Heterocycl. Commun., Vol. 17(1-2), pp. 7–9, 2011 • Copyright © by Walter de Gruyter • Berlin • Boston. DOI 10.1515/HC.2011.008

Preliminary Communication

Stereochemistry of enacyloxins. Part 6: Synthesis of C16′-C23′ fragments of enacyloxins, a series of antibiotics from *Frateuria* sp. W-315

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Abstract

The C16′-C23′ fragments of enacyloxins, a series of antibiotics isolated from *Frateuria* sp. W-315, were synthesized from D-arabinose.

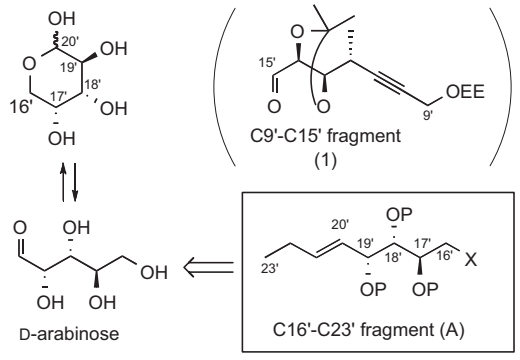
Keywords: antibiotics; D-arabinose; enacyloxins; *Frateuria* sp. W-315; synthesis; Wittig-Horner reaction.

In the preceding paper, we described our synthesis of a C9′-C15′ fragment **1** of enacyloxins (ENXs) (Furukawa et al., 2011). As a continuation, we began to prepare a C16′-C23′ fragment **A**, a nucleophilic counterpart of **1**, from D-arabinose to construct a C9′-C23′ polyol fragment (Scheme 1). The stereochemistry of 17′,18′,19′-positions could be derived from 2,3,4-positions of D-arabinose.

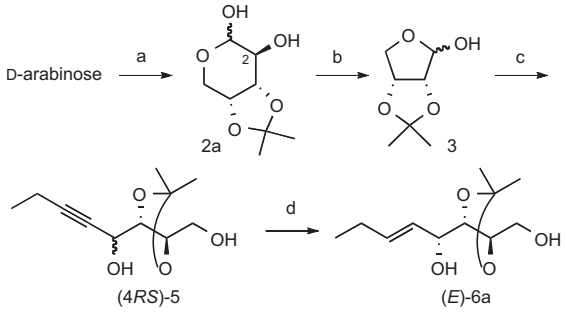
First, we chose a route via an alkyne (Scheme 2). 3,4-*cis*-Dihydroxy group of D-arabinose was selectively protected as an acetonide (**2a**) (Ballou, 1957; Kiso and Hasegawa, 1976). Oxidative fragmentation of **2a** was accomplished by León's procedure (León et al., 2006) to give erythrose derivative **3**. In our case, the intermediary formate was not isolated. Nucleophilic addition of 1-butynyllithium gave a diastereomeric mixture (4*RS*)-**5** (*R*/S=2.5:1). The undesired *S*-isomer could be removed after reduction of the triple bond [(*E*)-**6a**]. Although (*E*)-**6a** has the same stereochemistry with **A**, the elimination of the asymmetry of 2-position of **2a** and the separation of *R/S*-isomers are problems.

Thus, direct elongation of the anomeric 1-position of **2a** was examined. Several **2a** derivatives with a protection of the 2-hydroxy group were prepared (Scheme 3). Carbamoyl (**2b**), *p*-methoxyphenylmethyl (MPM, **2c**), and TBS (**2d**) (Enholm and Trivellas, 1989) ethers were prepared via a benzyl ether **7** (Ballou, 1957). Whereas the 1-position of **2a** was selectively oxidized with iodine (**4a**) (Stewart et al., 2002), the remaining 2-hydroxy group was protected as TBDPS and MOM ether to give **4e** and **4f**, respectively. The lactonic carbonyl group of **4e** was again reduced by DIBAL to give **2e**.

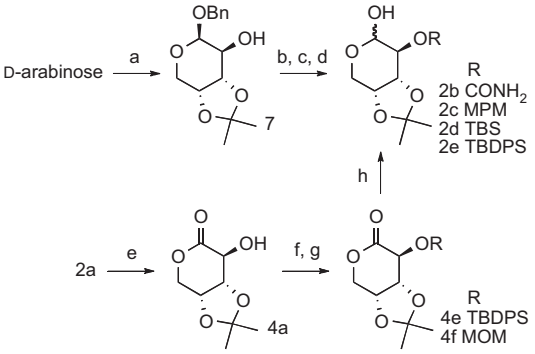
The representative results of Wittig and the related reactions of hemiacetals **2a**–**2e** are listed in Table 1. Usual conditions for Wittig reaction gave no olefin product (entry 1), and thus we applied Fitjer's harsh conditions (Fitjer and Quabeck, 1985). Unprotected and TBDPS protected hemiacetals **2a** and **2e** afforded olefin **6a** and **6e**, respectively, in 70% yield; however, these products (*E*/*Z*=1:1) were an inseparable mixture (entries 2 and 10). Ohira reagents (Ohira, 1989) gave an alkyne **9** in moderate yield (entry 4). The low reactivity of the carbamate **2b** was due to its high polarity (entries 5–7). Other reactions such as Julia olefination and Wittig-Schlosser reactions gave a complex mixture or recovered a starting material (data not shown).



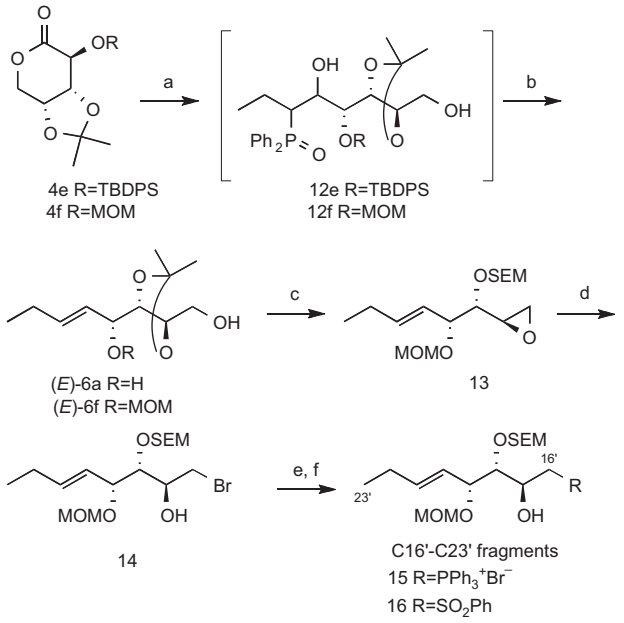
Scheme 1 Retrosynthetic analysis of the C16′-C23′ fragment.



Scheme 2 Alkyne route. (a) Kiso and Hasegawa, 1976. (b) $NaIO_4$, $NaHCO_3$, CH_2Cl_2-EtOH-H_2O (57%). (c) EtC≡CH, BuLi, THF, -78°C, (*R/S*=2.5:1, 76%). (d) i. $LiAlH_4$, ether, reflux. ii. separation (66%).



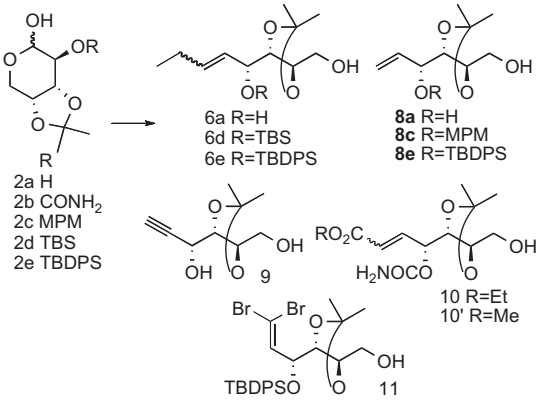
Scheme 3 Preparation of various substrates for chain elongation. (a) i. BnOH, AcCl. ii. 2,2-DMP, PPTS (97%, two steps). (b) i. NaOCN, TFA, CH_2Cl_2 (97%). ii. H_2, 10% Pd-C, EtOH. (c) i. NaH, MPMCl, DMSO (71%). ii. Raney Ni (W_2), EtOH (26%). (d) i. TBSCl, imidazole, DMF. ii. H_2, $Pd(OH)_2$, $NaHCO_3$, EtOH (95% from **7**). (e) i. I_2, $NaHCO_3$, acetone-H_2O (60%). (f) i. TBDPSCl, imidazole, DMF (78%). (g) MOMCl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2 (quant.). (h) DIBAL, CH_2Cl_2 (quant.).



Scheme 4 Synthesis of C9′-C15′ fragment. (a) i. $PrP(O)Ph_2$, BuLi, THF. ii. $NaBH_4$, EtOH-H_2O. (b) NaH, DMF [10% for (*E*)-**6a** and 54% for (*E*)-**6f**]. (c) i. TsCl, Et_3N, CH_2Cl_2. ii. AcOH-H_2O. iii. NaH, THF. iv. SEMCl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2 [41%, four steps from (*E*)-**6f**]. (d) $MgBr_2$, CH_2Cl_2 (quant.). (e) PPh_3, THF (15%). (f) PhSSPh, $NaBH_4$, EtOH. ii. $Mo_7O_{24}(NH_3)_6{\cdot}4H_2O$, H_2O_2, EtOH (40%).

Because the separation or isomerization of the *E/Z*-isomers (**6a**, **6d**, and **6e**), chain elongation of alkenes (**8e** and **11**), and alkyne **9** failed, Wittig-Horner reaction (Buss and Warren, 1985) with lactones **4e** and **4f** was examined (Scheme 4). Nucleophilic attack of the anion derived from diphenylpropylphosphine oxide to **4e** followed by reduction with $NaBH_4$

Table 1 Wittig and related reactions of the hemiacetals.



Entry	Hemiacetal	Conditions	Product (*E/Z*)	Yield (%)
1	**2a**	Ph_3PPrI, NaH, CH_2Cl_2, 0°C–20°C	–	–
2	**2a**	Ph_3PPrBr, KO*t*-Bu, toluene, reflux	**6a** (50:50)	70
3	**2a**	Ph_3PMeBr, KO*t*-Bu, toluene, reflux	**8a**	78
4	**2a**	Ohira reagent, K_2CO_3, MeOH	**9**	40
5	**2b**	$Ph_3P{=}CHCO_2Et$, toluene, 50°C	**10** (43:57)	5
6	**2b**	$Ph_3P{=}CHCO_2Me$, CH_2Cl_2, 50°C	**10′** (10:90)	21
7	**2b**	$(EtO)_2P(O)CH_2CO_2Et$, NaH, DMF	–	–
8	**2c**	Ph_3PMeBr, KO*t*-Bu, toluene, reflux	**8c**	70
9	**2d**	Ph_3PPrI, BuLi, toluene	**6d** (0:100)	32
10	**2e**	Ph_3PPrBr, KO*t*-Bu, toluene, reflux	**6e** (50:50)	70
11	**2e**	Ph_3PMeBr, KO*t*-Bu, toluene, reflux	**8e**	10
12	**2e**	$(Ph_3PCHBr_2)Br$, Zn, 1,4-dioxane	**11**	15

afforded **12e**. As ^{1}H NMR was very complex, crude **12e** was treated with NaH. Only *E*-isomer without TBDPS group (*E*)-**6a** was isolated in 10% yield. The same reaction sequence was performed using alkaline tolerable MOM protecting group, giving (*E*)-**6f** in 40% yield. The corresponding (*Z*)-isomer was not detected. (*E*)-**6f** was converted to a 3-SEM-oxy 1,2-epoxide **13** to discriminate 2,3-oxygen functions, and the epoxy ring was cleaved with $MgBr_2$ in CH_2Cl_2 to give a bromohydrin **14**. Finally, the C16′-C23′ fragments, Wittig salt **15**, and Julia sulfone **16** were prepared.

In conclusion, the C16′-C23′ fragments, Wittig salt **15**, and Julia sulfone **16** were prepared in diastereomerically pure forms from D-arabinose using Wittig-Horner reaction as the key step. Coupling reactions of the C16′-C23′ fragments with the C9′-C15′ aldehyde are under investigation.

Acknowledgments

The authors thank Dr. Toshihiko Watanabe for useful discussion. Financial support by grant-in-aid from the Japan Society for the Promotion of Science (No. 17580092), the Naito Foundation, the Intelligent Cosmos Foundation, and the Kuribayashi Ikuei Foundation are gratefully acknowledged.

References

Ballou, C. E. A new synthesis of D-erythrose derivatives from D-arabinose. *J. Am. Chem. Soc.* **1957**, *79*, 165–166.

Buss, A. D.; Warren, S. The stereocontrolled Horner-Wittig reaction: synthesis of disubstituted alkenes. *J. Chem. Soc., Perkin Trans 1* **1985**, 2307–2325.

Enholm, E. J.; Trivellas, A. Samarium(II) iodide mediated transformation of carbohydrates to carbocycles. *J. Am. Chem. Soc.* **1989**, *111*, 6463–6465.

Fitjer, L.; Quabeck, U. The Wittig reaction using potassium-*tert*-butoxide high yield methylenations of sterically hindered ketones. *Synth. Commun.* **1985**, *15*, 855–864.

Furukawa, H.; Hoshikawa, H.; Igarashi, W.; Yaosaka, M.; Yamada, T.; Kuwahara, S.; Kiyota, H. Stereochemistry of enacyloxins. Part 5: Synthesis of a C9′-C15′ fragment of enacyloxins, a series of antibiotics from *Frateuria* sp. W-315. *Heterocycl. Commun.* **2011**, *17*, 3–5.

Kiso, M.; Hasegawa, A. Acetonation of some pentoses with 2,2-dimethoxypropane-*N*,*N*-dimethylformamide-*p*-toluenesulfonic acid. *Carbohydr. Res.* **1976**, *52*, 95–101.

León, F.; Brouard, I.; Rivera, A.; Torres, F.; Rubio, S.; Quintana, J.; Estévez, F.; Bermejo, J. Isolation, structure elucidation, total synthesis, and evaluation of new natural and synthetic ceramides on human SK-MEL-1 melanoma cells. *J. Med. Chem.* **2006**, *49*, 5830–5839.

Ohira, S. Methanolysis of dimethyl (1-diazo-2-oxopropyl) phosphonate: generation of (diazomethyl)phosphonate and reaction with carbonyl compounds. *Synth. Commun.* **1989**, *19*, 561–564.

Stewart, A. J.; Evans, R. M.; Weymouth-Wilson, A. C.; Cowley, A. R.; Watkin, D. J.; Fleet, G. W. J. 2-Deoxy-L-ribose from an L-arabinono-1,5-lactone. *Tetrahedron: Asymmetry* **2002**, *13*, 2667–2672.

Received April 19, 2011; accepted April 26, 2011