The furanoeremophiloids are present in plant terpenoids. A number of bicyclic and tricyclic eremophilane-furanoeremophilane sesquiterpenoids have been isolated and their structures determined. The fused 3-methylfuran structures and their biological activities have aroused interest and stimulated considerable synthetic efforts. In this paper we describe the total synthesis of racemic ligularone (2)1—3) a representative furanoeremophiloid isolated from Ligularia sibirica Coss., and its thermal isomerization product, isoligularone (18)4,5) by furannulation reaction with the cis-4aß,5,6,7,8,8a-hexahydro-8ß,8aß-dimethylnapthalen-1,3(2H,4H)-dione (11) by furannulation reaction with diethylprop-2-ynylsulphonium bromide, prepared from diethyl sulfide and propargyl bromide.

Key words furanoeremophiloid; ligularone; isoligularone; furannulation reaction; synthesis

The furanoeremophiloids are present in plant terpenoids. A number of bicyclic and tricyclic eremophilane-furanoeremophilane sesquiterpenoids have been isolated and their structures determined. The fused 3-methylfuran structures and their biological activities have aroused interest and stimulated considerable synthetic efforts. In this paper we describe the total synthesis of racemic ligularone (2),1—3) a representative furanoeremophiloid isolated from Ligularia sibirica Coss., and its thermal isomerization product, isoligularone (18)4,5) by furannulation reaction with diethylprop-2-ynylsulphonium bromide, prepared from diethyl sulfide and propargyl bromide.

In previous papers, we have reported the synthesis of 2,4,5,6,7,7a-hexahydro-4ß-hydroxy-3,6,6-trimethyl-1-benzofuran-2-one (7) as a model 6ß-hydroxyeremophilone (1), as shown in Chart 1.8) This reaction proceeded from dimeredone (4) to compound 7 by C-alkylation, followed by lactonization. Firstly, we planned to study the synthetic route involving condensation of the bicyclic 1,3-diketone 11 with ethyl 2-iodopropionate (5) as well as a model route. Compound 11 was prepared starting from 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (8) and 2-methyl-2-cyclohexenone (9) in ten steps as reported by Miyashita et al. and shown in Chart 2.5)

Although an attempt at alkylation of 11 with ethyl 2-iodopropionate (5) under basic conditions gave two O-alkylated compounds, cis-3-[1-(ethoxycarbonylethoxy)]-8ß,9ß-dimethyl-2-octalin-1-one (12) and cis-1-[1-(ethoxycarbonylethoxy)]-8ß,9ß-dimethyl-1-octalin-3-one (13), the desired C-alkylated bicyclic diketone 14 was not obtained, as shown in Table 1. Therefore, we changed the synthetic target from 6ß-hydroxyeremophilone (1) to ligularone (2) using the key bicyclic 1,3-diketone 11.

Firstly, we investigated the synthesis of 3,6,6-trimethyl-6,7-dihydrobenzofuran-4(5H)-one (15) as a model compound. The synthesis of compound 15 has involved the furannulation reaction of dimeredone (4) with 1-nitro-1-(phenylthio)propane, KF or diethylprop-2-ynylsulphonium bromide as shown in Chart 3.5,7) Initially, we studied the C-alkylation of 4 with acetal to give 3-hydroxy-2-[1,2-dihydroxy-1-methyl]ethyl]-5,5-dimethyl-2-cyclohexen-1-one. Al-
though the furannulation reaction of 4 with acetol under basic conditions was unsuccessful, treatment of 4 with acetol in the presence of KF in benzene afforded the dimeric condensation product, namely, 16, C\textsubscript{19}H\textsubscript{28}O\textsubscript{5}, mp 139—140.5 °C, (21.3% yield). The IR spectrum showed absorption bands at 3420 and 3250 cm\textsuperscript{-1} due to hydroxy groups, at 1734 and 1703 cm\textsuperscript{-1} due to ketonic groups, and at 1630 cm\textsuperscript{-1} due to an olefinic group. The 1H-NMR spectrum showed the presence of five methyl groups at \(\delta\): 0.78 (3H, s), 1.09 (6H, s), 1.20 (3H, s), and 1.30 (3H, s), two hydroxy protons at \(\delta\): 1.45 (1H, s), and 1.77 (1H, s), ten methylenic protons at \(\delta\): 2.04—2.89 (8H, m), and 4.49 (2H, d, \(J=2.2\) Hz), and a methinic proton at \(\delta\): 4.76 (1H, s). Thus, compound 16 was assigned as 6-ace-toxymethyl-1,2,3,4,7,8,9,10-octahydro-3,3,6,9,9-pentamethyl-6H-dibenzo[b,d]pyran-1,7-dione, which is the tricyclic product.

Next, we investigated the furannulation reaction using 11. As the furannulation reaction of 11 with acetol was unsuccessful, we planned to study the formation of the fused 3-methylfuran by reaction of the enolate anion of 11 with the allenic sulfonium salt, diethylprop-2-ynylsulphonium bromide, which was obtained by reaction of diethyl sulfide and propargyl bromide. Reaction of 11 with diethylprop-2-ynylsulphonium bromide using NaOMe in MeOH or tert-BuOK afforded the tricyclic 6\textsubscript{H}-dibenzo[b,d]pyrane product, namely, 17, C\textsubscript{21}H\textsubscript{28}O\textsubscript{5}, a colorless oil (82.3% yield). The IR spectrum showed an absorption band at 1765 and 1660 cm\textsuperscript{-1} due to ketonic groups and at 1635 cm\textsuperscript{-1} due to an olefinic group. The 1H-NMR spectrum showed the presence of six methyl groups at \(\delta\): 1.06 (9H, s), 1.14 (3H, s), 1.52 (3H, s), and 2.13 (3H, s), and ten methylenic protons at \(\delta\): 2.18—2.47 (8H, m), and 4.39 (2H, d, \(J=0.7\) Hz). Thus, compound 17 was assigned as 6-ace-toxymethyl-1,2,3,4,7,8,9,10-octahydro-3,3,6,9,9-pentamethyl-6\textsubscript{H}-dibenzo[b,d]pyran-1,7-dione, which is the tricyclic product.

Table 1. Alkylation of Bicyclic 1,3-Diketone 11 with Ethyl 2-Iodopropionate (5)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Yield (%)\textsuperscript{a)</th>
<th>12</th>
<th>13</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH</td>
<td>DMSO</td>
<td>r. t., 15 h</td>
<td>34</td>
<td>33</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>NaH</td>
<td>Benzene</td>
<td>r. t., 15 h</td>
<td>No reaction</td>
<td>24</td>
<td>21</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>n-BuLi</td>
<td>THF</td>
<td>0 °C, 1 h—r. t., 15 h</td>
<td>30</td>
<td>32</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>K\textsubscript{2}CO\textsubscript{3}</td>
<td>Acetone</td>
<td>r. t., 15 h</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

\(\textsuperscript{a) Isolated yield.  b) r. t. = Room temperature. — Not isolated. DMSO: Dimethyl sulfoxide. THF: Tetrahydrofuran.}\)
in tetrahydrofuran (THF) afforded two tricyclic furannulation products. In this, diethylprop-2-ynylsulphonium bromide was added to the THF solution of 11 and tert-BuOK. The mixture was reacted for 6 h at 10 °C to afford (±)-ligularene (2), C_{12}H_{20}O_2, mp 62—64 °C (lit. 13) mp 68—70 °C, (25.0% yield), and (±)-isoligularene (18), C_{15}H_{20}O_2, mp 110—113 °C (lit. 14) mp 111—114 °C (41.7% yield). The racemic ligularene and isoligularene obtained were compared spectroscopically with data from authentic samples.

Experimental
All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR-200 spectrometer, and 1H-NMR and 13C-NMR spectra on a JEOL JNM-EX90 or JEOL JNM-α500 spectrometer, with tetramethylsilane as an internal standard. MS were recorded on a JEOL JMS-D 300 spectrometer. Elemental analyses were obtained using on a Yanaco CHN-corder MT-3. Wakogel C-200 (silica-gel) and Merck Kieselgel G nach Stahl (silica-gel) were used for column chromatography and thin-layer chromatography (TLC), respectively. All runs were carried out under argon.

cis-3-[1-(Ethoxycarbonyl)ethoxy]-8β,9β-dimethyl-2-octalin-1-one (12) and cis-1-[1-(Ethoxycarbonyl)ethoxy]-8β,9β-dimethyl-1-octalin-3-one (13)
A solution of cis-4aβ,5,6,7,8,8α-hexahydro-8β,8α-dimethylnapthalen-1,3(2H,4H)-dione (11) 19 (30 mg) in dry dimethyl sulfoxide (DMSO) (0.5 ml) was added to a mixture of NaH (7.8 mg) and dry DMSO (1.0 ml) and stirred at room temperature for 30 min. A solution of ethyl 2-isopropionate (119 mg) in dry DMSO (0.5 ml) was then added and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and the aqueous layer was acidified with 10% HCl and extracted with chloroform. The organic layer was washed with 10% HCl, sat. NaHCO_3, then dried (MgSO_4) and concentrated. The residue was subjected to silica-gel chromatography (ether–hexane, 1 : 3), and the eluate gave 25.9 mg (25.0%) 2 as colorless needles (ether–hexane, mp 62—64 °C (lit. 15 mp 68—70 °C). IR (KBr) cm^{-1}: 1665, 1640, 1570. 1H-NMR (CDCl_3) δ: 0.88 (3H, d, J = 7.0 Hz, -Me), 1.12 (3H, s, -Me), 1.33—1.66 (6H, m, methylene H), 2.20 (3H, d, J = 1.2 Hz, -Me), 2.21—2.26 (2H, m, methine H), 2.75 (1H, d, J = 13.4 Hz, methylene H), 2.91 (1H, d, J = 15.6 Hz, methylene H), 7.06 (1H, t, J = 0.6 Hz, olefinic H). High-resolution EI-MS m/z: Caled for C_{15}H_{20}O_2 (M^+): 232.1463. Found: 232.1467. The second eluate gave 49.9 mg (41.7%) 2 as colorless needles (ether–hexane, mp 110—113 °C (lit. 15 mp 111—114 °C). IR (KBr) cm^{-1}: 1670, 1550. 1H-NMR (CDCl_3) δ: 0.93 (3H, d, J = 6.7 Hz, -Me), 1.31 (3H, s, -Me), 1.41—1.62 (5H, m, methylene H), 1.78—1.85 (1H, m, methylene H), 1.90 (1H, q, J = 6.6 Hz, methine H), 5.10 (1H, s, olefinic H). High-resolution EI-MS m/z: Caled for C_{15}H_{20}O_2 (M^+): 232.1463. Found: 232.1473. Both synthetic products obtained were identified by comparison with data from authentic samples.5)

References