Synthesis of Optically Active NC-1800, a Therapeutic Agent for Urinary Disturbance

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A new synthetic method for chiral oxazolidinone derivatives, therapeutic agents for treating urinary disturbance, is described. The condensed compound obtained from chiral 1-amino-3-phenyl-2-propanol and 1-phenyl-3-morpholino-1-propanone was reduced with Me 2 NBH(OAc) 2 to give the intermediate, 1-(3-morpholino-1-phenylpropyl)amino-3-phenyl-2-propanol (MAPP) in 34% diastereomeric excess (d.e.). MAPP was converted to an urethane and purified by recrystallization of its methanesulfonate, to afford a single isomer, (2R)-1-[N-[1S]-3-morpholino-1-phenylpropyl]-N-ethoxycarbonyl]amino-3-phenyl-2-propanol methanesulfonate (4-A · methanesulfonate).

Key words: urinary; NC-1800; optically active; oxazolidine; crystallization

Recently, the number of patients suffering from urinary disturbance caused by prostatic hypertrophy, cerebrovascular disease, and various neurogenic dysfunction have been increasing. Many drugs have been developed for treating urinary disturbance and involve a number of different mechanisms of action. α 1 -Adrenoceptor blocking agents, antiandrogens, steroid 5α-reductase inhibitors, anticholinergic drugs, smooth muscle relaxants, and α- or β-adrenergic drugs have been investigated in clinical trials. 1–6 Extensive reviews on the types of drugs advocated for treating disorders of the micturition have been published by Anderson 5 and Wein. 6 At present, anticholinergic drugs such as oxybutynin 7–9 are the most widely used for treating bladder instability and cystitis. However, anticholinergic drugs produce a variety of side effects, such as dry mouth, blurred vision, constipation and tachycardia, that many patients find intolerable.

Previously, we found that alkylenediolamine derivatives, especially one of the racemic diastereoisomers of 5-benzyl-3-(3-morpholino-1-phenylpropyl)-1,3-oxazolidin-2-one fumarate [NC-1800 (code number, Nippon Chemiphar Co., Ltd., Tokyo, Japan); (±)-1-fumarate (Fig. 1)] showed the novel function of relieving the urinating contraction that is observed under high intracystic pressure. 4,10–11 We have also reported that the absolute configuration of (±)-1 was determined to be 1R, 5S by X-ray crystallographic analysis. 12

In this paper, we report the synthesis of chiral NC-1800 [(−)-1 fumarate], by way of reduction of the condensation product between (2R)-1-amino-3-phenyl-2-propanol [(R)·2] 13–15 and 1-phenyl-3-morpholino-1-propanone (3), followed by recrystallization of the methanesulfonate of the urethane form (4-A).

Results and Discussion

Synthesis of Diaminoalcohol (±)-1-(3-Morpholino-1-phenylpropyl)amino-3-phenyl-2-propanol [±)-MAPP] (±)-MAPP was obtained by reduction of the condensation product of (±)-1-amino-3-phenyl-2-propanol (2) 10,16 and 1-phenyl-3-morpholino-1-propanone (3) 10 in benzene, as a mixture of racemic diastereoisomers. The reduction of this compound was examined in situ using various reducing agents since instability prevented its isolation. The experimental results are summarized in Table 1.

As shown in Table 1, reduction with LiAlH 4 , NaBH 4 , or catalytic reduction with hydrogen, gave the two racemic diastereoisomers [(±)-MAPP-A and (±)-MAPP-B] with poor diastereoselectivity. One of racemic diastereoisomers was obtained from the fast eluted fraction on silica gel column chromatography (hexane/ethyl acetate) and was referred to as (±)-MAPP-A, from which NC-1800 is derived; the other diastereomer (±)-MAPP-B was also obtained (Table 1, entries 1, 2, 3). However, in the reductions with triacetoxymethane derivatives, such as NaBH(OAc) 2, (±)-MAPP-A was obtained with moderate diastereoselectivity [22% d.e. for (±)-MAPP-A, B] (Table 1, entry 4). The ratio of racemic diastereoisomers formed was calculated on the basis of HPLC peak area %. When Me 2 NBH(OAc) 2 was used in ethanol, diastereoselectivity was further improved and (±)-MAPP-A was obtained in 38% d.e. (Table 1, entry 6).

Synthesis of Optically Active NC-1800 via Diastereoselective Synthesis of Diaminoalcohol (MAPP) A new synthetic method for optically active NC-1800 by employing the reduction described above was next examined (Chart 1). The crude condensation product formed between the optically active amine ((R)-2) 13–15 and 3, was reduced using Me 2 NBH(OAc) 2 to give the two diastereoisomers (1S,2R)-MAPP-A and (1R,2R)-MAPP-B in a ratio of 67/33 (34% d.e., yield 31%). Reaction of the oily mixture of (1S,2R)-MAPP-A and (1R,2R)-MAPP-B with ethyl chloroformate afforded the corresponding urethane, which was then subjected to crystallization with various acids to increase the diastereomeric purity. As shown in Table 2, the crystalline salt was obtained only when maleic acid and methanesulfonic acid were used. However, whilst the ratio of diastereoisomers [4-A/4-B; urethane compound derived from (1S,2R)-MAPP-A is designated as 4-A and the other as 4-B] of the maleate was almost the same as that of the original (1S,2R)-MAPP-A–(1R,2R)-MAPP-B mixture (87/13, Table 2, entry 2), the

Fig. 1. Structure of NC-1800 [(±)-1-Fumarate]

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diastereoisomeric ratio of the methanesulfonate was improved to 98/2. Consequently, diastereoisomer 4-A of high purity was obtained as the methanesulfonate (yield 32%, Table 2, entry 3). After cyclization of 4-A with potassium carbonate, the resulting (1S,5R)-I was converted to optically active NC-1800.

![Chemical diagram]

Table 1. Reduction of the Condensation Compound between (±)-1-Amino-3-phenyl-2-propanol(2) and 1-Phenyl-3-morpholino-1-propanone(3) with a Variety of Reducing Agents

| Entry | Reductant (eq) | Solvent | Reaction temperature | (±)-MAPP Yielda | (±)-MAPP-A/(-)-MAPP-B
<table>
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<tbody>
<tr>
<td>1</td>
<td>LiAlH4 (2.5)</td>
<td>THF</td>
<td>Reflux</td>
<td>28%b</td>
<td>48/52</td>
</tr>
<tr>
<td>2</td>
<td>NaBH4 (2.5)</td>
<td>MeOH</td>
<td>t.t.</td>
<td>74%</td>
<td>49/51</td>
</tr>
<tr>
<td>3</td>
<td>H2/Pd-C (2.5)</td>
<td>EtOH</td>
<td>t.t.</td>
<td>55%</td>
<td>46/54</td>
</tr>
<tr>
<td>4</td>
<td>NaBH(OAc)2 (2.5)</td>
<td>MeOH</td>
<td>t.t.</td>
<td>73%</td>
<td>61/39</td>
</tr>
<tr>
<td>5</td>
<td>Me2NBH(OAc)2 (2.5)</td>
<td>MeOH</td>
<td>t.t.</td>
<td>68%</td>
<td>64/36</td>
</tr>
<tr>
<td>6</td>
<td>Me2NBH(OAc)2 (2.5)</td>
<td>EtOH</td>
<td>t.t.</td>
<td>59%</td>
<td>69/31</td>
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</tbody>
</table>

a) Calculated on the basis of HPLC peak area % of crude MAPP-A and B mixture.  b) Isolated yield.

Table 2. Crystallization and Separation of the Diastereoisomers of 4

| Entry | Acid            | Solvent | State of salt | 4-A Acid salt | Yield (%) | 4-A/4-B
<table>
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<tr>
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<tbody>
<tr>
<td>1</td>
<td>Fumaric acid</td>
<td>E</td>
<td>No crystallization</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>Maleic acid</td>
<td>D</td>
<td>Crystallization</td>
<td>29b</td>
<td>87/13</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>Methanesulfonic acid</td>
<td>C</td>
<td>Crystallization</td>
<td>43b</td>
<td>98/2</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>Hydrochloric acid</td>
<td>A, B, C</td>
<td>No crystallization</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>Sulfonic acid</td>
<td>A, B, C</td>
<td>No crystallization</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>Hydrobromic acid</td>
<td>A, B, C</td>
<td>No crystallization</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>7</td>
<td>Benzoic acid</td>
<td>A, B, C</td>
<td>No crystallization</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>p-Toluene sulfonic acid</td>
<td>A, B, C</td>
<td>No crystallization</td>
<td>—</td>
<td>—</td>
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</table>

a) Calculated on the basis of 4-A and -B mixture (A/B=85/15), ethoxycarbonylation was 62% yield.  b) Calculated on the basis of MAPP-A and -B mixture (A/B=67/33).

A, AcOEt/hexane; B, benzene/hexane; C, Et2O; D, AcOEt/isopropyl ether; E, AcOEt/Et2O.
Experimental

Melting points were determined on a Yamato MP-21 and are uncorrected. Specific rotation values were obtained on a JASCO DIP-360 digital polarimeter. H-NMR spectra were recorded on a JEOL JNM-A400 NMR spectrometer with tetramethylsilane as the internal standard. IR spectra were recorded on a JEOL JIR-6500 IR spectrometer. Elemental analyses were performed on a Foss Heraeus CHN-O-RAPID analyzer. The HPLC system consisted of a JASCO BIP-1 HPLC pump and a JASCO UVIDEC 100-V UV-Vis spectrometer, with monitoring at 215 nm. The column contained Cosmosil SC-18 AR* (4.6 × 250 mm); Nacalai Tesque (Kyoto, Japan). The mobile phase was composed of acetonitrile and 2 M sodium dihydrogenphospho-

Synthesis of Racemic MAPP [(-)-MAPP] A solution of (-)-MAPP (454 mg, 3.00 mmol) and 1-phenyl-3-morpholino-1-propanone (658 mg, 3.00 mmol) in benzene (30 ml) was refluxed for 24 h using a Dean Stark trap. Evaporation of benzene gave 1.06 g of the residue as a yellow oil, which was used without purification. Under a N₂ atmosphere, to a cold solution of the residue (353 mg) in methanol (10 ml) was added sodium triacetoxysilox-

Synthesis of Optically Active NC-1800. (2R)-[1-(1SR)-MAPP] A mixture of (R)-2 (5.00 g, 33.1 mmol), 1-phenyl-3-morpholino-1-propanone (7.26 g, 33.1 mmol), molecular sieves (3 Å, 10 g) and benzene (100 ml) was stirred at 80 °C for 24 h. Molecular sieves were removed and washed with benzene (25 ml×2). Under a N₂ atmosphere, to the combined benzene solution was added methanol (150 ml) and teftramethylammonium triacetoxyborohydride (28.8 g, 109 mmol). After stirring at room temperature for 18 h, the mixture was concentrated to dryness, the residue was taken up in a solution of water (100 ml) and saturated aqueous NaHCO₃, and pH adjusted to 8. This mixture was the extracted with ethyl acetate (150 ml×2). The ethyl acetate layer was washed with water (150 ml×2), saturated aqueous NaCl solution (10 ml), dried over Na₂SO₄, and concentrated to dryness. The residue was puri-

References and Notes

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