AN ALTERNATIVE METHOD FOR LACTONIZATION OF $\beta, \gamma$-ENOIC ACIDS AND ITS APPLICATION TO VERTICILLENE-10-CARBOXYLIC ACID

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Abstract-The reaction with iodine in refluxing acetic acid was found to be an alternative method for the lactonization of $\beta, \gamma$-enoic acids. Application of the method to verticillene-10-carboxylic acid (6) resulted in the formation of three $\gamma$-lactones (7, 12, and 13), 12 being an unexpected product.

The diterpene alcohols, verticillol (1) and 12-epiverticillol (2), are the constituent of an evergreen wood of conifer Sciadopitys vertilillata and a moss, Jackiella javanica, respectively. In spite of the early discovery of verticillols, there had been no report on the synthesis of the natural products excepting the construction of the hydrocarbon, verticillene. The bicyclic verticillene is biogenetically related to tricyclic taxane nucleus and is the putative biogenetic intermediate from the geranylgeranyl pyrophosphate (Scheme 1). The novel IN OUT structure of verticillols as well as their biogenetical relation with tricyclic taxane skeleton prompted us to elaborate the synthetic
route of 1 and 2, in which 10-cyanoverticillene (3) was settled as a key intermediate. Furthermore, Lewis acid promoted cyclization of the bicyclic intermediate (3) and its derivatives to a taxane skeleton is much interested from biogenetical viewpoints. 

verticillol (1) : R1=OH, R2=Me
12-epi-verticillol (2) : R1=Me, R2=OH

Figure 1. Structure of Verticillols

Thus, we have explored the synthetic route and reactivity of the intermediate (3), from which epoxide (4) and allyl alcohol (5) were derived (Chart 1). Since our trials to convert 4 or 5 to the epiverticillol (2) were all unsuccessful, we were compelled to adopt an alternative route, being the lactonization of verticillene-10-carboxylic acid (6) to \( \gamma \)-lactone (7) (Figure 2). The \( \gamma \)-lactone (7) is expected a promising intermediate, from which 2 may be synthesized by decarbonylation. For this purpose, lactonization of acid (6) derived from 3 was tried under several typical conditions including reactions with Lewis acid such as H\(_2\)SO\(_4\) and SnCl\(_4\) and also oxymercuration and iodo-lactonization. Since all attempts led to unsuccessful results, we have, therefore, searched an alternative lactonization conditions using homogeranic acids as model
compounds. This paper concerns with our results of exploration of lactonization conditions and their application to the verticillene-10-carboxylic acid (6), leading to the formation of three lactonic products (7, 12 and 13).

Lactonization of Homogeranic Acids (8 and 9). After considerable experiments, we have ultimately found that monocyclohomogeranic acid (8) was effectively converted to the corresponding \( \gamma \)-lactone (10) when treated with iodine (1.5 mol equiv) in refluxing acetic acid. No iodine atom was introduced in the lactone (10), differing from the product obtainable by the usual iodolactonization conditions (\( K_2CO_3 \) and iodine). Both iodine and acetic acid are substantial for the lactonization. Although exact mechanism is unclear, iodine or some active species derived therefrom in acetic acid may activate the double bond to make the lactone ring. In order to get insight into the mechanism, the reaction of acyclic homogeranic acid (9) was examined under several conditions, the result being summarized in Table 1. It was found that cyclization followed by lactonization occurred in high yield under the same conditions (run 1). In the meanwhile, reaction at room temperature for 1 h resulted in the formation of complex
Table 1. Conditions of Lactonization Reactions of 9

<table>
<thead>
<tr>
<th>run</th>
<th>reagent (equiv.)</th>
<th>solv.</th>
<th>temp. (°C)</th>
<th>time</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I₂ (1.5)</td>
<td>AcOH</td>
<td>120</td>
<td>1 h</td>
<td>84%</td>
</tr>
<tr>
<td>2</td>
<td>I₂ (1.5) + NaOAc (3.2)</td>
<td>AcOH</td>
<td>120</td>
<td>1 h</td>
<td>5%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>I₂ (1.5)</td>
<td>'BuCOOH</td>
<td>120</td>
<td>1 h</td>
<td>68%</td>
</tr>
<tr>
<td>4</td>
<td>I₂ (1.5)</td>
<td>AcOH</td>
<td>80</td>
<td>1 h</td>
<td>70%</td>
</tr>
<tr>
<td>5</td>
<td>I₂ (1.5)</td>
<td>AcOH</td>
<td>room temperature</td>
<td>1 h</td>
<td>mixture</td>
</tr>
<tr>
<td>6</td>
<td>I₂ (1.5)</td>
<td>AcOH</td>
<td>room temperature</td>
<td>1 day</td>
<td>58%</td>
</tr>
<tr>
<td>7</td>
<td>I₂ (0.03)</td>
<td>AcOH</td>
<td>120</td>
<td>1 h</td>
<td>40%</td>
</tr>
<tr>
<td>8</td>
<td>CH₂COOH (1.5)</td>
<td>AcOH</td>
<td>120</td>
<td>1 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>9</td>
<td>CICH₂COOH (1.5)</td>
<td>AcOH</td>
<td>120</td>
<td>1 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>10</td>
<td>54% aq HI (1.5)</td>
<td>AcOH</td>
<td>room temperature</td>
<td>1 h</td>
<td>mixture</td>
</tr>
<tr>
<td>11</td>
<td>54% aq HI (1.5)</td>
<td>AcOH</td>
<td>80</td>
<td>1 h</td>
<td>mixture</td>
</tr>
</tbody>
</table>

<sup>a</sup>; 5-(4-Methyl-3-penteny)-5-methylbutenolide (11) was isolated in 40% yield.
mixture, probably being composed of double bond isomers (run 5). After one day treatment at room temperature, the final product (10) was yielded in moderate yield (run 6). The result in run 7 indicated iodine acted catalytically. When sodium acetate was added (run 2), the lactone (10) was isolated in only 5% yield and the major product obtained in 40% yield was 5-(4-methyl-3-pentenyl)-5-methylbutenolide (11), probably formed by normal iodolactonization followed by dehydroiodination. By the action of halogenated acetic acids (runs 8 and 9) or hydroiodic acid (runs 10 and 11), the lactone (10) was not isolated from the reaction mixture. The results in Table 1 demonstrate clearly that I$_2$-AcOH system promotes cyclization as well as lactonization reactions of acyclic homogeranic acid (9).

**Application of I$_2$-AcOH to Verticillene-10-carboxylic Acid (6).** In our model experiments, we have revealed that the double bond of homogeranic acid is activated and cyclization followed by lactonization occurs easily and efficiently by the action of iodine in refluxing acetic acid. Since verticillene skeleton is considered as a putative biogenetic progenitor of tricyclic taxane skeleton (Scheme 1), it seems, therefore, intriguing to examine the reactivity of 6 with iodine in refluxing acetic acid from view points of both achievement of verticillol synthesis and also examination of cyclization to the taxane skeleton.

By treatment of 6 with iodine in refluxing acetic acid, three \( \gamma \) lactonic products (7, 12 and 13) were isolated in 20, 28 and 8% yields, respectively (Chart 2). The product (12) possesses tetracyclic ring system with \( \gamma \) lactone ring (1770 cm$^{-1}$). At the outset of our study, 12 could not be differentiated from the expected taxane skeleton (14) by usual means of \(^1\)H and \(^{13}\)C nmr spectra. Ultimately, the structure (12) was unequivocally determined by X-ray crystallographic analysis. The structures (7 and 13) were deduced from physical evidence.

Although formation mechanism of 12 is still unclear, protonization at C11 double bond
\[ \Delta E = +6.3 \text{ kcal/mol} \]

Bond distance:
- C3-C8: 4.03 Å
- C4-C9: 3.23 Å
- C3-C8: 3.52 Å

Figure 3. Molecular mechanics minimization and bond distances
from β face of 6 with concomitant lactonization (path A) leads to lactone (7). Protonization from α face followed by isomerization of double bond would transform to a plausible intermediate (B) (path B), from which the tetracyclic product (12) may be formed by cyclization-lactonization as demonstrated in Scheme 2. Our preliminary MM2 calculation\textsuperscript{11} allows us to estimate that the intermediate (B) is energetically more stable, having distance between C4 and C9 enough for ring closure, as compared with those of starting material (6) and hypothetical intermediate (A*), derived by deprotonization from an intermediate (A) (Figure 3). The lactone (7) remained unchanged when subjected to the conditions of iodine in refluxing acetic acid, indicating the path A is irreversible. Thus, we have demonstrated that iodine in acetic acid is an alternative lactonization conditions of β, γ -enoic acids. Application of the present method to verticillene-10-carboxylic acid furnished the expected lactone (7) although the yield is not satisfactory. Transformation of the lactone (7) to the natural product, verticillol (2) is now in progress.

**EXPERIMENTAL**

Melting points (measured on Yanaco-MP) are uncorrected. Unless otherwise noted, \textsuperscript{1}H nmr and \textsuperscript{13}C nmr spectra were recorded on solutions in CDCl\textsubscript{3} with SiMe\textsubscript{4} as internal standard with JEOL spectrometers. Chemical shifts are reported in δ-units with δ\textsubscript{H} (\textsuperscript{1}H nmr) and δ\textsubscript{C} (\textsuperscript{13}C nmr), and J-values are in Hz. The mass spectra were measured with Hitachi M-80 and M-80A spectrometers. The infrared spectra were measured with Hitachi 270-30 spectrophotometer in solution. The characteristic absorption bands were reported with ν\textsubscript{max}, the solvent being indicated in parentheses. The usual work-up involved dilution of the reaction mixture with water, extraction with ether, washing of the organic extracts with water and brine, followed by drying over Na\textsubscript{2}SO\textsubscript{4}, and
evaporation at aspirator pressure. Column chromatographic purification was carried out on Kiesel gel 60, Art 7734 (70-230 mesh), the elution solvents being indicated.

**Lactonization of Monocyclohomogeranic Acid (8).** A mixture of homogeranic acid (8) (56.6 mg, 0.31 mmol) and iodine (119 mg, 0.47 mmol, 1.5 eq) in acetic acid (4 ml) was refluxed for 1 h under argon atmosphere. After cooling, the reaction mixture was diluted with ether, washed successively with aq saturated NaHCO₃, aq saturated Na₂S₂O₃ and brine. The ether was removed and the residue was chromatographed with hexane-AcOEt 50:1 and then 1:1 to afford γ-lactone (10) (48 mg, 84%) as colorless oil.

\[ \nu_{\text{max}} (\text{CCl}_4) 1784 \text{ cm}^{-1}. \delta H (90 \text{ MHz}) 0.96 (3H, s), 1.06 (3H, s), 1.53 (3H, s), 2.41 (1H, s), 2.54 (1H, d, J=4.8 Hz). \delta C (23 \text{ MHz}) 175.5, 85.8, 51.8, 34.6, 33.5, 33.1, 32.1, 29.9, 28.3, 26.8, and 18.9. \text{HRms Found: m/z 182.1301. Calcd for C}_{11}\text{H}_{18}\text{O}_{2}: M, 182.1307. \]

**General Procedure of Reaction of Homogeranic Acid (9) in Table 1.**

Homogeranic acid (9) (30 mg) in acetic acid (6 ml) was treated under the conditions listed in Table 1. The reaction mixture was treated as in the case of 8.

9. \[ \nu_{\text{max}} (\text{CCl}_4) 1712 \text{ cm}^{-1}. \delta H (90 \text{ MHz}) 1.61 (3H, s), 1.66 (3H, s), 1.69 (3H, s), 2.05 (4H, s), 3.10 (2H, d, J=7.2 Hz), 5.10 (1H, br s), and 5.33 (1H, br t, J=7.2 Hz). \]

**Reaction of Homogeranic Acid (9) with Iodine and Sodium Acetate.** A mixture of homogeranic acid (9) (43.4 mg, 0.24 mmol), I₂ (90.7 mg, 0.36 mmol, 1.5 eq) and NaOAc (62.5 mg, 0.76 mmol, 3.2 eq) in AcOH (7 ml) was refluxed for 1 h under argon atmosphere and the reaction mixture was treated as in the case of 8.

Column chromatography afforded butenolide (11) (17.1 mg, 40%), cis-lactone (10) (2.5 mg, 6%) and trans-lactone (1.8 mg, 4%).

11. \[ \nu_{\text{max}} (\text{CCl}_4) 1768 \text{ cm}^{-1}. \delta H (90 \text{ MHz}) 1.48 (3H, s), 1.57 (3H, s), 1.68 (3H, s), \]
Lactonization of Verticillene-10-carboxylic Acid (6). A mixture of verticillene-10-carboxylic acid (6) (110 mg, 0.348 mmol) and iodine (132 mg, 0.532 mmol, 1.5 eq) in acetic acid (20 ml) was refluxed for 1 h under argon atmosphere. After cooling, the reaction mixture was diluted with ether, washed successively with aq saturated NaHCO₃, aq saturated Na₂S₂O₃ and brine. The ether was removed and the residue was chromatographed with hexane-AcOEt 50:1 and then 1:1 to afford 7 (22.4 mg, 20%), 12 (30.4 mg, 28%) and 13 (9.3 mg, 8%). 7 colorless powder, mp 169-170°C (hexane). ν max (CCl₄) 1766 cm⁻¹. δ H (200 MHz) 0.62 (3H, s), 0.93 (3H, s), 1.53 (6H, s), 1.56 (3H, s), 4.96 (1H, br d, J=10.0 Hz), and 5.32 (1H, br d, J=12.3 Hz). δ C (50 MHz) 180.6 (s), 134.7 (s), 132.7 (d), 132.2 (s), 123.7 (d), 86.1 (s), 46.9 (d), 41.9 (t), 41.5 (t), 40.2 (d), 40.1 (d), 34.5 (s), 32.8 (t), 31.5 (t), 29.4 (q), 28.4 (q), 26.6 (t), 25.7 (q), 23.4 (t), 16.3 (q), and 16.0 (q). HRms Found: m/z 316.2400. Calcd for C₂₁H₃₂O₂: M, 316.2402. 12 colorless prisms, mp 118-120°C (hexane). Crystal System: orthorhombic. Cell Constant: a=13.120 (4), b=16.479 (1), c=16.413 (2) Å. V=3648.5 (1.7) Å³. Dcocl: 1.184 g/cm³. Z: 8. ν max (CCl₄) 1770 cm⁻¹. δ H (500 MHz) 0.96 (3H, s), 1.06 (6H, s), 1.33 (3H, s), 1.53 (3H, s), 2.55 (1H, br s), 2.70 (1H, dd, J=1, 13 Hz), and 5.54 (1H, m). δ C (50 MHz) 181.4 (s), 132.8 (s), 125.5 (d), 84.5 (s), 57.9 (d), 46.9 (d), 42.9 (t), 40.8 (d), 39.8 (t), 38.8 (d), 37.6 (t), 35.6 (s), 34.5 (s), 33.3 (q), 28.3 (t), 26.9 (q), 24.8 (q), 24.3 (t), 22.4 (q), 20.6 (t), and 19.3 (q). HRms Found: m/z 316.2421. Calcd for C₂₁H₃₂O₂: M, 316.2402. 13 colorless needles, mp 173-175°C (hexane). δ H (200 MHz) 0.99 (3H, s), 1.11 (3H, s), 1.33 (3H, s), 1.63 (3H, s), 1.65 (3H, s), 2.74 (1H, m), 3.28 (1H, br d, J=10.3 Hz), 5.18 (1H, br d, J=12.0 Hz). δ C
(50 MHz) 180.5 (s), 133.7 (s), 130.9 (s), 129.0 (s), 127.6 (d), 87.3 (s), 44.1 (d), 43.0 (d), 41.1 (t), 38.1 (t), 37.7 (s), 36.6 (t), 34.0 (t), 32.5 (t), 31.8 (q), 26.7 (q), 26.1 (q), 25.5 (t), 22.2 (q), 20.2 (t), and 15.5 (q). HRms Found: m/z 316.2400. Calcd for C\textsubscript{21}H\textsubscript{32}O\textsubscript{2}: M, 316.2402.

REFERENCES

10. Unpublished results in our laboratory.

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