The Nakanishi Symposium

on Natural Products & Bioorganic Chemistry

March 23, 2022

Sponsored by
The Chemical Society of Japan
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The American Chemical Society

Takenori Kusumi

Professor Emeritus, Tokushima University
Special Professor, Tokyo Institute of Technology

■EDUCATION

- B.Sci. Department of Chemistry, Tokyo University of Education 1966
- Ph.D. Chemistry, Tokyo University of Education 1973

■CAREER

- Tokyo University of Education 1973–1976
  Assistant Professor, Department of Chemistry
- Tsukuba University 1976–1992
  Lecturer, Department of Chemistry
- Columbia University 1979–1980
  Postdoctoral fellow, Department of Chemistry, K. Nakanishi's group

- Tokushima University 1992–2008
  Professor, Faculty of Pharmaceutical Sciences
- Tokyo Institute of Technology 2008–2021
  Special Professor, Department of Chemistry

■RESEARCH TOPICS

- Structure elucidation of natural products
- Absolute configuration of organic compounds
- Chiral anisotropic reagents for absolute configuration determination
- NMR spectroscopy

■SELECTED PUBLICATIONS

1. Novel Diterpenes with a Cyclobutenone Moiety from the Brown Alga Pachydictyon coriaceum, M. Ishitsuka, T. Kusumi, H. Kakisawa, Y. Kawakami, Y. Nagai, T. Sato, *J. Org. Chem.*, **1983**, *48,* 1937.
2. High-field FT NMR Application of Mosher's Method. The Absolute Configurations of Marine Terpenoids, I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc*., **1991**, *113*, 4092.
3. Cyanoviridin RR, a Toxin from the Cyanobacterium (Blue-green Alga) Microcystis viridis, T. Kusumi, T. Ooi, M. M. Watanabe, H. Takahashi, H. Kakisawa, *Tetrahedron Lett*., **1987**, *28*, 4695.
4. Microviridin, a Novel Tricyclic Depsipeptide from the Toxic Cyanobacterium Microcystis viridis, M. O. Ishitsuka, T. Kusumi, H. Kakisawa, K. Kaya, M. M. Watanabe, *J. Am. Chem. Soc.*, **1990**, *112*, 8180.
5. The Structures of Quatromycins A_1, A_2, and A_3: Novel Macrocyclic Antiviral Antibiotics Possessing Four Tetronic Moieties, T. Kusumi, A. Ichikawa, H. Kakisawa, M. Tsunakawa, M. Konishi, T. Oki, *J. Am. Chem. Soc.*, **1991**, *113*, 8947.
6. NMR Spectroscopic Determination of the Absolute Configuration of Chiral Sulfoxides via *N*- (Methoxyphenylacetyl)sulfoximines, T. Yabuuchi, T. Kusumi, *J. Am. Chem. Soc.*, **1999**, *121*, 10646.

■AWARD

The Chemical Society of Japan Award for Creative Work for 2004.

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Nakanishi Symposium 2022

Organized by：Nakanishi Symposium Organizing Committee
Co-organized by: Chemical Society of Japan,
Division of Natural Products Chemistry & Biological Science

Date　March 23rd, 2022, 13:00–15:40 Zoom Webinar

Program

■13:00-13:20　Award Ceremony of Nakanishi Prize 2022
Congratulatory Address: Prof. Hiroaki Suga,
President-elect, The Chemical Society of Japan
Prize Winner of the Nakanishi Prize 2022:
Prof. Takenori Kusumi; Professor of Tokyo Institute of Technology

■13:20-15:40　Nakanishi Symposium
Presider Prof. Noritaka Chida (Keio University)

13:30-　"*NMR-based Determination of Absolute and Relative Configuration Inspired by the Kusumi's Method*"
Prof. Michio Murata (Osaka University)

13:45-　"*Studies on Biosynthesis of Marine Toxins Based on The Chemical Structures*"
Prof. Mari Yotsu-Yamashita (Tohoku University)

14:00-　"*Marine Natural Product Chemistry: Isolation, Structural Determination, Synthesis, and Molecular Mechanism of Biological Action*"
Prof. Hideo Kigoshi (Tsukuba University)

14:15-　"*Discovery of Marine Natural Products: Standing on the Shoulders of Giants*"
Prof. Higeki Matsuhaga (The University of Tokyo)

14:30-14:40　---Break---

■14:40-　**Award Lecture**
Presider Prof. Keisuke Suzuki; Tokyo Institute of Technology
"*Perpetually Fascinated by Natural Products Chemistry: with the Advancement of NMR*"
Prof. Takenori Kusumi

15:35-　Closing Remarks by Prof. Koichi Fukase (Osaka University)

NMR-Based Determination of Absolute and Relative Configuration Inspired by the Kusumi's Method

Michio Murata
Graduate School of Science, Osaka University
murata@chem.sci.osaka-u.ac.jp

Determination of stereochemistry of natural products and synthetic intermediates is one of the major topics of instrumental analytical methods. With the availability of high-field and high-resolution NMR instruments, which have been realized in the last 20-30 years, Dr. Kusumi has succeeded in establishing a reliable method for stereochemistry analysis by optimizing the classical Mosher method. This achievement has greatly accelerated the progress of structure determination and synthesis of natural products in the past 30 years. Inspired by the so called Kusumi method, various conformational analysis techniques have been developed, including those invented by himself.

Recently, new methodologies have been used that do not require chiral auxiliaries; e.g., computer-based approaches to deduce NMR chemical shifts of organic compounds have become more reliable. The scope and limitations of these methods will also be discussed.

References:

1. Ohtani, I., Kusumi, T., Kashman, Y., Kakisawa, H. *J. Am. Chem. Soc.*, **1991,** *113*, 4092–4096.
2. 岩下孝、楠見武徳、村田道雄 「特論 NMR 立体化学」講談社, 2012 年.

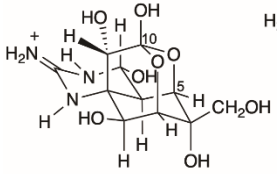
Studies on Biosynthesis of Marine Toxins Based on The Chemical Structures

Mari Yotsu-Yamashita

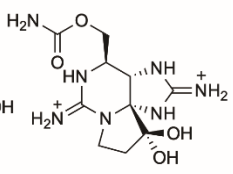
Graduate School of Agricultural Science, Tohoku University

mari.yamashita.c1@tohoku.ac.jp

Tetrodotoxin (TTX) and saxitoxin (STX) are potent Na_v blockers. TTX, a puffer fish toxin, has been identified in a wide range of marine animals and terrestrial amphibians. Biosynthesis of TTX has been a mystery for long time. We have approached this problem by identifying many structurally related compounds to TTX from puffer fish and newts. Based on the structures of these compounds, multiple oxidation steps from the spiro-fused bicyclic guanidino compounds have been suggested in TTX biosynthesis in marine environments.[1] In terrestrial environments, C5-C10 directly bonded TTX analogues and bi- and tricyclic guanidino compounds have been identified from newts, suggesting monoterpene origin of TTX.[2] Concerning STX biosynthesis, putative biosynthetic genes and functional expression of some corresponding enzymes have been reported. The mechanism of tricyclic structure formation in STX biosynthesis and order of oxidation steps are the current issues of interest. We are challenging to solve these questions using synthetic intermediates and originally developed analytical methods.[3]



Tetrodotoxin (TTX)



Saxitoxin (STX)

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1. N. Ueyama, K. Sugimoto, Y. Kudo, K. Onodera, Y. Cho, K. Konoki, T. Nishikawa, M. Yotsu-Yamashita, *Chem. Eur. J.*, **2018**, *24*, 7250-7258.
2. Y. Kudo, C.T. Hanifin, M. Yotsu-Yamashita, *Org. Lett.,* **2021**, *23*, 3513-3517.
3. S. Tsuchiya, Y. Cho, R. Yoshioka, K. Konoki, K. Nagasawa, Y. Oshima, M. Yotsu-Yamashita, *Angew. Chem. Int. Ed.,* **2017**, *56*, 5327-5331.

Marine Natural Product Chemistry: Isolation, Structural Determination, Synthesis, and Molecular Mechanism of Biological Action

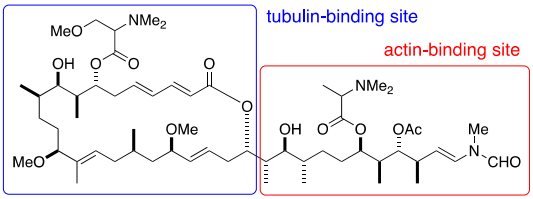
Hideo Kigoshi

Faculty of Pure and Applied Sciences, University of Tsukuba

kigoshi@chem.tsukuba.ac.jp

Marine natural products provide us scientific knowledge to understand life. There have been interesting compounds with unique structures and remarkable bioactivites from marine organisms.

Aplyronine A is a potent antitumor macrolide isolated from the Japanese sea hare *Aplysia kurodai*. We determined the structure in spectroscopic and organic synthetic manners. Total synthesis of the natural product and its artificial analogs was achieved, which provided the SAR information. Bioorganic study using artificial analogs and chemical probes revealed that an aplyronine A–actin–tubulin ternary complex disrupts microtubule dynamics to lead tumor cells to apoptosis. In this presentation, synthesis of aplyronine analogs and bioorganic study using the analogs will be discussed.



aplyronine A

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1. Yamada, K.; Ojika, M.; Kigoshi, H.; Suenaga, K. *Nat. Prod. Rep.*, **2009**, *26*, 27-43.
2. Kita, M.; Kigoshi, H. *Nat. Prod. Rep.*, **2015**, *32*, 534-542.
3. Ohyoshi, T.; Kigoshi, H. *Chem. Lett.*, **2021**, *50*, 580-584.

Discovery of Marine Natural Products: Standing on the Shoulders of Giants

Shigeki Matsunaga

Department of Aquatic Bioscience, The University of Tokyo

assmats@mail.ecc.u-tokyo.ac.jp

Compounds with a vast structural diversity have been isolated from marine organisms, especially sponges. Appropriately chosen methods should be used for their precise structure elucidation. Two examples from our group will be discussed.

Marine sponge *Cladocroce* sp. contained a new glycosylated bipolar sphingolipid. The relative configuration of 1,2-amino-alcohol unit in each end was assigned after converting to the bis-oxazolidinone derivative. The absolute configuration of the secondary alcohol in each end was determined by the modified Mosher's method. There was an isolated ketone in the middle of a long aliphatic chain, whose position was determined after converting to a mixture of positional isomers of the amides.[1]

Sesquiterpens related to manoalide and with less oxidation state were isolated from a marine sponge *Luffariella* sp. There was a chiral dihydropyran ring whose absolute configuration was assigned by a combination of asymmetric dihydroxylation and analysis of the ^{1}H NMR data. The conclusion drawn from this analysis was confirmed by the modified Mosher's method.[2]

References:

1. K. Sugawara, H. Watarai, Y. Ise, H. Yokose, Y. Morii, N. Yamawaki, S. Okada, S. Matsunaga, *Marine Drug*, **2021**, *9*, 287.
2. D. Kanki, K. Imai, Y. Ise, S. Okada, S. Matsunaga, *J. Nat. Prod.*, **2021**, *84*, 1676-1680.

Perpetually Fascinated by Natural Products Chemistry: with the Advancement of NMR

Takenori Kusumi

Professor Emeritus, Tokushima University

Special Professor of Tokyo Institute of Technology

kusumi.t.ab@m.titech.ac.jp

—Dedicated to late Professor Harry Stone Mosher—

Historically, natural products have been the centerpiece of organic chemistry, because they exist in common organisms surrounding human beings, some showing fascinating colors, and some having medicinal activities. Among the properties of natural products, the complexity of their chemical structures has intrigued organic chemists, who work in syntheses and structure analyses.

We have been studying the structure elucidation of natural products, mainly of those separated from marine organisms. The works were heavily dependent on NMR spectroscopy, starting from 60 MHz in the 1960th to modern 600 MHz instruments. The first significant results were obtained from the works on the seaweeds of *Dictyota* family, which produced a series of unique diterpenes composed of 4- to 11-memberbed rings.[1] With the aid of newly developed pulse sequences such as TOCSY, ROESY, HSQC and HMBC, the structures of the unusual compounds such as a marine alkaloid composed of a guanidine and a spermidine groups[2], a hepatotoxic monocyclic peptide[3] and a tricyclic depsipeptide[4] from a lake-water cyanobacterium, a novel macrocyclic antiviral antibiotics possessing four tetronic moieties,[5] and a highly unsaturated antibiotic alkaloid (using INADEQUATE)[6] were elucidated.

In the middle of 1980th, most of the compounds we isolated from marine organisms turned out to be 'known compounds'. In fact, one of the graduate students was sighing in front of the heap of cembranoids (monocyclic diterpenoids), whose structures were all known. There was no way to publish the known structures in a journal. She, however, found that, although the relative stereochemistry of them was clarified, the absolute configurations were not elucidated. Therefore, we focused on the method capable of determination of their absolute configurations. That was the time when the modified Mosher's method[7] was established based on Professor Mosher's original findings.[8] The method is easy to use and reliable, it was utilized world-widely until recently.

The method depends on the anisotropic effect of the phenyl group of the MTPA moiety. Later, we developed new chiral reagents possessing a naphthyl or an anthracenyl groups, which shows stronger anisotropic effect.[9] Also, the methods for absolute configurations of chiral carboxylic acids[10] and sulfoxides[11] were newly developed.

Because collection of marine organisms became more and more difficult from the ecological point of view, our focus was shifted to marine-derived fungi, which were easily cultivated in the laboratory.[12]

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1. (a) M. Ishitsuka, T. Kusumi, J. Tanaka, H. Kakisawa, *Chemistry Lett.*, **1982**, 1517. (b) T. Kusumi, D. M. Nkongolo, M. Goya, M. Ishitsuka, T. Iwashita, H. Kakisawa, *J. Org. Chem.*, **1986**, *51*, 384 and references cited therein.
2. (a) I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc*., **1991**, *113*, 4092. (b) I. Ohtani, T. Kusumi, H. Kakisawa, Y. Kashman, S. Hirsh, *J. Am. Chem. Soc.*, **1992**, *114*, 8472.
3. T. Kusumi, T. Ooi, M. M. Watanabe, H. Takahashi, H. Kakisawa, *Tetrahedron Lett.*, **1987**, *28*, 4695.

4. M. O. Ishitsuka, T. Kusumi, H. Kakisawa, K. Kaya, M. M. Watanabe, *J. Am. Chem. Soc.*, **1990**, *112*, 8180.
5. T. Kusumi, A. Ichikawa, H. Kakisawa, M. Tsunakawa, M. Konishi, T. Oki, *J. Am. Chem. Soc.*, **1991**, *113*, 8947.
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8. J. A. Dale, H. S. Mosher., *J. Am. Chem. Soc.* **1973**,*95*, 512.
9. T. Kusumi, T. Ooi, Y. Ohkubo, T. Yabuuchi, *Bull. Chem. Soc, Jpn*, **2006**, *79*, 965 and references cited therein.
10. T. Yabuuchi , T. Kusumi, *J. Org. Chem.*, **2000**, *65*, 397.
11. T. Yabuuchi, T. Kusumi, *J. Am. Chem. Soc.*, **1999**; *121*, 10646.
12. (a) M. Iida, T. Ooi, K. Kito, S. Yoshida, K. Kanoh, Y. Shizuri, T. Kusumi, *Org. Lett*., **2008**, *10*, 845. (b) R. Ookura, K. Kito, T. Ooi, M. Namikoshi, T. Kusumi, *J. Org. Chem.,* **2008**, 73, 4245.

Michio Murata: born in 1958, Osaka, graduated and PhD from Tohoku University (Prof. Takeshi Yasumoto), Research Staff, Suntory Institute for Bioorganic Research (1983-1985, Prof. Nakanishi), Research Associate, Tohoku University (1985-1993, Prof. Yasumoto), Post-Doctoral Research Fellow, NIDDK, National Institutes of Health (1989-1991, Dr. J. W. Daly), Associate Professor, The University of Tokyo (1993-1999, Prof. Kazuo Tachibana), Professor, Department of Chemistry, Osaka University (1999-).

Mari Yotsu-Yamashita: born in 1961 and graduated from Tohoku University (B. 1984), PhD from Tohoku University (1989, Prof. Takeshi Yasumoto), Junior researcher (Technical official) (1984-1998), Visiting Scholar, Department of Chemistry, Ohio State University (Prof. Viresh H. Rawal) (1994-1995), Associated Professor, Faculty of Agriculture, Graduate School of Agricultural Science, Tohoku University (1998-2004), Professor, Graduate School of Agricultural Science, Tohoku University (2004-). JSBBA Award for Young Scientists (2000).

Hideo Kigoshi: born in Gifu, 1959 and graduated from Nagoya University (B. 1981) PhD, Nagoya University (Prof. Kiyoyuki Yamada) 1989, Assistant Professor, Faculty of Science, Nagoya University (1984-1994), Postdoctoral fellow, Harvard University (1990-1991, Prof. E.J. Corey), Associate Professor, Faculty of Science (1994-1998) and Research Center for Materials Science, Nagoya University (1998-2000), Professor, Department of Chemistry (2000-2011) and Faculty of Pure and Applied Sciences, University of Tsukuba (2011-). Chemical Society of Japan Award for Young Chemists (1993).

Shigeki Matsunaga: born in Tokyo in 1957 and educated at The University of Tokyo (B., 1979; M., 1981; PhD, 1984) (Prof. Shoji Konosu). JSPS Postdoctoral Fellow, The University of Tokyo (1984-1988), postdoctoral fellow at University of Hawaii (1988-1989, Prof. R. E. Moore), and National Cancer Center Research Institute (1990-1991, Dr. Hirota Fujiki), Assistant Professor, Faculty of Agriculture, The University of Tokyo (1991-1995), Associate Professor (1995-2004), and Professor (2004-2022) at the same campus. Throughout his research career he has been fascinated by the incredibly designed structures of biologically active natural products.

The Recipients of the Prize hereto are:

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1997 Frank H. Westheimer
1998 Albert J. Eschenmoser*
1999 Jeremy R. Knowles
2000 Satoshi Ōmura*
2001 John D. Roberts
2002 Sir Jack Baldwin*
2003 A. Ian Scott
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2006 Takeshi Yasumoto*
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2010 Shosuke Yamamura*
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2021 Mei Hong
2022 Takenori Kusumi*

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