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Total synthesis and stereochemical determination of yoshinone A

Seiichi Shinomiya [a], Arihiro Iwasaki [a], Osamu Ohno [b], Kiyotake Suenaga [a, *]

[a] Department of Chemistry, Keio University, 3-14-1, Hiyoshi, Kohoku-ku, Yokohama, Kanagawa 223-8522, Japan
[b] Department of Chemistry and Life Science, Kogakuin University, 2665-1, Nakano-Machi, Hachioji, Tokyo 192-0015, Japan

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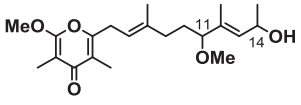
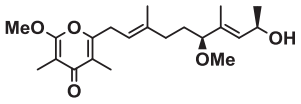
ABSTRACT

In 2014, the γ-pyrone-containing polyketide, yoshinone A, was isolated from the marine cyanobacterium *Leptolyngbya* sp. and its structure was determined. Yoshinone A inhibited differentiation of 3T3-L1 cells into adipocytes, with an EC_{50} value of 420 nM without any cytotoxicity, and therefore is expected to be a lead compound for obesity drugs. To establish its absolute configuration, and to provide sufficient amounts for further research, the total synthesis of yoshinone A was achieved through synthesis of its two possible diastereomers.

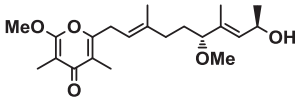


1 (Yoshinone A)

Fig. 1. The structure of yoshinone A (**1**).



1a



1b

Fig. 2. Two possible diastereomers of yoshinone A (**1a** and **1b**).

1. Introduction

Marine cyanobacteria produce interesting compounds with useful biological activities (Blunt et al., 2015). Some of these compounds, such as dolastatin 10, have been applied to the development of drugs (Costa et al., 2012). Against this background, secondary metabolites of marine cyanobacteria have been investigated and several biologically active compounds were discovered, including kurahamide (Iwasaki et al., 2014a), maedamide (Iwasaki et al., 2014b; Takayanagi et al., 2015), and jahanyne (Iwasaki et al., 2015), respectively. In a series of studies, the γ-pyrone-containing polyketide, yoshinone A (**1**) (Fig. 1), was isolated from the marine cyanobacterium *Leptolyngbya* sp. and its structure was determined in 2014 (Inuzuka et al., 2014). Yoshinone A (**1**) inhibited differentiation of 3T3-L1 cells into adipocytes with an EC_{50} value of 420 nM without any cytotoxicity. In addition, a recent study established that kalkipyrone (Graber and Gerwick, 1998) had anti-obesity activity in an *in vivo* experiment in mice (Koyama et al., 2016). Therefore, γ-pyrone compounds like yoshinone A are potential lead compounds for development of anti-obesity drugs. Furthermore, Bertin et al. recently reported that yoshinone A (**1**) showed toxicity against *Saccharomyces cerevisiae* ABC16-Monster

* Corresponding author.
E-mail address: suenaga@chem.keio.ac.jp (K. Suenaga).

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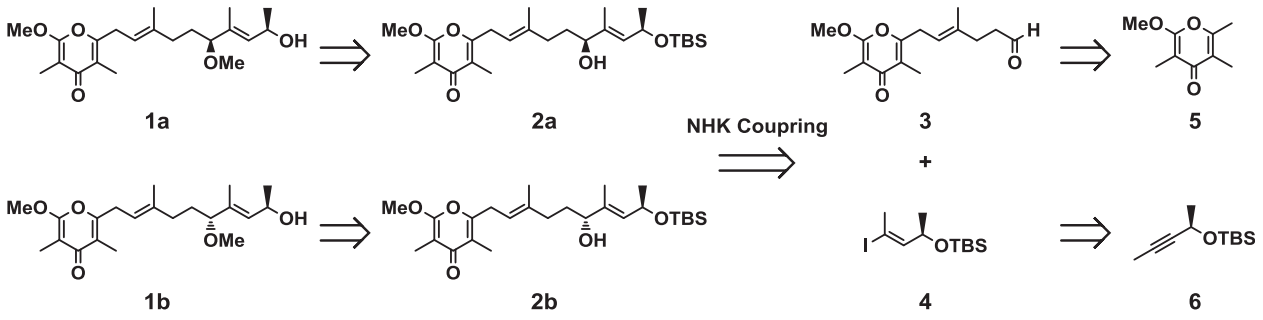
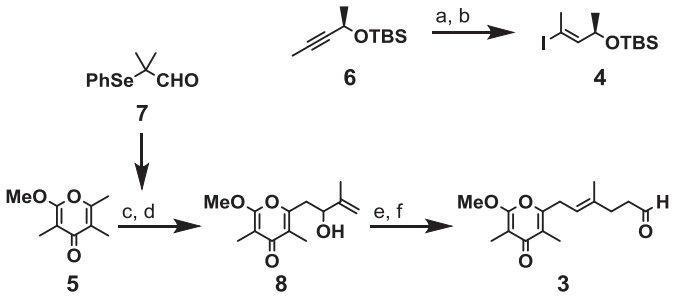
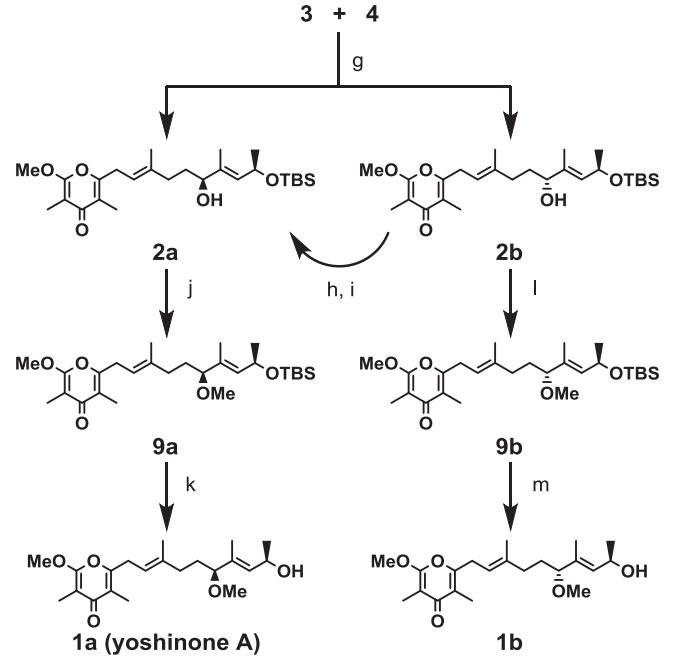


Scheme 1. Retrosynthetic analysis of yoshinone A.



Scheme 2. Synthesis of vinyl iodide **4** and aldehyde **3**: (a) $Pd(PPh_3)_2Cl_2$, $HSnBu_3$, hexanes, rt, 1 h; (b) I_2, CH_2Cl_2, 0 °C, 10 min, 49% in two steps; (c) LHMDS, THF, −78 °C, 2 h; then addition of compound **7**, 0 °C, 1 h; (d) mCPBA, CH_2Cl_2, −15 °C, 20 min; Et_3N, 0 °C, 20 min, 44% in two steps; (e) ethyl vinyl ether, $Hg(OCOCF_3)_2$, rt, 41 h; (f) toluene, reflux, 19 h, 76% in two steps.



Scheme 3. Synthesis of **1a** and **1b**: (g) $CrCl_2$, $NiCl_2$, DMSO, 35 °C, 60 h, **2a** 40%, **2b** 37%; (h) DMP, $NaHCO_3$, CH_2Cl_2, rt, 10 min; (i) (*R*)-2-methy-CBS-oxazaborolidine, $BH_3{\cdot}SMe_2$, toluene, 0 °C, 50 min, 42% in two steps; (j) $Me_3O{\cdot}BF_4$, proton sponge, CH_2Cl_2, rt, 40 min, 66%; (k) pyr·HF, pyridine, THF, rt, 4 h, 82%; (l) $Me_3O{\cdot}BF_4$, proton sponge, CH_2Cl_2, rt, 30 min, 59%; (m) pyr·HF, pyridine, THF, rt, 7 h, 92%.

strain (IC_{50} 63.8 μM) (Bertin et al., 2016). Despite the potential usefulness of **1** as described above, there are two obstacles to be overcome. The first is the scarcity of yoshinone A (**1**). To study its further biological activity, including animal experiments, more than 50 mg of **1** are needed. However, it is most difficult to obtain such amounts of yoshinone A from the marine cyanobacterium, because of its low content (*e.g.* 1.0 mg from 600 g of the cyanobacterium) and also its difficulty in cultivation of the cyanobacterium itself. This scarcity of **1** has limited further biological evaluations, and an alternative way of supplying **1** is required. Another issue is the uncertainly of the stereochemistry of yoshinone A (**1**), for which possesses two chiral centers at C-11 and C-14 (Fig. 1), and whose stereochemistries have not been established. Therefore, there are four possible stereochemical structures for yoshinone A (**1**), two diastereomers and the respective enantiomers. This uncertainty prevented a detailed structure-activity investigation of yoshinone A (**1**). The synthesis of two possible diastereomers (**1a** and **1b**) (Fig. 2), followed by comparison of the NMR data of these compounds with those of natural yoshinone A (**1**) can, however, establish the relative stereochemistry of yoshinone A (**1**). In addition, the comparison of the specific optical rotation of the synthetic standard with that of natural yoshinone A (**1**) can clarify its absolute stereochemistry.

To overcome the obstacles described above, a synthetic study on yoshinone A (**1**) was carried out through the synthesis of two possible diastereomers **1a** and **1b** (Fig. 2).

2. Results and discussion

The retrosynthetic analysis of the diastereomers **1a** and **1b** is outlined in Scheme 1. Compounds **1a** and **1b** could be synthesized from alcohols **2a** and **2b**, respectively, with the latter two being prepared simultaneously by Nozaki-Hiyama-Kishi coupling (Jin et al., 1986; Okuda et al., 1977) of aldehyde **3** and vinyl iodide **4** followed by separation. Aldehyde **3** could be assembled from the known γ-pyrone **5** (Leiris et al., 2010; Shimamura et al., 2007), whereas vinyl iodide **4** could be prepared from known alkyne **6** (Marshall and Yanik, 2000).

First, aldehyde **3** and vinyl iodide **4** were synthesized as shown in Scheme 2. The known alkyne **6** (Marshall and Yanik, 2000) was then converted into vinyl iodide **4** through *E*-selective hydrostannylation, followed by tin-iodine exchange with iodine (Smith et al., 2001).

Meanwhile, deprotonation of the known γ-pyrone **5** (Leiris et al., 2010; Shimamura et al., 2007) with LHMDS, followed by nucleophilic addition to α-phenylselenoaldehyde **7**, provided the corresponding alcohol. Subsequent oxidation of the alcohol by mCPBA and syn-elimination furnished allylic alcohol **8**. The latter was converted to the desired aldehyde **3** by mercury-mediated etherification and Claisen rearrangement (Jeso and Micaizio, 2010). The configuration of trisubstituted olefin of **3** was established as to be *E*, based on a carbon chemical shift of the vinyl methyl group (δ 16.6 ppm), which is sterically compressed (Carey et al., 1983).