Communications

[5+2] Oxidopyrylium Ion Cycloaddition Reaction with Vinylsilane: Construction of Core Structure of Biogenic Intermediates of Arteminolides

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Arteminolides A-D (**1-4**), natural products isolated from the aerial parts of *Artemisia*, have been reported to possess an inhibitory activity on farnesyltransferase (FTase).[1] The target proteins of FTase include members of the Ras superfamily of small GTP-binding proteins critical to cell cycle progression, resulting in several FTase inhibitors undergoing testing as anti-cancer agents.[2] The arteminolides also exhibited the inhibition of tumor cell growth in a dose-dependent manner and, in particular, arteminolide C (**3**) blocked in vivo growth of human colon and lung tumor xenograft without the loss of body weight in nude mice.[1] In spite of their intriguing biological profile and structural complexity, there has been no report on the synthesis of these natural products since their first isolation in 1998.

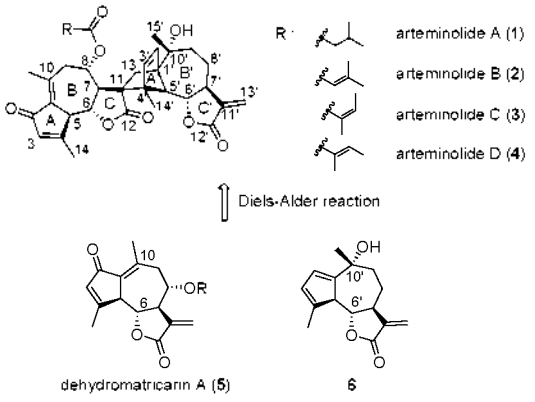
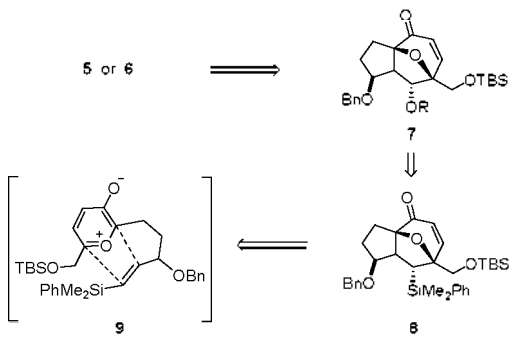


Figure 1. Structure of arteminolide A-D (**1-4**) and their biogenic precursors.

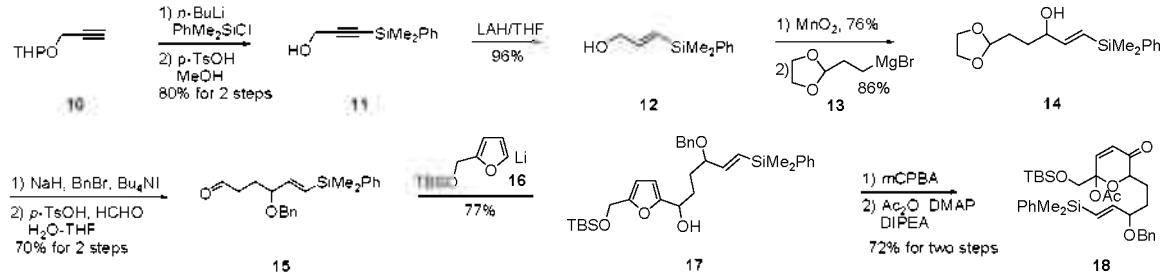


Scheme 1. Retrosynthetic analysis.

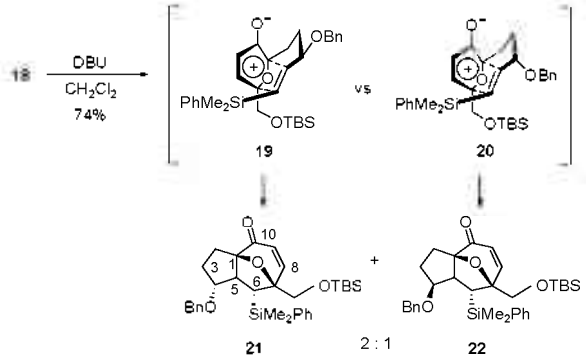
The biogenesis of arteminolides *via* Diels-Alder reaction between left- and right halves has been proposed,[1a,3] and the left biogenic precursor, dehydromatricarin (**5**) and analogues of the right precursor **6** have been identified.[3b] It was deemed logical to design a total synthesis of arteminolides through the biogenic Diels-Alder reaction. We envisioned that both of the two precursors, enone **5** and diene **6** could be obtained from the common intermediate **7**. The ether bridge of **7** would allow stereoselective introduction of stereocenters of **5** and **6**, and **7** in turn can be obtained through an intramolecular [5+2] cycloaddition reaction of the silylvinyl oxidopyrylium ion **9** as the key step (Scheme 1). Since the required enolether from the precursor of **7** would be too reactive during the synthetic sequence toward the oxidopyrilium ion, the silyl compound **8** was devised to serve as a surrogate for the hydroxyl corresponding to C6- and C6`-OH. The silyl group would be stable under various reaction conditions and readily converted to the hydroxyl with the retention of the configuration.[4,5]

While the 1,3-dipolar [5+2] oxidopyrylium cycloaddition reactions with olefins to form seven-membered rings with four stereocenters have been extensively studied and successfully applied to the total synthesis of natural products,[7] the cycloaddition reaction with substituted olefins were rare either in intermolecular or intramolecular reaction.[8] Thus, the effects of substituents that influence the electron density of the olefins on the reactivity or regio-/stereoselectivity have not been reported. In the case of the heteroatom attached allenes, we observed that the cycloaddition reaction proceeded well and electron rich methoxy allenes were more reactive than neutral- or electron deficient ones.[9] These results were encouraging for the synthesis of the key intermediate **8** which could be prepared through the intramolecular cycloaddition reaction with silylated olefin.

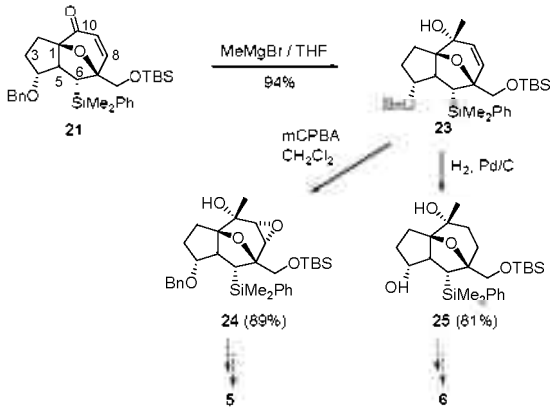
The synthesis of **8** commenced with the silylation of THP-protected propargyl alcohol **10**, followed by the removal of THP to afford **11** (Scheme 2). The $LiAlH_4$ reduction[10] of **11** was carried out to obtain, in high yield, necessary trans allylic alcohol **12** which was then oxidized using MnO_2 and coupled with Grignard reagent **13** to furnish **14**. After the hydroxyl in **14** was protected as benzyl ether, the deprotection of dioxolane gave the desired aldehyde **15**, which was coupled with **16** to afford furfuryl alcohol **17**, in good overall yield. As the precursor to the oxidopyrylium ion, pyran **18** was prepared in two-steps inclu-



Scheme 2. Synthesis of the precursor to the oxidopyrylium ion.



Scheme 3. [5+2] oxidopyrylium ion cycloaddition reaction of **18**.



Scheme 4. Stereoselective introduction of Me and hydroxyl onto C10 and C8 respectively.

ding oxidation-rearrangement of **17** using *m*CPBA followed by acetylation of tertiary hydroxyl generated.[9]

Treatment of pyran **18** in methylene chloride with DBU generated the oxidopyrylium ion, and in situ cycloaddition reaction proceeded well to give a separable mixture of two isomers at the OBn center with the ratio of 2:1 (**21**/**22**), in 74% yield (Scheme 3)[6]. The transition state, in which silyl group is positioned exclusively for endo cycloaddition reaction and OBn group exists preferably at pseudo-equatorial position over pseudo-axial, explains the stereochemistry of silyl group as well as the diastereomeric ratio of the mixture of the cycloadducts. The ratio of diasteromers is of little consequence since the benzyl ether will be eliminated or converted to the ketone for the diene **6** or dienophile **5**, respectively. Through this route, we could synthesize the desired common ring skeleton of the AB- and A'B'-rings of arteminolides in 14.4% overall yield from the THP-protected propargyl alcohol.

Further studies moved forward to investigation of the necessary stereoselective introduction of Me and hydroxyl onto C10 and C8 respectively. When cycloadduct **21** was treated with MeMgBr, alcohol **23** with desired stereochemistry was obtained in high yield as a sole product (Scheme 4). The introduction of hydroxyl moiety onto C8 in **23** was performed by epoxidation using *m*CPBA to afford epoxide **24** with the desired stereochemistry as a single isomer.[6] which is a desirable intermediate to the dienophile **5**. When alcohol **23** was subjected to hydrogenation conditions the deprotection of benzyl ether and reduction of double bond were achieved simultaneously to furnish diol **25** which is a desirable intermediate to the diene **6**.[6]

In summary, we prepared compound **8** which is the common ring skeleton of the AB- and A'B'-rings of arteminolides in eleven steps and 14.4% overall yield from the THP-protected propargyl alcohol, through a route that featured an intramolecular [5+2] oxidopyrylium cycloaddition reaction with silyl olefin as the key step. Compound **8** allowed for the essential stereoselective introduction of Me and hydroxyl moiety onto C10 and C8 respectively, and studies directed toward the completion of the synthesis of arteminolides are currently underway.

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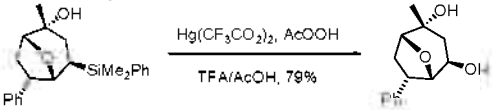
5. Model study was achieved.



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