Professor Keiichiro Fukumoto

A Tribute

This Special Issue of Arkivoc is to celebrate the 70th anniversary of Professor Keiichiro Fukumoto's birth

Professor Keiichiro Fukumoto was born in Shodo Island, Kagawa prefecture, on February 10, 1934. He graduated from the Pharmaceutical Institute, Osaka University in 1956 and obtained his Ph.D. degree from Osaka University in 1964, studying the synthesis of isoquinoline alkaloids, cularine, and related ones, under the guidance of the late Professor Tetsuji Kametani. He was appointed Assistant Professor of the Pharmaceutical Institute, Tohoku University, in 1959, and promoted to Associate Professor in 1972 and Full Professor in 1981. In 1997 he retired from Tohoku University and became Emeritus Professor. From 1964, he spent one year at the University of Alberta with Professor S. Masamune and one year at the University of Sussex, with Professor A. I. Scott, as a postdoctoral fellow.

Professor Fukumoto has won a number of awards such as The Pharmaceutical Society of Japan (The PSJ) Award for Young Scientists in 1976, The PSJ Award in 1997, the Academic Award of The Society of Synthetic Organic Chemistry, Japan, in 1993, and Medal of Honor with Purple Ribbon in 2000. He has served the chemical community in many ways: he has acted for a long period as the Editor of *Heterocycles*, after Professor Kametani passed away in 1988.

Professor Fukumoto's research interests have ranged widely over synthetic chemistry; in developments of novel synthetic methodologies and syntheses of biologically active compounds. He has synthesized over 200 natural products and published 633 scientific papers. Selected papers are listed according to categories at the end of this Tribute. I give here a brief description of his selected research activities. His research career as an organic chemist started in 1955, and his first project was the synthesis of isoquinoline- and indole alkaloids. He obtained his Ph.D. with the accomplishment of the total synthesis of cularine, as mentioned above. Until the early 1970s, his main interest was the synthesis of isoquinoline alkaloids by biomimetic approaches utilizing phenol oxidation, the modified Pschorr reaction, and so on. A number of isoquinoline

alkaloids such as the morphine-, aporphine-, proaporphine-, protoberberine-, hasbanan-, benzophenanthridine-, and sendaverine types, the phenethylisoquinoline type, *Erythrina*-, *Amaryllidaceae*- and *Ipecac*- alkaloids, were totally synthesized. His books, "The Chemistry of the Isoquinoline Alkaloids, vols. 1 and 2", published along with the late Professor Kametani in 1968 and 1974, respectively, contributed tremendously to this field.

The principle of 'Retro Mass Spectral Synthesis' that he proposed together with the late Professor Kametani in 1974 was especially brilliant and fruitful. Various biologically active natural products such as steroids, diterpenes, triterpenes, protoberberine-, phthalideisoquinoline-, quinazolinocarboline-, spiro-benzylisoquinoline- alkaloids, *Ipecac* alkaloids, and indole-, and diterpene alkaloids, were elegantly synthesized. In particular, the syntheses of estrone, (+)-estradiol, alnusenone and friedelin using the intramolecular Diels–Alder reaction of benzocyclobutene, based on the principle, are outstanding. Applications utilizing pericyclic reactions of *o*-quinodimethane developed by his group are regarded as leading research in synthetic chemistry.

As an extension of pericyclic reactions, he and his associates studied the development of new cascade reactions, forming plural bonds in a stereo- and regioselective manner in one procedure. The intramolecular double-Michael reaction and the intramolecular Michael–aldol reactions, elaborated by them, are useful tools for the synthesis of polycyclic natural products. It was established that both cascade reactions could be performed by treatment with lithium amides or treatment with various combinations of Lewis acids and amines. They showed many advantages, owing to the characteristic features of the intramolecular reaction and cascade reaction. The intramolecular double-Michael reaction is applicable not only to carbocyclic compounds but also to heterocyclic compounds. The alkaloids epilupinine and tylophorine, were effectively synthesized by the intramolecular aza- double- Michael reaction. Syntheses of terpenoids, pentalenene, pentalenic acid, 8,14-cedranediol and atisirene, were carried out in highly stereoselective manners by employing the intramolecular double-Michael reaction. The asymmetric synthesis of the *Aconitium* alkaloid atisine, accomplished by this methodology, is a beautiful example. Unique polycyclic ring systems fused to cyclobutane were constructed efficiently by the intramolecular Michael–aldol reaction. The method has recently been further extended to other new types of cascade reactions by his associates.

In every respect, Professor Fukumoto has been a brilliant and productive chemist. Furthermore, he is an outstanding human being and an excellent educator. We have always been stimulated to do our best for research by his encouragement. He was a good baseball player when he was a high- school student. With an attitude similar to sports, he has been at the forefront of research in new areas and has tackled the most difficult problems with the deepest insight. We all wish Professor Fukumoto a healthy and happy life with Mrs Fukumoto.

Masataka Ihara
Sendai
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List of Selected Publications

Isoquinoline Alkaloids

1. A Total Synthesis of (±)-Cularine, Kametani, T.; Fukumoto, K. *J. Chem. Soc. (C)* **1963**, 4289.
2. Synthesis of Morphinandienone Alkaloids by Phenol Oxidation and the Pschorr Reaction, Kametani, T.; Fukumoto, K. *J. Heterocyclic Chem*. **1971**, *8,* 341.
3. Photochemical Synthesis of Isoquinoline Alkaloids, Kametani, T.; Fukumoto, K. *Acc. Chem. Res*. **1972**, *5*, 212.
4. Application of Phenolic Oxidation to the Total Syntheses of the Isoquinoline and Related Alkaloids; Biogenetic Type Syntheses, Kametani, T; Fukumoto, K. *Synthesis* **1972**, 657.

Indole Alkaloids

1. Asymmetric Total Synthesis of Tacamonine (Pseudovincamone I) via Radical Cyclization, Ihara, M.; Setsu, F.; Shohda, M. (nee Hosoda); Taniguchi, N; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem*. **1994**, *59,* 5317.
2. Stereoselective Construction of the Diterpene Part of Indole Alkaloids, Radarins, by Way of Intramolecular Diels–Alder Reaction, Ihara, M.; Katsumata, A.; Egashira, M.; Suzuki, S.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1995**, *60*, 5560.

Quinoline Alkaloids

1. Double Enamine Annelation of 3,4-Dihydro-1-methyl-β-carboline and Isoquinoline Derivatives with 6-Methyl-2-pyrone-3,5-dicarboxylates and its Application for the Synthesis of (±)-Camptothecin, Ihara, M.; Noguchi, K., Ohsawa, T.; Fukumoto, K.; Kametani T. *J. Org. Chem.* **1983**, *48*, 3150.
2. Total Synthesis of Hydrocinchonidine and Hydrocinchonine from an Indole Derivative via Oxidation with Singlet Oxygen, Ihara, M.; Taniguchi, N.; Noguchi, K.; Fukumoto, K.; Kametani, T. *J. Chem. Soc. Chem. Commun.* **1986**, 573.

Aconitium Alkaloids

1. A Facile Regiospecific and Stereocontrolled Synthesis of a Diterpene Alkaloid Intermediate from Benzocyclobutene, Kametani, T.; Kato, Y.; Honda, T.; Fukumoto, K. *J. Am. Chem. Soc.* **1976**, *98*, 8185.
2. Stereoselective Total Synthesis of (±)-Atisine via Intramolecular Double Michael Reaction, Ihara, M.; Suzuki, M.; Fukumoto, K.; Kametani, T. *J. Am. Chem. Soc.* **1988**, *110*, 1963.
3. Asymmetric Total Synthesis of Atisine via Intramolecular Double Michael Reaction, Ihara, M. ; Suzuki, M.; Fukumoto, K.; Kabuto, C. *J. Am. Chem. Soc.* **1990**, *112*, 1164.

Terpenes

1. Convenient and Stereoselective Route to Basic Frameworks for Synthesis of Unsymmetrical Pentacyclic Triterpenes Kametani, T.; Hirai, Y.; Shiratori, Y.; Fukumoto, K.; Satoh, F. *J. Am. Chem. Soc.* **1978**, *100*, 554.
2. A Stereoselective Total Synthesis of (±)-$\Delta^{9(12)}$Capnellene via the Intramolecular Diels–Alder Approach, Ihara, M.; Suzuki, T.; Katogi, M.; Taniguchi, N.; Fukumoto K. *J. Chem. Soc., Chem. Commun*. **1991**, 646.
3. The First Enantioselective Total Synthesis of (+)-Laurene, H. Nemoto, Nagamochi, M.; Fukumoto, K. *J. Chem. Soc., Chem. Commun.* **1992**, 1695.
4. Pd^{2+}-Promoted Cyclization in Linear Triquinane Synthesis. Total Synthesis of (±)-Hirsutene, Toyota, M.; Nishikawa, Y.; Motoki, K.; Yoshida, N.; Fukumoto, K. *Tetrahedron Lett.* **1993**, *34*, 6099.
5. Intramolecular Michael Reaction Using Trialkylsilyl Trifluoromethanesulfonates and Tertiary Amine Systems: Total Synthesis of (±)-Ricciocarpin A, Ihara, M.; Suzuki, S.; Taniguchi, N.; Fukumoto, K. *J. Chem. Soc., Chem. Commun.* **1993**, 755.
6. A Remarkable Substituent Effect on the Enantioselectivity of Tandem Asymmetric Epoxidation and Enantiospecific Ring Expansion of Cyclopropylidene Alcohols: A New Enantiocontrolled Synthesis of (-)-Debromoaplysin and (-)-Aplysin, Nemoto, H; Nagamochi, M.; Ishibashi, H.; Fukumoto, K. *J. Org. Chem*. **1994**, *59*, 74.
7. A Simple Total Synthesis of (±)-Spirojatamol and (±)-Erythrodiene via Intramolecular 1,3-Dipolar Cycloaddition, Tokunaga, Y.; Yagihashi, M.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Chem. Commun*. **1995**, 955.
8. Stereoselective Construction of Copaborneol and Longiborneol Frameworks by Intramolecular Double Michael Reaction, Ihara, M.; Makita, K.; Fujiwara, Y.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem*. **1996**, *61*, 6416.
9. Total Synthesis of (±)-Methyl Atis-16-en-19-oate via Homoallyl–Homoallyl Radical Rearrangement, Toyota, M.; Wada, T.; Fukumoto, K.; Ihara, M. *J. Am. Chem. Soc*. **1998**, *120*, 4961.

Steroids

1. A Formal Regio- and Stereoselective Total Synthesis of Estrone. A Convenient Synthesis of *D*-Homoestrone, Kametani, T.; Nemoto, H.; Ichikawa, H.; Shiroyama, K.; Fukumoto, K. *J. Am. Chem. Soc*. **1976**, *98*, 3378.
2. Asymmetric Total Synthesis of Estradiol by an Intramolecular Cycloaddition of Benzocyclobutene Derivative, Kametani, T.; Matsumoto, H.; Nemoto, H.; Fukumoto, K. *J. Am. Chem. Soc.* **1978**, *100*, 6218.
3. Chiral Synthesis of Androsterone through Intramolecular Diels–Alder Reaction, Ihara, M.; Sudow, I.; Fukumoto, K.; Kametani, T. *J. Org. Chem*. **1985**, *50*, 144.

4. A Novel Strategy for the Stereoselective Total Synthesis of C-17 Spiro Steroids. Total Synthesis of 19-Norcanrenone, a Formal Total Synthesis of 19-Norspironolactone, Nemoto, H.; Fujita, S.; Nagai, M.; Fukumoto, K.; Kametani, T. *J. Am. Chem. Soc.* **1988**, *110*, 2931.
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6. First Enantioselective Total Synthesis of (+)-Cortisone, Nemoto, H.; Matsuhashi, N.; Imaizumi, M.; Nagai, M.; Fukumoto, K. *J. Org. Chem.* **1990**, *55*, 5625.
7. A Novel Strategy for the Enantioselective Synthesis of the Steroidal Framework Using Cascade Ring Expansion Reactions of Small Ring System; Asymmetric Total Synthesis of (+)-Equilenin, Nemoto, H.; Yoshida, M.; Fukumoto, K.; Ihara, M. *Tetrahedron Lett*. **1999**, *40*, 907.

Synthetic Methodologies

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2. Total Synthesis of Natural Products by Retro Mass Spectral Synthesis, Kametani, T.; Fukumoto, K. *Acc. Chem. Res.* **1976**, *9*, 319.
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4. Synthesis of β-Lactam Antibiotics by the Sulfeno–Cycloamination, Ihara, M.; Haga, Y.; Yonekura, M.; Ohsawa, T.; Fukumoto, K.; Kametani, T. *J. Am. Chem. Soc.* **1983**, *105*, 7345.
5. Tandem Electrocyclic-Sigmatropic Reaction of Benzocyclobutenes. An Expedient Route to 4,4-Disubstituted Isochromanones, Shishido, K.; Shitara, E.; Fukumoto, K.; Kametani, T. *J. Am. Chem. Soc.* **1985**, *107*, 5810.
6. Enantioselective Construction of a Quaternary Asymmetric Carbon Center: A Versatile Synthesis of α-Alkyl α-Amino Acids, Ihara, M.; Takahashi, M.; Niitsuma, N.; Taniguchi, N.; Yasui, K.; Fukumoto, K. *J. Org. Chem.* **1989**, *54*, 5413.
7. Novel Construction of Polycyclic Systems Fused to Cyclobutane by Tandem Intramolecular Michael–Aldol Reaction, Ihara, M.; Ohnishi, M.; Takano, M.; Makita, K.; Taniguchi, N.; Fukumoto, K. *J. Am. Chem. Soc*. **1992**, *114*, 4408.
8. Synthesis of Polycyclic Cyclobutane Derivatives by Tandem Intramolecular Michael–Aldol Reaction under Two Complementary Conditions, TBDMSOTf–Et_3N and TMSI–$(TMS)_2NH$, Ihara, M.; Taniguchi, T.; Makita, K.; Takano, M.; Ohnishi, M.; Taniguchi, N.; Fukumoto, K.; Kabuto, C. *J. Am. Chem. Soc.* **1993**, *115*, 8107.
9. Syntheses of Polycyclic Natural Products Employing the Intramolecular Double Michael Reaction, Ihara, M.; Fukumoto, K. *Angew. Chem. Int. Ed. Engl*. **1993**, *32*, 1010.

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13. Stereocontrolled Synthesis of Indolo[2,3-*a*]quinolizines by Intramolecular Double Michael Reaction: Proof for Stepwise Mechanism, Ihara, M.; Ishida, Y.; Tokunaga, Y.; Kabuto, C.; Fukumoto, K. *J. Chem. Soc., Chem. Commun.* **1995**, 2085.
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15. Facile Construction of Bicyclo[6.4.0]dodecane System by Intramolecular Michael Addition of Sulfonyl Carbanion, Ihara, M.; Suzuki, S.; Tokunaga, Y.; Takeshita, H.; Fukumoto, K. *Chem. Commun*. **1996**, 1801.
16. 1,3-Dipolar Cycloaddition of 1-Carboxynitrone: Different Stereoselectivity Caused by Salt Effect, Tokunaga, Y.; Ihara, M.; Fukumoto, K. *Tetrahedron Lett*. **1996**, *37*, 6157.
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18. A Novel Palladium-Mediated Cascade Reaction Triggered by Strain Release of the Cyclobutane System. A New General Route to Benzo- and Naphthohydrindans, Nemoto, H.; Miyata, J.; Yoshida, M. ; Raku, N.; Fukumoto, K. *J. Org. Chem.* **1997**, *62*, 7850.

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2. An Efficient Synthesis of the Naphthalene Moiety of Neocarzinostatin Chromophore, Shishido, K.; Yamashita, A.; Hiroya, K.; Fukumoto, K. *Tetrahedron Lett*. **1989**, *30*, 111.
3. A Novel *o*-Quinodimethane Strategy for an Active Metabolite of Vitamin D_3. A Total Synthesis of 25-Hydroxy Windaus–Grundmann Ketone, Nemoto, H.; Ando, M.; Fukumoto, K. *Tetrahedron Lett*. **1990**, *31*, 6205.
4. Palladium-Catalyzed Intramolecular Allylic Alkylation Reaction in Marine Natural Product Synthesis: Enantioselective Synthesis of (+)-Methyl Pederate, a Key Intermediate in

Syntheses of Mycalamides, Toyota, M.; Hirota, M.; Nishikawa, Y.; Fukumoto, K.; Ihara, M. *J. Org. Chem*. **1998**, *63*, 5895.