The Nakanishi Symposium

on Natural Products & Bioorganic Chemistry

March 18, 2024

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Professor Minoru Isobe

Born in Nagoya, Japan, 1944 and graduated from Nagoya University (B. 1967), Nagoya Univ. (Prof. Toshio Goto) Dr. 1973, Postdoc, Columbia Univ. (G. Stork, 1973-75), Associate Prof. Faculty of Agriculture, Nagoya Univ. (1975-1991), Professor Nagoya Univ., Bioagric. Sciences, (1991-2008.3), Professor Emeritus Nagoya Univ. (2008-present), Chair Prof., National Tsing Hua Univ., Taiwan (2008.5- 2014.4), Chair Prof. National Sun Yat-Sen Univ., Taiwan (2014.6- 2015.9), Prof. Chulabhorn Research Institute, Thailand (2015.11-2016.10), Visiting Prof. Toyama Prefecture Univ. (2017-present). Imperial Awards: Medal with Purple Ribbon (2008.4), Princess Chulabhorn Gold Medal (2012.11), Order Sacred Treasure, Gold Rays (2018.4).

Academic Record

Nagoya University (bachelor) 1967 (Agricultural Chemistry)
Nagoya University (master) 1969 (bioluminescence)
Nagoya University (PhD) 1973 (silkworm diapause hormone, Prof. T. Goto)
Columbia University (postdoc., U.S.A.) (Prof. G. Stork, prostaglandin; 1973-1975)

Academic Apointment

Associate Professor, Nagoya University (1975-1991)
Professor, Nagoya University, Bioagricultural Sciences, (1991 – 2008.3 retired)
Professor, Institute of Advanced Research, Nagoya University (2005 – 2009.3)
Professor Emeritus, Nagoya University (2008.4-present)
NSC Chair Professor, National Tsing Hua University, Taiwan (2008.5-2014.4)
Visiting Professor, The Chinese University of Hong Kong (2015.1-4)
Chair Professor, National Sun Yat-sen University, Taiwan (2014.6-2015.9)
Professor, Chulabhorn Research Institute (2015.11-2016.10)
Visiting Chair Professor, National Cheng Kong University (2023.7-8)
Visiting Professor, Toyama Prefecture University (2017-present)

Research Field

Organic Chemistry, Natural Product Chemistry, Bioorganic Chemistry
Total Synthesis with Stereochemical Control
Synthetic Methodology
Bioluminescence (molecular mechanism on photoprotein)

Marine Toxins
Insect Hormone
Ion selective ionophore
Chemistry for biology (molecular interaction between natural product and target protein)

Awards

JSBBA Award for Young Scientists (1980)
Synthetic Organic Chemistry Award, Japan (1995)
JSBBA Award (2000)
紫綬褒賞 Medal with Purple Ribbon (2008.5.16)
Princess Gold Medal from H.R.H. Princess Chulabhorn of Thailand (2012.11)
瑞宝中綬章 The Order of the Sacred Treasure, Gold Rays with Neck Ribbon (2018.5.11)

Publication of Scientific Papers

458 + 40 (original articles 365; review articles and books 93) (plus others 40)

Invited Papers from authorized International Chemical Societies

>120

Contribution of International Service for Academic Area

Goto Memorial Lecture Organizer 1992-2000
Nagoya Medal Lecture Organizer 2002-2008
Sino-Japanese Symposium on Organic Chemistry for Young Scientists (2002-2005)
JSPS Coordinator Asian Core Program (Cutting-Edge Organic Chemistry in Asia (2005-2008)
IUPAC Division President of Organic & Biomolecular Chemistry (2004-2007)

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Nakanishi Symposium 2024

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

Date March 18th (Monday), 2024, 13:00–15:40

Venue Funabashi Campus, Nihon University

Program

■13:00-13:20 Award Ceremony of Nakanishi Prize 2024
Congratulatory Address: Prof. Hiroaki Suga,
President, The Chemical Society of Japan
Prize Winner of the Nakanishi Prize 2024:
Prof. Minoru Isobe; Professor of Nagoya University
Report on the Nakanishi Prize Selection: Chairman Michio Murata

■13:20-15:40 Nakanishi Symposium
Presider Prof. Kazuo Nagasawa (Tokyo University of Agriculture and Technology)

13:25- "*Natural Product Synthesis Using Cyclization Reactions of Alkyne-Dicobalt Complexes*"
Prof. Keiji Tanino (Hokkaido University)

Presider Prof. Hiroki Oguri (The University of Tokyo)

13:50- "*Collective Synthesis of Natural Products for Elucidation of Their New Biological Activities*"
Prof. Toshio Nishikawa (Nagoya University)

Presider Prof. Junko Okanda (Shinshu University)

14:15- "*Transition Metal Complexes in Chemical Biology*"
Prof. Mikiko Sodeoka (RIKEN)

■14:40- **Award Lecture**
Presider Prof. Minoru Ueda (Tohoku University)
"*BioOrganic Chemistry on Silkworm Diapause and Squid Bioluminescence*"
Prof. Minoru Isobe (Nagoya University)

15:35- Closing Remarks
by Prof. Hirokazu Arimoto (Tohoku University)

Natural Product Synthesis Using Cyclization Reactions of Alkyne-Dicobalt Complexes

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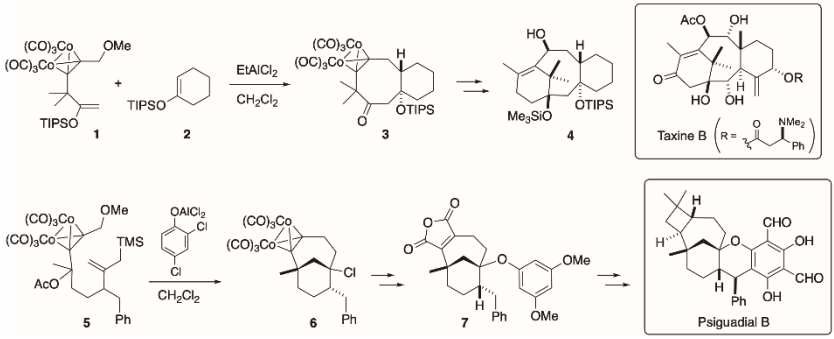
In this lecture, the development of annulation methods using alkyne-dicobalt complexes will be presented. The formal [6+2] cycloaddition reaction[1] of cobalt complex **1** with enol silyl ether **2** afforded bicyclic ketone **3** which was converted to tricyclic alcohol **4**, a model compound of taxane diterpenoids.[2] On the other hand, the double cyclization reaction of cobalt complex **5** was designed as the key step of the total synthesis of Psigusial B, giving rise to bicyclic compound **7** through introduction of the aromatic ring.[3]



References:

1. K. Mitachi, T. Shimizu, M. Miyashita, K. Tanino, *Tetrahedron Lett*. **2010**, *51*, 3983.
2. R. Hanada, K. Mitachi, K. Tanino, *Tetrahedron Lett.* **2014**, *55*, 1097.
3. M. Kinebuchi, R. Uematsu, K. Tanino, *Tetrahedron Lett*. **2017**, *58*, 1382.

Collective Synthesis of Natural Products for Elucidation of Their New Biological Activities

Toshio Nishikawa

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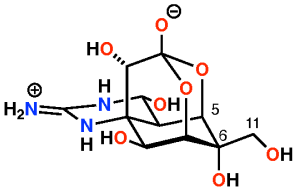
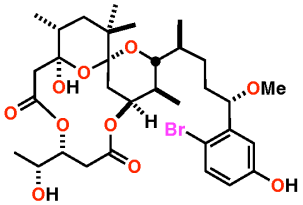
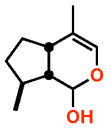
Natural products exhibiting unique and potent biological activities have played significant role not only in drug discovery but also in the development of life sciences. However, biological activities of the most of natural products isolated so far have not been fully investigated because of their small amounts isolated from natural sources. To explore new and unique biological functions of natural products, we have synthesized several natural products collectively. In this symposium, collective synthesis of natural products shown below and our efforts to explore their new biological activities will be presented.



tetrodotoxin (TTX)



aplysiatoxin (ATX)



nepetalactol

References:

1. (a) T. Nishikawa, M. Isobe, *Chem. Rec.* **2013**, *13*, 286. (b) Y. Noguchi *et al. Sci. Rep.* **2022**, article No.15087 (d) T. Suzuki *et al*. *Chem. Senses 47*, **2022**, bjac011.
2. K. Hada *et al. J. Org. Chem.*, **2022**, *87*, 15618.
3. R. Uenoyama *et al. Science Advances* **2021**, eabd9135.

Transition Metal Complexes in Chemical Biology

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RIKEN Center for Sustainable Resource Science
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We have been working on the development of transition metal-catalyzed reactions, as well as chemical biology research to elucidate the molecular mechanisms of action of small bioactive molecules. As a research linking transition metal chemistry and chemical biology, we have recently developed several purification techniques for peptides modified with bioactive small molecules based on the formation of transition metal complexes. These techniques facilitate the identification of target proteins/binding sites of bioactive molecules.

We have found conditions under which β-ketoamide-labeled peptides can be selectively enriched by catch and release processes using polymer-supported Pd aqua complex.[1] Covalent binding site of an enzyme inhibitor was successfully determined by using this method.

Furthermore, alkynes are widely used as a primary tag, with fluorophores and biotin introduced later via a copper-mediated click reaction for imaging and target and binding site identification. Two methods for direct enrichment of alkyne-tagged peptides based on the formation of alkyne cobalt complexes[2] and silver acetylide, respectively, were also established.

References:

1. Hayamizu, K.; Koike K.; Dodo, K.; Sodeoka, M. *Chem. Sci.* **2023**, *14*, 8249.
2. Miyazaki, A.; Asanuma, M.; Dodo, K.; Egami, H.; Sodeoka, M. *Chem. Eur. J.* **2014**, *20*, 8116.

BioOrganic Chemistry on Silkworm Diapause and Squid Bioluminescence

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We have been studying on bioorganic chemistry from multidisciplinary strategy through collaboration with biological specialists about the research topics such as bioluminescence, insect diapause, protein phosphatase inhibition, toxic substances, etc. One of the major strategies is chemical synthesis including total synthesis of natural and unnatural products, which are required to perform for solving biological questions. List of our total synthesis is shown in **Figure 1**. The other strategy is ultra-microanalysis usable to figure out samples in pico-/femto-mol level availability. We have spent a lot of time to prepare enough ability by exploring our house-assembled nano-HPLC-MS system. An example is illustrated in **Figure 2**. Our outstanding research environments have also supported us for the structural studies with the dynamic aspects of natural product chemistry along these lines.

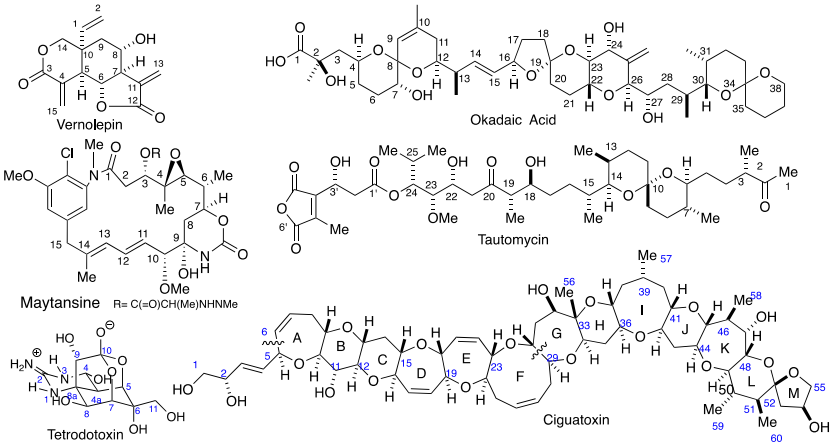


Figure 1. Natural products achieved by total synthesis with highly stereo-controlled manner.

An **Okinawan squid** (TOBI-IKA) *Symplectoteuthis oualaniensis* is well known to emit blue light from its yellow photogenic organ on its mantle. In spite of notorious difficulty of the solvent extraction of the luminous substrate from the organ, we started studying on this bioluminescent system. We finally found that the light emission is due to a non-fluorescent substrate, dehydro-coelenterazine (DCZ) in 1993 through the first isolation of a fluorescent artifact. The related structures of coelenterazine are shown in **Figure 3**.[1] Reconstitution of DCZ was demonstrated with this photoprotein, which we named as *symplectin*. The size is 60 kDa to install the chromophore becoming fluororecent. This finding led us to prove that DCZ is the first example of photoprotein binding the luminous substrate through a covalent chemical bond.[2] The precise cysteine-binding process was suggested from model experiments including an isotope-analog 100%-$^{13}C_{(10)}$-DCZ(OMe) and HMBC method. We further proved the molecular mechanism of *Symplectoteuthis* bioluminescence using *apo-symplectin* and synthetic analogs through various spectroscopic manners including nano-HPLC-ESI-QTOF-MS.[2,3]

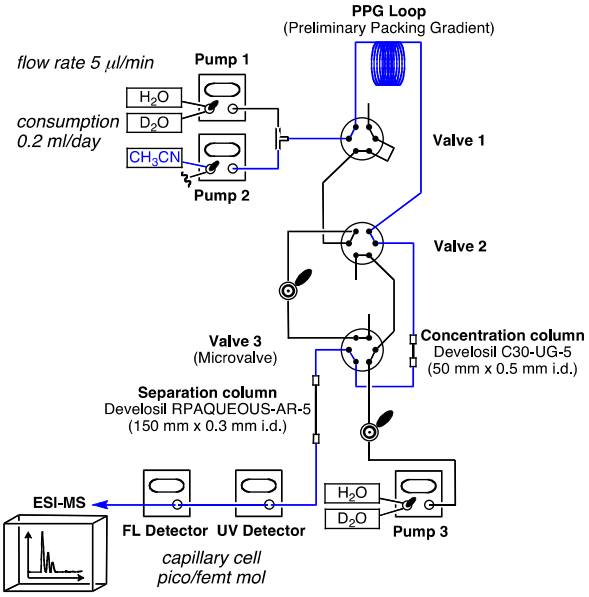


Figure 2. Example of house-assembled flow system equipped with PPG (pre-packed gradient), capillary UV, FL-detectors, into ESI-Q-TOF-MS.

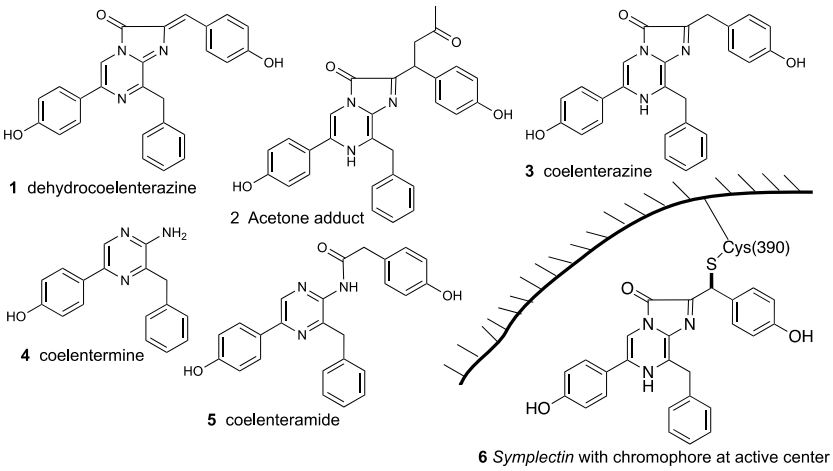


Figure 3. Chromophores related to *Symplectoteuthis* bioluminescence.

Generally *coelenterate* bioluminescence including dihydroimidazopyrazinone heterocycle (H_2-IDPZ, *Cypridina*, *Aequorin*, *Watasenia* etc) was discussed on the involvement of short life-time intermediates as hydroperoxides and dioxetanone until 1995. It was, however, limited to collect direct proof due to the instability. We came across to design a new method as shown in **Figure 4**: (i) synthesis of 4 compounds 100%-enriched-$^{13}C_{(2,\ 3,\ 5,\ 2\text{-}3)}$-$H_2$-IDPZ, (ii) photo-oxygenation at low temperatures (-78 °C) in magic solvents (CF_3CD_2OD-CD_3OD), (iii) measurements of ^{13}C-NMR and FTIR (1867 cm^{-1}). This method allowed us to collect the ^{13}C-data of aminopyrazyl-dioxetanone for the first time. We observed the emission spectra at 400 nm as neutral coelenteramide species from the dioxetanone; similarly at 470 nm as anionic amide from the peroxide as expected. It should also be noted that the luminescence from the 2-hydroperoxide in acidic media was observed only at 400 nm even strongly at lower temperature at -50 °C.[4] This is simply because that general chemiluminescence is observable only in alkaline (or neutral) media for the first oxidation in dipolar-aprotic solvents.

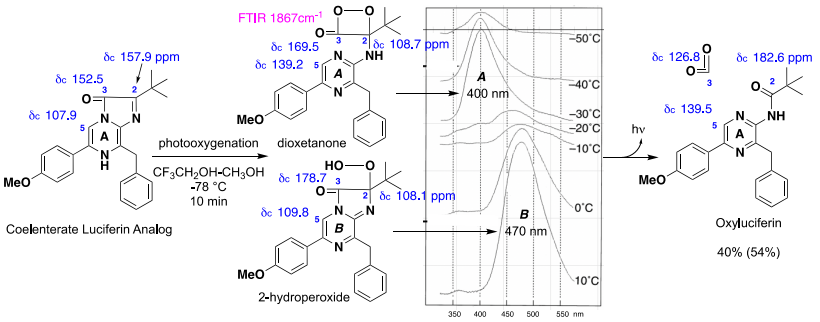


Figure 4. Photo-oxygenative preparation of dihydroimidazopyrazinone analogs containing 100% ^{13}C's in magic solvents at low temperatures, and ^{13}CNMR data of the short life-time dioxetanon and 2-peroxide. The luminescence spectra show the presence of 2 short lifetime intermediates.

Back to *symplectin* photoprotein, we elucidated its 501 amino acid sequence through nano-LC/MS*n* of the enzyme Lys-C hydrolysates (34 peptides) as well as cDNA dictation (from C-terminal). Furthermore, we observed a glyco-chain at 174-Asn (NSS), but no sugar at 436-Asn (NYT), 11 Cys (6 of them S-S), and 4 modified amino acids as shown in **Figure 5**.[5] The active site of *symplectin* was identified to be Cys390 by detecting the chromo-peptide CGLK (L26, m/z 843.55 before luminescence and m/z 831.53 after lumi.) using *aposymplectin* and a mono-fluorinated DCZ analog. Further studies using 2,4-diF-DCZ and other synthetic analogs allowed us to study the stereochemical process (using LC-CD) as well as the storage sites. Although the chromophore DCZ and luminescence product (aminopyrazine) have no stereogenic carbon, the intermediates should include 2 adjacent stereogenic carbons to play significant roles for the light emitting process. We call this type of stereochemical situation as *Dynamic Chirality* (**Figure 6**).[6] Design and new synthetic methods of the various DCZ analogs suggested assignment of the stereochemical process in *Symplectoteuthis* bioluminescence.[6,7] The difluorinated regioisomers (2,4-diF and 2,6-diF) are estimated to be different topological situation, which leads to largely different regio-isomers as *syn/anti* in the cysteine binding process. Balance of the kinetics of each step in **Figure 6** makes the 2,6-diF analog into intramolecular oxidation of the sulfur atom to give the sulfoxide as fatal damaging at the active site Cys390 of this protein. The selective luminescence

activity of these 2 isomers should be due to the *conformational constrain* in one of the substrates.

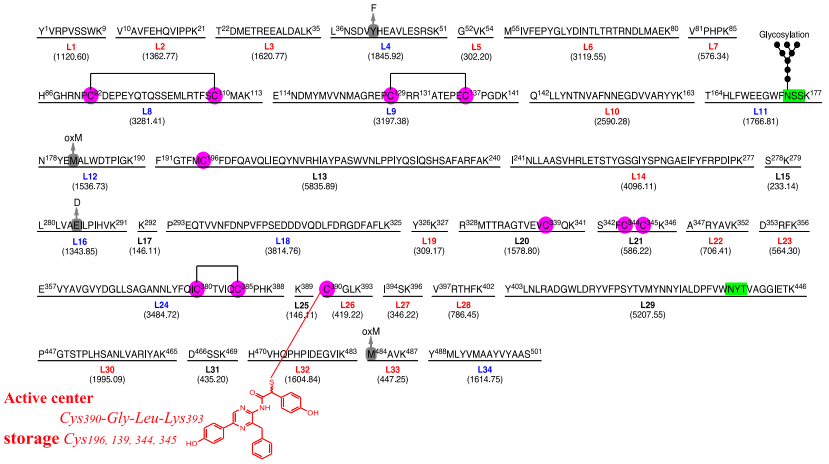


Figure 5. Amino acid sequence of *Symplectin*, the TOBI-IKA squid-photoprotein, showing Cys(390) as the active site and 4 free Cys's as storage sites.

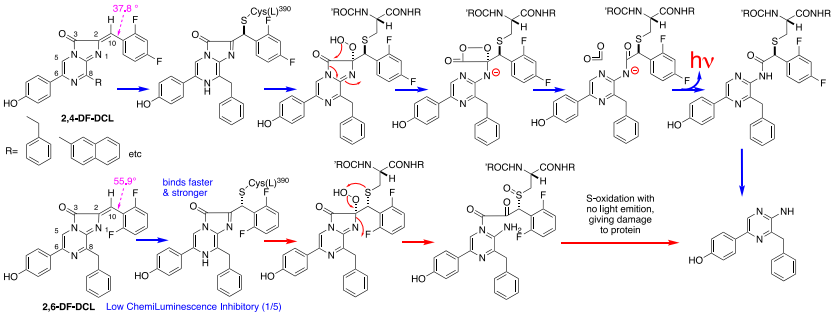
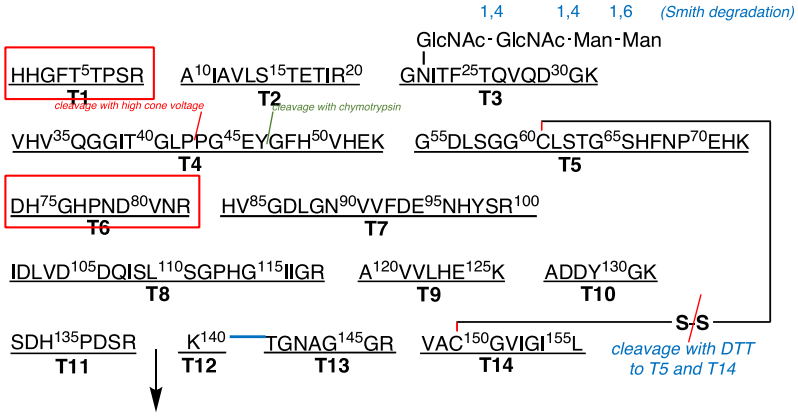


Figure 6. *Dynamic Chirality**: Two pathways explain the reasons why apo-symplectin and the 2 regio-isomeric di-F-dehydrocoelenterazine analogs behave differently (more luminescence or less light by damaging to active center Cys390. (*Stereogenic carbon is not included either in the starting material nor final product, but the stereochemistry exists in the intermediates only on the protein surface.)

Diapause (arrested embryonic development) in the silkworm, *Bombyx mori,* is a result of genetic adaptation to overwinter in the

stage of egg. Diapause is induced by diapause hormone (DH), which was found by Hasegawa in 1951.[8] In 1991, Imai et al reported the structure of DH to be a peptide of 24 amino acids having amide C-terminal.[9] Further gene-level studies were performed by Yamashita et al.[10] After terminating the diapause period, thousands of the eggs hatch within a few expected days as a result of overwintering (or kept at low temperatures). This mechanism is due to a program-conducted by the timer protein (TIME-EA4) and regulating peptide (PIN) to end up with the birth of the first instars. On the basis of such biological studies by Kai, we have collaborated from chemistry point of views. We first elucidated the amino acid sequences of TIME-EA4 and PIN, and estimated the (computer generated) 3D-structure of this protein as shown in **Figures 7a** and **7**.[11] We designed various experimental methodologies to tackle with the molecular mechanisms in dynamic aspects, and chemically concluded that the time measurement is due to the conformational change of TIME-EA4 molecule.

Fig. 7a Amino Acid Sequence of **TIME-EA4** by means of tryptic peptides on nano-LC-ESI-QTOF-MS/MS



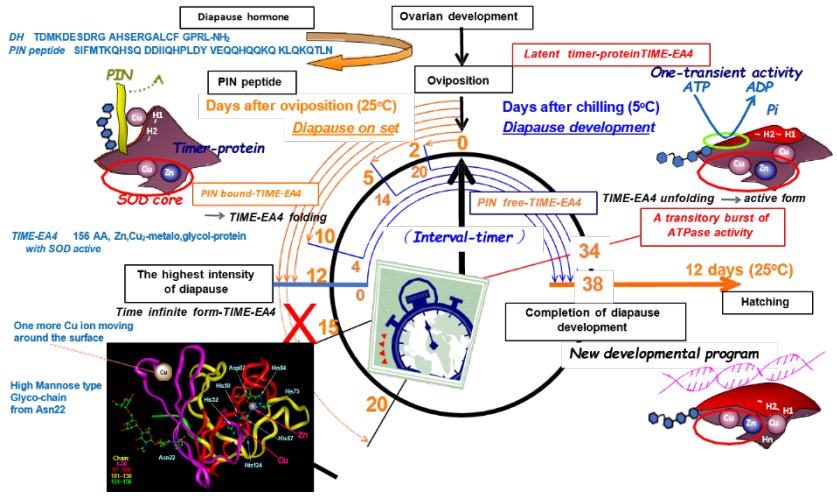


Figure 7. TIME-EA4 protein and PIN peptide regulate 'diapause termination' in the silkworm eggs. Conformational change of this metallo$_3$-glyco$_4$-protein was monitored through pin-point oxidation of moving His-ligands of copper ions by OH radical at different timings.

TIME-EA4, in fact, measures the termination of diapause duration on *Bombyx* diapause eggs. We have determined, in details, the amino acid sequence of TIME-EA4 protein as well as PIN-peptide (28~38 amino acids, obtained from C108 silkworm strain) by means of our nano-LC-ESI-QTOF-MS/MS method. TIME-EA4 comprises from 156 amino acids (apo-type m/z 17337.24)(under neutral ESI for metals: m/z 17461.70-CuZn, 17523.22-Cu_2Zn) both containing sugar-chain of a high-mannose type 4 sugars connected at Asn22.[11] The different structures of sugar linkage types were established in detail using various diapause strains of Thailand silkworm under ultra-micro scale analysis and nano-LC-MS (including Smith degradation, **Figure 7a**). We found varieties of 4 and 5 sugars with straight and branched structures extending from Asn(22).[12] Binding assay method, however, did not always match the results of our method using chemical modification and nano-LC-MS. Our recombinant TIME-EA4 (m/z 16607.20) prepared from a gene transplanted *E. coli* without the sugar chain allowed us to find additional metal (Cu^{++}) also from the neutral

ESI-MS (m/z 16732.00-CuZn, 16795.30-Cu_2Zn). This protein, however, does not exhibit any timer function such as transitory ATPase activity, which is usually observable in the native TIME-EA4. This is due to the fact that the regulation of TIME-EA4 timer function is given rise to form PIN & TIME-EA4 complex, and that its carbohydrate moiety is indispensable for the time measurement function. These results suggests that the sugar chain contributes some specific folding structure of this protein, and the conformational change might be related to the time measurement mechanism.[13] To prove such hypothesis through the chemical experiments, we implemented our 'site-specific *pin-point oxidation* method' to obtain the structural features using such a dynamic protein modification established in 2001.[14] This method includes changing His to OxoHis, so that the molecular weight being increased in 16 Da. The OxoHis residues are detected through MS/MS fragmentation of the tryptic peptides. As expected, the Zn,Cu-SOD core structure in TIME-EA4 kept still, which was used as the standard values. On the other hand, the ligand His-residues of the second Cu were found to change in accordance with the different timing of diapause development. The pin-point oxidation method of TIME-EA4 in the presence of PIN concluded that the ligand His(5) of PIN peptide as well as His(1,2) of TIME-EA4 protein were modified. These site-specific protein modification data increasing 16 Da were monitored at different timing during diapause development to show different degrees of His-oxidation at different locations. These data suggested the conformational change of this protein during the diapause development. The travelling Cu ion on the TIME-EA4 protein surface finally arrived at His(77). These results must link to the proof of the conformational change of TIME-EA4. Namely the timer function is derived from such a conformational change of TIME-EA4 protein, including transitory ATPase activity.[15] The final conformation at the completion of diapause development exposes different surface, from which we have to find the important signal for starting the protein synthesis for embryonic development. Search for the signal is in progress with computational manner by collaboration with Supa.

Protein phosphatase inhibition has generally been understood as important action to regulate the protein functions, some of which are

once activated via phosphorylation by signal transduction. After our accomplishment of the total synthesis of okadaic acid, OKA in 1986, we became interested in tautomycin, TTM due to the fact that both of these natural products are assigned to be the non-protein-inhibitors selecting type 1 and 2, respectively.[16] After contribution for the structure elucidation of TTM through its synthetic partial proof,[17] we accomplished the total synthesis in 1995.[18] We collaborated with a biologist Takai for the bioorganic studies on searching the type-determining factor. We have developed a highly sensitive (femto-mol level) fast bioassay method using firefly luciferin phosphate as the substrate protein phosphatase-inhibition. This method detects the luminescent light with single photon counter as highly sensitive manner (**Figure 8**). It also led us to find that natural TTM anhydride is not active form, but TTM-diacid is the really active form as the inhibitor.[19]

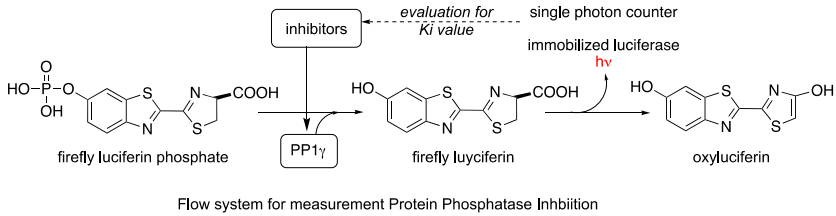
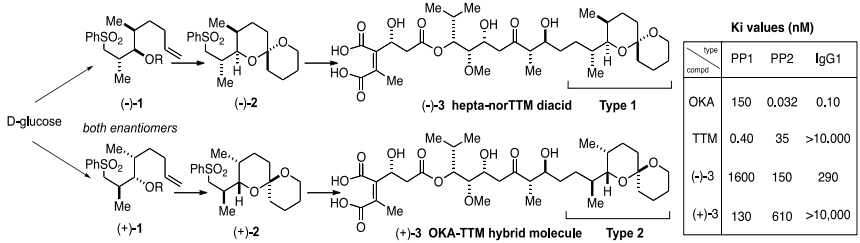


Figure 8. Fast Protein Phosphatase Inhibition measurement system using synthetic firefly luciferin phosphate as the substrate in ultra-micro scale (<femto mol).

During the course of our protein phosphatase inhibition studies, we have developed a new synthetic method to prepare both enantiomeric segments starting from D-glucose as the starting material. This method includes α-selective C-glycosylation with silyl acetylene and its epimerization to β-isomer via cobalt chemistry. We have designed and prepared 2 unnatural inhibitors on the basis of TTM/OKA, which led us to conclude that the chirality of the 6/6-spio moiety determined the type 1 and 2, respectively (**Figure 9**). The U-shape conformation of TTM was also chemically proven through fluorescence quenching effect between the two chromophores attached at the both ends of TTM. We found this result ahead of the X-ray crystallographic analysis.[19] We synthesized a TTM-diacid 100%-enriched

$^{13}C_4$($_{18,20,22,24}$)(see Figure 1 for numbering), which was subjected to the binding experiments in NMR tubing. It led us, however, only limited results due to strong binding as Ki value is ca. 4 *nM* level.[20] Various synthetic TTM analogs having the aliphatic terminal methyl-ketone moiety as oxime afforded different inhibitory activities.[21] Some of these inhibitor-phosphatase complexes were monitored by flow system using firefly phosphate as the substrate (**Figure 8**). One of them showed a stronger activity than the natural TTM-diacid. These TTM analogs would provide further experimental information of the binding mode through the protein modification followed by detecting the modified amino acids as we have demonstrated as nano-LC-MS.



Ki values (nM)

type / compd	PP1	PP2	IgG1
OKA	150	0.032	0.10
TTM	0.40	35	>10.000
(-)-3	1600	150	290
(+)-3	130	610	>10,000

Figure 9. Unnatural two protein phosphatase inhibitors (TTM-diacid analogs having partial enantiomeric moieties) were chemically synthesized from D-glucose, and the activity concluded (-)-**3** being Type 1 and (+)-**3** being Type 2, respectively.

Peptides, depsipeptides and peptaibols are quite popular natural products having unique biological activity. Some of them have been know extremely difficult to perform chemical and structural studies due to trace amount or unusual nature from ordinal peptides. We have collaborated with various biology groups to contribute for elucidating the chemical structures. ***GSS*** (gonado stimulating substance) of starfish was an insulin-like peptide[22] after decades of collaboration.[23] *Cereus toxin* has been known as a cause of food born illness to exhibit emetic toxicity. We elucidated the toxin's structure as a 36 membered cyclic depsipeptide centered by potassium ion, and named it as **cereulide**.[24] This is a K^+-selective ionophore and is comprised of alternative D- and L-aminoacid and oxyacid.[25] Cereulide has very similar structure as valinomycin, which is known as an antibiotic.

These 2 compounds have, however no cross biological activity at all.[26] We wondered the reason why such a toxin and a drug can be so similar structures. Finally, we concluded that the reason is from their 3D structures; namely, cereulide and valinomycin are mirror image with its frame as shown in **Figure 10**.

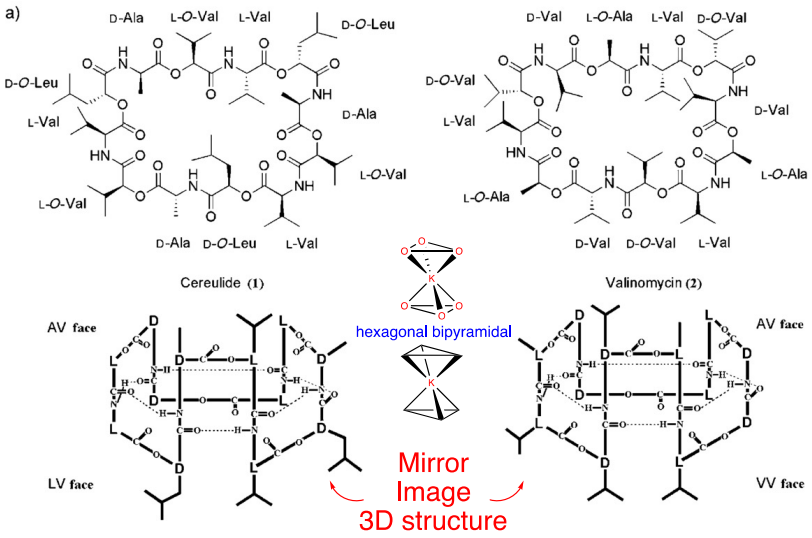


Figure 10. Emetic toxin *cereulide* was isolated from *B. cereus* and elucidated as cyclic depsipeptide with alternative D/L stereochemistry, very similar to valinomycin antibiotic. Both of these 36-membered compounds are K-selective ionophore having hexagonal bipyramidal structures. Why one is toxin and the other is drug? It is because these two compounds are pseudo-mirror image with 3D structures.

Acknowledgements:

We spent the great time for studying chemistry on natural products through heavy collaboration in the bioorganic area with people inside and outside of our Laboratory of Organic Chemistry, School of Bio-agricultural Sciences, Nagoya University and National Tsing Hua University. To perform our bioorganic studies mentioned

as above, we sometimes needed to develop necessary analytical instruments by our hands even we have been surrounded by outstanding scientific instruments. Organic synthesis brought us great supports by supplying necessary substances for the bioorganic studies. We are also thankful to the financial supports from funding agents. Finally, we are delighted to share with the collaborators for receiving such a high evaluation as Nakanishi Prize.

Natural Products be forever!

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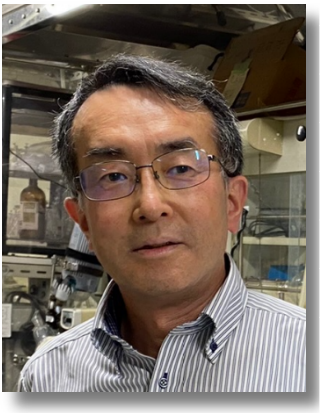

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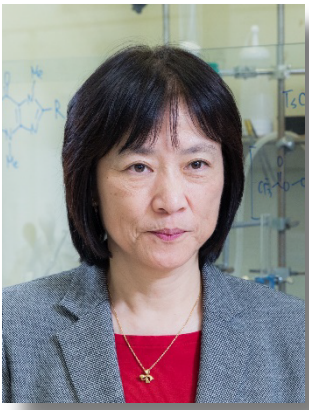

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