Optical Resolution by Preferential Crystallization of (1RS,3RS)-1,2,3,4-Tetrahydro-6,7-dihydroxy-1-methyl-3-isoquinolinecarboxylic Acid

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The racemic structure of (1RS,3RS)-1,2,3,4-tetrahydro-6,7-dihydroxy-1-methyl-3-isoquinolinecarboxylic acid [(1S,3S)-1] was examined based on the melting point, solubility, and IR spectrum, with the aim of optical resolution by preferential crystallization. (1RS,3RS)-1 was indicated from these results to exist as a conglomerate. The successive optical resolution by preferential crystallization of (1RS,3RS)-1 yielded (1S,3S)- and (1R,3R)-1 with optical purities of 85—95% at 66—81% degrees of resolution, which were fully purified by recrystallization.

Key words 1,2,3,4-tetrahydroisoquinoline; conglomerate; optical resolution; preferential crystallization

(1S,3S)-1,2,3,4-Tetrahydro-6,7-dihydroxy-1-methyl-3-isoquinolinecarboxylic acid [(1S,3S)-1] is the alkaloid from seeds of the genus Mucuna (Leguminosae). (1RS,3RS)-1 is a physiologically important compound and, for example, is potent in free radical-scavenging activity against hydroxyl and superoxide anion radicals. In addition, (1S,3S)- and (1R,3R)-1 are useful as chiral reagents in asymmetric syntheses; for example, (8S,13αR)-8-methyl-2,3,10,11-tetramethoxyberbine is synthesized from (S)-2-amino-3-(3,4-dihydroxyphenyl)propanoic acid [(S)-2; 1,3,4-dihydroxyphenylalanine (-DOPA)] via the (1S,3S)-1 intermediate. (1S,3S)-1 can be synthesized by condensation of (S)-2 with acetaldheyde in dilute aqueous mineral acid in vitro. By the condensation affords compound 1 as a mixture of two diastereoisomers, the major product (1S,3S)-1 (cis-form) and the minor product (1R,3S)-1 (trans-form), because of the generation of a new chiral center at the C-1 position of the 1,2,3,4-tetrahydroisoquinoline ring. From the mixture of the diastereoisomers, (1R,3S)-1 was removed by recrystallization from dilute hydrochloric acid to afford (1S,3S)-1 as the single diastereoisomer without formation of the hydrochloride, as described in Experimental. Although (1R,3R)- and (1S,3R)-1 can be also synthesized starting from (R)- and (RS)-2, respectively, in a manner similar to (1S,3S)-1, (R)-2 is not commercially available. Therefore we attempted to obtain both (1S,3S)- and (1R,3R)-1 by optical resolution by preferential crystallization of (1S,3S)-1 (Chart 1).

Optical resolution by preferential crystallization, which has been successfully employed to obtain enantiomers from racemates, is said to be a simple and useful method for large-scale chiral separation and is achieved by providing a small amount of one enantiomer as seed crystals in a racemic supersaturated solution. Racemates exist in the forms of racem compounds, racemic solid solutions, and conglomerates. However, only conglomerates, which are defined as mechanical mixtures of crystals of both enantiomers, can be optically resolved by preferential crystallization. Therefore we first examined the racemic structure of (1RS,3RS)-1.

The racemic structure was examined by comparing the melting point, solubility, and IR spectrum of the racemate with those of the enantiomer. Although (1RS,3RS)- and (1S,3S)-1 were decomposed by heating, (1RS,3RS)-1 was decomposed at a lower temperature during heating than was (1S,3S)-1. The IR spectrum of (1RS,3RS)-1 was identical to that of (1S,3S)-1. In addition, (1RS,3RS)-1 was more soluble than (1S,3S)-1; the solubility of (1RS,3RS)-1 at 10 °C was 1.396 g (100 ml of 0.1 mol/l HCl)−1; and the solubility of (1S,3S)-1 at 10 °C was 0.799 g (100 ml of 0.1 mol/l HCl)−1. Racemates that exist as conglomerates are known to have such characteristics. In addition, the ternary solubility diagram also showed that (1RS,3RS)-1 is expected to be a conglomerate (Fig. 1). The above results suggest that (1RS,3RS)-1 exists as a conglomerate.

(1RS,3RS)-1 was optically resolved by preferential crystallization in 0.1 mol/l hydrochloric acid at 10 °C. To optimize the conditions, the optical resolution was conducted by stirring solutions of (1RS,3RS)-1 in 50 ml of 0.1 mol/l hydrochloric acid at 140—170% supersaturation for 30—90 min; (1S,3S)-1 (0.100 g) was employed as seed crystals. The results are shown in Figs. 2 and 3. The yield of enantiomer [YE(g)], degree of resolution [DR(%)], and amount of crystallization [AC(1S,3S) and AC(1R,3S)] were calculated from

\[ YE(g) = \frac{[\text{yield (g)} \times 100]}{100} \]

\[ DR(\%) = \frac{\text{YE(g)} \times 100}{([1/2]\text{amount of (1RS,3RS)-1} - 0.698)) \]

\[ AC_{(1S,3S)}(g) = \frac{[1/2][\text{yield (g)} - \text{YE(g)} - 0.100]}{\text{AC}_{(1R,3S)}(g)} \]

Chart 1. Synthetic Route to Optically Active cis-1,2,3,4-Tetrahydro-6,7-dihydroxy-1-methyl-3-isoquinolinecarboxylic Acid (cis-1)
where the solubility of $$(1RS,3RS)$$-I was 0.698 g in 50 ml of 0.1 mol/l hydrochloric acid at 10°C, the yield is the sum of the amounts of the crystallized I and seed crystals, and the optical purity [OP(%)] of the obtained $$(1S,3S)$$-I is calculated on the basis of the specific rotation \([\alpha_D^\circ = -157^\circ] (c=1, 1 \text{ mol/l HCl})\) of $$(1S,3S)$$-I, which was synthesized from \((S)\)-2; \((1S,3S)$$-I, \([\alpha_D^\circ = -151.5^\circ] (c=1, 1 \text{ mol/l HCl})\); \((1R,3R)$$-I, \([\alpha_D^\circ = +157.4^\circ] (c=1, 1 \text{ mol/l HCl})\). The degree of resolution [DR(%)] is defined as the yield (%) of the seeded enantiomer, based on half of the supersaturating portion of a racemate, and indicates the efficiency of optical resolution; half of the supersaturating portion of a racemate means the theoretical yield (g) of the seeded enantiomer.

When the 140—155% supersaturated solutions were employed (Fig. 2), $$(1S,3S)$$-I with optical purities of about 90% were obtained with 49—63% degrees of resolution. When the solutions with 160% and 170% supersaturation were employed (Fig. 2), the optical resolutions gave $$(1S,3S)$$-I with optical purities of 71% and 37%, respectively, because of rapid crystallization of the unseeded \((1R,3R)\)-I. From these results, the optical resolution of the 155% supersaturated solution was determined at resolution times of 30—90 min (Fig. 3). Rapid crystallization of the unseeded \((1R,3R)\)-I was not observed for the first 70 min, but \((1R,3R)$$-I began to crystallize rapidly at 80 min. Therefore $$(1S,3S)$$-I with optical purity of 85% was obtained in the highest degree of resolution (70%) at resolution time of 70 min. Based on these results, successive optical resolution was attempted by stirring the 155% supersaturated solution, as the initial solution, for 70 min (Table 1). The degrees of resolution [DR(%)] of $$(1S,3S)$$- and \((1R,3R)$$-I obtained were calculated from

$$DR(\%) = YE(g) \times 100 / \text{operation amount of (1S,3S)- or (1R,3R)-I}$$

where the operation amount is the amount of $$(1S,3S)$$- and \((1R,3R)$$-I in the solution used in the optical resolution and those in runs 2—4 in Table 1 were calculated based on the yields and optical purities of \((1S,3S)$$- and \((1R,3R)$$-I obtained.

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Table 1. Successive Optical Resolution by Preferential Crystallization of \((1S,3R)$$-1,2,3,4-Tetrahydro-6,7-di-hydroxy-1-methyl-3-isooquinolinecarboxylic Acid (cis-I)

<table>
<thead>
<tr>
<th>Run</th>
<th>Amount of ((1RS,3RS)$$-I added (g)</th>
<th>Operation amount (g) ((1S,3S)$$-I-(1R,3R)-I</th>
<th>Resolution time (min)</th>
<th>Yield(%) (g)</th>
<th>Optical purity (%), YE(%) (g)</th>
<th>DR(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.082</td>
<td>0.541</td>
<td>70</td>
<td>(1S,3S)-(−) 0.276</td>
<td>84.7</td>
<td>0.134</td>
</tr>
<tr>
<td>2</td>
<td>0.176</td>
<td>0.474</td>
<td>80</td>
<td>(1R,3R)-(+) 0.320</td>
<td>92.4</td>
<td>0.196</td>
</tr>
<tr>
<td>3</td>
<td>0.220</td>
<td>0.572</td>
<td>60</td>
<td>(1S,3S)-(−) 0.285</td>
<td>87.0</td>
<td>0.148</td>
</tr>
<tr>
<td>4</td>
<td>0.186</td>
<td>0.498</td>
<td>80</td>
<td>(1R,3R)-(+) 0.307</td>
<td>94.9</td>
<td>0.191</td>
</tr>
</tbody>
</table>

*Conditions: seed crystals, 0.100 g of \((1S,3S)$$-I, solvent, 50 ml of 0.1 mol/l hydrochloric acid; temperature, 10°C. * Ye, yield of enantiomer. * DR, degree of resolution.*
in runs 1—3, respectively. Half of the solubility of (1RS,3RS)-1 is 0.349 g in 50 ml of 0.1 mol/l hydrochloric acid at 10 °C.

The optical resolution afforded (1S,3S)- and (1R,3R)-1 with optical purities of 85—95% at 66—81% degrees of resolution. The (1S,3S)- and (1R,3R)-1 obtained were recrystallized from 0.1 mol/l hydrochloric acid to afford the optically pure 1 enantiomers.

Experimental

General Specific rotations were measured at 589 nm and 20 °C with a Horiba Seisakusho SEPA-300 autopolarimeter equipped with a quartz cell with a 5.00-cm path length. IR spectra were obtained in the range of 4000—
400 cm⁻¹ with a Perkin-Elmer Model 1600 FT-IR spectrometer using the KBr disk method. 'H- and 13C-NMR spectra were recorded on a JNM-
FX270 FT NMR system in a deuterium oxide solution of deuterium chloride (DCI) with sodium 3-(trimethylsilyl)propionate-sulfonate (DSS) as an internal standard. Chemical shifts are reported in δ units downfield from DSS. Melting points were measured with a Yanaco MP-500 D micro melting point apparatus.

(1RS,3S)-, (1S,3S)-, and (1R,3R)-1,2,3,4-Tetrahydro-6,7-dihydroxy-1-methyl-3-isouquinolinemalononic Acid \([1R,3S,5S]-(1S,3S),\) and \([1R,3R,5R]-(1R,3R)-1\) To the solution of (RS)-2 (19.7 g, 0.100 mol) in 0.1 mol/l hydrochloric acid (1000 ml) acetaldehyde [49 g (about 90%), 1 mol] was added. After allowing to stand overnight at room temperature, the solution was evaporated to dryness in vacuo at 60 °C. A solution of the residue in 300 ml of boiling water for 1 h, \((1R,3S,5S)-1\) was collected quickly by filtration and dried.

(1RS,3S)-1: Yield: 16.5 g (74.0%); mp 270—275 °C (decomp.) (KBr) cm⁻¹: 3103, 1631, 1519, 1524, 1441, 1313, 852, 808, 624. 'H-NMR (270 MHz, 0.1 mol/l DCl, DSS) ℃: 6.82 (1H, s, arom. H), 6.77 (1H, s, arom. H), 4.59 (1H, q, J = 6.8 Hz, 1H-CH), 4.35 (1H, dd, J = 5.3, 12.0 Hz, 3-
CH), 3.32 (1H, dd, J = 5.4, 16.2 Hz, 4-CH2), 3.16 (1H, dd, J = 12.1, 16.0 Hz, 4-CH). 13C-NMR (67.5 MHz, 0.1 mol/l DCI, DSS) ℃=171.7 (C- COOH), 144.6 (arom. C), 144.1 (arom. C), 125.1 (arom. C), 123.0 (arom. C), 116.1 (arom. C), 113.3 (arom. C), 55.4 (1-C), 53.0 (3-C), 28.7 (4-C), 18.6 (CH). Anal. Calc for C11H13NO5C; C, 59.19; H, 5.87; N, 6.27. Found: C, 58.97; H, 5.70; N, 6.30.

(1S,3S)-1 was synthesized by reaction of (S)-2 (1.97 g, 10.0 mmol) with acetaldehyde (4.89 g, 0.100 mol), in a similar manner to that for \((1R,3S,5S)-1; [\alpha]_D^{20} = 139° (c = 1.00, 0.1 mol/l HCl). After vigorous stirring, a suspension of the crude \((1R,3S,5S)-1 (1.82 g) in 15 ml of 0.1 mol/l hydrochloric acid for 1 h at 80 °C and then at 10 °C for 3 h, the purified (1S,3S)-1 was collected by filtration, washed with a small amount of water, and dried.

(1S,3S)-1: Yield: 1.55 g (69.5%); mp 288—291 °C (decomp.) [mp 270—275 °C (1.000 g) in 40 ml of 0.1 mol/l hydrochloric acid for 1 h at 60 °C, followed by stirring for 10 h at 10 °C, the precipitated \((1R,3S,5S)-1 or (1S,3S)-1 was rapidly collected by filtration and thoroughly dried. The solubility at 10 °C was calculated on the basis of the weight of the precipitated \((1R,3S,5S)-1 \([25S,1]-1. Solubility of the \((1R,3S,5S)-1 at 10 °C: 1.396 g (100 ml of 0.1 mol/l HCl) \(^1\). Solubility of \((1S,3S)-1 at 10 °C: 0.799 g (100 ml of 0.1 mol/l HCl) \(^1\).

Preparing a ternary solubility diagram, the solubilities of mixtures of \((1R,3S,5S)-1 \) and \((1S,3S)-1 \) were measured at 10 °C similar to the method described above. The solid \(1 \) was filtered off and thoroughly dried and the specific rotation was measured. The amounts of \((1R,3S,5S)-1 \) and \((1S,3S)-1 \) in the solution were calculated based on the solubility of \(1 \) and the specific rotation of the solid \(1 \).

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