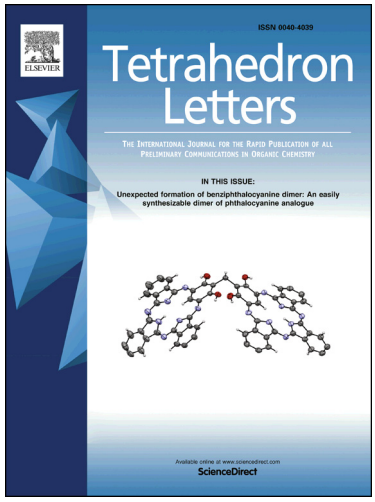

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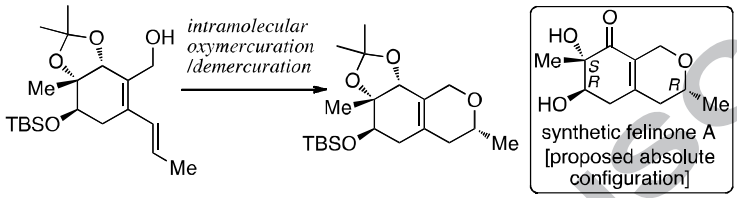

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Asymmetric total synthesis and revision of absolute configurations of azaphilone derivative felinone A

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ABSTRACT

The first total synthesis of the azaphilone derivative, felinone A, was accomplished. The absolute configuration of natural felinone A was revised to be 3*S*, 6*S*, and 7*R*.

Introduction

Azaphilones belong to a family of polyketide metabolites that possess highly oxygenated isochromene skeletons.[1] Recent reports demonstrated that many azaphilone derivatives possess biological activities, such as inhibition of p53–MDM2 protein–protein interactions,[2] inhibition of gp120–CD4 binding,[3] cytotoxicity, antimicrobial action, and anti-inflammatory actions.[4] Four similar azaphilone derivatives (Figure 1) have been reported recently. Felinone A (**1**)[5] was isolated by bioassay-guided fractionation of a culture extract of the marine-derived entomopathogenic fungus *Beauveria felina* EN-135 in 2014. The relative configurations of felinone A were determined using 1D and 2D NMR spectral data. Although the use of Mosher's method to determine the absolute configurations of **1** failed, its absolute configuration was tentatively assigned by comparison of CD spectral data with that of (*S*)-2-acetyl-3,6-dihydroxycyclohex-2-enone[6] to be 3*R*, 6*R*, and 7*S*.

In the following year, two azaphilone derivatives, fusaraisochromenone (**2**)[7] and hypoillexidiol (**3**),[8] which are diastereoisomers of felinone A, were isolated from the broth extracts of the endophytic fungus *Fusarium* sp. PDB51F5 and *Hypoxylon* sp. BCRC 12F 0687, respectively. Although the stereochemistry at the C3 position of fusaraisochromenone (**2**) was unclear, the absolute stereochemistry of **2** regarding a *cis*-diol moiety was assigned by the same method as that used for felinone A (**1**). The absolute configuration of hypoillexidiol (**3**),

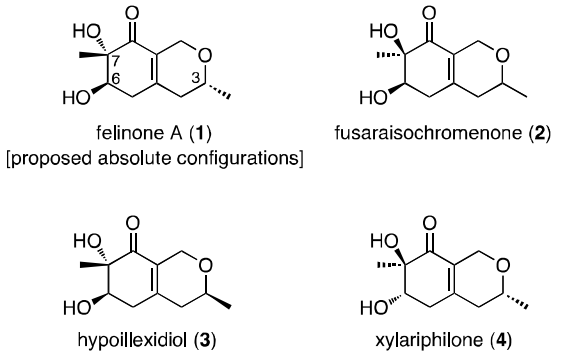

Fig. 1. Structures of azaphilone derivatives.

which is a diastereoisomer at the C3 position of felinone A (**1**), was not determined. The relative stereochemistry of hypoillexidiol was assigned only using NOESY analysis.

In 2016, Rukachaisirikul and co-workers reported the isolation and structural determination of a new azaphilone derivative **4**, named xylariphilone, from the seagrass-derived fungus *Xylariales* sp. PSU-ES163.[9] The relative configuration of xylariphilone (**4**) was assigned from coupling constants and selected NOEDIFF results. In addition, the absolute configuration of xylariphilone (**4**) was determined through

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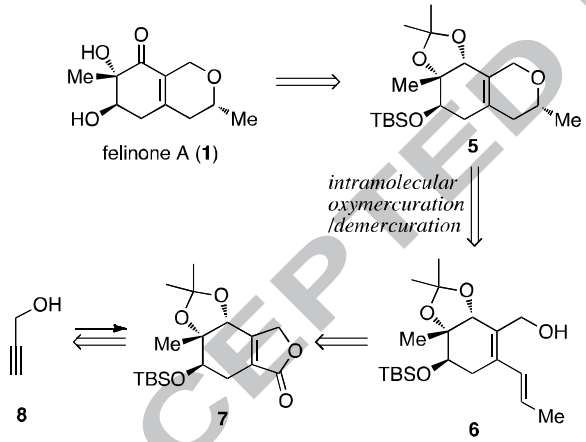
analysis of CD spectral data as 3*S*, 6*R* and 7*S*. The relative stereochemistry of xylariphilone (**4**) is identical with that of hypoillexidiol (**3**), but the sign of optical rotation is opposite [hypoillexidiol (**3**): $[\alpha]_D$ +231 (*c* 0.09, MeOH),[8] and xylariphilone (**4**): $[\alpha]_D$ –25.1 (*c* 0.50, $CHCl_3$)[9]]. Thus, hypoillexidiol is an enantiomer of xylariphilone, and the absolute configuration of hypoillexidion is 3*R*, 6*S* and 7*R*.

Very recently, we reported that the synthesis of polyketide having a dihydroxy-methylcyclohexenone nucleus was similar to that of felinone A (**1**).[10,11] Our previous study[11] based on Shi asymmetric epoxidation, regioselective epoxide ring opening, and diastereoselective dihydroxylation, was achieved *via* enantioselective construction of the dihydroxy-methylcyclohexenone skeleton of these azaphilone derivatives. The present report describes the asymmetric synthesis of felinone A using the previously reported methodology, leading to revision of its absolute configuration.

Results and discussion

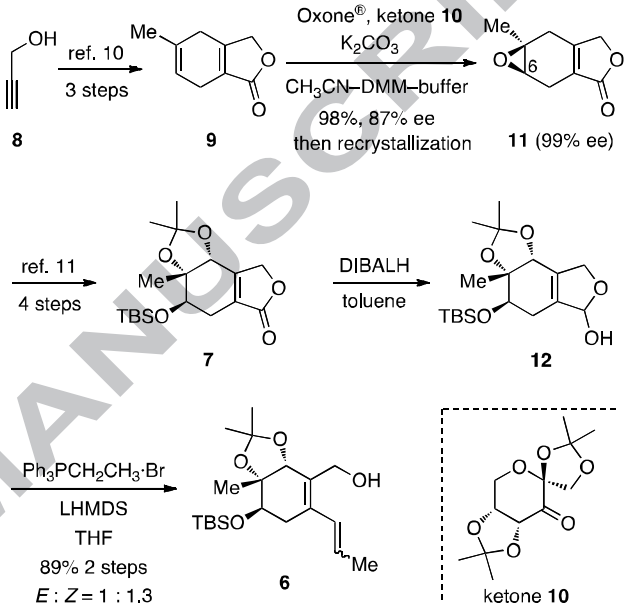
The synthetic plan is outlined in Scheme 1. Target molecule **1** would be synthesized from compound **5** by cleaving protective groups and transforming allyl alcohol to a conjugated enone part by oxidation. The bicyclic skeleton of hexahydroisochromene derivative **5** would be constructed by intramolecular oxymercuration/demercuration of the dienyl alcohol **6**, derived from the optically active bicyclic lactone **7** in two steps, reduction of the lactone ring to a cyclic hemiacetal moiety, followed by Wittig reaction. The optically pure (99% *ee*) bicyclic lactone **7** could be derived easily from propargyl alcohol (**8**) in eight steps using a previously reported method.[10,11]



Scheme 1. Synthetic plan for felinone A (**1**).

The synthesis began with installation of a conjugated diene moiety to the known bicyclic lactone **7**, prepared in an optically pure form from propargyl alcohol over eight steps, including chemo- and enantioselective epoxidation (Scheme 2). The bicyclic lactone **9**, which was a precursor of enantioselective epoxidation, was derived from propargyl alcohol (**8**) as a starting material in three steps using a previously reported method. Chemo- and enantioselective epoxidation of **9** with Oxone® and Shi catalyst **10** prepared from D-fructose gave the epoxide **11** in 98% yield with an 87% enantiomeric excess.[12-14] The absolute stereochemistry of the newly formed asymmetric carbon at C6 position was confirmed to be the *R* configuration using a modified Mosher's method.[11] After purification by recrystallization, transformation of enantiomerically pure **11** (99% ee) to the highly oxygenated bicyclic lactone gave **7** in four steps with high diastereoselectivity.

Construction of the conjugated diene on bicyclic lactone **7** was achieved in two steps: reduction of carbonyl group of **7** with DIBALH at –78 °C to hemiacetal **12**, followed by Wittig reaction of the resulting crude product **12** using a combination of ethyl triphenylphosphonium bromide and lithium hexamethyldisilazane in THF to afford alcohol **6** in 89% yield as a 1:1.3 mixture of *E*/*Z* isomers. Although many different reaction conditions for Wittig olefination (*e.g.*, bases, phosphonium reagents, solvents, temperatures) and for Julia olefinations were used, all attempts gave a 1:1 to 1:3 mixture of *E*/*Z* isomers.

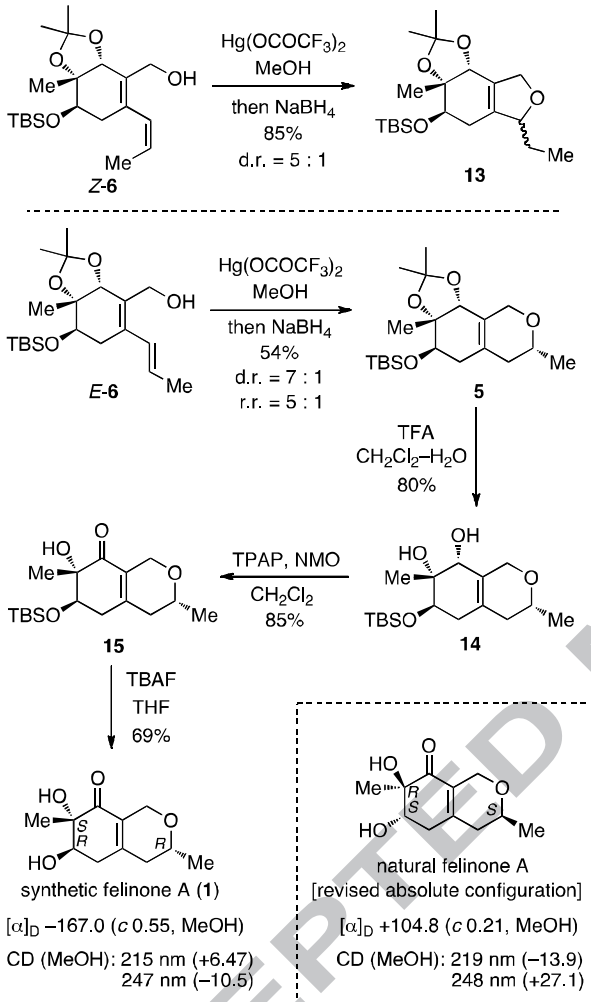


Scheme 2. Asymmetric synthesis of the oxymercuration precursor **6**.

After synthesis of alcohol **6** containing a conjugated diene, our efforts were focused on the synthesis of felinone A (**1**) *via* construction of a hexahydroisochromene skeleton through intramolecular oxymercuration, followed by demercuration. After separation of the *E*/*Z* isomers using HPLC, intramolecular oxymercuration of *E*- and *Z*-**6** were conducted as shown in Scheme 3. Intramolecular oxymercuration of *Z*-**6** with mercury(II) trifluoroacetate in methanol, followed by demercuration with 3 M NaOH and sodium borohydride gave the undesirable hexahydroisobenzofuran derivative **13** produced by 5-*exo* type cyclization as a 5:1 diastereomixture in 85% yield. In contrast, treatment of *E*-**6** with the same protocol afford the desired hexahydroisochromene derivative **5** in 54% yield with 7:1 diastereoselectivity and 5:1 regioselectivity. Although the relative configuration of **5** could not be confirmed, even after extensive spectroscopic analysis including NOESY experiments, the relative configurations of three asymmetric carbons were determined by X-ray crystallography of final compound **1**.[15] Although no details exist about the difference in oxymercuration reactions between *Z*-**6** and *E*-**6**, cyclization of *E*-**6** was thought to occur *via* cyclic mercurium ion to afford the desired product as a major cyclized product. However, reaction of *Z*-**6** occurred by cyclization *via* allyl cation species, because the hydroxyl group

and reaction point of the cyclic mercurium ion could not approach with the conformation of the transition state.

Treatment of **5** with trifluoroacetic acid (TFA) in CH_2Cl_2–H_2O for 1 h selectively cleaved the acetonide group to afford **14** in 80% yield. After Ley oxidation[16,17] of the diol **14** to **15**, treatment of the resulting ketone **15** with tetra-*n*-butylammonium fluoride (TBAF) provided the target compound **1** in 69% yield. Both ^{1}H- and ^{13}C-NMR spectral data were identical with data



Scheme 3. Synthesis of felinone A (**1**).

reported for **1**.[5] The optical rotation of synthetic 3*R*,6*R*,7*S*-**1** [$[\alpha]_D$ –167.0 (*c* 0.55, MeOH)] was opposite to that of natural felinone A [$[\alpha]_D$ +104.8 (*c* 0.21, MeOH)]. In addition, the circular dichroism spectra for synthetic **1** indicated a positive cotton effect at 215 nm and a negative effect at 247 nm, which were opposite of those for a natural sample[5] [negative effect at 219 nm, and positive effect at 248 nm]. To confirm the absolute configuration of synthetic **1**, a modified Mosher's method of **1** was carried out.[18] From the analysis of ^{1}H NMR spectra of MTPA esters derived from **1** with (*R*)- or (*S*)-MTPACl, the absolute stereochemistry of the asymmetric carbon at C6 position was reconfirmed to be the *R* configuration. Therefore, the absolute configuration of natural felinone A (**1**) was revised to be 3*S*, 6*S* and 7*R*.

In conclusion, the first total synthesis of azaphilone derivative felinone A was accomplished. The synthesis featured Shi asymmetric epoxidation of a bicyclic lactone, and intramolecular oxymercuration/demercuration for construction of the dihydropyrane ring. The absolute configuration of felinone A was revised to be 3*S*, 6*S*, and 7*R*.

Acknowledgments

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18. The detailed experimental results are described in the Supporting Information.

Supplementary Material

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Highlights

- Asymmetric total synthesis of azaphilone derivative felinone A was accomplished.
- The absolute configuration of felinone A was revised.
- Construction of the dihydropyrane ring by intramolecular oxymercuration/demercuration.