Stereoselective Synthesis of the C1-C12 Fragment of the Cytotoxic Macrolide FD-891

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Abstract: A stereoselective synthesis of the C1-C12 fragment of the naturally occurring, cytotoxic macrolide FD-891, is described. The initial chirality was created via an asymmetric Evans aldol reaction. Two other asymmetric reactions, a Sharpless epoxidation and an aldehyde Brown allylation were further key steps of the synthesis.

Key words: antitumor agents, aldol reactions, chiral auxiliaries, stereoselective synthesis, asymmetric allylations

The cytotoxic metabolite FD-891 was isolated from the fermentation broth of *Streptomyces graminofaciens* A-8890 and was found active against several tumor cell lines. In addition, it was found to potently prevent both perforin- and FasL-dependent CTL-mediated killing pathways. In contrast to the structurally related concanamycin A, however, it was unable to inhibit vacuolar acidification. According to the results of chemical degradations and X-ray diffraction analyses of the degradation products, the structure of FD-891 was reported two years ago to be that depicted below (Figure 1).[1] In line with this structural assignment, we performed a stereoselective synthesis of the whole side chain of the molecule, a fragment with seven stereocenters.[2] However, the group which investigated FD-891 two years ago reported this year a correction of its structure, which now turns out to be as shown in Figure 1.[3] While no changes in stereochemistry have resulted from this structural change, one olefinic bond has now been moved from inside the ring to the side chain. In view of this, we have seen ourselves in the need of carrying out a substantial modification of the initial synthetic plan. Fortunately, most of the ring part of the molecule has remained untouched by the structural amendment, so that we have been able to use a part of our previous synthetic sequence.

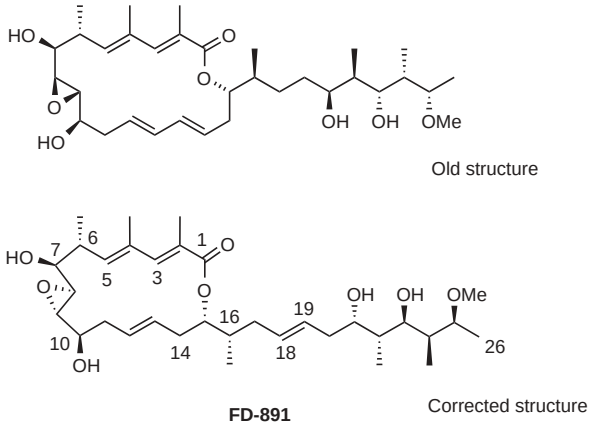
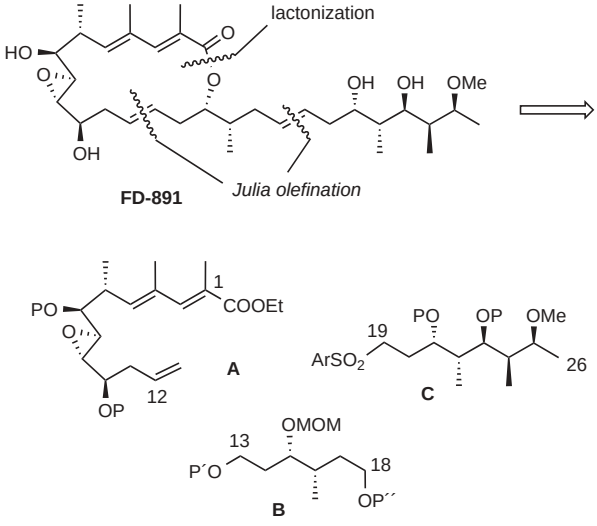


Figure 1



Scheme 1 Retrosynthetic analysis of FD-891.

For our modified synthesis of this bioactive metabolite, we have chosen the retrosynthetic plan shown in Scheme 1 (P, P′, P″ = protecting groups). According to it, the molecule of FD-891 is disconnected to fragments **A** (C1-C12, the extra carbon atom is to be removed later via oxidative cleavage), **B** (C13-C18) and **C** (C19-C26). The reactions planned to connect these three fragments are a macrolactonization[4] and two Julia olefinations.[5]

In the present communication, we describe the synthetic work performed to achieve the preparation of fragment **A** (P = TBDMS).[6] This fragment contains five out of the twelve sp^3 stereocenters of the molecule and was retrosynthetically disconnected as shown below in Scheme 2. One key structural retrotransformation (**A** → **I**) is the stereoselective allylation of a chiral α,β-epoxyaldehyde while the

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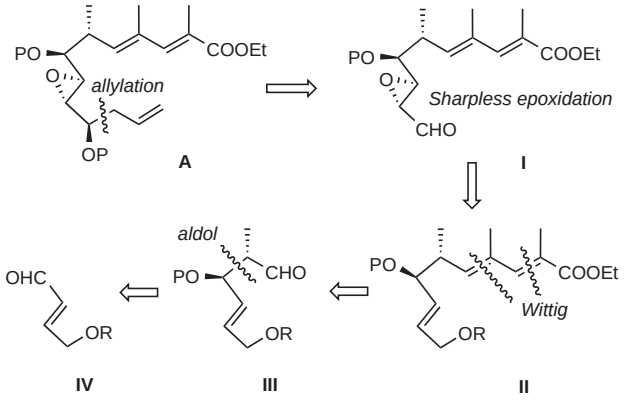
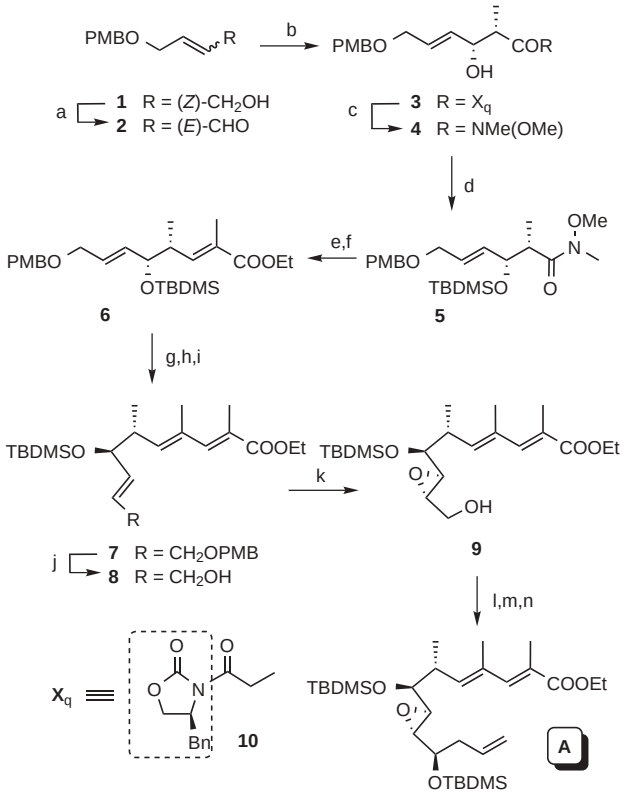
other (**III** → **IV**) is an aldol reaction intended to add the Me-C4-C5 propionate segment. The other two propionate segments are added via Wittig olefinations (**II** → **III**).



Scheme 2 Retrosynthetic analysis of fragment **A**.



Scheme 3 *Reagents and conditions*: a) PCC, CH_2Cl_2, r.t., 4 d, 52%; b) **10**, Bu_2BOTf, Et_3N, CH_2Cl_2, –78 °C, 30 min, then **2**, –40 °C, 12 h, 86%; (c) *N*,*O*-dimethylhydroxylamine, Me_3Al, THF, r.t., 1 h, then **3**, 3 h; (d) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, r.t., 1 h, 77% overall yield for the two steps; e) DIBAL, THF, –78 °C, 30 min; (f) Ph_3P=C(Me)COOEt, 1,2-dichloroethane, 60 °C, 12 h, 55% overall yield for the two steps; g) DIBAL, hexane, r.t., 1 h, 76%; h) MnO_2, CH_2Cl_2, Δ, 2 h; i) $(EtO)_2P(O)CH(Me)COOEt$, *n*-BuLi, THF, 0 °C, then addition of the crude aldehyde, 12 h, 84% overall yield for the two steps; j) DDQ, wet CH_2Cl_2, r.t., 2 h, 89%; (k) diethyl L-tartrate, $Ti(O\textit{i}\text{-}Pr)_4$, *t*-BuOOH, powdered 4 Å MS, CH_2Cl_2, –23 °C, 24 h, 60%; (l) Swern oxidation; (m) allylBIpc$_2$ [from (+)-DIP-Cl and allylmagnesium bromide, see text], Et_2O, 1 h, –90 °C, 66% overall yield for the two steps (dr, 85:15); (n) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, r.t., 1 h, 90%.

Scheme 3 depicts the actual synthetic sequence, which led to **A**. The commercially available (*Z*)-2-butene-1,4-diol was first converted into its monoprotected derivative **1** (= **IV** with R = PMB, *p*-methoxybenzyl),[7] PCC oxidation of which afforded the (*E*)-2-butenal **2**.[8] The aldol reaction which generates the initial chirality was performed with the aid of the Evans methodology.[9] To this purpose, *N*-propionyl oxazolidinone (**10**) was converted into its boron *Z*-enolate and added to aldehyde **2**. This furnished aldol adduct **3**, which was then converted into Weinreb amide **4**.[10] Since this product proved difficult to purify, it was used in crude form in the next silylation step. Compound **5** was then reduced with DIBAL to the corresponding aldehyde (H replacing NMeOMe), which, without chromatographic purification, was taken to the Wittig olefination step. This afforded the conjugated enoate **6**,[11] which was subjected to a second reduction–olefination sequence to yield the conjugated dienoate **7**. Cleavage of the PMB protecting group with DDQ[12] in wet CH_2Cl_2 was followed by an asymmetric Sharpless epoxidation.[13] The resulting epoxy alcohol **9** was then oxidized to the corresponding aldehyde and the latter was subjected in crude form to asymmetric allylation using the chiral B-allyl diisopinocampheylborane (allylBIpc$_2$) prepared from allylmagnesium bromide and (+)-DIP-Cl (diisopinocampheylboron chloride).[14] This procedure furnished in 66% overall yield a homoallyl alcohol as an 85:15 mixture of diastereomers. Subsequent silylation finally gave the desired product **A**.[15–17]

In summary, a stereoselective synthesis of the C1-C12 fragment of the cytotoxic macrolide FD-891 has been achieved. Studies towards the total synthesis of the natural product are underway and will be published in due course.

Acknowledgment

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(15) Compound **A**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.10 (br s, 1 H), 5.83 (m, 1 H), 5.55 (d, *J* = 10.0 Hz, 1 H), 5.10–5.00 (m, 2 H), 4.20 (q, *J* = 7.0 Hz, 2 H), 3.61 (dd, *J* = 5.0, 4.0 Hz, 1 H), 3.48 (dt, *J* = 5.5, 6.5 Hz, 1 H), 2.96 (dd, *J* = 5.5, 2.2 Hz, 1 H), 2.88 (dd, *J* = 4.0, 2.2 Hz, 1 H), 2.68 (ddq, *J* = 10.0, 5.0, 6.8 Hz, 1 H), 2.28 (t, *J* = 6.5 Hz, 2 H), 2.00 (d, *J* = 1.3 Hz, 3 H), 1.85 (d, *J* = 1.0 Hz, 3 H), 1.30 (t, *J* = 7.0 Hz, 3 H), 1.06 (d, *J* = 6.8 Hz, 3 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.09 (s, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H), 0.01 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.1, 142.7, 138.1, 134.5, 131.9, 125.9, 117.3, 73.6, 73.0, 60.6, 58.5, 57.2, 39.5, 37.7, 25.9 (× 3), 25.8 (× 3), 18.3, 18.2, 16.6, 15.7, 14.3, 14.0, –4.2, –4.4, –4.8, –4.9.
(16) None of the intermediates in the way towards **A** nor compound **A** itself was crystalline. Therefore, X-ray analyses aimed at configurational confirmation could not be performed. However, the key asymmetric transformations used here (Evans aldolization, Sharpless epoxidation and Brown allylboration) are well-known processes with safely predictable stereochemical outcomes. We are thus confident that the structure of synthetic intermediate **A** is that depicted in Scheme 3. Furthermore, a comparison of ^{1}H/^{13}C NMR chemical shift and coupling constants values within the relevant fragment of FD-891 with those of compound **A** (see Table 1 below, atom numbering is shown in Figure 1, coupling constant values are given in parenthesis) gives support to our structural assignment (the observed differences can be accounted for with the fact that the cyclic FD-891 is much more rigid than **A** from the conformational point of view; moreover, **A** bears two bulky TBSO groups instead of the free hydroxyls).
(17) Preliminary experiments have shown that oxidative cleavage of the terminal double bond in **A** can be performed via sequential osmylation and $NaIO_4$ oxidation to yield an unstable aldehyde.

Table 1 Comparison of Spectroscopic Data of Compounds **A** and FD-891

Atom	**FD-891**	**A**	Atom	**FD-891**	**A**
H-3	7.30, t (1.3)	7.10, br s	C-1	168.9	169.1
H-5	5.53, d (10.3)	5.55, d (10.0)	C-2	124.3	125.9
H-6	3.12, ddq (10.3, 4.1, 6.9)	2.68, ddq (10.0, 5.0, 6.8)	C-3	144.0	138.1
H-7	4.17, dd (6.0, 4.1)	3.61, dd (5.0, 4.0)	C-4	135.7	131.9
H-8	3.25, dd (6.0, 2.5)	2.88, dd (4.0, 2.2)	C-5	141.6	134.5
H-9	3.15, dd (2.5, 0.8)	2.96, dd (5.5, 2.2)	C-6	35.9	37.7
H-10	3.55, m	3.48, dt (5.5, 6.5)	C-7	70.8	73.0
H-11	2.55, m, 2 H	2.28, t, 2 H (6.5)	C-8	55.1	57.2
MeC_2	2.10, d (1.2)	2.00, d (1.3)	C-9	56.0	58.5
MeC_4	2.03, d (1.2)	1.85, d (1.0)	C-10	71.1	73.6
MeC_6	1.15, d (6.9)	1.06 d (6.8)	C-11	37.9	39.5
			MeC_2	13.6	14.0
			MeC_4	15.5	15.7
			MeC_6	16.5	16.6