Synthesis and Herbicidal Activity of Optically Active Ethyl 2-[4-(6-Chloro-2-quinoxalinyloxy)phenoxy]propanoate

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Optically active ethyl (R)-(+) and (S)-(-)-2-[4-(6-chloro-2-quinoxalinyloxy)phenoxy]propanoate ((R)-(+) and (S)-(-)-1) were synthesized from (S)-(+)lactic acid: (S)-(+)lactic acid was converted to ethyl O-(p-toluenesulfonyl)-(S)-(-)-lactate, ethyl O-methanesulfonyl-(S)-(-)-lactate, ethyl (R)-(+)2-chloro propanoate and ethyl (R)-(+)2-bromo propanoate, respectively. Each intermediate was condensed with 4-(6-chloro-2-quinoxalinyloxy)phenol (2) to afford (R)-(+) and (S)-(-)-1. Optical purities were determined by the 200 MHz 1H NMR spectroscopic measurement using shift reagent, Eu(HFC)3. It was assumed that optically pure (R)-(+)1 would have [α]D +35.2 (CHCl3, c=1.20%). The growth inhibiting activity against rice plants in petridish and the post-emergence herbicidal activity against Setaria viridis were examined. The strong correlation was observed between the content of (R)-(+)isomer and biological activity. It was assumed that optically pure (R)-(+)1 was approximately two fold more active than the racemate and optically pure (S)-(-)-1 was low active or inactive.

INTRODUCTION

Ethyl 2-[4-(6-chloro-2-quinoxalinyloxy)phenoxy]propanoate (I) [code No. NCI-96683] is a new novel selective herbicide discovered in 1979 and currently being developed by Nissan Chemical Industries, Ltd. It is a post-emergence herbicide for the selective control of annual and perennial grass weeds primarily in broadleaf crops. In our preceding paper, the syntheses and herbicidal activities of racemic NCI-96683 were reported. In this paper, we wish to report the syntheses of the optical active (R)-(+) and (S)-(−)-isomer of NCI-96683 by using (S)-(−)-lactic acid and the correlation between their specific rotations and optical purities and further to present their comparative biological activities.

MATERIALS AND METHODS

1. Apparatus

1H NMR spectra were obtained on a JEOL FX-90 and JEOL-200 spectrometer locked on the tetramethylsilane as an internal reference. IR spectra were measured on a JASCO A-3 Infrared Spectrophotometer. Mass spectra were measured on a JEOL D-300, JMA 3500 and DX-300, JMA 3100. Chemical purities were determined on a Shimadzu Liquid Chromatograph LC-3A and Shimadzu Gas Chromatograph GC-7A. Optical rotations were measured on a JASCO DPI-4 Digital Polarimeter. All melting points are uncorrected.

2. Syntheses of Compounds

2.1 Ethyl (S)-(−)-lactate

(S)-(−)-lactic acid (Sigma Chemical Co.) was esterified with ethyl alcohol containing a few drops of sulfuric acid in benzene. It had:
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by 77.0-78.5°C/48 mmHg; 1H NMR δ (ppm): 1.28 (3H, t, J=7.2Hz), 1.40 (3H, d, J=7.2Hz), 3.40 (1H, bs), 4.21 (3H, q, J=7.2Hz); [α]D 20 +7.7° (CH3OH, c=2.02%).

2.2 Ethyl O-(p-toluenesulfonyl)-(S)-(−)-lactate6)

Ethyl (S)-(−)-lactate dissolved in dry pyridine was cooled at 0-5°C and p-toluenesulfonyl chloride was added. The reaction mixture was stirred at room temperature, next allowed to stand overnight. It was worked up to obtain the solid, mp 34.0-35.5°C; 1H NMR TMS δ (ppm): 1.18 (3H, t, J=7.2Hz), 1.47 (3H, d, J=7.2Hz), 2.41 (3H, s), 4.07 (2H, q, J=7.2Hz), 4.87 (1H, q, J=7.2Hz), 7.29 (2H, d, J=7.8Hz), 7.78 (2H, d, J=7.8Hz); [α]D 20 +34.6° (CHCl3, c=2.95%).

2.3 Ethyl O-methanesulfonyl-(S)-(−)-lactate7)

Ethyl (S)-(−)-lactate and methanesulfonyl chloride were dissolved in anhydrous ether and cooled at 0-5°C. Triethylamine was slowly dropped and cooling was continued. Then the reaction mixture was stirred at room temperature, next allowed to stand overnight. It was worked up to obtain colorless liquid, bp 92.0-93.0°C/3 mmHg; 1H NMR δ (ppm): 1.29 (3H, t, J=6.6Hz), 1.59 (3H, d, J=6.6Hz), 3.11 (3H, s), 4.23 (2H, q, J=6.6Hz), 5.08 (1H, q, J=6.6Hz); [α]D 20 -55.3° (CHCl3, c=1.21%).

2.4 Ethyl (R)-(+) and (S)-(−)-2-[4-(6-chloro-2-quinoxalinyloxy) phenoxy] propanoate ((R)-(−)-1 and (S)-(−)-1)

Path 1. 4-(6-chloro-2-quinoxalinyloxy)-phenol (2) (5.43g, 20 mmol), ethyl O-(p-toluenesulfonyl)-(S)-(−)-lactate (5.44g, 20 mmol) and anhydrous potassium carbonate (5.52g, 40 mmol) were refluxed in 100 ml of acetonitrile for 8 hr. After cooling, solid was filtered off. The filtrate was evaporated and residue was dissolved in methylene chloride. Methylene chloride solution was washed with 2.5% sodium hydroxide, then water and dried over anhydrous sodium sulfate. Removal of solvent gave a pale-yellow solid, which was purified with column chromatography (silica gel, CH2Cl2) to obtain 6.86 g (92% yield) of chemically pure colorless solid; 1H NMR δ (ppm): 1.27 (3H, t, J=6.9Hz), 1.63 (3H, d, J=6.9Hz), 4.24 (2H, q, J=6.9Hz), 4.74 (1H, q, J=6.9Hz), 6.91 (2H, d, J=9.4Hz), 7.18 (2H, d, J=9.4Hz), 7.51 (1H, dd, J=9.2, 2.0Hz), 7.67 (1H, d, J=9.2Hz), 8.01 (1H, d, J=2.0Hz), 8.62 (1H, s); IR νmax cm−1: 3400, 2940, 1735, 1597, 1570, 1540, 1490, 1429, 1388, 1292, 1232, 1201, 1182, 920, 815; MS m/z: 372 (M+, base peak), 299, 271, 244, 163; [α]b 20 +28.5° (CHCl3, c=2.00%).

Path 2. 2 (5.43g, 20 mmol), ethyl O-methanesulfonyl-(S)-(−)-lactate (3.92g, 20 mmol) and anhydrous potassium carbonate (5.52g, 40 mmol) were refluxed in 100 ml of acetonitrile for 7.5 hr. Upon work-up and purification with column chromatography (silica gel, CH2Cl2), 6.71 g (90% yield) of colorless solid was obtained, [α]b 20 +15.7° (CHCl3, c=2.00%).

Path 3. 2 (5.45g, 20 mmol), ethyl (R)-(+) and (S)-(−)-2-chloropropanoate (3.00g, 22 mmol) and anhydrous potassium carbonate (5.52g, 40 mmol) were refluxed in 100 ml of acetonitrile for 7.5 hr. Upon work-up and purification with column chromatography (silica gel, CH2Cl2), 6.49 g (87% yield) of colorless solid was obtained, [α]b 20 -4.0° (CHCl3, c=2.00%).

Path 4. 2 (2.73g, 10 mmol), ethyl (R)-(+) and (S)-(−)-2-bromopropanoate (2.18g, 12 mmol) and anhydrous potassium carbonate (2.76g, 20 mmol) were refluxed in 50 ml acetonitrile for 8 hr. Upon work-up and purification with column chromatography (silica gel, CH2Cl2), 3.36 g (90% yield) of colorless solid was obtained, [α]b 20 -4.0° (CHCl3, c=2.00%).
3. Biological Test

The growth inhibiting activities of racemic, (R)-(+) and (S)-(−)-1 examined with seeds of rice plants (Oryza sativa) in petridish are shown in Table 1. Ten ml solutions of each compound containing 0.1% ethanol were poured in every petridish. Then, ten rice seeds were placed in each and incubated at 25°C under fluorescent lamps. One week after treatment, the length of shoot was measured. The post-emergence herbicidal activities against Setaria viridis (SETVI* determined in plastic boxes (15×22 cm and 6 cm in depth) under greenhouse conditions, is shown in Table 1. Each plastic box was filled with a sterilized clay loam soil and S. viridis was seeded 1.5 cm in depth. At the 5.5–6.5 leaf stage, plants were sprayed with a solution of each compound formulated as an emulsifiable concentrate. After four weeks, the plant shoot was harvested at soil level and weighed. The activity expressed as 190, 175 and 150 indicate the concentration level (ppm and g/a) required for the 90, 75 and 50% inhibition of the shoot growth to the control.

RESULTS AND DISCUSSION

1. Synthesis

Synthetic routes of ethyl (R)-(+) and (S)-(−)-2-[4-(6-chloro-2-quinoxalinyloxy)phenoxy]propanoate ((R)-(+) and (S)-(−)-1) are shown in Scheme 1.

Ethyl (S)-(−)-lactate, which was obtained from the esterification of (S)-(+)lactic acid, was converted into ethyl O-(p-toluenesulfonyl)-(S)-(−)-lactate, ethyl O-methanesulfonyl-(S)-(−)-lactate, ethyl (R)-(−)-2-chloropropanoate and ethyl (R)-(−)-2-bromopropanoate, respectively. The esterification of (S)-(−)-lactic acid and the tosylation or mesylation of ethyl (S)-(−)-lactate did not affect the bonds linked to the asymmetric carbon center, therefore, (S)-configuration were retained. On the other hand, the bromination or chlorination of ethyl (S)-(−)-lactate, proceeded with inversion of the configuration, therefore, the formation of (R)-isomer was accompanied.

These intermediates were condensed with 4-(6-chloro-2-quinoxalinyloxy)phenol (2) to afford optically active (R)-(+) and (S)-(−)-1. The reaction with 2 involved inversion of the configuration by the S_{2}2 mechanism.

2. Optical Purity

Optical purities of (R)-(+) and (S)-(−)-1 were determined by 1H NMR spectroscopic measurement using shift reagent. On attempts to separate both isomers, preliminary investigation was carried out by use of 90 MHz NMR spectrometer. The use of Eu(HF)_{3}, Eu(TF)_{3}, or Eu(TBC)_{3} as the shift reagent and carbon tetrachloride, deuteriochloroform or deuteriobenzene as the solvent were examined. When the shift reagent Eu(HF)_{3} was added to the carbon tetrachloride-deuteriobenzene(4:1) solution, A-methyl and B-methyl of (R)-(+)l-acid, was converted into ethyl O-(p-toluenesulfonyl)-
lated and the optical purity could be determined. However, when 90 MHz NMR spectrometer was used for the determination of their optical purities, the accuracy was still not satisfactory. If the ratio of (R)-(-) to (S)-(-)-isomer was extremely large or small, the signal for the minor isomer was included in the shoulder of the neighboring signals derived from the major one. More reliable optical purities were obtained by use of 200 MHz NMR spectrometer. The 1H NMR signals were separated as shown in Fig. 1.

The correlation between their specific rotations and optical purities (enantiometric excess) is shown in Fig. 2. As shown by the dotted line, it was assumed that optically pure (R)-(+)-1 have $[\alpha]_{D}^{10} -35.2^\circ$.

![Diagram of compound structure](image)

**Fig. 2** Correlation between the specific rotation and optical purity of ethyl 2-[4-(6-chloro-2-quinoxalinyloxy)phenoxy]propanoate.

![Graph](graph)

**Table 1** Growth inhibiting activity of ethyl (±), (R)-(+) and (S)-(-)-2-[4-(6-chloro-2-quinoxalinyloxy)phenoxy]propanoate.

<table>
<thead>
<tr>
<th>Compound</th>
<th>c.e. (%)*</th>
<th>$I_{90}$ (ppm)</th>
<th>$I_{75}$ (ppm)</th>
<th>$I_{50}$ (ppm)</th>
<th>$I_{90}$ (g/a)</th>
<th>$I_{75}$ (g/a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Racemate</td>
<td>0</td>
<td>0.076</td>
<td>0.056</td>
<td>0.034</td>
<td>1.30</td>
<td>0.25</td>
</tr>
<tr>
<td>(R)-(+)</td>
<td>81.5</td>
<td>0.040</td>
<td>0.030</td>
<td>0.020</td>
<td>0.43</td>
<td>0.10</td>
</tr>
<tr>
<td>(S)-(−)</td>
<td>11.4</td>
<td>0.090</td>
<td>0.070</td>
<td>0.050</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(S)-(−)</td>
<td>44.3</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>4.00</td>
<td>0.52</td>
</tr>
</tbody>
</table>

* Inhibition of shoot elongation.
  b) Inhibition of growth control.
  c) Enantiometric excess.
3. Biological Activity

Comparative biological activities of racemic, (R)-(−) and (S)-(−)-1 are shown in Table 1. When the shoot growth inhibiting activity against rice plants was examined in petridish, IC₅₀ for racemic, (R)-(−) and (S)-(−)-1 was 0.076, 0.040 and 0.090 ppm and the content of (R)-(−)-isomer was 50.0, 90.8 and 44.3%, respectively. The strong correlation was observed between the content of (R)-(−)-isomer and the shoot growth inhibiting activity. This means that optically pure (R)-(−)-1 is approximately two fold more active than the racemate, whereas optically pure (S)-(−)-1 is low active or inactive.

When the post-emergence herbicidal activity was examined with S. viridis, IC₅₀ for racemic, (R)-(−) and (S)-(−)-1 was 1.30, 0.43 and 4.00 g/a and the content of (R)-(−)-isomer was 50.0, 90.8 and 27.8%, respectively. Therefore, optically pure (R)-(−)-1 would be approximately three fold more active than racemate.

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Ethyl 2-[4-(6-chloro-2-quinoxalinyloxy)phenoxy]propanoate の光学活性体の合成とその除草活性

坂田五常，牧野健二，森本勝之

Ethyl (R)-(+) および (S)-(−)-2-[4-(6-chloro-2-quinoxalinyloxy)phenoxy]propanoate ((R)-(−)-1 および (S)-(−)-1) を (S)-(−)-lactic acid から合成した。 (S)-(−)-lactic acid を用いて、ethyl O-(p-toluenesulfonyl)-(S)-(−)-lactate, ethyl O-methanesulfonyl-(S)-(−)-lactate, ethyl-(R)-(−)-2-chloropropanoate および ethyl (R)-(−)-2-bromopropanoate を合成し、これら中間体を 4-(6-chloro-2-quinoxalinyloxy)phenol と反応させ、(R)-(−)-1 および (S)-(−)-1 を得た。光化学性はシフト試薬 Eu(HFC₃) を用いて、200 MHz NMR の測定から決定した。その結果、光学的に純粋な (R)-(−)-1 は、[α]D +35.2° (CHCl₃, c=1.20 %) の旋光度であることが推定できた。シャーレ試験におけるイネ幼苗植物の生長阻害活性と、イネ科植物を用いた薬剤除草活性を検討した結果、(R)-(−)-体の含量と除草活性の関係が明確であることがわかった。そして光学的に純粋な (R)-(−)-1 は、ラセミ体に比較して約 2 倍の除草活性を有すること、および (S)-(−)-1 は、低活性かあるいはほとんど活性を示さないことが推定された。