Total Synthesis of (−)-Fusarisetin A and Reassignment of the Absolute Configuration of Its Natural Counterpart

Research Interests
Divergent total synthesis of biologically active natural products based on biosynthetic hypothesis or privileged core structures
Desymmetrization strategy in natural product total synthesis
Ring strain-promoted reactions in natural product synthesis

Professional Experience
2010–present “Bairen Jihua” Professor, Shanghai Institute of Organic Chemistry
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Education
2004–2009 Ph.D., The Scripps Research Institute
Advisor: Prof. K. C. Nicolaou
2000–2004 B.Sc., Peking University
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Structures of (-)-Fusarisetin A
Retroynthetic analysis of fusarisetin (1)
(S)-(-)-citronellal

a) LiHMDS, 10, 71%
b) DIBAL-H, 98%
c) Ac₂O, Et₃N, 96%
Proposed structure of Fusarisetin A
\[ \alpha_{25}^D = -88.0 \ (c = 0.15 \text{ in MeOH}) \]

\[ \alpha_{25}^D = +84.6 \ (c = 0.2 \text{ in MeOH}) \]
总结：

1. 13 steps.
2. Lewis Acid-promoted intramolecular Diels-Alder reaction.
3. Pd-catalyzed O to C allylic rearrangement.
5. Dieckmann condensation/hemiketalization cascade.
one-pot radical cyclization and aminolysis

one-pot Dieckmann condensation and hemiacetalization

construction of DE rings

one-pot radical cyclization and aminolysis

construction of C ring

Wittig olefination

IMDA

(S)-(-)-citronellal (7)

(reaction)

olefin metathesis

5 Reformatsky reaction
1) Zn, ethyl bromoacetate
2) IBX, 80 °C
91% 2 steps

LiHMDS
then TEMPO
11
99%

99%

14
\[
\begin{align*}
14 & \quad \xrightarrow{\text{toluene, DMAP}} \quad 15 \\
\text{OH} & \quad \text{70\%, d.r. = ca. 1:1} \\
\text{13, DMAP} & \\
\text{one-pot radical cyclization and aminolysis} \\
\end{align*}
\]
1) Zn, AcOH
2) NaOMe
42%, 2 steps

(−)-fusarisetin A, 1
总结:

1, 9 steps, 10% (overall yield).
2, Protecting group-free.
3, Lewis Acid-promoted intramolecular Diels-Alder reaction.
4, One-pot TEMPO-induced radical cyclization/aminolysis.
Natural products serve as an abundant source in the search for anticancer agents due to unparalleled structural diversity and accompanying molecular modes of action. Recently, small molecules that inhibit cancer cell metastasis have received increasing interest in related drug discovery process, because such action may complement that of existing anticancer drugs such as the tubulin stabilizers/destabilizers and topoisomerase inhibitors. In May 2011, Ahn et al. reported the isolation of a biologically intriguing natural product, fusarisetin from a soil fungus, *Fusarium sp. FN080326*, which displays significant inhibition of acinar morphogenesis as well as cell migration and invasion without apparent cytotoxicity. The mechanism of action remains to be elucidated. The molecular structure of 1 was determined by employing X-ray crystallographic analysis (relative stereochemistry) and the exciton chirality circular dichroism method (absolute configuration). From a structural perspective, 1 exhibits a 6,6,5,5,5-fused pentacyclic ring system bearing 10 stereogenic centers. The interesting chemical structure as well as biological activity of fusarisetin A made it an attractive target for total synthesis. Herein, we report the first total synthesis of the proposed structure of this molecule.
In conclusion, we developed an efficient synthetic strategy for the total synthesis of the enantiomer of fusarisetin A, a newly discovered acinar morphogenesis inhibitor possessing an intricate structure, and reassigned the absolute configuration of the natural product through our synthesis. The synthesis featured an intramolecular Diels–Alder reaction, a Pd-mediated O→C allylic rearrangement, a chemoselective Wacker oxidation, and a Dieckmann condensation/hemiketalization cascade. The reported synthetic strategy and methods are expected to be applicable to the construction of other structurally or biosynthetically related natural products, as well as designed analogues of fusarisetin A, and thus to facilitate the exploration of its mechanism of action on a molecular level.