

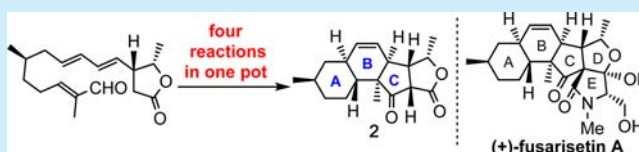
# Total Synthesis of (+)-Fusarisetin A Driven by a One-Pot Four-Reaction Process

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**S** Supporting Information

**ABSTRACT:** A concise, asymmetric total synthesis of (+)-fusarisetin A, a hybrid natural product, has been achieved. A one-pot four-reaction process efficiently delivered the tetracycle **2** which served as a key intermediate for the synthesis of the title natural product and its analogues through amino acid incorporation.



Hybrid natural products<sup>1</sup> are composed of two or more metabolic units with different biosynthetic origins and usually exhibit unique biological properties, thus providing many opportunities for developing new therapeutic agents. Inspired by nature, chemists artificially combine natural or unnatural molecules through covalent bonds, which plays an important role in modern pharmaceutical chemistry.<sup>2</sup>

As the essential biosynthetic building blocks for peptides and proteins, as well as alkaloids,<sup>3</sup> amino acid units have also been widely found in other bioactive natural products (Figure 1).

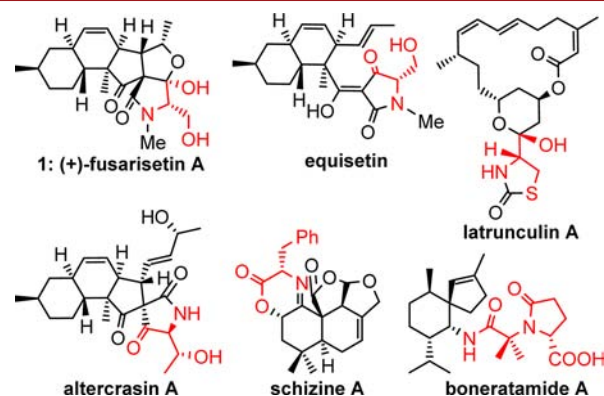


Figure 1. Hybrid natural products containing amino acids.

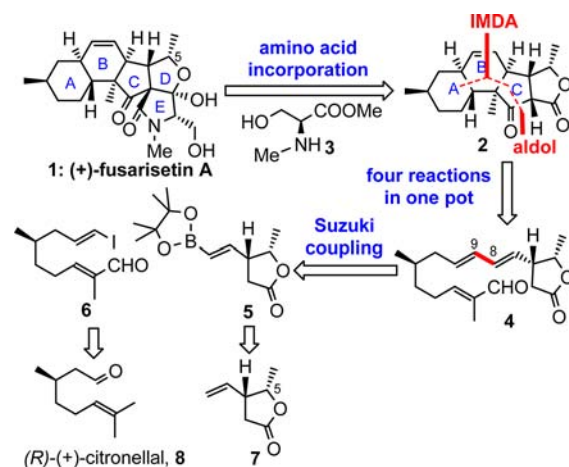
(+)-Fusarisetin A (**1**, Figure 1), isolated from the soil fungus *Fusarium* sp. FN080326, exhibited potent inhibition of metastasis in MDA-MB-231 breast cancer cells without significant cytotoxicity.<sup>4</sup> Structurally, fusarisetin A features a pentacyclic ring system comprising 10 continuous stereocenters, in particular, a complicated 5,5,5-angular tricycle motif containing a masked *N*-methyl serine. Its fascinating structure and promising therapeutic value have attracted considerable synthetic interest, thus culminating in several elegant total synthesis of **1** by the groups of Li<sup>5</sup> in 2011, Theodorakis<sup>6</sup> and Gao<sup>7</sup> in 2012, and Yang<sup>8</sup> in 2013. In the pursuit of this

molecule, a couple of novel strategies have been developed and some analogues have been prepared.<sup>9</sup>

With the goal of reducing time, cost, and waste production, one-pot reactions<sup>10</sup> have developed greatly in the past two decades. Herein, we describe a concise, asymmetric total synthesis of (+)-fusarisetin A driven by a one-pot four-reaction process. Furthermore, our convergent synthetic route and late-stage incorporation of amino acid units would greatly facilitate the diverted total synthesis<sup>11</sup> of the analogues.

Our modular strategy originates from the hypothesis that fusarisetin A could be viewed as a hybrid molecule of an amino acid and a polyketide-like compound. As outlined in Scheme 1, we anticipated that **1** could be assembled from tetracyclic polyketide-like compound **2** and the serine unit **3**.<sup>12</sup> Then rupture of the three indicated C–C bonds within **2**, through an intramolecular Diels–Alder reaction (IMDA)/Mukaiyama aldol/desilylation/oxidation sequence, revealed triene **4** as a

## Scheme 1. Retrosynthetic Analysis of (+)-Fusarisetin A (1)



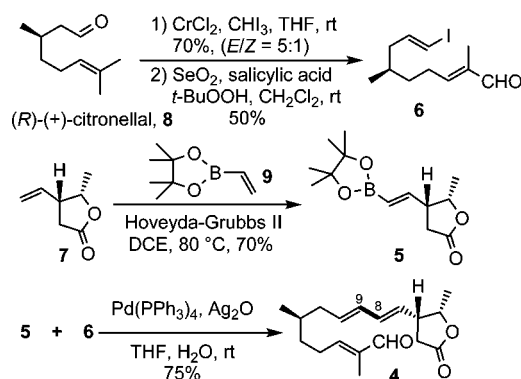
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possible precursor. To simplify the synthesis, we would practice these conversions in a one-pot manner, although the compatibility of reaction conditions and functional groups in each step is challenging. The retrosynthetic scission of the C8–C9 bond of precursor **4** led to vinyl borate **5** and iodide **6** as two similarly sized fragments, which could be connected through a Suzuki coupling. Finally, **5** and **6** could be prepared respectively from known lactone **7**<sup>13</sup> and (*R*)-(+)-citronellal **8**.

The stereoselective synthesis of trienaldehyde **4** commenced with the synthesis of two chiral building blocks **5** and **6** and proceeded as summarized in Scheme 2. Takai olefination<sup>14</sup> of

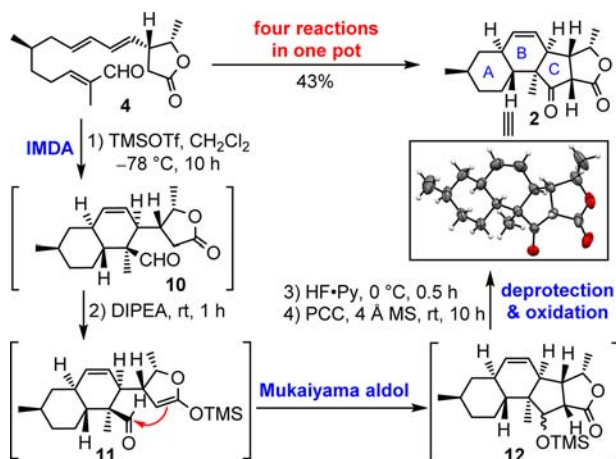
Scheme 2. Synthesis of Intermediate **4**



(*R*)-(+)-citronellal **8** afforded a vinyl iodide intermediate as an inseparable mixture of *E/Z* isomers in 70% yield,<sup>15</sup> which was converted to  $\alpha,\beta$ -unsaturated aldehyde **6** by a regioselective allylic oxidation. Fragment **5** was obtained via a Ru-catalyzed olefin cross metathesis<sup>16</sup> (Hoveyda–Grubbs' second generation catalyst) between lactone **7** and pinacol vinylborate **9** in 70% yield as a mixture of *E/Z* isomers (ca. 10:1). To our delight, the Suzuki cross-coupling of the vinyl borate **5** and vinyl iodide **6** in the presence of  $\text{Pd}(\text{PPh}_3)_4$  and  $\text{Ag}_2\text{O}$ <sup>17</sup> smoothly delivered (*E,E,E*)-trienal **4** in 75% yield.

With **4** in hand, we then focused on the key one-pot reaction sequence (Scheme 3). We first examined the intramolecular Diels–Alder reaction. Among the thermal conditions (benzene/150 °C/sealed tube, xylene/150 °C/microwave) and Lewis acidic conditions (e.g.,  $\text{Et}_2\text{AlCl}$ ,  $\text{BF}_3\cdot\text{OEt}_2$ ,  $\text{BBr}_3$ , and

Scheme 3. One-Pot Reaction for the Synthesis of Tetracycle **2**

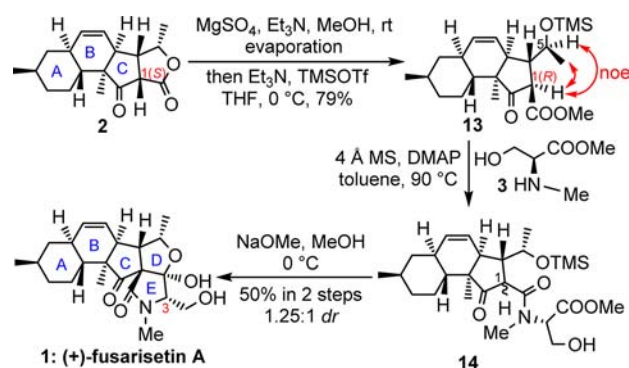


$\text{Sc}(\text{OTf})_3$ ) investigated,<sup>18</sup> 1.0 equiv of  $\text{BF}_3\cdot\text{OEt}_2$  in  $\text{CH}_2\text{Cl}_2$  at 0 °C gave the cycloadduct **10** in the highest yield of 60% (7:1 *endo/exo*). In spite of the failure of the intramolecular aldol addition with LDA or KHMDS as base, **10** was successfully converted to **12** probably via intermediate **11** under a Mukaiyama aldol<sup>19</sup> condition (TMSOTf and DIPEA) in 80% yield as a mixture of diastereomers (5:1 *dr*). However, the incompatibility between  $\text{BF}_3\cdot\text{OEt}_2$  and TMSOTf impeded the further exploration of the one-pot mechanics of these two steps.

Although TMSOTf is a poor activator for the dienophiles bearing  $\alpha,\beta$ -unsaturated carbonyls in intermolecular Diels–Alder reactions,<sup>20</sup> we reexamined the above-mentioned IMDA reaction with this Lewis acid. Rewardingly, subjection of **4** to 5.0 equiv of TMSOTf in  $\text{CH}_2\text{Cl}_2$  at –78 °C afforded **10** in 70% yield (9:1 *endo/exo*) if we quenched the reaction at this stage. To our great delight, the subsequent intramolecular aldol reaction proceeded smoothly only with the addition of 5.0 equiv of DIPEA to the preceding reaction mixture after warming to rt, thereby providing tetracycle **12** in a one-pot reaction manner. Encouraged by this success, we next explored the possibility of running the desilylation and oxidation in the same flask. After extensive screening of reaction conditions, the tetracyclic lactone **2** (as a pure  $\beta$ -keto lactone form) was obtained in 43% overall yield by sequential treatments with  $\text{HF}\cdot\text{Py}$  at 0 °C and PCC at rt.<sup>21</sup> Its structure was unambiguously confirmed by single crystal X-ray diffraction (Scheme 3). In this one-pot IMDA/Mukaiyama aldol/desilylation/oxidation sequence, three rings together with five stereogenic centers were built up. Of particular note was that the efficient one-pot four-reaction process only required sequential addition of the reagents at the corresponding reaction temperature.

With polyketide-like compound **2** in hand, our efforts were then focused on the incorporation of *N*-methyl serine unit **3** (Scheme 4). Direct aminolysis of five-membered lactone in **2**

Scheme 4. Completion of Total Synthesis

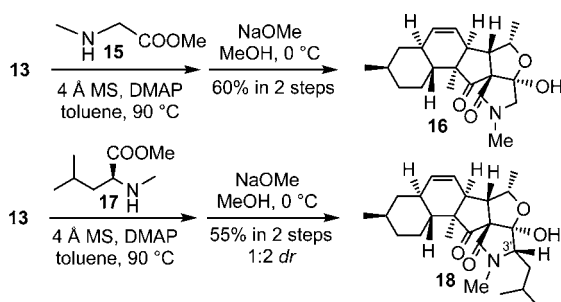


with **3** in the presence of the various additives<sup>22</sup> (e.g., DMAP,  $\text{Sn}(\text{OAc})_2$ , 2-hydroxypyridine, and  $\text{AlMe}_3$ ) did not produce any desired product, probably due to a combination of unfavorable entropic and enthalpic factors. However, this challenge was smoothly overcome by another one-pot two-step operation: **2** was first treated with  $\text{MeOH}/\text{Et}_3\text{N}$  (1:1)<sup>23</sup> in the presence of  $\text{MgSO}_4$ <sup>24</sup> at rt, and the resulting C5 alcohol was instantly protected as a TMS ether in the same flask (79% yield). NMR NOE studies indicated the inversion of the C1 stereocenter (*S*  $\rightarrow$  *R*) which was probably a major driving force for the transesterification. By treatment with the aminoester **3** and DMAP, **13** was converted to amide **14** as a pair of inseparable C1 epimers (1:1). Finally, when it was subjected to NaOMe in

MeOH at 0 °C, similar to Yang's observation,<sup>8</sup> (+)-fusarisetin A (1) and (+)-C3-*epi*-fusarisetin A were obtained in a 1.25/1.0 ratio in a combined yield of 50% in two steps.<sup>25</sup> The spectroscopic data (<sup>1</sup>H and <sup>13</sup>C NMR, HRMS, and optical rotation) for the synthetic sample (1)<sup>4</sup> and its C3-epimer<sup>8,26</sup> fully coincided with those reported.

After the successful synthesis of fusarisetin A, we examined the feasibility of our modular synthetic strategy in the diverted total synthesis of the analogues guided by a "hybridization" concept. Through the late-stage incorporation of amino acid units, as examples, two pentacyclic compounds 16 and 18 were synthesized respectively in 60% and 55% yield (1:2 *dr* at C3') from the advanced intermediate 13 (Scheme 5). It is noteworthy to mention that the epimerization at C3' seems inevitable under the current condensation conditions.<sup>18</sup>

**Scheme 5. Diverted Total Synthesis of the Analogues**



In summary, we have developed an efficient, modular synthetic strategy for the asymmetric total synthesis of (+)-fusarisetin A, featuring a Suzuki coupling and a novel one-pot four-reaction sequence (IMDA/Mukaiyama aldol/desilylation/oxidation). Our method is also viable for the diverted total synthesis of the analogues. We anticipated that this approach would provide a diverse array of analogues for further biological studies of tumor metastasis.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00036.

Experiment details and spectral data for all new compounds (<sup>1</sup>H NMR, <sup>13</sup>C NMR, IR, and HRMS) (PDF)

X-ray data for compound 2 (CIF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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Science (BNLMS). We also thank Ms. Fuling Liu of Xiamen University for solving the X-ray structure.

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(21) Direct treatment of **12** with PCC only gave compound **2** in low yield.

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(24) The promotion of the transesterification by  $\text{MgSO}_4$  was fortuitously found by the use of methanol dried over  $\text{MgSO}_4$ , in which a tiny amount of  $\text{MgSO}_4$  was dissolved.

(25) This enantiospecific synthesis required eight steps from (*R*)-(+)-citronellal and seven steps from known lactone **7** which could be prepared in large scale by procedures reported in ref [13](#).

(26) The stereochemistry of C3-*epi*-fusarisetin A was also confirmed by NMR NOE studies.