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Introduction—Biofunctional Molecules and Organic Synthesis

Synthetic organic chemistry is a discipline different from biology. The former, however, can be a very useful tool to solve problems in biology. This chapter explains the reason why organic synthesis is useful in the studies of biofunctional molecules, and also details the ideas and techniques employed in the synthesis of biofunctional molecules.

1.1 What are biofunctional molecules?

Biofunctional molecules are those compounds that control such characteristics of organisms as differentiation, growth, metamorphosis, homeostasis, aggregation and reproduction. Both small molecules and macromolecules are used as biofunctional molecules. Chemical synthesis of small biofunctional molecules will be the subject of this book, because I have been engaged in the chemical synthesis of small biofunctional molecules (molecular weight less than 1000) for half a century.

Biofunctional natural products with low molecular weights are classified as shown in Table 1.1. Chemical studies on vitamins, hormones and antibiotics started in the first half of the 20th century, while those on semiochemicals began in the middle of the 20th century. This book treats the chemical synthesis of hormones, pheromones and other bioregulators such as allelochemicals.

1.2 Developmental stages of studies on biofunctional molecules

Let us first consider the process by which the investigation of a biofunctional molecule develops. As shown in Figure 1.1, the careful observation of a biological phenomenon together with speculation on the cause of that phenomenon make up the first step in the discovery of a biofunctional molecule. In the studies on the plant-growth hormone gibberellin, the first step was the observation in Japan in 1898 that the infection of rice seedlings by fungus *Gibberella fujikuroi* causes elongation of the seedlings to bring about the so-called “bakanaé” (= foolish seedlings)\(^1\) disease, a destructive pest that reduces the yield of rice in Asia.\(^1\)
Table 1.1 Classification of biofunctional molecules

<table>
<thead>
<tr>
<th>Name</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamins</td>
<td>Biofunctional molecules that are taken in as food constituents; being essential to the proper nourishment of the organism. Derived from <em>vita</em> (L.) = life + amine</td>
</tr>
<tr>
<td>Hormones</td>
<td>Biofunctional molecules that are secreted and pass into the target organ of the same individual. Derived from <em>horman</em> (Gk.) = stir up</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Biofunctional molecules mainly of microbial origin that kill other micro-organisms. Derived from <em>anti</em> (Gk.) = against + <em>bios</em> (Gk.) = made of life</td>
</tr>
<tr>
<td>Semiochemicals</td>
<td>Biofunctional molecules that spread information between individuals. (They are also called signal substances.) Derived from <em>semio</em> (Gk.) = sign</td>
</tr>
<tr>
<td>(a) Pheromones</td>
<td>Biofunctional molecules that are used for communication between individuals within the same species. Derived from <em>pherein</em> (Gk.) = to carry + <em>horman</em> (Gk.) = stir up</td>
</tr>
<tr>
<td>(b) Allelochemicals</td>
<td>Biofunctional molecules that are used for communication between individuals belonging to different species. Derived from <em>allelon</em> (Gk.) = of each other</td>
</tr>
<tr>
<td>(1) Allomones</td>
<td>Biofunctional molecules that evoke advantageous reactions for their producers. Derived from <em>allos</em> (Gk.) = other</td>
</tr>
<tr>
<td>(2) Kairomones</td>
<td>Biofunctional molecules that evoke advantageous reactions for their receivers. Derived from <em>kairo</em> (Gk.) = opportune</td>
</tr>
<tr>
<td>(3) Synomones</td>
<td>Biofunctional molecules that evoke advantageous reactions for both their producers and receivers. Derived from <em>syn</em> (Gk.) = together with</td>
</tr>
</tbody>
</table>

Figure 1.1 Developmental stages of studies on biofunctional molecules: each stage is mutually interrelated with other stages

The second stage of the research is to prove the participation of a biofunctional molecule in that specific phenomenon. In gibberellin research, Kurosawa proved that small biofunctional molecules produced by *G. fujikuroi* caused the elongation of rice seedlings.2

Then, the third and crucial stage comes: the isolation and structure elucidation of the biofunctional molecules responsible for the phenomenon. In 1938, Yabuta and Sumiki isolated the plant hormone
gibberellins as crude crystals, which elongated rice seedlings.\textsuperscript{3} The correct gross structure of gibberelin A\textsubscript{3} (1, Figure 1.2) was proposed by Cross \textit{et al.} in 1959.\textsuperscript{4} With the established structure of a biofunctional molecule, one can proceed with further chemical or biological research. Chemists and biologists begin to clarify the biosynthesis, biodegradation and the mode of action of that biofunctional molecule. On the other hand, synthetic chemists attempt the synthesis of that compound. In the case of the gibberellins, their synthesis was undertaken by many groups, culminating in total synthesis by Nagata,\textsuperscript{5} Corey,\textsuperscript{6} Mander,\textsuperscript{7,8} Yamada and Nagaoka,\textsuperscript{9} Ihara and Toyota,\textsuperscript{10} and others. Mori’s relay synthesis of (\pm)-gibberellin A\textsubscript{4} (2) in 1969 was an early success in this area.\textsuperscript{11} As to the biosynthesis, biodegradation and mode of action of the gibberellins, chemists and biologist have been involved for many years.\textsuperscript{12}

Finally, application of a particular biofunctional molecule in agriculture and other bioindustries or health care and medicine is the practical goal of the research. Chemists will synthesize many analogs and derivatives, and biologists will evaluate their biological effects. If one can find a useful compound, it will be commercialized for practical application. For example, gibberellin A\textsubscript{3} (1) is used in Japan to produce seedless grapes.

1.3 \textbf{Small amounts of the samples are now sufficient for the elucidation of the structures of biofunctional molecules}

Thanks to the development of microanalytical techniques and efficient separation methods, it is now possible to determine the structure of a biofunctional molecule with less than 1 mg of the material. In Table 1.2, examples are given with regard to the amounts of the samples employed for the structure elucidation of biofunctional molecules.

When Butenandt \textit{et al.} studied bombykol (3), the female sex pheromone of the silkworm moth (\textit{Bombyx mori}) in 1961, they isolated 12 mg of the crystalline 4-(\textit{p}-nitrophenylazo)benzoate of bombykol (3) from half a million pheromone glands of the female silkworm moth obtained from more than a million silkworm cocoons bought in Germany, Italy and Japan.\textsuperscript{13} A highly recommendable account of the reflection on the study of bombykol was published by Hecker and Butenandt.\textsuperscript{14} More recent examples\textsuperscript{15–19} in Table 1.2 show that the structures have been clarified even with microgram quantities.

A unique example of structural identification of a biofunctional molecule was reported recently by Hughson and coworkers in 2002.\textsuperscript{19} Autoinducer-2 (AI-2) is a universal signal for interspecies communication (quorum sensing) in bacteria, which allows bacteria to coordinate gene expression. The structure of AI-2 remained elusive until 2002, when the X-ray crystallographic analysis of AI-2 sensor protein (Lux P) in a complex with AI-2 was successfully carried out. As shown in Table 1.2, the bound ligand AI-2 was a furanosyl borate diester 8.\textsuperscript{19} In this particular case, the structure of a biofunctional molecule could be elucidated even without isolating it.
### Table 1.2 Amounts of the samples employed for the structure elucidation of some biofunctional molecules

<table>
<thead>
<tr>
<th>Researchers and year of the work</th>
<th>Name of compound</th>
<th>Structure(^a)</th>
<th>Amounts of sample (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butenandt et al.(^{13}) 1961</td>
<td>Bombykol (pheromone of Bombyx mori)</td>
<td><img src="image1" alt="Structure 1" /></td>
<td>12 (as a derivative)</td>
</tr>
<tr>
<td>Röller et al.(^{15}) 1967</td>
<td>Juvenile hormone I (from Hyalophora cecropia)</td>
<td><img src="image2" alt="Structure 2" /></td>
<td>0.3</td>
</tr>
<tr>
<td>Persoons et al.(^{16}) 1976</td>
<td>Periplanone-B (pheromone of Periplaneta americana)</td>
<td><img src="image3" alt="Structure 3" /></td>
<td>0.2</td>
</tr>
<tr>
<td>Oliver et al.(^{17}) 1992</td>
<td>Pheromone of Biprorulus bibax</td>
<td><img src="image4" alt="Structure 4" /></td>
<td>0.075</td>
</tr>
<tr>
<td>Wakamura et al.(^{18}) 2001</td>
<td>Posticlure (pheromone of Orgyia postica)</td>
<td><img src="image5" alt="Structure 5" /></td>
<td>0.01</td>
</tr>
<tr>
<td>Hughson et al.(^{19}) 2002</td>
<td>Al-2 (bacterial quorum-sensing signal)</td>
<td><img src="image6" alt="Structure 6" /></td>
<td>trace</td>
</tr>
</tbody>
</table>

\(^a\)Except for \(^8\), the stereostructures including cis/trans-isomerism were determined later by synthesis.

### 1.4 Why must biofunctional molecules be synthesized?

One may think that there is no need for the synthesis of biofunctional molecules, because they always exist in organisms, and can be extracted and isolated. This is quite untrue, because the amounts of biofunctional molecules in organisms are usually very small. Due to their extremely low concentrations effective in organisms, biofunctional molecules can be isolated only in very small amounts, as shown in Table 1.2. It is therefore impossible to isolate hormones, pheromones and other bioregulators in gram quantities.

The limited availability of biofunctional molecules often makes it difficult to determine their precise stereostructures at the time of isolation. Accordingly, synthesis has become important as a tool to determine the structures of biofunctional molecules unambiguously. Advances in analytical techniques enabled chemists to propose the structures of biofunctional molecules even when they are available in extremely small quantities. Because of that, synthesis has become even more important than ever.

When we want to use biofunctional molecules practically in agriculture or medicine, of course we have to provide them in quantity. Organic synthesis is a method of choice for their large-scale production together with biotransformation and fermentation. More importantly, organic synthesis can provide useful
compounds with better utility than the natural products themselves. Therefore, we must synthesize biofunctional molecules. Only after sufficient supply of the materials, biologists can examine their bioactivities in full depth. Biologists are always waiting for the cooperation and service of synthetic chemists.

1.5 How can we synthesize biofunctional molecules?

1.5.1 What is synthesis?

Synthesis is a process by which we can convert a simple compound $A$ to a more complicated compound $B$. For that purpose we must employ an appropriate chemical reaction $C$. Synthesis is therefore a function involving the three parameters $A$, $B$, and $C$. There are three kinds of synthetic studies.

(a) Synthesis with a fixed target molecule $B$. Synthesis of natural products is the typical example in this category. Many of the syntheses in this book belong to this category.

(b) Synthesis with a fixed starting material $A$. In industries, it is always necessary to think about a clever new use of cheap starting materials in-house.

(c) Synthesis as achieved by using a particular reaction $C$. Discoverers of new reactions usually attempt to determine the scope and limitations of their new reactions by applying them to the synthesis of a certain target molecule. People in academia quite often work along this line.

Of course there is another type of synthesis. That is synthesis of any kinds of target molecules from any kinds of starting materials to generate compounds with the desired physical or biological properties. This is the way popular in materials science and medicinal chemistry.

1.5.2 What kind of consideration is necessary before starting a synthesis?

In synthesizing biofunctional molecules, one must select a target molecule. There are a number of criteria for selecting a target. The impact and significance of the synthetic achievement must be taken into consideration. What kind of target can be regarded as the one with a great impact? It quite often depends on personal taste. It may happen that a target is chemically interesting but biologically nonsense or vice versa. So, like paintings, one and the same synthetic achievement can be highly appreciated by a certain fraction of chemists, while it can be disputed by others. Accordingly, the choice of a target molecule reflects the taste of the chemist who works with that target. There is no other way than to choose one’s favorite molecule as the target. However, it happens that someone requests you to synthesize a sample for him or her. In my experience, such a request quite often brings about an interesting result. Chemists should be flexible to respond to others.

Next, one must choose the starting material(s). All the synthesis starts from readily available commercial products. It is therefore important for a chemist to look at catalogs of big reagent manufactures like Aldrich. By reading catalogs we can have knowledge on the prices of many possible starting materials. It is also important to be familiar with the industrial intermediates in the chemical and pharmaceutical industries. We may be able to obtain such intermediates by the courtesy of people in these industries.

Then, it is the time to make a gross plan of the synthesis. One must decide the key reaction to be employed. In the case of an enantioselective synthesis, the timing of introducing the required asymmetry correctly is always of great importance. Of course, one must think about each of the steps, and the order must be fixed by which each step is to be executed. There are many possible synthetic routes for a biofunctional molecule. At the beginning it is not so easy to devise the best route. Through experimentation
one can determine realistic routes. If a certain step does not go as expected, one must reconsider and modify
the synthetic route. Finally, one can make the target molecule. In many cases, if one can dream it, one
can make it.

1.5.3 Synthon

According to Corey, *synthon* is defined as structural units within a molecule that are related to possible
synthetic operations. Some people recently regard a synthon as a synonym of a building block. This is
different from Corey’s original usage.

So as to understand the concept of synthon, let us analyse the synthesis of keto ester A in Figure 1.3.
There are many different ways to disconnect the C–C bond in A, and eight structural units (a)–(h)
are conceivable as possible synthons. Disconnection of a target molecule to possible synthons is called
*retrosynthetic analysis*. If there is a reaction to connect the possible synthons to build up A, then we
can select realistic synthons. In the case of A, (d) and (e) are two synthons, which can be connected by
employing the Michael addition.

Retrosynthetic analysis is the basic operation in planning organic synthesis. Knowledge on synthetic
reactions and insight to determine a useful reaction are of basic importance in planning synthesis. The
higher the number of synthons in a target molecule, the more difficult it is to synthesize. Corey emphasizes
in depth the importance of retrosynthetic analysis.21

1.5.4 Molecular symmetry and synthesis

Recognition of explicit or implicit symmetry in a target molecule often simplifies its synthetic plan. A
classic and well-known example, as shown in Figure 1.4, is the synthesis of (±)-usnic acid (9) by Barton
*et al.*22 A lichen constituent usnic acid is dissymmetric at a glance. But by employing oxidative coupling
reaction of phenols, usnic acid (9) can be dissected into a single starting material.

Our synthesis of magnosalicin (10), a medicinally active principle from a plant Magnolia salicifolia,
was achieved in a single step, as shown in Figure 1.5, considering the symmetry of the molecule.23 The
details of this synthesis will be discussed later in Section 2.4.2.

1.5.5 Criteria for ‘A Good Synthesis’

It sometimes happens that over twenty or thirty different syntheses are published for a single biofunctional
molecule, because so many different synthetic routes are possible for that target. Then, how can we regard

![Figure 1.3 Retrosynthetic analysis: disconnection of A to give two synthons (d) and (e)](image)
a single one of the syntheses as superior to others? This is a good question, just like it is difficult to judge a painting, a composition or a novel to be better than others. Personal tastes of a researcher as a designer are always reflected on his or her achievements. The following three points, however, are the prerequisites for a particular synthetic plan to be judged as a good one.

(a) Each step of the synthesis proceeds with a good yield. Highly efficient regio- and stereoselective reactions must be employed.

(b) As to the pivotal step in a synthetic route, there should be available an alternative method to achieve that transformation. Otherwise, the synthesis may come to a dead end, and a graduate student as a practitioner may not be able to get his or her Ph.D. degree.

(c) The simpler the synthetic route, the better the synthesis. This is my own view.

In order to achieve an efficient synthesis, a convergent route is always preferred to a linear route. In the case of a linear route, as shown in the left part of Figure 1.6, the starting material A will be converted to the final product ABCDEFGH through seven steps in a linear sequence. With this linear route, the overall yield of the final product will be 48% even in the case in which the yield of each step is 90%. Usually, the yield of each of the seven steps may be 70%. Then, the overall yield will drop to only 8%. If the yield of each step is 50%, the overall yield will result in a miserable figure of only 1%. As shown in the right part of Figure 1.6, a convergent route generates blocks like AB, CD, EF and GH. Then, these will be connected twice to give the final product. The necessary steps to complete this convergent synthesis
are the same seven steps. But the overall yield of the convergent route can be surprisingly better than what can be realized by the linear route. Thus, when each step can give the next product in 90% yield, the overall yield will be as high as 73%. Even in the case when the yield of each step is 50%, the overall yield of the convergent route will remain as still acceptable 13%. It is clear that a convergent synthesis is more efficient than a linear synthesis.

Recognition of possible synthons in a target molecule is the most important factor to make its synthesis simple or complicated. Let us compare the efficiency and simplicity of three different syntheses of (8E,10E)-8,10-dodecadien-1-ol (11), the female-produced sex pheromone of the codling moth, *Cydia pomonella*. This moth is a notorious pest of apple orchards.

Figure 1.7 summarizes the synthesis of 11 reported by Descoins and Henrick in 1972.24 In their retrosynthetic analysis, they dissected 11 into two parts by breaking the C–C bond between C-5 and C-6. Cyclopropyl bromide was converted to 3,5-heptadienyl bromide (A), while tetrahydropyran furnished another building block B. Coupling of the Grignard reagent C derived from B with A in the presence of lithium tetrachlorocuprate was followed by the removal of the THP protective group to give 11. The pure pheromone 11 was found to be crystalline, and could be purified by recrystallization. This synthesis is convergent. But the two starting materials are expensive, and the synthetic route is not short enough for economical manufacturing of 11.

Mori’s synthesis of 11 in 1974 was also convergent, as shown in Figure 1.8.25 In this synthesis, the C–C bond at between C-6 and C-7 was disconnected to enable the use of two cheap C6 starting materials, sorbic acid and hexane-1,6-diol. The former was converted to the building block A, while the latter was
converted to another building block B. Coupling of the Grignard reagent prepared from B with A yielded 11 after deprotection.

Further improvement of Mori’s synthesis was reported by Henrick in 1977 (Figure 1.9). Coupling of (2E,4E)-2,4-hexadienyl acetate (A) with the Grignard reagent B yielded the desired and crystalline product 11 in 60–70% overall yield based on (2E,4E)-2,4-hexadien-1-ol. This convergent synthesis was employed
for the commercial production of 11. Improvement of a synthetic manufacturing process, so-called “process chemistry”, is important in realizing the practical use of biofunctional molecules.

1.6 What kind of knowledge and techniques are necessary to synthesize biofunctional molecules?

Of course, knowledge in synthetic reactions and techniques in organic experiments including purification methods are essential requirements to execute synthesis of biofunctional molecules. However, two additional things must be learned.

1.6.1 Stereochemistry and reactivity

Many biofunctional molecules are chiral and nonracemic. It is therefore important to know the relationship between stereochemistry and reactivity. Let us examine the following two examples.

We first think about the different reactivities of axial and equatorial isomers through the examples shown in Figure 1.10. Esters 12 and 13 are called methyl 4-epidehydroabietate (12) and methyl dehydroabietate (13). Dehydroabietic acid can be esterified with methanol and sulfuric acid to give 13, while 4-epidehydroabietic acid cannot be esterified under the same conditions. Ester 12 can be prepared only through methylation with diazomethane. Although ester 13 can be hydrolysed with sodium hydroxide in methanol, the stereoisomer 12 cannot be hydrolysed under the same conditions. This reduced reactivity

![Figure 1.10: Reactivity of the two stereoisomers of resin acid methyl ester](image-url)
of 12 originates from the steric congestion around the ester group, because it is in axial orientation. The equatorial counterpart 13 is more reactive, because the ester group of 13 is not sterically hindered.

Figure 1.11 shows the second example. Triterpene alcohol 14 with an axial hydroxy group can be dehydrated smoothly by treatment with phosphorus oxychloride in pyridine to give 16 through conventional E2 elimination mechanism. However, dehydration of the equatorial alcohol 15 leads to a rearrangement product 17 through the mechanism as shown in Figure 1.11. This type of simple stereochemical knowledge is very useful in synthetic planning.

1.6.2 Stereochemistry and analytical methods

Knowledge on analytical methods is very important for quick elucidation of the structures of synthetic intermediates. It is also very important for the unambiguous identification of the final synthetic product with the natural product. Two examples will be given here.

The first example illustrates the importance of NMR spectroscopy in modern organic synthesis. Commercial NMR spectrometers manufactured by Varian Associates in the USA became available to chemical communities in late 1950s to early 1960s. In Japan, the first NMR spectrometer that became available was Varian V4300C operating at 56.4 MHz. In 1960 I synthesized (±)-lactone 18 by the route shown in Figure 1.12.²⁷ It is worthwhile for you to think about the mechanisms of conversion of A to B and that of C to E via D.

The racemic lactone (±)-18 was obtained as a pure and crystalline compound, and its relative stereochemistry had to be determined. I thought, in 1960, ¹H NMR analysis to be the most appropriate method to solve the problem, because it had already been known to use a vicinal coupling constant for the stereochemical studies of cyclohexane compounds including terpenoids and steroids. Figures 1.13(a) and (b)
Figure 1.12 Synthesis of (+)-lactone 18. Modified by permission of Shokabo Publishing Co., Ltd

show two $^1$H NMR spectra of (+)-18, one (a) measured at 56.4 MHz in 1960 and the other (b) measured at 400 MHz in 2008. The $^1$H NMR spectrum of the tosylate of (+)-18 is also shown in Figure 1.13 (c).

I was able to deduce the relative stereochemistry of (+)-18 by examining its $^1$H NMR spectrum measured in 1960. I noticed the presence of a signal at $\delta = 3.54$ (1H, dd, $J = 3, 10$ Hz) due to the CHOCH proton.

Figure 1.14 shows the stereoformulas 18A–18D of the stereoisomers of (+)-18. The formula shows one of the two enantiomers. The Newman projections depicted in the middle row show the stereochemical relationships between the substituents at C-2 and C-3, while the Newman projections in the bottom row indicate the situations at C-2 and C-1. The Karplus equation, as follows, is known to correlate the magnitude of the coupling constant $J$ with the dihedral angle $\phi$.

$$J = \begin{cases} 8.5\cos^2\phi - 0.28 & 0^\circ \leq \phi \leq 90^\circ \\ 9.5\cos^2\phi - 0.28 & 90^\circ \leq \phi \leq 180^\circ \end{cases}$$

Let us first examine the projections in the middle row. In the case of 18A, the dihedral angle $\phi$ between the bonds C–Ha and C–Hb is 180°, which demands $J = 9$ Hz according to the Karplus equation. In the cases of 18B, 18C and 18D, that dihedral angle $\phi$ is 60°. Therefore, in these three cases, the magnitude of $J$ will be 1.8 Hz according to the Karplus equation. As you can see from the two Newman projections in the bottom row, the dihedral angle $\phi$ between the bonds C–Ha and C–Hc is fixed at 60°, which demands $J = 1.8$ Hz. Accordingly, only in the case of the stereoisomer 18A, we can observe a large constant $J = 9$ Hz. The $^1$H NMR spectrum of (+)-18 as shown in Figure 1.13(a) shows the
Figure 1.13 $^1$H NMR spectra of (±)-18 measured at (a) 56.4 MHz in CHCl$_3$ in 1960, and (b) 400 MHz in CDCl$_3$ in 2008. $^1$H NMR spectrum of the corresponding tosylate is also shown in (c) at 400 MHz in CDCl$_3$ in 2008.
magnitude of the coupling constant $J_{\text{HaHb}}$ as 10 Hz. Therefore, the relative configuration of (±)-18 was determined unambiguously as 18A. NMR spectroscopy is useful and important as a tool to determine the stereostructures of the synthetic products.

The second example shows the usefulness of X-ray crystallographic analysis in modern organic synthesis. Advances in computer science made this technique a routinely useful one. In 1986 I was interested in clarifying the steric course of the oxidation reaction as shown in Figure 1.15. The reaction had been studied by Schmauder et al., and the product reported as 21. Because the product could be recrystallized from isopropyl alcohol as a beautiful monoclinic with mp 96–97 °C, its X-ray crystallographic analysis was carried out. Figure 1.16 shows the molecular structure of the product. It was not 21 but 20. This information was used immediately for the synthesis of a very similar and bioactive lignan called magnosalicin (10, see Section 2.4.2).

There are many other useful analytical methods. Chromatographic methods such as gas chromatography (GC) and high-performance liquid chromatography (HPLC) are used daily for identification and estimation of the purity of a synthetic product. Chiroptical methods, such as circular dichroism (CD) spectroscopy, are also important especially in studying the relationships between absolute configuration and bioactivity of biofunctional molecules. In later chapters I will give some examples of application of CD spectroscopy in enantioselective synthesis.
Figure 1.14  Four possible stereoisomers A–D of (±)-18. Modified by permission of Shokabo Publishing Co., Ltd

Figure 1.15  Synthesis of 20 by means of oxidative dimerization of anethole (19). Modified by permission of Shokabo Publishing Co., Ltd
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Figure 1.16 Structure 20 as clarified by X-ray crystallographic analysis

References
