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Total Synthesis of Pseudodehydrothyrsiferol

Hideaki Hioki,* Masatoshi Motosue, Yasuhiko Mizutani, Akira Noda, Tomoaki Shimoda, Miwa Kubo, Kenichi Harada, Yoshiyasu Fukuyama, and Mitsuaki Kodama

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770-8514, Japan

hioki@ph.bunri-u.ac.jp

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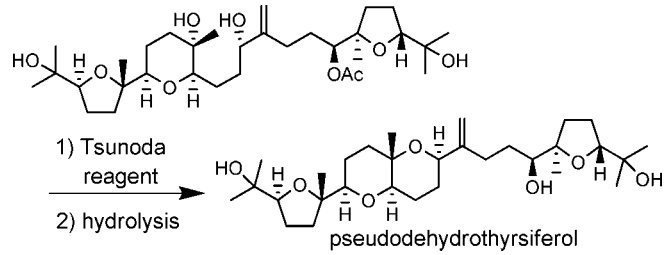
ABSTRACT



An enantioselective total synthesis of pseudodehydrothyrsiferol has been accomplished. The synthetic sequence highlights formation of the highly strained tetrahydropyran C-ring by a Mitsunobu-type S_N2 reaction with an oxygen nucleophile.

Pseudodehydrothyrsiferol (**1**), belonging to the thyrsiferol family, was isolated along with other related compounds from the red alga *Laurencia viridis* by Fernández et al.[1] Several members of the thyrsiferol family exhibit a potent and specific inhibitory effect on protein phosphatases 2A[2] and strong cytotoxic activity.[3] This family has attracted synthetic attention because of their unique structures of squalene-derived polyether combined with interesting biological activities. The characteristic structural feature of this family includes the strained tetrahydropyran C-ring adopting a twist-boat conformation to avoid an unfavorable 1,3-diaxial interaction between the angular methyl group and the side chain (Figure 1). Three groups have already completed the syntheses of thyrsiferol, thyrsiferol 23-acetate, and venustatriol among this family.[4] The key step in their syntheses was how to construct the strained tetrahydropyran C-ring. Herein we report the first enantioselective total synthesis of

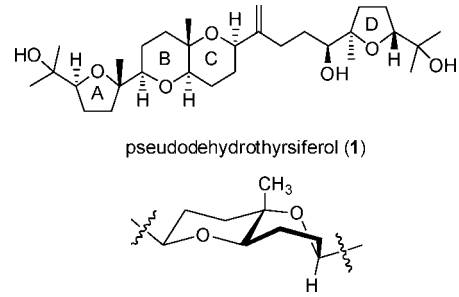


Figure 1. Structure of pseudodehydrothyrsiferol (**1**) and twist-boat conformation of C-ring in **1**.

(1) Manríquez, C. P.; Souto, M. L.; Gavín, J. A.; Norte, M.; Fernández, J. J. *Tetrahedron* **2001**, *57*, 3117–3123.

(2) (a) Matsuzawa, S.; Suzuki, T.; Suzuki, M.; Matsuda, A.; Kawamura, T.; Mizuno, Y.; Kikuchi, K. *FEBS Lett.* **1994**, *356*, 272–274. (b) Souto, M. L.; Manríquez, C. P.; Norte, M.; Leira, F.; Fernández, J. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1261–1264.

(3) Fernández, J. J.; Souto, M. L.; Norte, M. *Nat. Prod. Rep.* **2000**, *17*, 235–246.

(4) (a) Corey, E. J.; Ha, D. C. *Tetrahedron Lett.* **1988**, *29*, 3171–3174. (b) Hashimoto, M.; Kan, T.; Nozaki, K.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *J. Org. Chem.* **1990**, *55*, 5088–5107. (c) González, I. C.; Forsyth, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 9099–9108.

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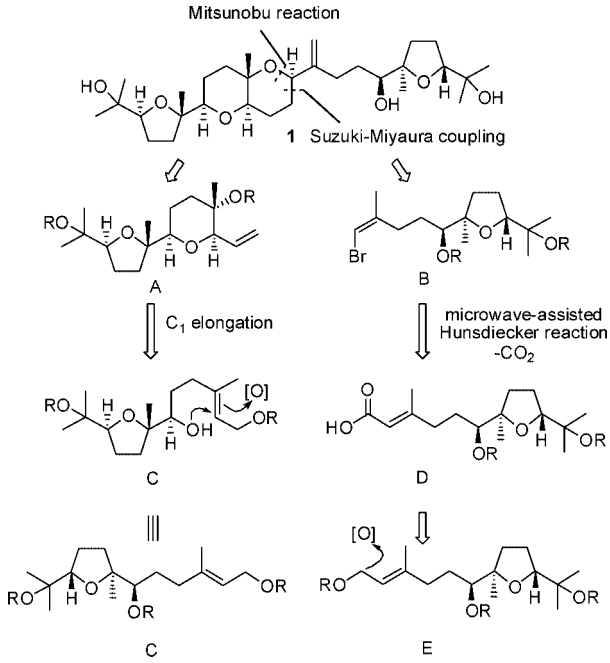
Scheme 1. Retrosynthesis of Pseudodehydrothyrsiferol (**1**).

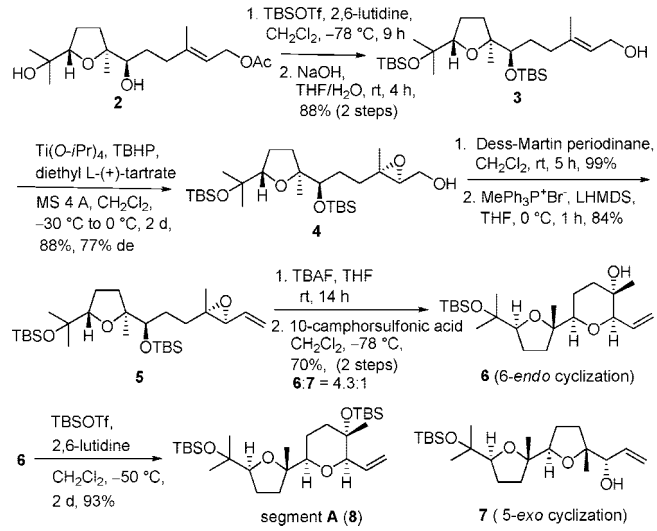


pseudodehydrothyrsiferol (**1**) featuring unique C-ring closure by a Mitsunobu-type S_N2 reaction.

Our retrosynthetic analysis is illustrated in Scheme 1. Disconnection of the target molecule at the central part leads to C_{16} segment **A** and C_{14} segment **B**, both of which have a 1,3-*trans* tetrahydrofuran ring with different configuration. They would be connected by Suzuki−Miyaura coupling. We envisioned that the key cyclization to form the C-ring would be realized by ring closure with an oxygen nucleophile. Segment **A** with tetrahydropyran ring would be synthesized from C_{15} unit **C** by oxidation and C_1 elongation. On the other hand, segment **B** would be synthesized from C_{15} unit **E**, which is the antipode of **C**, by oxidation of the primary hydroxy group. The carboxylic acid **D** would be converted to segment **B** by a stereospecific Hunsdiecker-type reaction.

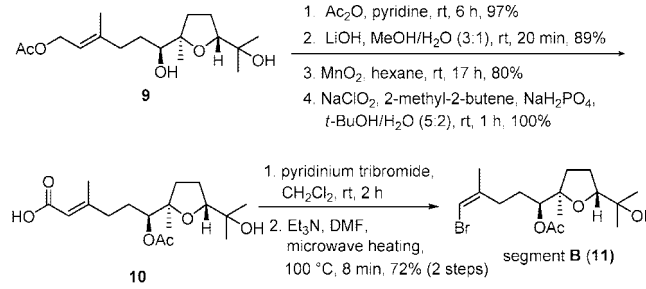
Preparation of the segments **A** and **B** began with the 1,3-*trans* tetrahydrofuran derivative **2** and its enantiomer **9**, which were prepared from the same precursor as reported previously.[5] A synthetic scheme for the segment **A** is shown in Scheme 2. After protection of two hydroxy groups in **2** as TBS ethers, the terminal acetate was hydrolyzed. The resulting allylic alcohol **3** was converted into epoxide **4** (77% de) by Sharpless asymmetric epoxidation using diethyl L-(+)-tartrate.[6] The primary alcohol in **4** was oxidized followed by Wittig methylenation to afford allyl epoxide **5**. After deprotection of the secondary TBS group in **5**, the resulting epoxy alcohol was subjected to cyclization under acidic conditions. 6-*endo* Cyclization product **6** was expected to

Scheme 2. Synthesis of Segment A



be favored over 5-*exo* product **7** because the terminal vinyl group can assist cleavage of next C−O bond.[7] The epoxy alcohol was easily cyclized even in the presence of a small amount of acid in $CDCl_3$. However, *endo*-*exo* ratio was low (**6**/**7** = 2:1). The ratio was improved to 4.3:1 when the reaction was performed at −78 °C in the presence of 0.2 equiv of 10-camphorsulfonic acid. TBS protection of the tertiary alcohol in **6** completed the synthesis of the segment **A** (**8**).

Scheme 3. Synthesis of Segment B



Segment **B** was synthesized according to the following procedure shown in Scheme 3. Starting from **9**, the secondary hydroxy group was acetylated and then terminal acetate was selectively hydrolyzed. The resulting allylic alcohol was oxidized to carboxylic acid **10** in further two steps. After bromination of **10**, the resulting dibromide was subjected to microwave assisted stereospecific decarboxylation along with debromination according to Tokuda's procedure.[8] (*Z*)-vinyl

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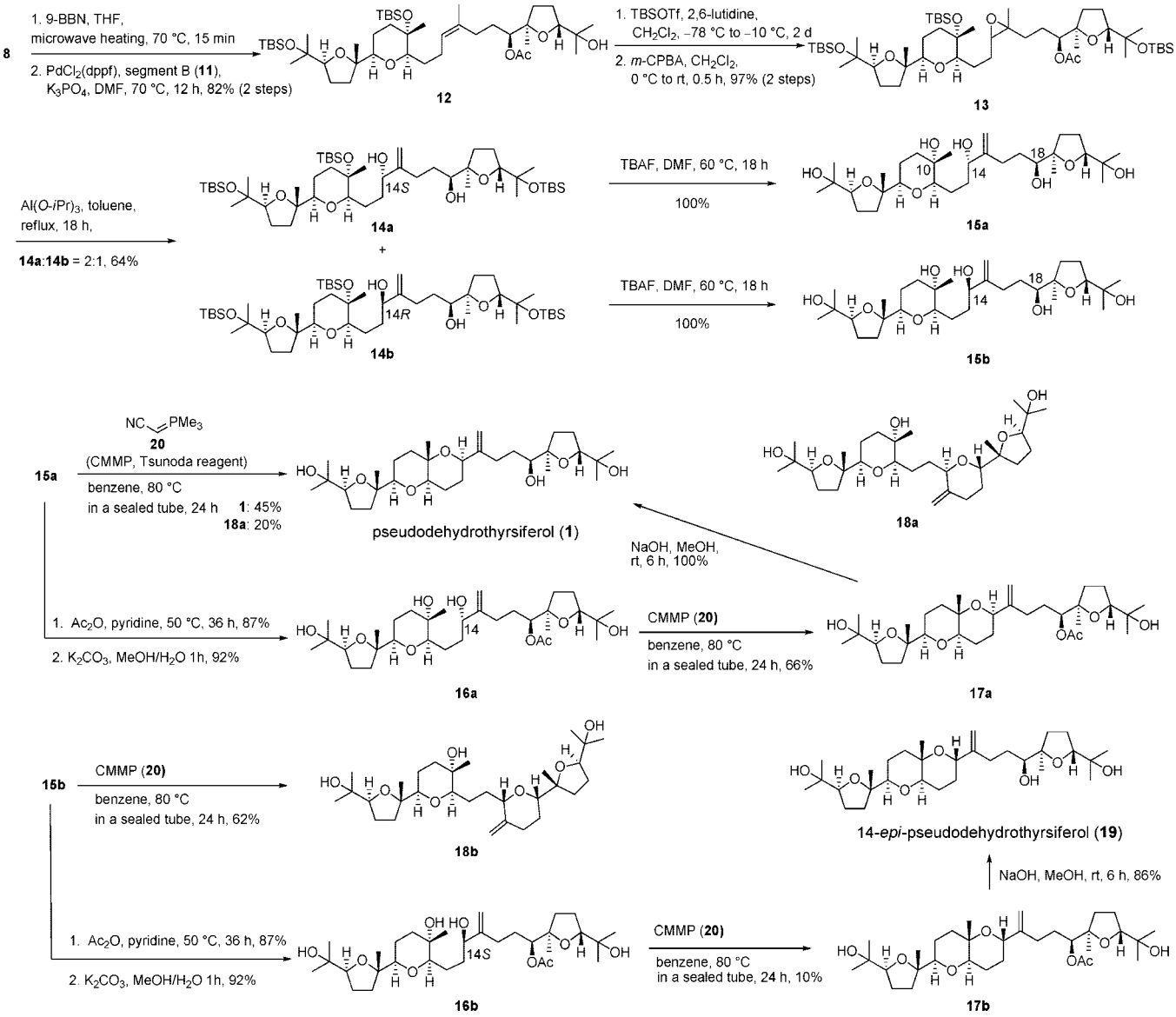
(6) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.

(7) (a) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C. K. *J. Am. Chem. Soc.* **1989**, *111*, 5330–5334. (b) Matsukura, H.; Morimoto, M.; Koshino, H.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 5545–5548.

(8) Kuang, C.; Senboku, H.; Tokuda, M. *Tetrahedron Lett.* **2001**, *42*, 3893–3896.

Scheme 4. Syntheses of Pseudodehydrothyrsiferol (**1**) and Its C-14 Epimer (**19**)



bromide **11** was mainly obtained with 20:1 stereoselectivtiy with regard to the olefin geometry.[9]

The total synthesis of **1** was achieved as shown in Scheme 4. After hydroboration of the segment **A** (**8**) with 9-BBN, microwave-assisted Suzuki−Miyaura cross-coupling[10] with the segment **B** (**11**) was carried out to give **12** in good yield. Terminal hydroxy group in **12** was protected as TBS ether and then trisubstituted alkene was converted to epoxides **13** as a 2:1 mixture of inseparable diastreomers by treatment with *m*-CPBA. This mixture was subjected to Al(O-*i*-Pr)$_4$-catalyzed isomerization to give allyl alcohols **14a** and **14b**, accompanied by deprotection of the acetate. Two diastereomers were separable by simple column chromatography at this stage. The major isomer was assigned to be 14*S* by Kusumi's method[11] after converting **14a** to (*R*)- and (*S*)-MTPA esters. Walden inversion at C-14 in **14a** is required to lead pseudodehydrothyrsiferol **1**. Tsunoda et al. reported a dehydrative cyclization of 1,5-diol to tetrahydropyran by phosphorane-type Mitsunobu reagents (Tsunoda reagent).[12] We applied this method to **1**, although they only reported nucleophilic substitution at primary carbon. The least hindered allyl alcohol at C-14 in **15a** expected to be phosphorylated among five hydroxy groups at first and subsequent intramolecular nucleophilic substitution at C-14 would take place with the inversion of configuration. A hydroxy group at C-10 is necessary to attack on C-14 for

(9) Unexpectedly, the reaction proceeded without the aid of microwave heating; however, the selectivity was slightly reduced (10:1).

(10) Navarro, O.; Kaur, H.; Mahjoor, P.; Nolan, S. P. *J. Org. Chem.* **2004**, *69*, 3173–3180.

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(12) Tsunoda, T.; Ozaki, F.; Shirakata, N.; Tamaoka, Y.; Yamamoto, H.; Itô, S. *Tetrahedron Lett.* **1996**, *37*, 2463–2466.

leading to **1**, even in the presence of another oxygen nucleophile. Upon treatment of **15a** with CMMP **20**,[13] the most reactive Tsunoda reagent, in benzene at 80 °C for 24 h, the desired pseudodehydrothyrsiferol **1** was obtained in 45% yield, along with 20% of isomer **18a** formed by an undesired nucleophilic substitution with a hydroxy group at C-18. The reaction proceeded with the complete inversion of configuration at C-14. The ^{1}H and ^{13}C NMR spectra of synthetic compound **1** were in agreement with those of the natural product **1**. The synthetic sample showed negative optical rotation in accordance with the natural compound, however the value was much smaller than that of the natural product. ($[\alpha]^{25}_{D}$ −2.7, lit.[1] $[\alpha]^{25}_{D}$ −13.1). Interestingly, when C-14 epimer **15b** was applied to the same cyclization condition, 14-*epi*-pseudohydrothyrsiferol (**19**) was not obtained but isomer **18b** in 62% yield. The secondary alcohol at C-18 in both isomers **15a** and **15b** was protected by an acetyl group in two steps to avoid the undesired cyclization by the C-18 oxygen nucleophile. The yield of the cyclization for **16a** was improved to 66% as expected. On the other hand, the reaction of **16b** did not proceed smoothly. **17b** was obtained in only 10% yield along with 55% of stating material. Pseudodehydrothyrsiferol (**1**) and 14-*epi*-pseudodehydrothyrsiferol (**19**) were synthesized by hydrolysis of the acetate in **17a** and **17b**. In these cyclizations, ring closure to strained C-ring with a twist-boat conformation occurred more easily than less-strained C-ring with chair conformation. Shirahama et al. reported adverse results in case of intramolecular cyclization of epoxy alcohol.[4b] The striking difference is intriguing but ambiguous at this stage.

In summary, the first total synthesis of pseudodehydrothyrsiferol (**1**) has been completed. The present synthesis emphasizes the effective formation of the strained tetrahydropyran C-ring, which is the crucial issue in the synthesis of thyrsiferols. Dehydrative cyclization between secondary and tertiary 1,5-diol to form a strained tetrahydropyran C-ring was successfully achieved along with complete Walden inversion at C-14 utilizing the Tsunoda reagent. Our synthesis exemplifies a new approach to form highly strained cyclic ethers. It would be applicable to various hindered diols.

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Supporting Information Available: Experimental procedures, characterization data, and ^{1}H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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