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Total Synthesis of (−)-Chamobtusin A

Hikaru Suzuki and Sakae Aoyagi*

School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, Horinouchi, Hachioji, Tokyo 192-0392, Japan

aoyagis@toyaku.ac.jp

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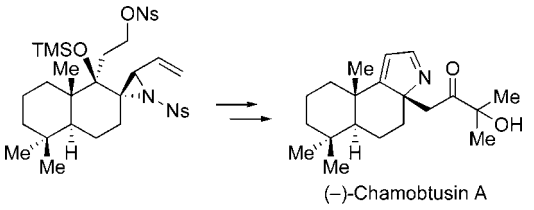
ABSTRACT

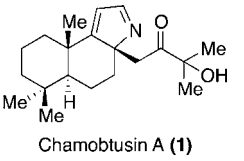


The first asymmetric total synthesis of a structurally unique alkaloid, chamobtusin A (1), is described. The route features a novel aziridine formation from the 1,2-oxazine derivative and a palladium-mediated annulation of the vinylaziridine intermediate.

Chamobtusin A (**1**), isolated by Tan and co-workers from *Chamaecyparis obtusa* cv. *tetragon* in 2007, is the first alkaloid from the order Pinales, as well as the first diterpene alkaloid from the family *Cupressacea*. Its structure was established mainly on the basis of 2D NMR techniques (Figure 1) and was confirmed by single-crystal X-ray diffraction analysis, but the absolute configuration has not been assigned.[1] To date, two syntheses of racemic chamobtusin A have been reported independently by Watanabe's group[2] and our group[3] using an approach that featured an intramolecular aza-Michael reaction to construct the key nitrogen-bearing quaternary center. We now report the first enantioselective total synthesis of (−)-chamobtusin A (**1**).

Our retrosynthetic analysis for chamobtusin A is shown in Scheme 1. Chamobtusin A (**1**) would be derived from perhydrobenzoindole **2** by manipulation of the keto alcohol side chain and the 2*H*-pyrrole moiety. The key C-8 stereocenter of **2** could be introduced through a stereoselective allylation of tricyclic 1,2-oxazine **3** bearing the siloxy group at C-9, which could be derived from octahydronaphthalenone **4**.

As depicted in Scheme 2, our synthesis commenced with the preparation of the known α-hydroxy ketone **5**[4] from the known ketone **4**,[5] which was obtained in optically pure



Chamobtusin A **(1)**

Figure 1. Structure of chamobtusin A (**1**).

form from (*S*)-(+)-Wieland−Miescher ketone[6] in seven steps, following the published procedure.[7] Oxidation of the obtained **5** with Dess−Martin periodinane and treatment of the resulting diketone with LHMDS followed by TBSCl trapping of the enolate gave the corresponding *tert*-butyldimethylsilyl enol ether **6**, which was successively treated with vinyl Grignard reagent and tetrabutylammonium fluoride (TBAF) in THF to produce the desired vinyl alcohol **7** as a single diastereomer in 77% yield over four steps from **5**. Having successfully constructed the requisite C-9 stereocenter, we set out to synthesize the tricyclic 1,2-oxazine **3**. Thus, **7** was subjected to hydroboration with dicyclohexylborane (Chx_2BH)[8] followed by oxidation of the alkylborane intermediate to afford primary alcohol **8** in

(1) Zhang, Y.-M.; Tan, N.-H.; Lu, Y.; Chang, Y.; Jia, R.-R. *Org. Lett.* **2007**, *9*, 4579–4581.
(2) Kuzuya, K.; Mori, N.; Watanabe, H. *Org. Lett.* **2010**, *12*, 4709–4711.
(3) Suzuki, H.; Aoyagi, S. *Chem. Commun.* **2011**, *47*, 7878–7879.
(4) Ihara, M.; Toyota, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2151–2161.
(5) Hatzellis, K.; Pagona, G.; Spyros, A.; Demetzos, C.; Katerinopoulos, H. E. *J. Nat. Prod.* **2004**, *67*, 1996–2001.
(6) Buchschacher, P.; Fürst, A.; Gutzwiller, J. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, pp 368−372.
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(8) (a) Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic Press: London, 1988. (b) Kabalka, G. W.; Yu, S.; Li, N.-S. *Tetrahedron Lett.* **1997**, *38*, 5455–5458.

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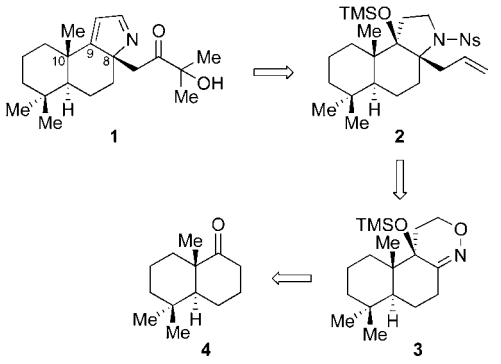
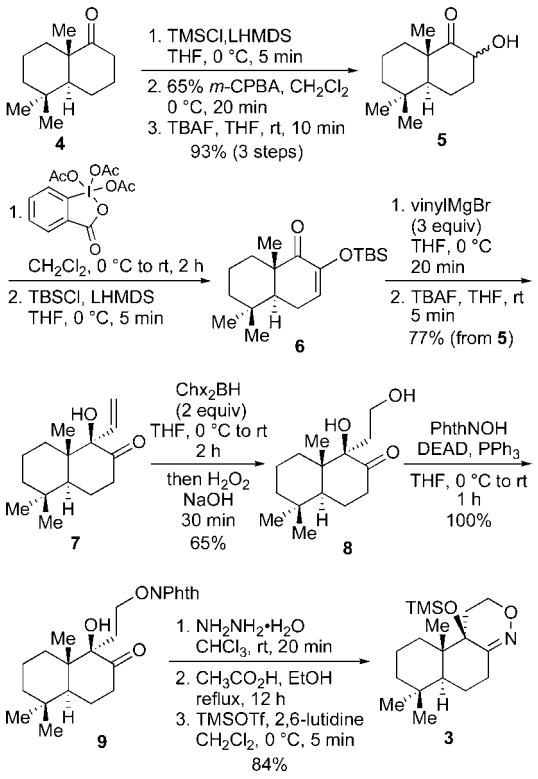
Scheme 1. Retrosynthetic Analysis for Chamobtusin A (**1**)



65% yield.[9] Treatment of **8** with *N*-hydroxyphthalimide under Mitsunobu conditions gave **9** in quantitive yield. Deprotection of the phthalimide group of **9** by treating with hydrazine monohydrate, heating of the formed hemiaminal with acetic acid in EtOH, and exposure to TMSOTf and 2,6-lutidine resulted in an 84% yield of the oxime ether **3**.

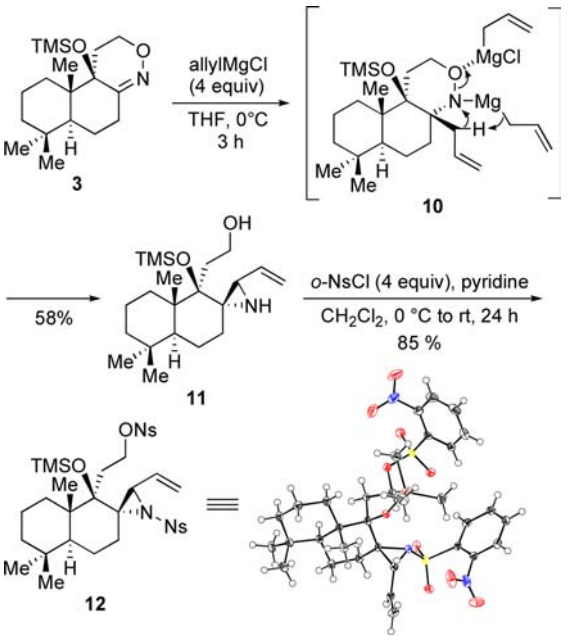
Scheme 2. Preparation of 1,2-Oxazine **3**



With the desired oxime ether **3** in hand, we next focused on stereoselective construction of the pyrrolidine moiety and elaboration of the necessary side chain of perhydrobenzoindole **2** (Scheme 3). Thus, in order to stereoselectively introduce the allyl group at C-8, **3** was subjected to

(9) Treatment of **7** with borane reagents such as 9-BBN, disiamylborane, or thexylborane gave low yields or complex mixtures.

Scheme 3. Formation of Vinylaziridine Derivative **12**



reaction with allylmagnesium chloride (4 equiv) in THF at 0 °C. To our surprise, however, this reaction provided the unexpected spiro aziridine **11** in 58% yield, presumably via initial abstraction of an allylic hydrogen by an appropriately oriented proximal allyl component on the nitrogen of allylated intermediate complex **10**, followed by simultaneous aziridine ring formation/N−O bond cleavage.[10] The stereostructure of **11** was confirmed by X-ray crystallographic analysis of the *N*,*O*-dinosyl derivative **12**, derived in 85% yield from **11**.

Our next task was to elaborate the tricyclic framework of chamobtusin A. For this, we envisioned use of a palladium-mediated ring-expansion,[11] in which a π-allylpalladium intermediate **13** derived from vinylaziridine derivative **12** by palladium-catalyzed hydrogenolysis,[12] would serve as a precursor for an intramolecular S_N2-like amination (Scheme 4). Thus, when **12** was subjected to the standard conditions for palladium-catalyzed hydrogenolysis ($Pd_2(dba)_3CHCl_3$, PBu_3, formic acid, Et_3N), the cascade reaction occurred to generate the desired perhydrobenzoindole **2**, albeit in low yield (21%). The use of PPh_3 as a ligand, however, greatly increased the yield of **2** to 92%.

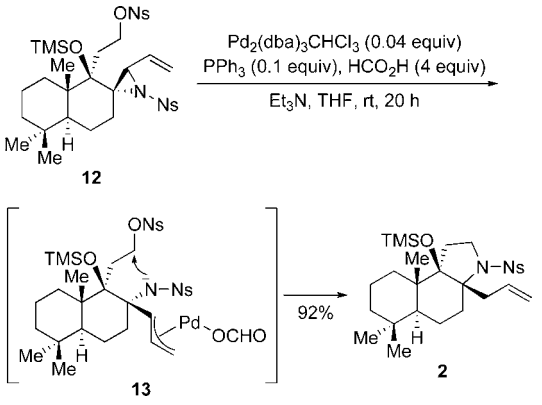
Subsequent transformation of the C-8 allyl moiety into the 3-hydroxy-3-methyl-2-butanone side chain was accomplished by means of our previously developed sequence

(10) For related examples of the preparation of aziridines from oximes, see: (a) Kotera, K.; Takano, Y.; Matsuura, A.; Kitahonoki, K. *Tetrahedron* **1970**, *26*, 539–556. (b) Freeman, J. P. *Chem. Rev.* **1973**, *73*, 283–292.

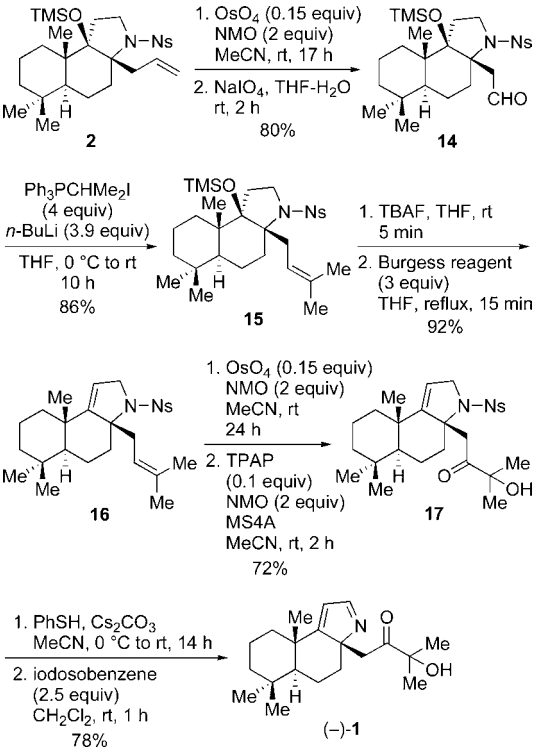
(11) For related palladium-mediated annulation of vinylaziridines, see: Lowe, M. A.; Ostovar, M.; Ferrini, S.; Chen, C. C.; Lawrence, P. G.; Fontana, F.; Calabrese, A. A.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 6370–6374.

(12) (a) Tsuji, J.; Minami, I.; Shimizu, I. *Synthesis* **1986**, 623–627. (b) Mandai, T.; Matsumoto, T.; Kawada, M.; Tsuji, J. *J. Org. Chem.* **1992**, *57*, 1326–1327. (c) Tsuji, J.; Mandai, T. *Synthesis* **1996**, 1–24.

Scheme 4. Synthesis of Perhydrobenzoindole **2**



Scheme 5. Synthesis of (−)-Chamobtusin A



(Scheme 5). Dihydroxylation of **2** with OsO_4 and NMO, followed by $NaIO_4$ cleavage of the resulting diol, provided aldehyde **14** in 80% yield. Wittig reaction gave alkene **15** in 86% yield. At this stage, the silyl protecting group of **15** was removed, and the resulting tertiary alcohol was treated with Burgess' reagent[13] in THF at reflux to cleanly afford dihydropyrrole **16** in 92% yield for these two steps. Regioselective dihydroxylation of the side chain of **16**, in preference to the ring double bond with OsO_4, followed by TPAP oxidation of the resulting diol gave keto alcohol **17** in 72% yield over two steps. Finally, the nosyl group was removed using Fukuyama's conditions,[14] and the resulting secondary amine was oxidized with iodosobenzene[15] in CH_2Cl_2 at room temperature, furnishing (−)-chamobtusin A (**1**) in 78% yield over two steps. The spectroscopic data (^1H and ^{13}C NMR, and IR) and optical rotation [$[\alpha]^{25}_D$ −233.2 (*c* 0.14, MeOH) (lit.[1] $[\alpha]^{24}_D$ −220.1 (*c* 0.24, MeOH))] of synthetic **1** were in accord with those reported for the natural product.

In summary, we have completed the first asymmetric synthesis and determined the absolute configuration of (−)-chamobtusin A. The key features of this synthesis include a novel aziridine formation from the corresponding 1,2-oxazine derivative and a palladium-mediated annulation of the vinylaziridine derivative.

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Supporting Information Available. Experimental procedures and compound characterization data including X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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