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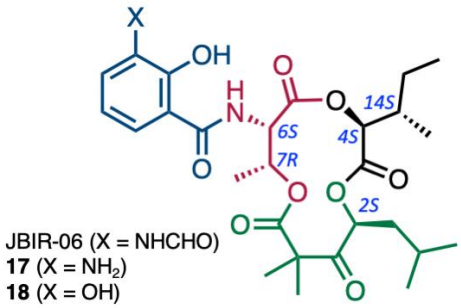
Total Syntheses and Configuration Assignments of JBIR-06 and Related Depsipeptides

Chie Hamada, Yoshinosuke Usuki,* Daiki Takeuchi, Hikaru Ogawa, Ryota Abe, and Tetsuya Satoh

Department of Chemistry, Graduate School of Science, Osaka City University, 3-3-138 Sugimoto, Sumiyoshi, Osaka 558-8585, Japan

Supporting Information



ABSTRACT: The first total syntheses of JBIR-06 and two analogous depsipeptides, 12-membered antimycin-class antibiotics, have been accomplished via Shiina macrolactonization. Comparison of the spectroscopic data of the synthesized compounds with those reported for natural products verified that the absolute configutation of the natural products was (*2S*, *4S*, *6S*, *7R*, *14S*).

Antimycin-class antibiotics contain a macrocyclic ring (9-, 12-, 15-, or 18-membered) with a 3-(formylamino)-2-hydroxybenzoic acid attached to an L-threonine moiety via an amide bond.[1] The ring size and ring substitution result in much structural diversity. Antimycin-type antibiotics have attracted significant interest because of their diverse biological activities, including anticancer, antifungal, and immunosuppressant properties.[2] The biosynthetic pathway for a common cyclic skeleton toward antimycin family production with high structural diversity has been investigated, and the construction of analogues of this scaffold from natural sources has been attempted.[3]

JBIR-06 (**1**) was isolated from *Streptomyces* sp. ML-55 by Shin-ya and co-workers.[4] Compound **1** showed inhibitory activity against glucose-regulated protein 78 (GRP78) expression in 2-deoxy-D-glucose (2DG)-treated HT1080 cells (IC_{50}: 262 nM). High levels of GRP78 have been implicated in cancer growth and chemoresistance because of its upregulation in tumor cells.[5] GRP-78 downregulators, which accelerate apoptosis of cancerous cells, would be promising agents for targeted cancer therapies. The inhibitory activity of JBIR-06 against GRP78 expression was 130-fold lesser than that of prunustatin A (**2**),[6] a 15-membered antimycin antibiotic, suggesting that the ring size is crucial for the inhibition of increased GRP78 expression induced by 2-DG treatment (Figure 1).

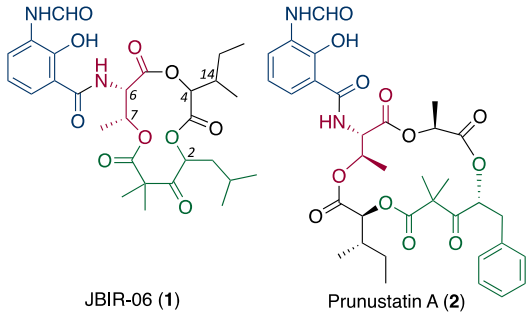


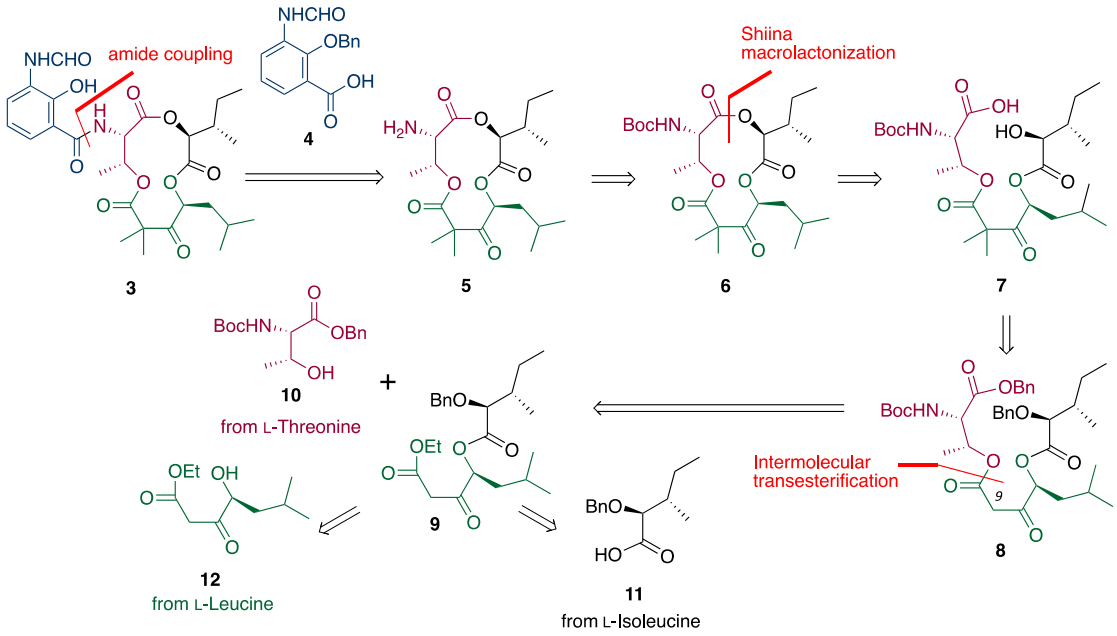
Figure 1. Structures of JBIR-06 (**1**) and Prunustatin A (**2**).

2D NMR analyses revealed that **1** is a new member of the antimycin family, and that it features a 12-membered trilactone. The absolute configuration of the threonine moiety of **1** was elucidated to be L by Marfey's method; however, the other three stereogenic centers were not determined. During our studies on the total syntheses of antimycin-type antibiotics,[7] we focused on the total synthesis and stereochemical elucidation of **1**. Recently, Awakawa and Abe et al. have reported the production of JBIR-06 and related ring-expansion compounds with reprogramming of the antimycin NRPS (nonribosomal peptide synthase)/PKS (polyketide synthase) assembly line.[8] They carried out the acid-catalyzed degradation of their products and GC-MS analyses with a chiral column to confirm that the stereochemistry of each building block in JBIR-06 was L. Therefore, we

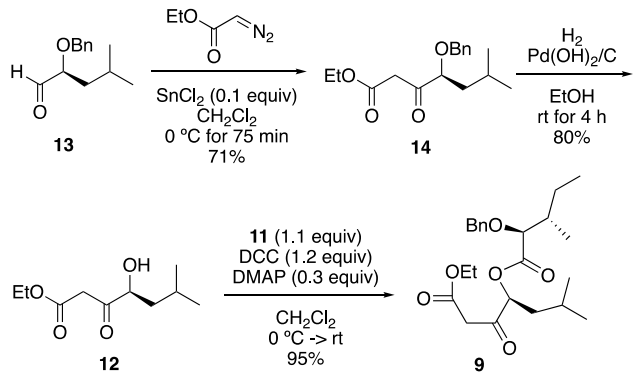
focused on the synthetic confirmation of the reported stereochemistry of **1**. Herein, we report our endeavors for the preparation of 12-membered trilactone derivatives.

We presumed that JBIR-06 has the (*2S*, *4S*, *6S*, *7R*, *14S*) configuration. We embarked on a synthetic route to the desired compound **3** by cyclization via Shiina macrolactonization[9] for the construction of the 12-membered trilactone core, followed by amidation of **4** with **5** and deprotection (Scheme 1). Conceptually, bis-benzyl protected **8** would be prepared by the intermolecular transesterification[10] of **9** and *N*-Boc-L-threonine benzyl ester **10**. Mechanistic studies suggest that the transesterification of β-keto esters proceeds via the corresponding acyl ketene intermediate;[10c,d] that is the other ester moieties in **9** and **10** would not be effective during the conversion into **8**. Compound **9** would be obtained by the condensation of **11**,[11] which is derived from L-isoleucine, with β-ketoester **12**.

Scheme 1. Retrosynthesis of the Target Molecule (3)



Scheme 2. Synthesis of Fragment 9



The reaction of aldehyde **13**, derived from L-leucine, with ethyl diazoacetate in the presence of $SnCl_2$ (0.1 equiv) provided the corresponding β-keto ester **14** in 71% yield as a tautomeric and rotameric mixture.[12] Hydrogenolysis of **14** in the presence of $Pd(OH)_2$ in EtOH resulted in removal of the benzyl ether protecting group to afford compound **12** in 80% yield. Fragment **9** was prepared by coupling **11** with **12** in the presence of DCC and DMAP in 95% yield (Scheme 2).

Slow addition of **10** in toluene to the mixture of **9** and anhydrous $CuSO_4$ (0.7 equiv) in toluene over 3 h at 100 °C and subsequent reflux for overnight successfully furnished intermolecular transesterification to provide the desired **8** in 59% yield. Double methylation at the C9 position of **8** was achieved using iodomethane (2.9 equiv) and Na_2CO_3 (9.2 equiv) in DMSO at rt for 4 h to provide the corresponding **15** in 83% yield. Reductive deprotection of the benzyl groups in the presence of $Pd(OH)_2$ in EtOAc under H_2 atmosphere afforded the desired seco acid **7** in quantitative yield (Scheme 3).

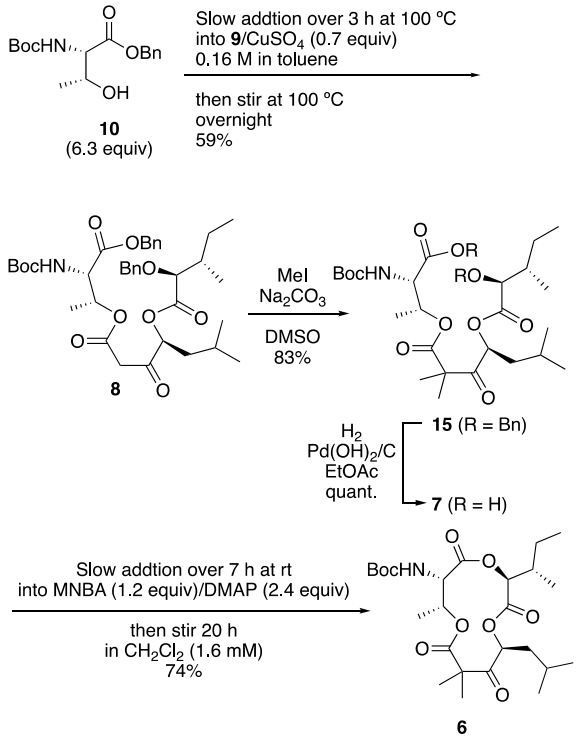
We next adapted Shiina macrolactonization with MNBA (2-methyl-6-nitrobenzoic anhydride)/DMAP for the ring closure of **7**,[9,13] and examined several sets of conditions. In each case, dimer formation was not observed by ESI/MS. Finally, we found that under high-dilution condition (1.6 mM), slow addition of **7** into MNBA /DMAP over 7 h at rt and subsequent stirring for 20 h successfully furnished the key 12-membered trilactone **6** in 74% yield. The *gem*-dimethyl effect facilitated this macrolactonization: seco acid without a *gem*-dimethyl group would not cyclize under these conditions.[14]

At endgame of the total synthesis of **3**, the Boc group of **6** was removed with TFA in dichloromethane to afford amine **5**. Subsequent condensation of **5** with benzyl ether **4**[15] using EDCI, HOBt, and NMM in DMF provided the corresponding amide **16** in 85% yield from **6**. Finally, reductive removal of the benzyl ether protecting group was accomplished in the presence of $Pd(OH)_2$ in EtOAc under H_2 atomosphere and the desired **3** was obtained in 91% yield (Scheme 4).

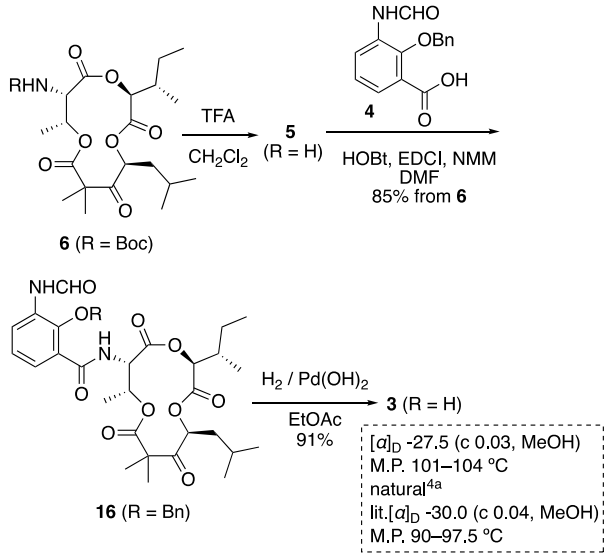
The spectral data of synthetic **3** were identical to those reported for the natural product (Table S1). The optical rotation of synthetic **3** ($[\alpha]_D$ -27.5, c 0.03, MeOH) was in good agreement with that of the natural sample ($[\alpha]_D$ -30.0, c 0.04, MeOH). Comparison of the spectroscopic data between the synthetic **3**

and natural **1** verified the absolute configuration of **1** is (*2S*, *4S*, *6S*, *7R*, *14S*).

Scheme 3. Intermolecular Transesterification and Double Deprotection/Macrocyclization



Scheme 4. Completion of the Synthesis of 3



Magarvey reported two analogous 12-membered depsipeptides **17** and **18** from *Streptomyces* sp. ML-55,[4b] whose NMR data were similar to those of JBIR-06 (**1**), except for the signals pertaining to the benzoic acid moiety. An advanced Marfey's method suggested that the threonine residue found in **17** and **18** had the L-configuration. Comprehensive analysis of 2D NMR data revealed the planar structure of **17** and **18**, as shown in Figure 2, which would be confirmed by total synthesis.

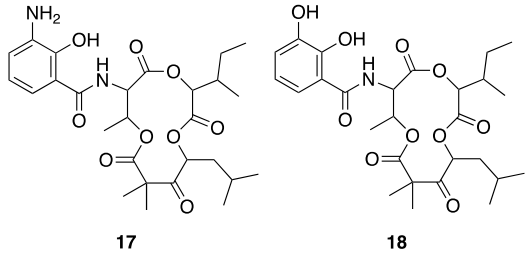
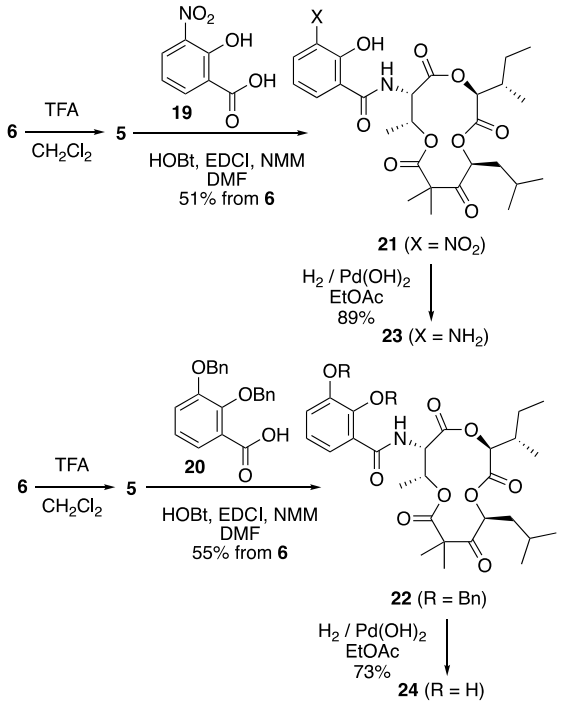


Figure 2. Structures of Two Analogous Depsipeptides **17** and **18**.

Removal of the Boc group of **6** with TFA in dichloromethane, followed by condensation of **5** with the commercially available 3-nitrosalicylic acid **19** or dibenzyl ether **20**[16] using EDCI, HOBt, and NMM in DMF provided the corresponding amide **21** or **22** in 51% or 55% yield from **6**. Reduction of **21** in the presence of $Pd(OH)_2$ in EtOAc under H_2 atmosphere afforded the desired **23** in 89% yield. Reductive removal of the benzyl ether protecting groups from **22** in the presence of $Pd(OH)_2$ in EtOAc under H_2 atmosphere provided **24** in 73% yield (Scheme 5).

Scheme 5. Endgame to the Synthesis of 23 and 24



Unfortunately, the optical rotation values of the natural products **17** and **18** are not available. The other spectral data for the synthetic **23** and **24** were in good agreement with those reported for the natural **17** and **18** (Table S2 and S3): The absolute configuration of natural **17** and **18** was assigned as (*2S*, *4S*, *6S*, *7R*, *14S*) based on the total synthesis.

In conclusion, the first total syntheses of JBIR-06 and related two depsipeptides were accomplished by Shiina macrocyclization with MNBA/DMAP. Synthetic confirmation of the absolute configuration of **1**, **17**, and **18** was thus achieved. Further studies aimed at the biological evaluation of these 12-membered trilactone antibiotics are in progress, and the results will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publication website.

Comparisons of NMR Data of Natural and Synthetic compounds (Table S1, S2 and S3), Synthetic procedures and characterization data for compounds **3**, **5**, **6**, **8**, **9**, **12**–**16**, and **21**–**24** including ^{1}H and ^{13}C NMR spectra (PDF).

AUTHOR INFORMATION

Corresponding Author

*E-mail: usuki@sci.osaka-cu.ac.jp

Author Contributions

All authors have approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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