J. Pestic. Sci. **45**(3), 177–183 (2020)
DOI: 10.1584/jpestics.J20-03

Society Awards 2020
(on prominent achievement)

Synthetic studies of biologically active natural products contributing to pesticide development

Hiromasa KIYOTA*

Grad. Sch. Environmental & Life Science, Okayama University,
1–1–1 Tsushima-Naka, Kita, Okayama 700–8530, Japan

(Accepted July 1, 2020)

Natural product research, including total synthesis, is becoming increasingly important for the discovery of pesticide seeds and leads. Synthetic studies of biologically active compounds such as antibiotics (enacyloxins, polynactin, pamamycins, spirofungin A and B, glutarimides and antimycins), phytopathogenic toxins (pyricuol, pyriculariol, tabtoxinine-β-lactam, gigantenone, phomenone and phaseolinone), marine derived products (pteroenone, β-D-Asp-Gly, didemniselinolipid B, cortistatin A, sanctolide A and gizzerosine), POPs (dieldrin, endosulfan, HCB), plant hormones (abscisic acid and jasmonic acid), insect pheromones (*endo*-brevicomin *etc.*), especially using a variety of biotransformation are described.

Keywords: total synthesis, antibiotics, marine natural products, phytotoxins, plant hormones, pheromones, biotransformation.

Introduction

Since it was found that natural products (generally, low molecular weight organic compounds and secondary metabolites that exist in nature) govern the growth of living organisms and communication between individuals, humans have used natural products or compounds that mimic natural products as pesticides. Utilization of pesticides has further developed through diversification and increased production of crops. While "planar drugs" centering on heterocyclic aromatic compounds are dominant, drug design based on *in silico* analysis of target receptors is also in progress. While various heterocycles have been tried as effective central structures and structural modifications have been made to respond to the development of resistance, "natural products" that possess a steric skeleton have returned as prime targets. Novel scaffold compounds potentially possess many biological activities (including known and unknown mechanisms) and achievement of total synthesis in itself contributes to the birth of new drug leads and the development of new synthetic methods. Therefore, we have determined the structures of various bioactive natural products (antibiotics, phytopathogenic toxins, marine natural products, plant components, insect pheromones *etc.*), elucidated their biosynthetic pathways and structure–activity relationships, and developed synthetic pathways for their production.

1. Organic Compounds Derived from Microorganisms

1.1. Antibiotics

Enacyloxins (ENXs) produced by acetobacter *Frateuria* sp. W-315 are expected to be next-generation drug leads because of their characteristic structure and selective antibacterial activity based on inhibition of protein elongation factor EF-Tu.[1,2] The complete structure of enacyloxin IVa was solved from partial synthesis of natural enacyloxin degradation products and spectroscopic analyses including NMR with *J*-resolved HMBC (Fig. 1).[3–6] A new organocopper mediated coupling reaction with acid chloride was found during the synthetic studies.[7–9] Polynactin produced by *Streptomyces actinomycetes* comprises a series of unique tetrameric macrolides in which monomeric enantiomers are alternately ester-bonded.[10] *Streptomyces* polynactin was once used as an acaricide, but later it has been commonly applied as a immunosuppressant and an antibiotic for multidrug resistant bacteria.[11,12] From the result of structure–activity relationship studies, analogs having bulky *i*-Pr group (macrotetrolide α) and CF_3 group (macrotetrolide β) in the side chain were designed and synthesized (Fig. 1).[13–15] The key reactions were a selective iodoetherification to form the *cis*-tetrahydrofuran ring and a Mukaiyama–Corey–Gehlach macrolactonization. A de-

* To whom correspondence should be addressed.
E-mail: kiyota@okayama-u.ac.jp
Published online July 22, 2020

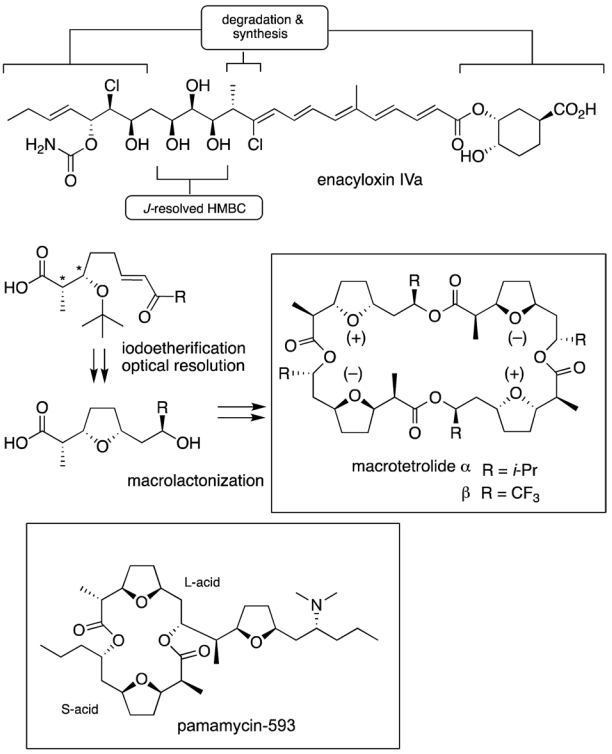

Fig. 1. Antibiotics: enacyloxins, polynactin, and pamamycins.

signed isopropyl-type biosynthetic mimic of nonactin was transformed to macrotetrolide *α* by polynactin producing *Streptomyces griseus*.[16]

In a similar manner, the L-acid and S-acid fragments of pamamycin congeners, aerial hyphal differentiation inducers of *Streptomyces alboniger*, were synthesized.[17–20]

The proposed structures of spirofungin A and B produced by *Streptomyces* spp., were revised after synthesis of spiroacetal core fragments as C-15 epimers,[21,22] and the formal total synthesis was also achieved (Fig. 2).[23] A series of related glutarimide antibiotics including actiketal,[24,25] streptimidone,[26] and antimycins[27] were also synthesized. 9-Methylstreptimidone was later found to induce selective apoptosis in adult T-cell leukemia cells.[28]

1.2. Phytotoxins

Pyricularia oryzae, a persistent phytopathogen of rice, produces salicylaldehyde-type toxins that induce brown lesions on rice leaves.[29] Several derivatives including plausible biosynthetic intermediates were synthesized in either racemic and/or optically active forms *via* coupling reactions (Fig. 3).[30–35] Through synthetic studies, it was clarified that the blast fungus produces optically active toxins such as pyriculol and pyricuol under shaking culture conditions, while pyriculariol and dihydropyriculariol resulting from aeration and agitation culture are racemic.[36]

Pseudomonas syringae pv. *tabaci*, the causative fungus of tobacco wildfire disease, produces tabtoxin which is converted into tabtoxinine-*β*-lactam by a plant peptidase, leading to inhibition of glutamine synthetase and the non-selective death of

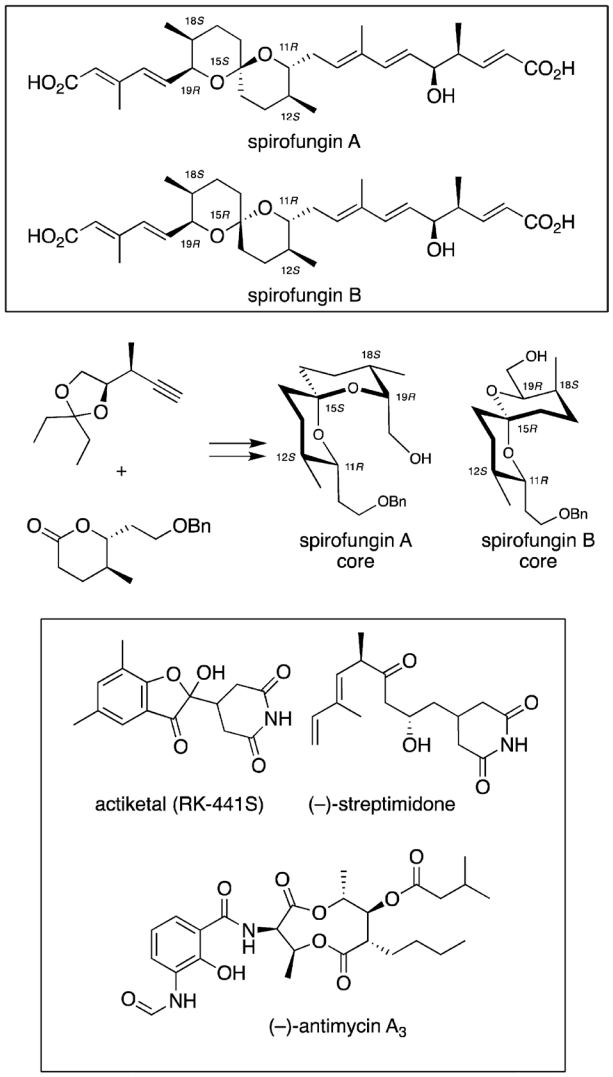

Fig. 2. Antibiotics: spirofungin, glutarimides, and antimycin.

plants (Fig. 4).[37] Tabtoxin derivatives are expected to be effective herbicides for crops which contain a resistance-conferring transgene, and total synthesis was therefore performed for practical use.[38,39]

Total synthesis of phytopathogenic compounds of an eremophilane-type such as gigantenone (phytohormone mimic isolated from *Drechslera gigantea*), phomenone (*Phoma exigua*) and phaseolinone (*Macrophomina phaseolina*) was achieved by using baker's yeast asymmetric reduction as the key step.[40]

2. Marine Natural Products

2.1. Antifeedants

Many characteristic compounds have been discovered in marine animals. Pteroenone is a repellent substance from *Clione antarctica* found in the Southern Ocean, and it is extremely interesting example as an adapted defense response of the amphipod *Hyperiella dilatata*.[41] This defensive polyketide is simple but easy to decompose, and the four stereoisomers were synthesized using

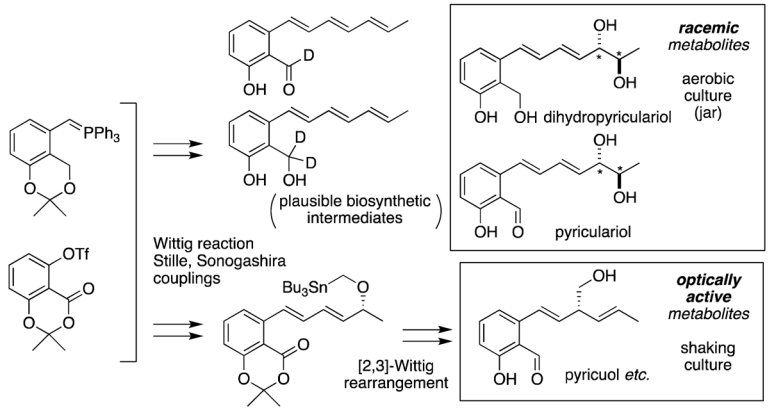

Fig. 3. Salicylaldehyde-type phytotoxins from *Pyricularia oryzae*.

Evans' aldol reaction as a key step (Fig. 5).[42,43] β-D-Asp-Gly found from *Aplysia kurodai* also showed repellent activity to saltwater fish, but was ineffective against freshwater fish.[44]

2.2. Antitumor compounds

We performed total synthesis of a new skeleton, serine glycerol didemniserinolipid B, which is produced by ascidian from Indonesia (Fig. 6).[45] Here, the absolute configuration was determined, the proposed structure was corrected, and a sulfate ester was clarified, for didemniserinolipid B.[46] In addition, several analogs of cortistatin A and sanctolide A were synthesized.[47]

2.3. Gizzerosine

Gizzerosine is a byproduct of fish feed processing that causes the

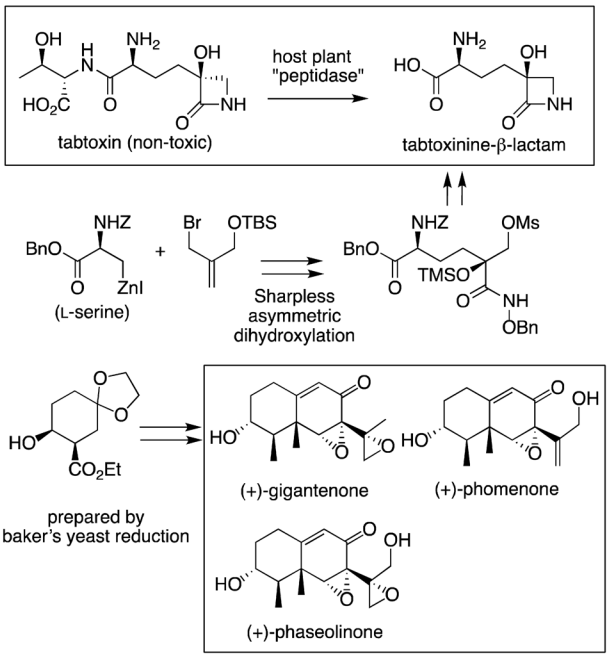

Fig. 4. Tabtoxinine-β-lactam, and eremophilane-type phytotoxins.

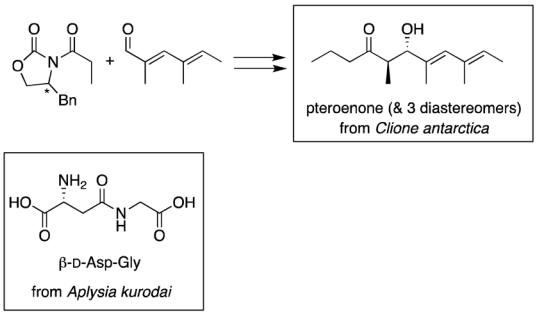

Fig. 5. Marine antifeedants.

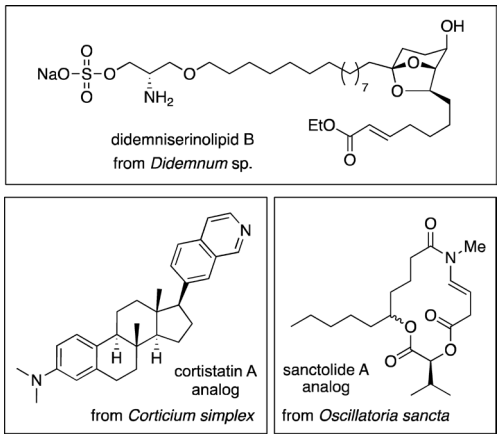

Fig. 6. Antitumor compounds and analogs from marine source.

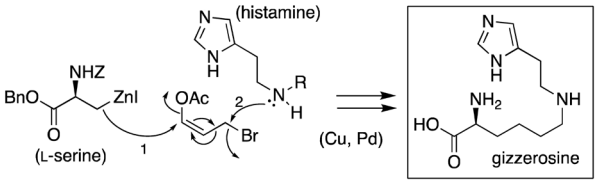

Fig. 7. Synthesis of gizzerosine.

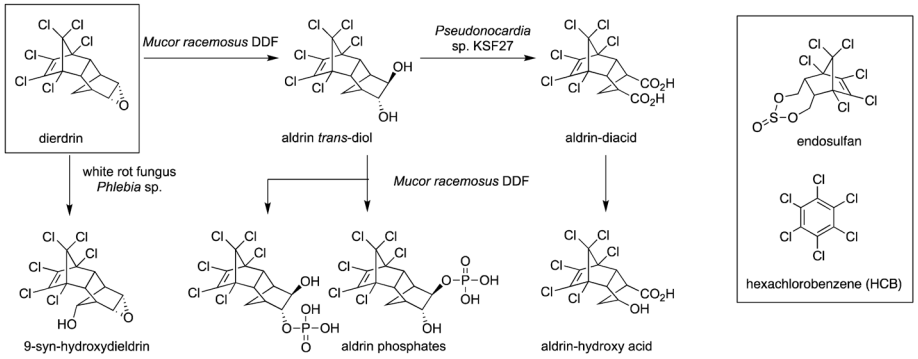

Fig. 8. Proposed degradation pathway of dieldrin, and structures of endosurfan and HCB.

formation of muscle gastric erosions and gastric ulcers in chickens (Fig. 7).[48] Therefore a gizzerosine standard is necessary for better fish feed quality control. The total synthesis of this basic amino acid was performed from L-serine and histamine using a continuous two-step metal coupling reaction.[49,50]

3. Degradation Pathway of Dieldrin

In recent years, bioremediation has attracted attention as a measure against POPs (persistent organic pollutants) that are distributed in agricultural soil at low concentrations. Although the insecticide dieldrin was once widely used, its persistence in agricultural soil or crops is a serious problem due to its high stability. In Japan, cucumber and other Cucurbitaceae vegetables have a concentration (0.02 ppm) that exceeds the standard value, and soil has a maximum concentration of 2.6 ppm. Based on the synthesis of various putative dieldrin intermediates in a joint research with the National Institute for Agro-Environmental Sciences and Kyushu University, a metabolic pathway for dieldrin was proposed as Fig. 8.

1. The filamentous fungus, *Mucor racemosus* DDF, hydrolyzes dieldrin to aldrin-*trans*-diol, followed by phosphorylation. Synthetic studies have determined that there are two common stereoisomers of the phosphate ester. This phosphate conjugation phenomenon has only been reported in a few cases from insects, and is the first case with a microbial metabolite.[51,52]
2. The aerobic bacterium *Pseudonocardia* sp. strain KSF27, which was discovered by selective culturing in the presence of charcoal, oxidizes aldrin-*trans*-diol to aldrin-diacid, and further converts the diacid to a hydroxy acid by oxidative decarboxylation.[53]
3. The white-rot fungus *Phlebia* sp. (a type of mushroom) oxidizes dieldrin to 9-*syn*-hydroxydieldrin.[54]

Degradation pathways of other POPs such as endosulfan and hexachlorobenzene (HCB) were also studied.[55–57]

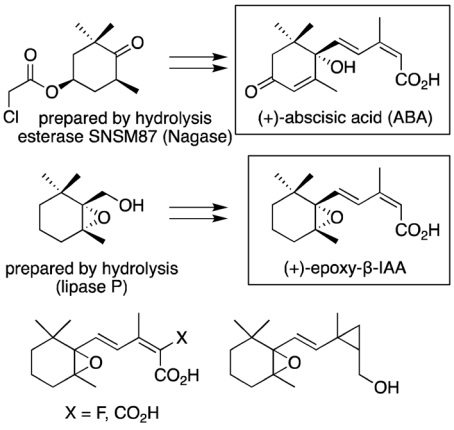

Fig. 9. Abscisic acid and related compounds.

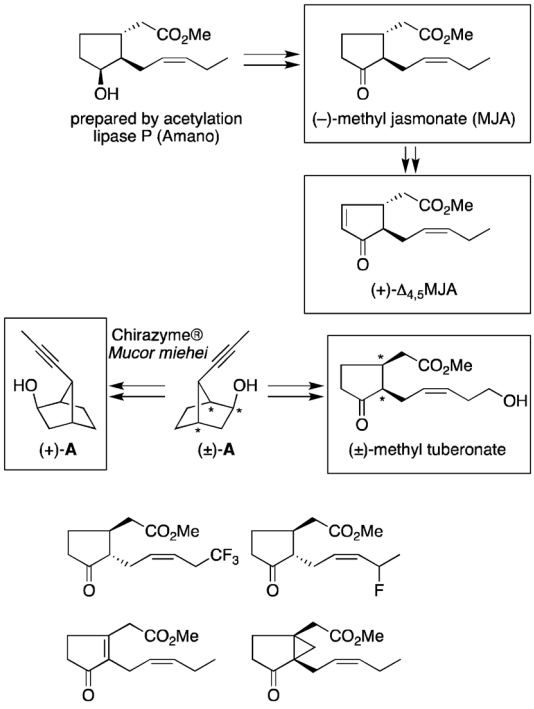

Fig. 10. Jasmonic acid and related compounds.

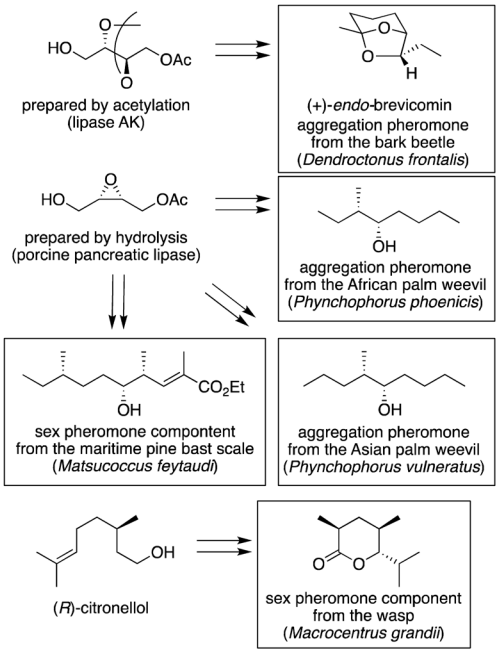

Fig. 11. Synthesis of insect pheromones.

4. Plant Hormones

4.1. Abscisic acid

Abscisic acid (ABA) is a plant hormone that induces dormancy, growth suppression, and stomatal closure.[58] Epoxy-β-ionylideneacetic acid (epoxy-β-IAA) was developed as an ABA analog that can be converted into active ABA in plants. The key synthetic intermedial alcohols for ABA and epoxy-β-IAA were prepared by the use of enzyme-catalyzed transesterification or hydrolysis (Fig. 9).[59] Synthetic studies were carried out with the key to the enzyme-catalyzed reaction of these compounds and derivatives.[60] Several analogs were also synthesized.[61]

4.2. Jasmonic acid

Jasmonic acid is a plant hormone that induces ripening and aging of fruits and breaks dormancy.[62] Practical preparation of both enantiomers of methyl jasmonate (MJA) has been developed using lipase-catalyzed hydrolysis/transesterification (Fig. 10).[63] (±)-Methyl tuberonate, a potato tuber-forming substance, was firstly synthesized *via* an intermediate (±)-**A** (Fig. 10).[64] Its enzymatic optical resolution leading to (+)-**A**, a common intermediate for MJA derivatives, succeeded.[65] Several natural MJA and their analogs were also prepared.[66–75]

5. Insect Pheromones

Pheromones have been found in a variety of species throughout lower organisms such as bacteria and brown algae to mammals such as mice and elephants, among which these natural products have been extensively studied in insects.[76] Insect pheromones have been put into practical use as pesticides by taking advantage of their high species specificity, high attracting activity and high volatility. Several insect pheromones were synthesized to determine the absolute configuration using enzyme-catalyzed asymmetric reactions as shown in Fig. 11.[77–81]

Concluding Remarks

The central dogma dictates that the origin of life is one and that all living organisms share a common biochemical language. Secondary metabolites consisting of limited elements such as C, H, O, N and S are common in multiple organisms. For example, jasmonic acid-related compounds were first discovered as jasmine aromas, but later were recognized as insect pheromones, phytopathogenic toxins, and now as plant hormones. Furthermore, the fact that secondary metabolites often play roles in multiple pathways suggests that a single novel pesticide lead may have potential to uncover multiple mechanisms of action. Therefore, we will continue to pursue synthetic research aimed at discovering new pesticide seeds, and targeting key substances that determine various life phenomena.

Acknowledgements

I would like to thank Pesticide Science Society of Japan for giving me the award. My thanks are due to my former supervisers, Professor Emeritus the late Kenji Mori (The University of Tokyo), Professor Emeritus Takeshi Kitahara (The University of Tokyo), Professor Emeritus Takayuki Oritani (Tohoku University), Professor Shigefumi Kuwahara (Tohoku University), the late Dr. Takeyoshi Sugiyama, and Professor Steven V. Ley FRS CBE (Cambridge University, UK). I express my sincere gratitude to all the staff and members of the laboratories at the University of Tokyo, Tohoku University and Okayama University, and many collaborators. I thank the collaborator and my senior Dr Kazuhiro Takagi (the National Institute for Agro-Environmental Sciences) for giving me the opportunity to resume soil research. These works were partially supported by grant-aid for scientific research, from Japan Society for the Promotion of Science, and from Japan Ministry of Education, Culture, Sports, Science and Technology (KAKENHI). Support was also given by Naito Foundation, Agricultural Chemical Research Foundation, Intelligent Cosmos Foundation, Kuribayashi Ikuei Gakujutsu Foundation, Tokyo Ohka Foundation for The Promotion of Science and Technology, Nagase & Co., Ltd., and Sumitomo Chemical Co., Ltd.

References

1) T. Watanabe, T. Sugiyama, M. Takahashi, J. Shima, K. Yamashita, K. Izaki, K. Furihata and H. Seto: *Agric. Biol. Chem.* **54**, 259–261 (1990).
2) A. Parmeggiani, I. M. Krab, T. Watanabe, R. C. Nielsen, C. Dahlberg, J. Nyborg and P. Nissen: *J. Biol. Chem.* **281**, 2893–2900 (2006).
3) T. Fujimori, O. Nakayama, H. Kiyota, Y. Kamijima, T. Watanabe and T. Oritani: *Heterocycl. Commun.* **7**, 327–330 (2001).
4) T. Watanabe, H. Kiyota, R. Takeuchi, K. Enari and T. Oritani: *Heterocycl. Commun.* **7**, 313–316 (2001).
5) R. Takeuchi, H. Kiyota, M. Yaosaka, T. Watanabe, T. Sugiyama and T. Oritani: *J. Chem. Soc., Perkin Trans.* **1**, 2676–2681 (2001).
6) H. Furukawa, H. Kiyota, T. Yamada, M. Yaosaka, R. Takeuchi, T. Watanabe and S. Kuwahara: *Chem. Biodivers.* **4**, 1601–1604 (2007).
7) H. Furukawa, H. Hoshikawa, W. Igarashi, M. Yaosaka, T. Yamada, S. Kuwahara and H. Kiyota: *Heterocycl. Commun.* **17**, 3–5 (2011).
8) W. Igarashi, H. Hoshikawa, H. Furukawa, T. Yamada, S. Kuwahara and H. Kiyota: *Heterocycl. Commun.* **17**, 7–9 (2011).

9) A. Saito, W. Igarashi, H. Furukawa, T. Yamada, S. Kuwahara and H. Kiyota: *Biosci. Biotechnol. Biochem.* **78**, 766–769 (2014).
10) R. Corbaz, L. Ettlinger, E. Gäumann, W. Keller-Schierlein, F. Kradolfer, L. Neipp, V. Prelog and H. Zähner: *Helv. Chim. Acta* **38**, 1445–1448 (1955).
11) Y. Tanouchi and H. Shichi: *Immunology* **63**, 471–475 (1988).
12) N. B. Marie, P. Elene, F. Marina and G.-S. Aelette: *Eur. J. Biochem.* **223**, 125–133 (1994).
13) H. Kiyota, M. Abe, Y. Ono and T. Oritani: *Synlett* **1997**, 1093–1095 (1997).
14) K. Takai, T. Hanadate, T. Yamada, S. Kuwahara and H. Kiyota: *Tetrahedron* **67**, 7066–7072 (2011).
15) K. Takai, T. Hanadate, S. Oi, T. Yamada, S. Kuwahara and H. Kiyota: *Synthesis*, 3741–3748 (2011).
16) T. Hanadate, K. Takai, T. Yamada, S. Kuwahara and H. Kiyota: *Heterocycl. Commun.* **17**, 93–98 (2011).
17) Y. Furuya, H. Kiyota and T. Oritani: *Heterocycl. Commun.* **6**, 427–430 (2000).
18) H. Kiyota, Y. Furuya, S. Kuwahara and T. Oritani: *Biosci. Biotechnol. Biochem.* **65**, 2630–2637 (2001).
19) A. Miura, H. Kiyota and S. Kuwahara: *Tetrahedron* **61**, 1061–1067 (2005).
20) A. Miura, S. Takigawa, Y. Furuya, Y. Yokoo, S. Kuwahara and H. Kiyota: *Eur. J. Org. Chem.* **2008**, 4955–4962 (2008).
21) Y. Shimizu, H. Kiyota and T. Oritani: *Tetrahedron Lett.* **41**, 3141–3144 (2000).
22) L. G. de Oliveira, L. C. Dias, H. Sakauchi and H. Kiyota: *Tetrahedron Lett.* **47**, 2413–2418 (2006).
23) H. Sakauchi, E. Higashi, Y. Shimizu, M. Kojima, Y. Asamitsu, S. Kuwahara, M. Izumi and H. Kiyota: *Heterocycl. Commun.* **21**, 337–343 (2015).
24) H. Kiyota, Y. Shimizu and T. Oritani: *J. Pestic. Sci.* **25**, 93–95 (2001).
25) H. Kiyota, Y. Shimizu and T. Oritani: *Tetrahedron Lett.* **41**, 5887–5890 (2000).
26) H. Kondo, T. Oritani and H. Kiyota: *Eur. J. Org. Chem.* **2000**, 3459–3462 (2000).
27) H. Kondo, T. Oritani and H. Kiyota: *Heterocycl. Commun.* **6**, 211–214 (2000).
28) M. Takeiri, E. Ota, S. Nishiyama, H. Kiyota and K. Umezawa: *Oncol. Res.* **20**, 7–14 (2012).
29) M. Nukina, T. Sassa and M. Ikeda: "Shokubutsu Byogai no Kagaku," eds. by A. Ichihara and T. Ueno, Gakkai Shuppan Center, Tokyo, pp. 74–83, 1997 (in Japanese).
30) H. Kiyota, R. Ueda, T. Oritani and S. Kuwahara: *Synlett*, 219–220 (2003).
31) Y. Nakamura, H. Kiyota, R. Ueda and S. Kuwahara: *Tetrahedron Lett.* **46**, 7107–7109 (2005).
32) A. Sasaki, K. Tanaka, Y. Sato, S. Kuwahara and H. Kiyota: *Tetrahedron Lett.* **50**, 4637–4638 (2009).
33) K. Tanaka, Y. Nakamura, A. Sasaki, R. Ueda, Y. Suzuki, S. Kuwahara and H. Kiyota: *Tetrahedron* **65**, 6115–6122 (2009).
34) K. Tanaka, A. Sasaki, H.-Q. Cao, T. Yamada, M. Igarashi, I. Komine, H. Nakahigashi, N. Minami, S. Kuwahara, M. Nukina and H. Kiyota: *Eur. J. Org. Chem.* **2011**, 6276–6280 (2011).
35) A. Saito, K. Hiramatsu, H.-Q. Cao, Y. Nagashima, K. Tanaka, A. Sasaki, T. Yamada, S. Kuwahara, M. Nukina and H. Kiyota: *Heterocycl. Commun.* **20**, 185–188 (2014).
36) H. Kiyota: *J. Synth. Org. Chem. Jpn.* **77**, 173–180 (2019) (in Japanese).
37) W. W. Stewart: *Nature* **229**, 174–178 (1971).
38) H. Kiyota, T. Takai, M. Saitoh, O. Nakayama, T. Oritani and S. Kuwahara: *Tetrahedron Lett.* **45**, 8191–8194 (2004).
39) H. Kiyota, T. Takai, Y. Shimasaki, M. Saitoh, O. Nakayama, T. Takada and S. Kuwahara: *Synthesis* **2007**, 2471–2480 (2007).
40) T. Kitahara, H. Kiyota, H. Kurata and K. Mori: *Tetrahedron* **47**, 1649–1654 (1991).
41) W. Y. Yoshida, P. J. Bryan, B. J. Baker and J. B. McClintock: *J. Org. Chem.* **60**, 780–782 (1995).
42) Y. Nakamura, H. Kiyota and S. Kuwahara: *Synlett*, 635–636 (2005).
43) H. Asao, Y. Nakamura, Y. Furuya, S. Kuwahara, B. J. Baker and H. Kiyota: *Helv. Chim. Acta* **93**, 1933–1944 (2010).
44) H. Kiyota, H. Asao, Y. Nakamura, Y. Furuya, S. Kuwahara, K. Takatsuto, S. Nakano, T. Yamaguchi, M. Sato and K. Yamamori: *Abstr. 8th Annu. Meeting Chemical Ecology Soc. Jpn.* (2013).
45) N. Gonzalez, J. Rodriguez and C. Jiminez: *J. Org. Chem.* **64**, 5705–5707 (1999).
46) H. Kiyota, D. J. Dixon, C. Luscombe, S. Hettstedt and S. V. Ley: *Org. Lett.* **4**, 3223–3226 (2002).
47) Y. Sato, H. Kamiyama, T. Usui, T. Saito, H. Osada, S. Kuwahara and H. Kiyota: *Biosci. Biotechnol. Biochem.* **72**, 2992–2997 (2008).
48) T. Okazaki, T. Noguchi, K. Igarashi, Y. Sakagami, H. Seto, K. Mori, H. Naito, T. Masumura and M. Sugahara: *Agric. Biol. Chem.* **47**, 2949–2952 (1983).
49) M. Shimasaki, H. Kiyota, M. Sato and S. Kuwahara: *Synthesis* 3191–3192 (2005).
50) M. Shimasaki, H. Kiyota, M. Sato and S. Kuwahara: *Tetrahedron* **62**, 9628–9634 (2006).
51) R. Kataoka, K. Takagi, I. Kamei, H. Kiyota and Y. Sato: *Environ. Sci. Technol.* **44**, 6343–6349 (2010).
52) K.-I. Yamazaki, K. Takaga, R. Kataoka, M. Kotake, T. Yamada and H. Kiyota: *Int. Biodet. Biodeg.* **92**, 36–40 (2014).
53) F. Sakakibara, K. Takagi, R. Kataoka, H. Kiyota, Y. Sato and S. Okada: *Biochem. Biophys. Res. Commun.* **411**, 76–81 (2011).
54) P.-F. Xiao, T. Mori, I. Kamei, H. Kiyota, K. Takagi and R. Kondo: *Chemosphere* **85**, 218–224 (2011).
55) K. Ito, F. Kawashima, K. Takagi, R. Kataoka, M. Kotake, H. Kiyota, K. Yamazaki, F. Sakakibara and S. Okada: *Biochem. Biophys. Res. Commun.* **473**, 1094–1099 (2016).
56) K. Ito, K. Takagi, R. Kataoka, H. Kiyota and A. Iwasaki: *J. Pestic. Sci.* **44**, 171–176 (2019).
57) K. Ito, K. Takagi, R. Kataoka and H. Kiyota: *J. Pestic. Sci.*
58) T. Oritani and H. Kiyota: *Nat. Prod. Rep.* **20**, 414–425 (2003).
59) R. Okazaki, H. Kiyota and T. Oritani: *Biosci. Biotechnol. Biochem.* **64**, 1444–1447 (2000).
60) H. Kiyota, M. Nakabayashi and T. Oritani: *Tetrahedron Asymmetry* **10**, 3811–3817 (1999).
61) H. Kiyota, T. Masuda, J. Chiba and T. Oritani: *Biosci. Biotechnol. Biochem.* **60**, 1076–1080 (1996).
62) C. Wasternack and M. Strnad: *Int. J. Mol. Sci.* **19**, 2539 (2018).
63) H. Kiyota, E. Higashi, T. Koike and T. Oritani: *Tetrahedron Asymmetry* **12**, 1035–1038 (2001).
64) H. Kiyota, D. Nakashima and T. Oritani: *Biosci. Biotechnol. Biochem.* **63**, 2110–2117 (1999).
65) H. Kiyota, D. Nakashima, S. Kuwahara and T. Oritani: *Z. Naturforsch.* **63b**, 1441–1442 (2008).
66) H. Kiyota, M. Saitoh, T. Oritani and T. Yoshihara: *Phytochemistry* **41**, 1259–1262 (1996).
67) H. Kiyota, Y. Yoneta and T. Oritani: *Phytochemistry* **46**, 983–986 (1997).
68) H. Kiyota, T. Koike, E. Higashi, Y. Satoh and T. Oritani: *J. Pestic. Sci.* **25**, 96–99 (2001).

69) H. Kiyota, E. Higashi, T. Koike and T. Oritani: *Flavour Fragrance J.* **16**, 175–179 (2001).
70) H. Kiyota, T. Koike, E. Higashi and T. Oritani: *Flavour Fragrance J.* **17**, 267–271 (2002).
71) Y. Ishii, H. Kiyota, S. Sakai and Y. Honma: *Leukemia* **18**, 1413–1419 (2004).
72) Y. Nakamura, R. Miyatake, A. Matsubara, H. Kiyota and M. Ueda: *Tetrahedron* **62**, 8805–8813 (2006).
73) Y. Asamitsu, Y. Nakamura, M. Ueda, S. Kuwahara and H. Kiyota: *Chem. Biodivers.* **3**, 654–659 (2006).
74) H. Tsumura, M. Akimoto, Y. Ishii, H. Kiyota, H. Ishikura and Y. Honma: *Leukemia* **23**, 753–760 (2009).
75) M. Ueda, G.-Q. Yang, Y. Ishimaru, T. Itabashi, S. Tamura, H. Kiyota, S. Kuwahara, S. Inomata, M. Shoji and T. Sugai: *Bioorg. Med. Chem.* **20**, 5832–5843 (2012).
76) H. Kiyota: "Trend in Pesticide Discovery Research—Development of Safer and Environmentally Friendly Pesticides—," ed. by N. Umetsu, CMC Publishing, Tokyo, pp. 302–306, 2018 (in Japanese).
77) K. Mori and H. Kiyota: *Liebigs Ann. Chem.* **1992**, 989–992 (1992).
78) K. Mori, H. Kiyota and D. Rochat: *Liebigs Ann. Chem.* **1993**, 865–870 (1993).
79) K. Mori, H. Kiyota, D. Rochat and C. Malosse: *Liebigs Ann. Chem.* **1993**, 1201–1204 (1993).
80) H. Kiyota and K. Mori: *Biosci. Biotechnol. Biochem.* **58**, 1120–1122 (1994).
81) K. Mori, T. Fruuchi and H. Kiyota: *Liebigs Ann. Chem.* **1994**, 971–974 (1994).