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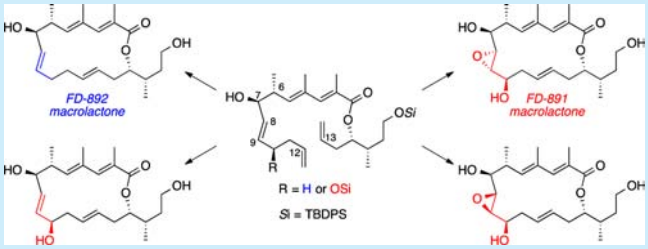
# A Concise and Unified Strategy for Synthesis of the C1−C18 Macrolactone Fragments of FD-891, FD-892 and Their Analogues: Formal Total Synthesis of FD-891

Naoki Kanoh,*[,†] Ayano Kawamata,[†] Tomohiro Itagaki,[†] Yuta Miyazaki,[†] Kenzo Yahata,[†] Eunsang Kwon,[‡] and Yoshiharu Iwabuchi[†]

[†]Graduate School of Pharmaceutical Sciences and [‡]Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University, 6-3 Aza-Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan

Supporting Information

**ABSTRACT:** A concise and unified strategy for the synthesis of C1−C18 macrolactone fragments of FD-891 and FD-892 as well as their analogues is reported. The strategy includes a stereoselective vinylogous Mukaiyama aldol reaction (VMAR) using chiral silyl ketene *N,O*-acetal to construct C6−C7 stereocenters, an *E*-selective ring closing metathesis to construct a C12−C13 olefin, and stereodivergent construction of a C8−C9 epoxide.




In 1994, FD-891 (**1**) and FD-892 (**2**) were isolated from the fermentation broth of *Streptomyces graminofaciens* A-8890 by the researchers of Taisho Pharmaceutical Co., Ltd.[1] Their structures were first proposed to be 18-membered macrolides[1b,c] but were later reassigned as 16-membered macrolides by Eguchi et al., as shown in Figure 1A.[2] These macrolides have

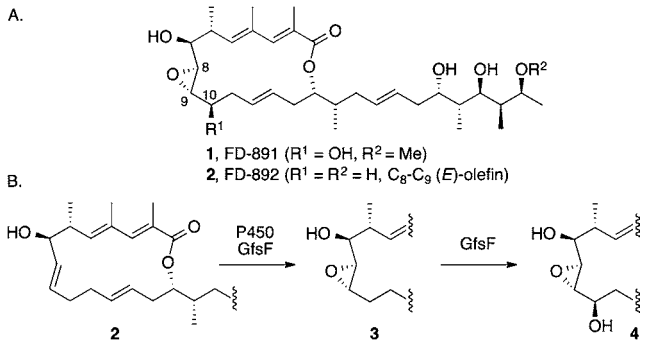



**Figure 1.** Chemical structure of FD-891 and FD-892, and introduction of the C8−C10 oxygen functionality of FD-891 catalyzed by the dual functionality of P450 enzyme GsfF.

been reported to show several biological activities,[1a,3] including cytotoxic activity against several tumor cell lines, when used at ten nanomolar for FD-891, **1**, and micromolar for FD-892, **2**, concentration ranges. Thus, FD-891, **1**, shows more than 100 times the potency of FD-892, **2**.[1a] Among the three structural differences between FD-891, **1**, and FD-892, **2**, the electrophilic C8−C9 epoxide is thought to be the origin of the high potency of FD-891, **1**.[1a] Although some SAR and biochemical studies on FD-891, **1**, have been carried out, its molecular target(s) and mode-of-action have not been clarified yet.

In addition to these structural and biochemical studies, Kudo et al. reported an interesting biosynthetic study regarding the origin of the C8−C10 oxygen functionality of FD-891, **1**.[4] During the characterization of the biosynthetic gene cluster of FD-891, **1**, they found that one cytochrome P450 enzyme named GfsF catalyzes not only epoxidation of the C8−C9 olefin but also C−H oxidation at C10 in a stepwise manner (*i.e.*, **2** → **3** → **4**) as shown in Figure 1B.

We are quite interested in the chemistry, biology, and biogenesis of FD compounds, including the substrate specificity of the GfsF enzyme. To study these matters in detail, we considered that it would be useful to develop a concise and unified strategy that could synthesize possible derivatives having altered C8−C10 oxygen functionality, because such derivatives are not always easy to obtain by fermentation. To date, three total syntheses[5] of FD-891, **1**, have been reported; however, all of them introduced the C8−C9 epoxide and C10 hydroxyl group in the early stage of the synthesis, and thus none are suitable for the modification of these portions. In addition, total synthesis of FD-892, **2**, has not been reported so far.

We therefore decided to develop a synthetic strategy that could be easily utilized for the synthesis of C1−C18 macrolactone fragments of FD compounds and their derivatives having different C8−C10 oxygen functionalities. Our strategy is summarized in Scheme 1.

C1−C18 macrolactones **5**−**8** were set as targets of our synthetic study because we wanted to test these compounds for cytotoxic activity and GfsF-catalyzed oxidation reaction, and the C18 primary hydroxyl group of these molecules would be used

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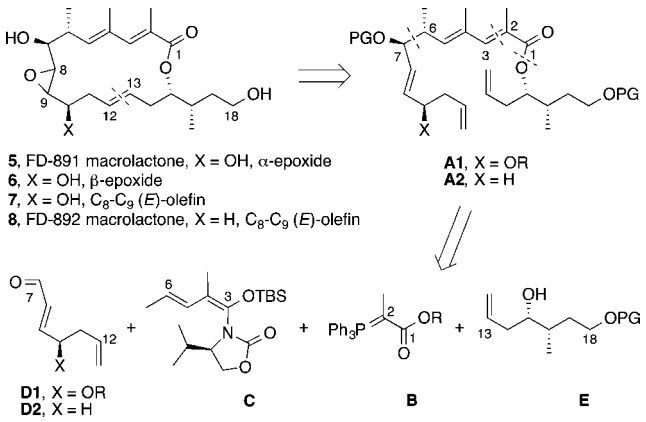
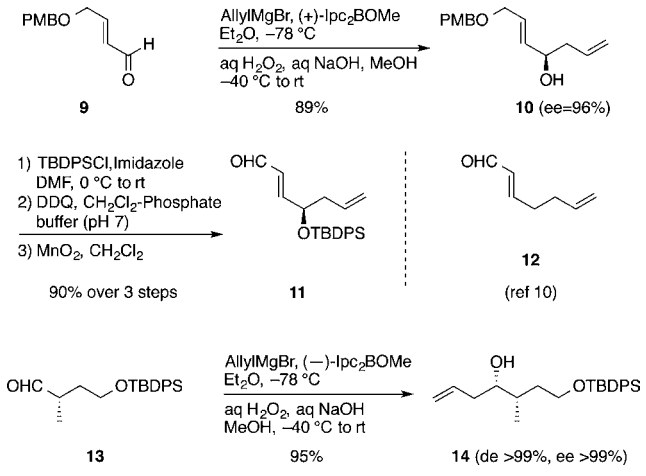
**Scheme 1. Retrosynthetic Analysis of the C1−C18 Macrolactone Part of FD Compounds**




for the further introduction of a side chain. Thus, the C8−C9 epoxide was retrosynthetically removed, and the C12−C13 olefin was cleaved to generate intermediates **A1** and **A2**, which were set as our common subtargets. We expected that the C8−C9 epoxide could be installed stereoselectively in the late stage of the synthesis by utilizing an adjacent C7 or C10 hydroxyl group. However, the construction of the C12−C13 (*E*)-olefin via the ring-closing metathesis (RCM) reaction of **A** could be challenging, because RCM between the C13 and C2 carbons has the potential to generate *δ*-lactone: However, we previously experienced a similar situation during the synthesis of polyene macrolactam glycoside,[6] in which the RCM between terminal monosubstituted olefins was predominant over the other RCMs to deliver the desired macrocycle. Thus, we expected that selective formation of the C12−C13 olefin was also feasible in the present case. The intermediates **A1** and **A2** were further divided into five fragments: i.e., C1−C2 Wittig reagent **B**, C3−C6 vinylketene *N,O*-acetal **C**, C7−C12 aldehydes **D1** and **D2**, and C13−C18 alcohol **E**. We envisioned that the C6 and C7 stereocenters could be constructed by a vinylogous Mukaiyama aldol reaction (VMAR) of fragments **D** and **C**.[7]

The synthesis commenced with the preparation of the fragment **D1** (Scheme 2). Known enal **9**[8] was subjected to Brown asymmetric allylboration/oxidation[9] using (+)-Ipc$_2$BOMe and allylmagnesium bromide to give homoallyl

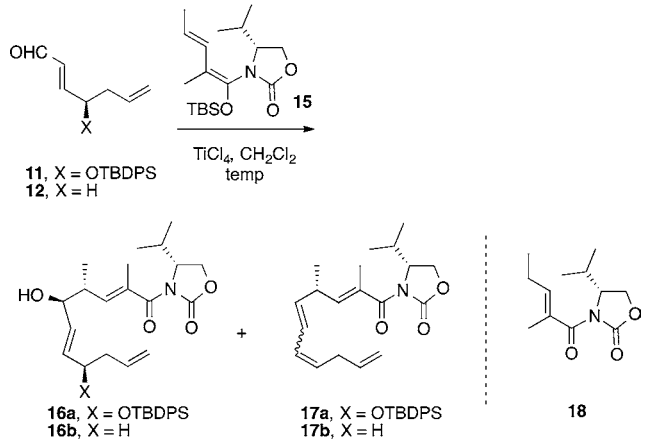
**Scheme 2. Synthesis of C7−C12 Fragments 11 and 12 and C13−C18 Fragment 14**




alcohol **10** in 89% yield and 96% ee (Scheme 2). Protection of its hydroxyl group as TBDPS ether followed by removal of the PMB group and $MnO_2$ oxidation afforded *γ*-silyloxy-*α,β*-unsaturated aldehyde **11** in 90% yield in three steps. The C7−C12 fragment **D2** (*i.e.*, **12**) was prepared from allyl vinyl ether according to the reported procedures with some modifications.[10] C13−C18 fragment **E** (*i.e.*, **14**) was synthesized by Brown allylboration of known aldehyde **13**[11] using (−)-Ipc$_2$BOMe and allylmagnesium bromide in 95% yield with high enantio- and diastereoselectivities.

Vinylogous Mukaiyama aldol reactions of vinylketene *N,O*-acetal **15** and C7−C12 fragments **11** and **12** were then examined (Table 1). Reaction of **15** (5 equiv) and aldehyde **11**

**Table 1. Vinylogous Mukaiyama Aldol Reactions of Vinylketene *N,O*-Acetal 15 and C7−C12 Fragments 11 and 12**[a]




| entry | aldehyde | temp (°C) | yield;[b] 16 | yield;[b] 17 |
|---|---|---|---|---|
| 1 | **11** | −78 to 0 | 95% | 0% |
| 2 | **12** | −78 to 0 | 27% | 33% |
| 3 | **12** | −78 to −20 | 42% | >9% |

[a]5 equiv each of acetal **15** and $TiCl_4$ were used. [b]Isolated yield.

in the presence of $TiCl_4$ (5 equiv) proceeded smoothly to give adduct **16a** in 95% yield (Table 1, entry 1). Relative and absolute stereochemistry of the newly generated stereocenters in **16a** was confirmed after leading to the known compound[12] and by the modified Moscher analysis, respectively (see the Supporting Information). To achieve a high yield and stereoselectivity, 5 equiv of **15** and $TiCl_4$ were necessary, but a total of 3 equiv of **15** and its desilylated product **18** were recovered and could be reused. When the same reaction conditions were applied for aldehyde **12** (Table 1, entry 2), desired adduct **16b** was obtained only in 27% yield and a considerable amount of dehydrated product **17b** (33%) was produced. However, the yield of **16b** could be improved just by changing the reaction temperature (Table 1, entry 3). Again, no stereoisomer was observed in this case.

With the desired C3−C12 fragments **16a** and **16b** in hand, we then introduced C1−C3 and C13−C18 moieties on these fragments by using our strategy of several unified procedures (Scheme 3). Protection of the C7 hydroxyl group followed by DIBAL-H reduction afforded aldehydes **19a** and **19b** in 90% and 72% yields, respectively. Wittig reactions using phosphonium salt **20**[13] and the following TMSOK[14] treatments gave carboxylic acids **21a** and **21b** in excellent yields. The C13−C18 fragment **14** was effectively coupled with these carboxylic acids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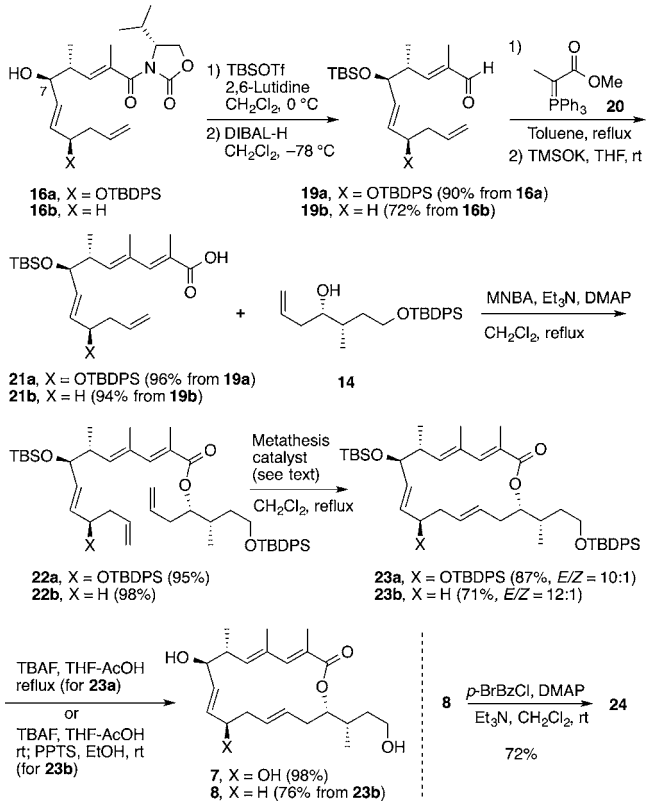
**Scheme 3. Synthesis of Macrolactones 7 and 8**




using 2-methyl-6-nitrobenzoic anhydride[15] (MNBA) to afford pentaenes **22a** and **22b**.

We next examined the RCM reaction of these substrates. To our delight, the desired RCM reactions of **22a** and **22b** were successfully catalyzed by a Grubbs second generation catalyst[16] and a Hoveyda-Grubbs second generation catalyst[17] (20 mol % each), respectively, to produce macrolactones **23a** (87%) and **23b** (71%) with high *E*-selectivity.[18] Note that no $\delta$-lactone was obtained, as discussed earlier. Finally, deprotection of the silyl-protecting group furnished macrolactone **7** and FD-892 macrolactone **8** in good yields. The structure of **8** was unambiguously confirmed by X-ray crystal analysis after leading to its *p*-bromobenzoate **24** (Figure 2).

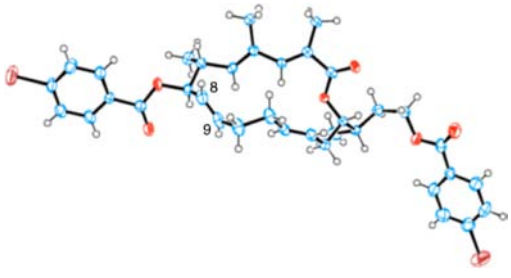
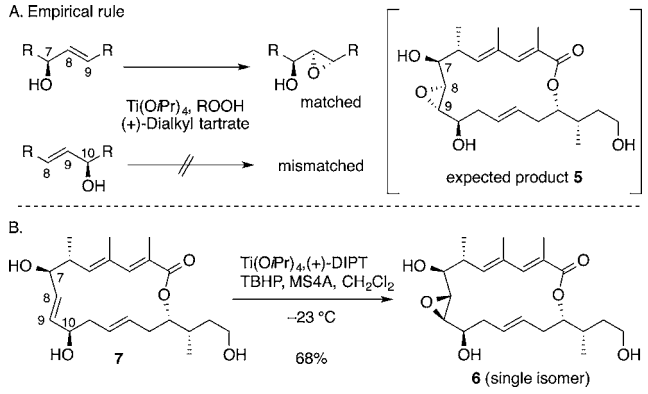


**Figure 2.** X-ray crystal structure of *p*-bromobenzoate, **24**.

Next, we examined the stereoselective introduction of the C8−C9 epoxide in **7** (Scheme 4). We originally planned to obtain $\alpha$-epoxide **5** via a "matched" reagent-controlled Sharpless asymmetric epoxidation using Ti(O*i*Pr)$_4$, (+)-dialkyl tertarate, and *tert*-butyl hydroperoxide (*t*BuOOH).[19] In this case, we utilized the empirical rule prediction from which complexation of Ti, (+)-DIPT, and the C7 hydroxyl group of **7**

**Scheme 4. Allylic Epoxidation of Triol 7**

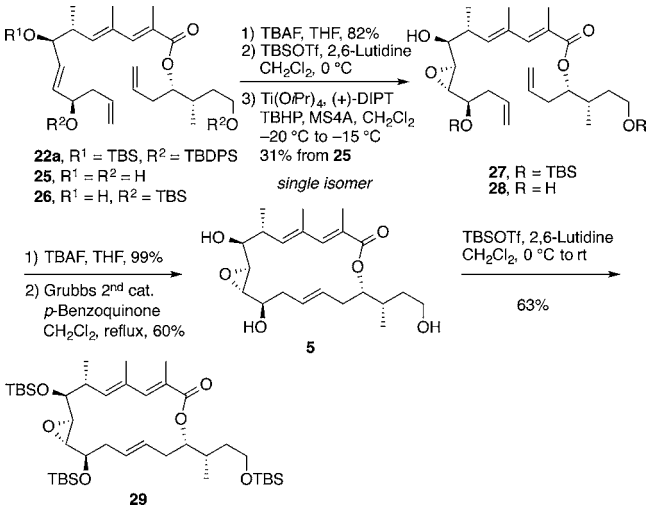



resulted in the generation of the desired C8−C9 $\alpha$-epoxide (Scheme 4A). However, reaction of triol **7** under the Sharpless conditions with (+)-DIPT cleanly gave $\beta$-epoxide **6** in 68% yield as a single isomer (Scheme 4B). Moreover, all efforts to invert the face selectivity of the epoxidation of macrolactones derived from **7** were found to be unsuccessful: for example, epoxidation of **7** using vanadyl acetylacetonate and *t*BuOOH and Sharpless epoxidation of **7** with (−)-DIPT both gave **6** as a major product (data not shown).

Inspection of the X-ray structure of **24** (Figure 2) as well as the NMR-based solution structure of triol **7** in $CDCl_3$ (see the Supporting Information) indicated that these macrocycles **7** and **24** have similar local conformations around the C8−C9 olefin, which could enforce hydroxyl-group-directed and peripheral epoxidation to give the $\beta$-epoxide.

Thus, we next examined the epoxidation of the C8−C9 double bond before the ring-closing metathesis reaction. To this end, tetraene **22a** was treated with TBAF to afford triol **25** in 82% yield (Scheme 5). Gratifyingly, epoxidation of **25** under

**Scheme 5. Synthesis of $\alpha$-Epoxides 5 and 29**




the Sharpless conditions with (+)-DIPT generated a 3:1 mixture of C8−C9 epoxides, with the desired $\alpha$-epoxide as a major isomer (data not shown). The following inspection of the substrate structure and reaction conditions on the face selectivity of C8−C9 epoxidation revealed that the C7 free hydroxyl group, protected C10 hydroxyl group, and (+)-tartrate ligand are important for the $\alpha$-selectivity. After considerable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experimentation, we finally found that epoxidation of diTBS ether **26**, which was prepared from **25**, under the Sharpless conditions with (+)-DIPT afforded $\alpha$-epoxide **27** in modest yield but as a single isomer (Scheme 5). The RCM reaction proceeded efficiently, when triol **28** was used as a substrate, to give macrolactone **5** in 60% yield. Macrocyclic triol **5** was further converted to triTBS ether **29**, whose spectral data were in accord with those of a synthetic intermediate for Crimmins' and Yadav's total synthesis,[5a,f] which means that formal total synthesis of FD-891, **1**, was accomplished at this stage.

In summary, we accomplished not only the concise and unified synthesis of C1−C18 macrolactones **5**−**8** (15-, 13-, 12-, and 9-step longest linear sequence from known starting materials, respectively), but also the formal total synthesis of FD-891. Stereoselective VMAR to construct C6−C7 stereocenters, *E*-selective RCM to introduce the C12−C13 olefin, and stereodivergent epoxidation of the C8−C9 olefin are the key features of the present synthesis. Macrolactones **5**−**8** would be important intermediates and substrates for studying the relationship between the structure of the FD compounds and its antitumor activity, GsfF-catalyzed C8−C10 oxygenation reactions, and GsfF−substrate interaction. These are in progress in our laboratory and will be reported in due course.

## ■ ASSOCIATED CONTENT

### Supporting Information

Full experimental and characterization details for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: nkanoh@m.tohoku.ac.jp.


### Notes

The authors declare no competing financial interest.

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