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

Shinichi YOSHIDA,*[a,b] Masao YAMAMOTO,[b] Nobutaka MOCHIZUKI,[b] and Hiroyuki NOHIRA[a]

Department of Applied Chemistry, Faculty of Engineering, Saitama University,[a] Shimo-Ohkubo, Urawa, Saitama 338–8570, Japan and Research Laboratories, Nippon Chemiphar Co., Ltd.,[b] Hikokawato, Misato, Saitama 341–0005, Japan.
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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 $Me_4NBH(OAc)_3$ 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, (2*R*)-1-[*N*-[(1*S*)-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 neurogonic 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—4] Extensive reviews on the types of drugs advocated for treating disorders of the micturition have been published by Andersson[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 alkylenediamine 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 1*R*, 5*S* 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 (2*R*)-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;[11] the other diastereoisomer (±)-MAPP-B was also obtained (Table 1, entries 1, 2, 3). However, in the reductions with triacetoxyborane derivatives, such as $NaBH(OAc)_3$, (±)-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 $Me_4NBH(OAc)_3$ 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 $Me_4NBH(OAc)_3$ to give the two diastereoisomers (1*S*,2*R*)-MAPP-A and (1*R*,2*R*)-MAPP-B in a ratio of 67/33 (34% d.e., yield 31%). Reaction of the oily mixture of (1*S*,2*R*)-MAPP-A and (1*R*,2*R*)-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 (1*S*,2*R*)-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 (1*S*,2*R*)-MAPP-A–(1*R*,2*R*)-MAPP-B mixture (87/13, Table 2, entry 2), the

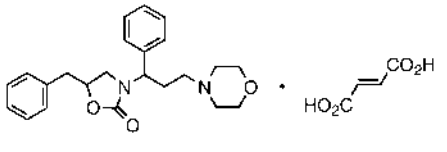


Fig. 1. Structure of NC-1800 [(±)-**1**·Fumarate]

* To whom correspondence should be addressed.

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 (1*S*,5*R*)-**1** was converted to optically active NC-1800.

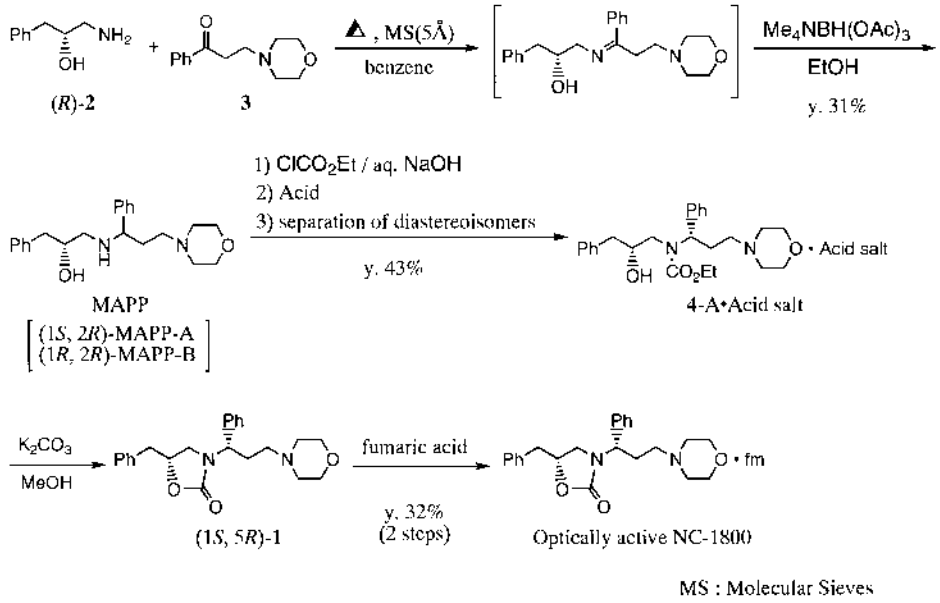
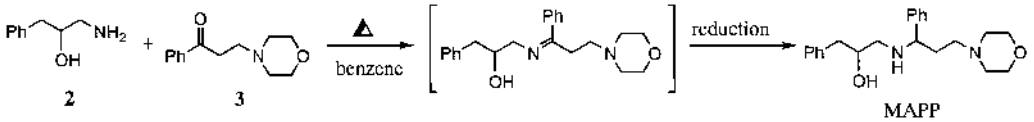


Chart 1

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	
				Yield[a]	(±)-MAPP-A/(±)-MAPP-B[a]
1	$LiAlH_4$ (2.5)	THF	Reflux	28%[b]	48/ 52
2	$NaBH_4$ (2.5)	MeOH	r.t.	74%	49/51
3	H_2/Pd–C (2.5)	EtOH	r.t.	55%	46/54
4	$NaBH(OAc)_3$ (2.5)	MeOH	r.t.	73%	61/39
5	$Me_4NBH(OAc)_3$ (2.5)	MeOH	r.t.	68%	64/36
6	$Me_4NBH(OAc)_3$ (2.5)	EtOH	r.t.	59%	69/31

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** · Acid salt	
				Yield (%)	**4**-A/**4**-B
1	Fumaric acid	E	No crystallization	—	—
2	Maleic acid	D	Crystallization	29[a]	87/13
		A, B, C	No crystallization	—	—
3	Methanesulfonic acid	C	Crystallization	43[b]	98 / 2
		A, B	No crystallization	—	—
4	Hydrochloric acid	A, B, C	No crystallization	—	—
5	Sulfonic acid	A, B, C	No crystallization	—	—
6	Hydrobromic acid	A, B, C	No crystallization	—	—
7	Benzoic acid	A, B, C	No crystallization	—	—
8	*p*-Toluenesulfonic acid	A, B, C	No crystallization	—	—

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, Et_2O; D, AcOEt/isopropyl ether; E, AcOEt/Et_2O.

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. ^{1}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 HOLC pump and a JASCO UVIDEC 100-V UV-spectrometer, with monitoring at 215 nm. The column contained Cosmosil 5C18-AR® (4.6×250 mm); Nacalai Tesque (Kyoto, Japan). The mobile phase was composed of acetonitrile and 2 M sodium dihydrogenphosphate in a ratio of 3/10—7/10 (v/v). The chiral column contained Chiralcell® OG (4.6×250 mm); Daicel Chemical Industries, Ltd. (Tokyo, Japan). The mobile phase was composed of ethanol and hexane in a ratio of 1/5 (v/v). The flow rate was maintained at 1.0 ml/min and the procedure was carried out at room temperature.

Synthesis of Racemic MAPP [(±)-MAPP] A solution of (±)-**2** (454 mg, 3.00 mmol) and 1-phenyl-3-morpholino-1-propanone (658 mg, 3.0 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 N_2 atmosphere, to a cold solution of the residue (353 mg) in methanol (10 ml) was added sodium triacetoxyborohydride (530 mg, 2.50 mmol). After stirring at room temperature for 18 h, the reaction mixture was concentrated to dryness. The residue was dissolved in ether (50 ml), and the ether layer was washed with saturated aqueous $NaHCO_3$ solution (50 ml×2), water (50 ml), and saturated aqueous NaCl solution (50 ml), dried over Na_2SO_4, and concentrated to dryness to give 284 mg of crude (±)-MAPP as a pale yellow oil [(±)-MAPP-A/B=61/39; determined by HPLC [mobile phase in a ratio of 3/10 (v/v)]]. (±)-MAPP-A: ^{1}H-NMR (CD_3OD) (corresponding to 0.61H) δ: 1.72—1.83 (1H, m), 1.93—2.04 (1H, m), 2.10—2.48 (8H, m), 2.59—2.75 (2H, m), 3.58—3.68 (5H, m), 3.85—3.93 (1H, m), 7.13—7.32 (10H, m). (±)-MAPP-B: ^{1}H-NMR (CD_3OD) (corresponding to 0.39H) δ: 1.72—1.83 (1H, m), 1.93—2.04 (1H, m), 2.10—2.48 (8H, m), 2.59—2.75 (2H, m), 3.58—3.68 (5H, m), 3.78—3.85 (1H, m), 7.13—7.32 (10H, m).

In the same manner, (±)-MAPP [(±)-MAPP-A/B=69/31] was obtained by using tetramethylammonium triacetoxyborohydride as the reducing agent and ethanol as solvent.

Synthesis of Optically Active NC-1800. (2*R*)-1-(1*RS*)-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 (5 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 N_2 atmosphere, to the combined benzene solution was added ethanol (150 ml) and tetramethylammonium 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 $NaHCO_3$, 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 (100 ml), dried over Na_2SO_4, and concentrated to dryness. The residue was purified by silica gel column chromatography (methanol/chloroform) to give 3.60 g of MAPP as a yellow oil [(1*S*,2*R*)-MAPP-A/(1*R*,2*R*)-MAPP-B=67/33; determined by HPLC [mobile phase in a ratio of 3/10 (v/v)]]. (1*S*,2*R*)-MAPP-A: ^{1}H-NMR (CD_3OD) (corresponding to 0.67H) δ: 1.72—1.83 (1H, m), 1.93—2.04 (1H, m), 2.10—2.48 (8H, m), 2.59—2.75 (2H, m), 3.58—3.68 (5H, m), 3.85—3.93 (1H, m), 7.13—7.32 (10H, m). (1*R*,2*R*)-MAPP-B: ^{1}H-NMR (CD_3OD) (corresponding to 0.33H) δ: 1.72—1.83 (1H, m), 1.93—2.04 (1H, m), 2.10—2.48 (8H, m), 2.59—2.75 (2H, m), 3.58—3.68 (5H, m), 3.78—3.85 (1H, m), 7.13—7.32 (10H, m)

(2*R*)-1-[*N*-[(1*S*)-3-Morpholino-1-phenylpropyl]-*N*-ethoxycarbonyl] amino-3-phenyl-2-propanol Methanesulfonate (4-A·Methanesulfonate) To an ice-cooled solution of MAPP [(1*S*,2*R*)-MAPP-A/(1*R*,2*R*)-MAPP-B=67/33, 3.30 g] in dichloromethane (10 ml) was added 2 M sodium hydroxide (14 ml). With vigorous stirring, a solution of ethyl chloroformate (1.34 ml, 14.0 mmol) in dichloromethane (3 ml) was added dropwise to the mixture over 10 min and the reaction mixture then stirred at the same temperature for 1 h and at room temperature for 1 h. After the dichloromethane layer was separated, the water layer was extracted with dichloromethane (10 ml). The combined dichloromethane solution was washed with saturated aqueous NaCl solution (20 ml), dried over Na_2SO_4, and concentrated to dryness. To a solution of the yellow oily residue in ethyl acetate (20 ml) was added methanesulfonic acid (0.49 ml, 7.77 mmol), and the mixture was concentrated to dryness. The residue was dissolved in ethyl acetate (2 ml) with heating. After cooling and adding ether (1000 ml) the mixture was stirred in an ice bath for 24 h. The precipitate was collected by filtration and recrystallized from a mixture of ethyl acetate (1 ml) and ether (500 ml) to give 1.41 g of **4** (**4**-A/**4**-B=98/2; determined by HPLC [mobile phase in a ratio of 3/7 (v/v)]) as a colorless solid, mp 85—88 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.09—1.39 (3H, m), 1.44—3.18 (12H, m), 3.44—4.37 (11H, m), 5.24—5.56 (1H, m), 7.08—7.46 (10H, m), 10.60—11.02 (1H, m). IR (KBr) cm^{-1}: 3440, 2933, 1686, 1454, 1408, 1329, 1228, 1198, 1076, 1053, 876, 791, 24 702, 567, 534. $[\alpha]_D^{24}$ +0.2 ° (*c*=2, $CHCl_3$). *Anal*. Calcd for $C_{26}H_{38}N_2O_7S$: C, 59.75; H, 7.33; N, 5.36. Found: C, 58.82; H, 7.41; N, 5.39.

(5*R*)-5-Benzyl-3-[(1*S*)-3-morpholino-1-phenylpropyl]-1,3-oxazolidin-2-one Fumarate, Optically Active NC-1800 A mixture of **4**-A (523 mg, 1.00 mmol), potassium carbonate (691 mg, 5.00 mmol), methanol (4.8 ml) and water (1.2 ml) was refluxed for 15 h. After cooling to room temperature, the mixture was diluted with water (2.5 ml) and the methanol evaporated. The residue was extracted with ethyl acetate (10 ml×2) and the combined ethyl acetate extracts washed with saturated aqueous NaCl solution (10 ml), dried over Na_2SO_4, and concentrated to dryness. The residue was taken up in ethanol (5 ml) and the solvent evaporated. To a solution of the residue in ethanol (2 ml) was added a solution of fumaric acid (116 mg, 1.00 mmol) in ethanol (5 ml), hexane (21 ml) was added the mixture and stirred at room temperature for 18 h. The deposit was collected by filtration and recrystallized from a mixed solvent of ethanol (16 ml) and hexane (8 ml) to give 157 mg of optically active NC-1800 as a colorless solid, mp 134—136 °C (131—132 °C[10]). ^{1}H-NMR ($CDCl_3$) δ: 1.94—2.14 (4H, m), 2.50 (4H, br s), 2.89—2.96 (2H, m), 3.22—3.24 (2H, m), 3.56—3.58 (4H, m), 4.71—4.82 (2H, m), 6.61 (2H, s), 7.25—7.34 (10H, m). IR (KBr) cm^{-1}: 3435, 3032, 2465, 1736, 1476, 1431, 1369, 1254, 1182, 1090, 1045, 984, 760, 704, 648. $[\alpha]_D^{24}$ −0.4° (*c*=1, MeOH); 100% ee. (determined by HPLC). *Anal. Calcd* for $C_{27}H_{32}N_2O_7$: C, 65.31; H, 6.50; N, 5.64. Found: C, 65.17; H, 6.38; N, 5.75.

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