An enantiocontrolled entry to the tricyclic polar segment of (+)-fusarisetin A

Aki Kohyama, Naoki Kanoh, Eunsang Kwon, Yoshiharu Iwabuchi

PII: S0040-4039(15)30464-0
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.12.049
Reference: TETL 47096

To appear in: *Tetrahedron Letters*

Received Date: 13 October 2015
Revised Date: 1 December 2015
Accepted Date: 9 December 2015

Please cite this article as: Kohyama, A., Kanoh, N., Kwon, E., Iwabuchi, Y., An enantiocontrolled entry to the tricyclic polar segment of (+)-fusarisetin A, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.12.049

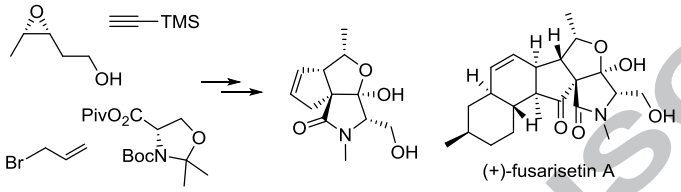
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

An enantiocontrolled entry to the tricyclic polar segment of (+)-fusarisetin A

Leave this area blank for abstract info.

Aki Kohyama, Naoki Kanoh, Eunsang Kwon, and Yoshiharu Iwabuchi



ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

An enantiocontrolled entry to the tricyclic polar segment of (+)-fusarisetin A

Aki Kohyama[a], Naoki Kanoh[a], Eunsang Kwon[b] and Yoshiharu Iwabuchi[a]*

[a] *Graduate School of Pharmaceutical Sciences, Tohoku University, Aobayama 6-3, Sendai 980-8578, Japan*
[b] *Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University, Aobayama 6-3, Sendai 980-8578, Japan.*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

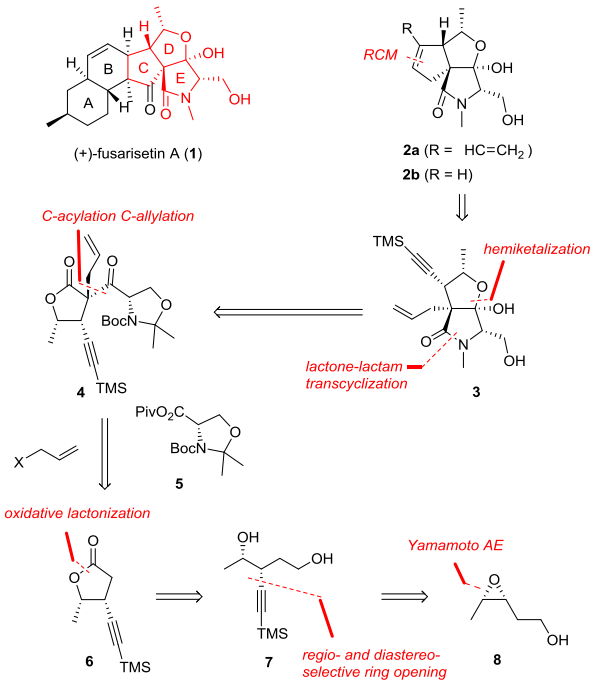
Keywords: Fusarisetin A, Yamamoto asymmetric epoxidation, epoxide ring opening, oxidative lactonization

ABSTRACT

The tricyclic polar segment of fusarisetin A, designed for preparing analogues for structure–activity relationship studies of the aliphatic segment thereof, has been constructed in an enantiocontrolled manner, featuring the Yamamoto asymmetric epoxidation of a homoallylic alcohol, C3-selective ring-opening of a 3,4-epoxy alcohol, stereocontrolled merger of a γ-lactone with Garner's counterpart, and ruthenium-catalyzed ring-closing metathesis.

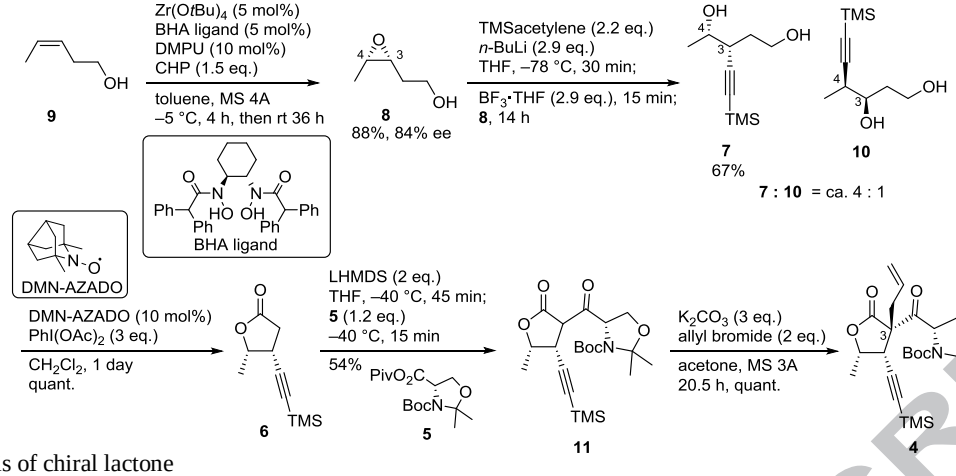
Considerable interest has surrounded the fungal metabolite (+)-fusarisetin A (**1**), isolated from the soil fungus *Fusarium* sp. FN08326, as an emerging class of anticancer agents owing to its potent inhibitory activity against acinar morphogenesis, cell migration, and cell invasion in MDAMB-231 cells.[1] The unprecedented complex molecular architecture coupled with a promising pharmacological properties has spurred intense synthetic efforts, some of which have culminated in elegant total syntheses.[2] Fascinated by the dense array of polar functional groups related to tetramic acid class of pharmacophore, our group also embarked on a synthetic study of fusarisetin A to gain insight into the structure–activity relationship (SAR) regarding the aliphatic polycyclic substructure. Herein, we report a concise entry to the tricyclic polar segment of fusarisetin A, in which the Yamamoto asymmetric epoxidation[3] of a homoallyic alcohol and Garner's counterpart[4] were employed to secure chiral centers.

Our retrosynthetic analysis of the polar tricylic segment of fusarisetin A (**1**) is depicted in Scheme 1. We set bicyclic lactam-lactol **3** as the crucial strategic intermediate, the ring closing metathesis (RCM) of which should provide the tricyclic segments **2a** and **2b**. 1,3-Diene **2a** serves as a platform amenable to extend additional rings for the SAR *via* Diels-Alder reaction, and tricycle **2b** can be regarded as the simple polar tricyclic CDE segment of (+)-fusarisetin A. The construction of **3** would be attained *via* the deprotection of **4**, the subsequent transcyclizations, and intramolecular hemiketalization. Foresight with respect to the inherent diastereopreference of an enolate derived from γ-lactone **6** led us to anticipate the stereocontrolled construction of the quarternary center of **4** *via* the sequential *C*-acylation of **6** with mixed anhydride **5**[4] and subsequent *C*-allylation. γ-Lactone **6** would be readily accessed from 1,4-diol **7** *via* the oxidative lactonization. Enantiomerically enriched 1,4-diol **7** is a logical product of the Yamamoto asymmetric epoxidation of the corresponding (*Z*)-homoallylic alcohol[3] and the following regio- and diasteroselective ring opening[5] of 3,4-epoxy alcohol **8** with a TMS-acetylide.



Scheme 1. Retrosynthetic analysis

* Corresponding author. Tel.: +81-22-795-6846; fax: +81-22-795-6845; e-mail: y-iwabuchi@m.tohoku.ac.jp

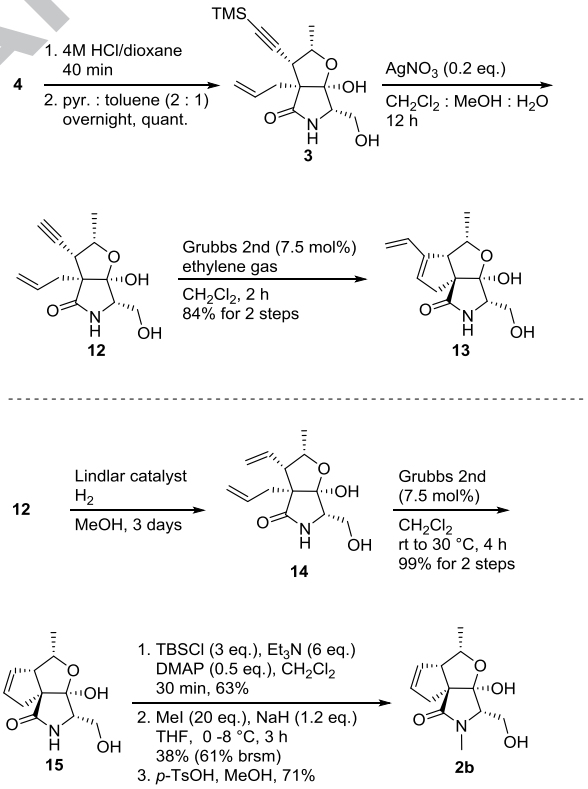


Scheme 2. Synthesis of chiral lactone

According to the procedure described by Yamamoto and coworkers,[3] commercially available (*Z*)-pent-3-en-1-ol **9** was treated with cumene hydroperoxide in toluene from –5 °C (4 h) to rt (36 h) in the presence of 5 mol% (*R*,*R*)-bishydroxamic acid ligand, 5 mol% $Zn(OtBu)_4$, 10 mol% DMPU, and 4A MS to give (3*R*,4*S*)-epoxyalcohol **8** in 88% with 84% ee. The intended C3-selective nucleophilic ring opening of epoxide **8** with TMS-acetylide was best conducted under Yamaguchi conditions using $BF_3{\cdot}THF$[5a] at –78 °C, giving rise to a 4:1 mixture of regioisomeric acetylene adducts with preference for the 1,4-diol **7**. After chromatographic separation, 1,4-diol **7** was treated with $PhI(OAc)_2$ in the presence of 10 mol% DMN-AZADO[6] to furnish γ-lactone **6** in quantitative yield. After extensive experimentations, (*S*)-Garner's acyl counterpart amenable to condense with γ-lactone **6** in a cross-Claisen manner was identified to be mixed anhydride **5**.[4a] Thus, lithium enolate, generated *in situ* by treating **6** with 2 equiv. of LHMDS, was mixed with 1.2 equiv. of mixed anhydride **5** to give **11** in 54% as a single diastereomer. Although the use of a stoichiometric excess LHMDS was essential to conduct efficient condensation of **5** and **6**, stereochemical integrity derived from L-serine was completely retained. The treatment of **11** with allyl bromide in the presence of K_2CO_3 in acetone allowed *C*-allylation in exclusive stereoselectivity to furnish allylated compound **4** in quantitative yield (Scheme 2).[7]

Having assembled all the stereogenic centers and strategic functionalities, effort was focused on finding an expedient sequence for constructing the tricyclic polar segment of (+)-fusarisetin A (Scheme 3). The tasks were ultimately settled by adopting judicious reaction conditions. Thus, upon exposure to 4 M HCl in dioxane, both Boc and acetonide groups of **4** were cleanly removed, and the residue obtained by concentrating the reaction mixture *in vacuo* was treated with pyridine-toluene to give bicyclic lactam-lactol **3** in quantitative yield. It should be noted that introduction of the allyl group at C-3 is essential for the expedient transcyclization to be operative: attempted deprotection and lactamization of **11**, instead of **4**, and following functionalization was disappointingly low yield due to the base-labile property of the tetramic acid moiety.

Preliminary experiments with RCM suggested that the nonprotected hydroxyl group of the hemiacetal is crucial for efficient ring-closing eneyne metathesis in this particular case. As such, after deprotection of the TMS group of **3** under the Pale conditions using catalytic amount of $AgNO_3$ in CH_2Cl_2-MeOH-H_2O,[8] ring-closing eneyne metathesis of **12** was effected by 2nd generation Grubbs catalyst to give the tricyclic segment **13** in 84% yield. The stereochemical arrangement and absolute configuration of **13** are confirmed by X-ray crystallography (Fig. 1). On the other hand, after the partial alkyne reduction of **12** to obtain diene **14**, the ring-closing metathesis of which using 2nd generation Grubbs catalyst furnished **15** in 99% yield.[9] Upon the TBS-protection of the primary hydroxyl group, *N*-methylation, and the deprotection of the TBS group, **15** furnished the tricyclic polar segment **2b**.



Scheme 3. Synthesis of tricyclic segments **13** and **2b**

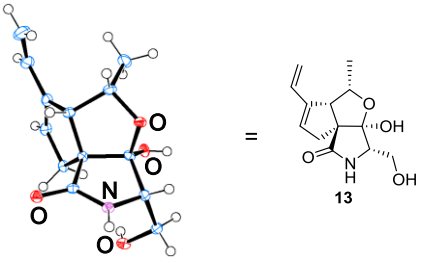


Fig. 1 ORTEP drawing of **13** showing thermal ellipsoids at the 50 % probability level.

In conclusion, we have successfully developed a concise enantiocontrolled entry to the tricyclic polar segment of fusarisetin A, which would enable the synthesis of various analogues for SAR studies. Our future work focusing on the preparation and evaluation of informative sets of derivatives will be reported in due course.

Acknowledgments

This research is partially supported by the Platform Project for Supporting in Drug Discovery and Life Science Research (Platform for Drug Discovery, Informatics, and Structural Life Science) from Japan Agency for Medical Research and Development, and Grant-in-Aid for Scientific Research on Innovative Areas“ Advanced Molecular Transformations by Organocatalysts” from MEXT, Japan, by a Grant-in-Aid for Scientific Research (B)(No. 24390001), and by a Grant-in-Aid for Young Scientists (A)(No. 23689001) from JSPS.

References and notes

1. Jang, J.-H.; Asami, Y.; Jang, J.-P.; Kim, S.-O.; Moon, D. O.; Shin, K.-S.; Hashizume, D.; Muroi, M.; Saito, T.; Oh, H.; Kim, B. Y.; Osada, H.; Ahn, J. S., *J. Am. Chem. Soc.* **2011,** *133*, 6865.
2. (a) Deng, J.; Zhu, B.; Lu, Z.; Yu, H.; Li, A., *J. Am. Chem. Soc.* **2012,** *134*, 920; (b) Xu, J.; Caro-Diaz, E. J.; Trzoss, L.; Theodorakis, E. A., *J. Am. Chem. Soc.* **2012,** *134*, 5072; (c) Yin, J.; Wang, C.; Kong, L.; Cai, S.; Gao, S., *Angew. Chem. Int. Ed. Engl.* **2012,** *51*, 7786; (d) Xu, J.; Caro-Diaz, E. J.; Lacoske, M. H.; Hung, C.-I.; Jamora, C.; Theodorakis, E. A., *Chem. Sci.* **2012,** *3*, 3378; (e) Huang, J.; Fang, L.; Long, R.; Shi, L.-L.; Shen, H. J.; Li, C.; Yang, Z., *Org. Lett.* **2013,** *15*, 4018; (f) Yin, J.; Kong, L.; Wang, C.; Shi, Y.; Cai, S.; Gao, S., *Chem.-Eur. J.* **2013,** *19*, 13040; (g) Caro-Diaz, E. J.; Aung, A.; Xu, J.; Varghese, S.; Theodorakis, E. A., *Org Chem Front* **2014,** *1*, 135; (h) Kong, L.; Rao, M.; Ou, J.; Yin, J.; Lu, W.; Liu, M.; Pang, X.; Gao, S., *Org. Biomol. Chem.* **2014,** *12*, 7591; (i) Nagaraju, K.; Mainkar, P. S.; Chandrasekhar, S., *Tetrahedron Lett.* **2015,** *56*, 404.
3. Li, Z.; Yamamoto, H., *J. Am. Chem. Soc.* **2010,** *132*, 7878.
4. (a) Cutarelli, T.; Fu, X.; McAllister, T.; Reeder, M.; Yin, J.; Yong, K.; Zhang, S., US-Patent, US20080045718A1, 2008; (b) Garner, P., *Tetrahedron Lett.* **1984,** *25*, 5855; (c) Liang, X.; Andersch, J.; Bols, M., *J. Chem. Soc., Perkin Trans. 1* **2001**, 2136.
5. (a) Evans, A. B.; Knight, D. W., *Tetrahedron Lett.* **2001,** *42*, 6947; (b) Yamaguchi, M.; Hirao, I., *J. Chem. Soc., Chem. Commun.* **1984**, 202.
6. (a) Doi, R.; Shibuya, M.; Murayama, T.; Yamamoto, Y.; Iwabuchi, Y., *J. Org. Chem.* **2015,** *80*, 401; (b) Hansen, T. M.; Florence, G. J.; Lugo-Mas, P.; Chen, J.; Abrams, J. N.; Forsyth, C. J., *Tetrahedron Lett.* **2003,** *44*, 57.
7. Teixeiraa, L. H. P.; Souzab, M. C. B. V. d.; Ramosa, M. d. C. K. V.; Netoa, F. R. d. A.; Barreiroa, E. J.; Fragac, C. A. M., *Synth. Commun.* **2002,** *32*, 505.
8. Orsini, A.; Vitérisi, A.; Bodlenner, A.; Weibel, J.-M.; Pale, P., *Tetrahedron Lett.* **2005,** *46*, 2259.
9. Hansen, E. C.; Lee, D., *Acc. Chem. Res.* **2006,** *39*, 509.