ANNULATED FURAN SYNTHESIS BY USING ALLENIC SULFONIUM SALT AND ITS APPLICATION TO THE SYNTHESIS OF NATURALLY OCCURRING FURAN COMPOUNDS

王子田, 彰夫
Graduate School of Pharmaceutical Sciences, Kyushu University

https://doi.org/10.11501/3081194
ANNULATED FURAN SYNTHESIS BY USING ALLENIC SULFONIUM SALT AND ITS APPLICATION TO THE SYNTHESIS OF NATURALLY OCCURRING FURAN COMPOUNDS

Akio Ojida
1995
ANNULATED FURAN SYNTHESIS BY USING ALLENIC SULFONIUM SALT AND ITS APPLICATION TO THE SYNTHESIS OF NATURALLY OCCURRING FURAN COMPOUNDS

A Dissertation
for the Degree of Doctor of Pharmaceutical Sciences
Institute of Synthetic Organic Chemistry
Faculty of Pharmaceutical Sciences
Kyushu University

Akio Ojida
1995
PREFACE

This dissertation has been carried out during 1989-1994 under the direction of

Professor Dr. Ken Kanematsu

at the Institute of Synthetic Organic Chemistry, Faculty of Pharmaceutical Sciences, Kyushu University.

This thesis presents the "Annulated Furan Synthesis by Using Allenic Sulfonium Salt and Its Application to the Synthesis of Naturally Occurring Furan Compounds".

The author would like to express his sincerest gratitude to Professor Dr. Ken Kanematsu for his kind and helpful suggestion and encouragement throughout the course his work.

He would like to make grateful acknowledgement to Dr. Mariko Aso for her profound interest and helpful discussions. He also thanks Dr. Takanori Yasukouchi, Dr. Shigeru Nagashima, Dr. Sin-Koo Yeo, Dr. Yoshiyasu Baba for their valuable discussions.

He is deeply indebted to Miss Chizuru Yoshimura, Miss Fumiyo Tanoue, and Mr. Akira Abe for their collaboration.

He extends his thankfulness to Mr. Izumi Ikeda, Mr. Takeshi Sagara, Mr. Ma-Se Lee and the rest of the members in the Laboratory of Professor Ken Kanematsu for their occasional discussions and hearty cooperation.

He also extends his thankfulness to Dr. Ryuichi Isebe, Mr. Yoshitsugu Tanaka and Ms. Yasuko Soeda for the measurement of MS and NMR spectra.

He thanks to Professor Dr. Eiji Osawa, Toyohashi University of Technology, for performing MO calculations.

Finally, acknowledgement must be made to his parents and brothers for their patience and understanding, without which this work would not have been possible.

Akio Ojida
CONTENTS

CHAPTER I
INTRODUCTION
1 Chemistry of Furan 1
2 Synthesis of Furan 5

CHAPTER II
CONSTRUCTION OF ANNULATED FURAN RING
1 General Aspect 7
2 Synthesis of Annulated Furan Compound 11
2-1 Annulated Furan Synthesis 11
2-2 Scope and Limitations of Annulated Furan Synthesis 14
2-3 Substituted Furan Synthesis via Furannulation/Ene Route 19
3 Discussion 22

CHAPTER III
SYNTHESIS OF NATURALLY OCCURRING FURAN COMPOUND
1 Synthesis of Menthofuran 27
2 Synthesis of Maturome 29
2-1 General Aspect 29
2-2 Synthetic Strategy for Maturome 30
2-3 Synthesis of Maturome 31
2-4 Discussion of the Regioselectivity in the Diels-Alder Reaction of Benzofuranquione 37
3 Synthesis of Marine Furanosesquiterpenoids, tubipofurans 43
3-1 General Aspect 43
3-2 Synthetic Strategy for Tubipofurans 44
3-3 Synthesis of Tubipofurans 46

SUMMARY OF THE ORIGINAL WORK 53

EXPERIMENTAL SECTION 54

REFERENCES AND NOTES 83

LIST OF PUBLICATIONS 90
Furans are the most prominent class of heteroaromatic compounds and show structural diversity in nature. Since the first isolation of 2-furoic acid (pyromucis acid) by Scheele in 1780, a large number of furans have been isolated from a variety of natural sources—plants, fungi, marine organisms, and microorganisms. Among them, many furans have been found to exhibit interesting biological activities and received wide interests. Recent attractive one is the family of marine furanocembranolide, such as pseudopterolide (Figure 1). Their unique structures and potent biological activities (cytotoxic, neurotoxic, and anti-inflammatory activities) have attracted considerable interest of organic chemists and pharmacologists. In addition, many furans can be found in the commercially important pharmaceuticals (Figure 1). Ranitidine (Zantac) is the most representative \( H_2 \) receptor histamine antagonist and the inhibitor of gastric acid secretion. Nitrofurantoin is a broad spectrum antibacterial agent, which is used for the treatment of urinary tract infections. Befunorolol, a benzofuran derivative, is the \( \beta \)-adrenergic blocking agent and effective in the treatment of angina and arrhythmia.
Furthermore, furans are of great importance in fragrances and flavors. Rosefuran is an essence of one of the most prized fragrances, oil of rose (Figure 1). Coffee owes some of its flavors to furylmethanethiol and related compounds.

Equally significant is the role of furan derivatives as versatile synthetic intermediate for the preparation of a wide range of cyclic and acyclic organic compounds. As shown in Figure 2, furan ring can be converted into a variety of five-membered oxygen-containing heterocyclic ring systems which are also present in numerous biologically active natural products. These conversions have been successfully applied to the total syntheses of many natural products. 

The oxidation of a furan ring has been used to express the latent functionality present within this heterocyclic system. Furan ring has been recognized as 1,4-dicarbonyl equivalent and this characteristic feature has sometimes been utilized in the strategy for the synthesis of natural product. The oxidation of furan derivatives by the treatment of Br\textsuperscript+ ROH or MCPBA affords 1,4-dicarbonyl compounds and the subsequent transformations allow the syntheses of a variety of functionalized compounds. Successful applications reported by Honda et al. and Albizati et al. are described in Scheme 1. Furan ring is also recognized as a latent carboxylic acid and the oxidative cleavage of furan ring provides the terminal carboxylate. Mukaiyama et al. employed this furan-to-acid conversion in the synthesis of methyl D-glucosaminate (Scheme 1).

Another significant feature of furan derivative as a versatile synthetic intermediate emerges from its inter- or intramolecular Diels-Alder reaction (Scheme 2). The cycloaddition of furan provides the oxabicyclo[2,2,1]heptene ring system which can be converted into a variety of cyclic compounds after the cleavage of carbon-carbon or carbon-oxygen bond. Smith et al. reported the high-pressure Diels-Alder reaction of bicyclic methoxyfuran and adduct of which was successfully applied to the total synthesis of jatrophaolones (Scheme 2). In the author’s laboratory, the intramolecular Diels-Alder reaction of furfuryl allenyl ether, so-called furan ring transfer (FRT) reaction, has been fully explored in which a variety of benzo[c]furan derivatives were directly obtained. This method has been successfully applied to the syntheses of naturally occurring furan compounds such as euryfuran, furoscrobiculin B, and spongia-13(16),14-diene.

**Figure 2**

**Scheme 1**

**Honda et al.**

- NBS, aq. THF (98%)

**Albizati et al.**

- DDH, aq. MeCN

**Mukaiyama et al.**

- RuO\textsubscript{2}/Na\textsubscript{2}O\textsubscript{4} (75%)
- CH\textsubscript{2}N\textsubscript{2} (78%)
In connection with the above-mentioned significant features of furan, numerous furan ring construction methods have been developed over the years. The classical furan synthesis was based on the cyclization of 1,4-diketones (Paal-Knorr furan synthesis) (Scheme 3). Acid catalyzed dehydration of 1,4-diketones followed by cyclization of the monoenols provided a variety of substituted furans. This method is useful for all 1,4-diketones which are not sterically hindered. Some carbohydrates have been recognized as the useful synthetic precursors for 2,3-disubstituted furans. The formation of furfural from pentoses, 5-methylfurfural from methylpentoses, and 5-hydroxymethylfurfural from hexoses under acidic conditions has long been known. These furan syntheses involve the similar cyclization step to Paal-Knorr furan synthesis. So far several modifications of Paal-Knorr furan synthesis have also been reported.

A number of furan syntheses have been developed until the early 1980s and reviewed in some texts, however, in recent years, more efficient and convenient furan syntheses have been devised (Scheme 4). Danheiser et al. reported the [3+2] furan annulation method by the reaction of allenylsilanes with acid chlorides in 1989 which opened novel methodology for the synthesis of polysubstituted furans. It has long been known that furan ring have been prepared by the cyclization of acetylenic alcohol, and various modifications of this methodology have extensively been studied in recent years. For example, in 1992, Marshall et al. reported the new furan synthesis by the base catalyzed isomerization of alkynyloxiranes and subsequent cyclization. Furthermore, Jacobs et al. have applied the sequential intramolecular Diels-Alder—retro-Diels-Alder reaction of oxazole derivatives to the efficient annulated furan synthesis. In their continuing study, they successfully synthesized several naturally occurring furan compounds (Scheme 4). Consequently, the development of procedures for efficiently constructing furan rings possessing a variety of substituents and annulation systems have been continued unabated to the present day. However, it should be said that single-step convergent annulation approach still remain scarce.
In this dissertation, the author will describe a new annulated furan synthesis by using allenic sulfonium salt, which is the single-step convergent approach to a certain furan ring system. The development of this method for the total synthesis of some naturally occurring furanoterpenoids will also be discussed in detail.
predominantly at the C-2 position. It was estimated that the C-2 : C-3 ratios for alkylation of furan ring under various conditions were in the range $8 \times 10^2$ to $6.8 \times 10^3$. Therefore, several procedures for direct alkylation of the C-3 position of furan ring have been devised in order to overcome this difficulty. The most noticeable one is the reactions of the furan derivatives possessing the highly reactive substituents (X=I, Bu3Sn, TMS) at the C-3 position in which C-3 alkylated furans are successfully obtained in moderate to high yields (Scheme 5). However, the preparations of these substrates are somewhat cumbersome and it might be difficult to utilize this methodology for annulated furan ring system. Thus, efficient and general methodology is still lacking and 3-substituted furan have generally been prepared by annulation of acyclic precursor which has substituent at the position destined to become the C-3 position of furan ring.

Scheme 5

In 1971, J. W. Batty et al. reported a novel polysubstituted furan synthesis by using propargyl sulfonium salt (1) and enolate anion of acyclic ketone possessing an electron-withdrawing group (ketone, ester, sulfone, and cyano group) at $\beta$-position (Scheme 6). The mechanism of this reaction has been proposed by them (Scheme 7). Propargyl sulfonium salt (1) initially isomerizes to allenic sulfonium salt under the basic condition. The nucleophilic attack of an enolate anion of ketone at the central carbon of allene and the following intramolecular substitution reaction result in the formation of oxygen-containing five membered ring. Finally, the isomerization of 3-methylideneurufan provides trisubstituted furan.

Scheme 6
Although this furan synthesis is a single-step convergent procedure providing a variety of substituted 3-methylfurans in high yields, this method has not been employed by organic chemists and has not been demonstrated its synthetic utility for long years. In order to devise a new procedure for efficient construction of "annulated" 3-methylfuran system, the author planned to take advantage of Batty's furan synthesis. If allenic sulfonium salt would react with cyclic 1,3-diketone, annulated 3-methylfuran could be obtained directly. This method should provide an efficient synthetic route to a variety of naturally occurring furan compounds.

In this chapter, the author describes the examination of the annulated 3-methylfuran synthesis by the reaction of allenic sulfonium salt and cyclic 1,3-diketone in detail.

### Chapter II

#### II-2 SYNTHESIS OF ANNULATED FURAN COMPOUND

#### II-2-1 ANNULATED FURAN SYNTHESIS

In the course of the author's plan aimed at the application of Batty's furan synthesis to the construction of annulated furan, a variety of conditions were initially examined in order to determine the optimal procedure for the effective furan ring annulation. The examination was carried out by the reaction of 1,3-cyclohexanedione (2a) and propargyl sulfonium salt (1) which was readily prepared from propargyl bromide and dimethyl sulfide in high yield (Scheme 8).

#### Scheme 8

![Scheme 8](image)

Table 1. Annulated 3-Methylfuran Synthesis by the Reaction of Allenic Sulfonium Salt with 1,3-Cyclohexanedione

<table>
<thead>
<tr>
<th>entry</th>
<th>1 (eq.)</th>
<th>base (eq.)</th>
<th>solvent</th>
<th>temp. (°C)</th>
<th>time (h)</th>
<th>4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>NaOEt (1.2)</td>
<td>EtOH</td>
<td>78</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>NaOEt (1.2)</td>
<td>EtOH</td>
<td>0</td>
<td>1</td>
<td>nr</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>NaOEt (1.2)</td>
<td>EtOH/CH3CN</td>
<td>78</td>
<td>1</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>NaH (1.2)</td>
<td>THF</td>
<td>et al.</td>
<td>12</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>NaH (1.2)</td>
<td>THF</td>
<td>67</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>K2CO3 (1.2)</td>
<td>DMF</td>
<td>0</td>
<td>20</td>
<td>37</td>
</tr>
<tr>
<td>7</td>
<td>1.5</td>
<td>K2CO3 (1.2)</td>
<td>DMF</td>
<td>2</td>
<td>20</td>
<td>37</td>
</tr>
<tr>
<td>8</td>
<td>1.5</td>
<td>t-BuOK (1.2)</td>
<td>THF</td>
<td>0</td>
<td>4</td>
<td>67</td>
</tr>
<tr>
<td>9</td>
<td>1.5</td>
<td>t-BuOK (1.2)</td>
<td>CH3CN</td>
<td>0</td>
<td>nr</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1.5</td>
<td>NaOEt (1.2)</td>
<td>THF</td>
<td>20</td>
<td>59</td>
<td></td>
</tr>
</tbody>
</table>

a) rt = room temperature
b) nr = no reaction
Chapter II
The results are summarized in Table I. The conditions employed in Batty's furan synthesis, i.e. refluxing in EtOH with sodium ethoxide as the base, were not effective for the annulated furan synthesis in which 4 was obtained in only 17% yield after the treatment with 5% HCl (entry 1). By using CH₃CN as a co-solvent, however, 4 was obtained in 44% yield (entry 3). The structure of 4 was well characterized by spectral analysis. The ¹H-NMR spectrum showed the C-2 aromatic proton on furan ring at 7.07 ppm (1H, br s) and the C-3 methyl proton at 2.20 ppm (3H, d, J=1.3 Hz). The IR absorption at 1660 cm⁻¹ and mass spectrum [m/z 150 (M⁺)] also indicated the structure of 4. The best yield (67%) was obtained when the reaction was conducted in THF at 0 °C with t-BuOK as the base (entry 8). Under these conditions, 1.5 eq. of 1 and 1.2 eq. of t-BuOK were employed. No change in the efficiency was observed employing the excess amounts (3 eq.) of 1 or t-BuOK.

Of particular interest in this reaction was that compound 3, an intermediate of the annulated furan synthesis, could be isolated when the acid treatment was not carried out. Batty et al. reported that the reaction of acyclic 1,3-diketones and 1 directly afforded 3-methylfuran compounds and did not isolate 3-methylidenefuran like 3.²⁵ The structure of 3 was well characterized by the analysis of ¹H-NMR, which showed the characteristic peaks of olefinic protons at 5.66 ppm (1H, t, J=3.3 Hz) and 4.83 ppm (1H, t, J=2.6 Hz) and methylene proton adjacent to oxygen atom at 5.07 ppm (2H, dd, J=3.3, 2.6 Hz). Compound 3 was extremely acid-sensitive and smoothly isomerized to 4 by the treatment with acid, e.g. 5% HCl in quantitative yield.

Although the annulated furan 4 could be obtained in modest yield under the optimal conditions (t-BuOK, THF, 0 °C), one problem was the formation of the byproduct 5 through a [2,3] sigmatropic rearrangement as shown in Scheme 9. For example, when the reaction was carried out under the optimal conditions, the formation of 5 (16%) was concomitant with that of the annulated furan 4 (67%). To overcome the problem, the author chose to employ diethyl prop-2-ynyl sulfonium salt (6) instead of 1. Barbarella et al. reported that base-catalyzed exchange of α-methyl hydrogens on trialkylsulfonium salt is much faster than that of α-methylene hydrogens (Table II).²⁷ Thus, the sulfonium salt 6 would avoid the base-induced anion formation on α-position of sulfur, which leads to the formation of 5 through a [2,3] sigmatropic rearrangement. The sulfonium salt 6 could be readily prepared by the reaction of diethyl sulfide and propargyl bromide in high yield (Scheme 10).²⁶ Compound 6 was a stable colorless salt and could be stored at 0 °C for several months. When employing the sulfonium salt 6, the reaction proceeded smoothly under the optimal conditions to afford the annulated furan 4 in high yield (82%) (Scheme 10). None of the byproduct 5 could be detected.

Table II. Second-order Rate Constants for Base-catalyzed H-D Exchange in D₂O at 35 °C²⁷

<table>
<thead>
<tr>
<th>Sulfonium Ion</th>
<th>10²k α-CH₃ (M⁻¹s⁻¹)</th>
<th>10²k α-CH₂ (M⁻¹s⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et₂MeS⁺</td>
<td>5.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Pr₂MeS⁺</td>
<td>4.3</td>
<td>1.4</td>
</tr>
<tr>
<td>t-Bu₂MeS⁺</td>
<td>3.7</td>
<td>-0.7</td>
</tr>
<tr>
<td>S⁻Me</td>
<td>7.3</td>
<td>1.2</td>
</tr>
<tr>
<td>S⁻Me</td>
<td>3.1</td>
<td>12</td>
</tr>
<tr>
<td>Me₂S⁺</td>
<td>3.1</td>
<td></td>
</tr>
</tbody>
</table>

Scheme 9
II-2-2 SCOPE AND LIMITATIONS OF ANNULATED FURAN SYNTHESIS

A variety of cyclic 1,3-diketones were employed to disclose the scope and limitations of the annulated 3-methylfuran synthesis using propargyl sulfonium salt (6). Some simple cyclic 1,3-diketones required for the annulated furan synthesis are commercially available. In addition, other variety of cyclic 1,3-diketones are also available as substrates for the annulated furan synthesis since various procedures for the synthesis of 1,3-diketone have been developed.

The results of the annulated 3-methylfuran syntheses employing several cyclic 1,3-diketones are summarized in Table III. Interestingly, when using 5-methyl-1,3-cyclohexanone (2b) as a starting material, (+)-evodone (7), a furanomonoterpene isolated from Evodia hortensis, was rapidly synthesized in 82% yield (entry 2). The spectral data of 7 were identical with that of natural material reported in the literature. This result demonstrates an useful aspect of the author's method. Reaction of 6 with 4-hydroxycoumarine (2d) afforded 9 possessing an unique furo[2,3-c]chromone system in 80% yield (entry 4). Furthermore, 1,3-cycloheptanone (2e) and 1,3-cyclooctanone (2f), both of which were prepared by Noyori's method, afforded the annulated furans 10 and 11 in 73% and 71% yields, respectively. Unfortunately, the highly strained cyclopenta[2,3-b]furanone could not be obtained from 1,3-cyclopentanone (entry 7). All furan compounds shown in Table 1 were well identified by the spectral analysis (1H-NMR, IR, mass, etc.).

<table>
<thead>
<tr>
<th>entry</th>
<th>1,3-dicarbonyl compound</th>
<th>furan (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>7 evodone</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>2e</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>2f</td>
<td>11</td>
</tr>
<tr>
<td>7</td>
<td>2g</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

Table III. Fused 3-Methylfuran Synthesis
Chapter II

The acid treatment, which promoted the isomerization of 3-methylidenefurans to the corresponding 3-methylfurans, was usually carried out with 5% HCl upon workup in a separatory funnel. In each case, the isomerization was completed within 10 min. However, in entry 4, the isomerization was conducted in CH₂Cl₂ with a catalytic amount of p-TsOH after the isolation of the stable 3-methylidenefuran.

The gratifying efficiency of the annulated 3-methylfuran synthesis raised an intriguing question concerning the siteselectivity on furan ring closure when unsymmetrical cyclic 1,3-diketone was employed as the starting material. The results of several examinations are summarized in Table IV. The reaction of the sulfonium salt 6 with 4-methyl-1,3-cyclohexanedione (2h) gave nearly equal amounts of 12 (40%) and 13 (45%) (entry 1). However, 4,4-dimethyl-1,3-cyclohexanedione (2i) afforded two isomers with a slight selectivity (ortho-14 : para-15 = 1.5 : 1) (entry 2). Compound 2j possessing a 1,3-dithiane group at its C-4 position provided two isomers in the same manner as entry 2 (ortho-16 : para-17 = 1.5 : 1) (entry 3). The reaction of 2k showed a moderate selectivity in which 18 and 19 were obtained in the ratio of 3.3 (47%) : 1 (13%) (entry 4). Furthermore, trans-decalin-1,3-dione afforded two tricyclic furan compounds, however none of selectivity was observed (20 : 21 = 1 : 1) (entry 5). Consequently, the sufficient siteselectivity could not be observed and the substituents of the 1,3-cyclohexanediones did not affect the direction of cyclization of furan ring. All furan compounds shown in Table IV were characterized by the spectral analysis (¹H-NMR, IR, mass, etc.). Furthermore, the structures of two regioisomers in each entry were well identified by the conversions to the corresponding silyl enol ethers (22-25) (Figure 4). These silyl enol ethers, which were readily obtained by the treatment with TBDMSOTf and NEt₃ from the annulated furans (13, 15, 19, and 21), showed the characteristic peaks of olefinic protons in the ¹H-NMR spectra. The analysis of the peak of olefinic proton definitely indicated whether the substituent was attached at C-5 (ortho) or C-7 (para) position. On the other hand, the structure of 17 was determined by the conversion to the benzofuranquinone 26 after the treatment with mercury perchlorate (MPC) (Scheme 11).

### Table IV. Fused 3-Methylfuran Synthesis

<table>
<thead>
<tr>
<th>entry</th>
<th>1,3-dicarbonyl compound</th>
<th>furan (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2h</td>
<td>12 (40%)</td>
</tr>
<tr>
<td>2</td>
<td>2j</td>
<td>14 (51%)</td>
</tr>
<tr>
<td>3</td>
<td>2j</td>
<td>16 (53%)</td>
</tr>
<tr>
<td>4</td>
<td>2k</td>
<td>18 (47%)</td>
</tr>
<tr>
<td>5</td>
<td>21</td>
<td>20 (45%)</td>
</tr>
</tbody>
</table>
Compound 3, which possesses an exomethylene group at the C-3 position of the dihydrofuran ring, could be isolated when the acid treatment did not carry out in the annulated 3-methylfuran synthesis. Compound 3 is extensively acid sensitive and tends to isomerize to the 3-methylfuran even upon chromatographic separation on SiO2. However, 3 could be prepared as a pure form in 76% yield after chromatographic separation on Al2O3 and following recrystallization (Scheme 12). During the course of this study, the author has found that 3 showed the high reactivity in ene reaction and provided the annulated furan compound possessing a variety of substituents at the C-3 position (Scheme 13).

Scheme 13

The results are summarized in Table V. The ene reaction of 3 with highly reactive enophiles such as diethyl azodicarboxylate (DEAD) and tetracyanoethylene (TCNE) proceeded even at room temperature and afforded adducts 27 and 28 in high yields, respectively (entry 1, 2). The 1H-NMR spectrum of 27 showed existence of the aromatic proton of furan ring at 7.35 ppm (1H, br s) and the mass spectrum [m/z 325 (M++H)] also indicated the structure of 27. The structure of 28 was characterized by the analysis of 1H-NMR and IR spectra, which indicated existence of the aromatic proton of furan ring at 7.57 ppm (s, 1H) and nitrile function at 2240 cm⁻¹, respectively. When using Eschenmoser's salt and ethyl glyoxylate34
Table V. Ene Reaction of 3 with Various Enophiles

<table>
<thead>
<tr>
<th>entry</th>
<th>enophile</th>
<th>time (hour)</th>
<th>temp. (°C)</th>
<th>furan (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NC=NC=NC</td>
<td>1</td>
<td>r.t.</td>
<td>27 (97%)</td>
</tr>
<tr>
<td>2</td>
<td>NC=NC=NC</td>
<td>0.5</td>
<td>r.t.</td>
<td>28 (88%)</td>
</tr>
<tr>
<td>3a)</td>
<td>NC=NC=NC</td>
<td>0.5</td>
<td>110</td>
<td>29 (93%)</td>
</tr>
<tr>
<td>4a)</td>
<td>NC=NC=NC</td>
<td>1</td>
<td>r.t.</td>
<td>30 (96%)</td>
</tr>
<tr>
<td>5b)</td>
<td>HC=CH</td>
<td>6</td>
<td>110</td>
<td>31 (85%)</td>
</tr>
<tr>
<td>6b)</td>
<td>H</td>
<td>3</td>
<td>110</td>
<td>32 (83%)</td>
</tr>
<tr>
<td>7b)</td>
<td>MeOOC-</td>
<td>24</td>
<td>110</td>
<td>33 (2%)</td>
</tr>
<tr>
<td>8(1,2)</td>
<td>CN</td>
<td>12</td>
<td>150</td>
<td>34 (88%)</td>
</tr>
<tr>
<td>9(1,2)</td>
<td>H</td>
<td>18</td>
<td>150</td>
<td>35 (87%)</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td></td>
<td></td>
<td>36 (52%)</td>
</tr>
</tbody>
</table>

a) Sodium acetate was added to trap trace amounts of acid.  
b) Reaction was carried out in a sealed tube.
Chapter II

II.3 DISCUSSION

The annulated 3-methylfuran synthesis examined in this chapter is defined as a formal [3+2] cycloaddition between allenic sulfonium salt and cyclic 1,3-diketone. Allenic sulfonium salt has two electrophilic sites: one is the central carbon of allene and the other is the terminal carbon of allene bearing sulfonium group. On the other hand, the enolate anion of cyclic 1,3-diketone is a typical ambident anion which also have two reaction sites. In principle, the [3+2] cycloaddition of these substrates can give rise to two isomeric furan compounds. However, the reaction proceeded exclusively in a regioselective fashion to provide the annulated 3-methylfuran compound as a sole product. The author supposes that this selectivity is well explained by the concept of HSAB (Hard and Soft Acids and Bases) (Scheme 15). Thus, the initial attack of the enolate anion takes place selectively at its α-carbon with the central carbon of allene moiety of the sulfonium salt where is the "softer" electrophilic site, and provides C-alkylated 1,3-diketone. Furthermore, subsequent ring closure occurs between the oxygen of the regenerated enolate anion and the α-position of the sulfonium salt where is the "harder" electrophilic site.

Several annulated furan construction methods involving formal [3+2] cycloaddition between cyclic 1,3-diketone and olefinic species have been reported (Scheme 16). The most representative one is "Feist-Beniary Furan Synthesis". Yoshikoshi et al. reported the sequential furan synthesis using 1-nitro-1-(phenylthio)propene as an olefinic species. Recently, Pirrung et al. reported the rhodium catalyzed dipolar cycloaddition of diazo-1,3-cyclohexanediones with vinyl ethers in which annulated furans were obtained in moderate yields. Among these annulated furan syntheses, the author's method have some advantages as follows: (i) propargyl sulfonium salt is readily available. (ii) a variety of annulated furans

Scheme 15

![Scheme 15 diagram]

Scheme 16

Feist-Beniary Furan Synthesis

\[
\text{O} \quad \xrightarrow{\text{NaHCO}_3, \text{HCO}_3, \text{RT}} \quad \text{H} \quad \xrightarrow{\text{H}^+} \quad \text{H}_2\text{O} \\
\text{O} \quad \xrightarrow{\text{KOH, water-MOH, H}^+} \quad \text{OH} \quad \xrightarrow{\text{H}^+} \\
\text{O} \quad \xrightarrow{\text{KF, benzene, } \Delta} \quad \text{OAc} \quad \xrightarrow{\text{Al}_2\text{O}_3} \\
\text{O} \quad \xrightarrow{\text{Na}_2\text{O}_4, \text{MeOH}} \quad \text{CCl}_3, \Delta, \text{Al}_2\text{O}_3 \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}2(\text{OAc})_4, \text{PhF}, \text{TsOH, benzene, } \Delta} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \xrightarrow{\text{P-TsOH, benzene, } \Delta} \\
\text{O} \quad \xrightarrow{1 \text{ mol} \% \text{ Rh}(\text{OAc})_3, \text{PhF}} \quad \text{OAc} \quad \x
can be directly obtained in high yields. (iii) the manipulation and purification are simple. (iv) the reaction can be readily conducted on a 10g-scale without lowering yield. (v) not only a methyl group, but also a variety of substituents can be introduced into the C-3 position of furan ring by employing the ene reactions of 3. Consequently, the author believes that the annulated furan synthesis by using allenic sulfonium salt is a highly efficient and practical method.

The reactions of allenic sulfonium salt (6) with several unsymmetrical cyclic 1,3-diketones provided two furan compounds without good site selectivity (Table IV). In this context, the annulated furan synthesis was conducted with the sulfonium salts 37 and 38 possessing the sterically more hindered alkyl groups on sulfur atom. The author expected the site selectivity on furan ring closure would change owing to the steric interaction between the substituents of cyclic 1,3-diketone and the hindered dialkyl groups of sulfonium salts. The results were described in Table VI. Unfortunately, the site selectivity did not change depending on the sulfur substituents and two isomeric furan compounds were obtained in almost the same ratios, respectively. Thus, it seems reasonable to conclude that the site selectivities observed in these reaction systems are probably due to the difference of stability of two isomeric enolate anions of 1,3-diketones (A and B), and therefore there are no steric interactions between the substituents on the reaction substrates (Scheme 17).

---

**Table VI**

<table>
<thead>
<tr>
<th>Sulfonium Salt</th>
<th>14 (%)</th>
<th>15 (%)</th>
<th>14 : 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 (Br, Si-Pr₂)</td>
<td>51</td>
<td>33</td>
<td>1.6 : 1</td>
</tr>
<tr>
<td>37 (Br, Si-Bu₂)</td>
<td>40</td>
<td>27</td>
<td>1.5 : 1</td>
</tr>
<tr>
<td>38 (Br, Si-Bu₂)</td>
<td>39</td>
<td>24</td>
<td>1.6 : 1</td>
</tr>
</tbody>
</table>

---

The thermal ene reaction of 3, an intermediate of the annulated furan synthesis, provided the furan compound possessing various C-3 substituents under the relatively mild conditions (room temperature - 150 °C) (Table V). The similar ene reactions employing the alicyclic isomers of aromatic compounds like 3 were reported in recent years. Miles et al. reported that the ene reaction of 1 (as a 4 : 1 mixture with 3-methylfuran) with the mono-substituted enophiles (Z=COCH₃, CN, CO₂CH₂CH₃) afforded the 3-substituted furan II under the conditions of refluxing in CH₂Cl₂ for 24-96 hr. Buchwald et al. reported the ene reaction of the alicyclic isomer of indole III with various enophiles under the conditions of heating in toluene at 85 °C. These ene reactions proceeded under the milder conditions compared with the typical ene reactions which usually occur at higher temperature. Miles et al. suggested that the driving force for the rapid ene reaction of 1 was the formation of the stable aromatic systems from the nonaromatic tautomer. Semiempirical molecular orbital calculations (PM3 implemented in MOPAC program) indicate that the energy of tautomerization of 3 (ΔHᵣ = -50.22 kcal/mol) to 4 (ΔHᵣ = -58.83 kcal/mol) is 8.61 kcal/mol (Figure 5). This value is almost the same that of the tautomerization energy difference between I (ΔHᵣ = -3.67 kcal/mol) and V (ΔHᵣ = -13.47 kcal/mol). Thus the author speculated that, as in the case for I, the large decrease of enthalpy accelerates the ene reaction of 3.
SYNTHESIS OF NATURALLY OCCURRING FURAN COMPOUND

In Chapter II, the author has developed a new furan ring construction method which directly provided the annulated 3-methylfurans in high yields. This method should become a powerful synthetic tool for approaching to naturally occurring furans since many of them possess the annulated 3-methylfuran system as a common structural unit. In this chapter, the author describes some applications of this method to the syntheses of the naturally occurring furanoterpenoids such as menthofuran, maturone, tubipofuran, and 15-acetoxytubipofuran.

III-1 SYNTHESIS OF MENTHOFRAN

Menthofuran (39)\textsuperscript{55} is a representative furanoterpenone, is one of the important perfumery isolated from peppermint oil (*Mentha piperita*). In addition, menthofuran is known as a proximate toxic metabolite of (R)-(+)­-plegone and can cause hepatic necrosis and death.\textsuperscript{46} Synthesis of menthofuran has been carried out by many groups.\textsuperscript{47} Scheme 19 shows recent syntheses of menthofuran. Padwa et al. reported a new furan synthesis using 2,3-dibromo-1-(phenylsulfonyl)-1-propene (DBP) and showed its utility in the total synthesis of (R)-menthofuran.\textsuperscript{48} Shishido et al. reported the synthesis of (R)-menthofuran from (+)-citronella\textsuperscript{49} by employing the intramolecular [3+2] cycloaddition of nitrile oxide.\textsuperscript{49}

As a first attempt to demonstrate the utility of the annulated furan synthesis using allenic sulfonium salt, the author also synthesized menthofuran from (±)-evodone (7), which was readily prepared from 5-methyl-1,3-cyclohexanedione in 82% yield. Treatment of (±)-evodone (7) with propanedithiol in the presence of zinc triflate afforded 40 in 85% yield (Scheme 20). Compound 40 was then treated with Raney Nickel (W-2) under the conditions of refluxing in EtOH to furnish (±)-menthofuran (39) in 55% yield as a volatile oil. The spectral data of synthetic menthofuran were identical with those of natural material reported in the literature.\textsuperscript{50}
Chapter III

III-2 SYNTHESIS OF MATURONE

III-2-1 GENERAL ASPECT

A number of furanophthalocyanine derivatives have been isolated from plants, particularly South American plants which have been used as folk remedy in Brazil. Some of these have been found to exhibit potent antitumor, antileukemic activities and received wide interest in recent years. Maturone (41), a norfuranosesquiterpene, was isolated from the roots of Cacalia decomposita A. Gray with several related compounds by Correa et al. in 1966. Maturone possesses a linear tricyclic furan nucleus bearing a hydroxymethyl group at the C-3 position and its structure was identified by spectroscopic analysis and chemical degradation. The structure of maturone was initially assigned to its C-8 methyl isomer, however, the revised structure was proposed by Thomson et al. and Kakisawa et al. on biogenetic ground to which possessed an aromatic methyl group at the C-5 position. Although, to the author's knowledge, the biological activity of maturone has not been examined in detail, the roots extract of Cacalia decomposita has been used for diabetes and other diseases in Mexico. The first synthesis of maturone has been achieved by Ghera et al. in 1986. They constructed the linear tricyclic skeleton of maturone by a regioselective annulation between an aromatic bromosulfone and γ-lactone (Scheme 21). This work established the validity of the revised structure of maturone.

The author planned an alternative effective synthesis of maturone to demonstrate the utility of the annulated furan synthesis by using allenic sulfonium salt. In this section, the total synthesis of maturone is described in detail.
III-2-2 SYNTHETIC STRATEGY FOR MATURONE

The retrosynthetic analysis of maturone is described in Scheme 22. The linear tricyclic skeleton of maturone would be constructed by the regioselective Diels-Alder reaction of the benzofuranquinone 42 and piperylene. The Benzofuranquinone 42, a crucial synthetic intermediate, would be prepared from 43 which possesses a hydroxymethyl group at the C-3 position on furan ring. Thus, the efficient introduction of a hydroxymethyl group into furan nucleus is required for the elegant synthesis of maturone based on this strategy. Compound 3 might be a possible substrate to obtain 43 because 3 possesses a highly reactive exomethylene moiety at its C-3 position, which might be readily transformed to hydroxymethyl group. An issue crucial to the success of the efficient synthesis of maturone based on this strategy is the regioselectivity of the Diels-Alder reaction of the benzofuranquinone 42 and piperylene. At the beginning of this study, the author did not have useful information about regioselectivity of Diels-Alder reaction of benzofuranquinone. Although Diels-Alder reactions of some quinone derivatives (p-benzoquinone, naphthoquinone, quinolinequinone etc.) are known to exhibit high regioselectivity under Lewis acid catalyzed conditions and their theoretical studies of the regioselectivity are also well documented, Lewis acid catalyzed Diels-Alder reaction of benzofuranquinone has been scarcely studied and few examinations have been reported. However, the author considered that high regioselectivity might be obtained if the Diels-Alder reaction of the benzofuranquinone 42 could be carried out under Lewis acid catalyzed conditions.

Scheme 22

III-2-3 SYNTHESIS OF MATURONE

The key intermediate, the benzofuranquinone 42, was prepared as shown in Scheme 23. The starting material was 3, which was readily prepared from 1,3-cyclohexanedione in 76% yield by employing the annulated furan synthesis (Scheme 12). Compound 3 readily reacted with N-bromosuccinimide (NBS) to give the 3-(bromomethyl)furan 44 in 68% yield. The $^1$H-NMR spectrum of 44 showed existence of the aromatic proton on furan ring at 7.40 ppm (1H, br s) and protons of bromomethyl moiety at 4.58 ppm (2H, br s). The mass spectrum [m/z 230 (M$^+$+1), 228 (M$^+$)] also supported the structure of 44. The plausible mechanism for the formation of 44 from 3 is described in Scheme 25. Hydrolysis of 44 with aq. NaHCO$_3$ afforded the 3-(hydroxymethyl)furan 43 in 75% yield. On the other hand, compound 43 could directly be obtained from 3 by the treatment with monoperoxyphthalic acid magnesium salt (MMPP) in 78% yield. The structure of 43 is well characterized by spectral analysis. The $^1$H-NMR spectrum showed existence of the aromatic proton of furan ring at 7.23 ppm (1H, br s) and the protons of hydroxymethyl moiety at 4.52 ppm (2H, br s). The IR absorption at 3400 and 1650 cm$^{-1}$ suggested existence of the hydroxyl and carbonyl functions, respectively. The mechanism for the formation of 43 is similar to that of 44 described in Scheme 25.
After protection of hydroxyl group of 43 as MOM ether (95%), 45 was transformed into the β-keto sulfoxide 46 by the treatment with methyl benzenesulfinate, which was readily converted to the phenol 47 via syn-elimination of the sulfoxide group (2 steps 82%). The aromatization of 43 was also achieved by using Saegusa's method (Scheme 24). Thus, the acetate 49 was converted into the corresponding silyl enol ether 50, which was then treated with Pd(OAc)₂ to afford 51 in 48% yield.

After treatment of 47 under the acidic conditions, the phenol 48 was treated with Fremy's salt to afford 42 in 69% yield (Scheme 23). The ¹H-NMR spectrum of 42 showed existence of the aromatic proton on furan ring at 7.66 ppm (1H, br s) and the olefinic protons on quinone moiety at 4.73 ppm (2H, br s). The mass spectrum [m/z 178 (M⁺)] also supported the structure of 42.

**Scheme 25**

With the benzofuranquinone 42 in hand, the stage was set for examination of the pivotal Diels-Alder cycloaddition. Compound 42 reacted with piperylene in methylene chloride at room temperature to afford the cycloadducts, which were oxidized by air to the mixture of regioisomers 52 and 53. Aromatization of these isomers by the treatment with chloranil gave a mixture of maturonone (41) and isomaturonone (54) (Scheme 26). Although separation of 41 and 54 by column chromatography was unsuccessful, the ratio of isomers could be determined.
by the $^{1}H$-NMR spectroscopy. The signals of aromatic methyl group of 41 and 54 were observed at 2.81 ppm and 2.83 ppm, respectively and the ratio was determined by comparison of integration of these peaks. Unfortunately, under the uncatalyzed conditions, the regioselectivity of cycloaddition was low and the ratio of 41 and 54 was almost same (2.81 ppm / 2.83 = 1.2 : 1) (Figure 6).

For the regioselective maturone synthesis, the Diels-Alder reaction of the benzofuranquinone 42 with piperylene was examined under a variety of Lewis acid catalyzed conditions. The results of the cycloaddition reaction in the presence and absence of Lewis acid were summarized in Table VII. In the presence of BF$_3$•Et$_2$O as a catalyst, the reaction proceeded smoothly and showed higher regioselectivity compared with the uncatalyzed reaction. Interestingly, the addition of the excess of BF$_3$•Et$_2$O (3 eq.) reversed the ratio of 41 and 54. On the other hand, using TiCl$_2$(Oi-Pr)$_2$ catalyst, which was freshly prepared from TiCl$_4$ and Ti(Oi-Pr)$_4$, resulted in higher regioselectivity than BF$_3$•Et$_2$O catalyst. It is to be noted that the ratio of cycloadducts was 20 : 1 when the reaction was performed at -50°C in the presence of 0.5 eq. of TiCl$_2$(Oi-Pr)$_2$ (Figure 7). The major isomer in TiCl$_2$(Oi-Pr)$_2$ catalyzed reactions could be easily isolated by recrystallization from acetone-hexane, and its $^{1}H$-NMR spectrum (Figure 8) was identical with that of maturone provided by Ghera. Other physical and spectral data (IR, mass, and m.p.) were also identical with those of maturone (41). Thus, the regioselective synthesis of maturone has been accomplished by the Lewis acid catalyzed Diels-Alder reaction of the benzofuranquinone 42.

### Table VII. Diels-Alder Reaction of Benzoquinone (42) and Piperylene.

<table>
<thead>
<tr>
<th>Lewis acid (eq.)</th>
<th>temp. (°C)</th>
<th>time* (h)</th>
<th>yield (%)</th>
<th>ratio 2.81 : 2.83 (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>none in CH$_2$C$_2$</td>
<td>r.t.</td>
<td>4 d</td>
<td>96</td>
<td>1.2 : 1</td>
</tr>
<tr>
<td>none in toluene</td>
<td>110</td>
<td>3 d</td>
<td>78</td>
<td>1.3 : 1</td>
</tr>
<tr>
<td>none in EtOH</td>
<td>r.t.</td>
<td>4 d</td>
<td>79</td>
<td>1 : 2</td>
</tr>
<tr>
<td>BF$_3$•Et$_2$O (0.5)</td>
<td>-40</td>
<td>6 h</td>
<td>61</td>
<td>3.3 : 1</td>
</tr>
<tr>
<td>BF$_3$•Et$_2$O (1.0)</td>
<td>-40</td>
<td>6 h</td>
<td>85</td>
<td>2 : 1</td>
</tr>
<tr>
<td>Ti(Oi-Pr)$_4$ (1.0)</td>
<td>-40</td>
<td>3 h</td>
<td>96</td>
<td>1 : 1.6</td>
</tr>
<tr>
<td>TiCl$_2$(Oi-Pr)$_2$ (0.5)</td>
<td>-50</td>
<td>17 h</td>
<td>66</td>
<td>20 : 1</td>
</tr>
<tr>
<td>TiCl$_2$(Oi-Pr)$_2$ (1.0)</td>
<td>-40</td>
<td>3 h</td>
<td>60</td>
<td>12.5 : 1</td>
</tr>
</tbody>
</table>

* d : day, h : hour

Figure 6. 270 MHz $^{1}H$-NMR of Maturone (41) and Isomaturone (54) [without catalyst in CH$_2$Cl$_2$]
III-2-4 DISCUSSION OF THE REGIOSELECTIVITY IN THE DIELS-ALDER REACTION OF BENZOFURANQUINONE

The synthesis of maturome was successfully accomplished via the regioselective Diels-Alder reaction of the benzofuranquinone 42. The effectiveness of Lewis acid in the Diels-Alder reaction of 42 prompted the author to gain the detailed understanding of regioselectivity shown by the experimental results. In order to elucidate the orientation of the regioselectivity, the author tried theoretical interpretation by performing molecular orbital calculations. The regioselectivity in Diels-Alder reaction has been successfully explained in terms of Frontier Molecular Orbital theory (FMO). Table VIII presents HOMO coefficients and energies of piperylene as obtained by PM3, AM1, CND0/2 and STO-3G. Contrary to the CND0/2 results which had indicated a larger coefficient at C-1 than at C-4 of piperylene, the STO-3G calculations reveal the reverse trend. PM3 and AM1 gives the same relative magnitude as STO-3G. For this reason and also in order to handle such large molecules as 42, the author uses the PM3 and AM1 results for these and all other molecules mentioned in this work. In the benzofuranquinone 42, the magnitude of the LUMO coefficient at C-5 is slightly greater than C-6. Hence the reaction paths 1 and 3 in Scheme 27 will be favorable than the reaction paths 2 and 4. The author expects, however, that the regioselectivity of this reaction is low because of the small difference of these coefficients. This observation is consistent with the observed regioselectivity of Diels-Alder reaction carried out in methylene chloride in the absence of catalyst (Table VII).
An interesting reversal of the regioselectivity has been observed when the reaction medium was changed from methylene chloride to ethanol (Table VII). The author studied the effects of intramolecular hydrogen bond formation between the C-4 carbonyl group and the hydroxyl group in 42 upon its LUMO coefficients, hoping to rationalize the experimental observation in terms of the destruction of intramolecular hydrogen bond in polar protic solvent such as ethanol. In the conformer 42 as depicted in Table VIII, PM3 results showed that the distance between the C-4 carbonyl oxygen and the O-9 hydroxyl hydrogen was 1.83 Å, which is sufficient to construct the intramolecular hydrogen bond. However, the destruction of the intramolecular hydrogen bond seems to cause the unfavorable change of the regioselectivity.

PM3 calculations of another conformer of benzofuranquinone 42', which can not form the intramolecular hydrogen bond, indicate that the coefficient of C-5 is larger than that of C-6 (Table IX). The changes of the magnitude of coefficients and the higher LUMO level compared with conformer 42 in Table VIII are probably due to the effect of the destruction of intramolecular hydrogen bond. Thus, in polar protic solvent, the reaction paths 1 and 3 in Scheme 27 will be favorable than the reaction paths 2 and 4, and the predicted regioselectivity based upon FMO theory is opposed to the experimental result. The observed reversal of regioselectivity may be the results of the differential solvation of the polar transition state. The effect of solvent would be larger in the polar transition state than in the ground state. The author assumes that this effect probably influences the observed change of regioselectivity.
has the lowest LUMO energy and the largest difference between C-5 and C-6 coefficients. This fact indicates that the complex C may react with piperylene faster than its competitors. However, the Lewis basicity of carbonyl oxygen at C-4 is greater than that of C-7. The charge density of carbonyl oxygen atom of C-4 is calculated to be -0.273 and that of C-7 is -0.229. This fact indicates the complex B is favorable than the complex C. Thus, clear result does not emerge from the interpretation based upon FMO theory. The author supposes an alternative explanation involving the polar transition structure (or the zwitterionic-like intermediate) formed from the complex B (Scheme 28). Among the possible polar transition structures, TS A is more stable than TS B because of the highly stabilized character of the positive charge. Thus, the formation of TS A from the complex B (and perhaps the closely related B1 as well) can be responsible for the observed regioselectivity favoring maturone (41) under the conditions of the low concentrations of BF3.

On the other hand, TiCl2(Oi-Pr)2 catalyzed reaction gave the higher regioselectivity (maturone : isomaturone = 20 : 11) compared with the reaction catalyzed by BF3•Et2O. TiCl2(Oi-Pr)2 seems to interact with 42 through the chelation complex E, which is formed by the alkoxy exchange between the hydroxyl group of 42 and i-PrOH followed by the coordination with the C-4 carbonyl oxygen (Figure 10). However, if such a species forms, the predicted regioselectivity based upon FMO theory is opposite to the experimental results. Thus, the author supposes that, as well as the low concentrated BF3•Et2O catalyzed reaction, the reaction of 42 with piperylene proceeds from the complex E through the polar transition structure (or the zwitterionic-like intermediate) like TS A. To observe the interaction of 42 with TiCl2(Oi-Pr)2, 1H-NMR study was attempted under low temperature (-50 °C), however, no informative result was obtained.
In conclusion, FMO theory does not rationalize the regioselectivities observed under various conditions. The author supposes an alternative explanation involving the polar transition structures (or the twitterionic-like intermediates), which well rationalizes the effects of the solvent and that of Lewis acid catalyses. In order to prove the validity of this supposition, detailed studies of transition states by performing MO calculations and additional experiments are required. The actual picture of regioselectivities observed in experiments still remains obscure.

Chapter III

III-3 SYNTHESIS OF MARINE FURANOSESQUITERPENOIDS, TUBIPOFURANS

III-3-1 GENERAL ASPECT

Furanosesquiterpenes, which possess a furanodecalin ring system, constitute a large and structurally varied group of natural products. From the first discovery of atracylone from the rhizomes of Atractylodes sp. in 1924, up to now, hundreds of furanodecalin compounds have been isolated from a wide variety of plants, particularly the family of Compositae.45,69 Several representative furanodecalins are shown in Figure 11.

Furanodecalins are conveniently classified into several types according to the basic carbon skeleton and, among them, the family of furanoeremophilanes is most abundantly present in plant sources. The structural feature of many furanodecalin is the 3-methyl[b]furan ring system as a common structural unit.

In recent years, many furanoterpenoids have been isolated from marine organisms, and some of these have potent biological activities and unique structures.70 The tubipofurans (55 and 56) were isolated from the Japanese stolonifer Tubipora musica Linnaeus by Yamada et al. in
1986 and were shown to be eudesmane-type marine furanosesquiterpenoids possessing a cis-fused decalin ring with a homoannular 1,3-diene system. These compounds showed an ichthyotoxicity toward a killifish *Orius latipes,* and 15-acetoxytubipofuran (56) showed a cytotoxicity against B-16 melanoma cells *in vitro.*

In this section, the author describes the first total syntheses of marine furanodecalins, two tubipofurans. These total syntheses demonstrate the utility of the annulated 3-methylfuran synthesis by using allenic sulfonium salt.

### III-3-2 SYNTHETIC STRATEGY FOR TUBIPOFURANS

**Scheme 29**

Bohlmann et al.\(^{100}\)

\[ \begin{align*}
\text{AcO} & \quad \text{EtOH} \quad 100-105^\circ \text{C} \quad \text{EtO} \quad \text{AcO} \\
(71\%) & \quad (12\%) \quad (\pm)-\text{lustralone}
\end{align*} \]

Yamakawa et al.\(^{100}\)

\[ \begin{align*}
\text{io} \quad \text{benzene, reflux} \quad \text{ii) recrystallization} \\
(75\%) & \quad (\pm)-\text{lustralone} \quad (\pm)-\text{furanoeremophilane}
\end{align*} \]

Several different synthetic approaches to furanodecalins have been developed over the years.\(^{71}\) Classical furanodecalin synthesis was based on construction of decalin system possessing substituents at required positions and subsequent furan ring annulation.\(^{710-12}\) In considering approach to tubipofurans, the author was attracted to the synthetic strategy developed by Bohlmann *et al.* and Yamakawa *et al.* in which the furanodecalin system were successfully constructed by the Diels-Alder reaction of benzofuranquinone (Scheme 29).\(^{56, 713}\) This strategy was thought to have some advantages for the synthesis of furanodecalin involving tubipofurans: (i) the cis-fused furanodecalin system of tubipofurans would be directly obtained. (ii) ketone groups adjacent to furan nucleus in cycloadduct would stabilize furan ring which is labile under acidic and oxidative conditions. (iii) the strategy is a convergent approach, which allows to employ a variety of electron-rich dienes possessing substituents at required positions, and therefore would be of value in the synthesis of other structurally varied furanodecalins.

Retrosyntheses of 55 and 56 are described in Scheme 30. The two tubipofurans 55 and 56 would be synthesized from the common intermediate 57. Compound 57 would be constructed by the Diels-Alder reaction of the benzofuranquinone 60 and Danishefsky diene 59\(^{72}\) in a regioselective fashion. Molecular orbital calculations indicated that favorable regioselectivity should be achieved on the basis of Frontier Molecular Orbital (FMO) theory: the magnitude of the coefficient of C-5 (c = -0.366) of 60 is larger than that of C-6 (c = 0.345).\(^{73}\) On the other hand, the magnitude of C-4 of 59 is larger than that of C-1. The benzofuranquinone 60 should be readily prepared from evodone (7), which can be obtained in multigram quantities by the reaction of 5-methyl-1,3-cyclohexanedione and allenic sulfonium salt (Scheme 10).

**Scheme 30**

\[ \begin{align*}
\text{R=H; tubipofuran} \\
\text{R=OAc; 15-acetoxytubipofuran}
\end{align*} \]
III-3-3 SYNTHESIS OF TUBIFOFRANS

The benzofuranquinone 60 was synthesized as shown in Scheme 31. The starting material was evodone (7), which was initially converted to the benzofuranquinone 60 by the following two steps: dehydrogenation of 7 with 10 % Pd-C gave the benzofuranol 61, which was oxidized to the benzofuranquinone 60 in 60% yield by treatment with Fremy's salt. The \(^1\)H-NMR spectrum of 60 showed existence of the aromatic proton on furan ring at 7.45 ppm (IH, br s) and the olefinic proton on quinone moiety at 6.50 ppm (IH, br s). The mass spectrum also indicated the structure of 60.

Scheme 31

\[
\begin{array}{c}
\text{7} \xrightarrow{10\% \text{ Pd-C}} \text{60} \\
\text{61} \xrightarrow{\text{Fremy's salt}} \text{60}
\end{array}
\]

Scheme 32

\[
\begin{array}{c}
\text{OMe} \text{TBDMSO} \xrightarrow{\text{toluene, } \Delta} \text{60} \\
60 \xrightarrow{\text{NaOCl}} \text{58} \xrightarrow{\text{TBDMSO}} \text{62}
\end{array}
\]

(80% after recrystallization)

The thermal Diels-Alder reaction of 60 with the diene 59, which was readily prepared according to Danishefsky's method, was conducted under the conditions of refluxing in toluene to afford a mixture of 58 (ortho-endo adduct) and 62 (para-endo adduct) in a ratio of 11 : 1 (98%). The structures of two regioisomers were well identified by the \(^1\)H-NMR analyses (Figure 12, 13). Furthermore, the structure of the major adduct 58 was specifically confirmed by the study of NOE correlation as shown in Figure 12. The major adduct 58 was the favored regioisomer as predicted by retrosynthesis, and was easily separated from the mixture of regioisomers by simple recrystallization (from hexane) in 80% yield.

Figure 12. \(^1\)H-NMR Analysis of 58

\[
\begin{array}{c}
3.17 \text{ppm (d, } \text{J=18.3 Hz)} \\
2.12 \text{ppm (br dd, } \text{J=18.4, 7.8 Hz)} \\
3.02 \text{ppm (d, } \text{J=7.8 Hz)} \\
2.07 \text{ppm (d, } \text{J=1.3 Hz)}
\end{array}
\]

Figure 13. \(^1\)H-NMR Analysis of 62

\[
\begin{array}{c}
3.48 \text{ppm (d, } \text{J=18.3 Hz)} \\
5.07 \text{ppm (d, } \text{J=4.3 Hz)} \\
3.69 \text{ppm (d, } \text{J=5.9 Hz)} \\
0.95 \text{ppm (s)}
\end{array}
\]

Reduction of 58 with NaBH₄ proceeded chemo- and stereoselectively to give 63 as a sole product (Scheme 33). This selectivity could be attributed to the steric hindrance of the tert-butyldimethylsiloxy group toward the C-4 carbonyl group and / or the poor electrophilicity of the C-4 carbonyl group, due to electron donation from the furan oxygen. Thus, chemoselective hydride attack at the C-9 carbonyl group would occur predominantly from the convex face of 58 to afford 63 as a sole product. Compound 63 was then converted to 64 by the treatment with CF₃COOH in 94% yield. The structure of 64 was characterized by \(^1\)H-NMR analysis, which showed existence of the aromatic proton on furan ring at 7.22 ppm (1H, br s), and the protons of enone moiety at 6.98 ppm (1H, d, J=10.2 Hz) and 6.08 ppm (1H, d,
To obtain the key intermediate 57, it was necessary to reduce the C-4 carbonyl oxygen and the C-9 hydroxyl group of 64. These conversions were successfully achieved by the Barton-McCombie radical deoxygenation method (Scheme 33). Other reductive methods (including treatment with P2I4,75 TMSI,76 acetylation followed by Birch reduction,71b tosylation or mesylation followed by reduction with LiEt3BH77) did not give good results in this furanodecalin system. Thus, after selective ketalization of the enone carbonyl group of 64 (92%), the corresponding ketal 65 was converted to the xanthate 66 under standard conditions, followed by radical reduction with Bu3SnH, affording 67 in 93% yield from 64. Reduction of the C-4 carbonyl group of 67 with LiAlH4 (98%), the xanthate 69 was obtained by employing the two-phase system CH2Cl2-50% aqueous NaOH.78 Unstable xanthate 69 was treated with Bu3SnH to give 70 which, upon deketalization, gave the key intermediate 57 in 53% yield from 68. The 1H-NMR spectrum of 57 showed existence of the aromatic proton on furan ring at 7.08 ppm (1H, br s), and the protons of enone moiety at 6.85 ppm (1H, d, J=9.9 Hz) and 5.93 ppm (1H, d, J=9.9 Hz). The IR absorption at 1650 cm⁻¹ and mass spectrum [m/z 216 (M⁺)] also indicated the structure of 57. In one attempt, the author tried the simultaneous removal of both hydroxyl groups of 71 to obtain 70 directly (Scheme 34). Compound 71, which was prepared from 65 by reduction with LAH, was converted to dixanthate followed by radical reduction with Bu3SnH, however 70 was obtained in poor yield (10%). Consequently, the author adopted the stepwise radical reductions depicted in Scheme 33, even though a few additional steps were required.

Scheme 34

During the sequence of chemical reactions depicted in Scheme 33, one of the major problems was epimerization of the cis-fused ring junction of the furanodecalin system. Several examples of epimerization have been reported in similar systems, even upon simple chromatographic separation on SiO2.56,71b The cis configuration could be confirmed by NOE correlation between the angular C-4a proton and the C-8a methyl proton in compounds 58 and 64. Furthermore, the assignment of cis configuration was also made with the help of unexpected
W-shape long range coupling. In compound 67, the author observed long range coupling between the C-4a proton (δ 2.00, ddd, J=13.2, 3.6, 1.7 Hz) and the C-8 proton (δ 5.80, dd, J=10.2, 1.7 Hz), which was specifically confirmed by spin decoupling experiments. This is explainable only in the case of cis stereochemistry with the non-steroidal conformation shown in Figure 14. Furthermore, this characteristic W-shape long range coupling was also observed in 64, 68, and 70. Consequently, the author concluded that no epimerization at the C-4a position occurred during the sequential conversion to the key intermediate 57.

Figure 14

Thus, with the key intermediate 57 in hand, the total synthesis of tubipofuran (55) was achieved by three step conversion depicted in Scheme 35. Methylation of 57 with Mel and LDA provided 72 as a mixture of epimers (β-methyl : α-methyl = 11 : 1) in 75% yield. After reduction of 72 with LAH (quant.), the conversion of the resulting 73 to tubipofuran (55) was examined. Among several approaches (dehydration catalyzed by p-TsOH, mesylation followed by β-elimination etc.), only the traditional dehydration method using Al₂O₃ in pyridine successfully afforded the synthetic tubipofuran (55) as a colorless oil.

Total synthesis of 15-acetoxytubipofuran (56) was also achieved from 57 (Scheme 36). Acylation of 57 with methyl cyanofonnate provided the β-keto ester 74 as a keto-enol tautomer in 75% yield. After selective reduction of 74 with NaBH₄ in the presence of CeCl₃ (68%), the resulting 75 was mesylated followed by β-elimination with DBU to give 76 (2 steps, 87%). Finally, reduction of 75 with LiAlH₄ followed by acetylation afforded the synthetic 15-acetoxytubipofuran (56) (83% from 76) as a colorless oil. The ¹H-NMR spectra of the synthetic tubipofuran (55) and 15-acetoxytubipofuran (56) (Figure 15 and 16) were identical with those of the natural materials provided by Yamada. Other spectral data (¹³C-NMR, IR, and MS) were also identical with those of the natural materials reported in the literature.
SUMMARY OF THE ORIGINAL WORK

This dissertation mainly deals with the new annulated 3-methyl[β]furan synthesis by using allenic sulfonium salt and its application to the synthesis of naturally occurring furanoterpenoids. The results of studies are summarized as follows:

1. Annulated furan compounds possessing an 3-methyl[β]furan system could be directly obtained by the reaction of allenic sulfonium salt and cyclic-1,3-diketones. The improved reaction conditions (diethyl prop-2-ynyl sulfonium salt (6) with t-BuOK in THF at 0°C) were the most suitable for the annulated furan synthesis and provided a wide variety of furans in high yields. This method is a single-step convergent approach and should be a valuable reaction in the repertoire of synthetic organic chemists.

2. The ene reaction of 3, an intermediate of the annulated furan synthesis, was examined. This ene reaction proceeded under the relatively mild conditions to afford the annulated furans possessing a variety of C-3 substituents, which could not be readily obtained by the direct alkylation of furan ring. The resulting ene adducts contain several reactive sites for subsequent conversions and should find useful application in organic synthesis.

3. The annulated furan synthesis was successfully applied to the total synthesis of naturally occurring furanoterpenoids such as menthofuran, maturone, tubipofuran, and 15-acetoxytubipofuran. Menthofuran was briefly synthesized from 5-methyl-1,3-cyclohexanone in only 3 steps. A new and efficient synthetic route to maturone have been developed wherein the pivotal step was the regioselective Diels-Alder reaction of benzofuranquinone (42) under the Lewis acid catalyzed conditions. Furthermore, the first total syntheses of marine furanosesquiterpenoids, tubipofuran and 15-acetoxytubipofuran have been successfully achieved via the common intermediate (57). Consequently, it is concluded that these successful total syntheses established the synthetic utility of the annulated furan synthesis.
EXPERIMENTAL SECTION

General

The melting point were measured with a Yanaco micro-melting point apparatus and are uncorrected. The \( ^1 \)H-NMR spectra were taken on JEOL GX-270 (270 MHz), JEOL FX-100 (100 MHz) and Hitachi R-1500 (60 MHz) spectrometer. The \( ^{13} \)C-NMR spectra were recorded on a JEOL GX-270 (67.8 MHz). Chemical shifts are reported in \( \delta \) units (part per million downfield from Me4Si). The IR spectra were determined on a JASCO IR A-100 infrared spectrophotometer. The mass spectra (MS) were determined on JEOL D-300 or JEOL DX-300. The elemental analyses were performed on a Yanaco MT2 CHN recorder. Analytical thin-layer chromatography (TLC) was performed on E. M. Merck precoated TLC plates (Kieselgel 60 F254, 0.2 mm). Nonflash chromatography separations were carried out on E. M. Merck Kieselgel 60 (70-230 mesh) or E. M. Merck Aluminium oxide 90 (70-230 mesh) as the stationary phase. Flash chromatography separations were conducted with E. M. Merck Kieselgel 60 (230-400 mesh). All solvents were purified and dried prior to use according to standard procedures. All reactions sensitive to moisture or air were performed under argon. Reaction vessels were flame-dried or oven-dried and allowed to cool under inert atmosphere for moisture-sensitive reactions.

CHAPTER II

54

Dimethylprop-2-ynyl sulfonium bromide (5). In a light-protected round bottomed flask, a solution of diethyl sulfide (3.67 mL, 50 mmol) and propargyl bromide (3.72 mL, 50 mmol) in anhydrous CH3CN (5 mL) was stirred for 16 h at room temperature. The salt crystallized was washed with anhydrous ether to give 8.19 g (90%) of 5 as a colorless solid. This material was used for the annulated furan synthesis without further purification.

3-Methyl-6,7-dihydrobenzofuran-4(5H)-one (4). To a solution of tert-BuOK (600 mg, 5.35 mmol) in anhydrous THF (10 mL) was added dropwise 1,3-cyclohexanedione (2a) (500 mg, 4.46 mmol) dissolved in anhydrous THF (5 mL). After stirring for 30 min at room temperature, the mixture was cooled to 0 °C and diethylprop-2-ynyl sulfonium bromide (6) (1.40 g, 6.69 mmol) was added. The reaction mixture was stirred for 6 h at 0 °C. After dilution with water, the resulting mixture was extracted with Et2O (x2). In a separatory funnel, the combined organic layers were treated with 5% HCl for about 10 min. The 5% HCl solution was extracted with Et2O and then the combined organic layers were washed with saturated NaHC03 followed by drying over Na2S04. After removal of the solvent in vacuo, the residue was purified by chromatography on silica gel (hexane : ethyl acetate = 10 : 1) to give 571 mg (82%) of 4 as a pale yellow solid: mp 62.5-63.5 °C; \( ^1 \)H NMR (CDCl3, 270 MHz) \( \delta \) 7.07 (br s, 1H), 2.83 (t, \( J=6.3 \) Hz, 2H), 2.49-2.44 (m, 2H), 2.20 (d, \( J=1.3 \) Hz, 3H), 2.17-2.10 (m, 2H); IR (CHCl3) 2950, 1660, 1560, 1415, 1410 cm\(^{-1}\); LRMS (EI, 30 eV) \( mlz \) (relative intensity) 150 (M\(^+\), 94), 122 (100), 94 (55), 66 (21). Anal. Calcd for C9H10O2: C, 71.98; H, 6.71. Found: C, 71.90; H, 6.70.

55

Experimental Section

5,5-Dimethylcyclohexane-1,3-dione (2c) (500 mg, 3.57 mmol) was used as a starting material. By the same procedure described for the synthesis of 4 and the purification by column chromatography on silica gel (hexane : ethyl acetate = 8 : 1), 8 was obtained as a pale yellow solid (545 mg, 86%): mp 75-76°C; \( ^1 \)H NMR (CDCl3, 270 MHz) \( \delta \) 7.08 (br s, 1H), 2.92 (br dd, \( J=15.8 \) Hz, 4.2 Hz, 1H), 2.54-2.17 (m, 4H), 2.19 (d, \( J=1.3 \) Hz, 3H), 1.16 (d, \( J=6.3 \) Hz, 3H); IR (CHCl3) 2950, 1660, 1550, 1430, 1410 cm\(^{-1}\); LRMS (EI, 30 eV) \( mlz \) (relative intensity) 164 (M\(^+\), 52), 122 (100), 94 (38). Anal. Calcd for C10H12O2: C, 73.15; H, 7.36. Found: C, 72.98; H, 7.33.

3,6-Dimethyl-6,7-dihydrobenzofuran-4(5H)-one (7) (7-evocone). 5-Methylcyclohexane-1,3-dione (2b) (500 mg, 3.96 mmol) was used as a starting material. By the same procedure described for the synthesis of 4 and the purification by column chromatography on silica gel (hexane : ethyl acetate = 20 : 1), 8 was obtained as a pale yellow solid (530 mg, 82%): mp 71-71.5 °C (lit.\(^{17c}\) 73 °C); \( ^1 \)H NMR (CDCl3, 270 MHz) \( \delta \) 7.08 (br s, 1H), 2.92 (br dd, \( J=15.8 \) Hz, 4.2 Hz, 1H), 2.54-2.17 (m, 4H), 2.19 (d, \( J=1.3 \) Hz, 3H), 1.16 (d, \( J=6.3 \) Hz, 3H); IR (CHCl3) 2950, 1660, 1550, 1430, 1410 cm\(^{-1}\); LRMS (EI, 30 eV) \( mlz \) (relative intensity) 164 (M\(^+\), 52), 122 (100), 94 (38). Anal. Calcd for C11H12O2: C, 73.15; H, 7.36. Found: C, 72.98; H, 7.33.
Experimental Section

3-Methylfuro[2,3-c]chromen-4-one (9). To a solution of tert-BuOK (249 mg, 2.22 mmol) in anhydrous THF (25 mL) was added dropwise 4-hydroxycoumarin (2d) (300 mg, 1.85 mmol) dissolved in anhydrous THF (5 mL). After stirring for 30 min at room temperature, diethylprop-2-ynyl sulfonium bromide (6) (581 mg, 2.78 mmol) was added and the mixture was stirred for 30 min. The reaction mixture was cooled to 0 °C and further stirred for 6 h at this temperature. The resulting mixture was diluted with water, acidified with HCl (ca. pH 3) and extracted with CH₂Cl₂ (x2). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane : ethyl acetate = 30: 1) to give 296 mg (80%) of 4, 5, 6, 7-dihydrobenzofuran-4(5H)-one (11). 3,5-Dimethyl-6,7-dihydrobenzofuran-4(5H)-one (13). 6-Methylcyclohexane-1,3-dione (2b) (280 mg, 2.22 mmol) was used as a starting material. By the same procedure described for the synthesis of 4 and the purification by column chromatography on silica gel (hexane : ethyl acetate = 50 : 1) to 20 : 1 → 18 : 1, 12 (145 mg, 40%) and 13 (163 mg, 45%) were obtained as a colorless solid and a pale yellow oil, respectively.

Spectral data of 11 is as follows: mp 40-42 °C; 1H NMR (CDCl₃, 270 MHz) δ 7.06 (br s, 1H), 2.89-2.84 (m, 2H), 2.54-2.40 (m, 1H), 2.26-2.16 (m, 1H), 2.19 (d, J=1.3 Hz, 3H), 1.97-1.82 (m, 1H), 1.21 (d, J=6.9 Hz, 3H); IR (CHCl₃) 1730, 1630 cm⁻¹; LRMS (FAB) m/z (relative intensity) 165 ([M+H]+, 52), 164 (M+, 25), 155 (50), 154 (51), 137 (79), 107 (27); HRMS (FAB) m/z 165.0918 ([M+H]+, calcd for C₁₀H₁₂O₂ 165.0916).

Spectral data of 13 is as follows: 1H NMR (CDCl₃, 270 MHz) δ 7.08 (q, J=1.0 Hz, 1H), 3.11-2.98 (m, 2H), 2.60-2.38 (m, 2H), 2.28-2.17 (m, 1H), 2.19 (d, J=1.0 Hz, 3H), 1.87-1.72 (m, 1H), 1.34 (d, J=6.9 Hz, 3H); IR (neat) 2960, 2930, 1670, 1550, 1440, 1420, 1410, 1060 cm⁻¹; LRMS (FAB) m/z (relative intensity) 165 ([M+H]+*, 100), 164 (M*, 65), 155 (52), 138 (53), 137 (75), 107 (31); HRMS (FAB) m/z 165.0909 ([M+H]+*, calcd for C₁₀H₁₂O₂ 165.0916).

3,5,5-Trimethyl-6,7-dihydrobenzofuran-4(5H)-one (14) and 3,7,7-Trimethyl-6,7-dihydrobenzofuran-4(5H)-one (15). To a solution of tert-BuOK (288 mg, 2.57 mmol) in anhydrous THF (5 mL) was added dropwise 4,4-dimethylcyclohexane-1,3-dione (2b) (300 mg, 2.14 mmol) dissolved in anhydrous THF (5 mL). After stirring for 30 min at room temperature, the mixture was cooled to 0 °C and diethylprop-2-ynyl sulfonium bromide (6) (671 mg, 3.21 mmol) dissolved in anhydrous THF (5 mL). After stirring for 30 min at room temperature, the mixture was concentrated in vacuo, the residue was purified by chromatography on silica gel (hexane : ethyl acetate = 40: 1) to 20 : 1 → 18 : 1, 12 (126 mg, 51%) and 15 (126 mg, 33%) as a colorless oil and a colorless solid, respectively.
Experimental Section

Spectral data of 14 as was follows: 1H NMR (CDCl3, 270 MHz) δ 7.07 (br s, 1H), 2.84 (t, J=6.3 Hz, 2H), 2.19 (d, J=1.3 Hz, 3H), 1.98 (t, J=6.3 Hz, 2H), 1.17 (s, 6H); IR (neat) 2970, 2930, 1670, 1560, 1450 1420, 1080, 1060 cm⁻¹; LRMS (EI, 30 eV) m/z (relative intensity) 178 (M⁺, 34), 122 (100), 94 (30); HRMS (FAB) m/z 179.1085 ([M+H]+, calcd for C14H19O4 179.1084).

Spectral data of 15 as was follows: mp 54.5-55.0 °C; 1H NMR (CDCl3, 270 MHz) δ 7.06 (q, J=1.3 Hz, 1H), 2.54 (t, J=6.4 Hz, 2H), 2.18 (d, J=1.3 Hz, 3H), 1.96 (t, J=6.4 Hz, 2H), 1.35 (s, 6H); IR (CHCl₃) 2970, 2930, 1650, 1540, 1420, 1400 cm⁻¹; LRMS (EI, 30 eV) m/z (relative intensity) 178 (M⁺, 50), 160 (100), 122 (27); HRMS (FAB) m/z 179.1072 ([M+H]+, calcd for C14H19O4 179.1073). The purification by chromatography on silica gel (hexane : ethyl acetate= 20 : 1) and the purification by column chromatography on silica gel (hexane : ethyl acetate= 20 : 1), 18 (165 mg, 47%) and 19 (45 mg, 13%) were obtained as the pale yellow oils, respectively.

Spectral data of 18 as was follows: 1H NMR (CDCl3, 270 MHz) δ 7.10 (br s, 1H), 4.18 (q, J=7.1 Hz, 2H), 3.25 (s, 1H), 3.07 (d, J=17.2 Hz, 1H), 2.61 (d, J=17.2 Hz, 1H), 2.18 (d, J=1.3 Hz, 3H), 1.27 (t, J=7.1 Hz, 3H), 1.22 (s, 3H), 1.15 (s, 3H); IR (neat) 2960, 1720, 1670, 1550, 1420, 1150 cm⁻¹; LRMS (FAB) m/z (relative intensity) 275 (M⁺H)+, 100, 250 (M⁺, 39), 205 (38); HRMS (FAB) m/z 251.1286 ([M+H]+, calcd for C14H19O4 251.1284).

Spectral data of 19 as was follows: 1H NMR (CDCl3, 270 MHz) δ 7.13 (br s, 1H), 4.22 (q, J=7.3 Hz, 2H), 3.62 (s, 1H), 2.88 (d, J=16.3 Hz, 2H), 2.20 (d, J=16.3 Hz, 1H), 1.29 (t, J=16.3 Hz, 3H), 1.20 (t, J=16.3 Hz, 3H), 1.17 (t, J=16.3 Hz, 3H), 1.16 (s, 3H); IR (neat) 2950, 1720, 1670, 1420, 1140 cm⁻¹; LRMS (FAB) m/z (relative intensity) 251 (M⁺H)+, 100, 250 (M⁺, 29), 177 (31); HRMS (FAB) m/z 251.1286 ([M+H]+, calcd for C14H19O4 251.1284).

Preparation of silyl enol ethers 22, 23, 24, and 25. To a cold (0 °C) solution of ketone (13, 15, 19, 21) (0.15-0.22 mmol) in anhydrous CH₂Cl₂ (2-3 mL) was added

Ethyl 4,5,6,7-Tetrahydro-3,6,6-trimethyl-4-oxo-5-benzofuran-2-carboxylate (18) and Ethyl 4,5,6,7-Tetrahydro-3,6,6-trimethyl-4-oxo-7-benzofuran-2-carboxylate (19). Ethyl 6,6-Dimethyl-2,4-dioxo-1-cyclohexanecarboxylate (2k) (300 mg, 1.39 mmol) was used as a starting material. By the same procedure described for the synthesis of 14 and 15, and the purification by flash chromatography on silica gel (hexane : ethyl acetate = 20 : 1 → 6 : 1), 18 (165 mg, 47%) and 19 (45 mg, 13%) were obtained as the pale yellow oils, respectively.
Experimental Section

dropwise NEt3 (2.5 eq.) followed by TBDSMOTf (1.5 eq.). After stirring for 20 min at 0 °C, the mixture was concentrated in vacuo. The residue was purified by short column chromatography on Al2O3 (hexane : ethyl acetate = 40 : 1) to the corresponding give silyl enol ether (22, 23, 24, 25). The structures of these materials were immediately determined by 1H NMR analyses.

**silyl enol ether of 13 (22):** 1H-NMR (CDCl3, 270 MHz) δ 6.99 (q, J = 1.0 Hz, 1H), 4.59 (br t, J = 4.5 Hz, 1H), 2.98-2.84 (m, 1H), 2.47 (dd, J = 16.2, 8.1, 1H, 1H), 2.13 (ddd, J = 16.2, 10.9, 4.3 Hz, 1H), 2.10 (d, J = 1.0 Hz, 3H), 1.21 (d, J = 6.6 Hz, 3H), 0.97 (s, 9H), 0.22 (s, 6H).

**silyl enol ether of 15 (23):** 1H-NMR (CDCl3, 270 MHz) δ 7.04 (br s, 1H), 4.39 (s, 1H), 4.15 (q, J = 6.9 Hz, 2H), 3.44 (s, 1H), 2.11 (d, J = 1.3 Hz, 3H), 1.24 (t, J = 6.9 Hz, 3H), 1.19 (s, 3H), 1.13 (s, 3H), 0.98 (s, 9H), 0.22 (s, 3H), 0.21 (s, 3H).

**silyl enol ether of 19 (24):** 1H-NMR (CDCl3, 270 MHz) δ 7.04 (br s, 1H), 4.39 (s, 1H), 4.15 (q, J = 6.9 Hz, 2H), 3.44 (s, 1H), 2.11 (d, J = 1.3 Hz, 3H), 1.24 (t, J = 6.9 Hz, 3H), 1.19 (s, 3H), 1.13 (s, 3H), 0.98 (s, 9H), 0.22 (s, 3H), 0.21 (s, 3H).

**silyl enol ether of 21 (25):** 1H-NMR (CDCl3, 270 MHz) δ 6.99 (q, J = 1.3 Hz, 1H), 4.48 (d, J = 2.0 Hz, 1H), 2.47-2.23 (m, 3H), 2.10 (d, J = 1.3 Hz, 3H), 1.86-1.76 (m, 3H), 1.43-1.26 (m, 4H), 0.97 (s, 9H), 0.23 (s, 3H), 0.21 (s, 3H).

3-Methylbenzofuran-4,7-dione (26). To a solution of 17 (57 mg, 0.22 mmol) in chloroform (3 mL) and MeOH (1 mL) was added dropwise a solution of mercury perchlorate (MPC) (228 mg, 0.49 mmol) dissolved in MeOH (3 mL). After stirring for 15 min at room temperature, the mixture was filtered and rinsed with CHCl3. The filtrate was washed with saturated NaHCO3 and extracted with CHCl3 (x2). The combined organic layers were washed with brine, dried over Na2SO4 followed by concentrated in vacuo. The residue was recrystallized from hexane-AcOEt to give 4.06 g (76%) of pure colorless crystals: mp 71-71.5 °C; 1H NMR (CDCl3, 270 MHz) δ 7.58 (dd, J = 8.9, 2.6 Hz, 1H), 6.67 (s, 1H), 2.29 (d, J = 1.2 Hz, 3H); IR (CHCl3) 1670, 1520, 1030 cm-1; LRMS (EI, 30 eV) mlz (relative intensity) 162 (M+*, 100), 108 (21), 52 (26).

**Diisopropylprop-2-ynyl sulfonium bromide (37).** In a light-protected round bottomed flask, a solution of diisopropyl sulfide (5.0 mL, 34.4 mmol) and propargyl bromide (3.1 mL, 34.4 mmol) in anhydrous CH2CN (3 mL) was stirred for 4 d at room temperature. The salt crystallized was washed with anhydrous ether to give 2.28 g (28%) of 37 as a colorless solid. This material was used for the annulated furan synthesis without further purification.

**Experimental Section**

Diisobutylprop-2-ynyl sulfonium bromide (38). In a light-protected round bottomed flask, a solution of diisobutyl sulfide (6.0 mL, 34.2 mmol) and propargyl bromide (3.1 mL, 34.2 mmol) in anhydrous CH2CN (3 mL) was stirred for 12 h at room temperature. The salt crystallized was washed with anhydrous ether to give 5.90 g (65%) of 38 as a colorless solid. This material was used for the annulated furan synthesis without further purification.

**Reaction of 37 with 6,6-dimethyl-cyclohexane-1,3-dione (2i).** 300 mg (2.24 mmol) of 2i was used as the starting material. By the same procedure described for the reaction of salt (6) and 2i, 14 (152 mg, 40%) and 15 (103 mg, 27%) were obtained as a colorless solid and a pale yellow oil, respectively.

**Reaction of 38 with 6,6-dimethyl-cyclohexane-1,3-dione (2i).** 300 mg (2.24 mmol) of 2i was used as the starting material. By the same procedure described for the reaction of salt (6) and 2i, 14 (148 mg, 39%) and 15 (91 mg, 24%) were obtained as a colorless solid and a pale yellow oil, respectively.

3-Methylidenel,1,2,4,5,6,7-hexahydrobenzofuran-4-one (3). To a solution of tert-BuOK (4.8 g, 42.8 mmol) in anhydrous THF (100 mL) was added dropwise 1,3-cyclohexanedione (4.0 g, 35.7 mmol) dissolved in anhydrous THF (40 mL) over 10 min. After stirring for 30 min at room temperature, the mixture was cooled to 0 °C and diethylprop-2-ynyl sulfonium bromide (6) (11.2 g, 53.6 mmol) was added. The reaction mixture was stirred for 6 h at 0 °C. After diluting with water (200 mL), the resulting mixture was extracted with Et2O (150 mL x 3). The combined organic layers were washed with brine and dried over Na2SO4. After removal of the solvent in vacuo, the residue was purified by chromatography on Al2O3 (300 g) (hexane / ethyl acetate = 30 : 1 → 10 : 1) to give 4.68 g of 3 as a pale yellow solid. This material was recrystallized from hexane-ACOEt to give 4.06 g (76%) of pure 3 as colorless crystals: mp 71-71.5 °C; 1H NMR (CDCl3, 270 MHz) δ 5.66 (t, J = 3.3 Hz, 1H), 5.07 (dd, J = 3.3, 2.6 Hz, 2H), 4.83 (t, J = 2.6 Hz, 2H), 2.55 (t, J = 6.3 Hz, 2H), 2.42-2.38 (m, 2H), 2.11-2.02 (m, 2H); IR (CHCl3) 1650, 1600, 1420, 1400 cm-1; LRMS (EI, 30 eV) mlz (relative intensity) 150 (M+*, 70), 12 (100). Anal. Calcd for C10H12O2: C, 71.79; H, 6.71. Found: C, 71.79; H, 6.78.

Diethyl N-[3-(4,5,6,7-Tetrahydro-4-oxo-benzofuran-1-yloxy)propyl]hydrazodicarboxylate (27). To a solution of 3 (100 mg, 0.66 mmol) in anhydrous CH2Cl2 (5 mL) was added diethyl azodicarboxylate (0.21 mL, 1.32 mmol) and the mixture was stirred for 1 h at room temperature. After removal of the solvent in vacuo, the residue was purified by chromatography on silica gel (hexane / ethyl acetate = 2 : 1 → 1 : 1) to give 210 mg (97%) of
Experimental Section

27 as a colorless solid: mp 92-93 °C; 1H NMR (CDCl$_3$, 270 MHz) δ 7.67 (br s, 1H), 7.35 (br s, 1H), 4.66 (br s, 2H), 4.19 (q, J = 7.3 Hz, 2H), 4.18 (q, J = 6.9 Hz, 2H), 2.86 (t, J = 6.3 Hz, 2H), 2.52-2.47 (m, 2H), 2.21-2.12 (m, 2H), 1.27 (t, J = 7.3 Hz, 3H), 1.25 (t, J = 6.9 Hz, 3H); IR (CHCl$_3$) 3000, 2990, 1740, 1710, 1670, 1440, 1300, 1250 cm$^{-1}$; LRMS (FAB) m/z (rel intensity) 325 ([M+H]$^+$, 100), 149 (54). Anal. Calc'd for C$_{13}$H$_9$O$_3$N$_2$: C, 55.55; H, 6.22; N, 8.64. Found: C, 55.36; H, 6.25; N, 8.73.

3-(4,5,6,7-Tetrahydro-4-oxo-benzofuranyl)-1,1,2,2-propanetetracarbonitrile (28). To a solution of 3 (200 mg, 1.33 mmol) in anhydrous CH$_2$Cl$_2$ (8 mL) was added freshly recrystallized tetracyanoethylene (170 mg, 1.33 mmol) and the reaction mixture was stirred for 30 min at room temperature. After removal of the solvent in vacuo, the residue was recrystallized from CH$_2$Cl$_2$-hexane to give 324 mg (88%) of 28 as colorless needles: mp 121 (dec.) °C; 1H NMR (CDCl$_3$, 270 MHz) δ 7.57 (s, 1H), 5.02 (s, 1H), 3.76 (s, 2H), 2.94 (t, J = 6.3 Hz, 2H), 2.59-2.54 (m, 2H), 2.28-2.19 (m, 2H); IR (KBr) 3000, 2950, 2760, 2500, 2240, 1640, 1550, 1450, 1350, 1180, 1000 cm$^{-1}$; LRMS (EI, 30 eV) m/z (rel intensity) 278 (M$^+$, 25), 251 (100), 223 (52), 213 (89), 149 (63), 121 (30), 55 (77), 27 (34). Anal. Calc'd for C$_{13}$H$_9$O$_3$N$_2$: C, 64.74; H, 3.62; N, 20.13. Found: C, 64.69; H, 3.66; N, 20.08.

3-(2-Dimethylaminoethyl)-6,7-dihydrobenzofuran-4(5H)-one (29). To a solution of 3 (100 mg, 0.66 mmol) and sodium acetate (27 mg, 0.33 mmol) in anhydrous CH$_2$Cl$_2$ (5 mL) was added N,N-dimethyl methylene ammonium iodide (Eschenmoser's salt) (244 mg, 1.32 mmol) and the reaction mixture was stirred for 30 min at room temperature. The resulting mixture was quenched with saturated NaHCO$_3$ and extracted with CH$_2$Cl$_2$ (2x). The combined organic layers were dried over Na$_2$SO$_4$ and the solvent was removed in vacuo. The residue was purified by chromatography on silica gel (hexane 2 : 1, then 2 : 1, then 4 : 1) to give 30 mg (86%) of 31 as a colorless oil: 1H NMR (CDCl$_3$, 270 MHz) δ 7.10 (s, 1H), 2.84 (t, J = 6.3 Hz, 2H), 2.65-2.59 (m, 2H), 2.51-2.44 (m, 4H), 2.20-2.10 (m, 2H), 2.15 (s, 3H), 1.93-1.82 (m, 2H); IR (neat) 3290, 1700, 1660, 1420, 1400, 1340, 1060, 990 cm$^{-1}$; LRMS (EI, 30 eV) m/z (rel intensity) 220 (M$^+$, 23), 163 (100), 162 (44), 153 (26); HRMS (FAB) M$^+$ 220.1108 (calc'd for C$_{13}$H$_{17}$O$_5$N 220.1100).

Ethyl 2-Hydroxy-3-(4,5,6,7-tetrahydro-4-oxo-benzofuranyl)-propionate (30). To a solution of 3 (100 mg, 0.66 mmol) and sodium acetate (27 mg, 0.33 mmol) in anhydrous CH$_2$Cl$_2$ (5 mL) was added dropwise ethyl glyoxylate (476 mg, 1.32 mmol) and the reaction mixture was stirred for 1 h at room temperature. The resulting mixture was diluted with water and extracted with CH$_2$Cl$_2$ (2x). The combined organic layers were dried over Na$_2$SO$_4$, and the residual glyoxylate (azeotropic removal with toluene) was removed in vacuo. The residue was purified by chromatography on silica gel (hexane / ethyl acetate = 2 : 1) to give 161 mg (96%) of 30 as a colorless oil: 1H NMR (CDCl$_3$, 270 MHz) δ 7.21 (s, 1H), 4.48 (br t, J = 3.6 Hz, 1H), 4.22 (dq, J = 7.1, 1.0 Hz, 2H), 3.94 (br d, J = 6.3 Hz, 1H), 3.19 (dd, J = 14.9, 4.0, 1.0 Hz, 1H), 3.01 (ddd, J = 14.9, 7.8, 0.8 Hz, 1H), 2.86 (t, J = 6.3 Hz, 2H), 2.53-2.48 (m, 2H), 2.21-2.12 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H); IR (neat) 3450, 2950, 1730, 1660, 1400, 1260, 1200, 1100, 1070, 1000 cm$^{-1}$; LRMS (FAB) m/z (rel intensity) 253 (M$^+$, 100), 252 (M$^+$, 20), 179 (67), 150 (39); HRMS (FAB) [M+H]$^+$ 253.1075 (calc'd for C$_{13}$H$_{17}$O$_5$N 253.1076).

Experimental Section
**Experimental Section**

(M+H)\(^+\), 100, 189 (96), 150 (36), 149 (30), 137 (28); HRMS (FAB) M\(^+\) 207.1024 (calcd for C\(_{12}\)H\(_{17}\)O\(_2\) 207.1022).

**Methyl 3-Methoxycarbonyl-4-(4,5,6,7-tetrahydro-4-oxo-benzofuranyl)-butanoate (34).** To a solution of 3 (100 mg, 0.66 mmol) in anhydrous toluene (5 mL) was added sodium acetate (27 mg, 0.33 mmol) and dimethyl fumarate (476 mg, 3.33 mmol) and the reaction mixture was stirred for 7 h at 45 °C. After removal of the solvent in vacuo, the residue was purified by chromatography on silica gel (hexane:ethyl acetate=4:1) to give 27 mg (88%) of 34 as a colorless solid: mp 70.92°C; 1H NMR (CDCl\(_3\), 270 MHz) \(\delta\) 7.17 (s, 1H), 3.77-3.69 (br m, 1H), 3.14 (br s, 1H), 2.92 (dd, \(J=14.4, 3.6, 0.7\) Hz, 1H), 2.86 (t, \(J=6.4\) Hz, 2H), 2.64 (ddd, \(J=14.4, 7.5, 0.7\) Hz, 1H), 2.53-2.48 (m, 2H), 2.22-2.12 (m, 2H), 1.51 (dq, \(J=7.6, 6.0\) Hz, 2H), 0.98 (t, \(J=7.6\) Hz, 3H); IR (neat) 2940, 2970, 1660, 1560, 1440, 1410, 1070, 1010 cm\(^{-1}\); LRMS (FAB) \(m/z\) (rel intensity) 295 ([M+H]\(^+\), 93), 294 (M\(^+\), 24), 263 (100), 203 (23), 202 (20), 175 (38); HRMS (FAB) M\(^+\) 294.1100 (calcd for C\(_{12}\)H\(_{17}\)O\(_3\) 294.1104).

**3-(4,5,6,7-Tetrahydro-4-oxo-benzofuranyl) propanecarbonitri le (35).** In a sealed tube, 3 (100 mg, 0.66 mmol), sodium acetate (27 mg, 0.33 mmol) and acrylonitrile (0.43 mL, 6.6 mmol) was dissolved in anhydrous xylene (5 mL) and the reaction mixture was heated at 150 °C for 12 h. After removal of the solvent in vacuo, the residue was purified by flash chromatography on silica gel (hexane:ethyl acetate=4:1) to give 116 mg (87%) of 35 as a colorless solid: mp 54-56°C; 1H NMR (CDCl\(_3\), 270 MHz) \(\delta\) 7.16 (s, 1H), 2.86 (t, \(J=6.3\) Hz, 2H), 2.76 (dd, \(J=7.3, 0.7\) Hz, 2H), 2.50-2.45 (m, 2H), 2.34 (t, \(J=6.9\) Hz, 2H), 2.21-2.12 (m, 2H), 1.99 (dt, \(J=7.3, 6.9\) Hz, 2H); IR (CHCl\(_3\)) 2950, 2250, 1660, 1560, 1540, 1440 cm\(^{-1}\); LRMS (EI, 30 eV) \(m/z\) (rel intensity) 209 (M\(^+\), 24), 163 (100), 119 (19). Anal. Calcd for C\(_{12}\)H\(_{17}\)O\(_3\)N: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.92; H, 6.45; N, 6.89.

**3-(2-Hydroxybuthyl)-6,7-dihydrobenzofuran-4(5H)-one (36).**

A) **Thermal condition:** In a cooled (-78 °C) solution of freshly distilled propionaldehyde (0.14 mL, 2.0 mmol) in anhydrous CH\(_2\)Cl\(_2\) (4 mL) was added dropwise hexane solution of EtAICh (0.96 M) (2.1 mL, 2.0 mmol). After stirring for 20 min at -78 °C, a solution of 3 (150 mg, 1.0 mol) in anhydrous CH\(_2\)Cl\(_2\) (2 mL) was added dropwise and the reaction mixture was stirred for 12 h at -78 °C. The reaction mixture was quenched with saturated NaHCO\(_3\) at -42 °C and poured into ether. After diluting with water, the resulting mixture was extracted with Et\(_2\)O (x3). The combined organic layers were washed with brine, dried over Na\(_2\)SO\(_4\) and concentrated in vacuo. The residue was purified by chromatography on silica gel to give 105 mg (50%) of 36 as a colorless oil: 1H NMR (CDCl\(_3\), 270 MHz) \(\delta\) 7.17 (s, 1H), 3.77-3.69 (br m, 1H), 3.14 (br s, 1H), 2.92 (dd, \(J=14.4, 3.6, 0.7\) Hz, 1H), 2.86 (t, \(J=6.4\) Hz, 2H), 2.64 (ddd, \(J=14.4, 7.5, 0.7\) Hz, 1H), 2.53-2.48 (m, 2H), 2.22-2.12 (m, 2H), 1.51 (dq, \(J=7.6, 6.0\) Hz, 2H), 0.98 (t, \(J=7.6\) Hz, 3H); IR (neat) 2940, 2970, 1660, 1440, 1410, 1070, 1010 cm\(^{-1}\); LRMS (FAB) \(m/z\) (rel intensity) 209 ([M+H]\(^+\), 100), 191 (60), 150 (37), 149 (26); HRMS (FAB) M\(^+\) 209.1174 (calcd for C\(_{12}\)H\(_{17}\)O\(_3\) 209.1178).
Experimental Section

CHAPTER III

SYNTHESIS OF MENTHOFURAN

6,7-Dihydro-3,6-dimethylspiro[1,3-dithiane-2,4'(5'H)-benzofuran] (40). To a suspension of zinc triflate (640 mg, 1.76 mmol) and 1,3-propanedithiol (0.3 mL, 3.0 mmol) in anhydrous dichloromethane (2 mL) was added 7 (146 mg, 0.89 mmol) dissolved in anhydrous CH2Cl2 (3 mL). The reaction mixture was stirred for 65 h at room temperature. The resulting mixture was diluted with water and extracted with ether-hexane (1:1 v/v) (x2). The combined organic layers were washed with 2% HCl (x2) and saturated NaHCO3 followed by drying over Na2SO4. After removal of the solvent and residual propanedithiol in vacuo, the residue was purified by chromatography on silica gel (hexane : ether= 30 : 1) to give 188 mg (83%) of 40 as a colorless solid: mp 84-85 °C; 1H NMR (CDCl3, 270 MHz) δ 7.03 (br s, 1H), 3.32-3.08 (m, 2H), 2.90-2.84 (m, 1H), 2.75-2.59 (m, 3H), 2.26 (d, J=1.3 Hz, 3H), 2.25-2.08 (m, 3H), 1.98-1.80 (m, 2H), 1.12 (d, J=6.3 Hz, 3H); IR (CHCl3) 2950, 2910, 1610, 1440-1390, 1260 cm⁻¹; LRMS (EI, 30 eV) m/z (relative intensity) 254 (M+, 51), 180 (100), 165 (34). Anal. Calcd for C13H1sOS2: C, 61.37; H, 7.13. Found: C, 61.61; H, 7.23.

3,6-Dimethyl-4,5,6,7-tetrahydrobenzofuran (menthofuran) (39). To a solution of 40 (37 mg, 0.145 mmol) in ether (1 mL) was added dropwise an ethanolic solution of Raney Nickel W-2 (10 mL) and the mixture was refluxed for 15 min with stirring. The reaction was monitored by TLC (pentane, detection with the Ehrlich reagent). The resulting mixture was filtered and rinsed with pentane. The filtrate was washed with water and dried over Na2SO4. After removal of the solvent in vacuo, the residue was purified by chromatography on silica gel with pentane to give 12 mg (55%) of 39 as a colorless oil. The spectral data (1H NMR, IR, Mass) were identical with that of natural menthofuran reported in the literature.50

3,6-Dimethyl-4,5,6,7-tetrahydrobenzofuran-4(SH)-one (44). To a solution of 3 (190 mg, 1.27 mmol) in DME / H2O (30 mL, 10:1, v/v) was added freshly recrystallized N-bromosuccimide (250 mg, 1.40 mmol) over 30 min at room temperature with stirring. The mixture was stirred for an additional 30 min during which time the pH is maintained within the range 7.0-8.0 by the addition of 10% NaHCO3 solution. The resulting mixture was extracted with ethyl acetate (x3). The combined organic layers were washed with brine and dried over Na2SO4. After removal of the solvent in vacuo, the residue was purified by chromatography on silica gel (hexane : ethyl acetate= 4:1) to give 197 mg (68%) of 44 as a colorless solid: mp 63-64 °C, 1H NMR (CDCl3, 60 MHz) δ 7.40 (br s, 1H), 4.58 (br s, 2H), 2.87 (t, J=6.0 Hz, 2H), 2.61-1.80 (m, 4H); IR (CHCl3) 2930, 1660, 1550, 1440, 1260 cm⁻¹; LRMS (EI, 30 eV) m/z (relative intensity) 230 (M+1, 16), 228 (M+), 149 (100). Anal. Calcd for C9H9O2Br: C, 47.10; H, 3.89. Found: C, 47.19; H, 3.96.

3-(Hydroxymethyl)-6,7-dihydrobenzofuran-4(SH)-one (43). A) Hydrolysis of 44: To a solution of 44 (192 mg, 0.84 mmol) in THF (25 mL) was added 10% NaHCO3 solution (10 mL) and the mixture was refluxed for 20 h with stirring. The resulting mixture was cooled to room temperature and extracted with ethyl acetate (x3). The combined organic layers were washed with brine and dried over Na2SO4. After removal of the solvent in vacuo, the residue was purified by chromatography on silica gel (hexane : ethyl acetate= 3:1) to give 104 mg (75%) of 43 as a colorless solid.

B) Reaction of 3a with MMPP: To a suspension of 3 (3.0 g, 20.0 mmol) and tetrabuthylammonium iodide (370 mg, 1.0 mmol) in dichloromethane (30 mL) was added dropwise aqueous solution of Raney Nickel W-2 (10 mL) and the mixture was refluxed for 15 min with stirring. The reaction was monitored by TLC (pentane, detection with the Ehrlich reagent). The resulting mixture was filtered and rinsed with pentane. The filtrate was washed with water and dried over Na2SO4. After removal of the solvent in vacuo, the residue was purified by chromatography on silica gel with pentane to give 12 mg (55%) of 39 as a colorless oil. The spectral data (1H NMR, IR, Mass) were identical with that of natural menthofuran reported in the literature.50

SYNTHESIS OF MATURONE

3-(Bromomethyl)-6,7-dihydrobenzofuran-4(SH)-one (44). To a solution of 3 (190 mg, 1.27 mmol) in DME / H2O (30 mL, 10:1, v/v) was added freshly recrystallized N-bromosuccimide (250 mg, 1.40 mmol) over 30 min at room temperature with stirring. The mixture was stirred for an additional 30 min during which time the pH is maintained within the range 7.0-8.0 by the addition of 10% NaHCO3 solution. The resulting mixture was extracted with ethyl acetate (x3). The combined organic layers were washed with brine and dried over Na2SO4. After removal of the solvent in vacuo, the residue was purified by chromatography on silica gel (hexane : ethyl acetate= 4:1) to give 197 mg (68%) of 44 as a colorless solid: mp 63-64 °C, 1H NMR (CDCl3, 60 MHz) δ 7.40 (br s, 1H), 4.58 (br s, 2H), 2.87 (t, J=6.0 Hz, 2H), 2.61-1.80 (m, 4H); IR (CHCl3) 2930, 1660, 1550, 1440, 1260 cm⁻¹; LRMS (EI, 30 eV) m/z (relative intensity) 230 (M+1, 16), 228 (M+), 149 (100). Anal. Calcd for C9H9O2Br: C, 47.10; H, 3.89. Found: C, 47.19; H, 3.96.

3-(Hydroxymethyl)-6,7-dihydrobenzofuran-4(SH)-one (43). A) Hydrolysis of 44: To a solution of 44 (192 mg, 0.84 mmol) in THF (25 mL) was added 10% NaHCO3 solution (10 mL) and the mixture was refluxed for 20 h with stirring. The resulting mixture was cooled to room temperature and extracted with ethyl acetate (x3). The combined organic layers were washed with brine and dried over Na2SO4. After removal of the solvent in vacuo, the residue was purified by chromatography on silica gel (hexane : ethyl acetate= 3:1) to give 104 mg (75%) of 43 as a colorless solid.
3-(Methoxymethoxymethyl)benzofuran-4-ol (47). To a solution of 43 (1.50 g, 9.03 mmol) in anhydrous THF (30 mL) was added disopropylethylamine (9.4 mL, 54.2 mmol) and chloromethyl methyl ether (3.4 mL, 45.2 mmol), and the mixture was stirred for 21 h at room temperature. The resulting mixture was quenched with water and extracted with ether. The organic layer was washed with 3% HCl and then the combined aqueous layers were extracted with ether (x2). The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. After removal of the solvent in vacuo, the residue was dissolved in anhydrous THF (2 mL) and then added methyl benzenesulfinate (230 mg, 1.47 mmol), acetic anhydride (1.60 mL, 17.0 mmol) and a catalytic amount of DMAP (180 mg, 1.47 mmol). The mixture was stirred for 90 min at 0 °C. After diluting with ethyl acetate, the organic layer was washed with 3% HCl and then the combined aqueous layers were extracted with ether (x2). The combined organic layers were washed with water and brine followed by drying over Na$_2$SO$_4$. After removal of the solvent in vacuo, the residue was purified by chromatography on silica gel (hexane : ethyl acetate = 2 : 1) to give 3.11 g (99%) of 46 as a colorless oil: $^1$H NMR (CDCl$_3$, 60 MHz) $\delta$ 7.66-7.63 (m, 2H), 7.57-7.53 (m, 3H), 7.37 (br s, 1H), 4.67 (d, J=1.3 Hz, one of C-3 methylene proton), 4.67 (d, J=1.3 Hz, one of C-3 methylene proton), 3.50-3.45 (m, 1H), 3.42 (s, 3H), 3.29-3.18 (m, 1H), 2.90-2.64 (m, 2H), 2.27-2.16 (m, 1H); IR (CHCl$_3$) 3575, 3575-3530 cm$^{-1}$; LRMS (FD, CHCl$_3$) $m/z$ (relative intensity) 210 (M$^+$+1, 16), 209 (94), 208 (100). The crude mixture of 46 was dissolved in anhydrous benzene (6 mL) and the solution was refluxed for 1 h with stirring. The resulting mixture was cooled to room temperature and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane : ethyl acetate = 10 : 1) to give 167 mg (82%) of 47 as a colorless solid: mp 44 °C; $^1$H NMR (CDCl$_3$, 100 MHz) $\delta$ 8.10 (br s, 1H, D$_2$O exchangeable), 7.45 (br s, 1H), 7.21 (dd, $J=7.8, 1.2$ Hz, 1H), 7.04 (dd, $J=7.8, 1.2$ Hz, 1H), 6.76 (dd, $J=7.6, 1.2$ Hz, 1H), 4.85 (s, 2H), 3.45 (s, 3H); IR (CHCl$_3$) 3300, 1580, 1490 cm$^{-1}$; LRMS (EI, 30 eV) $m/z$ (relative intensity) 208 (M$^+$, 23), 147 (30), 146 (100), 45 (45). Anal. Calcd for C$_{11}$H$_{12}$O$_4$: C, 63.45; H, 5.81. Found: C, 63.46; H, 5.82.

3-(Methoxymethoxymethyl)-6,7-dihydrobenzofuran-4(5H)-one (45). A 30-mL round-bottomed flask was charged with sodium hydride (60% dispersion in mineral oil) (59 mg, 1.47 mmol). To a stirred suspension was added dropwise TBDMSOTf (1.35 mL, 5.88 mmol) and the mixture was stirred for 45 min at 0 °C. The resulting mixture was quenched with saturated NaHC$_2$O$_3$ and extracted with hexane (x3). The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. After removal of the solvent in vacuo, the residue was purified by chromatography on silica gel (hexane : ethyl acetate = 3 : 1) to give 488 mg (48%) of 48 as a colorless solid: mp 94-96 °C; $^1$H NMR (CDCl$_3$, 60 MHz) $\delta$ 7.25 (br s, 1H), 5.08 (br s, 2H), 4.63 (d, $J=4.1$ Hz, 1H), 2.67-2.40 (m, 4H), 2.04 (s, 3H), 0.95 (s, 9H), 0.22 (s, 6H). To a solution of 49 (1.02 g, 4.90 mmol) and triethylamine (1.4 mL, 10.0 mmol) in anhydrous CH$_2$Cl$_2$ (10 mL) was added dropwise TBDMSOTf (1.35 mL, 5.88 mmol) and the mixture was stirred for 45 min at 0 °C. The resulting mixture was quenched with saturated NaHC$_2$O$_3$ and extracted with hexane (x3). The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. After removal of the solvent in vacuo, the residue was purified by chromatography on silica gel (hexane : ethyl acetate = 3 : 1) to give 248 mg (48%) of 50 as a pale yellow solid: $^1$H NMR (CDCl$_3$, 60 MHz) $\delta$ 7.20-7.04 (m, 3H), 6.68 (dd, $J=6.3, 2.4$ Hz, 1H), 5.29 (br s, 2H), 2.07 (s, 3H); IR (CHCl$_3$) 3575, 3575-3100, 1700, 1570, 1480, 1430, 1370, 1340, 1250 cm$^{-1}$; LRMS (EI, 30 eV) $m/z$ (relative intensity) 206 (M$^+$, 25), 147 (20), 146 (100). Anal. Calcd for C$_{11}$H$_{12}$O$_4$: C, 64.07; H, 4.89. Found: C, 63.80; H, 5.15.
Experimental Section

3-(Hydroxymethyl)benzofuran-4-ol (48).

A) Hydrolysis of 47: To a solution of 47 (150 mg, 0.72 mmol) in methanol (10 mL) was added 36% HCl (2 drops) and the mixture was refluxed for 70 min with stirring. The resulting mixture was cooled to room temperature and then added saturated NaHCO3 (5 drops). After removal of the solvent in vacuo, the residue was diluted with water and extracted with ethyl acetate (x2). The combined organic layers were washed with brine, dried over Na2SO4, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane : ethyl acetate = 4:1) to give 99 mg (84%) of 48 as a colorless solid.

B) Hydrolysis of 51: To a solution of 51 (332 mg, 1.61 mmol) in methanol (15 mL) was added 1M K2CO3 solution (7 mL) and the mixture was stirred for 30 min at room temperature. The resulting mixture was extracted with ethyl acetate (x3). The combined organic layers were washed with brine and dried over Na2SO4. After removal of the solvent in vacuo, the residue was purified by chromatography on silica gel (hexane: ethyl acetate = 1:1) to give 242 mg (92%) of 52 as a colorless solid: mp 100-102 °C; 1H NMR (CDCl3, 60 MHz) δ 7.37 (br s, 1H), 7.20 (dd, J=8.2, 7.6 Hz, 1H), 7.02 (dd, J=8.2, 1.2 Hz, 1H), 6.74 (dd, J=7.6, 1.2 Hz, 1H), 4.87 (d, J=1.0 Hz, 2H); IR (CHCl3) 3600, 3300, 1580, 1490, 1370, 1240 cm-1; LRMS (EI, 30 eV) m/z (relative intensity) 178 (M+, 100), 164 (M+, 53), 146 (100), 118 (25), 89 (21). Anal. Calcd for C9H6O4: C, 60.68; H, 3.39. Found: C, 60.63; H, 3.45.

(42) was purified by recrystallization (ethyl acetate-hexane) and was removed containing water by azeotropic distillation with toluene before use. Piperylene (cis-trans mixture) was distilled under argon and stored under MS 4A.

A) BF3 catalyzed Diels-Alder reaction: To a cold (-42 °C) solution of 42 (30 mg, 0.17 mmol) in anhydrous CH2Cl2 (5 mL) was added dropwise freshly distilled BF3·Et2O. After stirring for 20 min, piperylene (0.17 mL, 0.17 mmol) was added. The reaction mixture was stirred at -40 °C until the completion of the reaction. The resulting mixture was quenched with water and then warmed to room temperature. The resulting mixture was extracted with ethyl acetate (x2). The combined organic layers were washed with water and brine followed by drying over Na2SO4. After removal of the solvent in vacuo, the residue was purified by chromatography on silica gel (hexane : ethyl acetate = 2:1) to give the mixture of 52 and 53 as a brown oil.

B) TiCl2(Oi-Pr)2 catalyzed Diels-Alder reaction: To a cooled suspension of 42 (30 mg, 0.17 mmol) and powdered MS 4A (300 mg) in anhydrous CH2Cl2 (5 mL) was added CH2Cl2 solution (0.28 mL) of TiCl2(Oi-Pr)2 which was freshly prepared from equimolar amount of TiCl4 and Ti(Oi-Pr)4.60 After stirring for 1 h, piperylene (0.17 mL, 0.17 mmol) was added. The reaction mixture was stirred at low temperature until the completion of the reaction. By the same procedure described for BF3·Et2O catalyzed reaction, the mixture of 52 and 53 was obtained: Spectral data of the mixture of 52 and 53 is as follows: 1H NMR (CDCl3, 270 MHz) δ 7.59 (br s, 1H), 5.88-5.76 (m, 2H), 4.71 (d, J=1.0 Hz, one of C-3 methylene proton), 4.70 (d, J=1.2 Hz, one of C-3 methylene proton), 4.61 (d, J=0.8 Hz, one of C-3 methyl proton), 3.60-2.96 (m, 4H, D2O exchangeable); IR (CHCl3) 3450, 3100, 1660, 1580, 1530, 1360 cm-1; LRMS (EI, 30 eV) m/z (relative intensity) 244 (M+, 8), 242 (14), 226 (100); HRMS (EI, 30 eV) m/z 210.0900 (M+, calcld for C13H14O4 210.0901).
Aromatization of 52 and 53: maturone (41) and isomaturone (54). In a sealed tube, the mixture of 52 and 53 (46 mg, 0.19 mmol) was dissolved in m-xylene (15 mL). Chloranil (230 mg, 0.94 mmol) was added and the reaction mixture was heated for 24 h at 140 °C. After removal of the solvent in vacuo, the residue was purified by chromatography on silica gel (hexane: ethyl acetate= 3:1) to give the mixture of maturone (41) and isomaturone (54) (36 mg, 79%) as a yellow solid. Recrystallization of the mixture of 41 and 54 from acetone-hexane afforded pure maturone as yellow needles. The spectral data (1H NMR, IR, Mass) were identical with those of natural maturone reported in the literature.52,61

SYNTHESIS OF TUBIPOFURANS

3,6-Dimethyl-6,7-dihydrobenzofuran-4(5H)-one (7) (large scale procedure). To a solution of tert- BuOK (10.7 g, 95.4 mmol) in anhydrous THF (200 mL) was added dropwise 5-methyl-1,3-cyclohexanedione (10.0 g, 79.3 mmol) dissolved in anhydrous THF (150 mL) over 20 min. After stirring for 30 min at room temperature, the mixture was cooled to 0 °C and diethylprop-2-ynyl sulfonium bromide (6) (24.9 g, 119.0 mmol) was added. The reaction mixture was stirred for 6 h at 0 °C. After dilution with water (500 mL), the resulting mixture was extracted with Et2O (300 mL x 3). In a separatory funnel, the combined organic layers were treated with 5% HCl (400 mL) for about 10 min. The 5% HCl solution was extracted with Et2O (200 mL x 1) and then the combined organic layers were washed with saturated NaHCO3 followed by drying over Na2SO4. After removal of the solvent in vacuo, the residue was purified by chromatography on silica gel (300 g) (hexane: ethyl acetate= 20:1) to give 11.3 g (87%) of 7 as a pale yellow solid.

3,6-Dimethylbenzofuran-4-ol (61). In a sealed tube, a mixture of 7 (5.0 g, 30.6 mmol) and 10% Pd-C (6.0 g) in p-cymene (50 mL) was heated for 12 h at 200 °C. The resulting mixture was filtered and rinsed with ethyl acetate. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica gel (hexane : ethyl acetate = 8 : 1) to give 3.25 g (65%) of 61 as a colorless solid: mp 92-94 °C; 1H NMR (CDCl3, 60 MHz) 8 7.18 (br s, 1H), 6.84 (br s, 1H) 6.33 (br s, 1H), 5.13 (br s, 1H, D2O exchangeable), 3.37 (s, 3H), 3.35 (s, 3H); IR (CHCl3) 3600, 3350, 2900, 1630, 1610, 1580, 1420, 1320, 1240 cm⁻¹; LRMS (EI, 30 eV) m/z (relative intensity) 162 (M⁺ 100), 161 (52). Anal. Calcd for C10H10O2: C, 74.06; H, 6.21. Found: C, 74.11; H, 6.27.

3,6-Dimethylbenzofuran-4,7-dione (60). A solution of 61 (2.5 g, 15.4 mmol) in EtOH (70 mL) was cooled to 0 °C and an ice cooled aqueous buffer solution of freshly prepared Fremy’s salt (12.5 g, 46.6 mmol dissolved in 700 mL of 0.07 M KH2PO4 solution) was added dropwise over 1.5 h with stirring at 0 °C. The reaction mixture was further stirred for 1 h at 0 °C and then allowed to stand for 30 min at 0 °C. The red precipitate was filtered off, dissolved in ethyl acetate, washed with water and brine followed by drying over Na₂SO₄. After removal of the solvent in vacuo, recrystallization (from ethyl acetate / hexane x2) of the crude mixture gave 1.54 g (57%) of 60 as an orange-yellow solid. The filtrate was extracted with ethyl acetate (x2) and the combined organic layers were washed with water and brine followed by drying over Na₂SO₄. After removal of the solvent, the residue was purified by chromatography on silica gel (hexane : ethyl acetate = 2 : 1) to give an additional 75 mg (3%) of
Experimental section

60 as a yellow solid: mp 145-147 °C; ^1H NMR (CDCl3, 60 MHz) δ 7.45 (br s, 1H), 6.50 (br s, 1H), 2.27 (s, 3H), 2.12 (s, 3H); IR (CHCl3) 1650, 1530, 1380 cm⁻¹; LRMS (EI, 30 eV) m/z (relative intensity) 176 (M⁺, 100), 148 (25), 108 (23), 91 (30), 52 (22). Anal. Calcd for C10H13O3: C, 68.18; H, 4.58. Found: C, 68.20; H, 4.62.

(4αβ,8α,8αβ)-6-(tert-Butyldimethylsiloxy)-8-hydroxy-3,8a-dimethyl-4a,5,8,8a-tetrahydronaphtho[2,3-b]furan-4,9-dione (58) and (4αβ,5α,8αβ)-7-(tert-Butyldimethylsiloxy)-5-hydroxy-3,8a-dimethyl-4a,5,8,8a-tetrahydronaphtho[2,3-b]furan-4,9-dione (62). A mixture of 60 (3.10 g, 17.6 mmol) and diene 72 (59) (8.74 g, 40.8 mmol) in anhydrous toluene (150 mL) was refluxed for 12 h with stirring. After cooling to room temperature, the solvent was evaporated in vacuo. The residue was purified by chromatography on silica gel (hexane:ethyl acetate= 8: 1) to give the mixture of 58 and 62 (6.74 g, 98%) as a colorless solid. Recrystallization of the mixture from hexane (x2) afforded 5.50 g (80%) of 58 as colorless plates.

Spectral data of 58 is as follows: mp 134-135 °C; ^1H NMR (CDCl3, 270 MHz) δ 7.41 (br s, 1H), 5.05 (dm, J = 5.9 Hz, 1H), 3.69 (d, J = 5.9 Hz, 1H), 3.17 (d, J = 18.3 Hz, 1H), 3.02 (d, J = 7.8 Hz, 1H), 2.97 (s, 3H), 2.25 (d, J = 1.0 Hz, 3H), 2.12 (ddm, J = 18.3, 7.8 Hz, 1H), 1.40 (s, 3H), 0.96 (s, 9H), 0.24 (s, 3H), 0.20 (s, 3H); IR (CHCl3) 2950, 2930, 2850, 1680, 1520, 1380, 1260, 1250 cm⁻¹; LRMS (EI, 30 eV) m/z (relative intensity) 390 (M⁺, 16), 214 (30), 157 (41), 143 (100), 136 (55), 108 (63), 75 (25), 73 (29). Anal. Calcd for C21H32O3Si: C, 64.58; H, 8.22. Found: C, 64.20; H, 8.12.

To a cooled (0 °C) solution of 62 (2.79 g, 7.11 mmol) in CHCl3 (20 mL) was added NaHCO3 (912 mg, 3.13 mmol) was refluxed for 4 h with a Dean-Stark apparatus. After stirring for 10 min at 0 °C, the reaction mixture was poured into ice-cold water and brine followed by drying over Na2SO4. After removal of the solvent in vacuo, the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 2: 1) to give 1.64 g (94%) of 64 as a colorless solid: mp 115-116 °C; ^1H NMR (CDCl3, 270 MHz) δ 7.17 (br s, 1H), 5.04 (br d, J = 3.6 Hz, 1H), 4.82 (d, J = 6.4 Hz, 1H, D₂O exchangeable to singlet), 3.86 (m, 1H), 3.30 (s, 3H), 3.01 (d, J = 6.4 Hz, 1H, D₂O exchangeable), 2.81 (ddm, J = 16.9, 7.0, 1H), 2.60 (dd, J = 7.0, 6.4 Hz, 1H), 2.19 (d, J = 1.3 Hz, 3H), 2.15 (ddm, J = 16.9, 6.4 Hz, 1H), 1.21 (s, 3H), 0.92 (s, 9H), 0.17 (s, 6H); IR (CHCl3) 3550, 2950, 2850, 1670, 1360, 1250 cm⁻¹; LRMS (EI, 30 eV) m/z (relative intensity) 392 (M⁺, 10), 304 (24), 303 (100), 285 (23), 228 (26), 223 (30), 211 (20), 138 (60), 137 (42), 75 (33), 73 (42). Anal. Calcd for C21H32O3Si: C, 64.25; H, 6.82. Found: C, 64.20; H, 8.12.

(4αβ,8αβ,9α)-9-Hydroxy-3,8a-dimethyl-4a,5,8,8a-tetrahydronaphtho[2,3-b]furan-4,9-dione (64). To a cooled (0 °C) solution of 63 (2.79 g, 7.11 mmol) in CHCl3 (20 mL) was added CF₃COOH (3 mL) in one portion. After stirring for 10 min at 0 °C, the reaction mixture was poured into ice-cold water and brine followed by drying over Na₂SO₄ and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 2: 1) to give 1.64 g (94%) of 64 as a colorless solid: mp 137-138 °C; ^1H NMR (CDCl3, 270 MHz) δ 7.22 (br s, 1H), 6.98 (d, J = 10.2 Hz, 1H), 6.08 (d, J = 10.2 Hz, 1H), 4.90 (br d, J = 2.3 Hz, 1H), 3.41 (br s, 1H), 3.24 (dd, J = 17.4, 7.4 Hz, 1H), 2.87 (dd, J = 17.4, 5.1 Hz, 1H), 2.67 (dd, J = 17.3, 5.1 Hz, 1H), 2.19 (d, J = 1.0 Hz, 3H), 1.46 (s, 3H); IR (CHCl3) 3610, 3430, 2990, 2950, 2880, 1660, 1540, 1390, 1250 cm⁻¹; LRMS (EI, 30 eV) m/z (relative intensity) 246 (M⁺, 34), 228 (21), 158 (100), 110 (68), 109 (36). Anal. Calcd for C14H14O4: C, 72.88; H, 5.73. Found: C, 68.25; H, 5.69.

(4αβ,8αβ,9α)-4',5',8'a,9'-Tetrahydro-9-hydroxy-3',8'-dimethylsipo[1,3-dioxolane-2,6'-naphtho[2,3-b]furan-4'-one (65). A solution of 64 (1.54 g, 6.25 mmol), anhydrous benzene (150 mL), ethylene glycol (7.0 mL, 125 mmol) and collidine-p-toluenesulfonate (912 mg, 3.13 mmol) was refluxed for 4 h with a Dean-Stark apparatus. After cooling to room temperature, the reaction mixture was washed with water and cooled with brine followed by drying over Na₂SO₄. After removal of the solvent in vacuo, the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 1: 1) to give 1.66 g (92%) of 65 as a colorless solid: mp 137-138 °C; ^1H NMR (CDCl3, 270 MHz) δ 7.24 (q, J = 1.3 Hz, 1H), 5.93 (dd, J = 10.1, 1.7 Hz, 1H), 5.74 (d, J = 10.1 Hz, 1H), 4.52 (d, J = 2.6 Hz, 1H), 4.09-3.91 (m, 4H), 2.69 (dd, J = 13.9, 3.6 Hz, 1H), 2.43 (dd, J = 13.9, 12.9 Hz, 1H), 2.40 (d, J = 2.6 Hz, 1H), 2.23 (d, J = 1.3 Hz, 3H), 2.03 (ddd, J = 12.9, 3.6, 1.7 Hz, 1H), 1.42 (s, 3H); IR (CHCl3) 3580, 2970, 2880, 1680, 1560, 1420, 1240 cm⁻¹; LRMS (FAB) m/z (relative intensity) 414 (M⁺, 100), 370 (34), 304 (24), 303 (100), 285 (22), 228 (26), 223 (30), 211 (20), 158 (60), 137 (42), 75 (33), 73 (42).
Experimental section

intensity) 291 ([M+H]+, 100), 289 (21), 138 (27), 137 (45). Anal. Calcd for C_{16}H_{19}O_{4}: C, 66.22; H, 6.24. Found: C, 66.00; H, 6.27.

\[ \text{O} \cdot \{4'(a\beta, b\alpha, a\beta') - 4', 8'a, 9', 9'-\text{Tetrahydro-3', 8'a-dimethyl-4-oxospiro[1,3-dioxolane-2,6'\{5'H\} - naphtho[2,3-b]furan-9'-yl] S-Methyl Dithiocarbonate (66).} \]

To a cooled (0 °C) solution of LAH (120 mg, 3.17 mmol) in anhydrous THF (30 mL) was added carbon disulfide (1.1 mL, 18.3 mmol), iodomethane (1.1 mL, 17.7 mmol) followed by sodium hydride (60% dispersion in mineral oil) (206 mg, 5.16 mmol). After stirring for 20 min, the reaction mixture was quenched with a small amount of water and the solvent was evaporated in vacuo. The residue was diluted with water and extracted with Et_{2}O (x3). The combined organic layers were washed with brine, dried over Na_{2}SO_{4} and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane / EtOAc = 4 : 1) to give 795 mg (95%) of 67 (869 mg, 3.17 mmol) dissolved in anhydrous THF (7 mL). After stirred for 20 min, the reaction mixture was quenched with saturated NH_{4}Cl, filtered through Celite® and rinsed with Et_{3}O. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica gel (hexane / ethyl acetate = 1 : 1) to give 68 (α-OH : β-OH = 10.5 : 1) (858 mg, 98%) as a colorless solid. The major product (α-hydroxy epimer) was isolated by the recrystallization from ether. Spectral data of the α-hydroxy epimer of 68 is as follows: mp 142-143 °C; 1H NMR (CDCl_{3}, 270 MHz) δ 7.05 (br s, 1H), 5.81 (d, J=9.9 Hz, 1H), 5.50 (dd, J=9.9, 1.7 Hz, 1H), 5.03 (m, 1H), 4.06-3.90 (m, 4H), 2.62 (dd, J=17.0, 1.7 Hz, 1H), 2.36 (dd, J=17.0, 1.0 Hz, 1H), 2.24-2.11 (m, 2H), 2.10 (d, J=6.3 Hz, 1H), 1.50 (dd, J=14.1, 13.2 Hz, 1H), 1.08 (s, 3H); IR (CHCl_{3}) 3580, 3430, 2940, 2890, 1360 cm\(^{-1}\); LRMS (EI, 30 eV) m/z (relative intensity) 276 (M\(^+\), 36), 259 (60), 229 (24), 198 (27), 138 (27), 137 (50); HRMS (FAB) [M+H]+ 367.1035 (calcd for C_{16}H_{20}O_{4}S_{2} 367.1039).

\[ \text{O} \cdot \{4', 4'a, 8'a, 9', 9'-\text{Tetrahydro-3', 8'a-dimethylspiro[1,3-dioxolane-2,6'(5'H) - naphtho[2,3-b]furan-4'-yl] S-Methyl Dithiocarbonate (69).} \]

A solution of the 68 (459 mg, 1.66 mmol), CH_{2}Cl_{2} (10 mL), 50% (w/v) aqueous NaOH (10 mL), and Bu_{4}N\(^{+}\)HSO_{4}- (564 mg, 1.66 mmol) was vigorously stirred at room temperature. Carbon disulfide (1.0 mL, 16.6 mmol) was added and followed by iodomethane (0.52 mL, 8.3 mmol). After vigorously stirring for 20 min, the reaction mixture was poured into ethyl acetate. Water was added and extracted with ethyl acetate (x2). The combined organic layers were washed with brine, dried over Na_{2}SO_{4} and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane / ethyl acetate = 8 : 1) to give 69 (440 mg) as a yellow viscous oil with a small amount of inseparable contaminant. This material was used for the following step without further purification. The analytical sample was obtained by the further chromatography separation: 1H NMR (CDCl_{3}, 270 MHz) δ 7.07 (br s, one of C-2 proton), 7.03 (br s, one of C-2 proton), 6.85 (d, J=9.9 Hz, one of C-7 proton), 5.98 (d, J=9.9 Hz, one of C-8 proton), 5.83 (d, J=9.9 Hz, one of C-7 proton), 5.50 (dd, J=9.9, 1.7 Hz, one of C-8 proton), 5.25-5.19 (m, 1H), 4.07-3.89 (m, 4H), 2.84-2.03 (m, 4H), 2.48 (s, one of S-methyl proton), 2.46 (s, one of S-methyl proton), 2.01 (d, J=1.3 Hz, one of C-3 methyl proton), 1.99 (d, J=1.3 Hz, one of C-3 methyl proton), 1.62 (d, J=13.9, 1.3 Hz, one of C-8a methyl proton), 1.29 (s, one of C-8a methyl proton), 1.15 (s, one of C-8a methyl proton); IR (CHCl_{3}) 2970, 2930, 2880, 2850, 1360 cm\(^{-1}\); LRMS (EI, 30 eV) m/z (relative intensity) 276 (M\(^+\), 36), 259 (48), 173 (34), 172 (43), 171 (57), 147 (39), 146 (71), 124 (68), 109 (36), 73 (100), 45 (53). Anal. Calcd for C_{16}H_{23}O_{4}: C, 69.55; H, 7.29. Found: C, 69.32; H, 7.28.
(4aβ,8aβ)-4',4a,8'a,9'-Tetrahydro-3',8'a-dimethylspiro[1,3-dioxolane-2,6'-
(5'H)-naphtho[2,3-b]furan] (70). To a heated (110 °C) solution of Bu3SnH (3.0 mL, 11.6 mmol) with a catalytic amount of AIBN (5 mg) was added dropwise 69 (440 mg) dissolved in anhydrous toluene (3 mL) over 20 min. After refluxing for 5 h, during which time the color had changed from yellow to colorless, the reaction mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 10:1) to give 301 mg of 70 as a colorless solid: mp 69-69 °C; 1H NMR (CDCl3, 270 MHz) δ 7.08 (br s, one of C-2 proton), 7.03 (br s, one C-2 proton), 6.84 (d, J=9.9 Hz, one C-8 proton), 6.99 (d, J=9.9 Hz, 2.3 Hz, one C-8 proton), 5.93 (d, J=9.9 Hz, one C-7 proton), 5.85 (d, J=9.9 Hz, one C-7 proton), 2.66 (br s), 2.56 (m), 2.47 (m), 2.26 (d, J=13.2, 6.6 Hz, one C-5 proton), 1.95 (d, J=13.1 Hz, one C-3 methyl proton), 1.93 (ddd, J=13.2, 4.8, 2.5 Hz, one of C-4a proton), 1.87 (d, J=1.0 Hz, one of C-3 methyl proton), 1.20 (s, one of C-8a methyl proton), 1.15 (d, J=6.9 Hz, one of C-5 methyl proton), IR (CHCl3) 2960, 2910, 2870, 1640, 1440, 1360 cm⁻¹; LRMS (FAB) m/z (relative intensity) 261 ([M+H]+, 100), 259 (46), 109 (20), 108 (42); HRMS (FAB) [M+H]+ 260.1407 (calcd for C16H20O3 260.1413).

A solution of 70 (301 mg) in THF (5 mL) was treated with 2 N HCl (0.5 mL) and stirred for 10 min, the reaction mixture was quenched with saturated NaHCO3 (2 mL), diluted with water and extracted with Et2O (x3). The combined organic layers were washed with brine, dried over Na2SO4 and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 20:1) to give 46 mg (quant.) of 57.

Experimental section

4',4a,8'a,9'-Tetrahydro-3',8'a-dimethylspiro[1,3-dioxolane-2,6'-
(5'H)-naphtho[2,3-b]furan-4',9'-dien] (71). To a cold (0 °C) solution of LALH (12.5 mg, 0.33 mmol) in anhydrous THF (5 mL) was added dropwise 64 (96 mg, 0.33 mmol) dissolved in anhydrous THF (1 mL). After stirring for 20 min, the reaction mixture was quenched with saturated NH4Cl, filtered through Celite® and rinsed with Et2O. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 1:2) to give 71 (85 mg, 88%) as a colorless solid: 1H NMR (benzene-d6, 270 MHz) δ 6.94 (br s, 1H), 5.82 (dd, J=9.9, 1.3 Hz, one of C-8 proton), 5.76 (dd, J=9.9, 1.3 Hz, one of C-8 proton) 5.34 (d, J=9.9 Hz, one of C-7 proton), 5.18 (d, J=9.9 Hz, one of C-7 proton), 4.73 (br d, J=5.0 Hz), 4.45 (br a), 4.14 (s), 4.00 (s), 3.61-3.48 (m, 4H), 2.60-2.22 (m), 2.14 (dm, J=11.9 Hz), 2.03 (d, J=1.6 Hz, one of C-3 methyl proton), 1.90 (d, J=1.0 Hz, one of C-3 methyl proton), 1.76 (dm, J=13.2 Hz), 1.09 (s, one of C-8a methyl proton), 0.69 (s, one of C-8a methyl proton), IR (CHCl3) 3600, 3450, 2960, 2870, 1360, 1220 cm⁻¹; LRMS (FAB) m/z (relative intensity) 293 ([M+H]+, 8), 275 (100, 140 (43); HRMS (FAB) [M+H]+ 293.1383 (calcd for C16H20O3 293.1389).

3,5,8a-Trimethyl-4,4a,8a,9-tetrahydronaphtho[2,3-b]furan-6(5H)-one (72). To a cold (-42 °C) solution of LDA (from 0.18 mL (1.3 mmol) of disopropylamine and 0.87 mL (1.30 mmol) of 1.5 M BuLi) in anhydrous THF (5 mL) was added 57 (57 mg, 0.26 mmol) dissolved in anhydrous THF (1 mL). The reaction mixture was stirred for 30 min at -42 °C and then further stirred for 30 min at 0 °C. After recooling to -42 °C, HMPA (0.23 mL, 1.30 mmol) was added followed by iodomethane (0.16 mL, 2.60 mmol). The reaction mixture was warmed to 0 °C and further stirred for 30 min. After quenching with water, the resulting mixture was extracted with Et2O (x3). The combined organic layers were washed with brine, dried over Na2SO4 and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 4:1) to give 72 (87 %; mp 78-79 °C). 1H NMR (CDCl3, 270 MHz) δ 7.08 (br s, one of C-2 proton), 7.03 (br s, one C-2 proton), 6.84 (d, J=9.9 Hz, one C-8 proton), 6.99 (d, J=9.9, 2.3 Hz, one of C-8 proton), 5.93 (d, J=9.9 Hz, one C-7 proton), 5.85 (d, J=9.9 Hz, one C-7 proton), 2.66 (br s), 2.56 (m), 2.47 (m), 2.26 (d, J=13.2, 6.6 Hz, one C-5 proton), 1.95 (d, J=1.3 Hz, one of C-3 methyl proton), 1.93 (ddd, J=13.2, 4.8, 2.5 Hz, one of C-4a proton), 1.87 (d, J=1.0 Hz, one of C-3 methyl proton), 1.20 (s, one of C-8a methyl proton), 1.15 (d, J=6.9 Hz, one of C-5 methyl proton), IR (CHCl3) 2960, 2910, 2860, 1660, 1440, 1360 cm⁻¹; LRMS (EI, 30 eV) m/z (relative intensity) 230 (M⁺, 12), 108 (100); HRMS (FAB) [M+H]+ 231.1387 (calcd for C16H19O2 231.1386).

3,5,8a-Trimethyl-4,4a,8a,9-hexahydropyrido[2,3-b]furan-6-ol (73). To a cold (0 °C) solution of LAH (8.0 mg, 0.21 mmol) in anhydrous THF (3 mL) was added dropwise 72 (46 mg, 0.20 mmol) dissolved in anhydrous THF (1 mL). After stirring for 10 min, the reaction mixture was quenched with saturated NH4Cl, filtered through and rinsed with Et2O. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 4:1) to give 46 mg (quant.) of 73.
of C-3 methyl proton), 1.91 (d, J=1.3 Hz, one of C-3 methyl proton), 1.55-1.35 (m), 1.05 (s, one of C-8a methyl proton), 1.03 (d, J=6.3 Hz, one of C-5 methyl proton); IR (CHCl3) 3600, 3430, 2960, 2920, 2860, 1440, 1370, 1310, cm\(^{-1}\); LRMS (EI, 30 eV) \(m/z\) (relative intensity) 232 (\(M^+\)), 214 (14), 108 (100); HRMS (FAB) \(M^+\) 232.1466 (calcd for \(C_{15}H_{20}O_2\) 232.1464).

Tubipofuran (55). In a sealed tube, 73 (10.0 mg, 0.043 mmol) was dissolved in anhydrous pyridine (1 mL). Al\(_2\)O\(_3\) (ICN, neutral, activity grade I) was added and the reaction mixture was heated for 8 h at 200 °C. The resulting mixture was filtered and rinsed with MeOH. The filtrate was concentrated in vacuo and chromatography on silica gel (hexane / ethyl acetate = 30 : 1) to give 5.0 mg (54%) of tubipofuran (55) as a colorless oil. The spectral data (\(^1\)H NMR, IR, Mass) were identical with those of natural tubipofuran reported in the literature.\(^3\)

Methyl (4a\(\beta\),5\(\beta\),8a\(\beta\))-4,4a,5,6,8a,9-Hexahydro-3,8a-dimethyl-6-oxo-5-naphtho[2,3-\(b\)]furancarboxylate (74). To a cold (-42 °C) solution of LDA (from 0.24 mL (1.71 mmol) of diisopropylamine and 1.14 mL (1.71 mmol) of 1.5 M BuLi) in anhydrous anhydrous THF (5 mL) was added \(\beta\)-ketoester methyl cyanoformate (0.14 mL, 1.76 mmol). In this mixture was slowly warmed to 0 °C, and then further stirred for 30 min at 0 °C. After recooling to -42 °C, HMPA (0.30 mL, 1.71 mmol) was added followed by methyl cyanoformate (0.14 mL, 1.76 mmol). The reaction mixture was slowly warmed to 0 °C, quenched with water and extracted with Et\(_2\)O (x3). The combined organic layers were washed with brine, dried over Na\(_2\)SO\(_4\), and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane / ethyl acetate = 50 : 1) to give 14.9 mg (87%) of 74 as a colorless oil. \(^1\)H NMR (CDCl\(_3\), 270 MHz) \(\delta\) 11.79 (br s, enol proton), 7.09 (br s, one of C-2 proton), 7.01 (br s, one of C-2 proton), 6.95 (d, J=10.2 Hz, one of olefin proton), 6.10 (dd, J=9.8, 1.7 Hz, one of olefin proton), 5.99 (d, J=10.2 Hz, one of olefin proton), 5.94 (d, J=9.8 Hz, one of olefin proton), 3.81 (s, one of ester methyl proton), 3.79 (s, one of ester methyl proton), 3.34 (d, J=12.9 Hz, C-5 proton), 2.76-2.45 (m, 4H), 2.17-2.04 (m, 1H), 1.90 (d, J=1.3 Hz, one of C-3 methyl proton), 1.89 (d, J=1.3 Hz, one of C-3 methyl proton), 1.24 (s, one of C-8a methyl proton), 1.22 (s, one of C-8a methyl proton); IR (CHCl3) 2940, 2900, 2830, 1730, 1660, 1640, 1570, 1430, 1340, 1280, 1220 cm\(^{-1}\); LRMS (FAB) \(m/z\) (relative intensity) 275 (\([M+H]^+\), 100), 274 (\(M^+\), 55), 273 (40), 243 (61), 149 (32), 109 (44), 108 (68), 95 (31), 69 (32), 55 (30); HRMS (FAB) \(M^+\) 274.1211 (calcd for \(C_{16}H_{20}O_2\) 274.1205).

Experimental section

Methyl 4,4a,5,6,8a,9-Hexahydro-6-hydroxy-3,8a-dimethyl-5-naphtho[2,3-\(b\)]furancarboxylate (75). To a solution of 74 (20.4 mg, 0.074 mmol) in anhydrous MeOH (2.7 mL) and THF (0.3 mL) was added CeCl\(_3\)•7H\(_2\)O (447 mg, 1.2 mmol) followed by NaBH\(_4\) (3 mg, 0.079 mmol). The reaction mixture was stirred for 3 h at room temperature, during which time NaBH\(_4\) (3 mg, 0.079 mmol) was added for each 1 h. After quenching with water, the resulting mixture was extracted with ether (x3). The combined organic layers were washed with brine, dried over Na\(_2\)SO\(_4\), and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane / ethylene acetate = 20 : 1) to give 72 mg (75%) of 75 as a colorless oil. \(^1\)H NMR (CDCl\(_3\), 270 MHz) \(\delta\) 7.07 (br s, 1H), 5.85 (d, J=9.9 Hz, one of olefin proton), 5.78-5.70 (m, one of olefin proton), 5.57 (dd, J=9.9, 2.3 Hz, one of olefin proton), 4.62 (br d, J=9.2 Hz, one of hydroxy proton), 4.60 (br s, one of hydroxy proton), 3.74 (s, one of ester methyl proton), 3.72 (s, one of ester methyl proton), 2.70-1.99 (m, 7H), 1.90 (d, J=1.3 Hz, one of C-3 methyl proton), 1.89 (d, J=1.3 Hz, one of C-3 methyl proton), 1.8 (s, one of C-8a methyl proton), 1.09 (s, one of C-8a methyl proton); IR (CHCl3) 3610, 3450, 2940, 1730, 1440, 1380, 1310 cm\(^{-1}\); LRMS (FAB) \(m/z\) (relative intensity) 277 (\([M+H]^+\), 66), 276 (\(M^+\), 46), 259 (100), 258 (61), 199 (36), 137 (46), 109 (42), 108 (65), 69 (33); HRMS (FAB) \(M^+\) 276.1354 (calcd for \(C_{16}H_{20}O_2\) 276.1362).

Methyl (4a\(\beta\),8a\(\beta\))-4,4a,8a,9-Tetrahydro-3,8a-dimethyl-5-naphtho[2,3-\(b\)]furancarboxylate (76). To a cold (-42 °C) solution of 75 (21.7 mg, 0.079 mmol) in anhydrous CH\(_2\)Cl\(_2\) (1 mL) was added triethylamine (0.044 mL, 0.32 mmol), a catalytic amount of DMAP (3 mg) followed by methanesulfonyl chloride (0.012 mL, 0.16 mmol). After stirring for 30 min at 0 °C, the reaction mixture was poured into 3% HCl and extracted with ether (x3). The combined organic layers were washed with saturated NaHCO\(_3\) dried and concentrated in vacuo to give a crude mesylate as a pale yellow oil. This material was used for the following step without further purification. To a cooled (0 °C) solution of mesylate in anhydrous THF (1 mL) was added DBU (0.05 mL, 0.36 mmol) and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane / ethyl acetate = 20 : 1) to give 14.9 mg (87%) of 76 as a colorless oil. \(^1\)H NMR (CDCl\(_3\), 270 MHz) \(\delta\) 7.01 (br s, 1H), 6.98 (d, J=5.3 Hz, 1H), 6.04 (dd, J=9.5, 5.3 Hz, 1H), 5.90 (br d, J=9.5 Hz, 1H), 3.80 (s, 3H), 2.77 (dd, J=10.1, 5.9 Hz, 1H), 1.82-0.89 (m, 1H), 1.88 (d, J=13.5 Hz, 3H), 1.44 (s, 3H); IR (CHCl3) 2950, 2920, 1700, 1560, 1440, 1280, 1240 cm\(^{-1}\); LRMS (FAB) \(m/z\) (relative intensity) 259 (\([M+H]^+\), 80), 257 (42), 137 (23), 119 (29), 109 (45), 108 (100), 91 (21), 55 (24); HRMS (FAB) \([M+H]^+\) 259.1327 (calcd for \(C_{16}H_{20}O_2\) 259.1335).
(4aβ,8aβ)-5-Hydroxymethyl-3,8a-dimethyl-4,4a,8a,9-tetrahydronaphtho[2,3-b]furan (77). To a cooled (0 °C) solution of 76 (10.8 mg, 0.042 mmol) in anhydrous THF (2 mL) was added LAH (3.2 mg, 0.084 mmol) and stirred at 0 °C. After stirred for 20 min at 0 °C, the reaction mixture was quenched with saturated NaHCO3, filtered through and rinsed with Et2O. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 50:50) to give 18.0 mg (83%) of 77 as a colorless oil. 1H NMR (CDCl3, 270 MHz) δ 7.90 (br s, 1H), 5.93-5.86 (m, 2H), 5.55 (br d, J = 8.2 Hz, 1H), 4.23 (br s, 2H), 2.65 (br d, J = 16.5 Hz, 1H), 2.60-2.46 (m, 2H), 2.30-2.16 (m, 2H), 1.90 (d, J = 1.3 Hz, 3H), 1.15 (s, 3H); IR (KCl, cm⁻¹) 3025, 2920, 2860, 1440, 1380; LRMS (EI, 70 eV) m/z (relative intensity) 230 (M+), 212 (32), 108 (100); HRMS (FAB) M+ 230.1293 (calcd for C15H16O2 230.1293).

15-Acetoxytubipofuran (56). To a cooled (0 °C) solution of 77 (15.0 mg, 0.065 mmol) in 50% THF (2 mL) was added pyridine (0.021 mL, 0.26 mmol), acetic anhydride (0.011 mL, 0.12 mmol), and a catalytic amount of DMAP (3 mg). After stirring for 20 min at 0 °C, the reaction mixture was diluted with Et2O and washed with 1% HCl (x2). The aqueous layer was extracted with Et2O and then the combined organic layers were washed with saturated NaHCO3 followed by drying over Na2SO4. After concentration in vacuo, the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 9:1) to give 17.8 mg (quant.) of 15-acetoxytubipofuran (56) as a colorless oil. The spectral data (1H NMR, 13C NMR, IR, Mass) were identical with those of natural 15-acetoxytubipofuran reported in the literature.19

REFERENCES AND NOTES


30. 4-Methyl-1,3-cyclohexanedione (2b) and 4,4-dimethyl-1,3-cyclohexanedione (2i) were prepared from 1,3-cyclohexanedione as shown in the following scheme.

31. Spiro[1,3-dithiane-2,4'-cyclohexane-1',3'-dione] (2j) was prepared as shown in the following scheme.


43. The energy of tautomerization of A (ΔHt = -23.14 kcal/mol) to B (ΔHt = -25.37 kcal/mol) is only 2.23 kcal/mol.

44. The structures of 3, 4, i, and v were fully optimized by MM2.


61. We thank Professor E. Ghera, the Weizmann Institute of Science, for 1H NMR spectral data of maturone.

62. AM1 and PM3 calculations were performed using MOPAC program (version 6). All geometries were fully optimized by the eigenvector-following routine.

63. STO-3G calculations were performed using SPARTAN program.

64. In IR, benzo[1]furanoquinone (42) showed splitted two C=O absorption bands corresponding to two carbonyl groups at 1660 and 1680 cm⁻¹. In the case of the hydroxyl group protected silyl ether of 42 and 3-methylbenzo[4,7-quinone (26), the sharp singlet absorption band was observed at 1670 cm⁻¹ each other. On the other hand, under the high concentration condition, the protons of hydroxymethyl moiety of 42 showed a sharp signal in 1H NMR (CDCl₃). However, under the low concentration, somewhat a broad signal was observed. This phenomenon is probably due to the inhibition of free rotation of hydroxymethyl group by the formation of intramolecular hydrogen bond under the low concentration conditions.
65. AM1 results showed that the distance between the C-4 carbonyl oxygen and the O-9 hydroxyl hydrogen was 2.18 Å, which is too long to construct the intramolecular hydrogen bond. However, in general, PM3 reproduces hydrogen bond more correctly than AM1, the author uses PM3 results for discussions.


67. Distribution of BF3 on various basic sites of 42 can be in principle evaluated by the relative energies of geometry-optimized isomers which differ in the orientation of BF3. However, inferring the stabilities of these polar complexes in polar solvent from the vapor-phase energies seems too robust and we focus here only on the FMO features (Table X).


73. The coefficients of benzofuranquinone (60) were calculated by PM3 implemented in MOPAC program (version 6).


80. We thank Professor Y. Yamada, Tokyo College of Pharmacy, for 1H NMR spectral data of the tubipofurans.

LIST OF PUBLICATIONS

1. Regioselective Synthesis of Maturone via Lewis Acid Catalyzed Diels-Alder Reaction
   Mariko Aso, Akio Ojida, Guang Yang, and Ken Kanematsu

   Mariko Aso, Akio Ojida, Guang Yang, Ok-Ja Cha, Eiji Osawa, and Ken Kanematsu

3. Total Syntheses of Marine Furanosesquiterpenoids, Tubipofurans
   Akio Ojida, Fumiyo Tanoue, and Ken Kanematsu

4. Synthesis of Annulated Furans with Various 3-Substituents via a Sequential Furannulation/Ene Route
   Akio Ojida, Akira Abe, and Ken Kanematsu
   *Heterocycles* 1994, 38, 2585-2588.