The Nakanishi Symposium

on Natural Products & Bioorganic Chemistry

Tokyo University of Science
March 19, 2021

Sponsored by
The Chemical Society of Japan
&
The American Chemical Society

Yoshito Kishi
Professor Emeritus, Harvard University

■EDUCATION

Bachelor of Science, Nagoya University 1961
Doctor of Philosophy (Chemistry), Nagoya University
(Professors Yoshimasa Hirata and Toshio Goto) 1966
Postdoctoral Research Fellow (Chemistry), Harvard University
(Professor R. B. Woodward) 1966-1968

■ACADEMIC APPOINTMENT

Instructor of Chemistry, Nagoya University 1966-1970
Associate Professor of Agricultural Chemistry, Nagoya University 1970-1974
Visiting Professor of Chemistry, Harvard University 1972-1973
Professor of Chemistry, Harvard University 1974-1982
Morris Loeb Professor of Chemistry, Harvard University 1982-2002
Morris Loeb Professor of Chemistry, *Emeritus*, Harvard University 2002-

■RESEARCH TOPICS (chronological order)

1. **Chemical studies of bioluminescence:** The luminescent substance named luciferin is an unstable compound, making its structural determination extremely difficult. Dr. Kishi, however, determined the structures of luciferins, such as those in Cypridina, Genji fireflies, krill, dinoflagellates, and the luminous shellfish of Latia (1960s–1980s).

2. **Total synthesis of complex natural products:** The pufferfish toxin tetrodotoxin, the structure of which was determined in 1964, is still known as one of the most difficult natural products to synthesize due to its highly functionalized structural complexity. Dr. Kishi achieved the world's first total synthesis of this compound in 1972. Later, he achieved total synthesis of the paralytic shellfish toxin saxitoxin, the anticancer drug mitomycin C, the fungus toxin sporidesmin, and the β-lactam antibiotics (1970s–1980s).

3. **Development of acyclic stereocontrol in total synthesis of natural products:** Until the early 1970s, total synthesis of polyether antibiotics was almost impossible due to the presence of numerous asymmetric centers. However, Dr. Kishi developed a versatile stereoselective reaction based on a completely new concept of acyclic stereocontrol and achieved total synthesis of several complex natural products, such as the antibiotics lasalocid, monensin, narasin, and rifamycin. He showed the generality and usefulness of the acyclic stereocontrol methods, leading to explosive development in synthetic chemistry (late 1970s–1990s).

4. **Complete stereochemistry and total synthesis of palytoxin:** The highly toxic palytoxin is one of the largest and most complex natural marine products in the world, with a molecular weight of 2,681 Da. Dr. Kishi determined the fifty-one configurations of this molecule by making full use of organic synthesis, eventually completing its total synthesis. Except for biological macromolecules such as proteins and nucleic acids, palytoxin is the largest natural product ever synthesized by humankind, and its total synthesis is said to be a milestone in the history of chemistry (1980s–1990s).

5. **Development of a universal NMR database:** Dr. Kishi developed a universal NMR database which allowed a non-destructive determination of the configuration of acyclic compounds. With this

database, he determined the stereochemistry of maitotoxin, a large natural polyether marine product with a molecular weight of 3,422 Da, as well as the stereochemistry of mycolactone, the causative toxin of Buruli ulcer (1980s–present).

6. **Total synthesis of halichondrin and the development of the antitumor agents eribulin and C52-halichondrin-B amine:** The total synthesis of halichondrin B, a potent natural marine antitumor product, was completed using the NHK reaction developed during the synthesis of palytoxin. It was found that only the right side moiety of halichondrin B showed a similar antitumor activity as halichondrin. After more than ten years of the collaborative research with Eisai Co., a revolutionary antitumor agent, eribulin (trade name: Halaven), was developed. Eribulin has a complex structure, containing eighteen asymmetric centers, and is the most complex organic compound produced on a commercial basis. Most recently, this synthetic research led to the large-scale synthesis of C52-halichondrin-B amine, a new antitumor drug candidate currently in clinical trials (1990s–present).

■HONORS

- The Chemical Society of Japan Award For Young Chemists (1967)
- ACS Award for Creative Work in Synthetic Organic Chemistry (1980)
- Harrison Howe Award (1981)
- The 24th Naito Memorial Award (1992)
- Nagoya Gold Medal (1995)
- Prelog Medal (1994)
- Havinga Medal (1996)
- Imperial Prize of the Japan Academy 学士院賞恩賜賞 (1999)
- ACS Ernest Guenther Award in the Chemistry of Natural Products (2001)
- Tetrahedron Prize for Creativity in Organic Chemistry BioMedicinal Chemistry (2001)
- Person of Cultural Merit 文化功労者 (2001)
- Special Award in Synthetic Organic Chemistry, Japan (2010)
- The Order of the Sacred Treasure, Gold and Silver Star 瑞宝中綬章 (2013)
- Ryoji Noyori Prize (2018)

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Nakanishi Symposium 2020

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

Date　March 19th, 2021, 13:30–17:00 Zoom Webinar

Program

■13:30-13:50　Award Ceremony of Nakanishi Prize 2020
Congratulatory Address: Dr. Hiromitsu Kobayashi,
President, The Chemical Society of Japan
Prize Winner of the Nakanishi Prize 2020:
Dr. Yoshito Kishi; Professor Emeritus of Harvard University

■13:50-　**Award Lecture**
Presider Prof. Michio Murata; Osaka University
"*Chemistry and Biological Functions of Beyond Total Synthesis of Complex Natural Products*"
Prof. Yoshito Kishi

■15:00-17:00　Nakanishi Symposium
Presider Prof. Hirokazu Arimoto (Tohoku University)
15:00-　"*Synthetic Studies on Biologically Active Natural Products toward Practical Application*"
Prof. Kosuke Namba (Tokushima University)
15:30-　"*Synthesis of Polycyclic Alkaloids Based on Dearomative Oxidative Cyclization*"
Prof. Kazuo Nagasawa (Tokyo University of Agriculture and Technology)
15:30-15:40　---Break---
Presider Prof. Hideaki Oikawa (Hokkaido University)
15:40-　"*Lessons from Total Synthesis of Carthamin, A Red Pigment from Safflower (Benibana)*"
Prof. Keisuke Suzuki (Tokyo Institute of Technology)
16:10-　"*Studies on the Total Synthesis of Tetrodotoxin*"
Prof. Tohru Fukuyama (The University of Tokyo)
16:40-　Closing Remarks

Synthetic Studies on Biologically Active Natural Products toward Practical Application

Kosuke Namba

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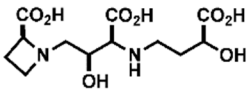
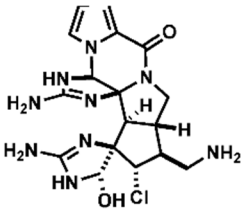
Despite advances in organic synthetic chemistry have been remarkable, total synthesis of biologically active natural products having complex carbon framework and many functional groups is still a difficult task. Therefore, although there are many useful natural products that are expected to contribute to the medical care and elucidation of life phenomena, the limited supply from natural sources is a major barrier to their practical application in many cases. In response to this problem, Prof. Kishi and collaborators have succeed in the practical application of a very complex natural product, halichondrin B, by supplying large quantities through chemical synthesis. The author worked on the part of this practical research and obtained valuable experience in Prof. Kishi's group. Now, the author believe that the solid supply of biologically active natural products is a significant issue for the future total synthesis. Based on this concept, in this presentation, I will discuss about our recent synthetic studies on mugineic acid[1] (**1**) and palau'amine[2] (**2**) in the view of the practical application of agrichemicals and pharmaceuticals.

Referecnes:

1. S. Takagi, *Soil Sci. Plant Nutr.* **1976**, *22*, 423.
2. R. B. Kinnel, H-P. Gehrken, P. J. Scheuer, *J Am. Chem. Soc*. **1993**, *115*, 3376.



mugineic acid (1)



palau'amine (2)

Synthesis of Polycyclic Alkaloids Based on Dearomative Oxidative Cyclization

Kazuo Nagasawa

Tokyo University of Agriculture and Technology

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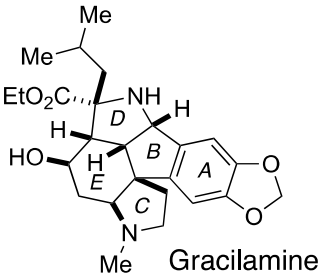
Some biologically active alkaloids have characteristic polycyclic ring systems with variety of functional groups including all-carbon quaternary center. To access the structures efficiently, number of approaches have been reported. In our group, we have examined the strategy for constructing the polycyclic ring system in the alkaloids with the following three steps; (i) connection of two aromatic rings one of which is a phenol, (ii) dearomative oxidative cyclization of phenol, and (iii) Michael type cyclization to the resulting dienones. In the process, it has an advantage that variety of functional groups can be installed in aromatic groups before constructing the polycyclic ring systems.

Based upon the strategy, we have demonstrated to construct 6-5-6, and 6-6-6 ring systems including heterocycles with multi-functional groups. Furthermore, an additional fused type ring is constructed by the Michael type cyclization reaction. In this presentation, synthesis of indole alkaloids of (+)-glacilamine[1] and hasubanan type alkaloids are discussed.



Gracilamine

Referecne:

1. M. Odagi, Y. Yamamoto, K. Nagasawa, A*ngew. Chem., Int. Ed.* **2018**, *57*, 2229.

Lessons from Total Synthesis of Carthamin, A Red Pigment from Safflower (Benibana)

Keisuke Suzuki

Department of Chemistry, Tokyo Institute of Technology

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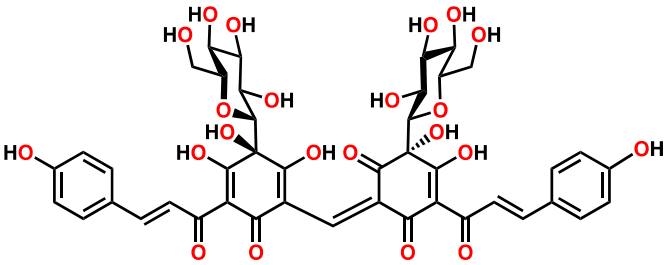
Carthamin is a traditional red pigment isolated from the petals of safflower, *Carthamus tinctorius* L (Benibana). The interest in the structural identity of the pigment traces back to 1910[1] or even earlier. From our interest in the natural products derived from type-II polyketide biogenesis,[2] we targeted this compound, having recently succeeded in the total synthesis.[3] In this talk, our lessons learned from the struggle will be discussed.



carthamin

References:

1. Kametaka, T.; Perkin, A. G. *J. Chem. Soc. Trans.* **1910**, *97*, 1415.
2. Suzuki, K. *Chem. Rec*. **2010**, *10*, 291.
3. Azami, K.; Hayashi, T.; Kusumi, T.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed.* **2019**, *58,* 5321.

Studies on the Total Synthesis of Tetrodotoxin

Tohru Fukuyama

Professor Emeritus, The University of Tokyo

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Tetrodotoxin (TTX) is one of the most famous natural products and is primarily known as a toxic principle of puffer fish. The potent toxicity of TTX is attributed to the inhibition of voltage-gated sodium channels (Na_Vs). Remarkable biological activities as well as unique structural features have made TTX a popular target for total synthesis. Several successful total syntheses and a number of synthetic approaches to TTX have been covered in a recent review.[1] As a young member of the TTX synthesis team of Prof. Kishi at Nagoya University, I was involved in the first total synthesis of racemic tetrodotoxin.[2] More recently, we focused our attention on an efficient asymmetric total synthesis of TTX which could be applied to design a probe to capture mammalian Na_Vs for structural studies. Brief accounts of our first[3] and second total syntheses of TTX as well as the most recent approach will be discussed in the lecture.

References:

1. Makarova, M.; Rycek, L.; Hajicek, J.; Baidilov, D.; Hudlicky, T. *Angew. Chem. Int. Ed.* **2019**, *58*, 18338.
2. Kishi, Y.; Fukuyama, T.; Aratani, M.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc*. **1972**, *94*, 9219.
3. Maehara, T.; Motoyama, K.; Toma, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem. Int. Ed*. **2017**, *56*, 1549.
4. I am deeply indebted to Prof. Satoshi Yokoshima, Graduate School of Pharmaceutical Sciences, Nagoya University, for his continued support and participation in the TTX project after my retirement.

Beyond Total Synthesis of Complex Natural Products

Yoshito Kishi

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With the halichondrin class of natural products as a case study, we have been searching for the coupling-reactions effective at a late-stage in a convergent synthesis of a complex molecule. In order to carry out a given convergent synthesis effectively, these coupling-reactions must meet with several demanding criteria, including the coupling efficiency with a ~1:1 ratio of the coupling partners, the functional group compatibility, the coupling rates, the stereoselectivity, and others. Thus far, we have focused on the development of Ni/Cr-mediated aldehyde/vinyl-iodide couplings[1] and Ni/Zr-mediated ketone synthesis,[2] leading us to the development of unified, efficient, and scalable total synthesis of the halichondrin class natural products.[3]

We will continue the research along these lines. At the same time, we realize that the current synthesis allows us to address the next level of our research-curiosity. In this presentation, we shall discuss three of these attempts. First, with collaboration with Eisai Tsukuba scientists, we have successfully demonstrated the scalability of the current synthesis, thereby showing that the drug-supply issue can be solved by a total synthesis even for complex natural products such as halichondrins.[4] Second, we have been creating a library of *in-vivo* active compounds on the basis of the halichondrin class of natural products. Using Xenograft models with 11 cancer-cell lines, we have

showed that: (1) each member in the library exhibits a unique profile against the cancer models and (2) many compounds in the library exhibit an outstanding *in-vivo* efficacy for these cancer models. Third, in order to gain further mechanistic in-sights on their anticancer effectiveness at a molecular level, we have synthetized and tested the *in-vitro* and *in-vivo* activity of complete- and half-antipode of halihondrin-B and homohalichondrin-B, thereby giving totally unexpected discoveries. In our view, these discoveries immediately suggest exciting new research-directions for both basic and applied research.

References

1. (a) H. Guo, C. Dong, D. Kim, D. Urabe, J. Wang, J. T. Kim, X. Liu, T. Sasaki, and Y. Kishi, *J. Am. Chem. Soc.* **2009**, *131*, 15387. (b) K. Yahata, N. Ye, K. Iso, S. R. Naini, S. Yamashita, Y. Ai, and Y. Kishi, *J. Org. Chem.*, **2017**, *82*, 8792 and references cited therein.
2. (a) V. P. Kumar, V. S. Babu, K. Yahata, and Y. Kishi, *Org. Lett.* **2017**, *19*, 2766. (b) Y. Ai, N. Ye, Q. Wang, K. Yahata, and Y. Kishi, *Angew. Chem. Int. Ed.* **2017**, *56*, 10791. (c) A. Umehara and Y. Kishi, *Chem. Lett.* **2019**, *48*, 947 and references cited therein.
3. K. Yahata, N. Ye, Y. Ai, K. Iso, and Y. Kishi, *Angew. Chem. Int. Ed.* **2017**, *56*, 10796 and references cited therein.
4. S. Kawano, K. Ito, K. Yahata, K. Kira, T. Abe, T. Akagi, M. Asano, K. Iso, Y. Sato, F. Matsuura, I. Ohashi, Y. Matsumoto, M. Isomura, T. Sasaki, T. Fukuyama, Y. Miyashita, Y. Kaburagi, A. Yokoi, O. Asano, T. Owa, and Y. Kishi, *Sci. Rep.* **2019**, *9*, 8656 and references cited therein.

Kosuke Namba: born in Osaka in 1972 and graduated from Osaka City University (B. 1996), PhD, Osaka City University (Prof. Y. Ohfune) 2001, Postdoctoral fellow, Colorado State University (2001-2003, prof. R. M. Williams) and Harvard University (2003-2005, Prof. Y. Kishi), Researcher, the Suntory Institute for Bioorganic Research (2005-2006), Assistant Professor, Tokushima Bunri University (2006-2008, Prof. M. Nishizawa), Lecturer and Associate Professor, Hokkaido University (2008-2013, Prof. K. Tanino), Professor, Pharmaceutical Science, Tokushima University (2013-). Incentive Award in Synthetic Organic Chemistry, Japan in 2009.

Kazuo Nagasawa: born in 1965 and graduated from Waseda University (B. 1988), PhD from Waseda University (1993, Prof. Isao Shimizu), Postdoctoral fellow, Harvard University (1997-1999, Prof. Yoshito Kishi), Researcher, RIKEN, (1993-2000, Prof. Tadashi Nakata), Associate Professor, Institute of Molecular and Cellular Biosciences, University of Tokyo (2001-2004), Associate Professor, Department of Technology, Tokyo University of Agriculture and Technology (2004-2009), Professor, Department of Technology, Tokyo University of Agriculture and Technology (2009-). Research Award in the Society of Synthetic Organic Chemistry, Japan (2000), The Pharmaceutical Society of Japan Award for Young Scientists (2003), Shionogi Award in the Society of Synthetic Organic Chemistry, Japan (2018). position.

Keisuke Suzuki: born in Chigasaki in 1954 and graduated from University of Tokyo (B. 1978), Dr. Sci., University of Tokyo (Prof. Teruaki Mukaiyama) 1983, Research Associate, Keio University (1983–1987), Lecturer (1987–1989), Associate Professor (1989–1994), Professor, Keio University (1994–1996), Professor, Tokyo Institute of Technology (1996–), Visiting Professor, ETH (1990–1991, Prof. Seebach), Member of Japan Academy (2018–). Chemical Society of Japan Award for Young Chemists (1986), Japan IBM Award (1994), Nagoya Silver Medal (1999), Synthetic Organic Chemistry Award, Japan (2003), Prizes for Science and Technology, MEXT Japan (2006), Chemical Society of Japan Award (2008), Humboldt Research Prize (2009), Purple Ribbon Medal (2010), Japan Academy Prize (2015).

Tohru Fukuyama: born in 1948 in Anjo, Japan. Nagoya University (B.A., 1971), Harvard University (Ph.D., 1977, Prof. Yoshito Kishi), Postdoctoral Fellow, Harvard University (1977-1978, Prof. Kishi), Assistant Professor (1978-1982), Associate Professor (1982-1988), Professor (1988-1995), Department of Chemistry, Rice University, Professor (1995-2012), Graduate School of Pharmaceutical Sciences, University of Tokyo, Professor (2012-2013), Designated Professor (2013-2018), Graduate School of Pharmaceutical Sciences, Nagoya University. A number of awards including ACS Award for Creative Work in Synthetic Organic Chemistry (2004) and Medal with Purple Ribbon.

The Recipients of the Prize hereto are:

1996 Yoshimasa Hirata*
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
2004 Isao Kitagawa*
2005 Stephen J. Benkovic
2006 Takeshi Yasumoto*
2007 Hung-wen Liu
2008 Michel Rohmer*
2009 JoAnne Stubbe
2010 Shosuke Yamamura*
2011 C. Dale Poulter
2012 Daisuke Uemura*
2013 Arthur G. Palmer, III
2014 Jerrold Meinwald*
2015 Fred McLafferty
2016 Shoichi Kusumoto*
2017 Martin Gruebele
2018 Nobuyuki Harada*
2019 Lewis E. Kay
2020 Yoshito Kishi*

*Selection and presentation made by the Chemical Society of Japan.

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Minoru Ueda (Tohoku University)
Keisuke Suzuki (Tokyo Institute of Technology)

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