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A divergent approach to apoptolidin and FD-891: asymmetric preparation of a common intermediate

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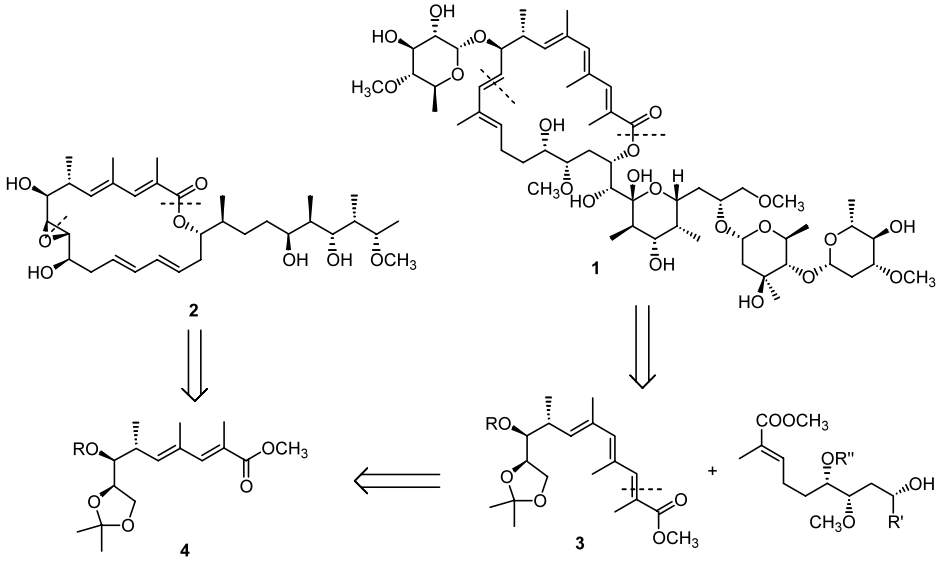
Abstract—Biologically active Apoptolidin and FD-891 have structural similarity in their macrocyclic cores. Asymmetric preparation of a common intermediate in the total synthesis of these two macrolides is presented. A modified Masuyama Sn-allylation was employed to control the relative stereochemistry in the synthesis of the intermediate.

Apoptolidin (Scheme 1, **1**) is a potent apoptosis-inducing agent isolated from *Nocardiopsis* sp.[1,2] It is found to induce apoptotic cell death selectively in rat glia cells transformed with the adrenovirus E1A oncogene ($IC_{50}=11$ ng/mL). In addition, this 20-membered macrocyclic lactone is also shown to be an inhibitor of the mitochondrial F0F1-ATP synthase.[3] The interesting biological activities and novel structure of apoptolidin make it a challenging target to the synthetic community.[4] Although the first total synthesis of this natural product was very recently reported by Nicolaou and co-workers, the numerous synthetic strategies associated with this molecule continue to be of great interest.[5] In 1994, FD-891 **2** was isolated from the fermentation broth of *Streptomyces graminofaciens* A-8890.[6] This 18-membered macrolide was found to induce morphological changes of HL-60 cells at low concentrations and has cytocidal activity against tumor cells in vitro.[7] Recently, the absolute stereochemistry of the macrolide was determined. It has a conjugated ester moiety **4**



Scheme 1.

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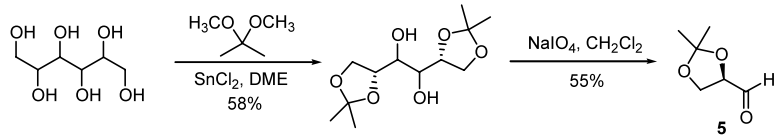
similar to that found in apoptolidin.[8] The structural similarity in these two natural macrolides suggested a divergent approach to the synthesis of their macrocyclic core structures.

The preparation of **4** began with the synthesis of the γ-homoallylic alcohol **6a**, which possesses the desired absolute stereochemistry at the hydroxyl carbon and the allylic position. Homoallylic alcohol **6a** can be obtained via a non-α-chelation controlled and *syn* selective allylation reaction of chiral aldehyde **5**, which in turn can be easily prepared through a two-step sequence from commercially available D-mannitol (Scheme 2).[9]

The allylation of aldehyde **5** to give homoallylic alcohol **6a** was actually quite difficult due to the acid sensitivity of the acetal-protecting group and the stereoselectivity which had to be achieved.[10] Thus, numerous methods including tin and indium-mediated reactions to effect the γ-allylation of aldehyde **5** either resulted in the cleavage of the acetal group or gave a non-selective mixture of isomers (**6a**–**d**, Table 1). The results are shown in Table 1.

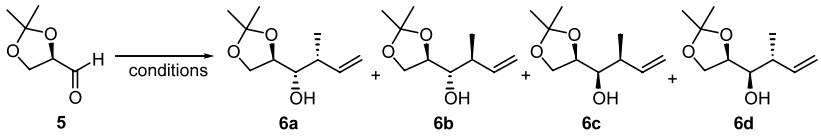
Masuyama has recently reported diastereocontrol in carbonyl allylation by 1-halobut-2-enes with tin(II) halides.[11] Although the use of tin(II) halide-mediated allylation also resulted in the cleavage of the protecting group, modification of the method by the use of tin metal afforded just two of the possible isomers (**6a**,**b**) in excellent yield and moderate diastereoselectivity, with the desired isomer **6a** as the major product (entry 11, Table 1). It is clear that with such a system, a non-α-chelation controlled reaction has taken place to give complete *anti* stereochemistry at the newly formed C–C bond. The diastereoselectivity of the allylic methyl relative to the hydroxyl group was found to be 75:25 by ^{1}H NMR analysis. Separation of the isomers by silica gel chromatography (4% ether in hexane) afforded the desired γ-homoallylic alcohol **6a** in 68% isolated yield.

The homoallylic alcohol **6a** was subsequently protected as benzyl ether **7** in good yield using benzyl bromide



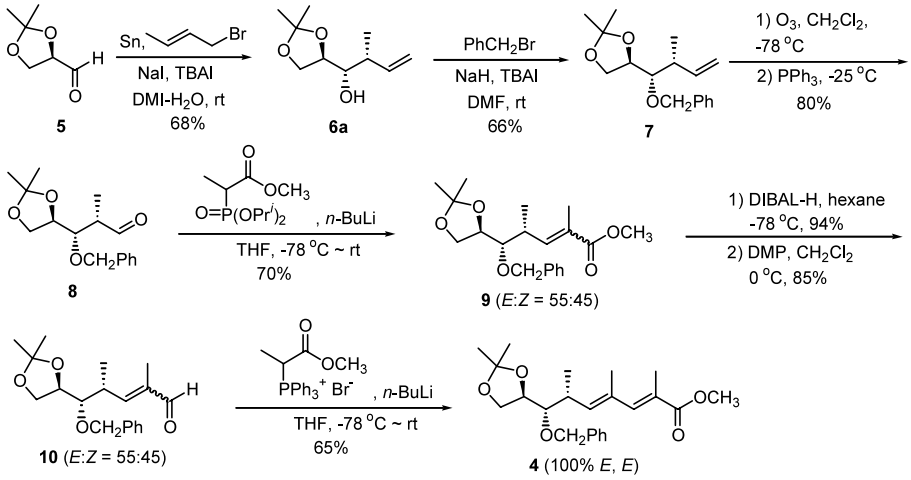
Scheme 2.

Table 1. Allylation of chiral aldehyde **5**

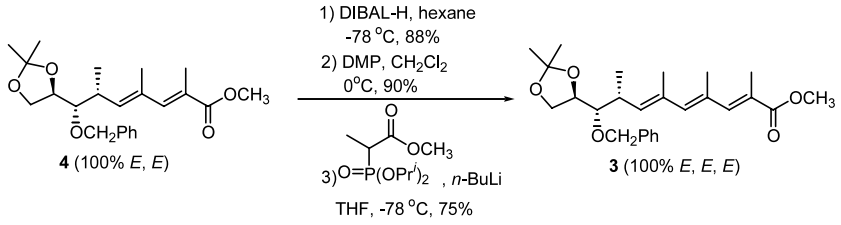


Entry	Allylic System	Conditions	Yield%[a] (a:b:c:d)[b]
1	Br	In, H_2O, rt	65 (18:53:21:8)
2	Br	In, DMF, rt	75 (24:54:15:7)
3	Br	In, $La(OTf)_3$, DMF, rt	70 (26:53:12:9)
4	Br	In, EtOH/H_2O (1:1), rt	78 (25:65:10:trace)
5	Br	In, THF/H_2O (1:1), rt	80 (30:51:15:4)
6	$SnBu_3$	TfOH, EtOH/H_2O (1:1), rt	0[c]
7	$SnBu_3$	$BF_3.OEt_2$, CH_2Cl_2, -78 °C to rt	76 (65:35:0:0)
8	Br	$SnCl_2$, NaI, TBAI, DMI-H_2O, rt	0[c]
9	Br	$SnBr_2$, NaI, TBAI, DMI-H_2O, rt	0[c]
10	Br	SnI_2, NaI, TBAI, DMI-H_2O, rt	0[c]
11	Br	Sn, NaI, TBAI, DMI-H_2O, rt	90 (75:25:0:0)

[a] Isolated Yields.
[b] Determined by ^{1}H NMR spectroscopy and comparison with literature values.
[c] Acetal protecting group was cleaved under these conditions.



Scheme 3.



Scheme 4.

under basic conditions (Scheme 3). Ozonolytic cleavage of the terminal olefin in **7** in CH_2Cl_2 from −78 to −25°C thus provided the enantiomerically pure aldehyde **8** in 80% yield. Performing the reaction at low temperatures, including quenching, prevented elimination of the β-alkoxyl group to form an enone.

Two successive Wittig reactions on aldehyde **8** should eventually bring us to the common intermediate of interest. However, the easy elimination of the β-alkoxyl group also gave rise to problems during the formation of conjugated ester **9**. Standard reflux conditions when reacting (carboethoxyethylidene)triphenylphosphorane with aldehyde **8** afforded only elimination products. In the many attempts to overcome the problem, the Horner–Emmons modification of the Wittig reaction using a diisopropyl phosphonate ester was successful.[12] Therefore, aldehyde **8** reacted with a diisopropyl phosphonate ester in the presence of *n*-butyllithium at −78°C to give conjugated ester **9** in 70% yield but with poor *E*:*Z* selectivity (55:45). This mixture of *E*:*Z* isomers **9** was subjected to a reduction–oxidation sequence to furnish aldehyde **10** in excellent yield. Fortunately, the subsequent Wittig reaction of (carboethoxyethyl)triphenylphosphonium bromide with aldehyde **10** in the presence of *n*-butyllithium at −78°C provided only the desired *E*,*E*-conjugated ester **4** (confirmed by NOE experiments). Despite the moderate yield of this final step, the common intermediate **4** in our synthetic approach to apoptolidin and FD-891 was successfully synthesized.

The *E*,*E*-conjugated ester **4** can be further homologated through a reduction–oxidation sequence and another Horner–Emmons–Wittig reaction to afford finally the *E*,*E*,*E*-conjugated ester **3** (Scheme 4) as one of the key fragments shown in our retrosynthetic analysis of apoptolidin.

Herein, we have reported an efficient synthesis of the common intermediate in our synthetic approach to apoptolidin and FD-891. The synthetic pathway is highlighted by an *anti–syn*-selective tin-mediated allylation reaction to control relative stereochemistry. The extended syntheses of apoptolidin and FD-891 from the common intermediate are being pursued and results will be reported in due course.

Acknowledgements

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