

# Total Synthesis of (+)-Arteannin M Using the Tandem Oxy-Cope/Ene Reaction

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## ABSTRACT



The first total synthesis of (+)-arteannin M was accomplished using the tandem oxy-Cope/transannular ene reaction as the key step to construct the bicyclic core of the natural product. The tandem reaction proceeded with high diastereo- and enantiomeric excess.

*Artemisia annua* L. (compositae) is found in the mountains of Sichuan province, Southern China and is the source of the sesquiterpene endoperoxide artemisin (1), one of the most important drugs for the treatment of malaria in South East Asia (Figure 1).<sup>1</sup> In 1998, Brown and co-workers isolated

2. To the best of our knowledge no synthesis of this molecule has yet been reported. We have recently established that the tandem oxy-Cope/transannular ene reaction of 1,2-divinylcyclohexanols provides a powerful method to rapidly construct polycyclic compounds possessing a bridgehead alcohol at the ring junction.<sup>3,4</sup> Our retrosynthetic analysis of arteannin M (2) took cognizance of the cadinane framework sesquiterpene 3, which can be directly obtained via the tandem oxy-Cope/ene reaction.

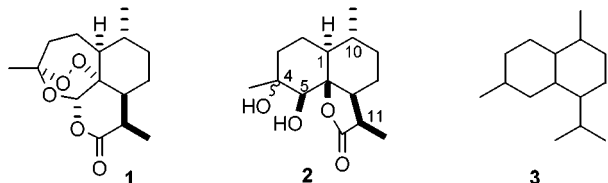


Figure 1.

from this plant a new sesquiterpene, arteannin M (2).<sup>2</sup> It is important to point out that the stereochemistry at C4 has not yet been defined, nor has the absolute configuration of

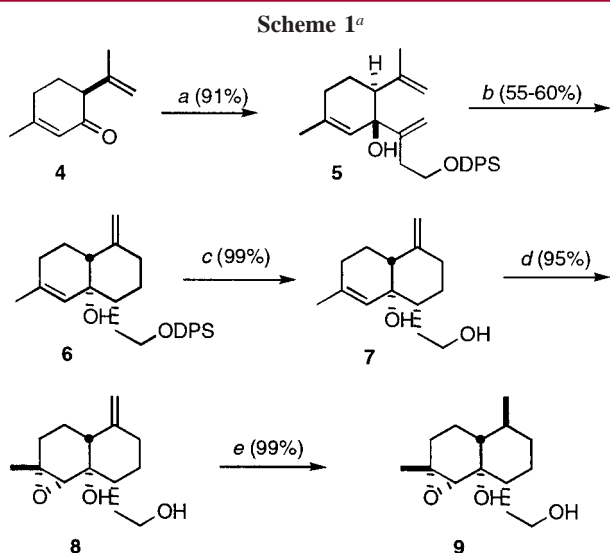
(1) Liu, J.-M.; Ni, M.-Y.; Fan, Y.-F.; Tu Y.-Y.; Wu, Z.-H.; Wu, Y.-L.; Zhou, W. S. *Acta Chim. Sin.* **1979**, 37, 129.

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(4) For other examples of transannular carbonyl ene reaction, see: (a) Mihailovic, M. L.; Lorenc, L.; Forsek, H.; Nesovic, G.; Snatzke, G.; Traska, P. *Tetrahedron* **1970**, 26, 557. (b) Yamamra, S.; Iguchi, M.; Nishiyama, M.; Niwa, M. *Tetrahedron* **1971**, 27, 5419. (c) Yamamra, S.; Iguchi, M.; Niwa, M. *Bull. Chem. Soc. Jpn.* **1976**, 49, 3148. (d) Yamamra, S.; Tereda, Y. *Tetrahedron Lett.* **1979**, 1623. (e) Lange, G. L.; McCarthy, F. C. *Tetrahedron Lett.* **1978**, 4749. (f) Williams, J. R.; Callahan, J. F. *J. Org. Chem.* **1980**, 45, 4479. (g) Wender, P. A.; Hubbs, J. C. *J. Org. Chem.* **1980**, 45, 365. (h) Williams, J. R.; Cleary, T. P. *J. Chem. Soc., Chem. Commun.* **1982**, 626.

The synthesis started with a halogen–metal exchange of 3-iodo-3-butenol silyl ether<sup>5</sup> using *tert*-butyllithium (1.7 M in pentane) in ether at  $-90\text{ }^{\circ}\text{C}$  followed by addition of the ketone **4**<sup>6</sup> (readily available from (+)-limonene). This sequence afforded the desired 1,2-divinylcyclohexanol **5** in 91% yield (Scheme 1). This compound was heated in toluene



<sup>a</sup> (a)  $\text{CH}_2=\text{CH}(\text{Li})\text{CH}_2\text{CH}_2\text{ODPS}$ ,  $\text{Et}_2\text{O}$ ,  $-90\text{ }^{\circ}\text{C}$ . (b) DBU, toluene,  $220\text{ }^{\circ}\text{C}$ . (c) TBAF, THF. (d)  $\text{VO}(\text{acac})_2$ , *t*-BuOOH,  $\text{CH}_2\text{Cl}_2$ . (e)  $\text{Ir}[(\text{COD})(\text{PCy}_3)]\text{PF}_6$ ,  $\text{H}_2$ ,  $\text{CH}_2\text{Cl}_2$ .

and DBU (5 equiv) for 5 h in a sealed tube to give **6** in 55–60% yield as the only detectable diastereoisomer.<sup>7</sup>

We have discovered that DBU is essential for the tandem oxy-Cope/ene reaction to proceed in good yield.<sup>8</sup> Indeed, in the absence of DBU a complex mixture of products was obtained from which it was impossible to isolate **6**.

The high diastereoselectivity observed in the tandem oxy-Cope/ene reaction can be explained by the proposed mechanism shown in Figure 2. Thermal rearrangement of **5** produces enol **10**, which immediately tautomerizes to ketone intermediate **11**. The macrocyclic ketone **11** can exist in two different conformations, which can each undergo an ene reaction via two competing reactive conformers, **A** and **B**, thus producing **12** and **6**, respectively. A close examination of **A** and **B** reveals that the alkyl chain in **A** is oriented pseudoaxially, whereas in **B** the alkyl group is in a pseudo-equatorial position, thus favoring the formation of **6** over **12**.

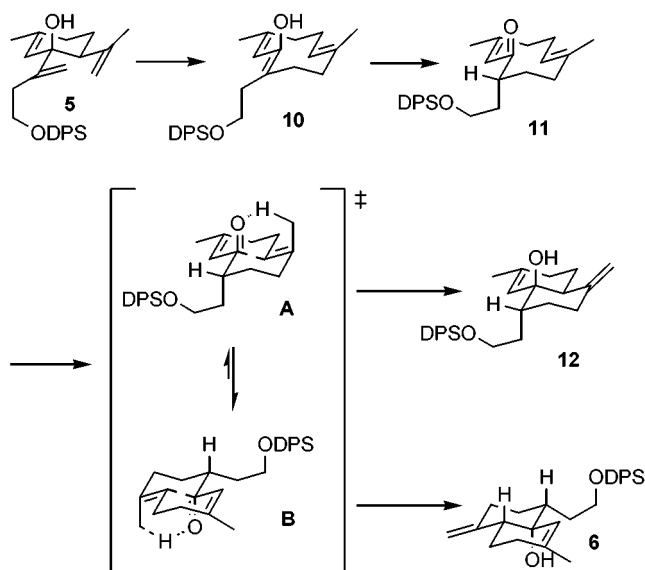
The chirality transfer of the tandem process was evaluated by 500 MHz  $^1\text{H}$  NMR analysis of the Mosher ester **8a** and **8b** (diastereomeric ratio of 89%) (Scheme 2). The high

(5) Prepared by treatment of 3-butenol with HI followed by alcohol protection with DPSCl, imidazole in THF.

(6) (+)-Limonene 98% ee was used. Dauben, W. B.; Lorber, M.; Fullerton, D. S. *J. Org. Chem.* **1969**, *34*, 3587.

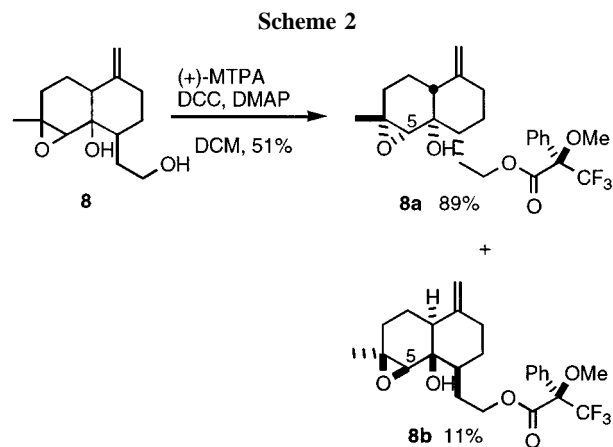
(7) No evidence of a second diastereoisomer was seen by 500 MHz  $^1\text{H}$  NMR.

(8) For examples of solvent-induced oxy-Cope reactions, see: (a) Fujita, Y.; Onishi, T.; Nishida, T. *Synthesis* **1978**, 934. (b) Onishi, T.; Fujita, Y.; Nishida, T. *J. Chem. Soc., Chem. Commun.* **1978**, 651. (c) Utagawa, A.; Hirota, H.; Ohno, S.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1207.



**Figure 2.** Transition state of the carbonyl ene reaction.

enantioselectivity control observed during the oxy-Cope rearrangement can be explained on the basis of the energy



barrier to invert **10** to *ent*-**10** and stereofacial protonation (Figure 3). The macrocycle **10** possesses a conjugated dienol (*E,Z*) and another *E* double bond (ene donor), which create a strained and rigid macrocyclic ring.

As a result, the conversion of **10** into *ent*-**10** requires that the enol moiety rotate inside the macrocycle, which is energetically demanding. At the same time, protonation of enol **10** can only occur from the  $\beta$ -face to yield ketone **11**. The preferential formation of ketone **11** over *ent*-**11** is thus readily explained.

Subsequent exposure of **6** to TBAF unmasked the primary alcohol **7** in quantitative yield. At this stage, diastereoselective oxirane formation and exo-cyclic olefin reduction took advantage of the C6 tertiary alcohol, which can be used as a coordinating source. Allylic epoxidation of **7** using VO-

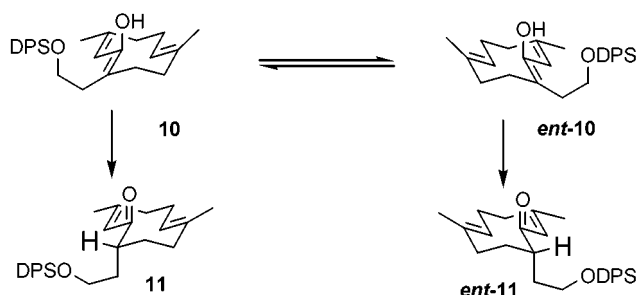


Figure 3.

(*acac*)<sub>2</sub> and TBHP in methylene chloride proceeded smoothly and led to the desired epoxide **8** in 95% yield.<sup>9</sup>

A second hydroxy-oriented reaction was performed using Crabtree's catalyst under H<sub>2</sub> atmosphere to reduce the double bond to afford **9** with the required C10 stereochemistry in 99% yield (diastereomeric ratio of 11:1 at C10).<sup>10</sup> The absolute configuration of **9** was established by X-ray analysis. Sequential oxidation of the diol **9** with TPAP and NMO in methylene chloride provided the lactone **13** in 90% yield (Scheme 3).<sup>11</sup> Installation of the C11 methyl in **13** required formation of the lithium enolate (LDA, THF -78 °C), which was then treated with iodomethane at -78 °C to give **14** in

72% yield. The methylation step reveals a high level of stereocontrol in that only the  $\beta$ -isomer **14** is produced (>98:2). Inversion of configuration at C11 by formation of the lithium enolate and subsequent protonation with ammonium chloride afforded the desired  $\alpha$ -isomer **15** in quantitative yield. NOESY experiments confirmed that **15** possess the 11*S* configuration (Scheme 3).

At this point in the synthesis, the remaining unsettled question concerned the possible stereochemistry of the C4–C5 diol. During the course of this synthesis, Brown et al. revised their stereochemical assignments at C4 and C5. They confirmed the presence of a C4–C5 *cis* diol in **2**, but they were unable to determine the relative configuration of C4 and C5. To assign these stereogenic centers correctly, regeneration of the double bond in ring A was imperative. Therefore, deoxygenation of **15** using Sharpless protocol successfully removed the epoxide and generated **16** in 67% yield.<sup>12</sup> Catalytic hydroxylation on the less indented face of **16** produced **17** having a *cis* diol *anti* to the lactone.

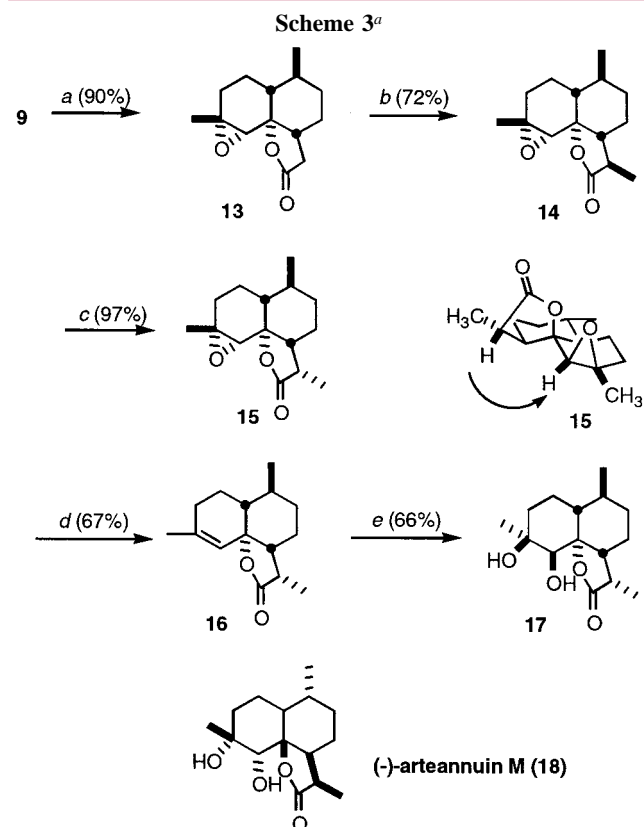
The 500 MHz <sup>1</sup>H and 125 MHz <sup>13</sup>C NMR spectra (CDCl<sub>3</sub>) of **17** were compared directly with those of the natural substance and were identical. This confirms without ambiguity the relative configuration of C4 and corrects the stereochemistry at C5. Furthermore, the positive optical rotation of **17** ([ $\alpha$ ]<sub>D</sub> = +34.1°, *c* 0.26 in CH<sub>2</sub>Cl<sub>2</sub>), which is the opposite sign of the natural product, establishes its absolute configuration as shown in **18** ([ $\alpha$ ]<sub>D</sub> = -31.1°, *c* 1.25 in CHCl<sub>3</sub>).

In summary, we have accomplished the total synthesis of (+)-arteannuin M (**17**) in 10 steps starting from readily available (+)-**4** (overall yield 14.1%). Expedient construction of the arteannuin M core **6** with high control of diastereoselectivity demonstrated the power and versatility of the tandem oxy-Cope/ene reaction of 1,2-divinylcyclohexanols. In addition, we have established the correct relative stereochemistry at C4 and C5, as well as the absolute configuration of the natural (-)-arteannuin M (**18**) as illustrated in Scheme 3.

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**Supporting Information Available:** Spectroscopic data and experimental procedures for **5–9** and **13–17**, ORTEP view of **9**, and copies of the <sup>1</sup>H and <sup>13</sup>C spectra of synthetic and natural arteannuin M. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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<sup>a</sup> (a) TPAP cat., NMO, molecular sieves 4 Å. (b) LDA, then MeI, THF, -78 °C. (c) LDA, then NH<sub>4</sub>Cl, THF, -78 °C. (d) WCl<sub>6</sub>, *n*-BuLi, LiI, THF, -78 to 25 °C. (e) OsO<sub>4</sub>, NMO, THF–H<sub>2</sub>O (4:1).

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