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Resolution of 3-(methylamino)-1-(2-thienyl)propan-1-ol, a new key intermediate for duloxetine, with (*S*)-mandelic acid

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Abstract—The resolution of racemic 3-(methylamino)-1-(2-thienyl)propan-1-ol **3**, a new key intermediate for duloxetine **1**, was studied. The conditions were optimized for an industrial-scale resolution of **3** by using (*S*)-mandelic acid **4** as a resolving agent and 2-butanol containing 2 equimolar amounts of water as a solvent. The (*S*)-**3**·(*S*)-**4**·H_2O diastereomeric salt was crystallized to give pure (*S*)-**3** with >99.9% e.e. after liberation of the amine. The absolute configuration of liberated (−)-**3** was determined as (*S*) by X-ray crystallography.

1. Introduction

To date, many new and attractive techniques for the production of enantiomerically pure compounds have been reported. Among them, resolution via diastereomeric salt formation is still useful to produce enantiomerically pure compounds on an industrial-scale, since it is, in general, simple, clean, and easy to reproduce laboratory-scale data on an industrial-scale operation.

Duloxetine (LY-248686), (*S*)-(+)-*N*-methyl-3-(1-naphthyloxy)-3-(2-thienyl) propylamine **1**, is expected to be not only a new potent antidepressant but also a norepinephrine (NE) reuptake inhibitor, a 5-HT (serotonin) reuptake inhibitor and a new drug for stress urinary incontinence.[1] In order to produce a key enantiopure intermediate for the synthesis of (*S*)-**1**, various strategies have been proposed, such as the enantioselective reduction of 3-(dimethylamino)-1-(2-thienyl)propan-1-one[2] and 3-chloro-1-(2-thienyl)propan-1-one[3] with Li(*ent*-Chirald®)$_2$AlH_2 and an oxazaborolidine catalyst, respectively, the enzymatic resolution of 3-chloro-1-(2-thienyl)propan-1-ol[4] using immobilized CALB (Novozyme 435, Novo-Nordisk A/S), and the resolution of 3-(dimethylamino)-1-(2-thienyl)propan-1-ol **2**[5] via diastereomeric salt formation. As a result, the resolution of (*RS*)-**2** via diastereomeric salt formation with (*S*)-mandelic acid **4** has been selected for an industrial-scale production together with efficient supporting techniques such as racemization of the antipode.[6] Duloxetine (*S*)-**1** is produced by the condensation of the chiral intermediate (*S*)-**2** with 1-fluoronaphthalene, followed by demethylation with 2,2,2-trichloroethyl chloroformate and Zn.[2] However, there are some critical problems in this process, such as low yield and considerable decomposition to give impurities. Thus, a direct synthesis starting from (*S*)-3-(methylamino)-1-(2-thienyl)propan-1-ol **3** is expected to be a new route for the production of (*S*)-**1**. However, the resolution of (*RS*)-**3** has not been reported.

We herein report the resolution of 3-(methylamino)-1-(2-thienyl)propan-1-ol **3** with (*S*)-mandelic acid **4**, where water molecules play an important role (Fig. 1).

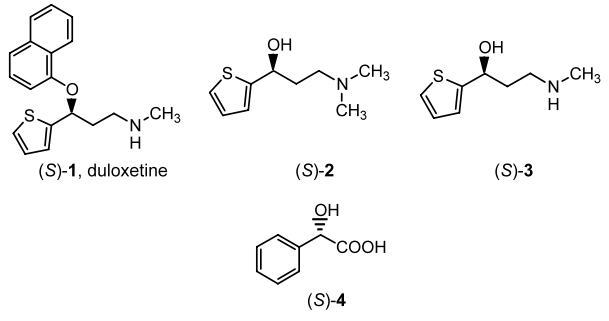

Figure 1.

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2. Results and discussion

In order to find a suitable resolving agent for (*RS*)-**3**, typical acidic resolving agents such as (*S*)-mandelic acid **4**, (*R*)-2-methoxy-2-phenylacetic acid **5**, (*R*)-phenylpropionic acid **6**, L-tartaric acid **7**, and its dibenzoyl derivative L-**8** and di-*p*-toluoyl derivative L-**9** were examined using EtOH as solvent. The results are summarized in Table 1. As can be seen from Table 1, (*R*)-**5** and L-**8** gave poor results (Table 1, entries 2 and 5), and (*S*)-**4**, (*R*)-**6** and L-**7** did not afford any crystals (Table 1, entries 1, 3, and 4). Although L-**9** showed the highest resolution efficiency (*E*),[7] the diastereomeric purity (d.p.)[8] of the salt was not satisfactory for an industrial-scale application (Table 1, entry 6).

Next, we checked in detail the conditions for the resolution of (*RS*)-**3** with (*S*)-**4**, commercially available in a large quantity and at a low price; in particular the resolutions were carried out using various solvents including those applied for the resolution of (*RS*)-**2** with (*S*)-**4**. The results are shown in Table 2. No crystals were obtained from solutions of MTBE (*tert*-butyl methyl ether) and MTBE–EtOH, which are favorable solvents in the resolution of (*RS*)-**2** with (*S*)-**4**, and from other organic solvents, such as 2-butanol, ethyl acetate, ethyl methyl ketone and ethyl ether (Table 2, entries 1–6). In sharp contrast, fine crystals with acceptable diastereomeric purity were obtained when water was used as a solvent (Table 2, entry 7). The spectral and elemental analyses revealed that the salt crystallized from water was monohydrated. These results suggest that water molecules play an important role in making the less-soluble diastereomeric salt crystal stable as a result of the close molecular packing of (*S*)-**3**, (*S*)-**4** and water molecules.

In order to improve resolution efficiency, namely to increase the yield of the less-soluble diastereomeric salt (*S*)-**3**·(*S*)-**4**·H_2O without any deterioration of the diastereomeric purity, we examined the effect of water in ethanol in a range of 2–75% (w/w) water content. The results are summarized in Table 3. Table 3 shows that the diastereomeric purity increased and then decreased with decreasing water content, and finally no crystals were obtained. On the basis of this result, we considered that the presence of water in a solvent is essential to form (*S*)-**3**·(*S*)-**4**·H_2O and that the three-component salt would be possible to deposit in a larger quantity from a solvent less polar than ethanol. Thus, we carried out the resolution by using less polar alcohols in the presence of a small amount of water. The results are summarized in Table 4. As shown in Table 4, the highest resolution efficiency (*E*) was achieved, when 2-butanol containing two molar amounts of water was used as a solvent (Table 4, entry 8). The diastereomeric salt crystals, obtained in all resolution systems shown in Table 4, contained an equimolar amount of water as a component. These results obviously revealed that water played a very important role to form stable diastereomeric salt crystals with satisfactory diastereomeric purity. The diastereomeric purity of the crude salt could be easily improved by recrystalliz-

Table 1. Resolution of (*RS*)-**3** with various resolving agents in EtOH

Entry	Resolving agent	Solvent/(*RS*)-**3** ratio (w/w)	Yield (%)	Diastereomeric purity (% d.p.)	Resolution efficiency (*E*, %)	Absolute configuration
1	(*S*)-**4**	3	Not crystallized		0	
2	(*R*)-**5**	2.3	4	63	5	*S*
3	(*R*)-**6**	5	Not crystallized		0	
4	L-**7**	5	Not crystallized		0	
5	L-**8**	5	74	9	13	*R*
6	L-**9**	5	47	53	50	*S*

4: Mandelic acid; **5**: 2-methoxy-2-phenylacetic acid; **6**: phenylpropionic acid; **7**: tartaric acid; **8**: dibenzoyltartaric acid; **9**: ditoluoyltartaric acid.
* Molar ratio of resolving agent: 1.0 equiv. versus racemate.

Table 2. Resolution of (*RS*)-**3** with (*S*)-mandelic acid **4** in various solvents[a]

Entry	Solvent[b]	Yield (%)	Diastereomeric purity (% d.p.)	Resolution efficiency (*E*, %)	Absolute configuration
1	MTBE	Not crystallized		0	
2	MTBE–EtOH[c]	Not crystallized		0	
3	2-BuOH	Not crystallized		0	
4	AcOEt	Not crystallized		0	
5	MEK	Not crystallized		0	
6	Ethyl ether	Not crystallized		0	
7	Water	20	75	30	*S*

[a] Resolving agent/(*RS*)-**3** = 1.0 (molar ratio).
[b] Solvent/(*RS*)-**3** = 1.9 (w/w).
[c] MTBE/EtOH = 2:1 (w/w).

Table 3. Resolution of (*RS*)-**3** with (*S*)-mandelic acid **4** in water/EtOH

Entry	Water/EtOH ratio (w/w)[a]	Yield (%)	Diastereomeric purity (% d.p.)	Resolution efficiency (*E*, %)
1	100/0	30	68	41
2	75/25	15	72	22
3	50/50	2	86	3
4	25/75	8	85	14
5	5/95	11	70	15
6	2/98	Not crystallized		0
7	0/100	Not crystallized		0

[a] Solvent/(*RS*)-**3** = 1.9 (w/w); 5% (w/w) of water means equimolar amount of (*RS*)-**3**.

Table 4. Optical resolution of (*RS*)-**3** with (*S*)-**4** in alcohols containing water[a]

Entry	Solvent[b]	Water/(*RS*)-**3** ratio [molar ratio]	Yield (%)	Diastereomeric purity (% d.p.)	Resolution efficiency (*E*, %)
1	*n*-PrOH	1.0	20	71	28
2	2-PrOH	1.0	32	74	47
3		2.0	47	55	52
4		3.0	40	71	57
5	*n*-BuOH	1.0	39	67	52
6		2.0	36	75	54
7	2-BuOH	1.0	40	63	50
8		2.0	45	70	63
9		3.0	39	73	57
10		4.0	32	76	49

[a] (*S*)-**4**/(*RS*)-**3** = 1.0 (molar ratio).
[b] Solvent/(*RS*)-**3** = 1.9 (w/w).

ing it once from aqueous 2-butanol; the diastereomeric purity of the recrystallized crystals was more than 95%. The final product (*S*)-**3** with more than 99.5% e.e. was obtained upon treatment of the recrystallized salt with aqueous sodium hydroxide, followed by extraction with 2-butanol and crystallization from toluene.[9]

In order to elucidate the role of water molecules in the formation of the stable less-soluble diastereomeric salt crystal, its crystal structure was determined by an X-ray crystallographic analysis. The crystal structure with hydrogen bonds is shown in Figures 2 and 3.

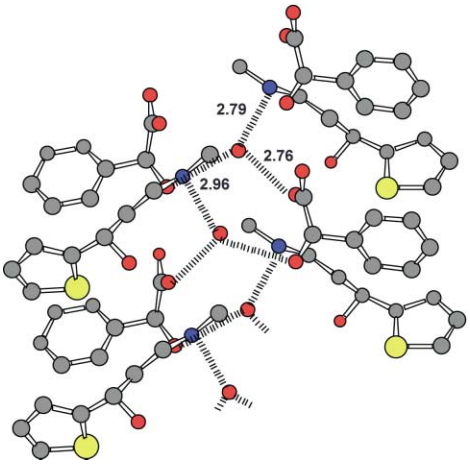

Figure 2. Molecular arrangement of (*S*)-**3**·(*S*)-**4**·H_2O: side view of the 2_1-columns.

As observed by the spectral and elemental analyses, water molecules participate in the crystal formation as connectors between the basic **3** and the acidic **4** molecules to form a hydrogen-bonded 2_1 column. In the crystals of the less-soluble diastereomeric salts consisting of mandelic acid and primary 1-arylalkylamines, such as 1-phenylethylamine, 1-(2-methylphenyl)ethylamine and 1-(3-methoxyphenyl)ethylamine, hydrogen bonds between the NH(amine) and the O(carboxylate) are essential to form a fundamental unit, and other NH(amine)···O(carboxylate) hydrogen bonds generally exist to form a 2_1-column.[10] Moreover, α-OH(acid)···O(carboxylate) hydrogen bonds result in the formation of a supramolecularly hydrogen-bonded sheet consisting of the 2_1 columns. In sharp contrast, a quite different hydrogen-bonding system is observed in this crystal; a fundamental unit is constructed from two molecules of **3** and two molecules of **4** through two water molecules by NH(amine)···HOH(water)···O(carboxylate) hydrogen bonds other than usual NH(amine)···O(carboxylate) hydrogen bonds. The insertion of water molecules between the NH(amine) and the O(acid) makes the distance between them longer, giving an enough space for the N–Me group to avoid steric congestion. In addition, the units are piled up by OH(hydroxyl in **4**)···O(carboxylate) hydrogen bonds to form a 2_1-column. As a result, the connection of the 2_1 columns is achieved by OH(hydroxyl in **3**)···O(carboxylate) hydrogen bonds to form a hydrogen-bonded supramolecular sheet. Thus, the less-soluble salt crystal is composed of a unique hydrogen-bonding network mediated by water molecules. The

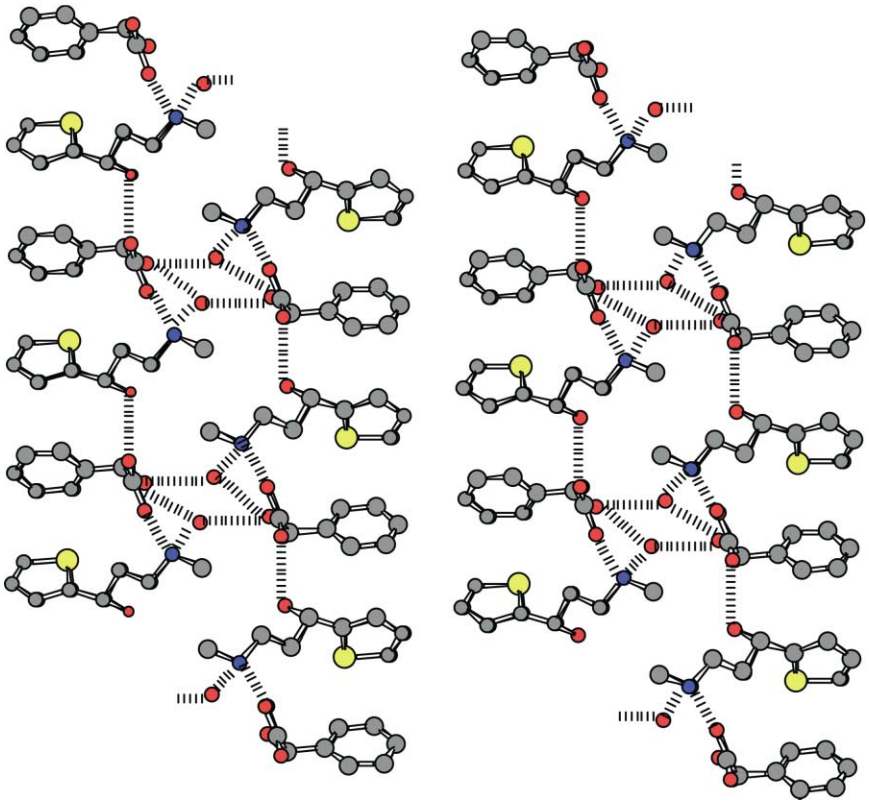

Figure 3. Molecular arrangement of (*S*)-**3**·(*S*)-**4**·H_2O viewed from the 2_1-columns.

formation of this unique hydrogen-bonding network would arise from the structural feature that **3** is a secondary amine.

3. Conclusion

An efficient industrial resolution process of 3-(methylamino)-1-(2-thienyl)propan-1-ol **3**, a new key intermediate for the synthesis of duloxetine, with (*S*)-mandelic acid **4** has been developed by using 2-butanol with a small amount of water as a solvent. From an X-ray crystal structure analysis, the existence of a unique hydrogen-bonding network mediated by water molecules was confirmed; water molecules gave a space for the bulky *N*-Me group of **3**. Absolute configuration of liberated (–)-**3** was determined as (*S*) by X-ray crystallography.

4. Experimental

4.1. General

Racemic **3** was obtained from Nippon Junryo Chemical (Osaka) and used without any purification. (*S*)-Mandelic acid (>99.5% e.e.) was made of Yamakawa Chemical (Tokyo). Other reagents were purchased from Tokyo Kasei Kogyo or Koso Chemical, unless otherwise indicated.

^{1}H NMR spectra were recorded on a JEOL JNM-ECP400 spectrometer in DMSO-d_6 or $CDCl_3$ with Me_4Si as an internal reference. IR spectra were measured on a JASCO IR-700 spectrometer using KBr pellets. Optical rotations were measured on a JASCO DIP-370 polarimeter with a circular temperature control unit. High-performance liquid chromatography was performed by a JASCO Intelligent HPLC system equipped with a 875-UV detector. Melting points were determined with a YAMATO MP-21 instrument and uncorrected. Water content in the salt was measured by the Karl Fischer method with a HIRANUMA Aquacounter AQV-5.

4.2. Determination of enantiomeric and diastereomeric purities

The enantiomeric purity of **3** and the diastereomeric purity of the salt, (*S*)-**3**·(*S*)-**4**·H_2O, were directly determined by HPLC using a Shiseido CD-Ph column (ID 4.6 mm×250 mm). Analytical conditions for the HPLC were as follows; 0.2 M $NaClO_4$:MeCN (70:30), 1 mL/min, 35°C, detected at 235 nm; injection sample 10 μL (15 mg/10 mL), Retention times: the (*R*)-enantiomer 9.8 min, the (*S*)-enantiomer 12.1 min. In the analysis of the diastereomeric purity of the salt, the peaks of the enantiomers of **3** were completely separated from that of (*S*)-**4** (retention time 2.6 min).

4.3. Preparation of the less-soluble diastereomeric salt, (*S*)-3·(*S*)-4·H_2O

Pilot scale runs usually gave better results than laboratory runs. A typical pilot run is described as follows: To

a 1000 L glass-lined reactor were added (*RS*)-**3** (100 kg, 584 mol), (*S*)-**4** (89 kg, 584 mol), 2-butanol (190 kg) and water (21 kg, 1168 mol; total amount including water in solvent-grade 2-butanol), and the mixture was stirred and heated up to about 50°C to give a clear solution. The solution was then gradually cooled, seeded (20 g) at 34–36°C, kept for 1 h at 29–32°C (corresponding to the crystallization temperature), and then cooled again to 20°C. After aging the suspension at the temperature for one hour, the crystals were collected by a centrifuge and washed twice with 2-butanol for each centrifugation (68 L in total; centrifugation six times) to afford the crude salt (83.2 kg, 244 mol, yield 42%, 75% dp, *E* 63%). The crude salt was recrystallized from a mixture of 2-butanol (165 kg) and water (7 kg; 11 kg (611 mol) in total including water in the crude salt, 2.5 equiv. versus the crude salt). The deposited salt was centrifuged, washed twice with 2-butanol (60 L in total; centrifugation five times), and dried at 50°C to give pure (*S*)-**3**·(*S*)-**4**·H_2O (66.1 kg, 194 mol, yield 79%, 95% d.p.).

(*S*)-**3**·(*S*)-**4**·H_2O: $[\alpha]_D^{20}$ +26.4 (*c* 1.00, EtOH); mp 70–71°C; IR (KBr) cm^{-1}: 3470, 3208, 1618, 1586, 1491, 1051, 701; ^1H NMR (DMSO-d_6, 400 MHz): δ 7.37–7.40 (m, 3H), 7.22–7.25 (m, 2H), 7.17 (d, $J=5.2$ Hz, 1H), 6.96 (dd, $J=3.2$, 5.2 Hz, 1H), 6.90 (d, $J=3.2$ Hz, 1H), 4.89 (dd, $J=4.8$, 8.0 Hz, 1H), 4.60 (s, 1H), 2.86–2.91 (m, 2H), 2.44 (s, 3H), 1.92–1.99 (m, 2H); water content (KF): calcd for a hydrate 5.25%, found 5.27%. Anal. calcd for $C_{16}H_{23}NO_5S$: C, 56.29; H, 6.79; N, 4.10; S, 9.39. Found C, 56.25; H, 6.64; N, 4.10; S, 9.36.

4.4. Preparation of (*S*)-3

The pure salt (*S*)-**3**·(*S*)-**4**·H_2O (66.1 kg) was treated with 1.2 M sodium hydroxide (194 L), and the liberated (*S*)-**3** was extracted with 2-butanol (124 L×3). The combined 2-butanol layers were concentrated under reduced pressure. To the condensate was added toluene, and remaining 2-butanol was removed upon evaporating repeatedly to change the solvent to toluene completely. To the final condensate was added toluene (322 L), and precipitated sodium (*S*)-mandelate was filtered off. The filtrate was concentrated to 95 L under reduced pressure. The suspension was heated at 50°C to dissolve the precipitates, then gradually cooled, seeded (20 g) at 45°C, kept for 1 h at around crystallization temperature (42°C), and then cooled again to 20°C. After aging the suspension at the temperature for 1 h, the crystals were collected by a centrifuge and washed twice with toluene for each centrifugation (24 L in total; centrifugation two times) to afford the white crystals of (*S*)-**3** (27.2 kg, 159 mol, Yield 82%, >99.9% e.e., total yield 27%).

(*S*)-**3**: $[\alpha]_D^{20}$ −16.5 (*c* 1.01, EtOH); mp 70.5–73.0°C; IR (KBr) cm^{-1}: 3384, 3284, 1489, 1303, 1178, 1110, 1085, 709; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.20 (d, $J=5.2$ Hz, 1H), 6.96 (dd, $J=3.2$, 5.2 Hz, 1H), 6.92 (d, $J=3.2$ Hz, 1H), 5.17 (dd, $J=3.2$, 8.0 Hz, 1H), 2.94 (ddd, $J=3.6$, 5.6, 8.0 Hz, 1H), 2.84 (ddd, $J=3.2$, 9.2, 12.0 Hz, 1H), 2.42 (s, 3H), 1.85–2.00 (m, 2H). Anal. calcd for $C_8H_{13}NOS$: C, 56.11; H, 7.65; N, 8.18; S, 18.72. Found C, 56.22; H, 7.56; N, 8.17; S, 18.79.

4.5. X-Ray crystal structure analysis

A colorless plate single crystal of (*S*)-**3**·(*S*)-**4**·H_2O salt (0.30×0.70×0.70 mm) was grown from the recrystallization conditions indicated above using the recrystallized salt crystals (>99.9% d.p.; (*S*)-mandelic acid >99.9% e.e.). The X-ray intensities were measured up to $2\theta_{max}=52.7°$ with graphite-monochromated MoKα radiation ($\lambda=0.71073$ Å) (MAC Science) at 296 K.

Data collection and refinement parameters for the salt are as follows: (*S*)-**3**·(*S*)-**4**·H_2O; $C_{16}H_{23}NO_5S$; formula weight 341.42; monoclinic; space group: $P2_1(\#4)$, $a=8.8150(4)$ Å, $b=5.8730(2)$ Å, $c=17.5500(9)$ Å, $\beta=92.573(2)°$, $V=876.77(6)$ $Å^3$, $Z=2$, $D_{calcd}=1.293$ g cm^{-3}, $\mu(MoK\alpha)=2.08$ cm^{-1}, $R=0.054$, $Rw=0.082$. Number of reflections measured: total=1961; unique=1959. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as a supplementary publication number CCDC 203963.

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7. Resolution efficiency (*E*, %)=yield (%)×diastereomeric purity (% d.p.)×2/100.

8. Diastereomeric purity (% d.p.) = |A−B|×100/(A+B), where A and B are both diastereomers.
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