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Total synthesis of (3*R*,16*E*,20*E*,23*R*)-(−)-eushearilide and structural determination of naturally occurring eushearilide

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ABSTRACT

An asymmetric total synthesis of the proposed structure of (16*Z*,20*E*)-eushearilide, a novel 24-membered macrolide, was achieved via an enantioselective aldol reaction and 2-methyl-6-nitrobenzoic anhydride-mediated macrolactonization. The obtained synthetic compounds were not identical to the natural product. The newly proposed most likely structure of eushearilide, (±)-(16*E*,20*E*)-eushearilide, was determined on the basis of detailed NMR analysis, and (3*R*,16*E*,20*E*,23*R*)-(−)-eushearilide was successfully synthesized. A comparison of the optical rotation of (3*R*,16*E*,20*E*,23*R*)-(−)-eushearilide with that of the natural product confirmed that the true structure of naturally occurring eushearilide is the (3*S*,16*E*,20*E*,23*S*)-(+)-form.

Introduction

Eushearilide (**1**) was first isolated from a culture of the fungus *Eupenicillium shearii* in 2006 by Hosoe et al.,[1] who then structurally characterized and demonstrated its antifungal activity against diverse fungi and yeasts (Fig. 1). The chemical structure of **1** was proposed to have a 24-membered lactone framework as the main structure, bearing two stereogenic centers (C3 and C23). Moreover, unlike general polyene macrolides, which mostly contain a conjugated polyene structure and a 1,3-polyol section, such as amphotericin B, nystatin, and pimaricin, which are extensively used as effective antifungal drugs, the present compound comprises a non-conjugated diene system (16*Z* and 20*E*) and a phosphorylcholine group in the molecule. Thus, compound **1** possesses unique structural characteristics and a promising structure–activity relationship; however, the absolute configuration at the C3 and C23 stereogenic centers of compound **1** has not been determined yet. During our research on the synthesis of eushearilide,[2] Higashiyama et al. reported the first total synthesis of **1**[3] but found that the synthetic product was not identical to the natural compound.

We have developed methods to synthesize carboxylic esters and lactones with diverse ring sizes using symmetrically substituted benzoic anhydrides, such as 2-methyl-6-nitrobenzoic anhydride (MNBA),[4] as condensing agents in the presence of a nucleophilic catalyst such as 4-(dimethylamino)pyridine (DMAP) or 4-(dimethylamino)pyridine *N*-oxide (DMAPO). As it has already been demonstrated that MNBA is one of the most effective dehydrating reagents to produce macrocyclic lactones by promoting basic catalysts,[5] we explored the asymmetric total synthesis of compound **1** using the proposed 24-membered lactone structure with the purpose of applying the present method to the total synthesis of a natural macrolide antibiotic.

Results and discussion

Our retrosynthetic analysis for compound **1** is depicted in Scheme 1.[2] We planned to exploit an MNBA-mediated lactonization to construct a 24-membered macrolide ring,[6] followed by the introduction of a highly polar phosphorylcholine[7] to a hydroxyl group at the C3 position in the final stage. The seco-acid containing a β-hydroxy ester moiety could be synthesized through the concurrent two-carbon elongation and construction of a stereogenic center using the asymmetric Mukaiyama aldol reaction[8] of aldehyde **3** with enol silyl ether. The aldehyde **3** containing (*Z*)-alkene could be stereoselectively constructed by the Wittig reaction of siloxyaldehyde **5**[9] with phosphonium ylide generated from **4**, which could be prepared through the conventional transformations from the simple and commercially available alkynyl primary alcohol and chiral propylene oxide.

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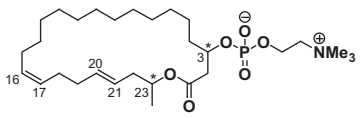
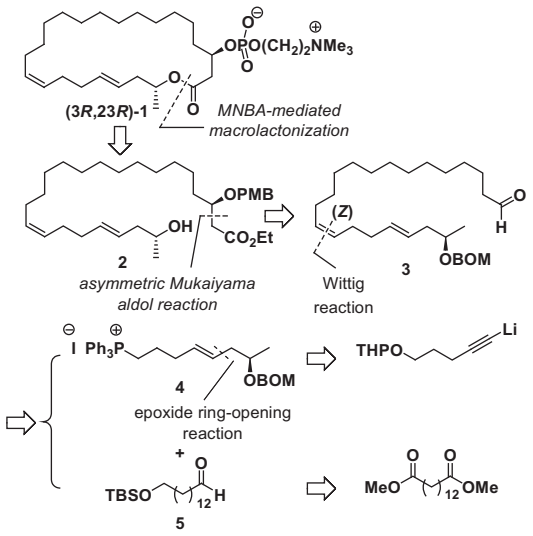


Figure 1. Proposed structure of eushearilide (**1**).



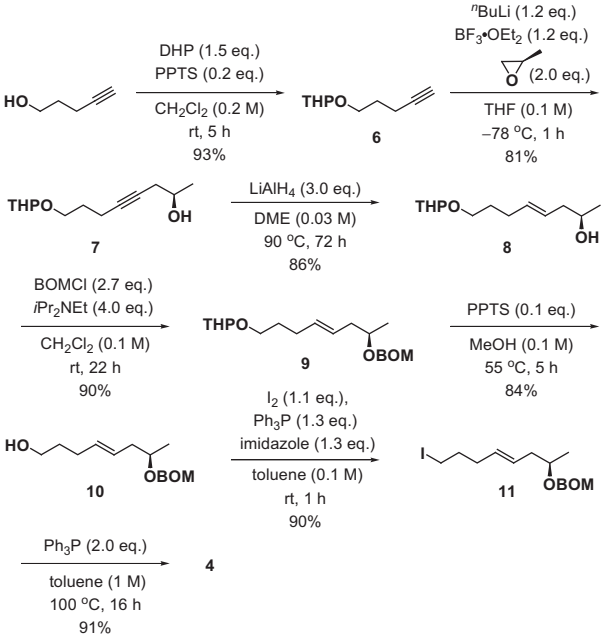
Scheme 1. Retrosynthetic strategy.

First, phosphonium salt **4** was synthesized starting with the readily available primary alkynyl alcohol, as shown in Scheme 2. Compound **6**, obtained from 4-pentyn-1-ol by the tetrahydropyranyl (THP) protection of the hydroxyl group, was subjected to the BF_3-mediated regioselective ring-opening reaction[10] of (*R*)-propylene oxide to afford the known alcohol **7**,[11] followed by reduction with $LiAlH_4$ to stereoselectively give *trans*-olefin **8** in high yields.[12] The obtained alcohol **8** was protected with a benzyloxymethyl (BOM) group, followed by the cleavage of the tetrahydropyranyl (THP) ether moiety using pyridinium *p*-toluenesulfonate (PPTS) to afford primary alcohol **10**. Treatment of alcohol **10** with Ph_3P and I_2 in the presence of imidazole furnished the desired iodide **11** in high yields, which was converted to phosphonium salt **4** by reaction with Ph_3P.

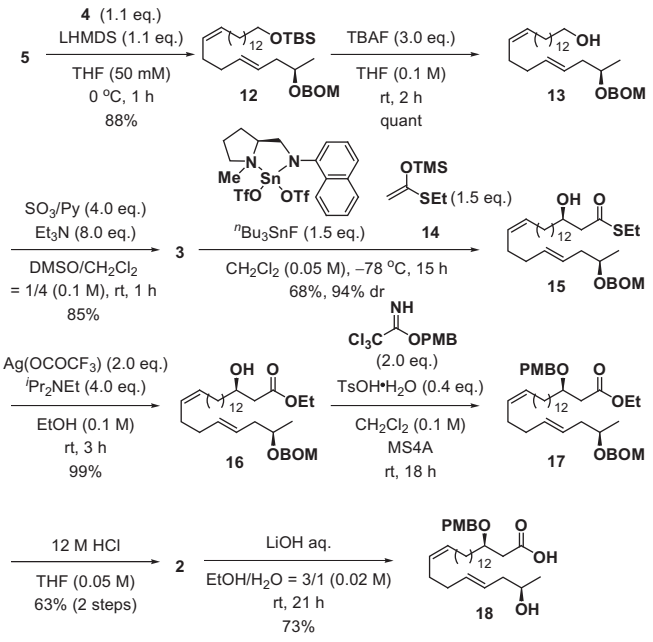
With the desired phosphonium salt in hand, the Wittig olefination of **4** with aldehyde **5** in the presence of LHMDS was performed to yield the desired (*Z*)-olefin **12**[13,14] as depicted by Scheme 3.[15] The successive deprotection of a terminal TBS group in **12** and the subsequent oxidation of the obtained alcohol **13** afforded the corresponding aldehyde **3** in high yields. The aldol product **15**, which has a (3*R*,23*R*)-configuration, was stereoselectively synthesized by the asymmetric Mukaiyama aldol reaction of 1-ethylthio-1-(trimethylsiloxy)ethene **14**, which was derived from *S*-ethyl propanethioate, with the obtained aldehyde **3** in the presence of (*S*)-diamine-Sn(II) complex as the catalyst with $^nBu_3$-SnF.[8] Next, the transesterification of thioester **15** with silver trifluoroacetate as the Lewis acid was performed to yield the corresponding ethyl ester **16**. The consecutive *p*-methoxybenzyl (PMB) protection of the secondary hydroxyl group in **16** and the deprotection of the BOM group followed by the deprotection of the ethyl ester moiety yielded the desired seco-acid **18**, a precursor of the ring-closing product, in good yields.

Next, we attempted the macrolactonization of the seco-acid eventually prepared by the MNBA method in the presence of DMAP or DMAPO as a nucleophilic catalyst (Table 1). An excess amount (6.0 equiv) of DMAP was employed with MNBA in dichloromethane at room temperature to give 24-membered lactone **19** in moderate yield (67%, entry 1). Increasing the reaction temperature to 40 °C slightly improved the yield (74%, entry 2). On the other hand, even if a catalytic amount (0.2 equiv) of DMAPO was used in the presence of excess triethylamine (3.0 equiv) as a co-base (entries 3 and 4), lactone **19** was obtained in a higher yield (81%, entry 3) under mild reaction conditions at room temperature.

Finally, after the successful completion of macrolactonization using MNBA, a choline residue was attached to the obtained macrolactone framework (Scheme 4). After the deprotection of the

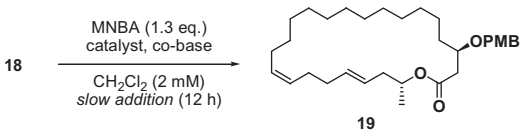


Scheme 2. Preparation of phosphonium salt **4**. Reagents and conditions.

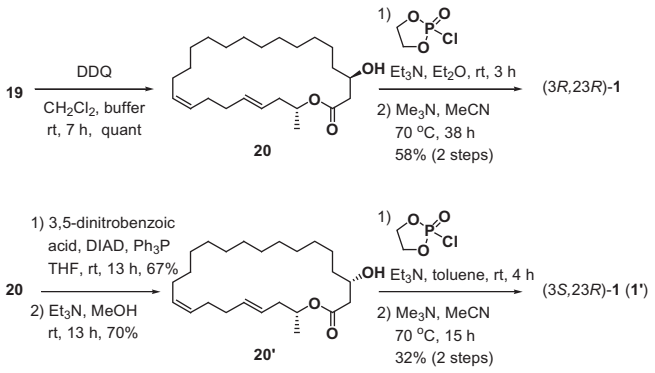


Scheme 3. Transformation of **5** to seco-acid **18**.

Table 1
Formation of lactone **19** by MNBA-mediated cyclization



Entry	Catalyst	Co-base	Temp. (°C)	Yield (%)
1	DMAP (6.0 equiv)	None	rt	67
2	DMAP (6.0 equiv)	None	40	74
3	DMAPO (0.2 equiv)	Et_3N (3.0 equiv)	rt	81
4	DMAPO (0.2 equiv)	Et_3N (3.0 equiv)	40	61



Scheme 4. Syntheses of (3*R*,23*R*)-1 and (3*S*,23*R*)-1 (1′).

PMB group in **19** with DDQ, a phosphoryl choline moiety[7] was introduced to the secondary hydroxyl group in **20** to yield the desired (3*R*,23*R*)-**1**. Moreover, a Mitsunobu inversion at the C3 position with 3,5-dinitrobenzoic acid in the presence of diisopropyl azodicarboxylate (DIAD) and Ph_3P, followed by the deprotection and attachment of a phosphoryl choline residue successfully afforded the corresponding diastereomer (3*S*,23*R*)-**1** (**1**′).

Thus, we achieved the asymmetric total synthesis of the proposed structure of eushearilide **1** and its diastereomer **1**′. However, the ^1H and ^{13}C NMR spectra of the synthetic products were not completely identical to those of the natural product reported in the literature.[16] In particular, as shown in the graphs in Figure 2, the ^{13}C NMR chemical shifts of the *cis*-olefinic carbons and their peripheral carbons around the C16–C17 double bond in both the synthetic products were evidently different from the reported values for the natural product.

On the basis of these results, we proposed an alternate structure **1**″, which has a *trans*-form rather than a *cis*-form at the C16–C17 double bond, and addressed the total synthesis of **1**″.[17] The stereoselective formation of the (*E*)-olefin moiety at C16 in **1**″ could be achieved by a *trans*-selective modified Wittig olefination, also known as the Schlosser modification.[18] Indeed, starting with aldehyde **5**, as shown in Scheme 3, the modified Wittig reaction of phosphonium salt **4** with **5** was performed to give the desired coupling product **12**″ in good yields, exclusively in the *trans*-form (Scheme 5).[19] Eventually, **12**″ was converted into the final product **1**″ using the same process as **1** (see Supporting information).

The ^1H and ^{13}C NMR spectra of (3*R*,16*E*,20*E*,23*R*)-eushearilide (**1**″) were in complete agreement with those of the natural product reported in the literature. As indicated in Figure 3, the ^{13}C NMR shifts of **1**″ were exactly identical to those of the natural product, whereas the optical rotation sense of **1**″ ($[\alpha]_D^{20}$ −10.9 (*c* 0.71, MeOH)) was the opposite of that reported for the naturally occurring eushearilide ($[\alpha]_D^{25}$ +12.8 (*c* 0.75, MeOH)). Therefore, it was inductively determined that the absolute configurations at C3 and C23 in natural eushearilide are both *S* (Fig. 4).

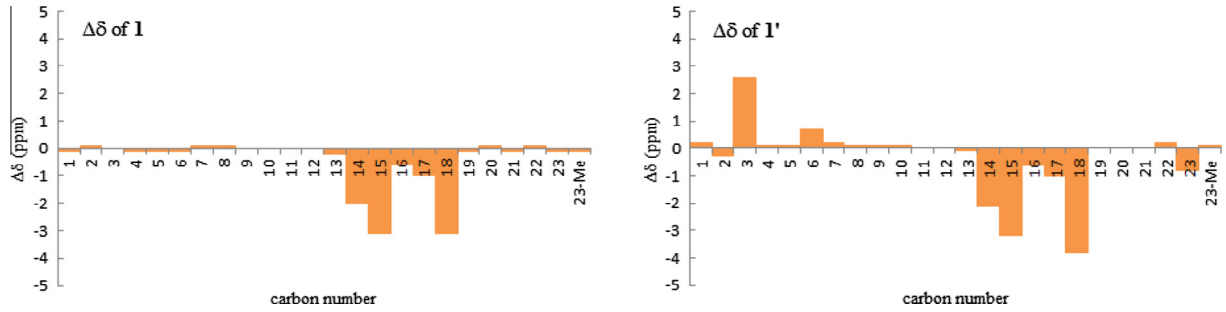
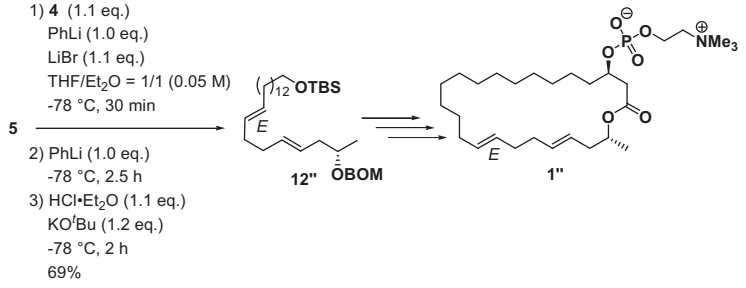


Figure 2. Δδ ppm of ^{13}C NMR chemical shifts in (3*R*,23*R*)-**1** and (3*S*,23*R*)-**1** (**1**′). Δδ corresponds to the difference in the chemical shift for natural and synthetic products (Δδ = δ (synthetic) − δ (natural)).



Scheme 5. (*E*)-Selective Wittig reaction by the Schlosser modification.

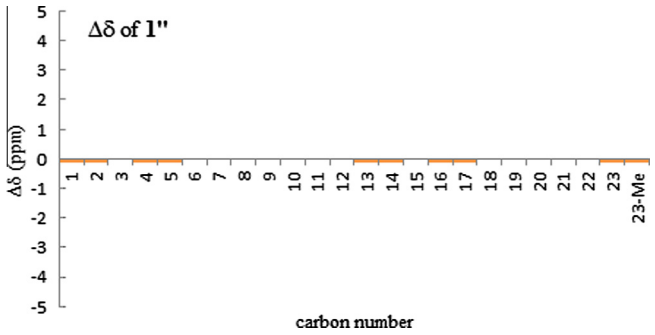
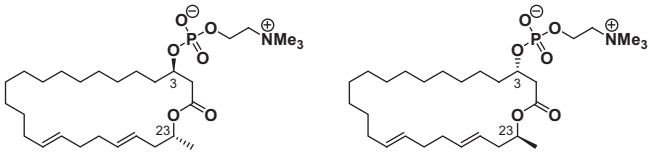


Figure 3. Δδ (ppm) of ^{13}C NMR chemical shifts in (3*R*,16*E*,20*E*,23*R*)-eushearilide (**1**″). Δδ corresponds to the difference in chemical shift for natural and synthetic products (Δδ = δ (synthetic) − δ (natural)).



(3*R*,16*E*,20*E*,23*R*)-(−)-Eushearilide (**1"**)
$[\alpha]_D^{20}$ −10.9 (c 0.71, MeOH)
(Synthetic)

(3*S*,16*E*,20*E*,23*S*)-(+)-Eushearilide (**1"'**)
$[\alpha]_D^{25}$ +12.8 (c 0.75, MeOH)
(Natural)

Figure 4. Structures of synthetic (**1**″) and natural (**1**‴) eushearilides.

Conclusion

In conclusion, we successfully performed the asymmetric total synthesis of the proposed structure of (3*R*,16*Z*,20*E*,23*R*)-eushearilide **1** and (3*S*,16*Z*,20*E*,23*R*)-eushearilide **1** (**1**′). Because the synthetic **1** and **1**′ were inconsistent with the reported natural product, the most likely structure of natural eushearilide, (±)-(16*E*,20*E*)-eushearilide, was proposed as an alternative. Consequently, (3*R*,16*E*,20*E*,23*R*)-(−)-eushearilide (**1**″) was successfully synthesized, and the optical rotation sense of **1**″ was found to be opposite to that of the natural product. The presently reported results show that naturally occurring eushearilide is (3*S*,16*E*,20*E*,23*S*)-(+)-eushearilide (**1**‴), an enantiomer of **1**″.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.01.181.

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12. The observed coupling constant of H-4 ($J_{4,5}$ = 14.9 Hz) in olefin **8** was ascribed to 4*E*.
13. The configuration of the double bonds in **12** and **12**″ obtained by Wittig olefination was determined by the chemical shifts of the allylic methylene (C7 and C10). See Ref. 14 and note 19.
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15. A small amount of the (*E*)-isomer was concurrently formed as an inseparable by-product, which was separated after the macrolactonization step.
16. Our results were in line with the conclusions reported by Higashiyama et al.[3]
17. As shown in Figure 2, in the case of Δδ of (3*S*,23*R*)-**1** (**1**′) compared to that of (3*R*,23*R*)-**1**, there was a comparatively larger difference of Δδ at C3, which convinced us that the relative configurations at two stereogenic centers (C3 and C23) were the same as those of **1**.
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19. The configuration of the double bond (C8–C9) in **12**″ was assigned as *E* based on the downfield shifts of the allylic methylene [δ_C 32.6 (C7) and δ_C 32.6 (C10)], while the *Z*-configuration was deduced for **12** from the upfield chemical shifts of the allylic methylene [δ_C 27.3 (C7) and δ_C 27.2 (C10)].[14]