

Synthesis of (*S*)-3-(*N*-Methylamino)-1-(2-thienyl)propan-1-ol: Revisiting Eli Lilly's Resolution–Racemization–Recycle Synthesis of Duloxetine for Its Robust Processes

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Abstract:

(±)-3-(*N,N*-Dimethylamino)-1-(2-thienyl)propan-1-ol (**6**), prepared from 2-acetylthiophene (**4**) in a two-step overall yield of 79%, is resolved into (*S*)-**6** of 93% ee as its diastereomeric salt (**8**) with (*S*)-mandelic acid (**7**) according to Eli Lilly's procedures developed for the resolution–racemization–recycle (RRR) synthesis of duloxetine (**2**) with some modifications in terms of practicality. On its liberation from **8**, (*S*)-**6** undergoes *N*-demethylative ethyl carbamate formation in two discrete but successive steps in an overall yield of 87% from **8**: (1) *O*-ethyl carbonate formation and (2) ethyl carbamate formation with concomitant loss of the *N*-methyl group. Alkaline hydrolysis then affords (*S*)-3-(*N*-methylamino)-1-(2-thienyl)propan-1-ol (**1**) of 100% ee, an alleged penultimate precursor to duloxetine (**2**), in 75% yield after a single recrystallization from ethylcyclohexane. In the overall process thus developed, PhMe is substituted successfully for *t*-BuOMe, a solvent that has been used favorably in Eli Lilly's original RRR synthesis of **2**.

Introduction

This communication will deal with the synthetic processes for (*S*)-3-(*N*-methylamino)-1-(2-thienyl)propan-1-ol (**1**) which were developed with modifications to Lilly's resolution–racemization–recycle (RRR) synthesis of duloxetine (**2**) (Figure 1).¹

Being a potent dual inhibitor of serotonin and noradrenalin reuptake, **2** has therapeutic potency to treat stress urinary incontinence as well as major depressive disorder.² In contrast, its ancestor, fluoxetine (**3**)³ which represents a selective serotonin reuptake inhibitor (SSRI), is prescribed only as an antidepressant (Figure 1). In addition, contrary to **3** that was approved as a racemate,⁴ **2** was supposed to reach the therapeutic market as a single enantiomer from the outset of its development. Thus, a wide range of chiral

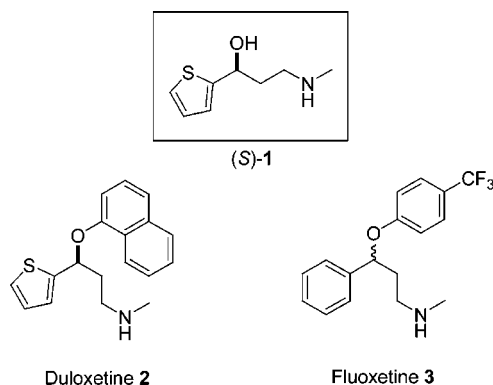


Figure 1. Structures of (*S*)-3-(*N*-methylamino)-1-(2-thienyl)propan-1-ol (**1**), duloxetine (**2**), and fluoxetine (**3**).

technologies has been explored to date for scalable processes that should provide **2** of high stereochemical purity;⁵ and among other things, resolution via diastereomeric salt formation seemed the most industrially viable as implied in Weigel's review.¹

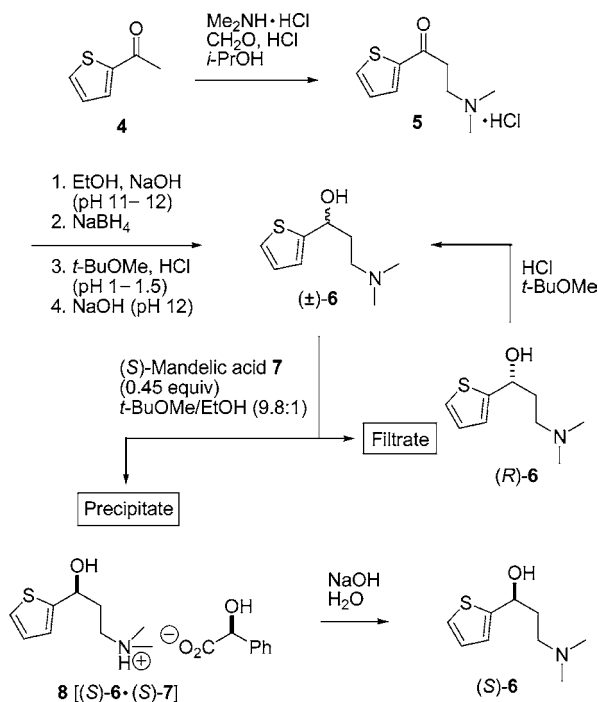
The resolution–racemization–recycle (RRR) synthesis of **2** developed at Eli Lilly starts with the Mannich reaction ($\text{Me}_2\text{NH}\cdot\text{HCl}$, CH_2O , HCl , *i*-PrOH) of 2-acetylthiophene (**4**) (Scheme 1).^{1,5b} The β -aminoketone freed from Mannich product (**5**) by base treatment (NaOH , EtOH; pH 11–12) is subjected to NaBH_4 -mediated reduction. After acidic workup (HCl ; pH 1–1.5) cleaving both B–O and B–N linkages, basification (pH 12) affords (±)-(*N,N*-dimethyl)aminoalcohol (**6**) as a free base,^{5b} which is extracted into *t*-BuOMe (MTBE). To the MTBE solution is added (*S*)-mandelic acid (**7**) (0.45 equiv) dissolved in EtOH. The resulting slurry [MTBE/EtOH (9.8:1)] is heated to reflux and then cooled to ambient temperature to allow (*S*)-**7** to form a diastereomeric salt with (*S*)-**6**, during which (*R*)-**6** is left unaffected and remains dissolved in the solution. The precipitated salt (**8**) [(*S*)-**6**·(*S*)-**7**] is collected by filtration and treated with aqueous NaOH solution to liberate (*S*)-**6**. In the meantime, the MTBE solution of (*R*)-**6** recovered as the filtrate (mother liquor) is treated with HCl to racemize (*R*)-**6** for another round of the resolution (recycling) as outlined in Scheme 1.¹

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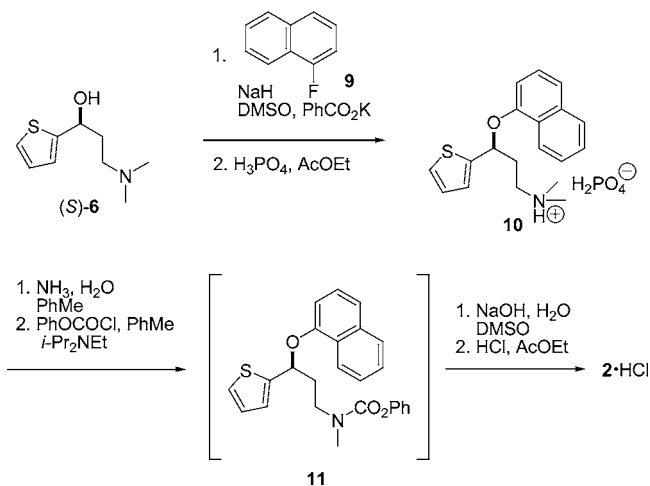
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 (4) (a) Hilborn, J. W.; Lu, Z.-H.; Jurgens, A. R.; Fang, Q. K.; Byers, P.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett.* **2001**, *42*, 8919. (b) Liu, H.-L.; Hoff, B. H.; Anthonsen, T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1767.

Scheme 1. Eli Lilly's RRR synthesis of (*S*)-3-(*N,N*-dimethylamino)-1-(2-thienyl)propan-1-ol (6**)**



Scheme 2. Eli Lilly's assemblage of 2·HCl from (*S*)-6****



When (*S*)-**6** is treated with NaH (1.0 equiv) in the presence of PhCO_2K (0.1 equiv) in DMSO,^{5b} it is allowed to participate in aromatic nucleophilic substitution on 1-fluoronaphthalene (**9**) (1.2 equiv), as depicted in Scheme 2. The coupled product is then isolated as its phosphate salt (**10**) of 91% ee in 79.6% yield from (*S*)-**6**. On basification under the biphasic conditions (NH_3 , H_2O , PhMe), the free amine liberated from **10** is taken up into PhMe. To the PhMe solution is added *i*-Pr₂NEt (0.10 equiv) followed by PhOCOCl (1.25 equiv), and the resulting homogeneous mixture is heated to 55 °C to implement *N*-demethylation. The resulting phenyl carbamate (**11**) is finally subjected to alkaline hydrolysis (NaOH, H_2O , DMSO) without isolation. Aqueous workup (acidification to pH 5.0–5.5 with AcOH, washing with *n*-hexane, basification to pH 10.5 with 50% aqueous NaOH solution, extraction with AcOEt) followed by salt formation with HCl in the AcOEt solution eventually

provides duloxetine hydrochloride (**2**·HCl) as a white solid in an overall yield of 32% from (*S*)-**6**.

Recently, it was suggested that (*S*)-3-(*N*-methylamino)-1-(2-thienyl)propan-1-ol (**1**) (Figure 1) should represent another penultimate precursor to **2** in place of **10**.⁶ Hence, as part of our process development program featuring resolution via diastereomeric salt formation,⁷ we chose to access (*S*)-**6** following the RRR tactics that had originated in Eli Lilly's protocol and then subject it to *N*-demethylation via carbamate formation in having a scalable access to (*S*)-**1** as will be discussed below in full detail.

Results and Discussion

Preparation of (\pm)-Alcohol (6**).** The Mannich reaction with **4** was first conducted under the same conditions as reported from Eli Lilly (Scheme 1). When a mixture of **4** (1.0 equiv), $\text{Me}_2\text{NH}\cdot\text{HCl}$ (1.26 equiv), paraformaldehyde (1.49 equiv), HCl (0.13 equiv), and *i*-PrOH (2.4 v/w) was heated to reflux all at once, there took place abrupt precipitation of the crystalline Mannich product (**5**) with vigorous bumping, which raised safety concerns. Thus, to prevent this unfavorable phenomenon, two countermeasures were taken: (1) To a solution of $\text{Me}_2\text{NH}\cdot\text{HCl}$ (1.25 equiv), paraformaldehyde (1.20 equiv) and 35% aqueous HCl solution (0.25 equiv) in *i*-PrOH (2.0 v/w) was added **4** in two halves; (2) prior to the addition of the second half of **4**, the reaction mixture was seeded with **5** to induce partial crystallization deliberately. As a result, these two modifications allowed **5** to be obtained as white crystals in 88% yield uneventfully in an industrially viable manner (Scheme 3).

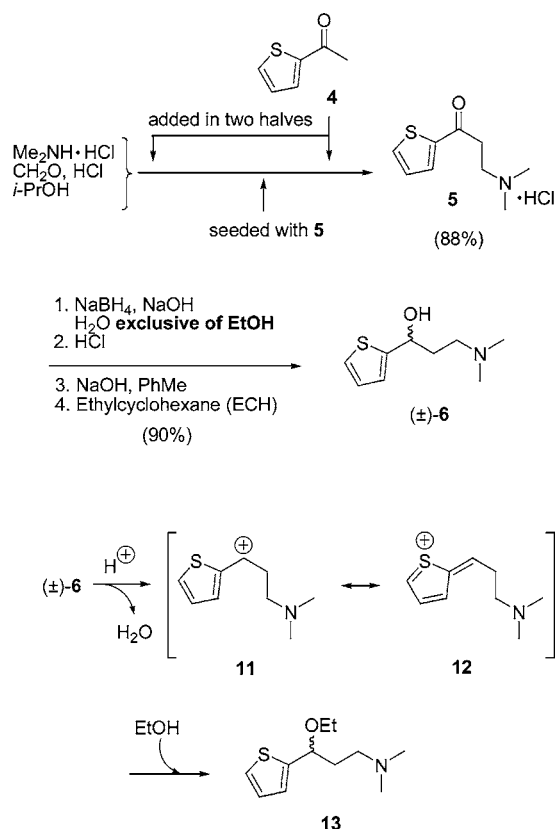
The free β -*N,N*-dimethylaminoketone liberated from **5** was reduced with NaBH_4 (0.50 equiv) in EtOH according to Eli Lilly's procedures as outlined in Scheme 1,^{5b} however, the acidic workup (HCl; pH 1–1.5) aimed at hydrolyzing both N–B and O–B bonds was inevitably accompanied by ethyl ether (**13**) being generated in a significant amount, which should arise from nucleophilic addition of EtOH to a cationic species that could be represented as two limiting structures, **11** and **12** (Scheme 3). To avoid such ether formation, the NaBH_4 -mediated reduction was conducted in an aqueous medium free of EtOH. The Mannich product (**5**) was added directly to an alkaline suspension of NaBH_4 (0.4 equiv) in an aqueous solution of NaOH (1.1 equiv). The reaction was then quenched with 35% aqueous HCl solution (1.65 equiv) to destroy all the boron complexes. The mixture was basified with 48% aqueous NaOH solution to liberate free (\pm)-(*N,N*-dimethyl)aminoalcohol (**6**), which was then extracted into PhMe. Eventually, crystallization from ethylcyclohexane (ECH) provided (\pm)-**6** as a white solid in 90% yield.

Resolution of (\pm)-6** into (*S*)-**6** as its Diastereomeric Salt with (*S*)-Mandelic Acid (**7**).** The resolution procedures established at Eli Lilly^{1,5b} were reexamined for further improvement. (\pm)-Alcohol (**6**) was combined with (*S*)-mandelic acid (**7**) (0.45 equiv) in a range of solvents listed

(6) Sakai, K.; Sakurai, R.; Yuzawa, A.; Kobayashi, Y.; Saigo, K. *Tetrahedron: Asymmetry* **2003**, *14*, 1631.

(7) Hirayama, Y.; Ikunaka, M.; Matsumoto, J. *Org. Process Res. Dev.* **2005**, *9*, 30.

Scheme 3. Preparation of (±)-6 free from ether byproduct (13)



in Table 1 to precipitate diastereomeric salt (**8**), which was analyzed for the enantiomeric purity of (*S*)-**6** contained in it by HPLC [column, Daicel OD i.d. 4.6 mm × 250 mm; eluent: *n*-hexane/*i*-PrOH/ Et_2NH (96.5:3.5:0.1); for more detail, see the analytical condition (2) in the Experimental Section]. When **8** was formed in MTBE doped with a protic solvent such as EtOH (10%; entry 1, Table 1) and H_2O (1%; entry 2, Table 1), efficient chiral separation was reproduced as reported from Eli Lilly.

MTBE being a solvent that has posed environmental concerns, other solvents of similar polarity, such as Bu_2O and *i*-PrOAc, were applied to the diastereomeric salt formation. While the use of $\text{Bu}_2\text{O}/\text{H}_2\text{O}$ (100:1) ended in less efficient resolution (entry 3, Table 1), that of *i*-PrOAc (entry 4, Table 1) enabled chiral separation as efficient as that recorded in the literature from Eli Lilly.^{5b}

The diastereomeric salt formation in question was next attempted in a solvent of low polarity. When **8** was allowed to precipitate from PhMe, its yield amounted to 43%, the enantiomeric purity of (*S*)-**6** contained in it being 94.4% ee (entry 5, Table 1). However, the enantiomeric purity of (*S*)-**6** contained in **8** suffered a decrease from 94.4% ee to 86.1% ee when the precipitated salt (**8**) was left suspended in the mother liquor [the PhMe solution of (*R*)-**6**] at 25 °C for 12 h.

It was then indicated from experimentation that diastereomeric salt (**8**) would gain the stereochemical stability in PhMe when it was doped with small amounts of a protic solvent; hence, PhMe doped with MeOH (2.5%) turned out to be the medium of choice in forming diastereomeric salt

(**8**) (entry 6, Table 1). Eventually, under these conditions, the precipitated salt was isolated in 41% yield, (*S*)-**6** contained in it being of 93.0% ee; and, what was better, the enantiomeric purity of (*S*)-**6** remained unchanged even after the salt had been suspended in the mother liquor containing (*R*)-**6** at ambient temperature for a day.

As a result, the solvent system of MTBE-EtOH (9.8:1) that had been employed for the diastereomeric salt formation at Eli Lilly was replaced successfully with that of PhMe-MeOH (40:1), which was more economical and environmentally benign: when (±)-**6** was combined with (*S*)-**7** (0.45 equiv) in PhMe (10 v/w)-MeOH (0.25 v/w), (*S*)-**6** was allowed to form a diastereomeric salt with (*S*)-**7** in a highly reproducible manner to give (**8**) in 41% yield with (*S*)-**6** of 93% ee being contained in it, as summarized in Scheme 4.

While the separated salt (**8**) was carried forward to the *N*-demethylation stage, the filtrate (mother liquor) was concentrated to recover (*R*)-**6**, which should be racemized for another round of the resolution, as discussed below.

Acid-Catalyzed Racemization of (*R*)-Alcohol (6). Racemization of the off-enantiomer, (*R*)-**6**, was also attempted according to the procedures devised at Eli Lilly.¹ When (*R*)-**6** of 70.8% ee at a concentration of 0.67 M was treated with 3 M aqueous HCl solution (3.0 equiv) at room temperature for 5 h, its enantiomeric purity declined to 1.8% ee. However, two kinds of byproducts were found to be generated in the course of the acid-induced racemization, as shown by HPLC analysis [YMC-Pack ODS-AM, i.d. 6.0 mm × 150 mm; $\text{H}_2\text{O}/\text{MeCN}/\text{CF}_3\text{CO}_2\text{H}$ (80:20:0.01); UV 254 nm; for more detail, see the analytical condition (3) in the Experimental Section]: t_R 2.8 min (10.2 area %) and t_R 4.8 min (6.7 area %).

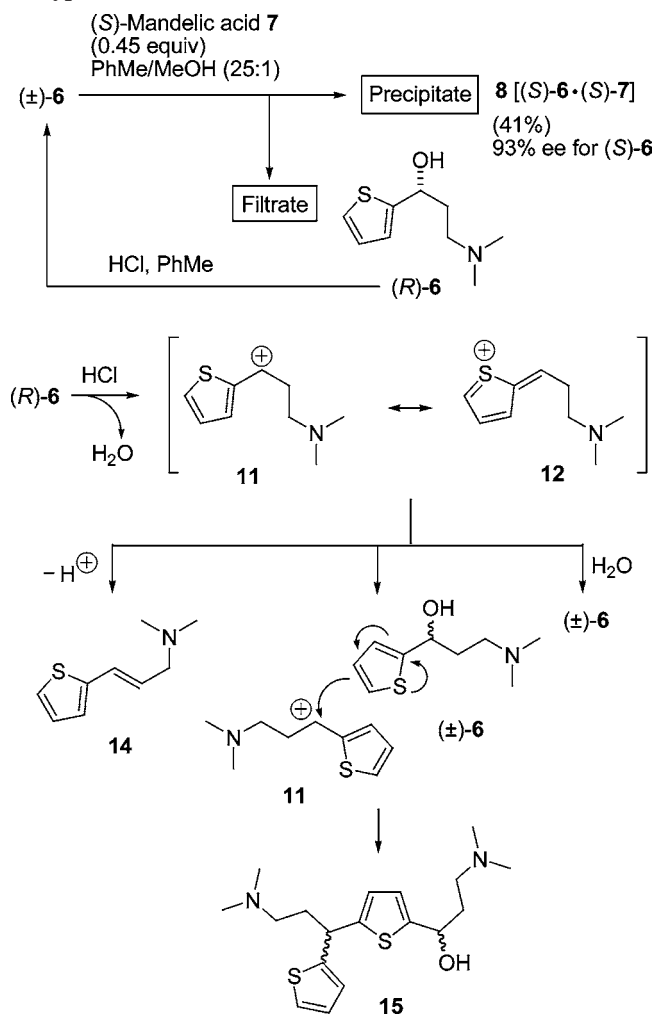
The slower-eluting byproduct (t_R 4.8 min) could be isolated using preparative TLC, and its structure was identified as olefin (**14**) by ^1H NMR and GC-MS analysis, which should arise from acid-catalyzed dehydration (Scheme 4). As regards the faster-eluting one (t_R 2.8 min), which was difficult to isolate in a pure state by silica gel chromatography, it was deduced from LC-MS (ESI) that its structure should be bis(2-thienyl)methine (**15**) based on $[\text{M} + \text{H}]^+ = 353$ ($\text{C}_{18}\text{H}_{28}\text{N}_2\text{OS}_2$); the plausible mechanism of the formation of **15** should involve electrophilic aromatic substitution as outlined in Scheme 4.

To prevent both **14** and **15** from being formed or at least to put their formation under stringent control, concentrations of (*R*)-**6** and amounts of HCl applied were varied for the best combination since both factors seemed to affect the chemical fate of **11** and/or **12**. When (*R*)-**6** (70.8% ee; 0.67 M) was treated with 2 M aqueous HCl solution (3.0 equiv) at 21 °C, it took 8 h until its enantiomeric purity dropped to below 5% ee, with **14** and **15** being produced in 7.1 and 12.7 area %, respectively, as shown by HPLC (entry 1, Table 2). When the concentration of (*R*)-**6** (70.8% ee) was kept constant at 0.67 M, increase in the amount of HCl (5 M) from 3.0 to 8.0 equiv accelerated the reaction rate 4 times, but it also raised the amounts of **14** and **15** to 18.9 and 37.8 area %, respectively (entry 2, Table 2).

Table 1. Solvent screen for the diastereomeric salt formation of (S)-6 with (S)-mandelic acid (7)

entry	solvent (v/w) ^a	yield (%) of 8	ee (%) of (S)-6 in 8 ^b	resolution efficiency ^c
1	MTBE (10), EtOH (1)	41.8	87.2	36.4
2	MTBE (10), H ₂ O (0.1)	42.4	91.0	38.6
3	Bu ₂ O (10), H ₂ O (0.1)	33.4	76.4	25.5
4	AcOPr ⁱ (10)	41.7	91.2	38.0
5	PhMe (10)	43.4	94.4	41.0
6	PhMe (10), MeOH (0.25)	41.0	93.0	38.1

^a A ratio of the solvent volume (mL) relative to the weight (g) of (±)-6. ^b Determined by HPLC under the analytical condition (2) detailed in the Experimental Section. ^c Calculated according to the following equation: [yield (%) of **8**] × [ee (%) of (S)-6 in **8**] × 0.01

Scheme 4. Resolution of (±)-6 via diastereomeric salt formation with (S)-mandelic acid (7) and acid-catalyzed racemization of (R)-6 accompanied by dehydrative formation of byproducts (14) and (15)

It was assumed that since **15** was produced by a bimolecular reaction, its amounts could be reduced by decreasing concentrations of (R)-6. When (R)-6 (70.8% ee) at a concentration of 0.34 M was treated with 2 M aqueous HCl solution (6.0 equiv) at 21 °C, its enantiomeric purity dropped to below 5% ee in 4 h with formation of **14** and **15** being reduced from 7.1 area % (entry 1, Table 2) to 5.6 area % and from 12.7 area % (entry 1, Table 2) to 7.5 area %, respectively (entry 3, Table 2).

When the reaction temperature was decreased from 21 to 9 °C, it took longer reaction time (24 h) for the

Table 2. Conditions for the acid-promoted racemization of (R)-6

entry	[(R)-6] (M)	HCl (equiv) [HCl] (M)	temp (°C)	time (h)	14 (area %) ^a	15 (area %) ^a
1	0.67	3/2	21	8	7.1	12.7
2	0.67	8/5	21	2	18.9	37.8
3	0.34	6/2	21	4	5.6	7.5
4	0.34	6/2	9	24	2.1	7.7
5	0.34	4.5/1.5	21	8	3.8	6.0
6	0.17	12/2	21	4	6.0	6.0

^a Determined by HPLC under the analytical condition (3) detailed in the Experimental Section.

enantiomeric purity of (R)-6 to decline to below 5% ee where formation of **14** was further lessened to 2.1 area % but that of **15** remained almost unchanged as 7.7 area % (entry 4, Table 2).

The acid-catalyzed racemization was next attempted using HCl in less amounts and at lower concentrations. In the presence of 1.5 M aqueous HCl solution (4.5 equiv), the enantiomeric purity of (R)-6 dropped from 70.8% ee to below 5% ee at 21 °C in 8 h during which accumulation of **14** and **15** could be suppressed to 3.8 and 6.0 area %, respectively (entry 5, Table 2). By comparison, (R)-6 (70.8% ee) at a more dilute concentration of 0.17 M was treated with as much as 12 equiv HCl (2 M aqueous solution) at 21 °C where the enantiomeric purity of (R)-6 dropped to below 5% ee in 4 h with a slight increase in the amount of **14** (6.0 area %), although that of **15** (6.0 area %) was almost unaffected when compared with entry 5 in Table 2 (entry 6, Table 2).

In the event, the racemization was best accomplished with (R)-6 (70.8% ee) at its concentration of 0.34 M by the action of 1.5 M aqueous HCl solution (4.5 equiv) at 21 °C, whereby formation of **14** and **15** could be suppressed to not more than 3.8 and 6.0 area %, respectively, both being the lowest level ever attained (entry 5, Table 2).

To telescope the racemization step in question into the previous resolution step, the PhMe solution of (R)-6 that had

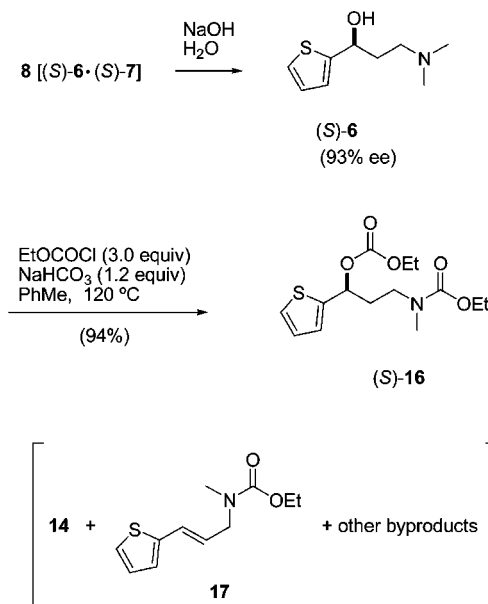
been separated from diastereomeric salt (**8**) by filtration was subjected directly to the racemization conditions identified as above. The PhMe solution of (*R*)-**6** (63% ee) obtained as the filtrate was washed with 1 M aqueous NaOH solution to remove (*S*)-**7** dissolved in it and with saturated aqueous NaCl solution. The PhMe solution was concentrated until its volume reached 0.42 times the original volume, whereby the MeOH dissolved in it was removed completely; unless the PhMe solution was freed of MeOH, the ensuing acid-mediated racemization would suffer from methyl ether formation as ethyl ether (**13**) formed in the presence of EtOH during the acidic workup of the NaBH₄-mediated reduction of **5** (Scheme 3). To the PhMe solution thus condensed was added 1.5 M aqueous HCl solution (4.5 equiv) and the resulting two-phase mixture was stirred at ambient temperature for 7 h. Finally, recrystallization from ECH (4 v/w) provided (\pm)-**6** in 79–83% yield, which was free of **14** but was contaminated with **15** in 3.0 area %.

As regards (\pm)-**6** that had been obtained from the above-mentioned process of acid-catalyzed racemization, its reuse was investigated. Regenerated (\pm)-**6** contaminated by **15** (3.0 area %) was combined with an equiamount of fresh (\pm)-**6** to prepare a sample of (\pm)-**6** that contained **15** in 1.5 area %, which was then subjected to the second round of resolution by (*S*)-**7** [0.45 equiv relative to (\pm)-**6**]. When (*S*)-**6** thus prepared was allowed to undergo *N*-demethylation under the conditions detailed below, there was produced (*S*)-**1** of 100% ee which was contaminated by bis-nor **15**, the byproduct arising from double *N*-demethylation of **15**, only in 0.46 area %; the product/byproduct ratios were measured arbitrarily in area % at 254 nm without correction based on the absorption coefficient of each compound.

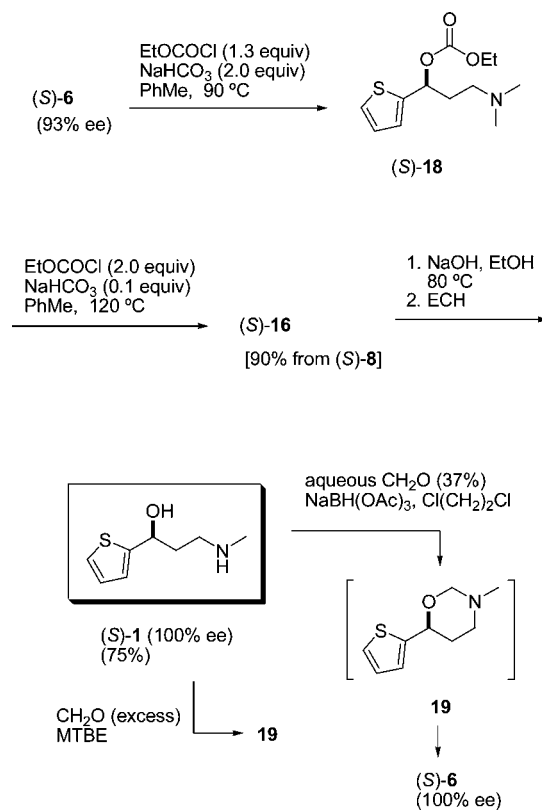
***N*-Demethylation of (*S*)-*N,N*-Dimethylaminoalcohol (**6**).** *N*-Demethylation of (*S*)-**6** of 93% ee, liberated from **8** by basification with an aqueous NaOH solution, was first attempted using Teva's procedures that had originally been applied to the synthesis of **3**.^{3b,8} A solution of (*S*)-**6** in PhMe was treated with ethyl chloroformate (3.0 equiv) in the presence of NaHCO₃ (1.3 equiv) with heating at reflux.⁸ The HCl evolving with the progress of the reaction was neutralized with solid NaHCO₃, and the resulting H₂O was removed by distillation as an azeotrope with PhMe. On complete consumption of (*S*)-**6**, aqueous workup provided (*S*)-*N,O*-bis-ethoxycarbonylated (**16**) in 94% yield (Scheme 5). However, the reaction turned out to be capricious and less reproducible, giving rise to a complex mixture of byproducts including dehydrated olefins, **14** and **17**.

The causative agent for such byproduct formation was assumed to be the HCl that survived the neutralization by NaHCO₃ under the heterogeneous conditions, considering that 2-thienyl carbinol (**6**) was so acid-sensitive a compound as discussed above and outlined in Schemes 3 and 4. Thus, to prevent (*S*)-**6** from entering into acid-promoted side reactions, such as dehydration, its hydroxyl group was converted to less acid-labile ethyl carbonate completely under mild conditions prior to *N*-demethylative ethoxycarbonyla-

Scheme 5. Attempted single-step procedures for *N*-demethylative ethyl carbamate formation from (*S*)-**6**



Scheme 6. Two-step procedures for *N*-demethylative ethyl carbamate formation from (*S*)-**6** and completion of the synthesis of (*S*)-**1**



tion, which would require harsh conditions, such as elevated reaction temperatures (Scheme 6). To a PhMe solution of (*S*)-**6** of 93% ee was added a PhMe solution of ethyl chloroformate (1.3 equiv) in the presence of solid NaHCO₃ (2.0 equiv) with heating at 90 °C. Aqueous workup followed by azeotropic removal of the generated water afforded a dried PhMe solution of (*S*)-**18**. To the PhMe solution was then added another PhMe solution of ethyl chloroformate (2.0

(8) Schwartz, R. E.; Kaspi, G. J.; Itov, R.-L. Z.; Pilarski, H. G. (Teva Pharmaceutical Industries Ltd.). U.S. Patent 5,225,585, 1993.

equiv) in the presence of solid NaHCO₃ (0.1 equiv) with heating at reflux to afford (*S*)-**16** of 91.1% chemical purity as a pale-yellow oil in 90% yield.

Both *N*- and *O*-ethoxycarbonyl groups were cleaved from (*S*)-**16** by alkaline hydrolysis.^{3b,8} To a solution of (*S*)-**16** in EtOH (1.7 v/w) and H₂O (2.2 v/w) was added 48% aqueous solution of NaOH (8.5 equiv) (Scheme 6). After stirring at 80 °C for 2 h, extraction with PhMe at 50 °C furnished crude (*S*)-**1** as a pale-yellow solid quantitatively; its enantiomeric purity was determined to be 93% ee by the method mentioned below, which indeed was the same as that of (*S*)-**6**.

Finally, recrystallization from ECH/PhMe (3:1) gave purified (*S*)-**1** (100 area %) as a white solid in 75% yield. It was then attempted to determine the enantiomeric purity of (*S*)-**1** in a direct way, but to no avail; hence, (*S*)-**1** thus obtained was reverted to (*S*)-**6**, and the latter was analyzed for enantiomeric purity. When a solution of (*S*)-**1** in Cl(CH₂)₂-Cl was treated with 37% aqueous solution of HCHO in the presence of NaBH(OAc)₃,⁹ reductive *N*-methylation proceeded via cyclic (*S*)-*N,O*-acetal (**19**) and eventually led to (*S*)-**6**; the intermediacy of **19** was confirmed by its unambiguous preparation in which (*S*)-**1** was treated with excess paraformaldehyde in MTBE. Eventually, HPLC analysis assured that (*S*)-*N,N*-dimethylamine (**6**) thus prepared was of 100% ee, and as such, the enantiomeric purity of the original (*S*)-**1** was confirmed to be of 100% ee.

Conclusions

2-Acetylthiophene (**4**) was converted to (*S*)-3-(*N*-methylamino)-1-(2-thienyl)propan-1-ol (**1**) of 100% ee, an alleged penultimate precursor to **2**, according to Eli Lilly's procedures (Schemes 1 and 2) with modifications aimed at dealing with the acid lability of the secondary alcohol function in 3-(*N,N*-dimethylamino)-1-(2-thienyl)propan-1-ol (**6**) in the following three situations: (1) NaBH₄-mediated reduction of the Mannich product (**5**) was effected in an aqueous medium exclusive of any alcoholic solvent, such as EtOH, to prevent ether formation in the course of acidic workup (Scheme 3). (2) As regards the acid-catalyzed racemization of the off-enantiomer, (*R*)-**6**, the conditions were tuned in terms of the substrate concentrations and the amounts of HCl applied such that dehydrated olefin (**14**) and bis(2-thienyl)methine derivative (**15**) should be formed in minimum amounts; when (*R*)-**6** (70.8% ee; 0.34 M) was treated with 1.5 M aqueous solution of HCl (4.5 equiv) at 21 °C, the racemization went almost to completion, giving (*R*)-**6** of not more than 5% ee, with **14** and **15** being formed in 3.8 and 6.0 area %, respectively (Scheme 4). (3) *N*-Demethylative ethoxycarbonylation of (*S*)-**6** to (*S*)-**16** was conducted through two-step discrete but successive operations to prevent the secondary alcohol of (*S*)-**6** from being eliminated by the action of the HCl that adventitiously survived neutralization by NaHCO₃; (*S*)-**6** was first converted to (*S*)-*O*-ethoxycarbonylated (**18**) at 90 °C, which was then subjected to *N*-demethylative ethoxycarbonylation at 120 °C to give (*S*)-

16 (Scheme 6). Last but not least, MTBE that had been employed in the original RRR synthesis of **2** was replaced with PhMe, a more favorable solvent in terms of safety and economy, throughout the modified processes.¹⁰

Experimental

General. Melting points were measured on an Electrothermal 1A8104 melting point apparatus and are uncorrected. ¹H NMR spectra were recorded at 400 MHz on a Varian UNITY-400 spectrometer in a CDCl₃ solution with tetramethylsilane as an internal standard. FT-IR spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. Mass spectra were recorded on a Hitachi M-8000 mass spectrometer (ESI). Elemental analyses were performed on an Elementar vario EL analyzer. Optical rotations were measured on a Horiba SEPA-200 polarimeter. Thin-layer chromatography (TLC) was performed on Merck Kieselgel 60 plates (0.25 mm thick, art 1.05714.).

Analytical Conditions. (1) HPLC to monitor the progress of the reduction of **5** to (±)-**6**: column, YMC-Pack ODS-AM, i.d. 6.0 mm × 150 mm; eluent, H₂O/MeCN/trifluoroacetic acid (90:10:0.01); flow rate, 1.0 mL/min; column temperature, 40 °C; detection, UV at 254 nm; *t*_R, 5.3 min for (±)-**6** and 6.0 min for **5**. (2) HPLC to determine the enantiomeric composition of **6**: column, Daicel CHIRAL-CEL OD i.d. 4.6 mm × 250 mm; eluent: *n*-hexane/*i*-PrOH/Et₂NH (96.5:3.5:0.1); flow rate, 0.7 mL/min; column temperature, room temperature; detection, UV at 230 nm; *t*_R, 15.8 min for (*R*)-**6** and 17.3 min for (*S*)-**6**. (3) HPLC to determine the chemical composition of **6** regenerated after acid-catalyzed racemization of (*R*)-**6**: column, YMC-Pack ODS-AM i.d. 6.0 mm × 150 mm; eluent, H₂O/MeCN/trifluoroacetic acid (80:20:0.01); flow rate, 1.0 mL/min; column temperature, 40 °C; detection, UV at 254 nm; *t*_R, 2.8 min for **15**, 3.2 min for **6**, and 4.8 min for **14**. (4) HPLC to monitor the progress of the reaction from (*S*)-**6** to (*S*)-**16** via (*S*)-**18**: column, YMC-Pack ODS-AM i.d. 6.0 mm × 150 mm; eluent, H₂O/MeCN/trifluoroacetic acid (50:50:0.01); flow rate, 1.0 mL/min; column temperature, 40 °C; detection, UV at 230 nm; *t*_R, 2.2 min for **6**, 2.6 min for **18** and 14.4 min for **16**. (5) HPLC to monitor the progress of the hydrolysis of (*S*)-**16** to (*S*)-**1** and to determine the chemical purity of (*S*)-**1**: column, YMC-Pack ODS-AM i.d. 6.0 mm × 150 mm; eluent, H₂O/MeCN/trifluoroacetic acid (50:50:0.01); flow rate, 1.0 mL/min; column temperature, 40 °C; detection, UV at 254 nm; *t*_R, 2.3 min for (*S*)-**1**, 3.0 min for bis-nor **15** (arising from double *N*-demethylation of **15**) and 14.1 min for **16**. (6) GLC to monitor the progress of the reductive *N*-methylation of (*S*)-**1** to (*S*)-**6**: column, Hicap (CBP1-M25-025), i.d. 0.25 mm × 25 m; column temperature, 130 °C; injection temperature, 250 °C; detection temperature, 275 °C; carrier gas, He, 90 mL/min; split ratio, 1:100; sample size, 2.0 μL; detection, FID; *t*_R, 15.7 min for (*S*)-**6**, 17.7 min for (*S*)-**1**, and 18.1 min for **19**.

(±)-**2**-[3-(*N,N*-Dimethyl)aminopropionyl]thiophen Hydrochloride (**5**). To a stirred solution of 35% aqueous

(9) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.

(10) The completed process was transferred to a contract manufacturer and enabled it to produce tens of kilograms of (*S*)-**1** in a reliable manner.

solution of HCl (1.15 g, 55 mmol) in *i*-PrOH (55 mL) were added paraformaldehyde (95%; 8.35 g, 264 mmol), Me₂NH·HCl (22.43 g, 275 mmol), and 2-acetylthiophene (**4**) (13.88 g, 110 mmol) in sequence at room temperature. The mixture was heated to 67–70 °C, and the stirring was continued with heating at the same temperature range for 1 h. The homogeneous mixture was seeded with a few crystals of **5** to induce partial crystallization. The resulting heterogeneous mixture was stirred with heating at the same temperature range for 1 h. The mixture was heated to reflux, and an additional amount of **4** (13.88 g, 110 mmol) was added. After the addition was complete, the stirred mixture was heated at reflux for 5 h. The mixture was allowed to cool to 5 °C with stirring and was kept at the same temperature for 0.5 h. The precipitated solid was collected by filtration under suction, washed with EtOH (20 mL × 2), and air-dried with heating at 50 °C to give **5** (42.37 g) as a white solid in 87.7% yield. Mp 176.0–178.1 °C (lit.:^{5a} mp 174–176 °C). IR ν (KBr) 3288, 3078, 3012, 2948, 2557, 2445, 2113, 1873, 1805, 1653, 1522, 1473, 1462, 1414, 1381, 1358, 1335, 1313, 1244, 1225, 1171, 1138, 1086, 1053, 1034, 1007, 976, 935, 860, 852, 798, 768, 731, 654, 590, 500 cm⁻¹. ¹H NMR (CDCl₃) for the free amine δ 7.74 (d, *J* = 3.6 Hz, 1H), 7.64 (d, *J* = 4.8 Hz, 1H), 7.13 (t, *J* = 4.0 Hz, 1H), 3.09 (t, *J* = 7.6 Hz, 2H), 2.76 (t, *J* = 7.6 Hz, 2H), 2.29 (s, 6H).

(±)-3-(*N,N*-Dimethylamino)-1-(2-thienyl)propan-1-ol (6). To a suspension of NaBH₄ (2.04 g, 54 mmol) in an aqueous solution of NaOH (48% aqueous solution of NaOH, 16.50 g, 198 mmol; H₂O, 118 mL) was added **5** (39.50 g, 180 mmol) in portions at room temperature over 1 h. The mixture was stirred at room temperature for 3 h. NaBH₄ (0.68 g, 18 mmol) was added, and the stirring was continued at room temperature for 2 h. The mixture was stirred with heating at 69–71 °C for 1 h, during which the progress of the reaction was monitored by HPLC as follows: From the reaction mixture was taken an aliquot (30 μ L), which was poured into MTBE (0.3 mL). The layers were separated, and the MTBE layer was concentrated in vacuo. To the residue was added MeCN (2 mL), and a portion (1 μ L) of the solution was injected to a chromatograph running under the analytical condition (1). On complete consumption of **5**, the mixture was cooled to 0 °C over 30 min. To the stirred mixture was added 35% aqueous solution of HCl (30.97 g, 297 mmol) carefully such that the inner temperature did not exceed 10 °C. The homogeneous mixture was washed with PhMe (10 mL × 2). To the aqueous layer was added 48% aqueous solution of NaOH (about 12 g) with occasional cooling at temperatures below 10 °C. The resulting turbid mixture was seeded with a few crystals of (\pm)-**6** to induce crystallization. Once crystals started to precipitate, 48% aqueous solution of NaOH (29.71 g, 357 mmol in total; inclusive of the amount added prior to the seeding) was added with cooling such that the inner temperature did not exceed 25 °C. The mixture was extracted with warm toluene (200 mL, 43–46 °C; 33 mL × 2, 30 °C). The combined toluene extracts (about 265 mL) were washed with saturated aqueous solution of NaCl (5 mL × 2). The toluene solution was concentrated in vacuo at 20 mmHg and 70 °C (bath temperature) to remove

water azeotropically until the residual volume diminished to about 115 mL. The residue was filtered while it was kept at 70 °C; the filtration suffered clogging unless it was conducted at temperatures over 70 °C. The filter cake was washed with warm PhMe (10 mL, 40 °C). The combined filtrate and washing were concentrated in vacuo at 70 °C (bath temperature) to give a pale-yellow and viscous oil (about 34 g). Ethylcyclohexane (ECH; 67 mL) was added, and the mixture was heated to 60–70 °C until the mixture turned homogeneous. The homogeneous mixture was allowed to cool to 5 °C over 1 h and kept at the same temperature for 30 min. Precipitated solid was collected by filtration under suction, washed with ice-chilled ECH (15 mL × 2), and air-dried with heating at 45 °C for 3 h to give (\pm)-**6** (30.59 g) in 90.1% yield as a white solid; prolonged heating should be avoided since (\pm)-**6** showed a tendency to sublime. Mp 71.0–72.0 °C. IR ν (KBr) 3080, 2943, 2829, 1801, 1742, 1689, 1591, 1548, 1468, 1383, 1302, 1242, 1221, 1178, 1165, 1134, 1076, 1040, 1013, 924, 901, 847, 739, 690, 573, 544 cm⁻¹. ¹H NMR (CDCl₃) δ 7.24 (br s, 1H), 7.21 (d, *J* = 4.8 Hz, 1H), 6.98–6.80 (m, 2H), 5.19 (dd, *J* = 4.0 Hz, 8.0 Hz, 1H), 2.70–2.50 (m, 2H), 2.29 (s, 6H), 2.00–1.88 (m, 2H).

(*S*)-*N,N*-Dimethyl-*N*-[3-hydroxy-3-(2-thienyl)propyl]ammonium (*S*)-Mandelate (8). To a stirred solution of (\pm)-**6** (9.25 g, 50 mmol) in PhMe (92.5 mL) and MeOH (2.3 mL) was added (*S*)-mandelic acid (**7**) (3.43 g, 23 mmol) at room temperature. The resulting suspension was stirred and heated to 80 °C to make the mixture homogeneous. The stirring was continued with heating at 80 °C for 0.5 h and the solution was allowed to cool to 25 °C at a rate of 0.5 °C/min. After stirring at 25 °C for 1 h, precipitated solid was collected by filtration under suction. The filter cake was washed once with PhMe (10 mL), air-dried with heating at 50 °C to give **8** (6.85 g) as a white solid in 41% yield. Mp 120.5–121.3 °C. [α]_D²⁰ +30.4 (*c* 1.00, MeOH). Anal. Calcd for C₁₇H₂₃NO₄S: C, 60.51; H, 6.87; N, 4.15; S, 9.50. Found: C, 60.3; H, 6.8; N, 4.1; S, 9.5. The enantiomeric purity of (*S*)-**6** contained in **8** was determined to be 93% ee by HPLC as follows: To a portion (2 mg) of **8** was added 2 M aqueous solution of NaOH (0.2 mL) followed by MTBE (0.2 mL). The layers were separated, and the MTBE layer was concentrated in vacuo. To the residue was added *i*-PrOH (2.0 mL), and a portion (1.0 μ L) of the solution was injected to a chromatograph running under the analytical condition (2).

Racemization of (*R*)-6. The filtrate (mother liquor) obtained in the course of the above-mentioned diastereomeric salt formation was analyzed by HPLC for the enantiomeric purity of (*R*)-**6**, and it was determined to be 63% ee as follows: From the filtrate was taken an aliquot (20 μ L) to which was added 2 M aqueous solution of NaOH (0.2 mL) followed by PhMe (0.2 mL). The layers were separated, and the PhMe solution was concentrated in vacuo. To the residue was added *i*-PrOH (2.0 mL), and a portion (1.0 μ L) of the solution was injected to a chromatograph running under the analytical condition (2). The filtrate [about 110 mL; a PhMe solution of (*R*)-**6** of 63% ee] was washed with 1 M aqueous solution of NaOH (5 mL) and saturated aqueous solution of

NaCl (5 mL). The PhMe solution was concentrated in vacuo until its volume diminished to 50 mL. To the residue was added 1.5 M aqueous HCl solution (89 mL), and the resulting two-phase mixture was stirred at 22 °C for about 7 h during which the progress of the reaction was monitored by HPLC as follows: From the aqueous layer was taken an aliquot (20 μ L) to which was added 2 M aqueous NaOH solution (0.2 mL) followed by MTBE (0.2 mL). The layers were separated, and the MTBE layer was concentrated in vacuo. To the residue was added *i*-PrOH (2.0 mL), and a portion (1.0 μ L) of the solution was injected to a chromatograph running under the analytical condition (2). When the enantiomeric purity of (*R*)-**6** diminished to below 5% ee, 48% aqueous NaOH solution (13 mL) was added to the stirred mixture. The layers were separated, and the PhMe layer was washed with saturated aqueous solution of NaCl (5 mL). The PhMe solution was concentrated in vacuo to give almost racemized **6** as an off-white solid (5.30 g). Its enantiomeric purity was determined to be 1.2% ee by HPLC as follows: To an aliquot (1 mg) of the solid was added *i*-PrOH (2.0 mL), and a portion (1.0 μ L) of the solution was injected to a chromatograph running under the analytical condition (2). It was also shown to be composed of **15** (5.4 area %), **6** (90.6 area %), and **14** (3.9 area %) by HPLC as follows: To an aliquot (2 mg) of the solid was added MeCN (2.0 mL), and a portion (5.0 μ L) of the solution was injected to a chromatograph running under the analytical condition (3). To the solid thus obtained (5.30 g) was added ECH (20 mL), and the mixture was heated to 60 °C where it became homogeneous. The resulting solution was allowed to cool to 47 °C over 0.5 h. The solution was seeded with a crystal of (\pm)-**6** and allowed to cool to 22 °C over 1 h. The heterogeneous mixture was stirred at 22 °C for 1 h. Precipitated solid was collected by filtration under suction, washed with ECH (5 mL \times 2), air-dried with heating at 45 °C to give (\pm)-**6** (4.60 g) in 86.8% yield as a white solid, an overall yield from virgin (\pm)-**6** being 49.7%. The racemic nature (0% ee) of the product was confirmed by HPLC conducted under the analytical condition (2), and it was shown to be composed of **15** (3.0 area %), **6** (97.0 area %), and **14** (0 area %) by HPLC analysis conducted under the analytical condition (3).

(S)-3-(N-Ethoxycarbonyl-N-methylamino)-1-ethoxy-carbonyloxy-(2-thienyl)propane (16). To **8** [10.1 g, 30.0 mmol; containing (*S*)-**6** of 93% ee] was added an aqueous solution of NaOH (48% aqueous solution of NaOH, 3.00 g, 36.0 mmol; H₂O, 12 mL). The mixture was extracted with PhMe (50 mL). To the PhMe extract was added solid NaHCO₃ (5.04 g, 60 mmol). The heterogeneous mixture was stirred and heated to 90 °C (inner temperature). A solution of EtOCOCl (4.23 g, 39 mmol) in PhMe (12 mL) was added dropwise over 15 min. The stirring was continued at 90 °C, and the progress of the reaction was monitored by HPLC as follows: From the reaction mixture was taken an aliquot (50 μ L), which was concentrated in vacuo. To the residue was added MeCN (2 mL), and a portion (2 μ L) of the solution was injected to a chromatograph running under the analytical condition (4). It took about 15 min until (*S*)-**6** was

consumed in >99.5%. The mixture was allowed to cool to room temperature, and ice-chilled H₂O (25 mL) was added; caution: when the aqueous mixture was left to stand at room temperature for 16 h, (*S*)-**18** produced suffered hydrolysis to give back (*S*)-**6** in 1–2% yield. The layers were separated, and the PhMe layer was washed with saturated aqueous NaCl solution (20 mL). The PhMe solution was concentrated in vacuo at 50 mmHg and 60 °C (bath temperature) until its volume reached 20 mL. To the residual PhMe solution were added PhMe (20 mL) and solid NaHCO₃ (0.25 g, 3.0 mmol). The resulting heterogeneous mixture was stirred and heated to reflux (bath temperature: 120 °C). A solution of EtOCOCl (6.5 g, 60 mmol) in PhMe (12 mL) was added dropwise over 20 min with the refluxing PhMe being circulated through a Dean–Stark apparatus. The mixture was stirred with heating at reflux where the refluxing PhMe was kept to circulate through the Dean–Stark apparatus. The progress of the reaction was monitored by HPLC as follows: From the reaction mixture was taken an aliquot (50 μ L), which was concentrated in vacuo. To the residue was added MeCN (2 mL), and a portion (2 μ L) of the solution was injected to a chromatograph running under the analytical condition (4). When (*S*)-**18** was consumed in >97%, the mixture was allowed to cool to room temperature. H₂O (20 mL) was added, and the layers were separated. The PhMe layer was washed with 0.5 M aqueous HCl solution (20 mL) and saturated aqueous NaCl solution (20 mL \times 2) and then was concentrated in vacuo at 60 °C (bath temperature) to give (*S*)-**16** as a pale-yellow oil (8.50 g) in 90.1% yield. IR ν_{\max} (KBr) 3491, 3107, 2982, 1747, 1699, 1487, 1404, 1371, 1254, 1005, 862, 841, 791, 771, 710 cm⁻¹; ¹H NMR (CDCl₃) δ 7.36–7.20 (m, 1H), 7.18–7.10 (m, 1H), 7.00–6.94 (m, 1H), 5.90–5.80 (m, 1H), 4.21–4.14 (m, 2H), 4.10 (q, *J* = 6.8 Hz, 2H) 3.50–3.20 (m, 2H), 2.89 (s, 3H), 2.38–2.10 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.24 (t, *J* = 6.8 Hz, 3H). MS *m/z* 338{[M + Na]⁺}. Chemical purity: 91.1% as determined by HPLC under the analytical condition (4).

(S)-3-(N-Methylamino)-3-(2-thienyl)propan-1-ol (1). To a stirred solution of (*S*)-**16** (4.50 g, 14.3 mmol) in EtOH (7.7 mL) and H₂O (12.0 mL) was added 48% aqueous NaOH solution (9.90 g, 11.9 mmol) dropwise. The mixture was stirred and heated at 82 °C for 3 h. H₂O (30 mL) was added, and the mixture was extracted with PhMe (50 mL \times 1, 30 mL \times 1, 20 mL \times 1) at 50 °C. The combined PhMe extracts were warmed to 50 °C and washed with saturated aqueous NaCl solution (20 mL). The PhMe solution was concentrated in vacuo until its volume diminished to 50 mL. To the residue was added Na₂SO₄ (0.3 g) to adsorb inorganic contaminants, but not for drying. The mixture was filtered, and the filtrate was concentrated in vacuo to give crude (*S*)-**1** as a pale-yellow solid (2.60 g). ECH (11.25 mL) and PhMe (3.75 mL), the ratio of ECH to PhMe being 3/1, were added, and the mixture was heated to 60 °C where it became homogeneous. The resulting solution was allowed to cool to 52 °C over 0.5 h. The solution was seeded with a crystal of (*S*)-**1** and allowed to cool to 25 °C over 1 h. The heterogeneous mixture was stirred at 25 °C for 1 h. Precipitated solid was collected by filtration under suction, washed with ECH (4 mL), and

air-dried with heating at 45 °C to give (*S*)-**1** (1.82 g) in 74.6% yield as a white solid. Mp 71.8–73.2 °C. $[\alpha]_{\text{D}}^{20} -13.3$ (*c* 10.0, MeOH) [lit.:^{5c} $[\alpha]_{\text{D}}^{22} -12.5$ (*c* 4.4, MeOH)]. IR ν_{max} (KBr) 3288, 3106, 2947, 2893, 2839, 1493, 1472, 1433, 1358, 1306, 1274, 1221, 1180, 1110, 1088, 939, 908, 715, 695 cm^{-1} . $^1\text{H NMR}$ (CDCl_3) δ 7.21 (dd, $J = 1.2$ Hz, 5.2 Hz, 1H), 6.98–6.90 (m, 2H), 5.20 (dd, $J = 3.2$ Hz, 8.4 Hz, 1H), 3.00–2.92 (m, 1H), 2.90–2.82 (m, 1H), 2.44 (s, 3H), 2.02–1.84 (m, 2H); signals due to two exchangeable protons (NH and OH) were too broad to discern. Anal. Calcd for $\text{C}_8\text{H}_{13}\text{NOS}$: C, 56.11; H, 7.65; N, 8.18; S, 18.72. Found: C, 56.0; H, 7.6; N, 8.1; S, 18.7. The chemical purity of (*S*)-**1** was determined to be 100% by HPLC as follows: To an aliquot (2 mg) of (*S*)-**1** was added MeCN (2.0 mL), and a portion (5.0 μL) of the solution was injected to a chromatograph running under the analytical condition (5). The enantiomeric purity of (*S*)-**1** was determined to be 100% ee as follows: To a stirred mixture of (*S*)-**1** (34.3 mg, 0.2 mmol), $\text{NaBH}(\text{OAc})_3$ (212 mg, 1.0 mmol), and 1,2-dichloroethane (3 mL) was added 37% aqueous solution of formaldehyde (17.8 mg, 0.22 mmol) at room temperature. The stirring was continued at room temperature for 1 h during which the progress of the reaction was monitored by GLC as follows: From the reaction mixture was taken an aliquot (100 μL) which was poured into 1.0 M aqueous solution of NaOH (0.5 mL). The mixture was agitated for 5 min, and a

portion (2.0 μL) of the 1,2-dichloroethane layer was injected to a chromatograph running under the analytical condition (6). When the presence of unconsumed (*S*)-**1** or cyclic (*S*)-*N,O*-acetal (**19**) was detected by the GLC analysis, a further amount (100 mg) of $\text{NaBH}(\text{OAc})_3$ was added, and the stirring was continued for another 1 h. To the mixture was added 3 M aqueous NaOH solution (4 mL). The mixture was extracted with MTBE (5 mL). The MTBE extract was concentrated in vacuo to give crude (*S*)-**6** as a white solid in about 90% yield. From the solid was taken an aliquot (1 mg) to which was added *i*-PrOH (2.0 mL). A portion (1.0 μL) of the solution was injected to a chromatograph running under the analytical condition (2).

(*S*)-3-Methyl-2-(2-thienyl)-perhydro-1,3-oxazine (19).

A solution of (*S*)-**1** (10 mg) and paraformaldehyde (100 mg) in MTBE was stirred at room temperature for 0.5 h. The usual aqueous workup provided (*S*)-**19**. TLC (*i*-PrOH) R_f 0.07 for (*S*)-**1** and 0.70 for (*S*)-**19**. $^1\text{H NMR}$ (CDCl_3) δ 7.27–7.25 (m, 1H), 7.01–6.90 (m, 2H), 4.73 (dd, $J = 11.2$ Hz, 2.4 Hz, 1H), 4.53 (dd, $J = 9.2$ Hz, 2.0 Hz, 1H), 4.27 (d, $J = 11.2$ Hz, 1H), 3.10–3.00 (m, 1H), 2.96–2.82 (m, 1H), 2.48 (s, 3H), 2.50–2.36 (m, 1H), 1.76–1.70 (m, 1H).

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