APPROACH TO NATURAL OCCURRING \( \alpha \)-METHYLENE BIS-\( \gamma \)-BUTYROLACTONES FROM (R)-1,2-O-ISOPROPYLDENEGLYCERALDEHYDE AS A CHIRAL TEMPLATE

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Abstract—Both 4-substituted tetrahydrofurano-\( \gamma \)-butyrolactones (12) and (16) which could be key intermediates leading to natural occurring \( \alpha \)-methylene bis-\( \gamma \)-butyrolactones were synthesized by regio and stereoselective haloetherification of (8) and (9), followed by a reductive coupling reaction for the preparation of (12), whereas a stereoselective hydrogenation of the enol ether (15) derived from the bromide (14) for the preparation of (16), respectively.

Avenaciolide (1), isoavenaciolide (2), ethisolide (3) and canadensolide (4), antifungal metabolites, have attracted much attention owing to unique \( \alpha \)-methylene bis-\( \gamma \)-butyrolactones skeleton as well as biological activities. In view of these, many efforts have been done toward the total syntheses of these compounds.\(^1\) However, preceding synthetic methods are limited and general synthetic method accessible to all of the compounds (1), (2), (3) and (4) had not been accomplished yet.

\[ \begin{align*}
1: \text{Avenaciolide} & \quad R^1=C_8H_{17}, \quad R^2=H \\
2: \text{Isoavenaciolide} & \quad R^1=H, \quad R^2=C_8H_{17} \\
3: \text{Ethisolide} & \quad R^1=H, \quad R^2=C_2H_5 \\
4: \text{Canadensolide} & 
\end{align*} \]
In a preceding paper,\textsuperscript{2,3} we described a general synthesis of 2,3-disubstituted $\gamma$-butyrolactones (8) and (9) via the esters (7) wherein a Claisen rearrangement of the allyl alcohol (6) derived from (R)-1,2-O-isopropylidenglyceraldehyde (5) was a key step.

![chemical structures]

As our extension of the total synthesis of natural products employing (R)-1,2-O-isopropylidenglyceraldehyde (5) as a chiral template,\textsuperscript{4} we have intrigued in a development of a general synthetic method of natural occurring $\alpha$-methylene-bis-$\gamma$-butyrolactones.

Our retrosynthetic analysis of (1), (2), (3) and (4) are shown in the following scheme. We envisaged that side chains in (2), (3) and (4) could be introduced by regio and stereoselective haloetherification of (a) and (e), subsequent catalytic hydrogenation of the enol ethers (c) and (d) from a less hindered $\beta$-side, whereas a side chain in (1) could be elaborated by a reductive coupling reaction of the bromide (b), derived from regio and stereoselective haloetherification of (a), with $\alpha,\beta$-unsaturated carbonyl compound.
Haloetherification\(^5\) of the known compound (8)\(^3\) with bromine provided regio and stereoselectively bicyclic tetrahydrofuranolactones (10)\(^6\),\(^7\) [mp 51-52\(^\circ\)C, \([\alpha]_D^{25}\) -16.1 (c=0.31, CHCl\(_3\)) and (11), ratio being 5:1, as would be expected from the kinetic preference of tetrahydrofuran over tetrahydropyran and the greater stability of transition state (A) over (B).
Since the bromide (10) was available, a reductive coupling\textsuperscript{8} of (10) with methyl acrylate was examined under several conditions and the results are summarized in the Table 1.

Table 1. Reductive coupling of the bromide (10) with methyl acrylate

<table>
<thead>
<tr>
<th>Reaction conditions</th>
<th>Products (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl acrylate (eq.)</td>
<td>AIBN (eq.)</td>
</tr>
<tr>
<td>8</td>
<td>0.4</td>
</tr>
<tr>
<td>4</td>
<td>0.4</td>
</tr>
<tr>
<td>8</td>
<td>0.4</td>
</tr>
</tbody>
</table>

* added over 20min.  ** added over 3h

As can be seen from the Table 1, a high dilution method is crucial for the preparation of (12) $[\alpha]_{D}^{25}$ -5.0° (c=0.15, CHCl\textsubscript{3}) in satisfactory yield, unless otherwise disappointing result was obtained.

Thus, a stereoselective introduction of the requisite side chain for (1) has been achieved. Since regioselective oxidation of cyclic ethers to a corresponding lactones has been known\textsuperscript{9}, this synthetic process would be useful for the enantioselective synthesis of (1).

Next our attention was focused on the synthesis of ethisolide (3). Haloetherification of the known compound (9)\textsuperscript{3}, followed by dehydrobromination of the bromide (14)\textsuperscript{10} provided the enol ether (15)\textsuperscript{11} [mp 113-115°C, $[\alpha]_{D}^{25}$ +227.9° (c=0.24, CHCl\textsubscript{3})] as a single isomer in 98.6% overall yield from (9).
Since the ether (15) was in our hand, catalytic hydrogenation was examined under a variety of conditions and the results are summarized in Table 2.

Table 2. Catalytic hydrogenation of the enol ether (15)

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Products (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catalyst Solvent</td>
<td>16</td>
</tr>
<tr>
<td>PtO₂ dry MeOH</td>
<td>0</td>
</tr>
<tr>
<td>PtO₂ dry EtOAc</td>
<td>38.3</td>
</tr>
<tr>
<td>PtO₂ dry Et₂O</td>
<td>44.4</td>
</tr>
<tr>
<td>10% Pd-C dry EtOAc</td>
<td>30.2</td>
</tr>
<tr>
<td>5% Rh on Al₂O₃ dry THF</td>
<td>90.3</td>
</tr>
</tbody>
</table>

As can be seen in Table 2, the best result was obtained by using Rhodium on alumina as a catalyst in dry tetrahydrofuran to provide exclusively the tetrahydrofuranolactone (16) \([\alpha]_D^{25} +8.16^\circ \text{ (c}=0.25,\text{CHCl}_3\)).

Thus, the methodology described herein is applicable to all of the known natural occurring \(\alpha\)-methylene bis-\(\gamma\)-butyrolactones. Based on this strategy, total syntheses of these natural products are now under investigation in this laboratory.


3. see the previous paper in this issue.


6. This compound is easily isolated from the reaction mixture by single crystallization from ether-hexane.

7. Melting points were measured on a Yazawa BY-1 micro melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO-DIP-4 automatic polarimeter. All compounds reported herein exhibited spectra consistent with assigned structures and gave satisfactory high resolution mass spectrometric determination.


10. The bromide (14) is a mixture of diastereoisomers (i) and (ii) whose ratio (5:1) were determined by reductive removal of bromine with tributyltin hydride to yield (17) and (16).
11. This compound is highly sensitive to moisture, however, it can be isolated as a crystalline solid through short silica gel pad after non-aqueous work-up and purified simply by recrystallization from n-hexane.


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