The Practical Synthesis of (2S)-7-Methoxy-1,2,3,4-tetrahydro-2-naphthylamine via Optical Resolution of 2-(3-Methoxybenzyl)succinic Acid

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We describe the practical synthetic route for (2S)-7-methoxy-1,2,3,4-tetrahydro-2-naphthylamine [(2S)-2-amino-7-methoxytetraline; (S)-AMT]. (2R)-2-(3-Methoxybenzyl)succinic acid [(R)-1] was obtained by the optical resolution of 2-(3-methoxybenzyl)succinic acid (1) as the salt of (1R,2S)-2-(benzylamino)cyclohexylmethanol (7), and (R)-1 was converted to the optically active (2S)-7-methoxy-1,2,3,4-tetrahydro-2-naphthoic acid [(S)-2] by the intramolecular Friedel-Crafts reaction followed by catalytic hydrogenation. (S)-AMT was obtained from the acid [(S)-2] by Hofmann rearrangement without racemization.

Key words optical resolution; (2S)-2-amino-7-methoxytetraline; (2R)-2-(3-methoxybenzyl)succinic acid; β-adrenoceptor

Recently, some new β2- and β2/β3-adrenoceptor agonists have been developed. In this field, currently, we are developing a new uterine relaxant KUR-1246 and a new ureteral relaxant KUL-1248,2 while Sanofi-Synthelabo is studying succinic acid derivatives. Evans’ s chiral enolate method provided the synthetic methods for the optically active benzylamino-7-methoxytetraline; (S)-AMT, because it is difficult to racemize the (S)-AMT also can be produced from commercially available L-aspartic acid (1), but this enzyme is not easily obtainable. (2) The optical resolution of racemic AMT as the salt of (1R,2S)-2-(benzylamino)cyclohexylmethanol (7) gave the corresponding methyl esters by treatment with trimethylsilyldiazomethane (TMS–CHN2).

Fig. 1

We thought that the optically active 2-(3-methoxybenzyl)succinic acid (1) or 7-methoxy-1,2,3,4-tetrahydrobenzylamino-7-methoxytetraline (25) was derived to (S)-AMT recovered from the mother liquor. (S)-AMT can be directly produced from 7-methoxy-2-tetralone using the specialized transaminase enzyme,2 but this enzyme is not easily obtainable. (S)-AMT also can be produced from commercially available L-aspartic acid and anisole,3) but it is necessary to use highly toxic reagents, PCl5, and SnCl4.

We described an efficient and practical method for the synthesis of (S)-AMT.

Some synthetic methods for (S)-AMT have been reported. One of them is the optical resolution of racemic AMT as the salt of (R)-mandelic acid.3 This is not an efficient method because it is difficult to racemize the (R)-rich AMT recovered from the mother liquor. (S)-AMT can be directly produced from 7-methoxy-2-tetralone using the specialized transaminase enzyme,2 but this enzyme is not easily obtainable. (S)-AMT also can be produced from commercially available L-aspartic acid and anisole,3) but it is necessary to use highly toxic reagents, PCl5, and SnCl4.

We thought that the optically active 2-(3-methoxybenzyl)succinic acid (1) or 7-methoxy-1,2,3,4-tetrahydrobenzylamino-7-methoxytetraline (25) was derived to (S)-AMT. Several groups have reported the synthetic methods for the optically active benzylamino-7-methoxytetraline derivatives. Evans’ s chiral enolate methodology6) needs the low temperature condition, and the asymmetric hydrogenation of benzylidenesuccinic acid derivatives with a chiral diphosphine complex of rhodium or ruthenium obtained unsatisfactory results.7) We tried optical resolution of the acids 1 or 2, because the racemates could be easily prepared under the usual reaction conditions in large quantity, and it was expected to racemize the other configuration of the acid components recovered from the mother liquors.

The acid 5 was prepared by the Stobbe condensation of 3-methoxybenzaldehyde (3) and diethyl succinate (4), followed by hydrolysis in 81% yield. After hydrogenation of 5 with 10% Pd–C, the acid 1 was obtained in 82% yield. The reaction of 1 with Ac2O followed by the intramolecular Friedel–Crafts reaction in the presence of AlCl3 produced the ketone 6 in 86% yield. The ketone 6 was reductively deoxygenated with 10% Pd–C and H2SO4 in AcOH to give the acid 2 in 88% yield.

The acid 1 or 2 and an optically active amine are dissolved in hot solvent and allowed to stand at room temperature. The precipitate was collected and recrystallized from the same solvent. The optical purity of the acids, the yield, the optical purity of the acids, and the resolution efficiency (RE) are shown in Tables 1 and 2. The optical purity of the acids 1 and 2 were determined by HPLC using a chiral column, after the transformation of the acids to the corresponding methyl esters by treatment with trimethylsilyldiazomethane (TMS–CHN2).

The optical resolution of the acid 1 using (1R,2S)-2-(benzylamino)cyclohexylmethanol (7) gave the corresponding salt in 37% yield with good optical purity of 90.1% ee. The salt of 1 and (1S)-1-phenyl-2-(4-tolyl)ethylylene (8) was obtained in 10% yield with the excellent optical purity of...
99.0% ee, however, the unsuitable (S)-configuration of 1 was obtained by using commercially available 8. The optically active 1-phenylethylamine performed the optical resolution of benzylsuccinic acid well in our previous report, but gave the unsatisfactory result in the one of 1. On the other hand, the acid 2 was resolved by the amine 7 and (1S)-1-(1-naphthyl)ethylamine as the corresponding salt in 17% yield with 93.4% ee and 17% yield with 84.5% ee, respectively. We calculated the RE value from the yield and the optical purity, and decided to use the combination of 1 and 7 in the optical resolution because of the best RE value of 33.

After the optimization of the optical resolution using 1 and 7, the salt 9a was given in 36% yield with 99.1% ee from 5% aqueous EtOH. The salt 9a was treated with hydrochloric acid to give the free acid (R)-1 in 95% yield with 99.0% ee (Chart 2). And the optically active amine 7 was recovered from the salt 9a in 97% yield. Furthermore, (S)-1 (60.2% ee) recovered from the mother liquor was racemized by heating for 3 h at 180 °C, followed by hydrolysis to give racemic 1. We tried to determine the configuration of (R)-1 using the X-ray analysis of the salt 9 but could not obtain a good crystal for the X-ray analysis. Therefore, we prepared the salt of the acid (R)-1 and (1R,2S)-norephedrine. This salt provided a good crystal for the X-ray analysis. It was determined that the acid (R)-1 had the (R)-configuration, as shown in Fig. 2.

The acid (R)-1 gave (R)-6 in 84% with 98.5% ee and (S)-2 in 86% with 97.8% ee using the same method as the racemate 1. The amide 10 was produced via the corresponding acyl chloride in 96% yield with 98.6% ee, and then the Hofmann rearrangement of 10 with Br₂ and tert-BuONa in tert-BuOH gave the tert-butoxycarbonyl (Boc) compound 11 in 87% yield with 98.0% ee. The Boc compound 11 was

### Table 1. Optical Resolution of the Acid 1 Using Chiral Amines

<table>
<thead>
<tr>
<th>Chiral amine</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>ee (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>RE&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1R,2S)-2-(Benzy lamino)cyclohexylmethanol (7)</td>
<td>EtOH</td>
<td>37</td>
<td>90.1 (R)</td>
<td>33</td>
</tr>
<tr>
<td>(1R,2S)-Norephedrine</td>
<td>EtOH</td>
<td>19</td>
<td>65.1 (R)</td>
<td>12</td>
</tr>
<tr>
<td>(1S)-1-Phenyl-2-(4-tolyl)ethylamine (8)</td>
<td>iso-PrOH</td>
<td>58</td>
<td>16.7 (R)</td>
<td>10</td>
</tr>
<tr>
<td>Quinine</td>
<td>EtOH</td>
<td>10</td>
<td>99.0 (S)</td>
<td>10</td>
</tr>
<tr>
<td>(1S,2R)-2-Amino-1,2-diphenylethanol</td>
<td>EtOH</td>
<td>17</td>
<td>93.4 (S)</td>
<td>16</td>
</tr>
<tr>
<td>(1S)-2-Amino-1-propanol</td>
<td>EtOH</td>
<td>17</td>
<td>84.5 (S)</td>
<td>14</td>
</tr>
<tr>
<td>(1R)-1-Phenylethylamine (2eq)</td>
<td>iso-PrOH</td>
<td>31</td>
<td>57.0 (S)</td>
<td>18</td>
</tr>
</tbody>
</table>

<sup>a</sup> The ee and configuration of the acid 1 are shown.  
<sup>b</sup> yield×ee = 100.

### Table 2. Optical Resolution of the Acid 2 Using Chiral Amines

<table>
<thead>
<tr>
<th>Chiral amine</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>ee (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>RE&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1S,2R)-2-Amino-1,2-diphenylethanol</td>
<td>H₂O–EtOH&lt;sup&gt;c&lt;/sup&gt;</td>
<td>46</td>
<td>11.4 (S)</td>
<td>5</td>
</tr>
<tr>
<td>(1S,2R)-2-Amino-1,2-diphenylethanol</td>
<td>H₂O–EtOH&lt;sup&gt;c&lt;/sup&gt;</td>
<td>16</td>
<td>46.0 (S)</td>
<td>7</td>
</tr>
<tr>
<td>(1S)-1-t-(1-Naphthyl)ethylamine</td>
<td>EtOH</td>
<td>17</td>
<td>84.5 (S)</td>
<td>14</td>
</tr>
<tr>
<td>(1S,2R)-2-(Benzy lamino)cyclohexylmethanol (7)</td>
<td>EtOH</td>
<td>37</td>
<td>93.4 (S)</td>
<td>16</td>
</tr>
<tr>
<td>(1S)-2-Amino-1-propanol</td>
<td>EtOH</td>
<td>17</td>
<td>84.5 (S)</td>
<td>14</td>
</tr>
<tr>
<td>Quinine</td>
<td>EtOH</td>
<td>10</td>
<td>36.0 (S)</td>
<td>3</td>
</tr>
</tbody>
</table>

<sup>a</sup> The ee and configuration of the acid 2 are shown.  
<sup>b</sup> yield×ee = 100.  
<sup>c</sup> 10% (v/v) aqueous EtOH.
treated with concentrated hydrochloric acid (conc. HCl) to give (S)-AMT·HCl (12) in 96% yield with 98.1% ee (Chart 3).

In conclusion, we established the efficient and practical route for the synthesis of (S)-AMT·HCl (10). We found that the optically active acid (R)-1 was obtained via the optical resolution of the racemic acid 1 as the salt of the optically active amine 7, and (S)-AMT was derived by the Hofmann rearrangement of the amide 10.

Experimental
All melting points were determined using a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet 510 FT-IR or AVATAR 320 FT-IR spectrometer. H- and 13C-NMR spectra were recorded in deuteriochloroform (DCl) or deuterioacetone (DAcO) for the aromatic protons and temperature was 25 °C. The chemical shifts (δ) were measured using tetramethylsilane as the internal standard. Mass spectra were determined using a JEOL JMS-SX102A mass spectrometer. Optical rotations were measured with a JASCO DIP-370 polarimeter.

The ee values of the prepared compounds were determined by HPLC using a chiral column (Chiralcel OD, 4.6 mm i.d.×250 mm, Daicel Chemical Industries Co., Ltd.) under the conditions of the flow rate of 1.0 ml/min, the detection of 220 nm (UV) and the indicated mobile phase.

2-(3-Methoxybezylidene)succinic Acid (5) 
Na (19.5 g, 0.85 g atom) was added to a benzene–AMX-400 (400 ml) suspension and the mixture was refluxed for 7 h at room temperature. The mixture was concentrated under reduced pressure. The Pd–C was filtered off, and the filtrate was concentrated under reduced pressure. Water (100 ml) was added to the resulting residue, and then the precipitate was collected by filtration to give 2 (8.62 g, 88%) as a white solid. An analytical sample was prepared by recrystallization from CHCl3 and the ee of the acid was determined by HPLC (mobile phase, hexane–iso-PrOH, 99 : 1). The ee of the methyl ester of 5 was determined by HPLC (mobile phase, hexane–iso-ProH, 4 : 1). The ee of the methyl ester of 2 was determined by HPLC (mobile phase, hexane–iso-ProH, 99 : 1).

(1R,2S)-2-(Benzylamino)cyclohexylmethanol (2a) 
The acid (1 or 2) (1.00 g) and an optically active amine (1.0 or 2.0 eq) were dissolved in hot solvent and allowed to react. The precipitate was washed with water (350 ml) for 12 h at 80 °C under atmospheric pressure. The Pd–C was filtered off, and the filtrate was concentrated under reduced pressure. Water (100 ml) was added to the resulting residue, and then the precipitate was collected by filtration to give 2 (8.62 g, 88%) as a white solid. An analytical sample was prepared by recrystallization from EtOH to give a white solid. mp 126—127 °C (HCl) (mp 127—127.5 °C). IR (KBr): 3194, 1712, 1650, 1599, 1532, 1416, 1377, 1246, 1185, 1137, 1107, 1050, 1001, 919, 746, 694, 621 cm−1. 1H-NMR (DMSO-d6): δ: 7.42—7.49 (2H, d, J=12.1 Hz), 7.42—7.49 (2H, d, J=12.7 Hz), 7.39—7.40 (2H, d, J=12.4 Hz), 7.00—7.02 (2H, d, J=12.5 Hz), 6.90—6.92 (2H, d, J=12.8 Hz), 5.88—5.90 (2H, d, J=12.9 Hz), 4.32—4.34 (2H, m, J=12.1 Hz), 2.12—2.14 (2H, m, J=12.4 Hz), 1.83—1.85 (2H, m, J=12.7 Hz), 1.13—1.16 (2H, m, J=12.9 Hz), 0.86 (3H, s, J=6.9 Hz). Anal Calcd for C20H25N2O4: C, 63.68; H, 6.49; N, 9.34. Found: C, 63.73; H, 6.34; N, 9.32.

(1R,2S)-2-(Benzylamino)cyclohexylmethanol (2b) 
The acid (1 or 2) (1.00 g) and an optically active amine (1.0 or 2.0 eq) were dissolved in hot solvent and allowed to react. The precipitate was washed with water (350 ml) for 12 h at 80 °C under atmospheric pressure. The Pd–C was filtered off, and the filtrate was concentrated under reduced pressure. Water (100 ml) was added to the resulting residue, and then the precipitate was collected by filtration to give 2 (8.62 g, 88%) as a white solid. An analytical sample was prepared by recrystallization from EtOH to give a white solid. mp 126—127 °C (HCl) (mp 127—127.5 °C). IR (KBr): 3194, 1712, 1650, 1599, 1532, 1416, 1377, 1246, 1185, 1137, 1107, 1050, 1001, 919, 746, 694, 621 cm−1. 1H-NMR (DMSO-d6): δ: 7.42—7.49 (2H, d, J=12.1 Hz), 7.42—7.49 (2H, d, J=12.7 Hz), 7.39—7.40 (2H, d, J=12.4 Hz), 7.00—7.02 (2H, d, J=12.5 Hz), 6.90—6.92 (2H, d, J=12.8 Hz), 5.88—5.90 (2H, d, J=12.9 Hz), 4.32—4.34 (2H, m, J=12.1 Hz), 2.12—2.14 (2H, m, J=12.4 Hz), 1.83—1.85 (2H, m, J=12.7 Hz), 1.13—1.16 (2H, m, J=12.9 Hz), 0.86 (3H, s, J=6.9 Hz). Anal Calcd for C20H25N2O4: C, 63.68; H, 6.49; N, 9.34. Found: C, 63.73; H, 6.34; N, 9.32.
lized from AcOEt-hexane to give (R)-1 (7.96 g, 95%) as a white solid. The ee of (R)-1 was determined to be 99.0% ee using dimethyl ester derived with TMS-CH2NH2 (10% solution in hexane) in CH2Cl2-MeOH by HPLC (mobile phase, hexane–iso-ProOH, 4:1); mp 89—89.5 °C. IR (KBr): 3355, 3190, 1660, 1624, 1503 cm−1; 1H-NMR (CDCl3): δ: 1.81—1.91 (1H, m), 2.09—2.16 (1H, m), 2.53—2.61 (1H, m), 2.76—3.02 (4H, m) 3.77 (3H, s), 5.63 (1H, br, s) 5.85 (1H, br, s), 6.35 (1H, δ, J = 2.4 Hz), 6.70 (1H, dd, J = 2.4, 8.3 Hz, 6.99 (1H, d, J = 8.3 Hz); 13C-NMR (CDCl3): δ: 27.25, 28.13, 32.93, 41.67, 56.56, 112.76, 114.04, 128.15, 130.12, 135.34, 158.10, 178.29. [α]D25 +60.8° (c = 1.0, MeOH). HRMS (FAB) m/z: Caled for C12H13NO4: M+ 205.1103. Found: 205.1104. Anal. Caled for C12H13NO4: C 60.48; H 5.92. Found: C 60.48; H 5.97.

Recovery of the Chiral Amino 7. The separated toluene solution in the synthesis of the acid (R)-1 was concentrated under reduced pressure, and the residue was crystallized from EtOH–water to give 7 (6.78 g, 88%) as a white solid. [α]D25 +25.0° (c = 1.0, MeOH). [Commercially available 7: [α]D25 +25.0° (c = 1.0, MeOH)]

Racemization of Recovered (S)-1. The (S)-1 (16.13 g, 60.2% ee) recovered from the mother liquor of the optical resolution was stirred for 50 °C for 24 h and was concentrated under reduced pressure. The resulting residue was suspended in hot AcOEt-hexane. After cooling, the solid was collected by filtration to give 7 (9.27 g, 58%, 1.0% ee as a white solid. [α]D25 +0.4° (c = 1.0, MeOH).

Crystal Structure of (1R,2S)-2-Amino-1-phenylprop-1-ol (2R)-2-(3-Methoxybenzyl)oxuccinate (1R,2S)-2-Amino-1-phenylprop-1-ol [1(2R)-3Norephedrine (76 mg, 0.50 mmol) and (R)-1 (120 mg, 0.50 mmol) were dissolved in EtOH (1.0 ml) at 50 °C, then cooled to room temperature. The precipitate was collected by filtration to give the title compound as a white solid (76 mg, 39%). A colorless crystal was obtained by recrystallization from EtOH (1.0 ml) at 50 °C, then cooled to room temperature. The pre-

The solution was acidified with conc. HCl (7.0 ml) and extracted with AcOEt (50 ml and 30 ml). The combined AcOEt layer was washed with brine (10 ml), dried over MgSO4, and concentrated under reduced pressure. The resulting residue was suspended in hot AcOEt-hexane. After cooling, the solid was collected by filtration to give 7 (9.27 g, 58%, 1.0% ee as a white solid. [α]D25 +0.4° (c = 1.0, MeOH).

The solution was acidified with conc. HCl (7.0 ml) and extracted with AcOEt (50 ml and 30 ml). The combined AcOEt layer was washed with brine (10 ml), dried over MgSO4, and concentrated under reduced pressure. The resulting residue was suspended in hot AcOEt-hexane. After cooling, the solid was collected by filtration to give 7 (9.27 g, 58%, 1.0% ee as a white solid. [α]D25 +0.4° (c = 1.0, MeOH).

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References and Notes

