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Nature-Inspired Total Synthesis of (−)-Fusarisetin A

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Supporting Information

ABSTRACT: A concise, protecting group-free total synthesis of (−)-fusarisetin A (**1**) was efficiently achieved in nine steps from commercially available (*S*)-(−)-citronellal. The synthetic approach was inspired by our proposed biosynthesis of **1**. Key transformations of our strategy include a facile construction of the decalin moiety that is produced via a stereoselective IMDA reaction and a one-pot TEMPO-induced radical cyclization/aminolysis that forms the C ring of **1**. Our route is amenable to analogue synthesis for biological evaluation.

Isolated from the soil fungus *Fusarium* sp. FN080326, fusarisetin A (**1**) (Figure 1) has attracted considerable attention due to its unprecedented complex molecular architecture and remarkable bioactivity.[1] The latter was shown to include potent inhibition of metastasis in MDA-MB-231 cells, a particularly invasive breast cancer cell line. Specifically, **1** was shown to inhibit acinar morphogenesis (77 μM), cell migration (7.7 μM), and cell invasion (26 μM) in these cell lines without any significant cytotoxicity.[1] These biological observations are particularly important due to the fact that tumor metastasis is the primary cause of death of cancer patients.[2] Thus, the chemical and biological investigation of fusarisetin could lead to the development of new and effective anticancer agents.[3]

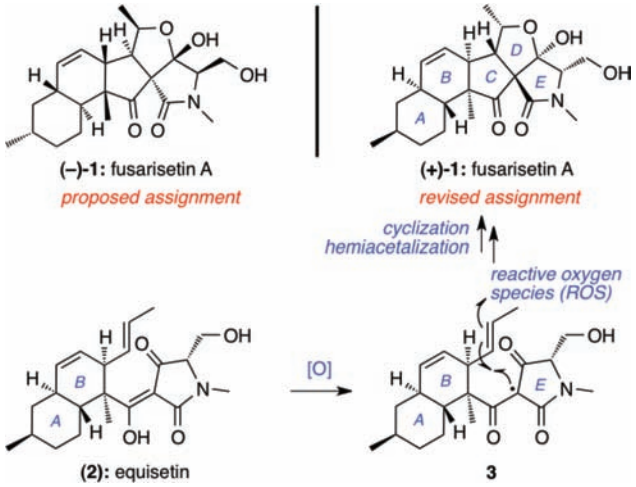
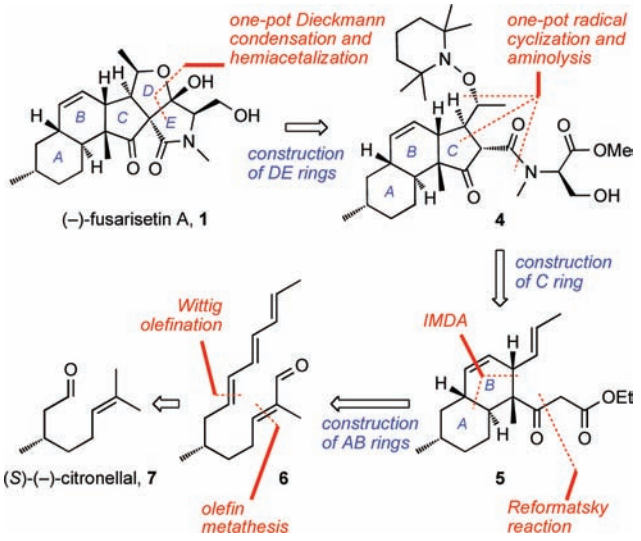


Figure 1. Fusarisetin A (**1**) and its proposed biosynthesis from equisetin (**2**).

From a structural point of view, fusarisetin is highlighted by the presence of an unprecedented pentacyclic motif containing 10 stereocenters. Close inspection of this framework reveals the fusion of a *trans*-decalin unit (AB ring system) with a tetramic acid moiety (E ring). These rings can also be found in the structure of equisetin (**2**),[4,5] another secondary metabolite from *Fusarium* sp., suggesting that both molecules arise from a common biosynthetic pathway. In fact, one possibility is that fusarisetin derives biogenetically from equisetin via a sequence that would involve formation of stabilized radical **3** (Figure 1). Radical cyclization at the pendant alkene followed by trapping by a reactive oxygen species (ROS)[6] and hemiacetalization would then produce **1**. Further evidence for this biosynthetic scenario was offered by a recent synthesis of **1** that revised its initially proposed absolute stereochemistry as shown in Figure 1.[7] Indeed, the revised structure of natural fusarisetin matches the absolute stereochemistry of equisetin.

Thorough evaluation of the pharmacological profile of fusarisetin A (**1**) would require a concise, high-yielding, and redox-economical synthetic process.[8] With this in mind and inspired by its proposed biosynthesis, we devised a synthesis of **1**, highlights of which are shown in Scheme 1.[9] We envisioned

Scheme 1. Strategic bond disconnections of fusarisetin A



that the pentacyclic motif of **1** could be constructed via a one-pot Dieckmann condensation and hemiacetalization of tricyclic

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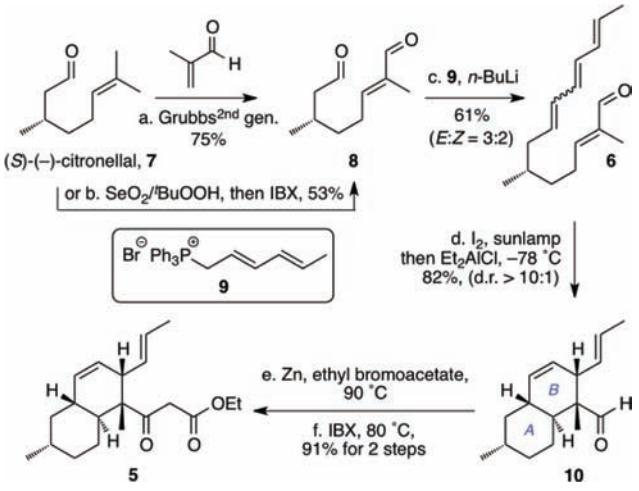
precursor **4** (construction of DE rings). A subsequent one-pot radical cyclization and aminolysis would then produce compound **4** from bicyclic motif **5** (construction of C ring). Decalin **5** could arise from a Lewis acid-promoted intramolecular Diels–Alder (IMDA) reaction of polyene **6** (construction of AB rings). Lastly, compound **6** could be obtained from commercially available (*S*)-(−)-citronellal (**7**) via a Ru-carbene catalyzed olefin metathesis or a regioselective allylic oxidation followed by a regioselective Wittig olefination.

Despite the high efficiency and stereoselectivity of the IMDA reaction,[10,11] the synthesis of decalin motifs via this process suffers from the preparation of the IMDA precursors that are usually synthesized via lengthy and tedious synthetic routes and/or proceed in low yields.[5b−d,7,10,11] This observation prompted us to develop a more straightforward synthetic route toward **6** (Scheme 2). Starting with (*S*)-(−)-citronellal (**7**), we were able to synthesize dialdehyde **8** via a Ru-catalyzed olefin cross-metathesis (Grubbs catalyst, second generation) with methacrolein[12] in 75% yield (90% brsm). Alternatively, **8** was obtained via a regioselective allylic oxidation[13] followed by sequential oxidation in 53% yield (64% brsm). Chemodifferentiation of the two aldehyde functionalities of **8** was expected to be a key factor of this approach. In fact, Horner–Wadsworth–Emmons reaction[5b,c] and Julia olefination[14] of **8** produced only small amounts of the desired triene **6**. We found, however, that Wittig olefination using phosphonium salt **9**[15] led to isolation of triene **6** in 61% yield, albeit with moderate stereoselectivity (*E*:*Z* = ∼3:2). This issue was addressed by an iodine-catalyzed photoisomerisation.[16] Thus, treatment of **6** with iodine (5 mol %) in dichloromethane under a sun-lamp (visible light, 5 min) led almost exclusively to the desired *trans*-alkene. Without any further purification, this diastereomeric mixture was treated with diethyl aluminum chloride (1.0 equiv) at −78 °C to form decalin **10** in satisfactory yield (82%) and good diastereoselectivity (>10:1, the minor diastereomer unassigned). This approach allows facile construction of the fusarisetin decalin ring moiety and can also be applied to the synthesis of other natural products possessing similar structural features, such as maklamicin,[17a] apiosporamide,[17b] simvastatin,[17c] lovastatin,[17d] oblongolides,[17e,f] and others.[17g−o] Treatment of the aldehyde functionality of **10** with ethyl bromoacetate under Reformatsky conditions[5d] followed by IBX oxidation of the resulting alcohol afforded *β*-ketoester **5** in 91% combined yield.

Scheme 2. Synthesis of decalin ester 5[a]



[a]Reagents and conditions: (a) methacrolein (2.0 equiv), Grubbs second- generation catalyst (5 mol %), CH_2Cl_2, 50 °C, 24 h, 75%, (90% brsm); (b) SeO_2 (3 mol %), ^tBuOOH (4.0 equiv), salicylic acid (0.1 equiv), CH_2Cl_2, 36 h, then IBX (1.4 equiv), DMSO, 1.5 h, 53%, (64% brsm); (c) **9** (1.0 equiv), *n*-BuLi (1.0 equiv), THF, −60 °C, 1 h, then −78 °C, **8**, 1 min (see SI), 61% (d) I_2 (5 mol %), sunlamp (visible light), CH_2Cl_2, 5 min, then −78 °C, Et_2AlCl (1.0 equiv), 18 h, 82%; (e) activated zinc dust (3.0 equiv), ethyl bromoacetate (1.2 equiv), PhH, 45 min, 90 °C; (f) IBX (2.0 equiv), DMSO, 80 °C, 10 min, 91% for 2 steps.

Next we sought to explore oxidative radical cyclization processes for the formation of the C ring of **1**. Although radical reactions have often been used in natural products for the construction of C–C bonds, their application to the synthesis of C–O bonds remains very limited.[18] In 2001, Jahn et al. reported the construction of 5-membered ring systems starting with a 1,3-dicarbonyl moiety and inactivated alkenes under TEMPO conditions.[19−21] Inspired by the similarities between this method and the proposed biosynthesis of fusarisetin A, we decided to evaluate this unexplored method in our synthesis.[22] Deprotonation of **5** with LiHMDS, followed by addition of TEMPO and ferrocenium hexafluorophosphate (**11**) as the oxidant, led to the isolation of **12** as an inseparable C-1 isomeric mixture in 99% yield. Importantly, the conversion of triene **6** to the key intermediate **12** needs only one column chromatography purification. Hence this method provides a convenient and scalable chemical process for the fusarisetin synthesis.

The radical cyclization of **12** proceeded cleanly upon heating in toluene at 90 °C over a period of 36 h. Tricyclic product **15** was isolated as a mixture of diastereomers at the C-5 center in good overall yield (80%, dr = ∼1:1) (Scheme 3). A reasonable mechanism of this cyclization would involve reversible generation of the stable radical **14** under heating followed by cyclization at the C-6 center to create the C-5 radical (5-*exo*-*trig* cyclization). Remarkably, the stereoselectivity of this cyclization is substrate-controlled and forms the desired isomer at the C-1 and C-6 centers. Subsequent irreversible trapping of the C-5 radical with TEMPO can give rise to compound **15**. To enhance the overall synthetic efficiency, we further performed this radical reaction in the presence of the amino acid **13**.[23] We were pleased to find that **13** did not interfere with the cyclization and readily aminolyzed the C-2 ester, to afford **4** and C_5-*epi*-**4** (dr = ∼1:1) in one-pot and 70% overall yield. Despite the moderate diastereoselectivity, this one-pot radical cyclization/aminolysis reaction cascade[24] offers a concise way to build up the fusarisetin core structure. Subsequently, the C-5 hydroxy group of compound **4** was liberated under Zn/AcOH conditions.[25] Treatment of the resulting C-5 alcohol under basic conditions (NaOMe) induced a one-pot Dieckmann condensation/hemiacetalization[5,7] (construction of DE rings) ultimately producing fusarisetin A (**1**) in 42% overall yield. Importantly, the C_5-*epi*-**4** could be also converted to fusarisetin A via a three-step sequence that included: (a) oxidative cleavage of the N–O bond with *m*CPBA[26] to form ketone **16**; (b) regioselective and stereoselective reduction of the C-5 ketone with $NaBH_4$ (dr = ∼3:1), and (c) one-pot Dieckmann condensation/hemiacetalization (38% yield over three steps).

The isolated sample of synthetic **1** was found to be identical in all aspects with naturally occurring fusarisetin A (^1H NMR, ^{13}C NMR, and HR-MS), except for the optical rotation [synthetic: $[\alpha]^{23}_D$ = −86.2 (*c* = 0.065 in MeOH); natural:

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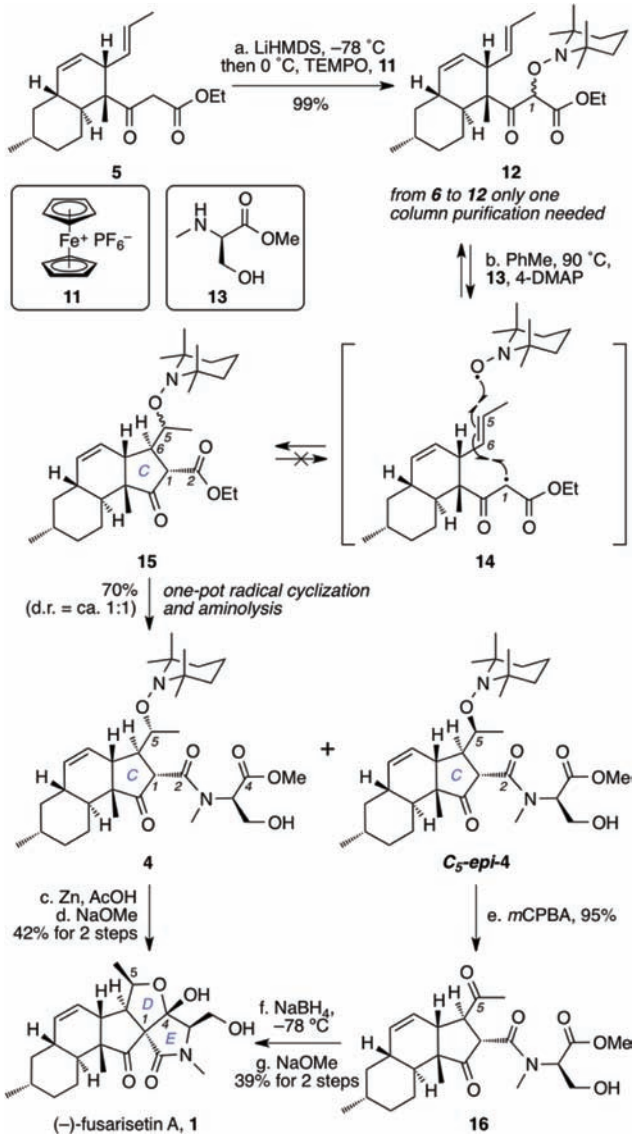
Scheme 3. Completion of the synthesis[a]



[a]Reagents and conditions: (a) LiHMDS (1.5 equiv), 1,2-dimethoxyethane, −78 °C, 30 min, then 0 °C, TEMPO (1.05 equiv), Cp_2FePF_6 (2.0 equiv), 5 min, 99%; (b) **13** (5.0 equiv), 4-DMAP (2 equiv), PhMe, 4 Å MS, 90 °C, 36 h, 70% (dr = ∼1:1); (c) activated zinc dust (100 equiv), AcOH/THF/H_2O (3:1:1), 70 °C, 12 h; (d) NaOMe (5.0 equiv), MeOH, 10 min, 42% for 2 steps; (e) *m*CPBA (1.2 equiv), CH_2Cl_2, 0 °C, 15 min, 95%; (f) $NaBH_4$ (0.6 equiv), MeOH, −78 °C (dr = ∼3:1); (g) NaOMe (5.0 equiv), MeOH, 10 min, 39% for 2 steps.

$[\alpha]^{25}_D$ = +84.6 (*c* = 0.2 in MeOH)[1], reported synthetic (−)-**1**: $[\alpha]^{27}_D$ = −88.0 (*c* = 0.15 in MeOH)[7]]. The chemical synthesis of **1** confirmed that the absolute stereochemistry of natural fusarisetin A is opposite to our synthetic **1** and provides support for its proposed biosynthesis.

In conclusion, we have accomplished a concise, nature-inspired and protecting-group-free[27] total synthesis of (−)-fusarisetin A (**1**). The overall synthesis proceeds in 9 steps and 10% overall yield. Our strategy is highlighted by: (a) a rapid stereoselective construction of decalin **5** (AB ring system) using an optimized sequence; (b) an efficient one-pot radical cyclization cascade/aminolysis that forms the C ring of **1** and installs the C-5 hydroxy group; and (c) a rapid Dieckman condensation/hemiacetalization reaction cascade that produces the DE rings of **1**. Our strategy also demonstrates for the first time the applicability of the TEMPO induced oxidative radical cyclization reaction in the context of complex molecule synthesis. We expect that this approach would be able to provide sufficient amounts of the natural (+)-fusarisetin A and related analogs for further biological investigations en route to the development of novel small molecule inhibitors of tumor metastasis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectral data for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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