Iodine Mediated Lactonization of Terpenic 3-Hydroxy Acids

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Abstract: Cyclization of terpenic 3-hydroxy acids in the presence of a catalytic amount of iodine gave bicyclic or tricyclic lactones in good yield.

Key words: iodine, lactonization, 3-hydroxy acid, terpenoid, lithium naphthalenide

Iodine-mediated lactonization of unsaturated acids has been recognized as “iodolactonization”, and utilized as a useful method for synthesis of iodolactone. This reaction proceeds via an iodonium-cation intermediate, which is formed by the addition of iodine to the double bond. Recently, Kim reported the exclusive formation of non-iodinated 4,4-dimethyl-γ-butyrolactones from the reaction of 4-methyl-4,5-pentenoic acids in the presence of a catalytic amount of iodine. The key feature of this reaction was the generation of hydrogen iodide, which was formed by the interaction of iodine with a free carboxy group.

In our laboratory, we have continuously studied the acid-catalyzed lactonization of 3-hydroxy acids. In this paper, we report that the lactonization of terpenic 3-hydroxy acids with a catalytic amount of iodine gives bicyclic or tricyclic lactones in good yield.

3-Hydroxy acids were prepared from cyclohexanone, 2-methylcyclohexanone and terpenic carbonyl compounds. Ketone was added to acetic acid dianion, which was prepared from acetic acid and lithium naphthalenide (Li-Nap.), and the reaction mixture was stirred for 24 hours to give the corresponding 3-hydroxy acid in 63–91% yield (Scheme 1).

An initial attempt of the lactonization of 3-hydroxy acid 1 with a catalytic amount of iodine was unsuccessful, and an intractable mixture was obtained (Scheme 2). This might be attributed to an ineffective hydride shift, and thus the secondary carbocation not being generated.

Next, we examined the lactonization of 3-hydroxy acid 2. When an acetonitrile solution of 2 and 0.2 equivalent of iodine was refluxed for 3 hours, the bicyclic lactone 9 was obtained in 51% yield (Table 1). The amount of catalyst needed was at least 0.2 equivalent, and 0.5 equivalent of the catalyst did not affect the chemical yield. An ethereal or hydrocarbon solvent was not effective for this reaction and 3-hydroxy acid 2 was recovered under these conditions. A plausible reaction mechanism of this reaction is illustrated in Scheme 3. Hydrogen iodide, which was initially formed by the interaction of iodine with free carbox-
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ylic acid, worked as an acidic catalyst, and the carbocation was generated by dehydration. Then, the hydride shift and the attack of carbonyl oxygen resulted in the stereoselective formation of the cis-lactone.

Various bicyclic or tricyclic lactones 10–16 were obtained in good yields through the iodine-catalyzed reaction of the corresponding terpenic 3-hydroxy acids 3–8 (Scheme 4, Table 2). The structure and the configuration of lactones were confirmed by 2D NMR and difference NOE experiments.

The 3-hydroxy acids 3 and 4 were readily converted to bicyclic lactones 10 and 11, respectively, in various solvents at room temperature without formation of any iodinated products. The other lactones 12–16 were formed in good yields only in acetonitrile, and the use of other solvents resulted in poor yields or no reaction. It seems that stabilization due to the formation of allylic cation intermediates facilitated a smooth reaction (Scheme 5).

Table 1 Lactonization of 3-Hydroxy Acid 2

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Temp.</th>
<th>Time (h)</th>
<th>I₂ (equiv)</th>
<th>Yield* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeCN</td>
<td>r.t.</td>
<td>12</td>
<td>0.2</td>
<td>trace</td>
</tr>
<tr>
<td>MeCN</td>
<td>reflux</td>
<td>3</td>
<td>0.2</td>
<td>51</td>
</tr>
<tr>
<td>MeCN</td>
<td>reflux</td>
<td>3</td>
<td>0.05</td>
<td>31</td>
</tr>
<tr>
<td>MeCN</td>
<td>reflux</td>
<td>3</td>
<td>0.5</td>
<td>58</td>
</tr>
<tr>
<td>THF</td>
<td>reflux</td>
<td>3</td>
<td>0.2</td>
<td>&lt;b&gt;</td>
</tr>
<tr>
<td>Hexane</td>
<td>reflux</td>
<td>3</td>
<td>0.2</td>
<td>&lt;b&gt;</td>
</tr>
<tr>
<td>Toluene</td>
<td>reflux</td>
<td>3</td>
<td>0.2</td>
<td>16</td>
</tr>
<tr>
<td>Et₂O</td>
<td>reflux</td>
<td>3</td>
<td>0.2</td>
<td>&lt;b&gt;</td>
</tr>
</tbody>
</table>

*a Isolated yield.

<b> 3-Hydroxy acid 2 was recovered.

ylic acid, worked as an acidic catalyst, and the carbocation was generated by dehydration. Then, the hydride shift and the attack of carbonyl oxygen resulted in the stereoselective formation of the cis-lactone.

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The lactonization of 3-hydroxy acid 5 led to the diastereomeric lactones 12 and 13. Epimerization of the C-4 atom might occur through dehydration and reprotonation (Scheme 6).

Tricyclic lactones 14, 15 and 16 were obtained from 3-hydroxy acids 6, 7 and 8, respectively. The reaction mechanism for the lactonization of 14 and 15 might involve a Wagner–Meerwein type rearrangement. The mechanism for the generation of 16 is illustrated in Scheme 7.

In conclusion, we have synthesized seven terpenic bicyclic or tricyclic lactones from 3-hydroxy acids. Especially, optically active tricyclic lactones 14–16 were prepared from commercially available natural compounds, so their use as an asymmetric catalyst or auxiliary is possible.

NMR spectra were recorded on a JEOL GSX-400 system or a Bruker DPX-300 system with TMS as an internal standard. IR spectra were recorded on a JASCO FT/IR-230 spectrometer. Mass spectra were recorded on a JEOL JMS-HX110. Optical rotations were mea-

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Table 2  Lactonization of 3-Hydroxy Acids 3–8

<table>
<thead>
<tr>
<th>Acid</th>
<th>Lactone</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
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<tr>
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<td>10</td>
<td>MeCN</td>
<td>r.t.</td>
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<td>61</td>
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<td>3</td>
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<td>MeCN</td>
<td>r.t.</td>
<td>16</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
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<td>reflux</td>
<td>3</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>Et₂O</td>
<td>r.t.</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>Et₂O</td>
<td>r.t.</td>
<td>16</td>
<td>73</td>
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<tr>
<td>3</td>
<td>10</td>
<td>Hexane</td>
<td>r.t.</td>
<td>16</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>MeCN</td>
<td>r.t.</td>
<td>3</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>MeCN</td>
<td>reflux</td>
<td>3</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>Et₂O</td>
<td>r.t.</td>
<td>3</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>Hexane</td>
<td>r.t.</td>
<td>3</td>
<td>75</td>
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<tr>
<td>5</td>
<td>12, 13</td>
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<td>r.t.</td>
<td>3</td>
<td>9 (12), 4 (13)</td>
</tr>
<tr>
<td>5</td>
<td>12, 13</td>
<td>MeCN</td>
<td>reflux</td>
<td>3</td>
<td>42 (12), 19 (13)</td>
</tr>
<tr>
<td>5</td>
<td>12, 13</td>
<td>Et₂O</td>
<td>r.t.</td>
<td>3</td>
<td>-b</td>
</tr>
<tr>
<td>5</td>
<td>12, 13</td>
<td>Hexane</td>
<td>r.t.</td>
<td>3</td>
<td>-b</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>MeCN</td>
<td>r.t.</td>
<td>3</td>
<td>83</td>
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<tr>
<td>6</td>
<td>14</td>
<td>MeCN</td>
<td>reflux</td>
<td>3</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>Hexane</td>
<td>r.t.</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>Et₂O</td>
<td>r.t.</td>
<td>3</td>
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<td>15</td>
<td>MeCN</td>
<td>r.t.</td>
<td>3</td>
<td>19</td>
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<td>7</td>
<td>15</td>
<td>MeCN</td>
<td>reflux</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>7</td>
<td>15</td>
<td>MeCN</td>
<td>reflux</td>
<td>3</td>
<td>91</td>
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<tr>
<td>7</td>
<td>15</td>
<td>MeCN</td>
<td>reflux</td>
<td>5</td>
<td>89</td>
</tr>
<tr>
<td>8</td>
<td>16</td>
<td>MeCN</td>
<td>r.t.</td>
<td>3</td>
<td>18</td>
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<tr>
<td>8</td>
<td>16</td>
<td>MeCN</td>
<td>reflux</td>
<td>3</td>
<td>54</td>
</tr>
<tr>
<td>8</td>
<td>16</td>
<td>Et₂O</td>
<td>r.t.</td>
<td>3</td>
<td>-b</td>
</tr>
</tbody>
</table>

a  Isolated yield.

b  Hydroxy acid was recovered.
verified on a JASCO DIP-370 or a HORIBA SEPA-300. Elemental analyses were performed on an Elementar vario EL. THF was distilled from CaH₂ and stored under Na wire. Toluene was distilled from phosphorus pentoxide. Other materials were obtained commercially.

3-Hydroxy Acids

The acids were prepared as reported previously.³

Compounds 1 and 2

Spectral data were reported previously.³

3-Hydroxy-5,9-dimethyldeca-4,8-dienoic Acid (3)

Viscous oil: (mixture of cis and trans, cis:trans = 1:1).

Yield: 11.6 g, 54 mmol (68%).

IR (neat): 2935, 1680 cm⁻¹.

³¹H NMR (300 MHz, CDCl₃): δ = 1.59, 1.60, 1.68, 1.69, 1.70, 1.71 (each-s, 9 H), 1.92–2.18 (m, 4 H), 2.49–2.60 (m, 2 H), 4.55–5.26 (m, 3 H), 6.92 (br s, 2 H).

³¹C NMR (75 MHz, CDCl₃): δ = 16.67, 16.87, 17.70, 23.31, 25.68, 26.29, 32.36, 39.44, 41.63, 64.68, 65.07, 123.74, 123.83, 125.11, 126.08, 131.83, 131.62, 133.69, 140.19, 176.22.


126.08, 131.85, 132.63, 139.96, 140.19, 176.50.

13C NMR (100 MHz, CDCl₃): δ = 18.50, 23.10, 26.52, 28.86, 30.12, 32.82, 39.11, 83.06, 123.44, 134.42, 171.37.


Iodine Mediated Lactonization of 3-Hydroxy Acids; General Procedure

I₂ (0.24 g, 0.94 mmol), 3-hydroxy acid (4.7 mmol), and MeCN (60 mL) were placed in a 100-mL flask and stirred at the appropriate temperature for 3 h. After stirring, the solution was quenched with 5% sodium thiosulfate to remove I₂. After usual extractive work-up, the crude product was purified by silica gel column chromatography (hexane–EtOAc, 8:1) to give the corresponding lactone.

Compound 9

Spectral data were reported previously.³

cis-2,2,8-Trimethyl-3-oxabicyclo[4.4.0]dec-7-en-4-one (10)

Viscous oil.

Yield: 0.39 g, 2.0 mmol (42%).

IR (KBr): ν = 2925, 1734 cm⁻¹.

³¹H NMR (300 MHz, CDCl₃): δ = 0.98 (d, 3 H, J = 6.3 Hz), 1.18–1.42 (m, 1 H), 1.43 (s, 3 H), 1.60–1.83 (m, 3 H), 1.91–2.06 (m, 2 H), 2.85–3.02 (m, 2 H).

¹³C NMR (75 MHz, CDCl₃): δ = 21.30, 24.60, 26.80, 27.19, 28.14, 30.89, 34.56, 37.26, 85.11, 122.64, 131.52, 170.12.


(8R)-2,2,8-Trimethyl-3-oxabicyclo[4.4.0]dec-1(6)-en-4-one (11)

Colorless crystals; mp 78.0–79.0 °C.

Yield: 0.80 g, 4.1 mmol (88%).

IR (KBr): ν = 2925, 1734 cm⁻¹.

³¹H NMR (300 MHz, CDCl₃): δ = 0.98 (d, 3 H, J = 6.3 Hz), 1.18–1.42 (m, 1 H), 1.43 (s, 3 H), 1.60–1.83 (m, 3 H), 1.91–2.06 (m, 2 H), 2.85–3.02 (m, 2 H).

¹³C NMR (75 MHz, CDCl₃): δ = 21.30, 24.60, 26.80, 27.19, 28.14, 30.89, 34.56, 37.26, 85.11, 122.64, 131.52, 170.12.


(1S,3S,6R)-3-Methyl-6-(1'-methylethyl)-7-oxabicyclo[4.3.0]nonan-8-one (12)

Viscous oil.

Yield: 0.39 g, 2.0 mmol (42%).

IR (KBr): ν = 2925, 1772 cm⁻¹.

³¹H NMR (400 MHz, CDCl₃): δ = 0.99 (d, 3 H, J = 6.2 Hz), 0.99 (d, 3 H, J = 6.8 Hz), 1.03 (d, 3 H, J = 6.8 Hz), 0.99–1.04 (m, 1 H), 1.27

References

1. PAPER Iodine Mediated Lactonization of Terpenic 3-Hydroxy Acids

\[(\text{ddd}, 1 \ H, J = 4.9, 12.3, 15.0 \ Hz), 1.50 \ (\text{ddd}, 1 \ H, J = 4.0, 11.8, 15.0 \ Hz), 2.01 \ (\text{sept}, 1 \ H, J = 6.8 \ Hz), 2.07-2.13 \ (\text{m}, 1 \ H), 2.48-2.59 \ (\text{m}, 2 \ H), 2.62-2.68 \ (\text{m}, 1 \ H). \]

\[^{13}\text{C} \text{NMR (100 MHz, CDCl}_3\text{): } d = 16.85, 17.65, 21.43, 25.43, 28.99, 29.60, 32.10, 33.59, 34.47, 35.99, 89.20, 176.71. \]

HRMS (FAB): m/z calcd for C\(_{12}\)H\(_{21}\)O\(_2\) [M + H]\(^+\): 197.1542. Found: 197.1551.

\((1\text{R},3\text{S},6\text{S})\)-3-Methyl-6-(1\text{¢}-methylethyl)-7-oxabicyclo[4.3.0]nonan-8-one (13)

Viscous oil.

Yield: 0.18 g, 0.9 mmol (19%).

\([\alpha]_D\text{25} = -23.8 \ (c \ 1.00, \text{CHCl}_3). \]

IR (KBr): 2950, 1773 cm\(^{-1}\).

\[^1\text{H} \text{NMR (400 MHz, CDCl}_3\text{): } d = 0.81 \ (\text{dt}, 1 \ H, J = 13.7, 11.9 \ Hz), 0.93 \ (d, 3 \ H, J = 6.2 \ Hz), 0.99 \ (d, 3 \ H, J = 6.6 \ Hz), 1.03 \ (d, 3 \ H, J = 6.6 \ Hz), 1.10 \ (\text{dtt}, 1 \ H, J = 3.9, 11.4, 13.2 \ Hz), 1.25-1.34 \ (\text{m}, 1 \ H), 1.48 \ (\text{ddd}, 1 \ H, J = 4.5, 13.2, 15.0 \ Hz), 1.53-1.59 \ (\text{m}, 1 \ H), 1.74-1.81 \ (\text{m}, 1 \ H), 1.91 \ (\text{sept}, 1 \ H, J = 6.7 \ Hz), 2.01 \ (\text{dt}, 1 \ H, J = 4.5, 11.4 \ Hz), 2.05 \ (d, 1 \ H, J = 17.3 \ Hz), 2.39 \ (\text{dt}, 1 \ H, J = 7.0, 11.9 \ Hz), 2.84 \ (\text{dd}, 1 \ H, J = 7.0, 17.3 \ Hz). \]

\[^{13}\text{C} \text{NMR (100 MHz, CDCl}_3\text{): } d = 16.54, 18.41, 22.15, 25.28, 28.95, 29.74, 34.49, 36.00, 38.14, 39.02, 89.69, 177.34. \]


Compounds 14 and 15

Spectral data were reported previously.\(^{4b}\)

\((1\text{R},5\text{R})\)-6,6-Dimethyl-4-oxatricyclo[5.2.1.0\text{1,5}]decan-3-one (16)

Viscous oil.

Yield: 0.48 g, 2.7 mmol (54%).

\([\alpha]_D\text{25} = +99.0 \ (c \ 1.35, \text{CHCl}_3). \]

IR (KBr): 2960, 1780 cm\(^{-1}\).

\[^1\text{H} \text{NMR (400 MHz, CDCl}_3\text{): } d = 1.06 \ (\text{s}, 3 \ H), 1.10 \ (\text{s}, 3 \ H), 1.10-1.32 \ (\text{m}, 2 \ H), 1.53-1.64 \ (\text{m}, 1 \ H), 1.71-1.80 \ (\text{m}, 3 \ H), 1.81-1.84 \ (\text{m}, 1 \ H), 2.48 \ (d, 1 \ H, J = 17.1 \ Hz), 2.56 \ (d, 1 \ H, J = 17.1 \ Hz), 3.65 \ (d, 1 \ H, J = 1.2 \ Hz). \]

\[^{13}\text{C} \text{NMR (100 MHz, CDCl}_3\text{): } d = 16.85, 22.72, 24.57, 25.46, 27.12, 35.23, 39.57, 42.66, 48.65, 53.09, 95.33, 177.01. \]


References


