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Preliminary Communication

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

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Abstract

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

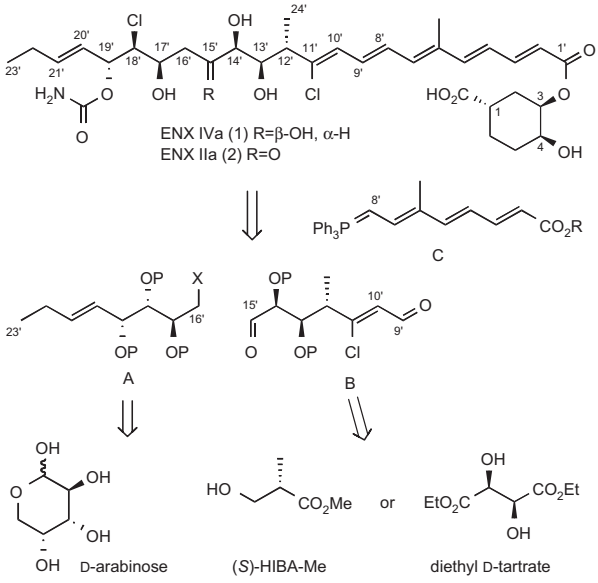
Keywords: antibiotics; diethyl D-tartrate; enacyloxins; *Frateuria* sp. W-315; synthesis.

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.

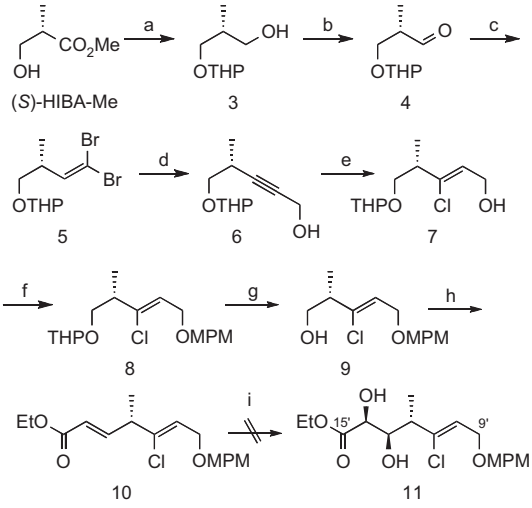
Scheme 1 shows our retrosynthetic plan. Disconnection of the whole molecule (**1** or **2**) leads to three fragments **A**, **B**, and **C**. The C8′-C9′ double bond could be formed by Wittig reaction and nucleophilic addition is suitable for the C15′-C16′ connection. The stereochemistry of fragments **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*-chlorosuccimide (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 ^{1}H NMR analysis of the corresponding (*S*)-MTPA ester (**13**). As a result, all



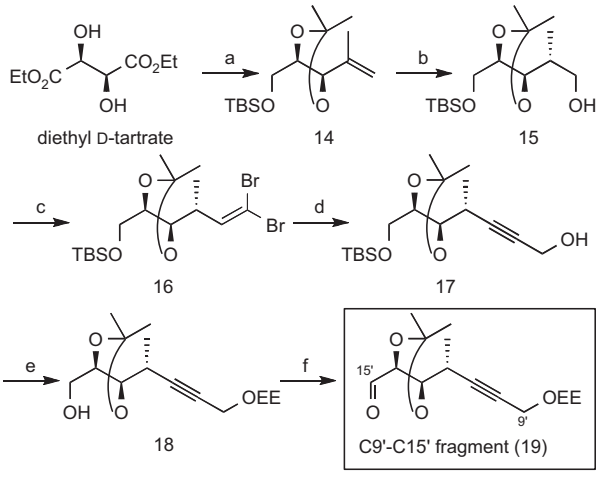
Scheme 1 Enacyloxins and their retrosynthetic analysis.



Scheme 2 Synthetic studies of C9′-C15′ fragment-1. (a) i. DHP, PPTS, $CHCl_3$. ii. $LiAlH_4$, THF. (b) Swern oxidation. (c) CBr_4, PPh_3, Et_3N, MeCN (69% from **3**). (d) BuLi, $(CH_2O)_n$, 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, CH_2Cl_2. ii. $Ph_3P{=}CHCO_2Et$, PhMe (77% from **9**). (i) AD-mix β, $MeSO_2NH_2$, *t*-BuOH-H_2O.

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.

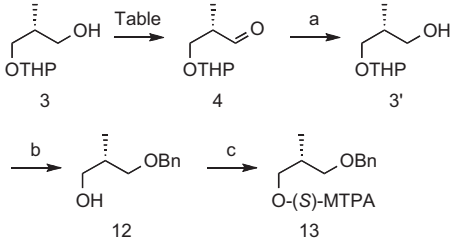
Next, we planned to use a dihydroxy moiety of D-tartrate for the C13′-C14′ position (Scheme 3). Araki et al. (2002) reported the conversion of diethyl D-tartrate to alcohol **15**, which had all the asymmetric center of the target fragment. Introduction of the asymmetric methyl group was performed by 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**.



Scheme 3 Synthesis of C9′-C15′ fragment 2. (a, b) Araki et al., 2002. (c) i. Swern oxidation (87%). ii. CBr_4, PPh_3, Et_3N, CH_2Cl_2 (43%). (d) BuLi, $(CH_2O)_n$, THF (43%). (e) i. ethyl vinyl ether, PPTS, CH_2Cl_2 (quant.). ii. TBAF, THF (76%). (f) Dess-Martin periodinane (68%).

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).

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



(a) $LiAlH_4$, THF. (b) i. NaH, BnCl, NaI, THF. ii. TsOH, MeOH (ca. 55% from **3**). (c) (*R*)-MTPACl, Py, CH_2Cl_2 (quant.).

Entry	Conditions	$[\alpha]_D$ of 12[a]	Optical purity (%)[b]
1	DMSO, $(COCl)_2$, Et_3N, -70°C to 0°C	–14.0°	81
2	DMSO, SO_3·Py, Et_3N, 0°C	–12.0°	69
3	Dess-Martin periodinane, CH_2Cl_2, 0°C	–14.6°	85
4	PCC, MS4Å, CH_2Cl_2, 0°C	–6.9°	40

[a]$[\alpha]_D$ (*c*=4.00, $CHCl_3$). [b]Optical purity was calculated based on *ent*-**12** {>98% ee, $[\alpha]_D$=+17.2° (*c*=3.24, $CHCl_3$)} reported by Nagaoka and Kishi (1981).

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