

HETEROCYCLES, Vol. 96, No. 9, 2018, pp. 1509 - 1527. © 2018 The Japan Institute of Heterocyclic Chemistry
Received, 27th February, 2018, Accepted, 21st May, 2018, Published online, 14th June, 2018
DOI: 10.3987/REV-18-885

DEVELOPMENTS TOWARD THE PRODUCTION OF DIVERSE NATURAL-PRODUCT-LIKE COMPOUNDS: DIVERSITY-ORIENTED SYNTHESIS AND DIVERSITY-ENHANCED EXTRACTS

Haruhisa Kikuchi* and Yoshiteru Oshima*

Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3, Aza-Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan. E-mails: hal@mail.pharm.tohoku.ac.jp and oshima@mail.pharm.tohoku.ac.jp

Abstract – Natural products and their derivatives have proven very useful in the search for biologically active compounds and in the development of new drugs because of their structural diversity. However, new approaches that may increase the chemical diversity of such natural products must be developed in order to retain the future usefulness of these compounds. Diversity-oriented synthesis (DOS) has recently emerged as an efficient methodology for constructing complex and diverse compounds from simple and similar precursors. Through the combination of natural product chemistry and DOS, we therefore propose a new approach, diversity-enhanced extracts, for increasing the diversity of natural-product-like compounds. This review describes recent developments toward the production of diverse natural-product-like compounds by DOS based on natural products and direct chemical derivatization of natural extracts, including diversity-enhanced extracts.

CONTENTS

1. Introduction
2. Diversity-oriented synthesis based on natural product scaffolds
3. Diversity-enhanced extracts and related direct chemical derivatization of natural extracts
4. Applications of diversity-enhanced extracts for the production of a pharmacological-activity-oriented chemical library
 - 4.1. Monoterpene indole alkaloid-like compound library
 - 4.2. Meroterpenoid-like compound library
5. Conclusion

1. INTRODUCTION

More than 50% of small-molecule drugs originate from natural products. The structures of these natural products have provided or inspired the subsequent development of drug structures.¹ Thus, the structural diversity of natural products and their derivatives have long contributed to the discovery of new drugs.² However, pharmaceutical research into natural products has recently declined because of factors such as the difficulty of collecting novel compounds bearing privileged structures.³ Therefore, new approaches to increase the chemical diversity of these products are crucial to retaining the usefulness of natural products and their derivatives.

Synthetic biology is a field that has been developed to translate encrypted microbial biosynthetic genes into diverse natural products.⁴ The manipulation of biosynthetic enzymes alters the functional groups and chemical skeletons of compounds, thereby creating unique analogs of natural products. Although the large-scale production of these compounds remains challenging,^{4c} this field will prove to be useful in natural-product-based drug discovery.

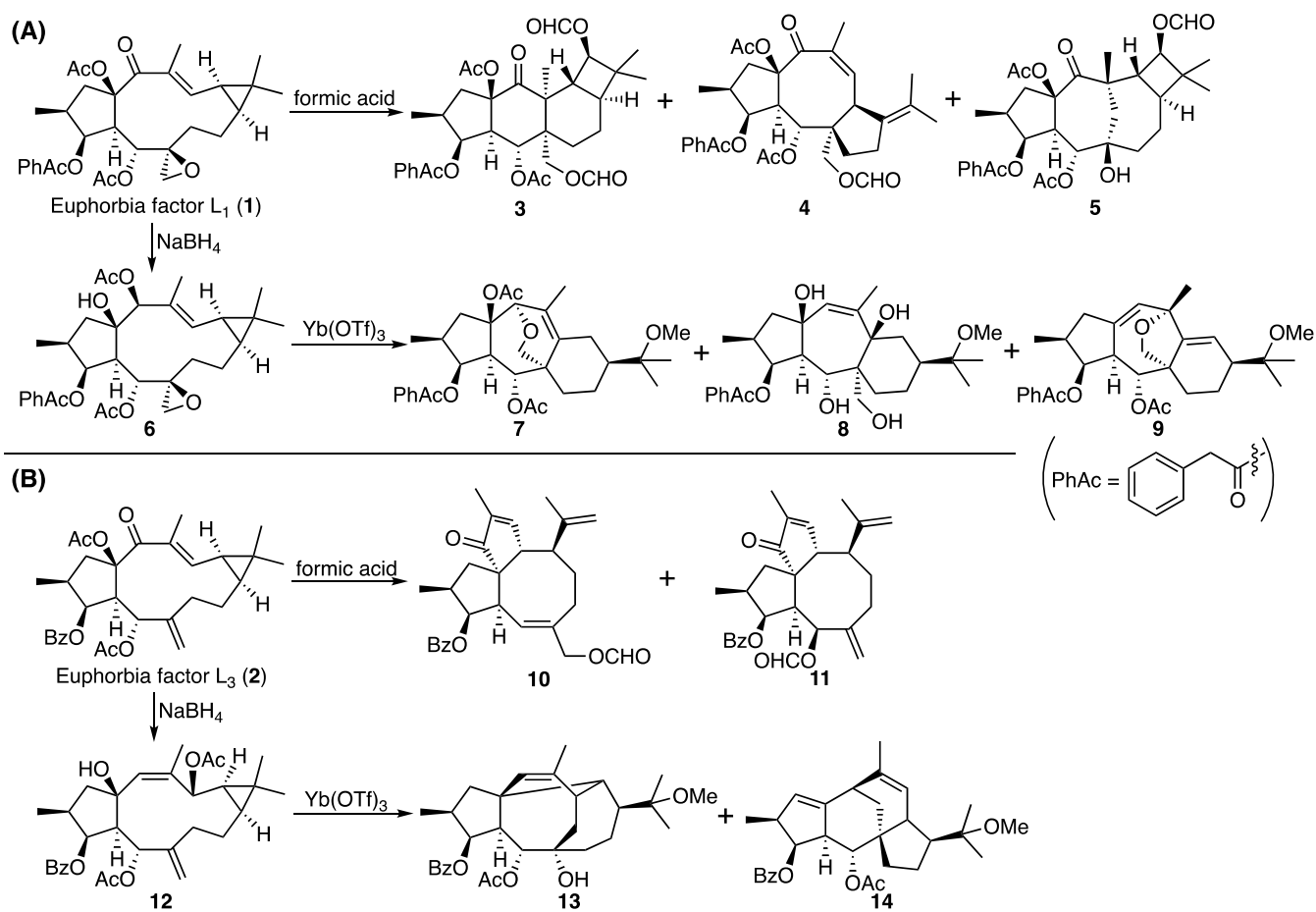
Another field of research, diversity-oriented synthesis (DOS), was pioneered by Schreiber and co-workers. It has emerged as an efficient methodology for the production of structurally diverse compounds.⁵ A diversity-generating reaction of simple substrates produces diverse products, which can be used as a chemical library for drug discovery. Recently, we proposed the use of “diversity-enhanced extracts”,^{6,7} an approach used to increase the chemical diversity of natural-product-like compounds through the combination of natural product chemistry and DOS. This review describes recent developments toward the production of diverse natural-product-like compounds by DOS based on natural products and direct chemical derivatization of natural extracts, including diversity-enhanced extracts.

2. DIVERSITY-ORIENTED SYNTHESIS BASED ON NATURAL PRODUCT SCAFFOLDS

As previously mentioned, the structural diversity of natural products and their derivatives plays an important role in drug discovery. Particularly, the production of a high level of three-dimensional-shape diversity derived from a high fraction of sp^3 carbon atoms (F_{sp^3}) in most natural products is very important.⁸ New approaches for augmenting the chemical diversity of natural products and their derivatives are therefore urgently required in order to retain the utility of these compounds. In this regard, DOS has emerged as an efficient method for constructing complex, diverse molecules from simple and similar precursors.⁵ The use of natural products as starting scaffolds is particularly effective in achieving chemically diverse libraries that are useful in drug discovery. Furthermore, easily accessible natural products can be used as a source for the synthesis of novel molecular scaffolds to avoid the use of a large number of reaction steps that may be required for *de novo* construction of complex natural-product-derived structures. The following examples represent some of the synthetic efforts that

have been made to transform natural products into diverse natural-product-like compounds.

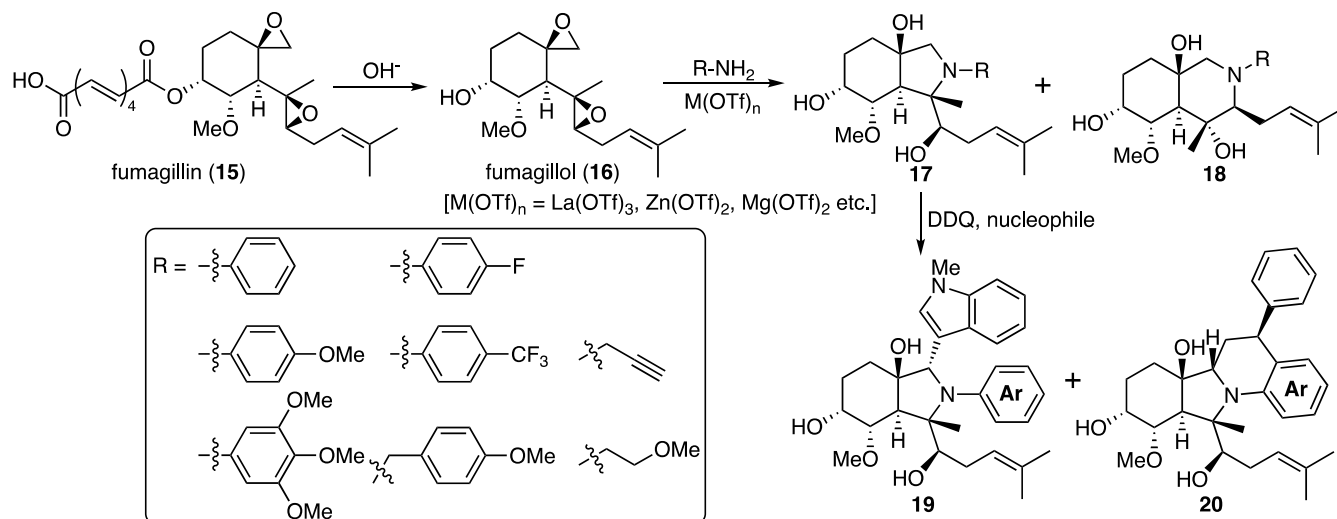
Sterner and co-workers reported upon the production of diverse polycyclic compounds from *Euphorbia* factors L₁ and L₃ (**1** and **2**, respectively), which are highly functionalized diterpenoids that are readily available in multigram quantities in the seeds of *Euphorbia laathyris* (**Scheme 1**).⁹ Various types of transannular reactions of these *Euphorbia* factors produced unnatural diterpene-type skeletons (**3–14**) that are not easily achieved by other methods.



Scheme 1. Transannular cyclization of *Euphorbia* factor L₁ (A) and L₃ (B) to produce a series of functionalized diterpene-type compounds

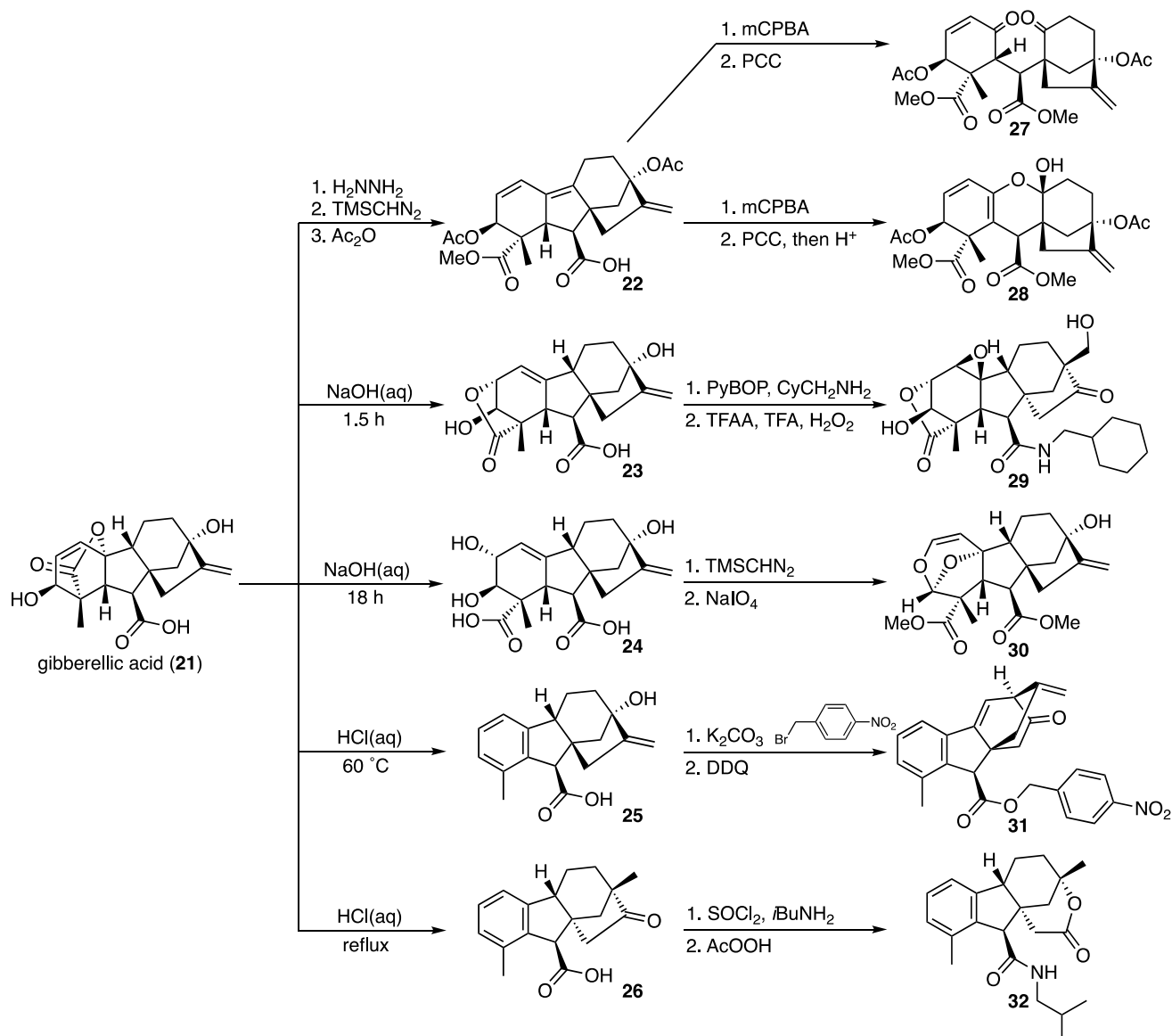
Porco, Jr. and co-workers reported upon the remodeling of fumagillol (**16**), a hydrolyzed product of fumagillin (**15**) that is readily available in the fermentation broth of *Aspergillus fumigatus*, into diverse nitrogen-containing compounds (**Scheme 2**).¹⁰ They used fumagillol because the adjacent two epoxides of this compound present sites for diversity-generating reactions, and the hydroxy and alkene groups offer additional functionality for further diversification. The 5-*exo*- or 6-*endo*-bis-epoxide opening reactions, which are dependent on the metal catalyst additive that is used, in the presence of several amines led to the formation of highly complex perhydroisoindoles (**17**) and perhydroisoquinolines (**18**). Subsequently,

the skeletal diversity of perhydroisindole (**17**) was further expanded into compounds **19** and **20** via oxygen-directed oxidation and subsequent Mannich reaction with several nucleophiles.¹¹



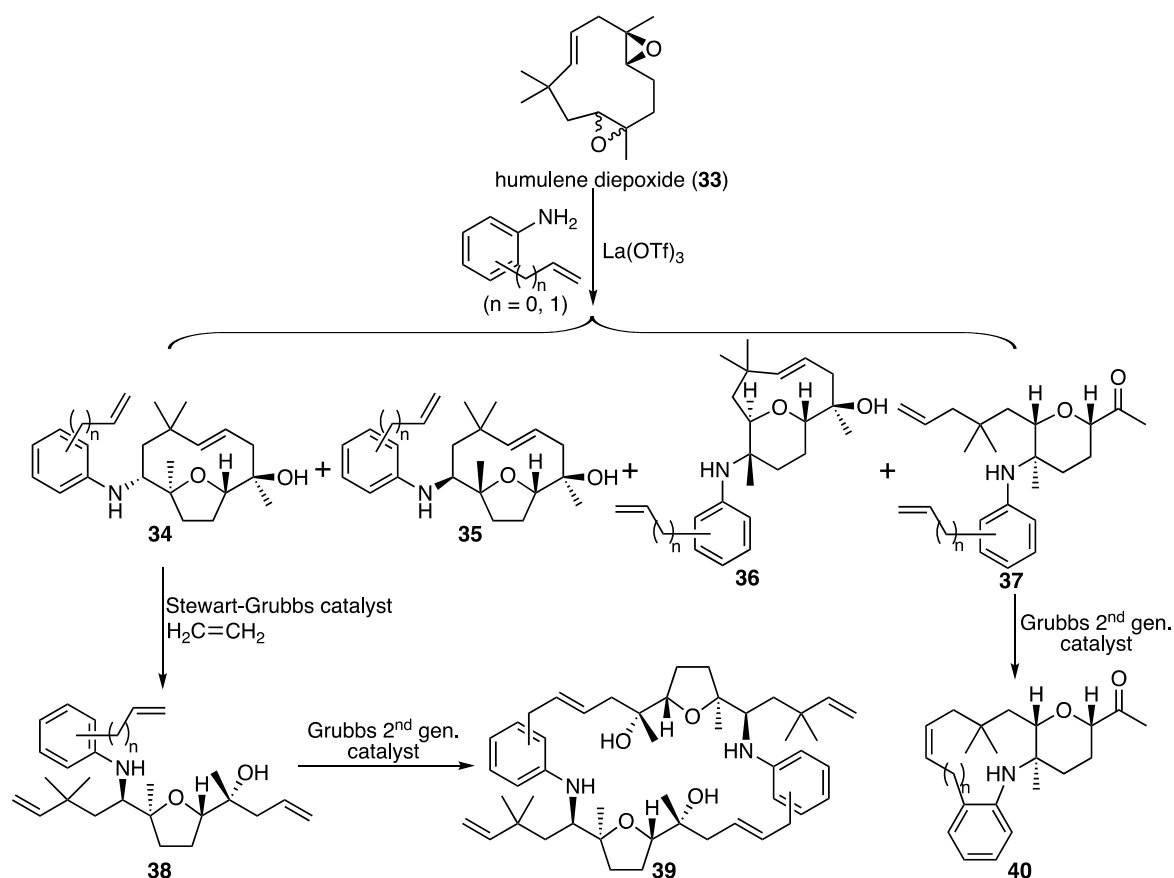
Scheme 2. Remodeling of fumagillol into perhydroisindoles and perhydroisoquinolines via ring opening of bisepoxides

Hergenrother et al. proposed the use of a ring-distortion strategy, wherein the core cyclic skeletons of structurally complex natural products are rearranged into diverse and distinct scaffolds by ring-distortion reactions.¹² For example, several ring-distorting reactions such as the opening reaction of a lactone ring, along with the rearrangement and oxidative cleavage of a ring system, were applied to gibberellic acid (**21**) to generate compounds **27–32**, which exhibited distinct and complex scaffolds (**Scheme 3**). By similar methods, adrenosterone and quinine were also converted into diverse natural-product-like compounds. Thus, a natural-product-like compound library including 49 markedly distinct molecular scaffolds was produced. This library had a higher F_{sp^3} value (0.59) and average number of stereocenters (5.17) than those of the commercial screening library (ChemBridge, with F_{sp^3} values of 0.23 and 0.24 stereocenter), properties that are suitable for a wide variety of biological and medicinal applications. The ring-distortion strategy was further applied to abietic acid,¹³ deltaline,¹⁴ sinomenine,¹⁵ and yohimbine¹⁶ to produce natural-product-like compounds possessing distinct molecular scaffolds.



Scheme 3. The ring-distortion strategy applied to gibberellic acid to build diverse natural product-like scaffolds

Recently, we reported upon the construction of a library of terpenoid alkaloid-like compounds based on humulene, an 11-membered-ring-containing sesquiterpenoid that is present in a wide range of plants such as hops (*Humulus lupulus*) (Scheme 4).¹⁷ Because of the medium-sized ring moiety of this compound, the introduction of a nitrogen-containing functional group during transannulation can produce diverse bicyclo-alkaloidal scaffolds. Thus, the ring-opening reactions of humulene diepoxide (33) by the use of vinyanilines or allylanilines produced several types of oxabicyclo compounds (34–36) and their ring-cleaved derivatives (37). The subsequent ring-opening/closing metathesis of these compounds afforded dimeric macrocycles (39) and tricyclic compounds (40). The constructed compound library contains 32 compounds comprising 10 monocycles, 17 bicycles, 2 tricycles, and 3 macrocycles, each possessing distinct scaffold.



Scheme 4. Our approach to the construction of a library of terpenoid alkaloid-like compounds based on humulene

3. DIVERSITY-ENHANCED EXTRACTS AND RELATED DIRECT CHEMICAL DERIVATIZATION OF NATURAL EXTRACTS

As described in the preceding section, DOS based on natural products is a powerful tool in the production of diverse compounds. On the basis of the aforementioned results, we recently proposed the use of “diversity-enhanced extracts”, which is an approach for increasing the chemical diversity of natural-product-like compounds via natural product chemistry and DOS (**Figure 1**).^{6,7} Diversity-enhanced extracts are obtained from chemical reactions that remodel molecular scaffolds directly in the extracts of natural resources. The subsequent isolation of each compound produced from such reactions results in the diverse natural-product-like compounds bearing new molecular scaffolds. There have been some studies using similar methods that chemically convert natural extracts (described in detail later). However, we defined diversity-enhanced extracts as natural extracts obtained by multiple diversity-generating reactions that not only convert functional groups, but also form new carbon–carbon bonds and modify molecular scaffolds similarly to DOS.

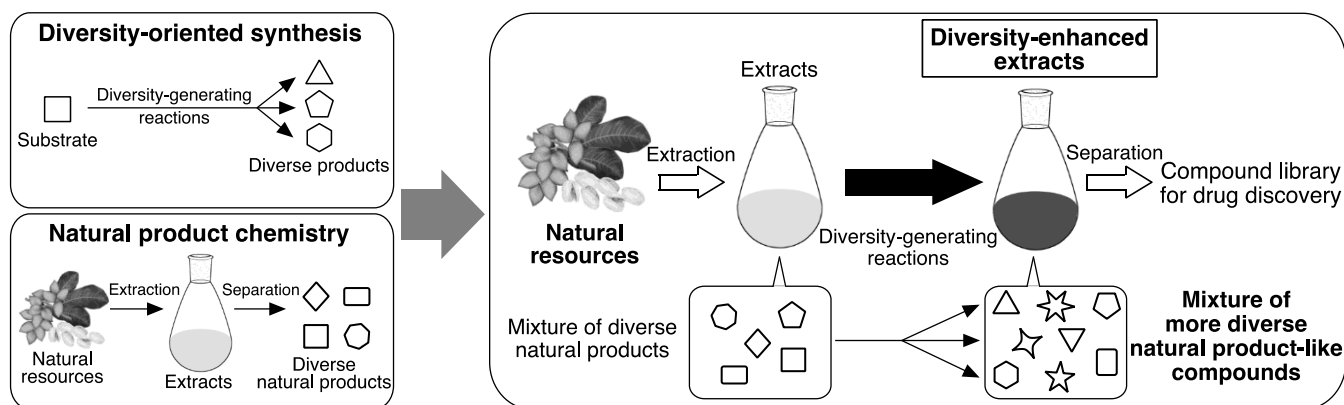
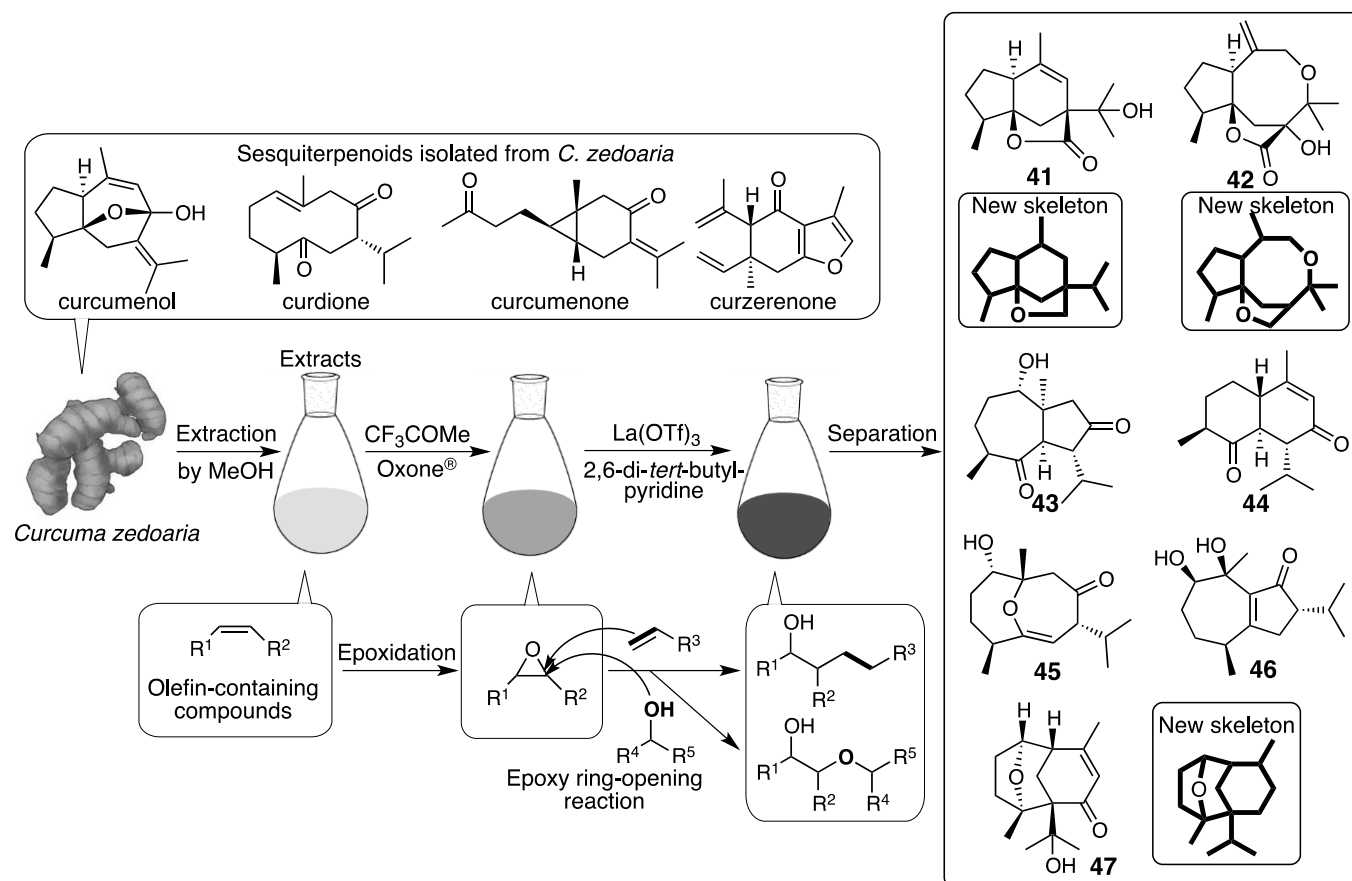


Figure 1. Schematic outline for the production of diversity-enhanced extracts

Commercially available traditional medicinal plants were chosen as starting materials to produce diversity-enhanced extracts. Because traditional medicinal plants contain diverse pharmacologically active natural products, the diversity-enhanced extracts of these products may be used to produce useful chemical libraries that contain very diverse natural-product-like compounds for subsequent drug discovery. For example, the method of diversity-enhanced extracts was applied to *Curcuma zedoaria* (white turmeric), a medicinal plant used as an aromatic stomachic (**Scheme 5**).⁶ Because of the several kinds of sesquiterpenoids¹⁸ in this plant that contain some carbonyl groups and olefins, epoxidation and a subsequent ring-opening reaction were used as diversity-generating reactions to prepare the diversity-enhanced extracts of *C. zedoaria*. These extracts were separated by repeated column chromatography to yield seven different sesquiterpene-type compounds (**41–47**). Compounds **41**, **42**, and **47** possessed unprecedented molecular skeletons, indicating that this method of producing diversity-enhanced extracts is useful in obtaining natural-product-like compounds bearing new molecular scaffolds.

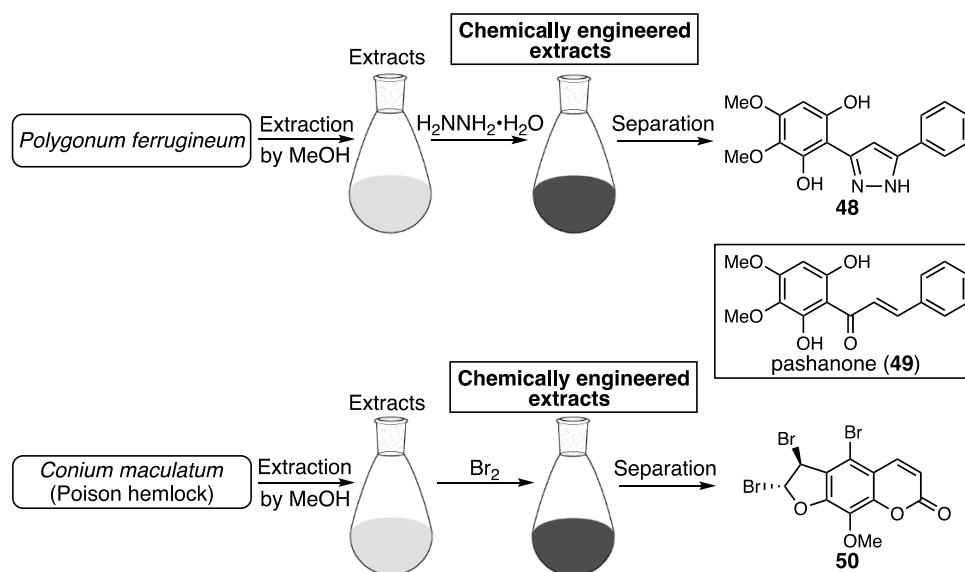
In fact, there have been several reports on the direct chemical derivatization of natural extracts for producing new natural product-like compounds. Furlan et al. reported upon “chemically engineered extracts”,¹⁹ which are chemically derivatized plant extracts that are used to prepare biologically active compounds based on natural products. The chemical reactions used to produce chemically engineered extracts were very simple and were suitable for the use of direct bioassays of the chemically altered extracts. Conversely, multiple harsh reactions were used in diversity-enhanced extracts to produce diverse and complex natural-product-like compounds. For example, the extracts of 17 species of plants, which were selected because they contained many kinds of carbonyl compounds, were treated with hydrazine monohydrate. As a result, a pyrazole-type compound (**48**) derived from a known chalcone, pashanone (**49**),²⁰ was isolated from the hydrazine-treated extracts of *Polygonum ferrugineum* through antifungal-assay-guided fractionation (**Scheme 6**).^{19a} Furlan et al. also reported upon the syntheses of a



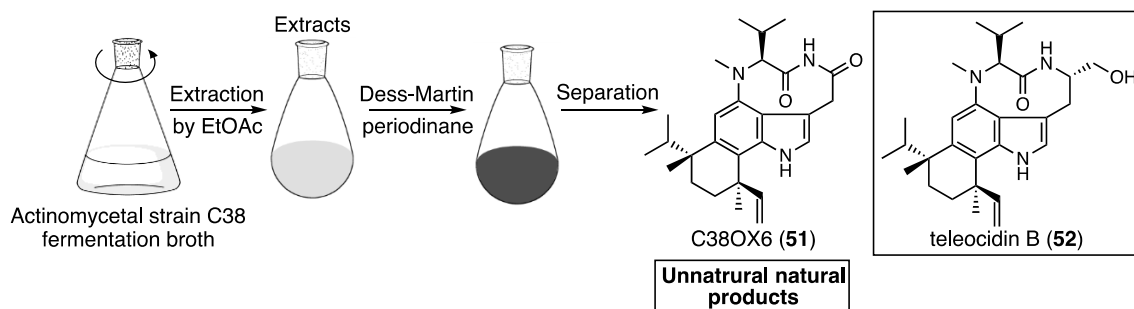
Scheme 5. Production of the sesquiterpenoid-like compounds isolated from the diversity-enhanced extracts of *Curcuma zedoaria*

tribromocoumarin (**50**) with acetylcholinesterase inhibitory activity that was isolated from the brominated extracts of *Conium maculatum*,^{19b} a histamine derivative with β -glucosidase inhibitory activity isolated from the sulfonylated extracts of *Urtica urens*,^{19d} and an anethole derivative with tyrosinase inhibitory activity isolated from the fluorinated extracts of *Ocimum basilicum*,^{19f} all of which they achieved using the method of chemically engineered extracts.

Imoto et al. referred to chemically modified microbial metabolites as “unnatural natural products”.²¹ They treated the extracts of an actinomycetal fermentation broth with either Dess–Martin periodinane, *m*CPBA, or sodium borohydride. The chemically modified extracts were then separated to construct the unnatural natural product library. From the broth of actinomycetal strain C38 treated with Dess–Martin periodinane, an XIAP (X-linked inhibitor of apoptosis) inhibitor, C38OX6, was isolated (**Scheme 7**). C38OX6 may be generated from an indole alkaloid, teleocidin B.



Scheme 6. Chemically engineered extracts and their products as reported by Furlan et al.

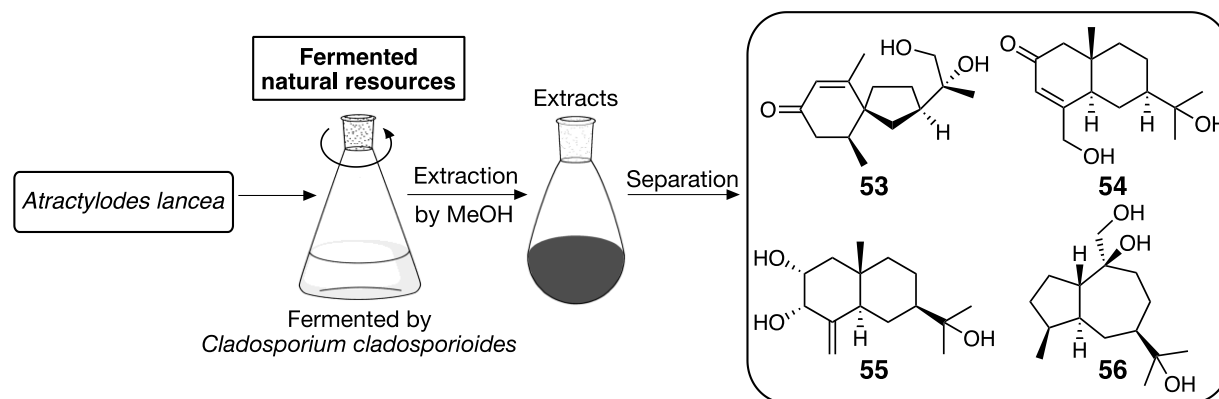


Scheme 7. Unnatural natural products derived from chemically modified microbial metabolites, reported by Imoto et al.

There exist several other reports on the direct chemical derivatization of natural extracts. Zhu et al. isolated cytochalasin derivatives, spicarins A–D, from acetylated extracts of the fermented broth of the fungus *Spicaria elegans*.²² Tomohara, Adachi, and co-workers performed the Bucherer–Bergs reaction directly, using the extracts of several plants and isolated compounds bearing imidazolidine-2,4-dione and 1,3-oxazinan-2-one skeletons.²³

Koyama et al. proposed an interesting approach for the fermentation of natural resources to enhance the chemical diversity of natural-product-like compounds.²⁴ In this approach, the whole constituents of natural resources are converted into their metabolites by microorganisms. For example, rhizomes of *Atractylodes lancea* were fermented by a marine-derived fungus, *Cladosporium cladosporioides*, and then extracted using chloroform. Next, dihydroxy- or trihydroxysesquiterpenoids were isolated from the fermented extracts (**Scheme 8**).^{24b} These polyhydroxy compounds were produced by the microbial oxidation of unactivated C–H bonds in known sesquiterpenoids, namely, β -eudesmol and hinesol, a

process that is difficult to achieve using synthetic chemistry techniques. Thus, this approach involving the fermentation of natural resources is valuable in enhancing the oxidation states of natural products.



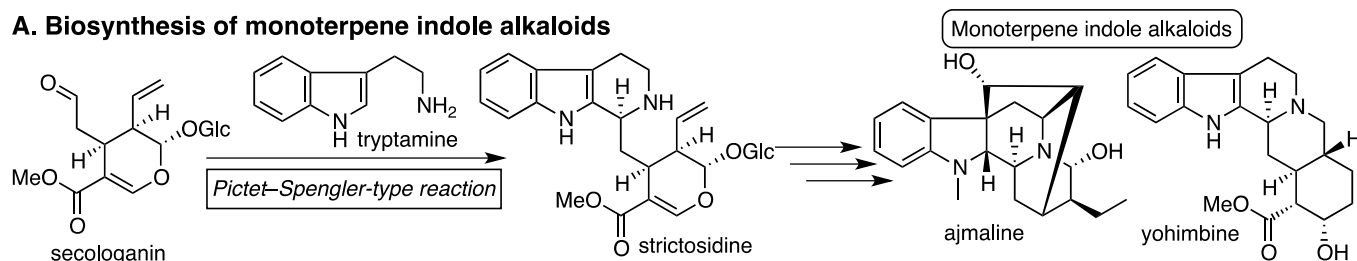
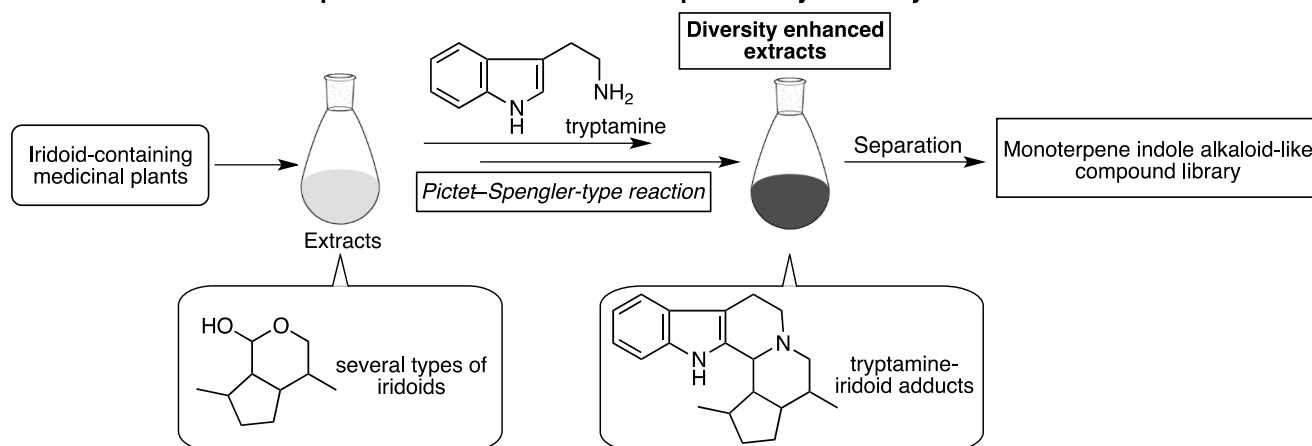
Scheme 8. Polyhydroxy sesquiterpenoids isolated from *A. lancea* fermented by *C. cladosporioides*

4. APPLICATIONS OF DIVERSITY-ENHANCED EXTRACTS FOR THE PRODUCTION OF A PHARMACOLOGICAL-ACTIVITY-ORIENTED CHEMICAL LIBRARY

As described in the preceding section, the use of diversity-enhanced extracts is an excellent approach for producing natural-product-like compounds bearing new molecular scaffolds. However, in order to produce a useful chemical library for drug discovery, it is not sufficient to produce only new molecular scaffolds; the production of new molecular scaffolds demonstrating biological or pharmacological activities should be sought. As such, the applications of the diversity-enhanced extracts obtained by this research group are discussed in the succeeding sections.

4.1. Monoterpene indole alkaloid-like compound library

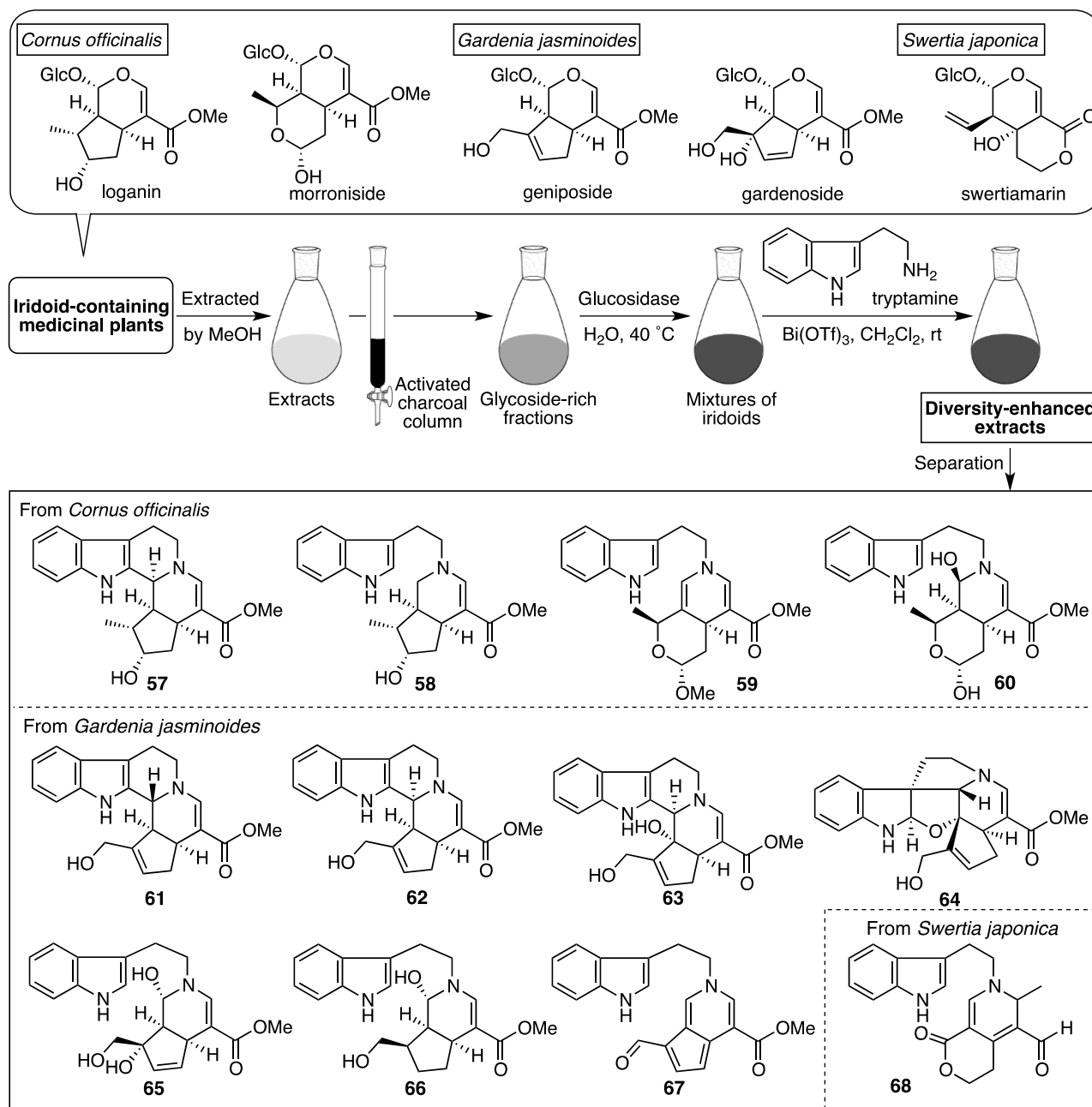
Many indole alkaloids such as ajmaline and yohimbine show significant biological activities; they are used either as drugs or as lead compounds for drugs.²⁵ Their structures contain sp^3 -rich terpenoid scaffolds and nitrogen-containing alkaloid scaffolds, which confer various pharmacological activities. In their biosynthetic pathways, strictosidine is produced via a Pictet–Spengler-type reaction²⁶ between tryptamine and secologanin catalyzed by strictosidine synthase, which cannot accept monoterpenes other than secologanin. Indole alkaloids containing several types of monoterpene moieties other than secologanin that could be produced here would be useful in constructing chemically diverse compound libraries for drug discovery (**Scheme 9**).

A. Biosynthesis of monoterpene indole alkaloids**B. Production of monoterpene indole alkaloid-like compounds by diversity-enhanced extracts**

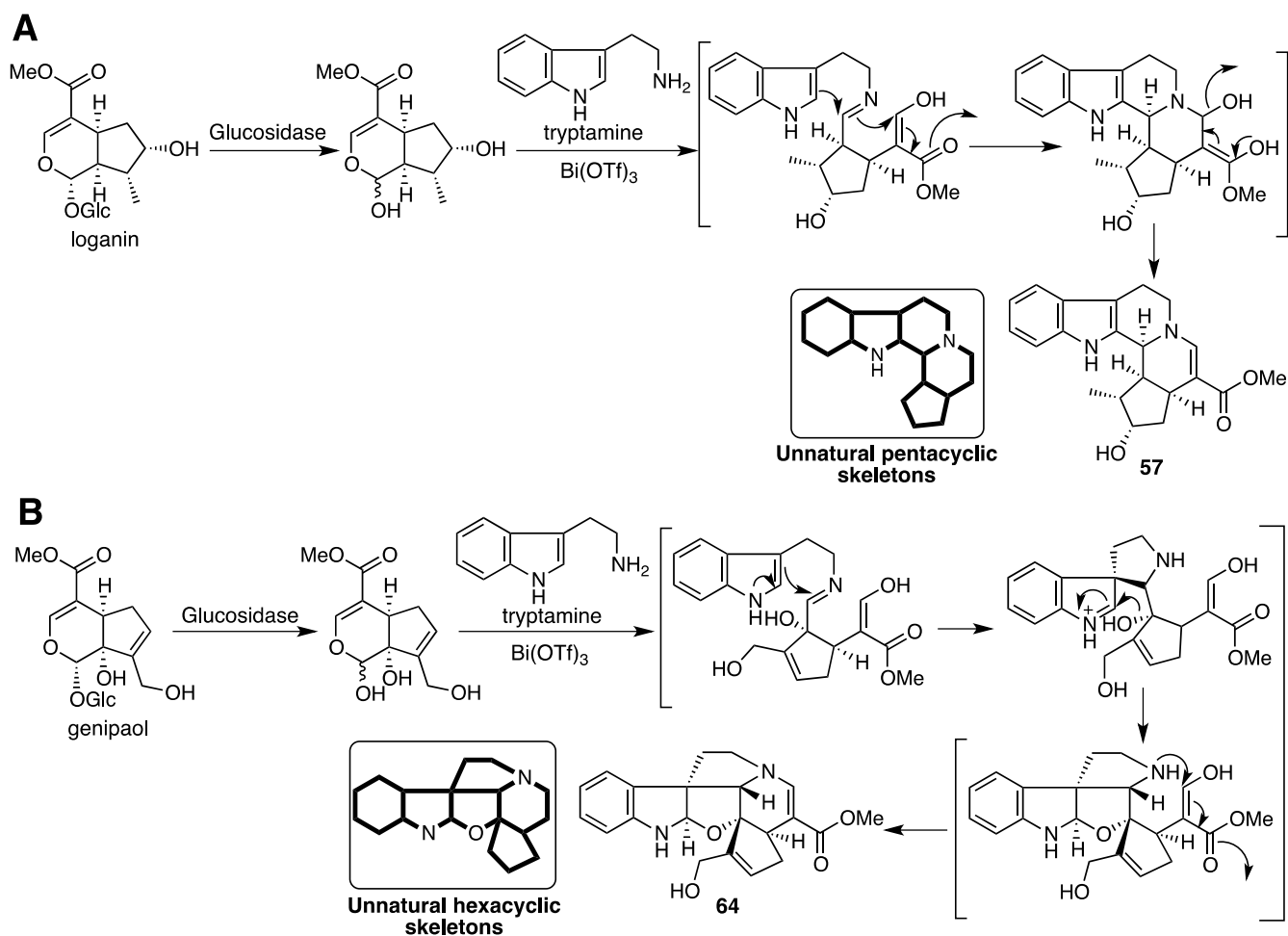
Scheme 9. Schematic diagrams for the biosynthesis of monoterpene indole alkaloids (A) and monoterpene indole alkaloid-like compounds produced from the diversity-enhanced extracts (B)

Thus, a library of compounds resembling indole alkaloids derived from iridoids, instead of secologanin, was built using the diversity-enhanced extracts of classical medicinal plants.⁷ The traditional medicinal plants *Cornus officinalis* and *Gardenia jasminoides*, which contain various kinds of iridoid glucosides, were used as starting materials (Scheme 10).^{27,28} Each plant was extracted using methanol. A large amount of sugars was removed from the extract by activated-charcoal column chromatography to produce a glycoside-rich fraction. Afterward, deglycosidation by glucosidase and a subsequent Pictet-Spengler reaction with tryptamine produced diversity-enhanced extracts containing indole alkaloid-like compounds, which were separated by repeated column chromatography. Four indole-conjugated compounds (**57–60**) were isolated from the extracts of *C. officinalis*, while seven compounds (**61–67**) were isolated from those of *G. jasminoides*. In addition, compound **68** was obtained from the diversity-enhanced extracts of *Swertia japonica*,²⁹ another medicinal plant that contains secoiridoid glucosides. Compound **57** has an unnatural pentacyclic skeleton, which has been reported upon only once³⁰ and was assumed to have been produced from loganin,²⁷ a constituent of *C. officinalis*, by sequential deglycosidation, imination, and Pictet-Spengler reaction (Scheme 11A). Compounds **61–63** also possess unnatural pentacyclic skeletons. On the other hand, compound **64** has an unexpected hexacyclic skeleton and possibly originates from genipaol, which reacts with tryptamine to produce an imine. Through its beta position, the indole attacks

the imine in a typical Pictet–Spengler reaction, producing a spiro intermediate. A tertiary alcohol attacks the alpha position of the indole, and tetrahydropyridine subsequently forms, affording compound **64** (Scheme 11B). This hexacyclic skeleton is unprecedented in both synthetic and natural compounds.



Scheme 10. Production of the monoterpene indole alkaloid-like compounds isolated from the diversity-enhanced extracts of iridoid-containing medicinal plants



Scheme 11. Plausible synthetic pathways for the production of the pentacyclic compound **57** (A) and the hexacyclic compound **64** (B)

To verify the usefulness of this library of iridoid-conjugated indole alkaloid-like compounds for the discovery of drugs and new pharmacologically active compounds, these compounds were screened for several types of biological activities. As a result, compound **57** decreased the production of anti-inflammatory IL-10 and inhibited the gene expression of the immune checkpoint protein, CTLA-4 (cytotoxic T-lymphocyte-associated protein 4), thus exhibiting potential use as a novel small-molecule immune checkpoint inhibitor.³¹

4.2. Meroterpenoid-like compound library

Meroterpenoids are natural products of mixed biosynthetic origins, which are partially derived from terpenoids.³² In particular, meroterpenoids derived from polyketide and terpenoid precursors contain sp³-rich terpenoid scaffolds and sp²-rich polyketide scaffolds, which confer various pharmacological activities. Although diverse in structure, phenolic meroterpenoids such as siccanin,³³ as well as pyrone-type meroterpenoids such as pyripyropene A,³⁴ have typical structures for polyketide-derived

meroterpenoids. That is, these compounds contain a cyclic ether moiety fused with a benzene or a pyrone ring (**Figure 2**). Thus, the construction of such cyclic ether moieties was undertaken to produce meroterpenoid-like compounds from diversity-enhanced extracts.

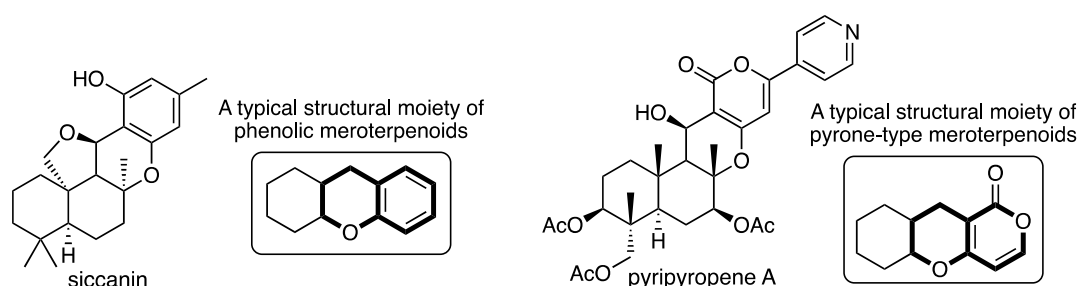
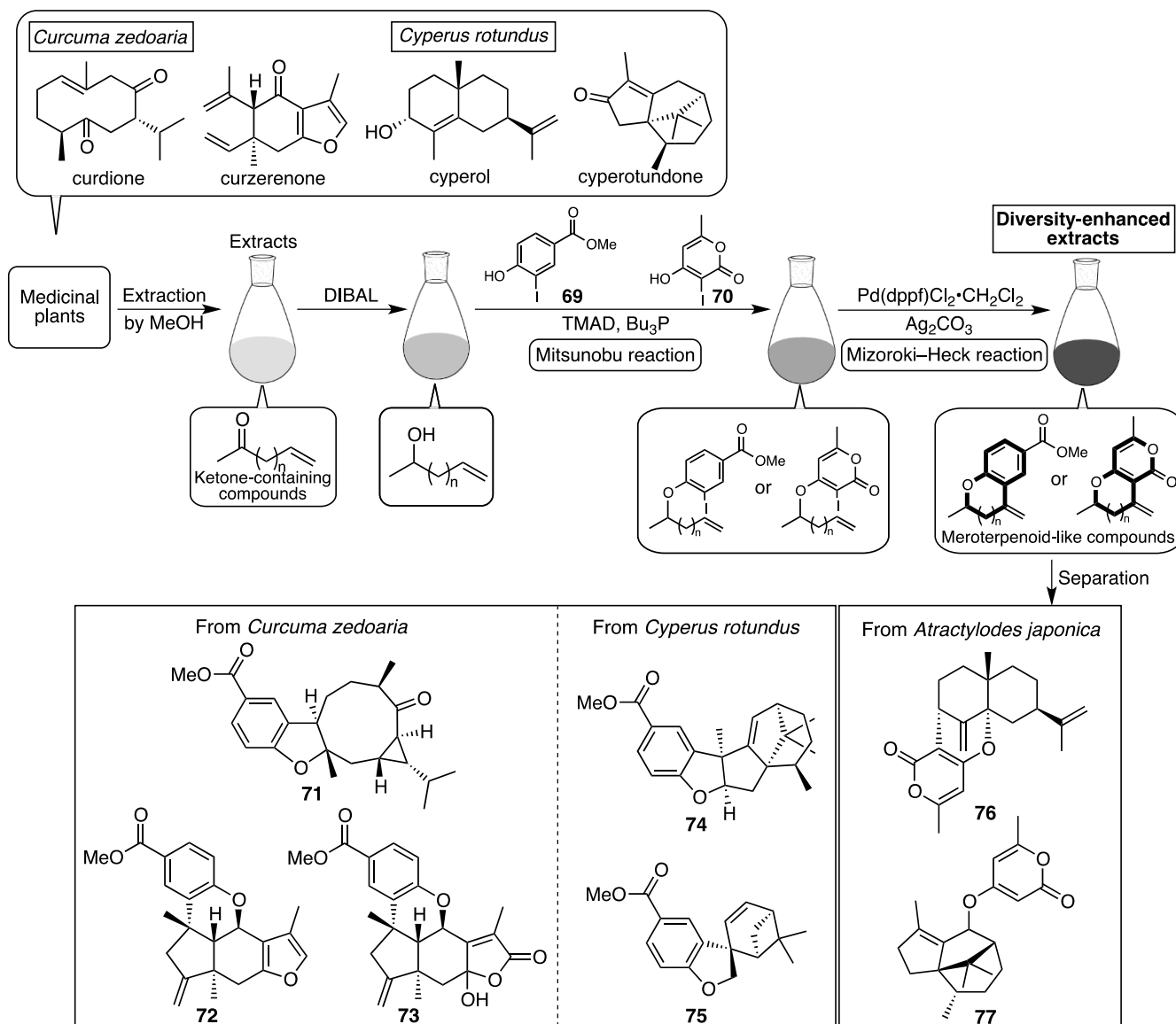


Figure 2. Typical structural moieties for polyketide-derived meroterpenoids

The traditional medicinal plant *Cyperus rotundus* contains sesquiterpenoids such as α -cyperone and cyperotundone (**Scheme 12**).³⁵ Methanol extracts of *C. rotundus* were treated with DIBAL to produce chemically reduced extracts. Next, the etherification of allyl alcohols with an *o*-iodophenol derivative (**69**) by the Mitsunobu reaction produced mixtures of aryl ethers. These were then subjected to intramolecular Mizoroki–Heck reaction conditions to obtain diversity-enhanced extracts containing compounds resembling phenolic meroterpenoids with cyclic ether moieties. On the other hand, the etherification of the chemically reduced extracts with an iodohydroxy- α -pyrone **70** instead of an iodophenol, and successive intramolecular Mizoroki–Heck reaction, produced diversity-enhanced extracts containing pyrone-type meroterpenoid-like compounds. *C. zedoaria*⁶ and *Atractylodes japonica*³⁶ are also traditional medicinal plants that are rich sources of sesquiterpenoids. Diversity-enhanced extracts containing meroterpenoid-like compounds were also prepared from the methanol extracts of these medicinal plants via similar procedures.

Separation of these diversity-enhanced extracts by repeated column chromatography provided phenolic meroterpenoids (**71–75**) and pyrone-type meroterpenoids (**76, 77**) (**Scheme 12**). These compounds have unique polycyclic ring systems, which have not yet been reported in natural products or synthetic compounds. Some of these compounds may be produced by unexpected reactions in addition to the Mitsunobu and Mizoroki–Heck reactions. For example, compounds **72** and **73** may be produced by the unexpected double Heck reactions of the iodophenyl ether derived from curzerenone, a main constituent of *C. zedoaria* (**Scheme 13A**). Compound **76** may be produced by an unexpected S_N2' -type Mitsunobu reaction and the subsequent Mizoroki–Heck reaction of cyperol, a main constituent of *C. rotundus* (**Scheme 13B**). Thus, these unexpected reactions enhance the diversity of the meroterpenoid library. Our research group is now screening the biological activities of these extracts.

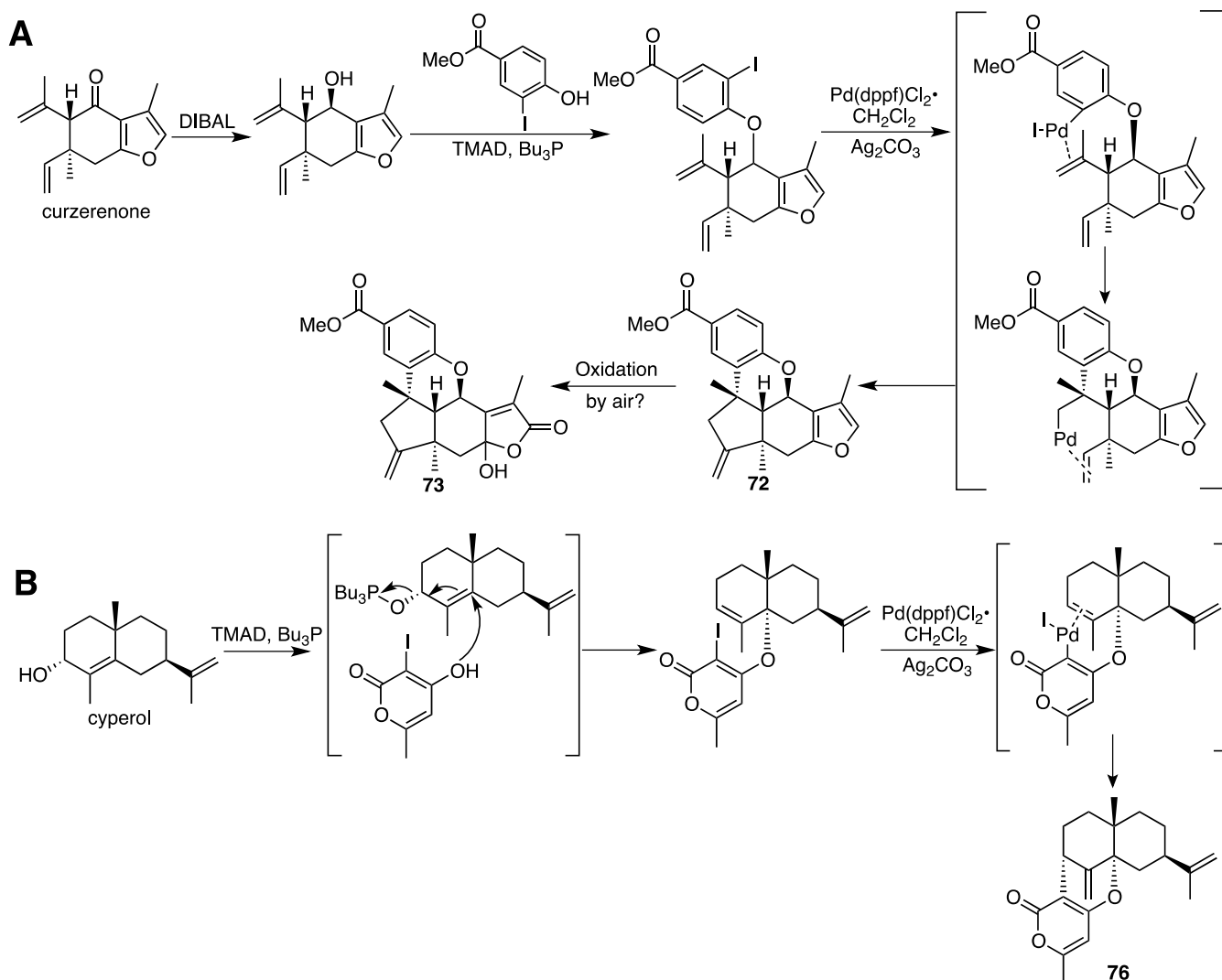


Scheme 12. Production of the meroterpenoid-like compounds isolated from the diversity-enhanced extracts of *C. zedoaria*, *C. rotundus*, and *A. japonica*

5. CONCLUSION

We have described the development for the production of diverse natural-product-like compounds by DOS and chemically derivatized natural extracts, including diversity-enhanced extracts.

The features of diversity-enhanced extracts that were developed by the authors were discussed. One advantage obtained by using diversity-enhanced extracts is that diverse natural-product-like compounds, which are difficult to obtain by other synthetic methods, can be obtained. In the preparation of diversity enhanced extracts, almost all compounds present in the natural extracts may be converted. Thus, unexpected unique compounds can be obtained by the conversion of minor or undiscovered components in natural extracts. Likewise, the unexpected conversion of components in natural extracts also results in the production of unexpected compounds. For example, compounds **42** and **47** obtained from the



Scheme 13. Plausible synthetic pathways for (A) phenolic meroterpenoids **72** and **73** and (B) a pyrone-type meroterpenoid **76**

diversity-enhanced extracts of *C. zedoaria* have highly oxidized and unprecedented scaffolds (**Scheme 5**). Although their origins are uncertain, they may be produced from minor components of *C. zedoaria*. Such compounds cannot be expected to be obtained by DOS based on isolated natural products.

The isolation of each natural-product-like compounds from the diversity-enhanced extracts seemed to be tedious in comparison with common chemical synthetic procedures, because they become complex mixtures including remaining reagents after diversity-generating reactions. However, only two or three successive column chromatography steps were necessary for the separation of these products, similar to the methods utilized for the isolation of common natural products. Methods such as solid-phase synthesis and fluororous synthesis should be investigated in order to improve the ease of separation.

On the other hand, there is a limited number of diversity-generating reactions, and the control of reaction conditions is difficult in the preparation of diversity-enhanced extracts because each compound of these natural extracts possess various functional groups. As such, if a natural compound is easily isolated from

a natural extract, it is more effective to apply the method of DOS based on the purified natural compound, as was introduced in Chapter 2, than it is to use the method of diversity-enhanced extracts. Nevertheless, the method of diversity-enhanced extracts is more effective than DOS based on natural products when the isolation of each compound from the natural extracts is difficult. A previous work reported that the isolation of many types of iridoid glucosides is very difficult,³⁶ but we were able to obtain iridoid-conjugated indole alkaloids by the use of diversity-enhanced extracts (**Scheme 10**). It is therefore important to properly apply both DOS and diversity-enhanced extracts.

In the future, the methodology for producing diversity-enhanced extracts will be applied to several natural resources, using a variety of diversity-generating chemical reactions, in order to create and discover new natural-product-like compounds that may be useful for drug discovery.

ACKNOWLEDGEMENTS

This work was supported in part by the Grants-in-Aid for Scientific Research (nos. 25350959 and 16H03279) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan; Platform Project for Supporting in Drug Discovery and Life Science Research (Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS)) from AMED under Grant Number JP17am0101095 and JP17am0101100; the Shorai Foundation for Science and Technology; Kobayashi International Scholarship Foundation; the Takeda Science Foundation; Suzuken Memorial Foundation; and the Uehara Memorial Foundation.

REFERENCES

1. D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, **2016**, *79*, 629.
2. M. Feher and J. M. Schmidt, *J. Chem. Inf. Comput. Sci.*, **2003**, *43*, 218.
3. (a) C. R. Pye, M. J. Bertin, R. S. Lokey, W. H. Gerwick, and R. G. Linington, *Proc. Natl. Acad. Sci. U.S.A.*, **2017**, *114*, 5601; (b) J.-L. Wolfender and E. F. Queiroz, *CHIMIA*, **2012**, *66*, 324; (c) J. W.-H. Li and J. C. Vederas, *Science*, **2009**, *325*, 161.
4. (a) M. J. Smanski, H. Zhou, J. Claesen, B. Shen, M. A. Fischbach, and C. A. Voigt, *Nat. Rev. Microbiol.*, **2016**, *14*, 135; (b) K. J. Weissman, *Nat. Prod. Rep.*, **2016**, *33*, 203; (c) E. Kim, B. S. Moore, and Y. J. Yoon, *Nat. Chem. Biol.*, **2015**, *11*, 649.
5. (a) S. L. Schreiber, *Science*, **2000**, *287*, 1964; (b) M. D. Burke, E. M. Berger, and S. L. Schreiber, *Science*, **2003**, *302*, 613; (c) M. D. Burke and S. L. Schreiber, *Angew. Chem. Int. Ed.*, **2004**, *43*, 46.
6. H. Kikuchi, K. Sakurai, and Y. Oshima, *Org. Lett.*, **2014**, *16*, 1916.
7. H. Kikuchi, K. Ichinohe, S. Kida, S. Murase, O. Yamada, and Y. Oshima, *Org. Lett.*, **2016**, *18*, 5948.
8. F. Lovering, J. Bikker, and C. Humblet, *J. Med. Chem.*, **2009**, *52*, 6752.

9. G. Appendino, G. C. Tron, T. Jarevång, and O. Sterner, [Org. Lett., 2001, 3, 1609](#).
10. B. R. Balthaser, M. C. Maloney, A. B. Beeler, J. A. Porco Jr., and J. K. Snyder, [Nat. Chem., 2011, 3, 969](#).
11. A. J. Grenning, J. K. Snyder, and J. A. Porco Jr., [Org. Lett., 2014, 16, 792](#).
12. R. W. Huigens III, K. C. Morrison, R. W. Hicklin, T. A. Flood Jr., M. F. Richter, and P. J. Hergenrother, [Nat. Chem., 2013, 5, 195](#).
13. R. J. Rafferty, R. W. Hichlin, K. A. Maloof, and P. J. Hergenrother, [Angew. Chem. Int. Ed., 2014, 53, 220](#).
14. Q.-F. Chen, F.-P. Wang, and X.-Y. Liu, [Chem. Eur. J., 2015, 21, 8946](#).
15. A. Garcia, B. S. Drown, and P. J. Hergenrother, [Org. Lett., 2016, 18, 4852](#).
16. N. G. Paciaroni, R. Ratnayake, J. H. Matthews, V. M. Norwood IV, A. C. Arnold, L. H. Dang, H. Luesch, and R. W. Huigens III, [Chem. Eur. J., 2017, 23, 4327](#).
17. H. Kikuchi, T. Nishimura, E. Kwon, J. Kawai, and Y. Oshima, [Chem. Eur. J., 2016, 22, 15819](#).
18. (a) H. Hikino, K. Meguro, Y. Sakurai, and T. Takemoto, [Chem. Pharm. Bull., 1965, 13, 1484](#); (b) H. Hikino, Y. Sakurai, H. Takahashi, and T. Takemoto, [Chem. Pharm. Bull., 1967, 15, 1390](#); (c) H. Hikino, Y. Sakurai, S. Numabe, and T. Takemoto, [Chem. Pharm. Bull., 1968, 16, 39](#).
19. (a) S. N. López, I. A. Ramallo, M. G. Sierra, S. A. Zacchino, and R. L. E. Furlan, [Proc. Natl. Acad. Sci. U.S.A., 2007, 104, 441](#); (b) L. Méndez, M. O. Salazar, I. A. Ramallo, and R. L. E. Furlan, [ACS Comb. Sci., 2011, 13, 200](#); (c) I. A. Ramallo, M. O. Salazar, L. Mendez, and R. L. E. Furlan, [Acc. Chem. Res., 2011, 44, 241](#); (d) M. O. Salazar, O. Micheloni, A. M. Escalante, and R. L. E. Furlan, [Mol. Divers., 2011, 15, 713](#); (e) P. García, I. A. Ramallo, M. O. Salazar, and R. L. E. Furlan, [RSC Adv., 2016, 6, 57245](#); (f) P. García, M. O. Salazar, I. A. Ramallo, and R. L. E. Furlan, [ACS Comb. Sci., 2016, 18, 283](#).
20. S. N. López, M. G. Sierra, S. J. Gattuso, R. L. Furlán, and S. A. Zacchino, [Phytochemistry, 2006, 67, 2152](#).
21. T. Kawamura, K. Matsubara, H. Otaka, E. Tashiro, K. Shindo, R. C. Yanagita, K. Irie, and M. Imoto, [Bioorg. Med. Chem., 2011, 19, 4377](#).
22. Z. Lin, X. Ma, H. Wei, D. Li, Q. Gu, and T. Zhu, [RSC Adv., 2015, 5, 35262](#).
23. (a) K. Tomohara, T. Ito, N. Hasegawa, A. Kato, and I. Adachi, [Tetrahedron Lett., 2016, 57, 924](#); (b) K. Tomohara, T. Ito, K. Furusawa, N. Hasegawa, K. Tsuge, A. Kato, and I. Adachi, [Tetrahedron Lett., 2017, 58, 3143](#).
24. (a) H. Kamauchi, T. Kon, K. Kinoshita, K. Takahashi, and K. Koyama, [Tetrahedron Lett., 2014, 55, 7203](#); (b) H. Kamauchi, K. Kinoshita, K. Takatori, T. Sugita, K. Takahashi, and K. Koyama, [Tetrahedron, 2015, 71, 1909](#); (c) H. Kamauchi, T. Kon, K. Kinoshita, K. Takatori, K. Takahashi,

- and K. Koyama, [Tetrahedron Lett.](#), 2015, **56**, 4377.
25. (a) G. A. Cordell, M. L. Quinn-Beattie, and N. R. Farnsworth, [Phytother. Res.](#), 2001, **15**, 183; (b) E. Vitaku, D. T. Smith, and J. T. Njardarson, [J. Med. Chem.](#), 2014, **57**, 10257; (c) V. Amirikia and M. Heinrich, [Phytochem. Lett.](#), 2014, **10**, 48.
26. E. D. Cox and J. M. Cook, [Chem. Rev.](#), 1995, **95**, 1797.
27. (a) T. Endo and H. Taguchi, [Yakugaku Zasshi](#), 1973, **93**, 30; (b) H. Inouye, S. Ueda, K. Inoue, and Y. Takeda, [Chem. Pharm. Bull.](#), 1974, **22**, 676.
28. T. Endo and H. Taguchi, [Chem. Pharm. Bull.](#), 1973, **21**, 2684.
29. T. Kubota and Y. Tomita, *Chem. Ind. (London)*, 1958, 229.
30. T. Arlette, G. Janine, R. Yves, and P. Jacques, *C. R. Acad. Sci. Ser. C*, 1979, **288**, 57.
31. J. L. Adams, J. Smothers, R. Srinivasan, and A. Hoos, [Nat. Rev. Drug Discov.](#), 2015, **14**, 603.
32. R. Geris and T. J. Simpson, [Nat. Prod. Rep.](#), 2009, **26**, 1063.
33. K. Hirai, S. Nozoe, K. Tsuda, Y. Iitaka, K. Ishibashi, and M. Shirasaka, [Tetrahedron Lett.](#), 1967, **8**, 2177.
34. S. Omura, H. Tomoda, Y. K. Kim, and H. Nishida, [J. Antibiot.](#), 1993, **46**, 1168.
35. (a) H. Hikino, K. Aota, and T. Takemoto, [Chem. Pharm. Bull.](#), 1965, **13**, 628; (b) H. Hikino, K. Aota, Y. Maebayashi, and T. Takemoto, [Chem. Pharm. Bull.](#), 1966, **14**, 1439.
36. H. Hikino, Y. Hikino, and I. Yoshioka, [Chem. Pharm. Bull.](#), 1962, **10**, 641.
-



Haruhisa Kikuchi is an associate professor at Graduate School of Pharmaceutical Sciences, Tohoku University. He graduated from Tohoku University in 1998, and then worked as a research associate in Tohoku University. He received Ph.D. degree from Tohoku University in 2005, and was appointed as an assistant professor in 2007 and an associate professor of Tohoku University in 2009. He received Award of 46th Symposium on the Chemistry of Natural Products in 2004, Award for Young Scientists of Tohoku Division of The Pharmaceutical Society of Japan in 2006, MCS Award, Division of Medicinal Chemistry, The Pharmaceutical Society of Japan in 2013. His research interests include the development of new methodologies producing diverse natural products and natural product-like compounds for drug discovery.



Prof. Yoshiteru Oshima is a specially appointed professor of Graduate School of Medicine, Tohoku University. He received his Ph.D. in 1981 from Tohoku University under the direction of (the late) Professor Hiroshi Hikino. Then, he worked natural product chemistry as an assistant professor in the same laboratory and was appointed as Professor at the Graduate School of Pharmaceutical Sciences, Tohoku University in 1996. He retired from Tohoku University in 2018.