Natural Products

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Asymmetric Synthesis and Biosynthetic Implications of (+)-Fusarisetin A**

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The fungal metabolite (+)-fusarisetin A [(+)-**1**; Figure 1], produced by the soil fungus *Fusarium* sp. FN080326, potently inhibits acinar morphogenesis, cell migration, and cell invasion in MDAMB-231 cells.[1] Tests of cell growth and cell death using the same cell line showed that (+)-**1** does not exhibit significant cytotoxicity. These findings suggest that (+)-**1** holds promise as a valuable anticancer agent. We aim to develop an efficient synthetic route to enable structure–activity relationship studies of this compound and facilitate the target identification studies. As a first step, we report herein a concise synthesis of (+)-**1** and its potential biosynthetic pathway.

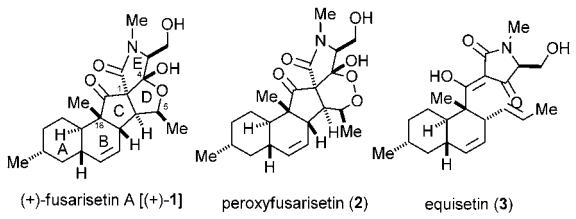
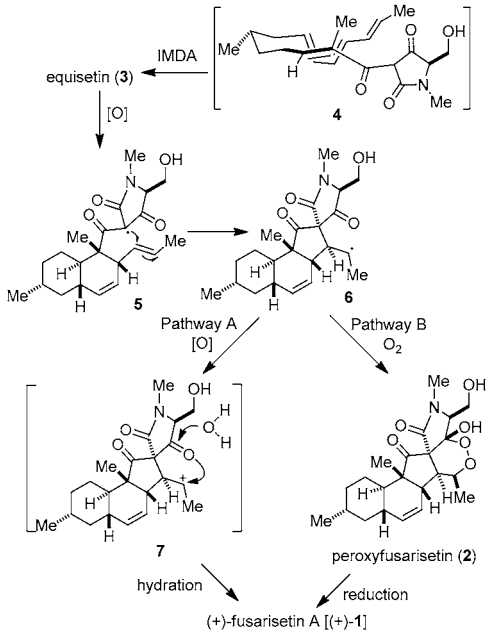


Figure 1. Fusarisetin A [(+)-**1**] and its proposed biosynthetic precursors peroxyfusarisetin (**2**) and equisetin (**3**).

(+)-Fusarisetin A (**1**) possesses unique structural characteristics: 1) a fused pentacyclic ring system (A,B,C,D,E) which contains a *trans* decalin (A,B), a spiroskeleton (C,E), and a tetramic acid moiety fused with a tetrahydrofuran ring (D,E); and 2) 10 stereocenters, including two all-carbon quaternary centers (C1, C16). Structurally related natural products possessing tetramic acid rings include equisetin (**3**),[2] diaporthichalasin,[3] integramycin,[4] tirandamycin,[5] and others.[6] Recently, Li and co-workers reported the first synthesis of (−)-**1** and revised its absolute configuration.[7] Theodorakis and co-workers later proposed **3** to be the biosynthetic precursor of **1** and accomplished a biomimetic synthesis of (−)-**1**.[8]

Equisetin (**3**) is another secondary metabolite isolated from *Fusarium* sp. and contains the basic skeleton (A,B, and E rings) of (+)-**1** but is at a lower oxidation state.[2] It is reasonable to assume that (+)-**1** is derived from **3** through an oxidative cascade sequence (Scheme 1).[8] According to this proposed biosynthetic pathway, single-electron oxidation of **3** would give the radical intermediate **5**, which would undergo



Scheme 1. Proposed biosynthetic pathway of (+)-fusarisetin A [(+)-**1**] and equisetin (**3**).

a 5-*exo* cyclization to yield **6**.[9] Under anaerobic conditions (Pathway A), a second single-electron oxidation would afford **1** via cation **7**. Under aerobic conditions (Pathway B), the radical **6** may trap oxygen to give peroxyfusarisetin (**2**), which could then be reduced to (+)-**1**. The *trans*-decalin unit of **3** is likely produced from the polyene tetramic acid **4** by an intramolecular Diels–Alder reaction (IMDA).[10] This IMDA strategy was first used by Dixon, Ley, and co-workers to synthesize **3** in 2000,[2e] and also adopted by Li and co-workers,[7] as well as Theodorakis and co-workers[8] to synthesize (−)-**1**.

Guided by this biosynthetic analysis, we developed the synthetic strategy outlined in Scheme 2. We envisioned that preparation of (+)-**1** could be achieved using either the biosynthetic Pathway A or B. The tetramic acid moiety of **3** could be installed through the aminolysis/Dieckmann cyclization of β-keto ester **8** and the (*S*)-serine derivative **9**.[2d] An

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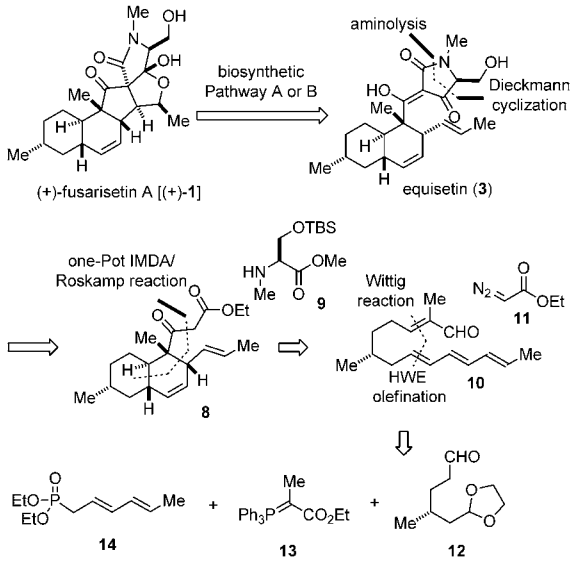
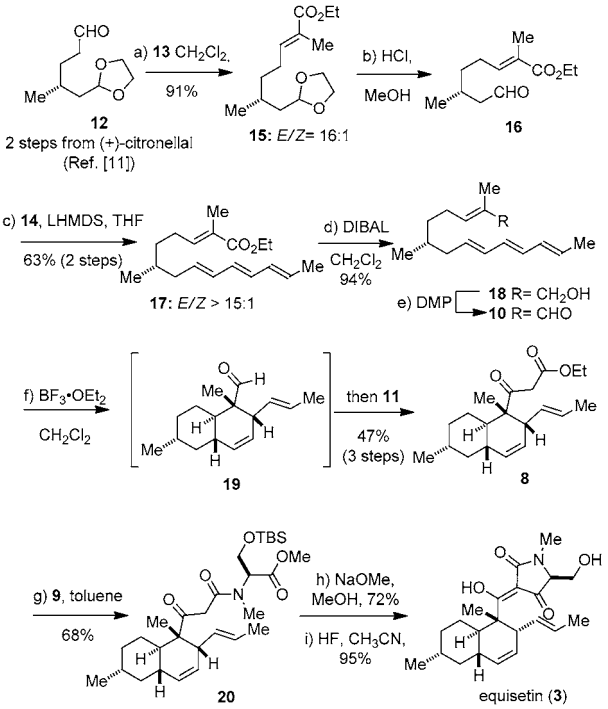


Scheme 2. Retrosynthetic analysis of (+)-fusarisetin A [(+)-**1**] and equisetin (**3**).



Scheme 3. Preparation of equisetin (**3**). Reagents and Conditions: a) **13** (1.1 equiv), 25 °C, CH_2Cl_2, 12 h, E/Z = 16:1, 91 %. b) HCl (1.0 N), 60 °C, 4 h, MeOH. c) **14** (1.3 equiv), LHMDS (1.4 equiv), 30 min, then **16** (1.0 equiv), −78 °C→25 °C, 16 h, THF, E/Z > 15:1, 63 % in 2 steps. d) DIBAL (2.2 equiv), CH_2Cl_2, −78 °C, 3 h, 94 %. e) Dess–Martin periodinane (1.5 equiv), H_2O (1.5 equiv), CH_2Cl_2, 10 min, 25 °C. f) $BF_3{\cdot}OEt_2$ (3.0 equiv), −78 °C, CH_2Cl_2, 20 min, then **11** (3.0 equiv), 0 °C, 1.5 h, 47 % in 3 steps. g) **9** (2.0 equiv), DMAP (2.0 equiv), toluene, 118 °C, 18 h, 68 %; h) NaOMe (1.0 equiv), MeOH, 25 °C, 2 h, 72 %. i) HF, CH_3CN, 25 °C 2 h, 95 %. DIBAL = diisobutylaluminum hydride, DMAP = 4-(dimethylamino)pyridine, LHMDS = lithium hexamethyldisilazide, THF = tetrahydrofuran.

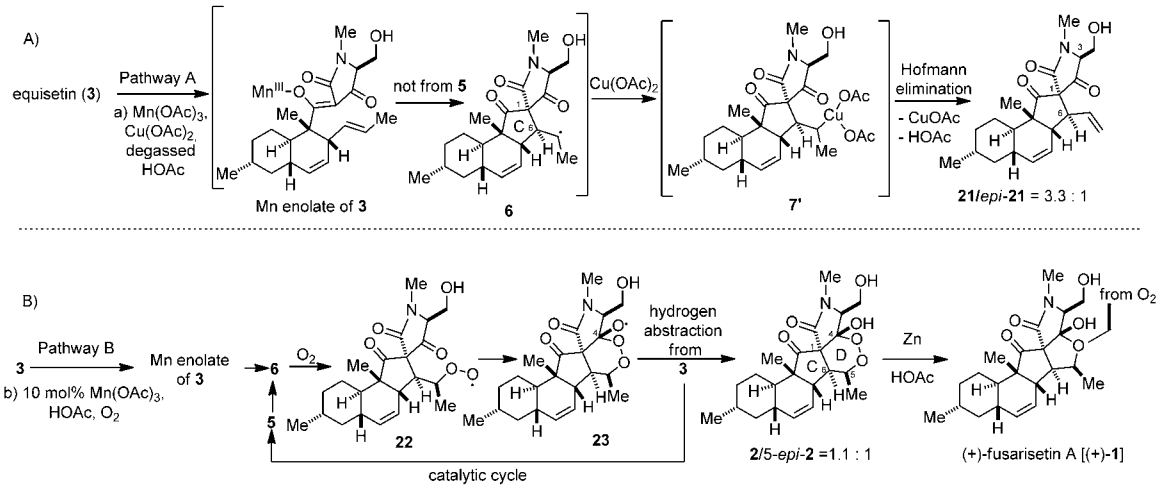
IMDA/Roskamp reaction could be used to construct the *trans*-decalin **8** from the polyene **10** and ethyl diazoacetate **11**.[2e,d] In turn, **10** could be easily prepared through Wittig and Horner–Wadsworth–Emmons (HWE) olefinations of **12** with the ylide **13** and phosphonate **14**.

Our synthesis commenced with the preparation of **12** from (+)-citronellal using a previously described two-step procedure (Scheme 3).[11] Treating **12** with the ylide **13** provided **15** in 91 % yield (E/Z = 16:1). Removal of the ethylene glycol gave **16**, which was used directly without purification. The HWE olefination of **16** and phosphonate **14**[2e] converted **16** into triene **17** in 63 % yield. The reduction of **17** with DIBAL yielded the allylic alcohol **18**, which was easily oxidized to polyene **10** using Dess–Martin periodinane (DMP). To construct the *trans*-decalin moiety, we extensively surveyed the reaction conditions and found that $BF_3{\cdot}OEt_2$, Et_2AlCl, or silica gel (during chromatography) promoted the IMDA reaction of **10** with good selectivity (d.r. = 9:1). We further found that the Roskamp reaction of the resulting aldehyde **19** and **11** could also be promoted by $BF_3{\cdot}OEt_2$ in one pot, thus giving **8** in 47 % yield over three steps from **18**. Finally, the total synthesis of **3** was completed using the aminolysis and Dieckmann cyclization sequence reported by Danishefsky.[2d]

We anticipated that **3** would be readily oxidized by single-electron oxidants as it contains a tricarbonyl system which exists as a mixture of keto/enol tautomers. Manganese(III) acetate has been shown to be an effective oxidant for enolizable carbonyl compounds.[12] The initial application of manganese(III) to oxidative radical cyclizations was reported by Corey and Kang,[13] Ernst and Fristad,[14] and Snider and co-workers[12a,c–g] in the 1980s. To date, radical reactions promoted by manganese(III) have been widely used in organic synthesis, especially natural product synthesis.[15] We therefore expected that the biomimetic oxidation of **3** could be realized with $Mn(OAc)_3$ to give (+)-fusarisetin A by either Pathway A or Pathway B.

We first found that, under anaerobic conditions, the C ring can be successfully formed by oxidizing **3** with $Mn(OAc)_3$, but all attempts to induce the formation of the D ring to yield (+)-**1** or trap **6** as an acetate failed (Scheme 4 A). The elimination product was obtained as the major product even in the presence of $Cu(OAc)_2$ or $Yb(OTf)_3$. For example, oxidation of **3** with $Mn(OAc)_3$ (2.0 equiv) and $Cu(OAc)_2$ (5.0 equiv) in degassed HOAc at room temperature gave **21** in 62 % yield (d.r. = 3.3:1).[16] On the basis of Snider's mechanistic studies,[12c–g] we believe that the highly acidic **3** first complexes with $Mn(OAc)_3$ to form the manganese enolate, which then cyclizes directly to give the radical **6** without the formation of **5**. Oxidation of **6** proceeded through the copper(III) intermediate **7'** to give **21** through a Hofmann elimination with loss of CuOAc and HOAc.[12c,h-j]

We next found that, under aerobic conditions,[17] both the C ring and "D ring" can be formed by oxidizing **3** with $Mn(OAc)_3$ (Scheme 4 B). Oxidation of **3** with $Mn(OAc)_3$ (2.0 equiv) in either air or 1 atm O_2 in HOAc at room temperature gave peroxyfusarisetin (**2**) and 5-*epi*-**2** as inseparable diastereomers in 62 % yield (d.r. = 1.3:1).[18] Reduction of **2** and 5-*epi*-**2** with Zn/HOAc furnished (+)-fusarisetin A (**1**) and 5-*epi*-**1**[7] in a 75 % combined yield. The spectroscopic



Scheme 4. Key transformations in the synthesis of (+)-fusarisetin A [(+)-**1**] from equisetin (**3**) and mechanistic analyses. Reagents and Conditions: a) $Mn(OAc)_3 \cdot 2H_2O$ (2.0 equiv), $Cu(OAc)_2$ (5.0 equiv), degassed HOAc, 2 h, 25 °C, d.r. = 3.3:1, 62 %. b) $Mn(OAc)_3 \cdot 2H_2O$ (0.1 equiv), air or 1 atm O_2, 25 °C, HOAc, 2 h, then Zn (30.0 equiv), 50 °C, 2 h, 41 %.

data (^{1}H and ^{13}C NMR spectra, as well as HRMS, and optical rotation) of synthetic (+)-**1** were fully consistent with the corresponding data for the natural product.[1]

Mechanistically, this reaction should also proceed through the radical **6**, which is trapped by O_2 instead of $Cu(OAc)_2$ to give **23** via **22**.[17] A hydrogen abstraction from **3** then yielded **2** and the radical **5**, which underwent a 5-*exo* cyclization to provide **6** again, thus creating a catalytic cycle. Indeed, we found that oxidation of **3** with 10 mol % $Mn(OAc)_3$ in either air or O_2 also gave **2** and 5-*epi*-**2** with a comparable 60 % yield (d.r. = 1.1:1).[18] The zinc reduction can be performed in situ to give (+)-**1** directly from **3** in 41 % yield. While the enolate of **3** was also involved in the radical initiation step, this aerobic oxidation proceeded mainly through radical **5**, which was not formed in the anaerobic oxidation of **3**. The observation of different diastereoselectivity in the Mn^{III}/Cu^{II} and Mn^{III}/O_2 oxidation reactions is explained by the different intermediates involved in the diastereoselectivity determining step.[19]

Our synthetic work suggests that the biosynthesis[20] of (+)-**1** may involve a single-electron transfer (SET) oxidation of **3** to generate **5** and lead to the formation of **2**. The labile peroxy group has been found in the antimalarial natural products artemisinin (Qinghaosu)[21] and yingzhaosu A[22] (Figure 2). We suggest that peroxyfusarisetin (**2**) is the biosynthetic intermediate of (+)-**1** and question if the reductive cleavage of the peroxide occurred during its isolation. This one-pot, biomimetic synthesis of (+)-fusarisetin A ((+)-**1**) and peroxyfusarisetin (**2**) from equisetin (**3**) allows us to easily access the natural product(s) for future biological studies. We are particularly interested in examining the antimalarial activity of **2**.

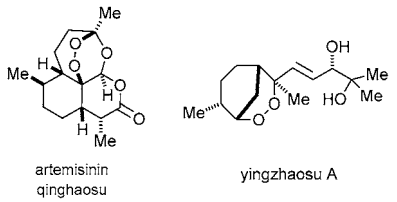


Figure 2. Structures of artemisinin and yingzhaosu A.

In summary, we have accomplished the first asymmetric synthesis of (+)-fusarisetin A ((+)-**1**). This efficient strategy relies on our proposed biosynthetic pathway involving 1) a one-pot IMDA/Roskamp reaction to construct the *trans*-decalin skeleton, and 2) biosynthetic oxidation of equisetin (**3**) promoted by Mn^{III}/O_2. Our synthetic approach has verified the absolute configuration of naturally occurring (+)-**1**, which matches that of its biosynthetic precursor **3**.

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