# New Madelalides Expand a Macrolide Series of Mitochondrial Inhibitors

LS 2018/01/06 Koichi Kamiya

## Contents

#### 1. Introduction

Mandelalide A and its Total synthesis by Smith, A. B.

#### 2. Main paper

McPhail, K. L.; Ishmael, J. E.; Smith, A. B.; Gallegos, D. A.; Anklin, C.; Nguyen, M. H.; Wan, X.; Serrill, J. D.; Nazari, M. *J. Med. Chem.* 2017, *60*, 7850–7862.





Isolation<sup>1)</sup> a new species of *Lissoclinum* ascidian (2012)

Biological Activity<sup>1)</sup> potent cytotoxity to human NCI-H460 lung cancer cells (IC<sub>50</sub> = 12 nM) and mouse Neuro-2A neuroblastoma cells (IC<sub>50</sub> = 29 nM)

Total Synthesis Ye, T. et al. (2014)<sup>2)</sup> Fürstner, A. et al. (2015)<sup>3)</sup> Altmann, K.-H. et al. (2016)<sup>4)</sup> Carter, R. G. et al. (2016)<sup>5)</sup> Smith, A. B. et al. (2016)<sup>6)</sup>

1) McPhail, K. L.; Ishmael, J. E. *et. al. J. Org. Chem.* **2012**, 77, 6066. 2) Ye, T.; Xu, Z. *et. al. Angew. Chem. Int. Ed.*, **2014**, *53*, 6533. 3) Fürstner, A.; Thiel, W. *et. al. Chem. Eur. J.*, **2015**, *21*, 10416. 4) Altmann, K.-H.; Bucher, P. *et. al. Chem. Eur. J.*, **2016**, *22*, 1292. 5) Carter, R. G.; McPhail, K. L.; Ishmael, J. E. *et. al. J. Am. Chem. Soc.* **2016**, *138*, 770. 6) Smith, A. B.; Kurogi, T. *et al. J. Am. Chem. Soc.* **2016**, *138*, 3675.

#### **Retro Synthesis of mandelalide A by Smith, A. B.<sup>1)</sup>**



## **Retro Synthesis of mandelalide A by Smith, A. B.<sup>1)</sup>**



#### **Synthesis of northern hemisphere**



#### **Synthesis of southern hemisphere**



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#### **Total Synthesis of mandelalide A**



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#### **Isolation of mandelalide analogues**



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#### **Total Synthesis of mandelalide L**



#### **Total Synthesis of mandelalide L**



## **Sideproduct of mandelalide**



seco mandelalide A methyl ester

# **Metabolic Pathway in Cancer Cells**



#### **Density-Dependent Changes in Sensitivity**



<sup>18</sup> 

#### **Oxidative Phosphorylation**





#### **OCR** analysis of mandelalide **B**



## **OCR** analysis of mandelalide A-C



Mandelalide A and B have the same function as oligomycin A. However, mandelalide C don't.

# **Cytotoxicity of A-type mandelalides**



## **Cytotoxicity of C-type mandelalide monosaccharide**



## **Cytotoxicity of C-type mandelalide aglycons**



#### **Cytotoxicity of B-type mandelalides**



## **Cytotoxicity of seco Mandelalide A methyl ester**



Macrolactone is needed for the cytotoxicity.

# Summary



It was revealed that mandelalides affect F1Fo-ATP Synthase.

SAR study revealed that monosaccharide is important for cytotoxicity, especially H-bond doner highlighted in purpole.

Generation of chemical probes for further analysis of the mandelalide binding target may be achievable by additional functionalization of the 24-OH (highlighted in yellow).