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Toward the stereochemical assignment of euvesperins A and B: total synthesis of the possible structures of the natural products†

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The possible structures of euvesperins A and B were synthesized. The results of our synthesis suggest that euvesperin A may be a mixture of the (2*R*,3*R*,4*S*,7*S*) and (2*S*,3*S*,4*R*,7*S*) isomers and euvesperin B may be a mixture of the (2*R*,3*S*,4*S*,7*S*) and (2*S*,3*R*,4*R*,7*S*) isomers in consideration of their putative biosynthetic pathways.

In 2016, euvesperins A (**1**) and B (**2**) were isolated from *Metarhizium* sp. FKI-7236 by Ōmura and Shiomi's research group (Fig. 1)^{1,2} and identified as new circumventors of arbekacin resistance in MRSA as part of their ongoing research.^{3–5} The structures of compounds **1** and **2** were deduced based on extensive NMR studies, which indicated that both of them were formed as diastereomeric mixtures at the C4 position. However, the relative and absolute configurations of the C2, C3, and C7 stereocenters remained unclear. Thus, determination of the stereochemical configurations of **1** and **2** has been strongly anticipated.

Previously, we completed the first total synthesis of L-755,807 (**3**), which has a molecular structure that is very similar to that of euvesperin A (Scheme 1).^{6–8} In our synthetic approach to **3**, a novel highly diastereoselective Darzens reaction between α -silyloxy aldehyde **4** and di-*tert*-butyl bromomalonate was developed,^{9,10} and late-stage coupling of ring segment **6** and side-chain segment **7** was accomplished using the Horner–Wadsworth–Emmons (HWE) reaction to effectively produce the desired compound **3**.

Comparing the structures of euvesperin A and L-755,807, we presumed that both of them have the same epoxide configuration. Hence, a mixture of (4*S*,7*S*)-**8** and (4*R*,7*S*)-**9** or a mixture of (4*S*,7*R*)-**10** and (4*R*,7*R*)-**11** were proposed as the putative structures of euvesperin A (Fig. 2), which could be pre-

pared by a synthetic strategy similar to the one we used for L-755,807. Additionally, euvesperin B could be obtained *via* a biomimetic conversion from euvesperin A as reported in the literature,¹ suggesting that its possible structures were a mixture of (4*S*,7*S*)-**12** and (4*R*,7*S*)-**13** or a mixture of (4*S*,7*R*)-**14** and (4*R*,7*R*)-**15**, as depicted in Fig. 2. Thus, we directed our attention toward the total synthesis and stereochemical assignment of these natural products. In this paper, we describe the synthesis of the possible isomers of euvesperins A and B and discuss the stereochemistries of the natural products.

Our retrosynthetic analysis of the putative structures of euvesperins A and B is shown in Scheme 2. As mentioned above, euvesperin B can be biomimetically derived from euvesperin A, and then we planned to obtain the four putative structures of euvesperin A **8–11** from enone **17** by a non-stereoselective Mukaiyama hydration, and **17** could be retrosynthetically disconnected *via* an HWE reaction into *n*-hexanal (**18**) and phosphonate **19**, which could be prepared from known Weinreb amide **20**.^{6–8}

Our synthesis commenced with the preparation of enone **17** from the known TES-protected Weinreb amide **20**^{6–8} (Scheme 3). According to a procedure from the literature,^{6–8} amide **20** was similarly converted into phosphonate **19** in 74% yield, which was then subjected to attempted coupling with *n*-hexanal (**18**) *via* an HWE reaction. After some unsuccessful experiments, we realized that phosphonate **19** to be unreactive, presumably owing to the bulkiness around the reactive site.

Next, we changed the enone-type intermediate from **17** to amination **24** or **26**, which were synthesized from **21**^{6–8} *via* amination

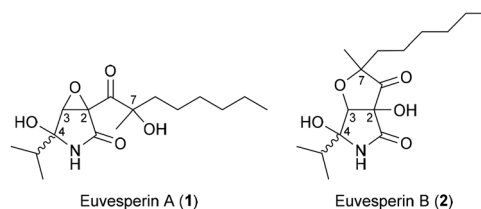


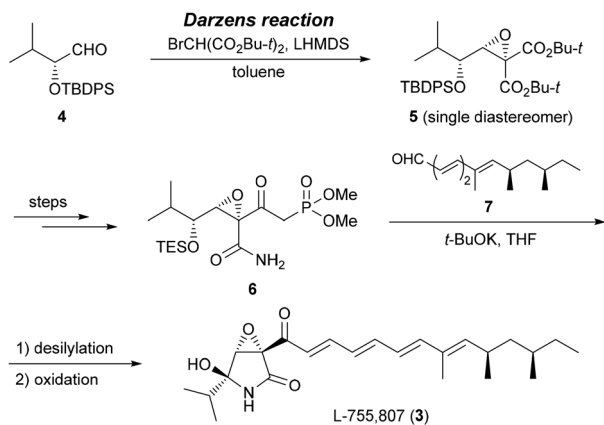
Fig. 1 Reported structures of euvesperins A (**1**) and B (**2**).

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Scheme 1 Our previous work on the synthesis of L-755,807 (3).

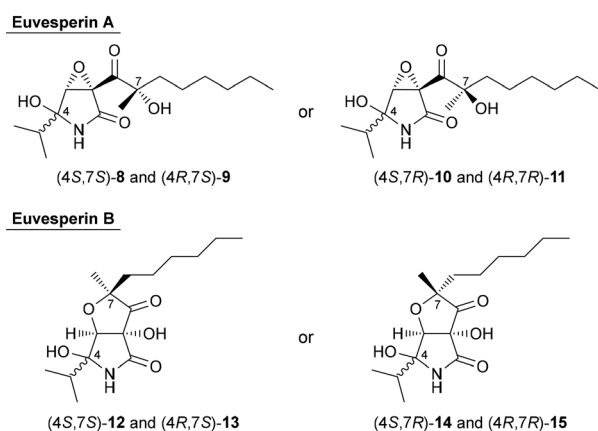
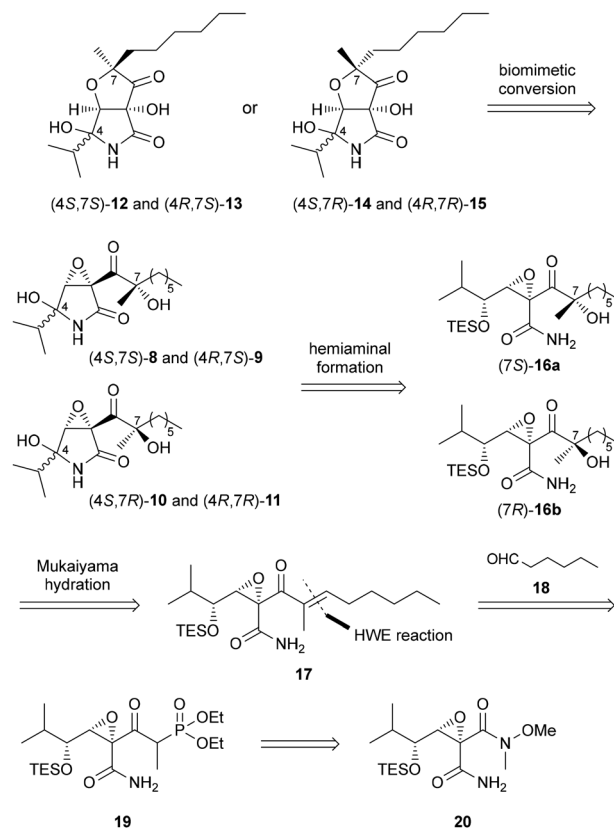


Fig. 2 Putative structures of euvesperins A and B.

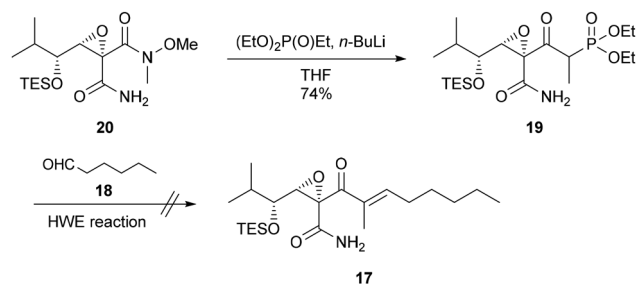
22 (Scheme 4). Alcohol **21** was initially oxidized with Dess–Martin periodinane, and the resulting hemiaminal was immediately converted into aminal **22** as a single diastereomer. The stereostructure of the aminal portion of **22** was confirmed through NOESY experiments, which revealed a correlation between the methine proton and aminal *O*-methyl protons, allowing us to determine the stereochemistry. The coupling reaction of aminal **22** with vinyl iodide **23**¹¹ afforded enone **24** in 51% yield. With iodide **25**,¹² which has a terminal double bond, enone **26** was obtained in high yield (88%). Therefore, we elected to use enone **26** for the subsequent hydration step.

Enone **26** was next subjected to Mukaiyama hydration with cobalt ($\text{Co}(\text{acac})_2$) or manganese ($\text{Mn}(\text{dpm})_3$) catalysts (Scheme 5).^{13,14} All conditions afforded a 1:1 mixture of the desired alcohols (7*S*)- and (7*R*)-**27**, although the yields were only moderate (31–53%) and it proved very difficult to separate the two isomers.

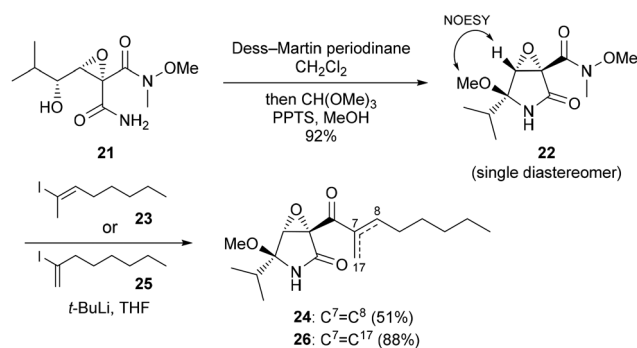
To overcome these issues, enone **26** was initially reduced with sodium borohydride in methanol to stereoselectively form allyl alcohol (6*S*)-**28** in 76% yield.¹⁵ Mukaiyama hydration of (6*S*)-**28** proceeded effectively to yield two diastereomeric



Scheme 2 Retrosynthetic analysis of euvesperins A and B.

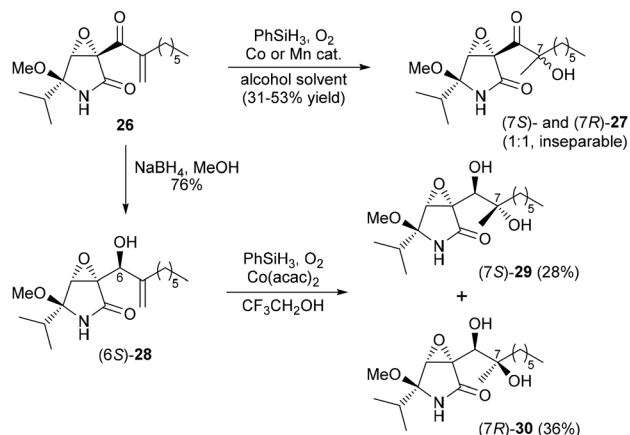


Scheme 3 Synthetic efforts toward enone **17**.



Scheme 4 Successful synthesis of enones **24** and **26**.



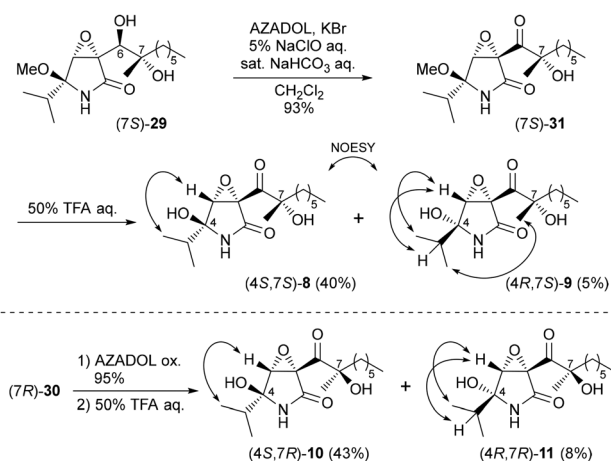


Scheme 5 Preparation of the two isomers with respect to the C7 stereocenter.

diols, which were easily separated to furnish (7*S*)-**29** and (7*R*)-**30** in 28% and 36% yields, respectively.¹⁶

Having prepared the two isomers (7*S*)-**29** and (7*R*)-**30**, the remaining tasks *en route* to our goal were oxidation of the C6 alcohol and hydrolysis of the aminal portion (Scheme 6). Accordingly, AZADOL oxidation^{17,18} of alcohol (7*S*)-**29** was conducted to afford ketone (7*S*)-**31** in 93% yield, which was finally hydrolyzed with aqueous trifluoroacetic acid (TFA) to furnish the 4*S* isomer of ketone **8** in 40% yield and the 4*R* isomer of ketone **9** in 5% yield. Similarly, (7*R*)-**30** provided (4*S*,7*R*)-**10** (43%) and (4*R*,7*R*)-**11** (8%) in two steps.

We performed NOESY experiments to determine the stereochemistry at the C4 position of the four synthetic compounds, and the key correlations are indicated in Scheme 6. As mentioned in the introduction, euesperin A was reported to be a diastereomeric mixture at the C4 position.¹ However, among the four synthetic compounds, (4*S*,7*S*)-**8** and (4*S*,7*R*)-**10** exhibited NMR spectra identical to those of the isomers of euesperin A, which implies that the stereochemistry of euesperin



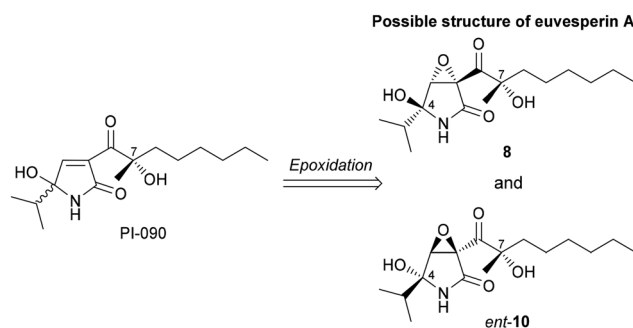
Scheme 6 Completion of the synthesis of four possible isomers of euesperin A.

A was incorrectly assigned. Consequently, four possible combinations were proposed for euesperin A: a mixture of **8** and **10**, a mixture of **8** and the enantiomer (*ent*) of **10**, a mixture of *ent*-**8** and **10**, or a mixture of *ent*-**8** and *ent*-**10**.¹⁹

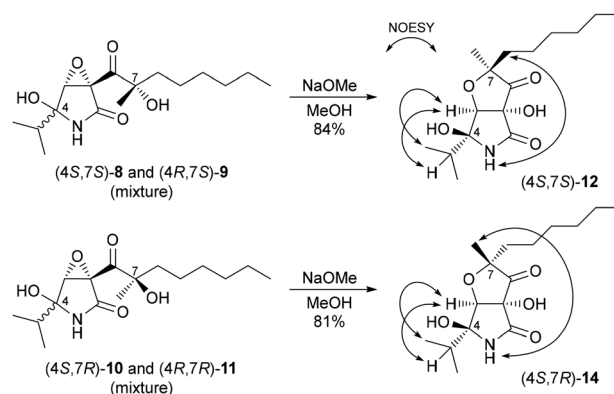
Natural euesperin A is anticipated to be biosynthetically produced from natural products PI-090²⁰ with the (7*S*) configuration *via* epoxidation (Scheme 7). Therefore, we consider that natural euesperin A may be a combination of **8** and *ent*-**10**.

With the proposed structures of euesperin A in hand, we turned our attention to the synthesis of euesperin B (Scheme 8). Treatment of a mixture of (4*S*,7*S*)-**8** and (4*R*,7*S*)-**9** with sodium methoxide in methanol gave (4*S*,7*S*)-**12** in 84% yield. Interestingly, (4*S*,7*S*)-**12** was obtained as a single diastereomer even though the starting materials **8** and **9** were a diastereomeric mixture at the C4 position. Similarly, (4*S*,7*R*)-**14** was formed as a sole isomer from a diastereomeric mixture of (4*S*,7*R*)-**10** and (4*R*,7*R*)-**11**. The stereochemistry of the products was deduced from the NOESY correlations shown in Scheme 8. The NMR spectra of synthetic (4*S*,7*S*)-**12** and (4*S*,7*R*)-**14** were identical to those of the isomers of euesperin B. Like euesperin A, euesperin B was previously reported to be a diastereomeric mixture at the C4 position; nevertheless, our work has ruled this out.

To determine the correct structure of euesperin B, we considered which of the combinations could be euesperin B: a

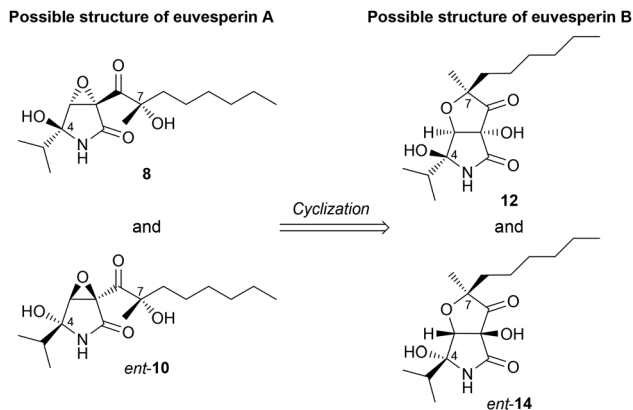


Scheme 7 Proposed biosynthesis of euesperin A.



Scheme 8 Synthesis of proposed structure of euesperin B.





Scheme 9 Proposed biosynthesis of euvesperin B.

mixture of **12** and **14**, a mixture of **12** and *ent*-**14**, a mixture of *ent*-**12** and **14**, or a mixture of *ent*-**12** and *ent*-**14**.¹⁹ As described in the literature, euvesperin A is presumed to be a biosynthetic precursor of euvesperin B.¹ Thus, euvesperin B should have the (*S*) configuration at C7, as in the case of euvesperin A. Consequently, we speculate that natural euvesperin B may be a mixture of **12** and *ent*-**14** (Scheme 9).

Conclusions

In conclusion, we completed the total synthesis of four possible structures of euvesperin A. By consideration of the putative biosynthetic pathway of this natural product, euvesperin A is proposed to be a mixture of compounds **8** and *ent*-**10**. In addition, two possible structures of euvesperin B were synthesized, and we propose that natural euvesperin B may be a mixture of compounds **12** and *ent*-**14**.

Data availability

Raw data were generated at Meiji Pharmaceutical University and Health Sciences University of Hokkaido. Derived data which supports the results of this study are available from the corresponding authors (Kenichi Kobayashi and Kosaku Tanaka III) upon request.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Education, Culture, Sports, Science and Technology (MEXT), Japan.

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