Chemical Biology Division Supported by Practical Organic Synthesis (Established：April 2018)

Group of Development and Application of the Practical Organic Synthesis

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Tsuneomi Kawasaki*	(Group Leader) Associate Professor, Department of Applied Chemistry, Faculty of Science
Takayuki Tonoi	Lecturer, Department of Applied Chemistry, Faculty of Science
Kenya Nakata	Visiting Associate Professor, Department of Chemistry, Graduate School of Natural Science and Engineering, Shimane University

Group of Chemical Biology and Research for the Development of Medicines

Motoyuki Shimonaka*	(Group Leader) Associate Professor, Department of Chemistry, Faculty of Science
Yoshikazu Higami	Professor, Department of Medicinal and Life Sciences, Faculty of Pharmaceutical Sciences
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Yukitoshi Nagahara	Visiting Professor, Division of Life Science and Engineering, Tokyo Denki University
Katsuhiko Kamei	Visiting Professor, Medical Mycology Research Center, Chiba University
Naruhiko Ishiwada	Visiting Associate Professor, Medical Mycology Research Center, Chiba University

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Chemical Biology Division Supported by Practical Organic Synthesis

Structure–Activity Relationship (SAR) and Mode of Action (MOA) Studies Using New Compounds Developed at the Tokyo University of Science

Group of Development and Application of the Practical Organic Synthesis

Synthesis of Ridaifens

Isamu Shiina*	Multi-component coupling reaction
Takayuki Tonoi	Dehydration condensation reaction
Kenya Nakata	Organocatalysis/Organometallics
	Pericyclic reaction

Asymmetric Synthesis/Total Synthesis

Isamu Shiina*	Nonsteroidal anti-inflammatory drugs
Tsuneomi Kawasaki*	Rare amino acids
Takayuki Tonoi	Borono-amino acids-^{10}B
Kenya Nakata	Natural product synthesis

Group of Chemical Biology and Research for the Development of Medicines

Project for Ridaifens

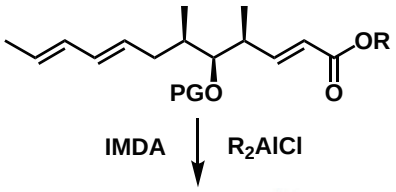
Motoyuki Shimonaka*	G1－G4 Ridaifens (*cf.* Ridaifen B, Drug for promotion of apoptosis induction)
Yoshikazu Higami	
Yasunari Mano*	G5 Ridaifens (RCOP) (Antitumor agent)
Kengo Morohashi	Transdermal drug（Skin cancer）
Kenichi Sakai	Lipoprofen（Antilipemic drug）
Go Hasegawa	M-COPA（Drug for TKI resistance）
Yukitoshi Nagahara	

SAR and MOA Studies

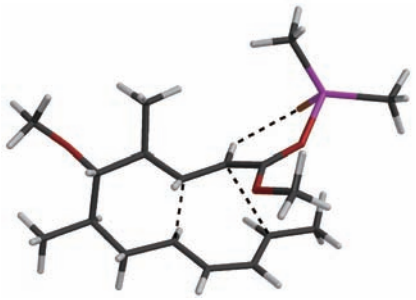
Motoyuki Shimonaka*	Boron neutron capture therapy (BNCT)
Yukitoshi Nagahara	
Katsuhiko Kamei	Macrolide antibiotics
Naruhiko Ishiwada	• Eushearilide, Nonactin, *etc.*
	Botcinin（Pesticide）
	EPM, BG, VA, *etc.*

Highlight of the Research Topics①

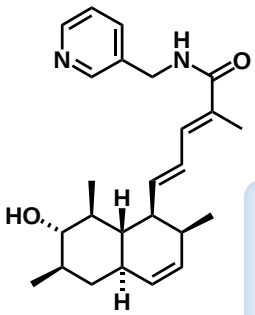
Asymmetric Synthesis of M-COPA, an Antitumor Agent



IMDA R_2AlCl



Favorable transition structure



M-COPA

14 steps
19% total yield

88.8% average yield
$(0.888)^{14} = 0.19$
$(0.80)^{14} = 0.04$
$(0.70)^{14} = 0.007$
$(0.60)^{14} = 0.0008$

Stereoselective total synthesis of M-COPA, a Golgi disruptor, was accomplished by the asymmetric C-C bond forming reactions.

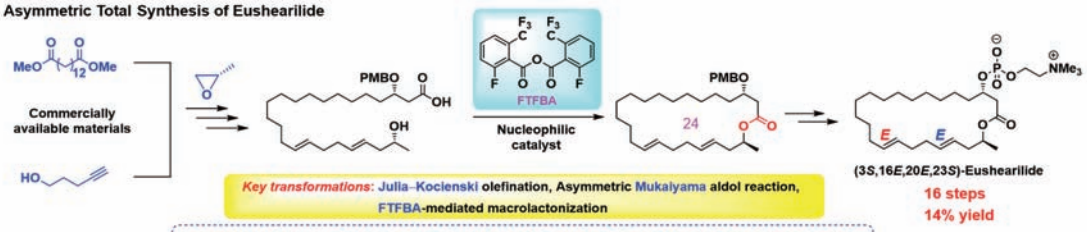
stereoisomers of IMDA rxn	stereogenic centers	stereoisomers
$2^4 = 16$	$2^3 = 8$	$2^7 = 128$

JP6143266 B2 (2017/5/19). （Materials and Manufacturing Methods）
PLOS ONE **12**(4), e0175514 (2017). （Anticancer Effect for Mast Tumor Cell）
Cancer Letters **415**, 1 (2018). （Anticancer Effect for Imatinib Resistant GIST）

Highlight of the Research Topics②

A Novel Antibiotic, Eushearilide

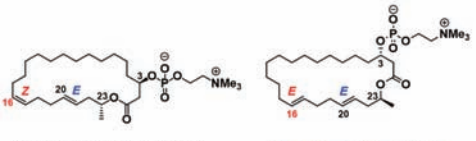
1. Asymmetric Total Synthesis of Eushearilide



Key transformations: Julia–Kocienski olefination, Asymmetric Mukaiyama aldol reaction, FTFBA-mediated macrolactonization

Convergent asymmetric total synthesis of a novel antibiotic, eushearilide, was accomplished through several key transformations starting with commercially available materials.

2. Determination of the Absolute Stereostructure of Eushearilide



Originally Proposed Structure (1)
(3*R*,16*Z*,20*E*,23*R*)-Eushearilide
$[\alpha]_D$ = +12.8° (*c* 0.75, MeOH)

Newly Proposed Structure (2)
(3*S*,16*E*,20*E*,23*S*)-(+)-Eushearilide
$[\alpha]_D$ = +11.3° (*c* 0.85, MeOH)

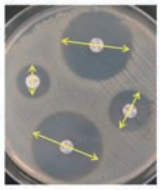
We successfully determined the absolute stereostructure of eushearilide for the first time.

3. Antimicrobial Activity of Eushearilide

microorganism	strain No.	compound[a] (3*S*,16*E*,20*E*,23*S*)-2
Trichophyton mentagrophytes	NBRC 5466	17.3
Aspergillus niger	NBRC 105649	4.3
Staphylococcus aureus	NBRC 12732	1.3
Staphylococcus aureus	IID 1677 (MRSA)	1.4
Staphylococcus aureus	ATCC 43300 (MRSA)	3.0
Enterococcus faecalis	ATCC 29212	7.8
Enterococcus faecalis	ATCC 51575 (VRE)	4.7

[a]The clear zone of inhibition (mm) around a paper disk impregnated with an antimicrobial agent at a concentration of 50 μg/disk.

Ref.) Disk Diffusion Test



Antimicrobial Susceptibility Test (Source: MAFF)

Eushearilde was found to exhibit antimicrobial activity not only against fungi, but even against bacteria including MRSA and VRE.

WO 2016068220 (2016/5/6). (Materials and Manufacturing Method)
Tetrahedron Letters **2015**, *56*, 1356–1359. (Total Synthesis of Eushearilide)
Journal of Antibiotics **2016**, *69*, 697–701. (Determination of the Stereostrucure of the Naturally Occurring Eushearilide)
Journal of Organic Chemistry **2018**, *83*, 7886–7899. (Total Synthesis and Antimicrobial Activity of Eushearilide Stereoisomers)