TOTAL SYNTHESIS OF ISLANDIC ACID I METHYL ESTER, ROSELLISIN AND ROSELLISIN ALDEHYDE

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Abstract. —— Total synthesis of islandic acid I methyl ester (2), rosellisin (3) and rosellisin aldehyde (4) has been accomplished starting from 4-hydroxy-5-hydroxymethyl-6-methyl-2H-pyran-2-one (9a) via formylation of 9a with dichloromethyl methyl ether and titanium tetrachloride as a key step.

Several 4-hydroxy-2H-pyran-2-one (α-pyrone) derivatives being fully substituted with oxygen containing functional groups have been isolated from natural sources. Among them islandic acid I (1) has shown potent cytotoxic activity against Yoshida sarcoma1–2 and rosellisin (3) has been reported to show antibacterial activity3–4. For the effective synthesis of these types of multiply substituted α-pyrone derivatives, it is necessary to establish selective introduction of oxygen containing functional groups to the 4-hydroxy-2H-pyran-2-one skeleton and selective conversion of these functional groups. We have already reported a facile synthesis of 5-carbomethoxy- and 5-carbethoxy-4-hydroxy-6-methyl-2H-pyran-2-ones (5a, 6a) and a new mild and selective reduction of the ester group at the C-5 position with borane-methyl sulfide complex (BMS) to the 5-hydroxymethyl derivative (9a).5 In this paper, we report the regioselective introduction of a formyl group to the C-3 position of the 4-hydroxy-2H-pyran-2-one skeleton and the application of the synthetic methods leading to the total synthesis of the natural α-pyrone derivatives shown below.

\[
\begin{align*}
\text{R=H} & \quad \text{Islandic acid I (1)} \\
\text{R=Me} & \quad \text{Islandic acid I methyl ester (2)} \\
\text{MeO} & \quad \text{Rosellisin (3)} \\
\text{MeO} & \quad \text{Rosellisin aldehyde (4)}
\end{align*}
\]
A variety of methods were attempted to achieve the introduction of a carbinol unit or an ester group to the C-3 position of α-pyrone derivatives. Treatment of 5a with formaldehyde or alkoxyethyl chloride, either in the presence of Et3N in refluxing benzene or in trifluoroacetic acid at room temperature, afforded bis (5-carbomethoxy-4-hydroxy-6-methyl-2-oxo-2H-pyr-3-yl)methane. Although the ethyl- and the 2,2,2-trichloroethylcarbomates of 5a were converted to the corresponding 3-carboalkoxy derivatives via Fries rearrangement using DMAP in toluene under reflux, the yields were low (~40%). Treatment of 5a under Friedel-Crafts' conditions with ClCO2Me and Lewis acid produced no reaction.

Poulton has reported that treatment of 4-methoxy-6-methyl-2H-pyrone-2-one (14b) with excess dichloromethyl methyl ether (MeOCHCl2)-TiCl4 produced the aldehyde (15b) in 37% yield. Additionally, he reported that similar treatment of the 4-hydroxy derivative (14a) did not produce the aldehyde (15a). When the procedure was applied to the 5-carbomethoxy-4-methoxy derivative (5b), 5b was completely recovered. However, it was found that treatment of the 4-hydroxy derivative (5a) with 15 eq. of MeOCHCl2 and 10 eq. of TiCl4 in dry CH2Cl2 under a continuous nitrogen flow while raising the reaction temperature from -10 °C to room temperature over a 1 d period (Method A) gave the 3-carboxaldehyde (7) [1H-Nmr (CDCl3): 9.86 (1H, s), 13C-Nmr (CDCl3): 99.8 (C-3), 108.2 (C-5), 159.6 (C-2), 174.0 (C-6), 176.3 (C-4), 193.6 (CHO)] in 89% yield.

**Table 1. Reaction of α-pyrone derivatives (5-14) under the conditions of Method A.**

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Method A:</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>R2</td>
<td>R3</td>
</tr>
<tr>
<td>5a</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>5b</td>
<td>H</td>
<td>Me</td>
</tr>
<tr>
<td>6a</td>
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<td>H</td>
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<tr>
<td>9a</td>
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<tr>
<td>9b</td>
<td>H</td>
<td>Me</td>
</tr>
<tr>
<td>11</td>
<td>H</td>
<td>Me</td>
</tr>
<tr>
<td>12</td>
<td>H</td>
<td>Me</td>
</tr>
<tr>
<td>14a</td>
<td>H</td>
<td>H</td>
</tr>
</tbody>
</table>
The 5-carbethoxypyrone (6a) was also converted to the aldehyde (8) in 88% yield under similar conditions, while the 4-methoxy derivative (6b) was unreacted. In the case of the 5-hydroxymethylypyrone (9a), introduction of a formyl group was similarly achieved using Method A. However, formylation was accompanied by substitution of the hydroxyl group to the chlorine atom, and 10a [1H-nmr (CDCl₃): 4.47 (2H, s), 9.85 (1H, s). 13C-Nmr (CDCl₃): 34.1 (CH₂), 193.8 (CHO)] was obtained in 86% yield. The 4-methoxy derivatives (9b, 11 and 12) did not undergo formylation and only substitution was effected which afforded the 5-chloromethyl derivative (13). Moreover, it was found that when 14a was treated under the conditions of Method A, the aldehyde (15a) was obtained in 77% yield. On the other hand, the 4-methoxypyrone (14b) was converted to the mixture of 15b and the rearranged acid (16) under the same conditions. Subsequent aqueous treatment of the reaction mixture for 1 d gave 16 as the sole product in 85% yield. Purification of the mixture by silica gel column chromatography also afforded 16 in 85% yield. The structure of 16 was confirmed by nmr spectral data and by conversion to the ester (17).

Thus the regioselective introduction of the formyl group to the C-3 and the chloromethyl group to the C-5 position have been demonstrated, which simplifies the independent derivatization on each position. With 10a in hand, attention was focused on the total synthesis of the natural products shown before. Attempted methylation of 10a with dimethyl sulfate-anhydrous K₂CO₃ or MeI under various conditions, and attempted reduction of 10a with BMS₅ or NaBH₄ resulted in the formation of complex mixtures. When 10a was treated with diazomethane, the 4-methoxy derivative (10b) was produced in 45% yield in addition to the 2-methoxy derivative (22) produced in 10% yield. Reduction of 10b with BMS at room temperature afforded the alcohol (18) in 80% yield together with the demethoxy derivative (23) in 15% yield. The 1,4-addition of BMS₅ was suppressed completely by lowering the reaction temperature to -78 °C and 18 was obtained in 98% yield. After
protection of the hydroxyl group of 18 with SEMCl (88%), substitution of the chlorine atom by the hydroxyl group was examined. When 19 was heated with AgNO₃ in the presence of 2,6-lutidine in acetone-water at 60 °C for 2 h, a mixture of 20 and the rearranged product (24) was obtained. The reaction mixture was treated with K₂CO₃ and heated for additional 4 h without purification to give 20 in 83% yield.

The THP ether (21) produced under standard conditions was alkylated with LDA-anhydrous methyl glyoxylate⁹ according to the procedure of Schreiber¹⁰ to afford 25 in 67% yield. Successive dehydration of 25 with p-TsCl-Et₃N gave the trans-isomer (26) in 84% yield along with a trace amount of the cis-isomer (27) (4%). Selective removal of the SEM group of 26 using n-Bu₄NF was proved difficult due to the degradation of the pyrone ring. However, when deprotection of the THP group was attempted with 0.1 eq. of PPTS in MeOH under reflux for 2 h, the hydroxy derivative (28) was obtained in 76% yield in addition to the dihydroxy derivative (3) produced in 12% yield. The minor product (3) was consistent with rosellisin by ¹H-nmr and ¹³C-nmr spectral data. Rosellisin aldehyde (4) was synthesized from 28 in 84% overall yield via PCC oxidation followed by deprotection of the SEM group with p-TsOH in 1,4-dioxane-water at 90 °C. Finally, after esterification of 4 with 22, 4E-hexadienoic acid,¹¹,¹² reduction of 30 with BMS gave islandic acid I methyl ester (2) selectively in 98% yield. The total synthesis of 2 was attained in 14 steps starting from 5a with an 8% overall yield.
ACKNOWLEDGMENT

The authors are thankful to Dr. Y. Fujimoto and Dr. T. Tatsuno for supplying of islandic acid I methyl ester and islandic acid II methyl ester2 (rosellisin) and for helpful discussions.

REFERENCES AND NOTES

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Received, 20th September, 1993