *in situ* [5+2] cycloaddition reaction proceeded *via* chair form of six-membered transition state **20** afforded the desired product **21** as a single diastereomer in 71% yield (Scheme 3).

To prepare the two biogenic precursors, **5** and **6**, we considered two routes for cleavage of the ether bridge in **21** using reductive deiodination. At first, conversion of PMB ether **21** to iodide **13** was performed through removal of PMB group using ceric ammonium nitrate (CAN), followed by iodination using triflic anhydride and tetrabutylammonium iodide. Cleavage of the ether bridge of iodide **13** was accomplished using purified Zn in refluxed EtOH to afford exo methylene **22** but the yield was not good (35%). The other route to cleave the ether bridge began with stereoselective reduction of carbonyl group of **21** to endo hydroxyl group (**23**) due to the intrinsic structural nature of **21**. Modified Tamao oxidation reaction using TBAF, H_2O_2 and $KHCO_3$ provided triol **24** in high yield.[3b,5a] Selective protection of the primary hydroxyl group with TBDPS group followed by dibenzoylation of the remaining secondary hydroxyl groups afforded **25**. Conversion of the PMB ether to corresponding iodide was accomplished to afford **26** in three-step sequence similar as the formation of iodide **13** from PMB ether **21**. The reaction conditions for cleavage of the ether bridge of **26** using Zn in refluxed EtOH previously used for **13** did not produce the desired product. Instead, the conditions with activation of Zn using AcOH in EtOH at room temperature resulted in the desired tertiary alcohol **27** in good yield (Scheme 4).

In summary, we have prepared a common intermediate to the biogenic precursors of arteminolides as single diastereomer *via* a route that featured silicon-tethered intramolecular [5+2] oxidopyrylium cycloaddition reaction. To move forward to total synthesis of arteminolides the cleavage of the ether bridge of the intermediate was achieved through two routes with reductive deiodination.

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