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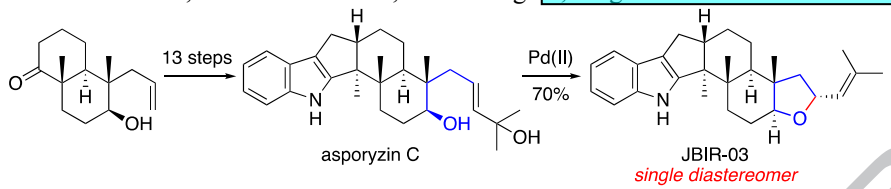

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Total synthesis of JBIR-03 and asporyzin C

Tetsuro Murokawa, Masaru Enomoto*, Takaaki Teranishi, Yusuke Ogura, Shigefumi Kuwahara*

Laboratory of Applied Bioorganic Chemistry, Graduate School of Agricultural Science, Tohoku University, 468-1 Aramaki-Aza-Aoba, Aoba-ku, Sendai 980-0845, Japan

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ABSTRACT

The first enantioselective total synthesis of JBIR-03 and asporyzin C, indole diterpenoids of fungal origin exhibiting a range of pharmacologically important biological activities, has been accomplished from a known bicyclic keto alcohol in 13 and 14 steps, respectively. A hydroxy-directed cyclopropanation and Pd(II)-mediated indole ring formation were exploited as the key steps to obtain a pivotal pentacylic intermediate, which was converted into asporyzin C via chain elongation using cross-metathesis and then into JBIR-03 by Pd(II)-catalyzed tetrahydrofuran ring formation in an exclusively diastereoselective manner.

Indole diterpenoids constitute a large family of fungal metabolites that are characterized by a hybrid molecular structure composed of an indole nucleus as a common unit and a cyclic diterpenoid moiety of high structural diversity [1]. Quite a few members of this family are known to exhibit pharmacologically important biological effects such as tremorgenic [2], antiviral [3], antitumor [4], insecticidal [5], and antimicrobial activities [6]. JBIR-03 (**1**) is an indole diterpene isolated first from *Dichotomomyces cejpii* var. *cejpii* NBRC 103559 [7] and later from a marine-derived strain of *Aspergillus oryzae* [8] and of *D. cejpii* [9] (Fig. 1). This fungal alkaloid features a tetrahydrofuran (THF) ring unit at the rightmost portion of the hexacyclic ring system, which is a rare structural motif in indole diterpenoids [1,7], and shows anti-MRSA, antifungal, and insecticidal activities with no cytotoxicity against human HT-1080 fibrosarcoma cells at a concentration of 100 μM [7,8]. It is also reported that **1** acts as an antagonist for cannabinoid receptors and the related orphan receptor GPR18 [9]. On the other hand, asporyzin C (**2**), a pentacylic indole diterpene isolated together with JBIR-03 (**1**) from *A. oryzae*, exerts potent antibacterial activity against *Escherichia coli* [8]. In spite of the promising biological properties as a potential lead for the development of various pharmaceuticals and agrochemicals, no synthetic studies on **1** and **2** have been reported so

* Corresponding author. Tel./fax: +81-22-757-4435; e-mail: shigefumi.kuwahara.e1@tohoku.ac.jp (S.K.), masaru.enomoto.a2@tohoku.ac.jp (M.E.).

far, which prompted our synthetic efforts toward the two indole diterpenoids. As part of our ongoing studies on the total synthesis of indole diterpenoids and related natural products [10], we describe herein the first enantioselective total total synthesis of **1** and **2** [11,12].

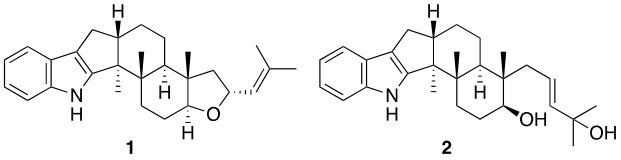
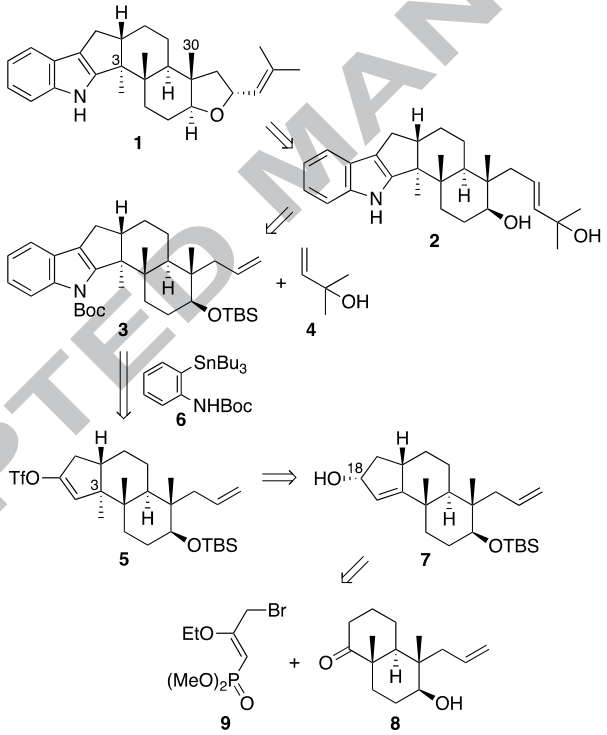


Figure 1. Structures of JBIR-03 (**1**) and asporyzin C (**2**).

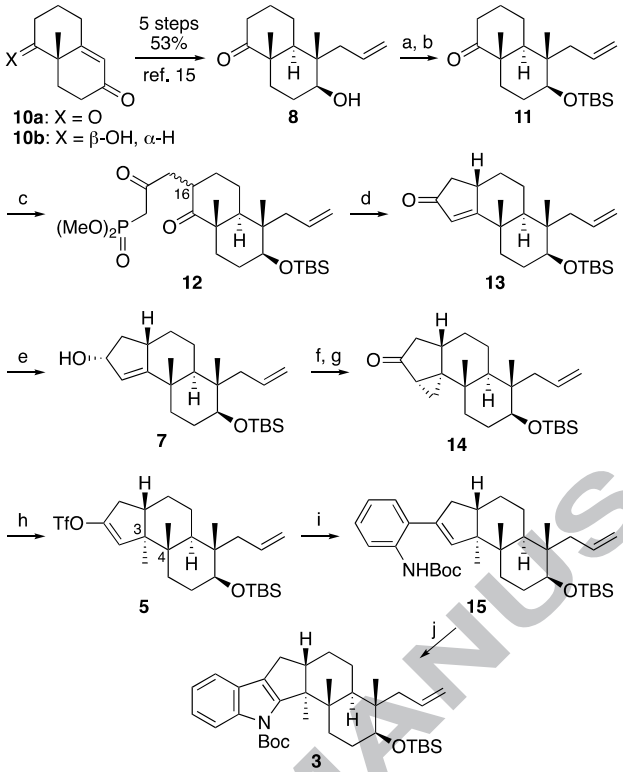
Our retrosynthetic analysis of JBIR-03 (**1**) and asporyzin C (**2**) is outlined in Scheme 1. We considered that the THP ring-containing hexacyclic compound **1** would be obtainable by Pd(II)-catalyzed ring closure of the pentacyclic olefinic diol **2**. The allylic alcohol moiety on the side chain of **2** would be installable by cross-metathesis between allyl-substituted pentacycle **3** and 2-methyl-3-penten-2-ol **4**. The preparation of **3** would be possible by following basically our synthetic strategy previously developed for the total synthesis of paspalinine [10b], a representative member of the hexacyclic tremorgenic indole diterpenoids which lack the C30 methyl group [13]. Thus, compound **3** was retrosynthetically dissected into tricyclic enol triflate **5** and *o*-stannylated aniline derivative **6** with the intention of assembling them by the Stille coupling reaction followed by Pd(II)-mediated indole ring formation. The enol triflate **5** bearing an α-oriented angular methyl group at C3 would be prepared from allylic alcohol **7** by a three-step sequence: (1) hydroxy-directed diastereoselective Simmons–Smith cyclopropanation to establish the C3 stereochemistry; (2) oxidation of the resulting cyclopropyl alcohol to the corresponding cyclopropyl ketone derivative; and (3) reductive opening of the cyclopropane ring followed by in situ trapping of the resultant enolate intermediate with Comins' reagent. The tricyclic alcohol **7** would be available by alkylation of a protected form of known bicyclic ketone **8** with bromo phosphorate **9** and a subsequent three-step manipulation that involves the installation of the α-oriented C18 hydroxy functionality by diastereoselective reduction of the corresponding tricyclic ketone intermediate.



Scheme 1. Retrosynthetic analysis of **1** and **2**.

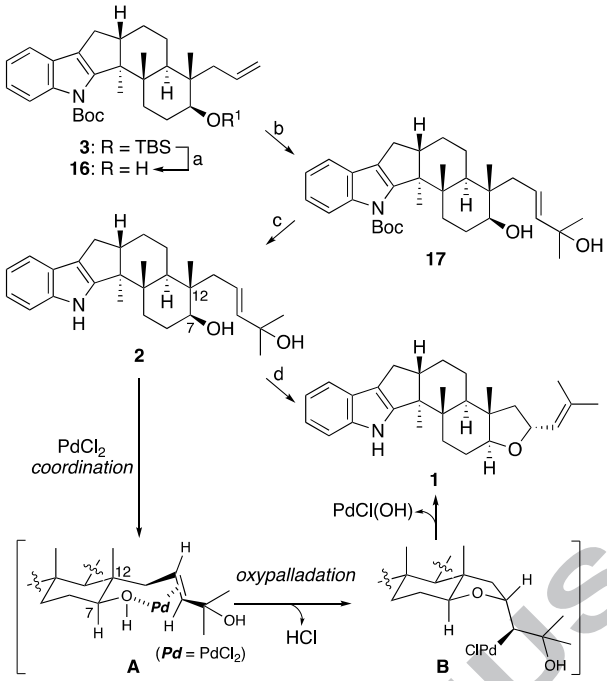
The preparation of the pentacyclic intermediate **3** is shown in Scheme 2. The bicyclic keto alcohol **8** employed as the starting material in this synthesis was obtained in 5 steps from optically enriched (+)-Wieland-Miescher ketone **10a** ($[\alpha]_D^{26}$ +102 (*c* 1.04, toluene)) [14] according to Smith's protocol [15]. The enantiomeric excees of **10a** was determined to be >99:1 by analyzing the ^{1}H NMR spectra of the (*R*)- and (*S*)-MTPA esters of alcohol **10b**, which was obtained by reduction of **10a** with $NaBH_4$ in $MeOH/CH_2Cl_2$ [16]. The alcohol **8** was treated with TBSOTf and 2,6-lutidine in CH_2Cl_2 to give the corresponding TBS ether **11** along with a small amount of its silyl enol ether, the latter of which (oversilylated by-product) could readily be converged into **11** by exposing the crude reaction mixture to aqueous HCl in acetone, furnishing **11** in 98% yield. Alkylation of **11** with the bromide **9** [17] and subsequent chemoselective hydrolysis of the enol ether moiety of the resulting product provided **12** as an epimeric mixture at the C16 position. Subjection of **12** to the intramolecular Horner–Wadsworth–Emmons reaction brought about a stereoconvergent cyclization to afford cyclopentenone derivative **13** as a single diastereomer, which was then reduced with L-Selectride® to give allylic alcohol **7** in a completely stereoselective manner. The hydroxy-directed Simmons–Smith cyclopropanation of **7** [18] and the Parikh–Doering oxidation of the resulting cyclopropyl alcohol afforded cyclopropyl ketone **14** in a diastereomerically pure form. Reductive cleavage of the cyclopropane ring of **14** was implemented by its exposure to sodium naphthalenide in THF in the presence of *t*-BuOH as a proton source, generating an enolate intermediate, which was then trapped with Comin's reagent to deliver enol triflate **5** with the *anti* stereochemistry between the contiguous C3/C4 quaternary stereocenters correctly installed. Finally, the Stille coupling of **5** with the

stannane **6** [19] under Corey's conditions [20] followed by Pd(II)-mediated oxidative indole ring formation [10b,21] from the resulting product **15** completed the preparation of **3**.



Scheme 2. Preparation of the pentacyclic core structure of **1** and **2**. Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 10 min; (b) 1 M aq. HCl, acetone, 0 °C, 1 h, 98% (2 steps); (c) LDA, **9**, THF/HMPA, –78 °C to rt, overnight, then 1 M aq. HCl, acetone, 0 °C to rt, 8 h; (d) Cs_2CO_3, DME, 50 °C, overnight, 38% (2 steps) (66% based on recovered **11**); (e) LiBH(*s*-Bu)$_3$, THF, –78 °C, 20 min, 89%; (f) CH_2I_2, Et_2Zn, CH_2Cl_2, 0 °C, 1 h, 63%; (g) DMSO, SO_3·Py, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h, 92%; (h) Na($C_{10}H_8$), *t*-BuOH, THF, –78 °C, 1 h, then Comins' reagent, THF/HMPA, –78 °C, 30 min, 50%; (i) **6**, $Pd(PPh_3)_4$, CuCl, LiCl, DMSO/THF, 60 °C, overnight, 81%; (j) $Pd(OCOCF_3)_2$, NaOAc, DMSO/THF, 60 °C, overnight, 63%.

With the pivotal intermediate **3** in hand, we proceeded to the final stage of the total synthesis of **1** and **2** (Scheme 3). Removal of the TBS protecting group in **3** was best performed by treating **3** with aqueous HCl in acetone/THF, giving **16** in 94% yield; other reaction conditions such as TBAF/THF, HF·Py/THF, and TFA/CH_2Cl_2 resulted in unsatisfactory outcomes. To install the side chain moiety of asporyzin C (**2**), the olefin **16** was subjected to cross-metathesis with 2-methyl-3-buten-2-ol (**4**) to provide **17** [10a]. Deprotection of the Boc group in **17** was conducted by heating a mixture of **17** and silica gel under reduced pressure [22], affording **2** in 85% yield. The ^{1}H and ^{13}C NMR spectra of the synthetic product were identical with those of natural asporyzin C. Cyclization of **2** into JBIR-03 (**1**) was achieved in an exclusively diastereoselective manner by exposing the olefinc diol **2** to a catalytic amount of $PdCl_2(MeCN)_2$ in THF at 0 °C according to a protocol reported previously by Uenishi and co-workers for analogous transformations [23]. Based on the mechanism proposed by them, we speculated the selective formation of **1** from **2** proceeded as follows: (1) coordination of $PdCl_2$ to the equatorially oriented C7-OH and the double bond on the side chain to form π-complex **A**; (2) *syn*-oxypalladation leading to σ-complex **B**; and (3) β-elimination of PdCl(OH) to afford **1**. The ^{1}H and ^{13}C NMR spectra of **1** were identical with those of natural JBIR-03 [7].



Scheme 3. Completion of the total synthesis of **1** and **2**. Reagents and conditions: (a) 2 M aq. HCl, acetone/THF, rt, 3 d, 94%; (b) **4**, 2nd-generation Grubbs catalyst, CH_2Cl_2, reflux, 1.5 h, 71%; (c) SiO_2, 100 °C, ca. 900 Pa, 20 min, 85%; (d) $(MeCN)_2PdCl_2$, THF, 0 °C, 10 min, 70%.

In conclusion, the first total synthesis of asporyzin C (**2**) has been accomplished from the known Wieland–Miescher ketone derivative **7** by a 13-step sequence that involves the highly diastereoselective installation of the α-oriented C3-methyl group (**7** → **14** → **5**), Pd(II)-mediated oxidative indole ring formation (**15** → **3**), and cross-metathesis to construct the side chain moiety (**16** → **17**). The exclusively diastereoselective ring closure of **2** to complete the first total synthesis of JBIR-03 (**1**) was efficiently achieved by Pd(II)-catalyzed tetrahydrofuran ring formation. Synthetic studies on related indole diterpenes such as asporyzins A and B are also in progress, and will be reported in due course.

Acknowledgments

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Supplementary Material

Supplementary data (experimental procedures, characterization data, and NMR spectra) associated with this article can be found, in the online version, at

Highlights

The first total synthesis of JBIR-03 and asporyzin C has been achieved.
Pd(II)-catalyst enables diastereoselective cyclization of asporyzin C into JBIR-03.
Hydroxy-directed cyclopropanation is useful for installation of an angular methyl.