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Synthetic Studies on Arglabin Diene; An Alleged Precursor to Arteminolides

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Arteminolides A-D (**1-4**), isolated from the leaves of *Artemisia sylvatica* Maxim, are triterpene lactones (Figure 1) and have been reported to be strong inhibitors of farnesyltransferase (FTase).[1] The FTase targets members of the Ras superfamily of small GTP-binding proteins critical to cell cycle progression[2] and, thus the arteminolides exhibited the inhibition of tumor cell growth in a dose-dependent manner.[1] In particular, arteminolide A (**1**) has been known to selectively inhibit recombinant rat FTase (IC_{50} = 360 nM) with no significant inhibition of rat squalene synthase (IC_{50} >> 200 μM) or geranylgeranyltransferase (GGTase, IC_{50} >> 200 μM).[1a] In addition, arteminolide C (**3**) blocked in vivo growth of human colon and lung tumor xenograft without the loss of body weight in nude mice.[1b] Because of their rigid skeleton, studies on the structure-activity relationships (SARs) with three-dimensional information using these natural products and analogues could provide valuable information for design of new inhibitor with high therapeutic value. For inhibition of FTase activity, our previously designed FTase inhibitors, **5** and **6**, with IC_{50} of 500 nM and 40 nM respectively,[3] and arteminolides must have a common structural feature. This idea in connection with SAR studies of arteminolide analogues can invoke the hypothesis on a similar three-dimensional topology of homologues functional groups in their bound or active conformations for binding to FTase. Overlaying of natural product **1** to tripeptide **5** and its nonpeptidic mimic **6** shows that the ester group (bottom box) and the carbonyl O of upper lactone (upper box) match the aryl hydrophobic group and the thiol group in **5** or **6**, respectively (Figure 1). The biologically favorable selectivity and in vivo activity, and structural complexity of these natural products are intriguing but, until now, there has been no report on the complete synthesis of these natural products since their first isolation in 1998.[4]

The biogenesis of arteminolides *via* Diels-Alder reaction between left half, dehydromatricarin (**7**), and right half, arglabin diene (**8**), has been proposed[5] and thus, both of which are most logical precursors for the total synthesis of arteminolides. While the dienophile **7** was isolated,[5b] the diene **8** has not been identified so far possibly due to its instability. Herein, we report the synthetic study on arglabin diene **8**, the right half of arteminolides. Scheme 1 delineates our synthetic strategy to the diene **8**. We envisioned that the diene could be obtained from sesquiterpene guaianolide **9**

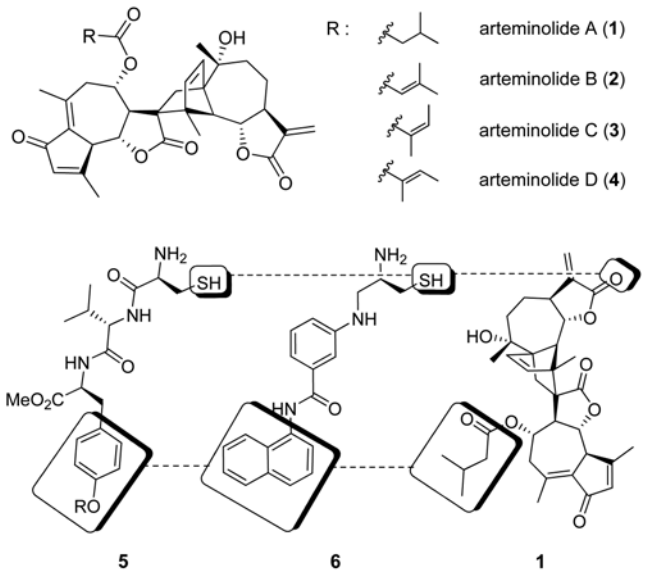
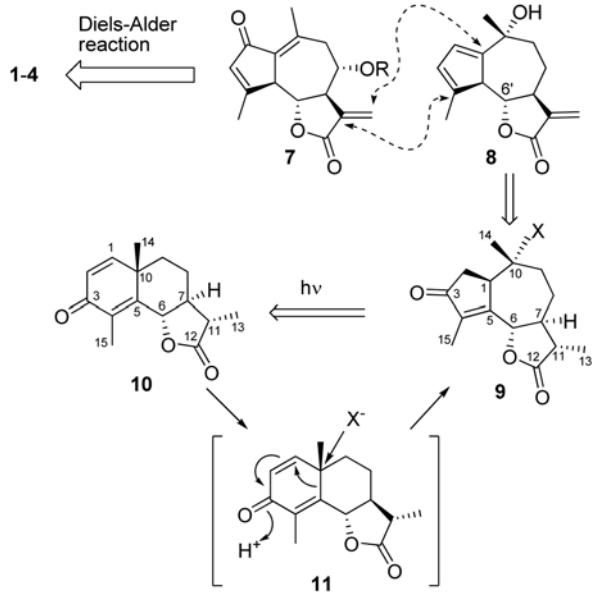


Figure 1. Structure of arteminolides A-D (**1-4**), and common structural feature between arteminolide A and tripeptidic or peptidomimetic FTase inhibitor.

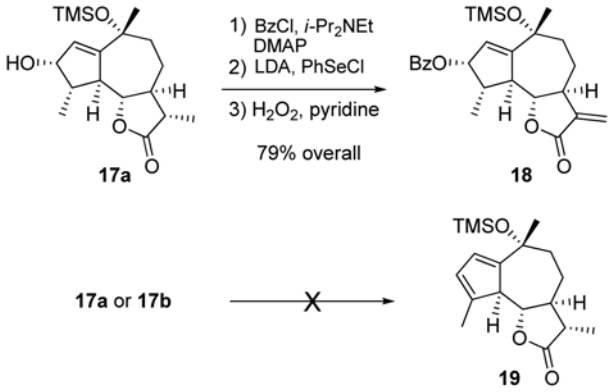


Scheme 1. The biogenesis of arteminolides *via* Diels-Alder reaction and retrosynthetic analysis of the right half precursor, arglabin diene (**8**).

which, in turn, was the product of the photochemical reaction of α-santonin (**10**). The transformation of eudesmane framework present in α-santonin into the guaiane framework was known to be promoted by UV irradiation, *via* photoactivation of **10** resulting in sufficiently energized molecule for occurrence of the acid-catalyzed rearrangement shown in **11**.[6] The anion X^- which is added to C10 can be either hydroxyl from water or acetate from the glacial acetic acid.[7]

The transformation of the eudesmane into a guaiane skeleton was carried out by a 300 nm UV promoted photochemical rearrangement in glacial AcOH solvent under Ar at room temperature for 20 h to afford guaianolide **12** in 35-40% yield. To obtain the desired stereochemistry of C5 by reduction the double bond with approach of hydrogen from less hindered α side, hydrogenation of **12** over Pd/C was accomplished. However, the reaction gave the saturated ketone[8] in low yield along with significant side-products. Alternatively, removal of acetyl group from **12** using methanolic KOH and then hydrogenation of the resulting alcohol **13**[7c] over Pd/C afforded the desired saturated ketone **14** in good yield. This unstable compound was converted to the stable epimer **15**[7d] using $NaHCO_3$ in MeOH in 99% yield. The stereochemistry of C4 is of little consequence, since C4 position should be oxidized in the preparation of diene. For the formation of the double bond between C1 and C2, we carried out re-protection of *tert*-OH in **15** as TMS ether, which was converted into enone **16** by the generation of silylenol ether followed by Saegusa oxidation.[9] Selective 1,2-reduction of enone **16** using $NaBH_4$ and $CeCl_3$ produced a mixture of enols **17a** and **17b** with a ratio of 1.6/1 in 85% yield (Scheme 2).

In order to prepare methylene group from methyl group at C11, major enol **17a** was protected as benzoyl ester, which was selenylated using LDA and PhSeCl, and eliminated using H_2O_2 and pyridine to afford **18** in 79% overall yield (Scheme 3).[10] Prior to synthesis of **8**, we attempted to synthesize diene **19** from **17a** or **17b** *via* mesylation or triflation of hydroxyl group, followed by reduction using diverse bases, but could not obtain the desired diene, presumably due to instability of the diene as mentioned earlier. Based on these results, it seems desirable that preparation of the diene



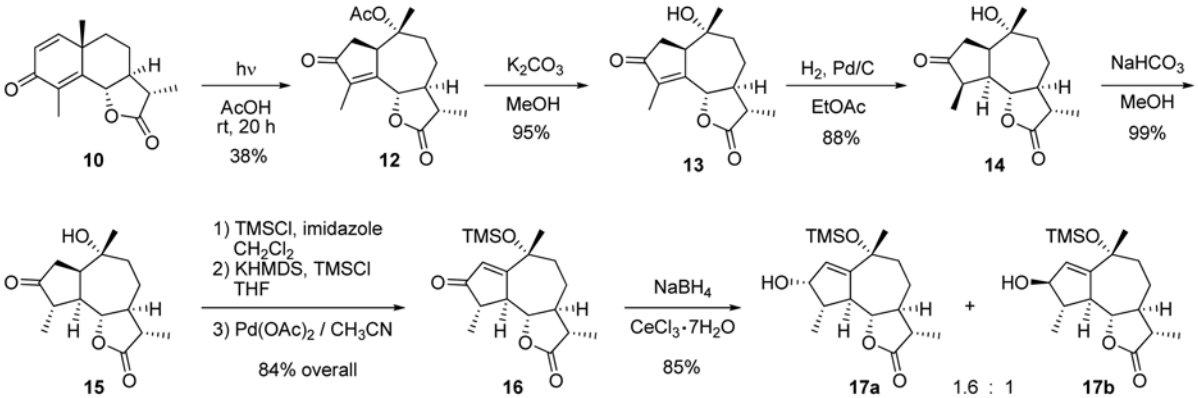
Scheme 3. Preparation of the methylene and the diene from compound **17**.

and the Diels-Alder reaction with **7** should be done in one pot and, due to its feasibility, the generation of methylene group at C11 could be achieved after the Diels-Alder reaction, which leads to avoid an unwanted reaction, dimerization of **8**.

In summary, we have synthesized a precursor to arglabin diene which is the right part biogenetic Diels-Alder precursor to arteminolides. The synthesis was achieved through a route that featured a photochemical rearrangement of α-santonin followed by several challenging transformations of functional groups. The current route offers an opportunity for asymmetric and short synthesis of arteminolides since the chiral starting material α-santonin already has necessary carbons and the photochemical rearrangement occurs stereoselectively.

Experimental Section

(3*S*,3a*S*,6*R*,6a*R*,9b*S*)-3,6,9-Trimethyl-2,8-dioxo-2,3,3a,4,5,6,6a,7,8,9b-decahydroazuleno[4,5-*b*]furan-6-yl acetate (12). A solution of 4.70 g (19.08 mmol) of a-santonin in 70 mL of glacial AcOH was irradiated under Ar for 20 h using a 300 nm UV lamp. The AcOH was evaporated under reduced pressure and the resulting oil was purified by column chromatography. The product was crystallized with EtOAc and *n*-hexane to afford 2.23 g (38%) of guaianolide **12**[7]: ^{1}H



Scheme 2. Synthesis of enol **17a** and **17b** from α-santonin (**10**).

NMR (400 MHz, $CDCl_3$) δ 4.77 (d, J = 10.9 Hz, 1H), 4.13 (m, 1H), 2.65 (m, 1H), 2.51-2.14 (m, 5H), 2.08 (m, 1H), 1.98 (s, 3H), 1.88 (m, 2H), 1.45 (m, 1H), 1.26 (d, J = 6.9 Hz, 3H). 1.06 (s, 3H)

(3*S*,3a*S*,6*R*,6a*R*,9*S*,9a*R*,9b*S*)-6-Hydroxy-3,6,9-trimethyloctahydroazuleno[4,5-*b*]furan-2,8(3*H*,9b*H*)-dione (15). To a solution of 500 mg (1.63 mmol) of **12** in MeOH (4 mL) was added K_2CO_3 (5 equiv) and the mixture was stirred overnight at ambient temperature. After solvent was evaporated, the concentrated mixture was diluted with Et_2O (40 mL) and washed with brine (10 mL × 2). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography to afford alcohol **13**[7c] (410 mg, 95%). Palladium on carbon (10%, 20 mg) was added to a solution of **13** (184 mg, 0.696 mmol) in EtOAc (4 mL) and the mixture was allowed to stir under H_2 atmosphere (balloon) for 5 h. The resulting mixture was filtered through a plug of silica and concentrated under reduced pressure. The crude product was purified by column chromatography to afford **14** (163 mg, 88%). To a stirred solution of **14** (135 mg, 0.507 mmol) in MeOH (3 mL) was added $NaHCO_3$ (5 equiv) and the mixture was stirred for 25 h at ambient temperature. After solvent was evaporated, the mixture was diluted with Et_2O (20 mL) and was then washed with brine (5 mL × 2). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography to afford **15**[7d] (133 mg, 99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (t, J = 9.6 Hz, 1H), 2.68 (m, 1H), 2.59 (m, 1H), 2.39-2.19 (m, 4H), 2.02-1.92 (m, 3H), 1.65 (m, 2H), 1.37 (m, 1H), 1.21 (d, J = 7.0 Hz, 3H), 1.17 (d, J = 7.0 Hz, 3H), 1.14 (s, 3H).

(3*S*,3a*S*,6*R*,9*S*,9a*S*,9b*S*)-3,6,9-Trimethyl-6-(trimethylsilyloxy)-3a,4,5,6,9,9a-hexahydroazuleno[4,5-*b*]furan-2,8(3*H*,9b*H*)-dione (16). To a stirred solution of **15** (372 mg, 1.40 mmol) in CH_2Cl_2 (3 mL) were added imidazole (380 mg, 5.58 mmol) and TMSCl (0.355 mL, 2.80 mmol), and the mixture was stirred for 2 h at room temperature. The resulting mixture was diluted with Et_2O (25 mL), washed with brine (5 mL × 2), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography to afford the corresponding TMS ether (429 mg, 91%). To a solution of KHMDS (0.5 M in $PhCH_3$, 4.56 mL) was added dropwise a solution of the TMS ether (594 mg, 1.75 mmol) in THF (7 mL), and the reaction mixture was stirred at –78 °C for 40 min. TMSCl (0.445 mL, 3.50 mmol) was added and the resulting mixture was stirred at –78 °C for 30 min. Et_3N (0.45 mL) was added, and the mixture was filtered through a silica gel pad and concentrated in vacuo. To a solution of the crude silylenol ether in CH_3CN (9 mL) was added $Pd(OAc)_2$ (473 mg, 2.10 mmol) and the reaction mixture was stirred for 12 h at room temperature. After solvent was removed under reduced pressure the residue was purified by column chromatography to afford enone 16 (544 mg, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 (d, J = 1.6 Hz, 1H), 3.79 (t, J = 10.4 Hz, 1H), 2.77 (m, 1H), 2.47 (m, 2H), 2.23-2.05 (m, 3H), 1.64-1.58 (m, 5H), 1.31 (m, 1H), 1.24 (m, 6H), 0.12 (s, 9H).

(3*S*,3a*S*,6*R*,8*S*,9*S*,9a*S*,9b*S*)-8-Hydroxy-3,6,9-trimethyl-6-(trimethylsilyloxy)-3a,4,5,6,8,9,9a,9b-octahydroazuleno[4,5-*b*]furan-2(3*H*)-one (17a) and (3*S*,3a*S*,6*R*,8*R*,9*S*,9a*S*,9b*S*)-8-hydroxy-3,6,9-trimethyl-6-(trimethylsilyloxy)-3a,4,5,6,8,9,9a,9b-octahydroazuleno[4,5-*b*]furan-2(3*H*)-one (17b). To a stirred mixture of **16** (40 mg, 0.119 mmol) and $CeCl_3 \cdot 7H_2O$ (44 mg, 0.119 mmol) in CH_2Cl_2-MeOH (4/1, 1 mL) was added portionwise $NaBH_4$ (4.5 mg, 0.119 mmol). After stirring at 0 °C for 30 min, the mixture was quenched with saturated aqueous NH_4Cl (3 mL) and was extracted with EtOAc (5 mL × 3). The organic layer was washed with brine (3 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography to afford **17a** (21 mg, 52%) and **17b** (13 mg, 33%). **17a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (m, 1H), 4.65 (m, 1H), 3.73 (m, 1H), 2.63 (m, 1H), 2.39 (m, 2H), 2.14-1.88 (m, 3H), 1.59-1.48 (m, 4H), 1.29-1.15 (m, 7H), 0.10 (s, 9H). **17b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (m, 1H), 4.29 (m, 1H), 3.87 (m, 1H), 2.41 (m, 2H), 2.18-1.97 (m, 4H), 1.63 (m, 1H), 1.50 (s, 3H), 1.33-1.17 (m, 7H), 0.07 (s, 9H).

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