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Stereoselective Synthesis of the $C_{25}-C_{36}$ Segment of Arenicolides A and B: Determination of the Configuration of the Trisubstituted Epoxide

Shinji Nagumo,[†] Taeko Nakano,[†] Kyomi Hata,[†] Megumi Mizukami,[‡] and Masaaki Miyashita*,[†]

Department of Applied Chemistry, Kogakuin University, Nakano 2665-1, Hachioji, Tokyo 192-0015, Japan, and Hokkaido Pharmaceutical University, School of Pharmacy, Katsuraoka 7-1, Otaru 047-0264, Japan

bt13149@ns.kogakuin.ac.jp

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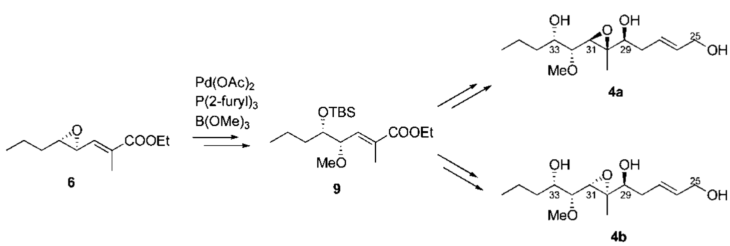
ABSTRACT



Two diastereomeric epoxides 4a and 4b corresponding to the $C_{25}-C_{36}$ fragment of arenicolides A and B were synthesized in a stereoselective manner involving the Pd(0)-catalyzed stereospecific methoxy substitution reaction of epoxy unsaturated ester 6 with $B(OMe)_3$ as the key step. Comparison of the ^1H NMR spectra of the synthetic compounds with that of arenicolide A revealed that the configuration of the epoxide in arenicolides A and B is 30*R* and 31*R*.

Marine organisms have been known to produce a wide variety of secondary metabolites to adapt themselves to the environment of the ocean. Searching for new compounds from these metabolites can often provide us with a good opportunity to find a promising candidate for drug development. In the course of their active research, Fenical and co-workers isolated salinosporamide A, a potent proteasome inhibitor, from the fermentation broth of marine actinomycete *Salinispora*.[1] The new molecule is currently in phase I of human clinical trials for cancer. Recently, three new compounds, arenicolides A−C (**1**−**3**), were discovered by the same group in the fermentation broth of *Salinospora arenicola* and arenicolide A (**1**) exhibited cytotoxicity against human colon adenocarcinoma cell lines.[2] The absolute structures of **1**−**3** were determined based on spectroscopic analyses and chemical degradation (Figure 1), although the configuration of the methyl group at the C_{12} position and that of the trisubstituted epoxide in arenicolides A and B (**1** and **2**) have yet remained undetermined. Evidently, the arenicolides are a new type of polyene macrolide composed of a 26-membered lactone ring containing three characteristic conjugated (*E*,*E*)-diene units and three or four sets of an

[†] Kogakuin University.
[‡] Hokkaido Pharmaceutical University.

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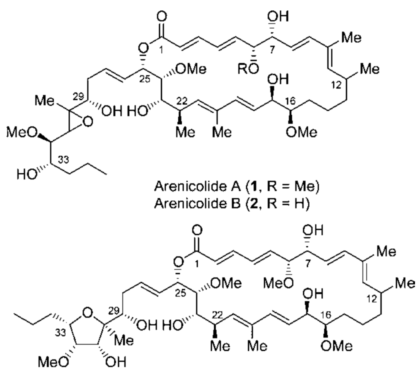


Figure 1. Structures of arenicolides A (**1**), B (**2**), and C (**3**).

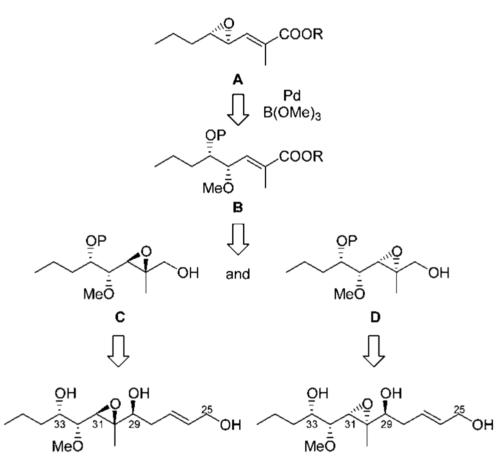
extremely rare vicinal hydroxy-methoxy structure, and a side chain bearing a trisubstituted epoxide (arenicolides A and B) or a fully substituted tetrahydrofuran ring (arenicolide C), in which fourteen asymmetric carbon atoms are included in total.

Very recently, Lee and co-workers have reported the synthesis of a $C_{26}-C_{36}$ segment bearing (30*R*, 31*R*)-epoxide, although the configuration of the epoxide in the arenicolides has not been clarified by their synthesis.[3]

The quite unique structures of the arenicolides, as well as their distinctive biological properties, prompted us to start a synthetic study on these natural products. To this end, we initially set about to determine the configuration of the trisubstituted epoxide in arenicolides A and B (**1** and **2**).

To determine the configuration of the epoxide unambiguously, we planned to synthesize two diastereomeric epoxides **4a** and **4b** corresponding to the $C_{25}-C_{36}$ segment in **1** and **2** (Scheme 1). In this regard, a chiral α-epoxy

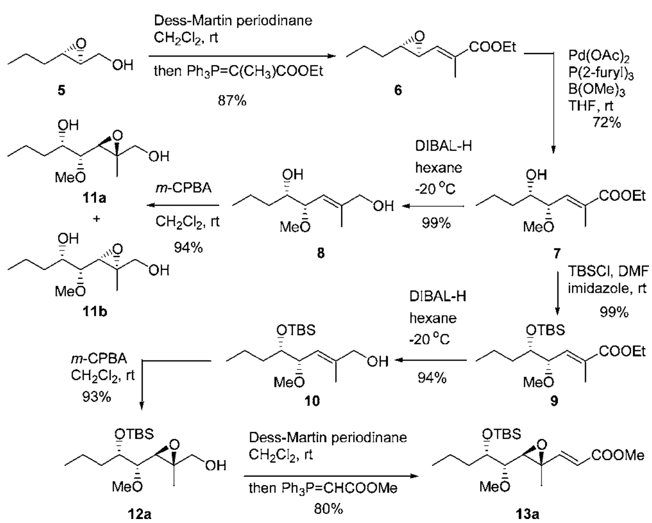
Scheme 1. Strategy for the Synthesis of Two Diastereomeric Epoxides **4a** and **4b**



unsaturated ester **A**, easily obtainable from commercially available (*E*)-2-hexen-1-ol, would be stereoselectively converted to unsaturated ester **B** bearing a *syn*-vicinal hydroxy-methoxy structure, by means of the Pd(0)-catalyzed stereospecific alkoxy substitution reaction of **A** with $B(OMe)_3$, which was recently developed by us.[4] The unsaturated ester **B** would be transformed into two diastereomeric epoxy alcohols **C** and **D**, from which the targeted compounds **4a** and **4b** would be derived via a similar synthetic reaction sequence, respectively.

The synthesis of the two requisite fragments **4a** and **4b** was performed according to Scheme 2. Thus, the chiral epoxy

Scheme 2. Synthesis of Intermediate **13a**



alcohol **5** prepared from (*E*)-2-hexen-1-ol, by the Katsuki–Sharpless asymmetric epoxidation,[5] was subjected to the Dess–Martin oxidation followed by a Wittig reaction to furnish epoxy unsaturated ester **6** in 87% yield. The key *syn*-methoxy substitution reaction of **6** at the γ-position was successfully performed by a combination of $Pd(OAc)_2$, P(2-furyl)$_3$, and $B(OMe)_3$ in THF[4] giving rise to the desired *syn*-δ-hydroxy-γ-methoxy unsaturated ester **7** in 72% isolated yield. Reduction of **7** with DIBAL-H in hexane produced diol **8** in 99% yield, which underwent epoxidation with *m*-CPBA to afford a nearly 1:1 inseparable mixture of diastereomers **11a** and **11b** in 94% combined yield. On the other hand, protection of the alcohol **7** with a TBS group followed by reduction of the ester **9** with DIBAL-H gave allylic alcohol **10** in 94% yield. Subsequent epoxidation of **10** with *m*-CPBA in CH_2Cl_2 stereoselectively occurred from the opposite side of the TBS group[6] giving rise to **12a** as a single product, which was then converted to epoxy unsatur-

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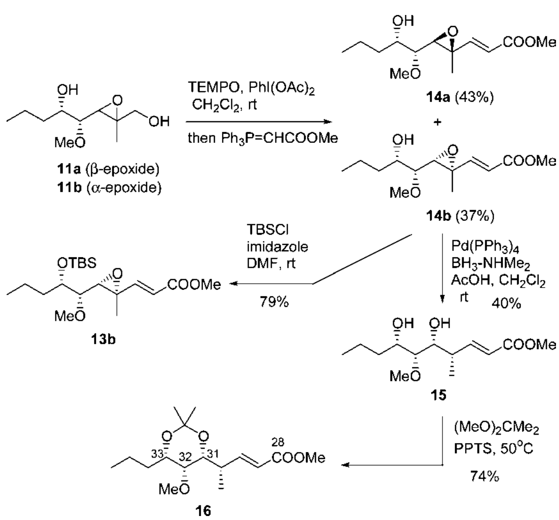
ated ester **13a** by the Dess−Martin oxidation[7] followed by a Wittig reaction in 80% overall yield.

To determine the stereochemistry of the two epoxides, the mixture of **11a** and **11b** was initially subjected to oxidation with TEMPO and BAIB[8] followed by a Wittig reaction to afford a mixture of epoxy unsaturated esters **14a** and **14b**, which was fortunately separated by silica gel column chromatography. First, the α-epoxy unsaturated ester **14b** was converted to acetonide **16** by a two-step reaction sequence: (1) reductive epoxide-opening with $[Pd(PPh_3)_4]$ and $BH_3{-}NHMe_2$ in CH_2Cl_2 in the presence of AcOH[9] and (2) acetonization of α-*syn*-diol **15** with $Me_2C(OMe)_2$ and PPTS.[10] The ^{13}C NMR spectrum of **16** exhibited peaks due to the methyl groups on the acetonide at 29.75 and 18.97 ppm, and a peak due to the acetal carbon atom at 98.86 ppm, which clearly indicated that the stereochemistry of the acetonide in **16** was *syn* (Scheme 3).[11] On the other hand,

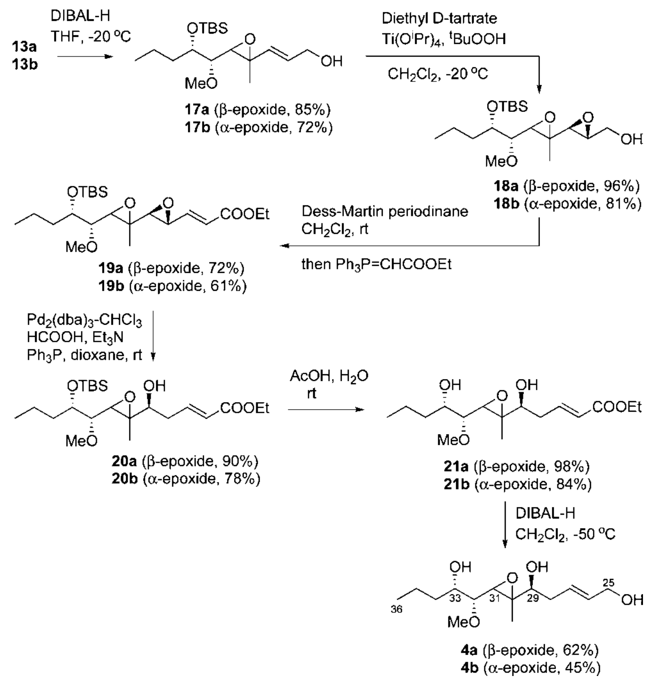
Scheme 3. Determination of the Stereochemistry of the Epoxide



protection of the alcohol **14b** with a TBS group furnished **13b** in 79% yield.

With the two requisite epoxy unsaturated esters **13a** and **13b** in hand, we next focused on the synthesis of **20a** and **20b** corresponding to the $C_{25}{-}C_{36}$ fragment. These conversions were carried out according to Scheme 4. Thus, reduction of **13a** and **13b** with DIBAL-H in THF followed by the Katsuki−Sharpless epoxidation[5] of the resulting allyl alcohols with (D)-(−)-tartrate afforded diepoxides **18a** and **18b** in high yields, respectively, which were converted to diepoxy unsaturated esters **19a** and **19b**, respectively,

Scheme 4. Synthesis of $C_{25}{-}C_{36}$ Segments **4a** and **4b**



by the same two-step reaction sequence: (1) Dess−Martin oxidation and (2) Wittig reaction. The subsequent crucial Pd(0)-catalyzed reductive epoxide-opening reaction of **19a** and **19b** with HCOOH[12] nicely occurred at the γ-position, giving rise to the desired products **20a** and **20b**, respectively. Finally, removal of the TBS group with aqueous AcOH and reduction of the resulting dihydroxy ester with DIBAL-H furnished the two targetted compounds **4a** and **4b**, respectively, corresponding to the $C_{25}{-}C_{36}$ segment in **1** and **2**.

The synthetic fragments **4a** and **4b** showed remarkable differences in their 400 MHz ^1H NMR spectra in $CDCl_3$, particularly, with respect to the chemical shifts of the protons at the C_{29}, C_{31}, C_{32}, and C_{33} positions as shown in Table 1. Namely, the chemical shifts of the protons at the C_{29}, C_{31}, C_{32}, and C_{33} positions in **4a** are very close to those of arenicolide A, whereas those of **4b** are obviously different from the latter, inter alia, the chemical shifts of the protons at the C_{29}, C_{31}, and C_{33} positions. Although each coupling constant of the particular protons in **4a** is apparently different from that in arenicolide A, it is presumed that the presence of four vicinal hydroxy-methoxy structures and two additional hydroxyl groups and an epoxide in the natural product might make extremely difficult the measurements of their coupling constants in the densely close chemical shifts. Thus, we concluded that the configuration of the trisubstituted epoxide in arenicolides A and B (**1** and **2**) is (30*R*,31*R*) by comparison of the chemical shifts of the protons at

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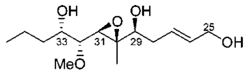
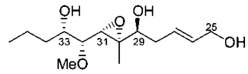
Table 1. The Characteristic Peaks in the 400 MHz ^{1}H NMR Spectra ($CDCl_3$) of **4a**, **4b**, and Arenicolide A (**1**)



4a



4b

	4a [ppm]	**4b** [ppm]	arenicolide A [ppm][2]
C_{29}−H	3.37 (br t, J = 6.1 Hz)	3.78 (t, J = 4.8 Hz)	3.39 (dd, J = 11.0, 2.5 Hz)
C_{31}−H	2.96 (d, J = 8.5 Hz)	3.32 (d, J = 8.0 Hz)	3.04 (s)
C_{32}−H	3.00 (dd, J = 8.5, 3.9 Hz)	3.00 (dd, J = 8.0, 2.0 Hz)	3.07 (d, J = 3.9 Hz)
C_{33}−H	3.70 (br m)	3.55 (m)	3.68 (dt, J = 8.3, 3.9 Hz)

the C_{29}, C_{31}, C_{32}, and C_{33} positions in **4a**, **4b**, and arenicolide A.

In conclusion, we synthesized the two diastereomeric epoxides **4a** and **4b** corresponding to the C_{25}−C_{36} fragment of arenicolides A and B (**1** and **2**) in a stereoselective manner and the configuration of the epoxide in **1** and **2** was determined to be 30*R* and 31*R* by comparison of the ^{1}H NMR spectra of the synthetic compounds with that of arenicolide A (**1**). Further synthetic studies toward total synthesis of arenicolides A−C are in progress in our laboratory.

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

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