

Preliminary Communication

Stereochemistry of enacyloxins. Part 5: Synthesis of a C9'-C15' fragment of enacyloxins, a series of antibiotics from *Frateuria* sp. W-315

Hiroyuki Furukawa, Hiroaki Hoshikawa, Wataru Igarashi, Manabu Yaosaka, Teiko Yamada, Shigefumi Kuwahara and Hiromasa Kiyota*

Graduate School of Agricultural Science, Tohoku University, 1-1 Tsutsumidori-Amamiya, Aoba-ku, Sendai 981-8555, Japan

*Corresponding author
e-mail: kiyota@biochem.tohoku.ac.jp

Abstract

The C9'-C15' fragment of enacyloxins, a series of antibiotics isolated from *Frateuria* sp. W-315, was synthesized from diethyl D-tartrate.

Keywords: antibiotics; diethyl D-tartrate; enacyloxins; *Frateuria* sp. W-315; synthesis.

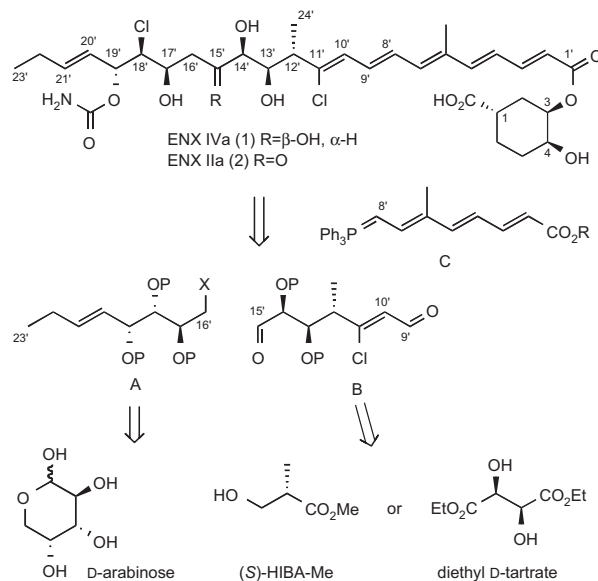
Enacyloxins (ENXs) are unique polyhydroxy-polyenic and yellow-colored antibiotics produced by *Frateuria* sp. W-315 in a Czapek-Dox medium spent by *Neurospora crassa* (Scheme 1) (Watanabe et al., 1990). ENXs show antibiotic activity against Gram-positive and Gram-negative bacteria, but inactive for yeast and fungi (Watanabe et al., 1990; Oyama et al., 1994). Its mode of action was considered to be an inhibition of peptide biosynthesis by hindering the release of EF-Tu GDP from the ribosome (Parmeggiani et al., 2006). Furthermore, ENXs have attracted considerable attention because of the inhibitory activity toward organelle protein synthesis in *Plasmodium falciparum* (Clough et al., 1999). The whole stereochemistry of ENXs [ENX IVa (1)] was elucidated by our synthetic (Fujimori et al., 2001; Takeuchi et al., 2001; Watanabe et al., 2001) and spectroscopic studies (Furukawa et al., 2007), and Parmeggiani's X-ray crystallographic analysis of the *Escherichia coli* EF-Tu/guanylyl iminodiphosphate-ENX IIa (2) complex (Parmeggiani et al., 2006). Continuing our chemical work of ENXs, we began the synthetic studies of the polyol fragment. Here, we describe an efficient synthesis of C9'-C15' fragment.

Scheme 1 shows our retrosynthetic plan. Disconnection of the whole molecule (1 or 2) leads to three fragments A, B, and C. The C8'-C9' double bond could be formed by Wittig reaction and nucleophilic addition is suitable for the C15'-C16' connection. The stereochemistry of fragments A

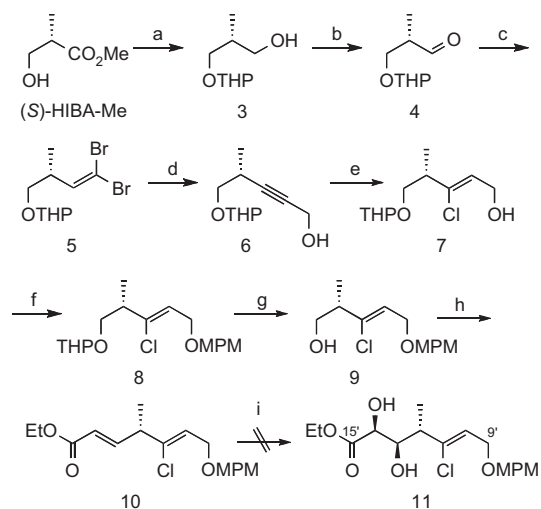
and B could make use of naturally occurring methyl (S)- β -hydroxyisobutyrate (HIBA-Me) or diethyl D-tartrate.

We first chose (S)-HIBA-Me as a starting material as its (S)-configuration was to be applied to the C12'-position of the C9'-C15' fragment (Scheme 2). (S)-HIBA-Me was converted to the known dibromide 5 according to the literature (Ley et al., 2009). A lithium acetylide formed by basic treatment of 5 was trapped with formaldehyde to afford a propargyl alcohol 6 in 88% yield. Hydroalumination followed by adding N-chlorosuccinimide (NCS) (Heathcock et al., 1984) gave a vinyl chloride 7. The hydroxy group of 7 was protected as p-methoxyphenylmethyl ether (8). Acidic removal of the THP group proceeded in 82%, however, sometimes suffered from concomitant dechlorination. TEMPO oxidation and Wittig reaction of 9 gave an enone 10; however, the next Sharpless asymmetric dihydroxylation resulted in a complex mixture.

In addition, it was found that partial epimerization occurred during the oxidation of 3. To confirm this and to elucidate optimized conditions, various oxidants were tested as shown in Table 1. The optical purity of aldehyde 4 was determined by derivatization to 12. Optical rotation value was compared with that of the known *ent*-12 (Nagaoka and Kishi, 1981). The optical purity of 12 was further confirmed by ¹H NMR analysis of the corresponding (S)-MTPA ester (13). As a result, all



Scheme 1 Enacyloxins and their retrosynthetic analysis.

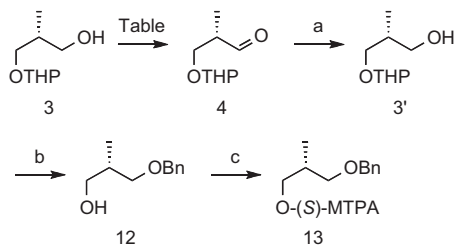


Scheme 2 Synthetic studies of C9'-C15' fragment-1. (a) i. DHP, PPTS, CHCl₃, ii. LiAlH₄, THF. (b) Swern oxidation. (c) CBr₄, PPh₃, Et₃N, MeCN (69% from **3**). (d) BuLi, (CH₂O)_n, THF (88%). (e) Red-Al[®], PhMe, then NCS (50%). (f) NaH, *p*-methoxyphenylmethyl chloride, NaI, THF (quant.). (g) PPTS, MeOH (82%). (h) i. TEMPO, KBr, aq. NaOCl, CH₂Cl₂. ii. Ph₃P=CHCO₂Et, PhMe (77% from **9**). (i) AD-mix β, MeSO₂NH₂, *t*-BuOH-H₂O.

the moderate conditions caused the epimerization. Thus, we thought HIBA-Me was insufficient as a starting material and formation of the vinylic chloride moiety should be introduced at a later step of synthesis.

Next, we planned to use a dihydroxy moiety of *D*-tartrate for the C13'-C14' position (Scheme 3). Araki et al. (2002)

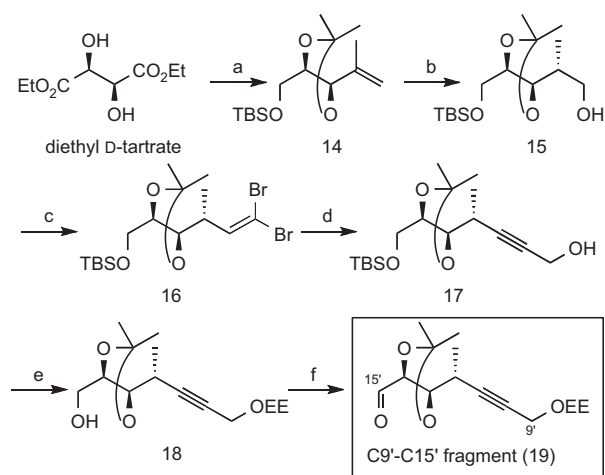
Table 1 Oxidation conditions for **3** and optical purity of derivative **13**.



(a) LiAlH₄, THF. (b) i. NaH, BnCl, NaI, THF. ii. TsOH, MeOH (ca. 55% from **3**). (c) (*R*)-MTPACl, Py, CH₂Cl₂ (quant.).

Entry	Conditions	[α] _D of 12 ^a	Optical purity (%) ^b
1	DMSO, (COCl) ₂ , Et ₃ N, -70°C to 0°C	-14.0°	81
2	DMSO, SO ₃ ·Py, Et ₃ N, 0°C	-12.0°	69
3	Dess-Martin periodinane, CH ₂ Cl ₂ , 0°C	-14.6°	85
4	PCC, MS4Å, CH ₂ Cl ₂ , 0°C	-6.9°	40

^a[α]_D (c=4.00, CHCl₃). ^bOptical purity was calculated based on *ent*-**12** {>98% ee, [α]_D=+17.2° (c=3.24, CHCl₃)} reported by Nagaoka and Kishi (1981).



Scheme 3 Synthesis of C9'-C15' fragment 2.

(a, b) Araki et al., 2002 (c) i. Swern oxidation (87%). ii. CBr₄, PPh₃, Et₃N, CH₂Cl₂ (43%). (d) BuLi, (CH₂O)_n, THF (43%). (e) i. ethyl vinyl ether, PPTS, CH₂Cl₂ (quant.). ii. TBAF, THF (76%). (f) Dess-Martin periodinane (68%).

reported the conversion of diethyl *D*-tartrate to alcohol **15**, which had all the asymmetric center of the target fragment. Introduction of the asymmetric methyl group was performed by hydroboration-oxidation of **14** with 9-BBN. The hydroxy group of **15** was converted to a dibromide **16** and then to a propargyl alcohol **17**. Epimerization of the methyl group was not detected. The TBS group was removed (**18**) and the resulting hydroxy group was oxidized to give C9'-C15' fragment aldehyde **19**. The overall yield was 8.3% in six steps from **14**.

In conclusion, the C9'-C15' fragment for the total synthesis of enacyloxin antibiotics was prepared from the known alcohol derived from diethyl *D*-tartrate. Preparation of a C16'-C23' is described by Igarashi et al. (2011).

Acknowledgments

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