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Synthetic studies on biologically active natural products with potential as agrochemicals

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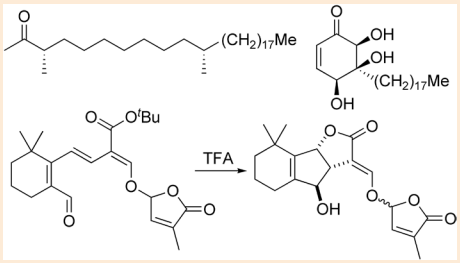
The chemical synthesis of biologically active natural products has diverse objectives and missions, including 1) determining the structures of the natural products, 2) providing synthetic samples for studying the activity and function, 3) providing a basis for applied research on these compounds, *etc*. I have studied various biologically active natural products and conducted synthetic studies on these compounds with various objectives. In this review, I present the results of my research, focusing on natural products with potential as agrochemicals.



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Introduction

It is extremely difficult for an ordinary academic researcher to "independently" develop a novel medical or agrochemical product. The reasons for this need no explanation. However, it is also true that there is an abundance of biologically active natural products with potential as agrochemicals. Therefore, it may be possible to contribute to the advancement of pesticide science or the development of agrochemicals by studying these compounds. The author has been engaged in synthetic studies on biologically active natural products for more than 35 years. Through these studies, I have provided several research results that could contribute to crop protection, if only we could ignore their feasibility. I would like to present some examples in this review, focusing on synthetic studies that I have performed bioassays.

1. Insect Pheromones

Pheromones, defined as semiochemicals (signal substances) that act between other individuals within the same species, play a very important role in chemical communication among organisms, especially in Insecta. It is well known that the properties of pheromones can be effectively exploited for pest management. However, since pheromones exist in nature in extremely small quantities, organic synthesis is considered necessary to provide pheromones for practical use. When discussing pheromone synthesis, no one can ignore Prof. Kenji Mori, the giant in this field.[1)] Since I am one of the graduates of Prof. Mori's school, I naturally started my own research career in pheromone synthesis.

1.1. Synthesis of the sex pheromone of the German cockroach

From all my 17 pheromone-related papers, I will select the most important pheromone synthesis "for me" and describe what this synthesis has taught not only to me, but also to us. The sex pheromone of the German cockroach *Blattella germanica*, one of the most famous sanitary pest insects, has been studied for a long time. In brief, 3,11-dimethyl-2-nonacosanone (**1**) was identified as the major component of the sex pheromone,[2)] and its absolute configuration was determined to be 3*S*,11*S* by Mori's synthesis.[3)] Among insect pheromones, which are well known for strict recognition of stereochemistry, this sex pheromone is quite exceptional because its four possible stereoisomers have been found to exhibit approximately equal biological activity. However, Mori-sensei was somewhat skeptical about this

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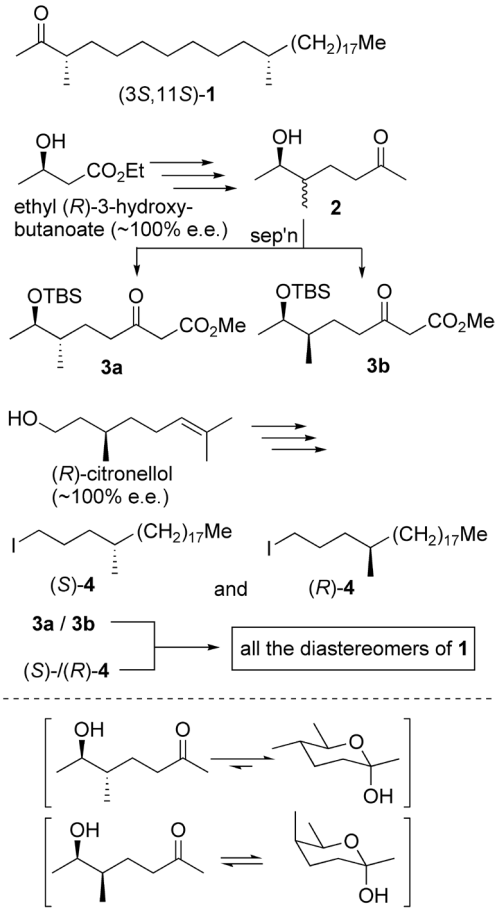


Scheme 1. Synthesis of the sex pheromone of the German cockroach (**1**).

structure–activity relationship (SAR) because the enantiomeric purity of the starting material used for this synthesis was 92% e.e. Thus, at the age of 22, I was given the task of synthesizing all the stereoisomers of **1** as pure as possible. As shown in Scheme 1, our synthesis commenced with two enantiomerically pure starting materials, ethyl (*R*)-3-hydroxybutanoate and (*R*)-citronellol. The highlight of this synthesis was the separation of the diastereomers of **2** based on intramolecular hemiacetalization (Scheme 1, bottom), which was my introduction to the joy and excitement of organic synthesis. Finally, we completed the synthesis of all four diastereomers of **1** in enantiomerically and diastereomerically pure states.[4] Subsequently, classical behavioral bioassays confirmed the previously reported SAR. However, later detailed electroantennogram (EAG) studies revealed a more surprising result that the natural (3*S*,11*S*)-isomer is less active than the other three stereoisomers at the very low concentrations found in nature.[5] To the best of our knowledge, such a SAR result was unprecedented, and even Mori-sensei did not expect it at all.

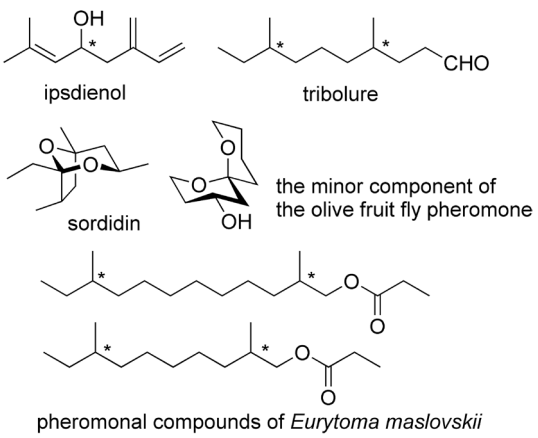


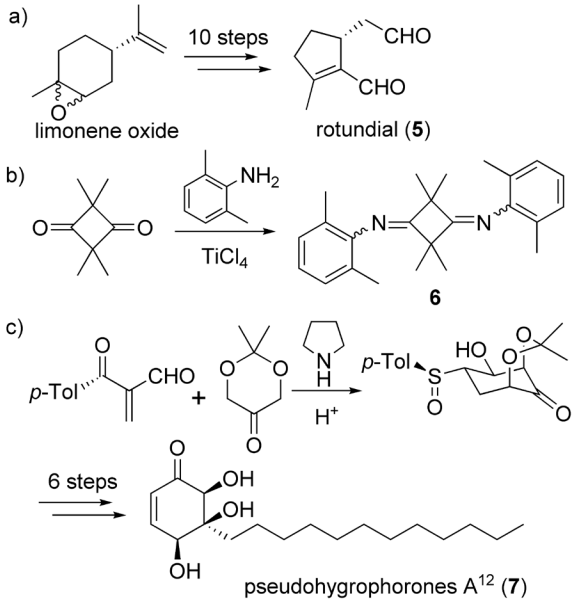
Fig. 1. Structures of other pheromones.

1.2. Others

Many other pheromone syntheses have been accomplished (Fig. 1); however, due to space limitations, I will only cite the original papers for a few syntheses here.[6–10]

2. Plant-derived and/or crop-protection-related natural products

Every natural product chemist knows that plants produce a wide variety of secondary metabolites. It is also known that a considerable number of them have potential as agrochemicals. It is also well known that many groups of compounds in natural products derived from other species, such as microorganisms, can be exploited for crop protection. However, the profiles of these compounds have rarely been studied in detail, and one of the main reasons for this is the scarcity of naturally occurring compounds. I have been engaged in synthetic studies on a group of compounds that show potential as agrochemicals and will present some of these results for which we have performed bioassays.



Scheme 2. Synthesis of **5**, **6**, and **7**.

2.1. *Synthesis of rotundial*

Rotundial (**5**) is a novel natural mosquito repellent isolated from the medicinal plant *Vitex rotundiforia*, and its mosquito repellent activity has been reported to be superior to that of *N*,*N*-diethyl-*m*-toluamide (Deet®), the best known and most widely used insect repellent.[11] We synthesized both enantiomers of **5** by starting from (*R*)/(*S*)-limonene oxide (Scheme 2, top).[12] Bioassays of the synthesized enantiomers of **5** showed that there is no significant difference in mosquito repellent activity between the enantiomers and also that their activity is not very potent.

2.2. *Synthesis of 2,2,4,4-tetramethyl-N,N′-bis(2,6-dimethylphenyl)cyclobutene-1,3-diimine*

In 1993, Miles *et al.* isolated 2,2,4,4-tetramethyl-*N*,*N*'-bis(2,6-dimethylphenyl)cyclobutene-1,3-diimine (**6**) from *Arundo donax* as an antifeedant against the ball weevil (*Anthomus grandis*).[13] At first glance, the structure of compound **6** is so unusual for a natural product that it is hard to believe that this compound exists in nature. One-step synthesis of **6** was successfully performed by condensation of 2,2,4,4-tetramethylcyclobutane-1,3-dione and 2,6-dimethylaniline (Scheme 2, middle), and several diimine analogs were also prepared in the same manner. Bioassays of the synthesized **6** and its analogs showed that none of them exhibited any definite antifeedant activity.[14]

2.3. *Synthesis of pseudohygrophorone A*[12]

In 2016, pseudohygrophorone A[12] (**7**) was isolated from the fruiting bodies of the basidiomycete *Hygrophorus abieticola*[15] and reported to exhibit potent antibacterial activity against *Septoria tritici*, *Botrytis cinerea*, and *Phytophthora infestans*. As shown in Scheme 2 (bottom), our enantioselective synthesis of **7** featured the diastereoselective Michael-aldol cascade cyclization as the key reaction. Biological evaluation of the synthetic **7** and other derivatives against *S. tritici*, *B. cinerea*, *P. infestans*, *etc.* revealed that the anti-phytopathogenic activity of synthetic (+)-**7**, the natural enantiomer, was moderate but considerably higher than that of synthetic (±)-**7**.[16]

2.4. *Others*

A considerable number of plant-derived natural products and/or natural products with crop protection potential have been synthesized during my research career (Fig. 2). However, due to space limitations, I will only cite the original papers for some of these syntheses.[17–25]

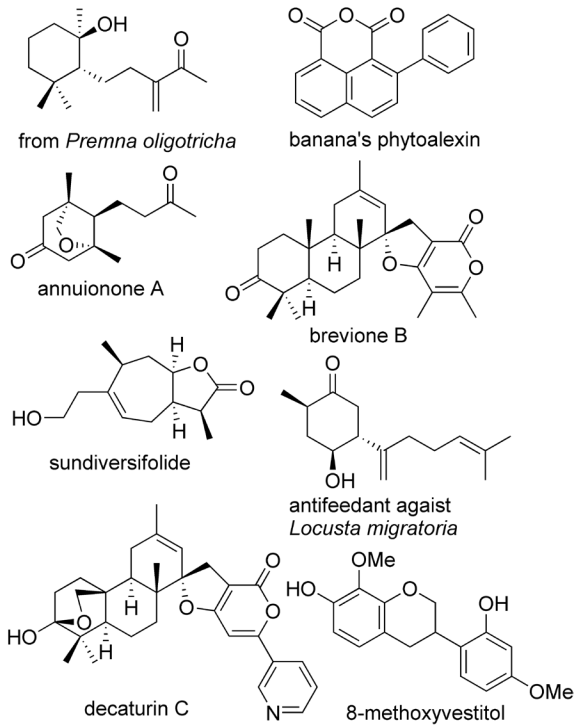


Fig. 2. Structures of other plant-derived and/or crop-protection-related compounds.

3. Strigolactones

Strigolactone (SL) is the collective name for a group of apocaronoids isolated as germination stimulants for the seeds of root parasitic weeds, such as *Striga* and *Orobanche* spp. However, SLs are now recognized not only as rhizosphere semiochemicals but also as plant hormones. SLs have received the most attention in the field of plant natural product chemistry, although a detailed discussion or explanation of this interest in SLs will not be presented here. I have been engaged in SL research for more than 15 years with the following three keywords in mind: synthesis, application, and biosynthesis. Therefore, I would like to present our achievements very briefly.

3.1. *SLs as synthetic targets*

I have already reported more than 10 original papers on the synthesis of natural and pseudo-natural SLs (Fig. 3). However, due to space limitations, I will not mention them here, so please refer to selected references.[26–31]

3.2. *Induction of suicidal germination*

As mentioned above, SLs are a group of semiochemicals that induce seed germination of root parasitic weeds. Since the 1970s, it has been proposed that this intrinsic ability of SLs can be ex-

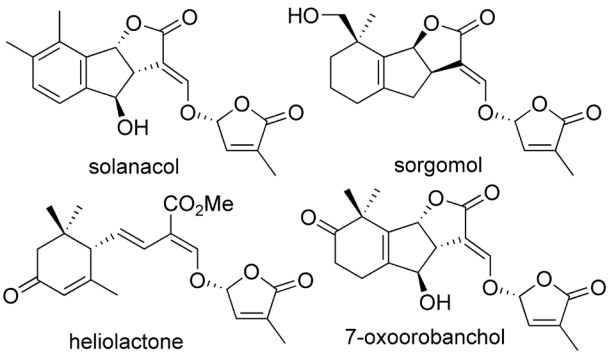


Fig. 3. Structures of synthetic target SLs.

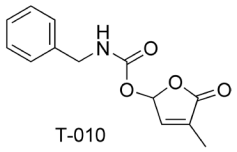
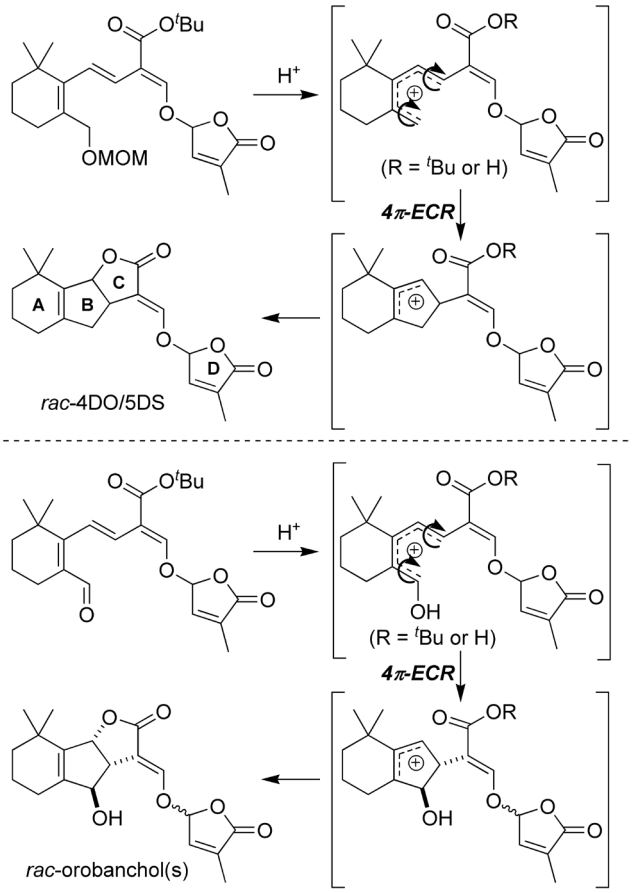


Fig. 4. Structure of T-010.

ploited to control root parasitic weeds. The core of this proposal is "suicidal germination," which refers to a concept and methodology for artificially germinating the seeds of parasitic weeds by applying SL (or its analogs) in an environment where no host is present and killing the weeds. To realize this concept, it has been considered necessary to develop SL analogs with simpler structures than SLs, because SLs are rare in nature and not easy to synthesize. Unfortunately, at the same time, this method of weed control has been considered to have low feasibility for various reasons. However, the Kobe University team, including myself, made a breakthrough in this field. Namely, by rejecting the widely accepted hypothesis on the mechanism of SL perception,[32] this team created novel analogs with a dramatically simplified structure.[33] As a result, the developed carbamate analog, codenamed T-010 (Fig. 4), was effective in controlling parasitic weeds in field trials conducted in Sudan.[34] Thus, parasitic weed control through "suicidal germination," which had been considered as an unfeasible concept, proved to be a methodology that could implemented in practice.



Scheme 3. Acid-mediated cascade cyclization to 4DO/5DS (top) and orobanchol(s) (bottom).

3.3. Insight into SL biosynthesis

Since SLs have attracted considerable attention for their diverse functions, their biosynthesis has been extensively studied. However, until recently, the process of BC-ring formation, which constructs the basic skeleton of canonical SL, has remained a mystery. Therefore, in order to gain insight into this unexplored cyclization, I dreamed of attempting the BC-ring formation "in flask" and consequently succeeded in synthesizing *rac*-4DO/5DS[35] and also *rac*-orobanchols[36] *via* acid-mediated cascade cyclization (Scheme 3). I believe that this acid-mediated cascade cyclization is based on 4π-ECR and is quite similar to that *in planta*. These results are crucial to the overall understanding of SL biosynthesis. In other words, what we have achieved here are the syntheses that anticipate our understanding of biosynthesis and are thus fundamentally different from the usual biomimetic or bioinspired synthesis. Incidentally, the acid-mediated cascade cyclization performed in these biosynthesis-oriented studies was employed for the novel and efficient synthesis of not only *rac*-orobanchol[31] but also optically active orobanchols.[37]

Concluding remarks

The chemical synthesis of biologically active natural products has diverse meanings and purposes, and its ultimate goal may be to contribute to human welfare. From this point of view, one of the best possible outcomes would be for our research to lead directly to the development of novel medical or agrochemical products. However, it is well known that it is extremely difficult for an ordinary academic researcher to achieve this goal, and I have not been actively engaged in research aimed at practical application and social implementation. Rather, as a synthetic organic chemist or natural product chemist, I have studied biologically active natural products from the perspective of curiosity-driven research. Therefore, to be honest, I am not proud that our research results have contributed to the progress of pesticide science. Nevertheless, I would be happy if our research results were recognized as making even a small contribution to the advancement of pesticide science.

Acknowledgements

I would like to express my deepest gratitude to the late Prof. Kenji Mori and Prof. Mitsuru Sasaki, who introduced me to the field of chemistry and pesticide science, respectively. I also thank all those who gave me the opportunity to start and/or develop this series of research and all the people and organizations that supported my research. I would also like to express my sincere gratitude to all my collaborators, especially my students, who have worked and sweated to realize my ideas and plans (and sometimes a kind of fantasy). Finally, I would like to thank my wife Aya, my son Ryotaro, and my daughter Nozomi, who have supported me over the years and whose very existence is a driving force within me.

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