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Synthesis of (±)-Chamobtusin A by a Presumed Biomimetic Aza-Cyclization

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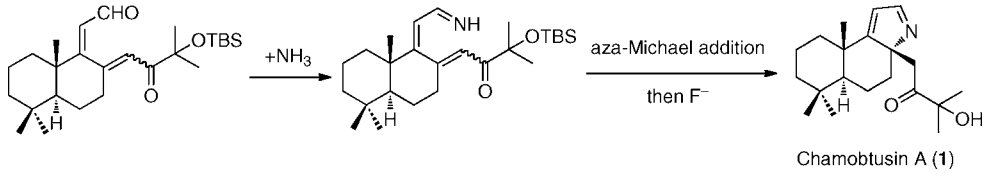
ABSTRACT



A total synthesis of (±)-chamobtusin A has been accomplished on the basis of our presumed biosynthetic pathway: the imine formation of keto aldehyde followed by intramolecular aza-Michael addition.

Chamobtusin A (**1**) was isolated from the branches and leaves of *Chamaecyparis obtusa* cv. tetragon by Tan and co-workers in 2007, and its relative stereochemistry was elucidated unambiguously by X-ray crystallographic analysis (Figure 1).[1] Although Tan reported that chamobtusin A (**1**) showed no cytotoxic activities on A549 and K562 human tumor cell lines, it is expected to possess antitumor, antimalarial, or antibacterial activities. In addition to that, chamobtusin A (**1**) has a novel structure with an unsaturated five-membered ring including a nitrogen atom. Its unique structure as well as a possibility of discovering new biological activities inspired us to start a synthetic study of chamobtusin A (**1**). Herein, we report a first total synthesis of (±)-chamobtusin A (**1**) based on a presumed biosynthetic pathway.

Our proposed biosynthetic route and retrosynthetic plan of chamobtusin A (**1**) are shown in Scheme 1. Oxidative cleavage of benzene ring of **C**[2] with a well-known abietane skeleton would generate keto aldehyde **B**. In the presence of ammonia, **B** would be transformed into imine **A**, and subsequent Michael addition of the nitrogen atom to C8 position would produce chamobtusin A. In our synthesis,

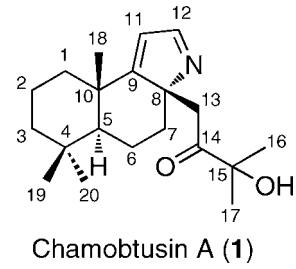


Figure 1. Structure and numbering of chamobtusin A.

we selected aza-Michael addition[3] as a key reaction. Intermediate **B** would be synthesized from **D** by introducing aldehyde unit at C11 position followed by side-chain elongation at C13. **D** would be obtained from known alchohol **E**,[4] which can be easily prepared by Diels−Alder reaction of diene **F** and dimethyl acetylenedicarboxylate (**G**) followed by hydroboration−oxidation.

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(3) For reviews, see: (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992. (b) Xu, L.-W.; Xia, C.-G. *Eur. J. Org. Chem.* **2005**, 633–639. (c) Vicario, J. L.; Badía, D.; Carrillo, L.; Etxebarria, J.; Reyes, E.; Ruiz, N. *Org. Prep. Proc. Int.* **2005**, *37*, 513–538.

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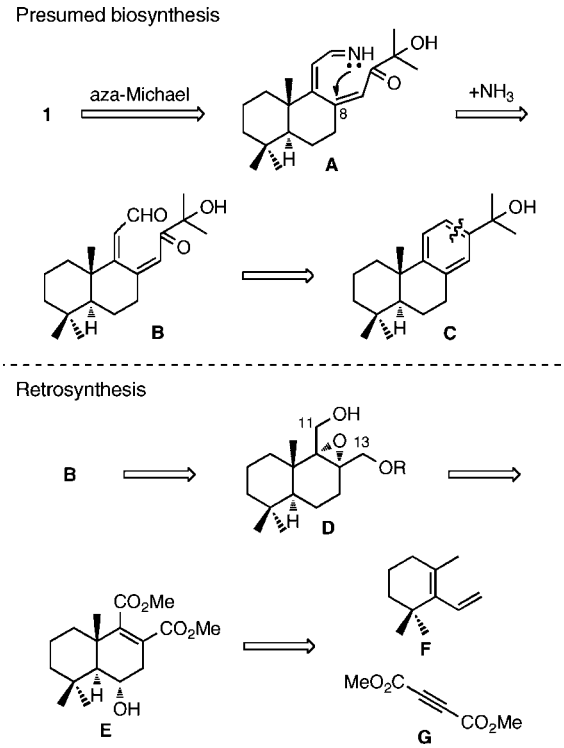
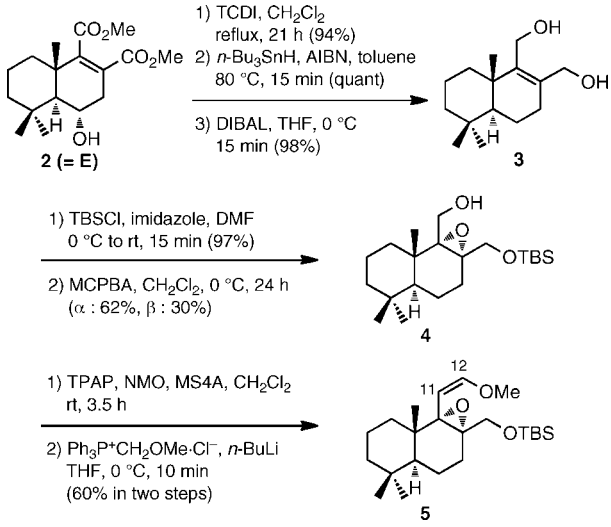
Scheme 1. Presumed Biosynthesis and Retrosynthesis of Chamobtusin A



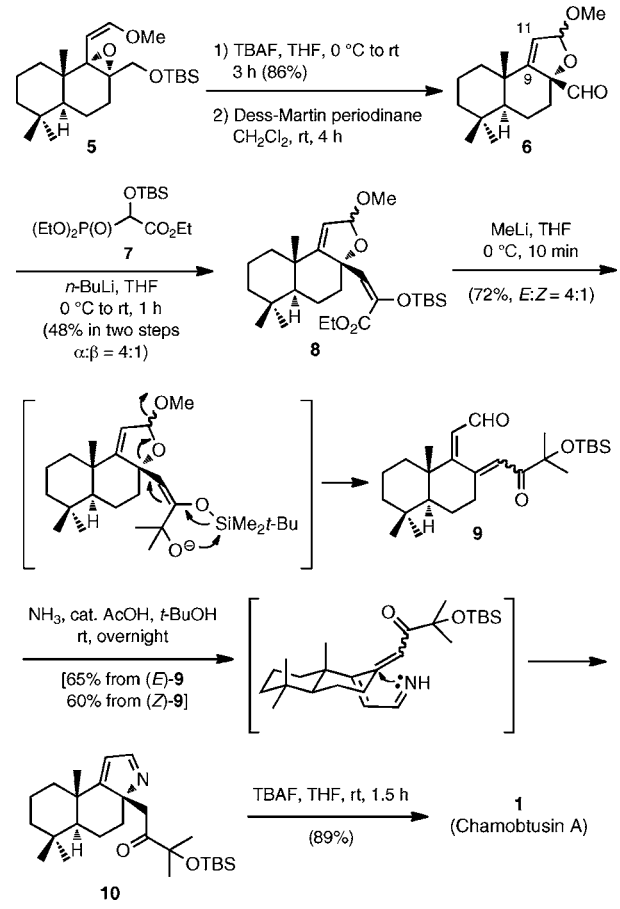
The first stage of the synthesis is shown in Scheme 2. As mentioned above, we selected known alchohol **2**[4] (= **E**) as a starting material. The hydroxy group of **2** was converted into thiocarbamate, which was then deoxygenated[5] by treatment with *n*-Bu_3SnH and AIBN, and the resulting diester was reduced with DIBAL to give diol **3**[6] in high yield. The less hindered primary alchohol of **3** was selectively protected as the TBS ether. *m*-CPBA oxidation of the double bond gave a mixture of α- and *β*-epoxides[7] in a ratio of 2.1:1, which were separated by silica gel column chromatography, and the major α-epoxide **4** was used in the next reaction. After TPAP oxidation[8] of the primary hydroxy group of **4**, Wittig reaction of the resulting aldehyde with the ylide generated from (methoxymethyl)triphenylphosphonium chloride and *n*-BuLi afforded enol ether **5** in which the geometry of the double bond was completely *Z* ($J_{11,12}$ = 6.6 Hz).

Scheme 2. First Stage of the Synthesis



The completion of the synthesis was performed as shown in Scheme 3. The TBS group of **5** was removed with TBAF, and the liberated primary alchohol was oxidized with Dess−Martin periodinane[9] to give cyclic product **6** in which reaction, eliminative epoxide opening, and acetalization

Scheme 3. Completion of the Synthesis



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(6) Other methods for preparing **3** have been reported. See: (a) Razmilic, I.; Sierra, J.; Lopez, J.; Cortes, M. *Chem. Lett.* **1985**, 1113–1114. (b) Hueso-Rodrigues, J. A.; Rodrigues, B. *Tetrahedron* **1989**, *45*, 1567–1576. (c) Abad, A.; Agulló, C.; Cuñat, A. C.; Pardo, D. *Tetrahedron Lett.* **2003**, *44*, 1899–1902.

(7) The stereochemistry of the epoxide was determined by comparing ^{1}H NMR chemical shifts with those of similar compounds. Benites, J.; Preite, M. D.; Cortés, M. *Synth. Commun.* **2001**, *31*, 1347–1354.

might have been promoted by acetic acid generated in situ. Fortunately, by this unexpected cyclization, the desired *Z* geometry of the newly generated C9−C11 double bond of **6** could be controlled. Horner−Wadsworth−Emmons reaction of **6** with phosphonate **7**[10] gave **8** (α/β = 4:1), whose stereochemistries were determined by NOE experiments as shown in Figure 2. To our delight, **8** could be converted

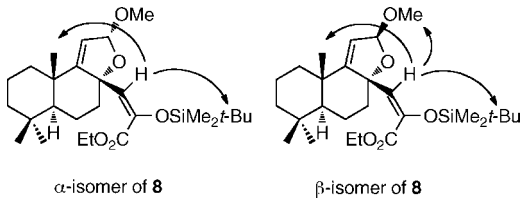

Figure 2. NOE correlations of **8**.

directly into the cyclization precursor **9** by treatment with MeLi. The alkoxide generated by the addition of 2 equiv of MeLi trapped the neighboring TBS group, and subsequent ring-opening of methyl acetal gave desired keto aldehyde **9** (*E*/*Z* = 4:1) in 72% yield. As we expected, imine formation and subsequent intramolecular aza-Michael addition smoothly proceeded from both geometrical isomers of **9** by treatment with ammonia in the presence of acetic acid to afford **10** as a single diastereomer (65% from *E* isomer, 60% from *Z* isomer).

Finally, the TBS group was removed with TBAF to give (±)-chamobtusin A. ^{1}H NMR and ^{13}C NMR spectra of our synthetic **1** were in good accordance with those of the natural compound.

In conclusion, we achieved a first total synthesis of (±)-chamobtusin A based on a presumed biomimetic pathway. The overall yield of **1** starting from **2** was 5.3% in 13 steps. To determine the absolute configuration of the natural product, synthetic study of optically active chamobtusin A from natural abietane diterpenoid (**C** → B → **1**) is now in progress and the results will be reported in due course.

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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