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Development of a Large-Scale Stereoselective Process for (1*R*,4*S*)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-amine Hydrochloride

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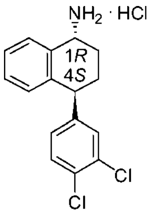
Abstract:

A convenient, multikilogram-scale, stereoselective process for the synthesis of (1*R*,4*S*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-amine hydrochloride 1 is described. The key steps involve synthesis of sulfinyl imine (R_s,4*S*)-5 from (*S*)-tetralone (4*S*)-3 and (*R*)-*tert*-butylsulfinamide (R_s)-4, and its stereoselective reduction with 9-BBN to produce the (1*R*)-amine center of 1. The process has been scaled up to multikilogram scale and gives 1 in an overall yield of >50% with a chemical purity of 99.7 A% by HPLC and stereochemical purity of >99.9% by chiral HPLC.

Introduction

Recently, drug candidates for blocking the monoamine reuptake transporters have sparked considerable interest in the pharmaceutical industry for treatment of central nervous system disorders. Various candidates[1,2] are in clinical evaluation in addition to numerous others at the preclinical stage. Sertraline **2** is a selective serotonin reuptake inhibitor (SSRI), marketed by Pfizer as Zoloft for depression. (1*R*,4*S*)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-amine hydrochloride[3] **1** is structurally similar to sertraline **2** and is currently under investigation for a number of potential central nervous system disorder indications at Sepracor.



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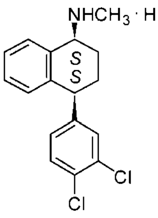

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There are numerous synthetic approaches documented in the literature for the synthesis of sertraline **2**.[4,5] However, most of the approaches reported for sertraline are not applicable to the synthesis of **1** due to the substrate preference for the formation of the cis diastereomer. Fortunately, a great variety of chemical approaches to optically active amine compounds have been explored in recent years.[6] Depending on substrate reactivity and cost of goods, methodologies ranging from stoichiometric chiral auxiliary-based transformations to catalytic processes have been developed. When successful, these processes have been applied to the plant-scale manufacture of advanced pharmaceutical intermediates. Herein we describe a practical, scalable, stereoselective synthesis of the compound *trans*-**1** at multikilogram scale.

Results and Discussion

Initial Chemical Synthesis. Our discovery chemistry colleagues synthesized compound **1** utilizing a route, which is not suitable for the manufacture of API at multikilogram scale (Scheme 1). The discovery route[3] involved preparation of (*S*)-tetralone **(4*S*)-3** from racemic tetralone **(4*RS*)-3** via chromatographic separation of sulfinyl imine **(R_s,4*RS*)-5** diastereomers, followed by hydrolysis. The sulfinyl imine isomers were generated by condensation with (*R*)-*tert*-butylsulfinamide[7] ((*R*)-TBSA), **(R_s)-4**, in the presence of titanium ethoxide. The yield of sulfinyl imine diastereomer **(R_s,4*S*)-5** was ~15% after chromatographic purification. The low recovery yield was due to chromatographic loss and the instability of compound **5** on silica gel. The resulting (*S*)-tetralone **(4*S*)-3** was converted to *N*-formyl amine **(1*RS*,4*S*)-6** as a mixture of two diastereomers that were again separated

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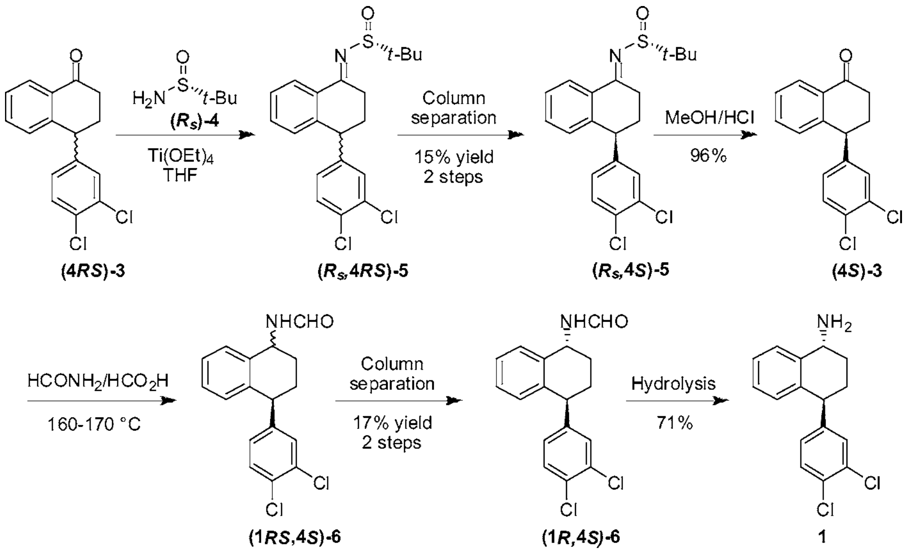
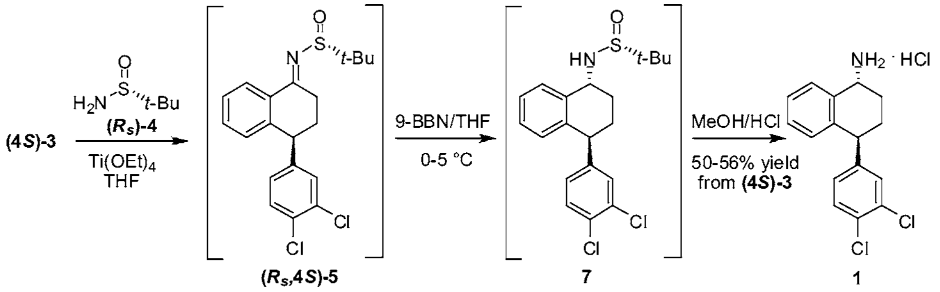
10.1021/op7000589 CCC: $37.00

Scheme 1. **Discovery chemistry synthesis**



Scheme 2. **GMP synthesis approach to 1**



by chromatography to afford the desired diastereomer **(1*R*,4*S*)-6** in 17% yield over two steps. (1*R*,4*S*)-*trans*-norsertraline **1** was obtained after the acidic hydrolysis of **(1*R*,4*S*)-6** in 71% yield. The overall yield of this route was less than 2% and involved two chromatographic purifications, making it impractical for an efficient large-scale synthesis of **1**.

GMP Synthesis. On the basis of the discovery work and a tight schedule, it seemed prudent to use the (*S*)-tetralone **(4*S*)-3** as starting material for the GMP synthesis, without consideration of its cost. This approach allowed us to focus on setting the 1*R*-amine chiral center. Also, this ketone starting material can now be readily obtained from commercial sources of sertraline[5] **2** and already contains one of the two asymmetric centers present in the target structure **1**. Unfortunately, all of our efforts made to take advantage of the 4*S* chiral center of **(4*S*)-3** in a substrate-controlled fashion to set the amine center stereochemistry of the API favored the undesirable cis product.[8] With a desire to rapidly and more efficiently produce cGMP supplies, we turned our attention to a chiral auxiliary-based approach to the amine stereocenter in **1**. With the intermediate **(*R*s,4*S*)-5** from the discovery route as a lead, we explored the use of chiral sulfinamide-directing groups to control formation of the new chiral center. The key step in this approach involves the stereoselective reduction of sulfinyl imine **(*R*s,4*S*)-5**, derived from **(4*S*)-3** without isolation, leading to sulfinamide **7** by in situ reduction. Advantageously, the directing capacity of the chiral auxiliary **(*R*s)-4** is strong enough to overcome the intrinsic substrate bias of the tetralone-derived 4*S* center favoring the cis diastereomer. Conducting the two-step sequence in a telescoped fashion, without purification of intermediates, avoids the possible degradation of **(*R*s,4*S*)-5,** which is highly susceptible to hydrolysis. The sulfinamide **7**, resulting from the asymmetric reduction, is then easily hydrolyzed to **1** (Scheme 2).

Formation of Sulfinyl Imine (*R*s,4*S*)-5. Condensation of enantiopure primary sulfinamides with ketones and aldehydes is well documented in the literature.[7,9,10] The reaction calls for a Lewis acid dehydrating agent such as titanium alkoxide or molecular sieves. Ellman et al. have reported an extensive optimization of the condensation of *tert*-butylsulfinamide with aldehydes and ketones.[10] They found that magnesium sulfate and copper sulfate are effective for condensation with a wide range of aldehydes including sterically demanding substrates, such as isobutyraldehyde, and electron-rich

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(8) Hydrogenation of various imine derivatives derived from **(4*S*)-3** provided predominantly cis product.

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Table 1. **Effect of solvent and temperature on the conversion of (4*S*)-3 to (R_s,4*S*)-5**

entry	reagent	solvent, temp. (°C)	% conv.[11] to **(R_s,4*S*)-5** (HPLC)
1	Ti(OPr)$_4$, neat	THF, 75	<50
2	Ti(O^{i}Pr)$_4$, neat	THF, 75	<50
3	Ti(OEt)$_4$ 20 wt % soln in EtOH	THF/toluene, 80−90 1:1 (v/v)	<70 with byproducts
4	Ti(OEt)$_4$ 20 wt % soln in EtOH	THF, 70−75	>95

compounds, such as *p*-anisaldehyde. Unreactive substrates, such as pivaldehyde, required more Lewis acidic titanium ethoxide or isopropoxide. Only titanium alkoxides in THF solvent were found to be effective for the condensation of ketones.

The strongly Lewis-acidic reagents titanium isopropoxide, *n*-propoxide, and ethoxide initially worked with only moderate success for our ketone substrate **(4*S*)-3** (Table 1). We optimized these reaction conditions by screening different solvent systems. When THF was used as the single solvent, at 75 °C, less than 50% conversion[11] was obtained as measured by HPLC (Table 1, entries 1 and 2). Higher conversion was seen using a THF and toluene solvent mixture, which enabled an increase of the reaction temperature to 80−90 °C, but the 70% conversion was accompanied with byproduct formation (entry 3). Meanwhile, reduced temperatures gave lower conversions with ethanolic Ti(OEt)$_4$ solution. The best conversion, i.e., >95%, was obtained using an ethanolic solution of titanium ethoxide in THF at 70−75 °C (Table 1, entry 4). The amount of ethanol charged with the titanium ethoxide (20 wt % in ethanol) was sufficient to generate a 1:1 (v/v) mixture with THF and allowed the reaction to proceed to completion without significant formation of byproducts.

After reaction completion, as evidenced by HPLC analysis, the mixture was quenched with an aqueous solution of sodium chloride. Although the titanium byproducts precipitated out of solution, filtration of the resulting suspension was extremely slow. Diluting the slurry with methyl *tert*-butyl ether or ethyl acetate before filtration did not improve the filtration rate. However, when the slurry was diluted with THF, the filtration rate improved significantly. Excess THF from the reaction mixture was removed by distillation under reduced pressure prior to extracting the product into toluene. This aromatic solvent was selected for extraction owing to the favorable solubility of the sulfinyl imine **(R_s,4*S*)-5**. In addition, toluene also enabled the removal of water from the product by azeotropic distillation prior to the next step where anhydrous conditions were required with 9-borabicyclo-[3.3.1]nonane (9-BBN).

Stereoselective Reduction of Sulfinyl Imine (R_s,4*S*)-5 to Sulfinamide 7. Although the asymmetric reduction of sulfinyl imines, in general, has previously been explored,[12] in 1999 Ellman et al.[13] reported the first screening of asymmetric reduction of *tert*-butylsulfinyl imines. Using various borohydride reagents, Ellman's group achieved excellent selectivity with acetophenone-derived substrates. In order to evaluate the stereoselectivity of the reduction, we screened reducing agents using a purified sample of our substrate **(R_s,4*S*)-5**. We also briefly evaluated the reduction of the sulfinyl imine **(R_s,4*S*)-5T** derived from (*R*)-*p*-toluenesulfinamide[9] **(R_s)-4T**, which was prepared using conditions[14] similar to those that were used for **(R_s,4*S*)-5** yet that gave poor yields (i.e., 25−30% unoptimized, Scheme 3).

Scheme 3. **Preparation and reduction of *p*-toluene sulfinyl imine (R_s,4*S*)-5T**

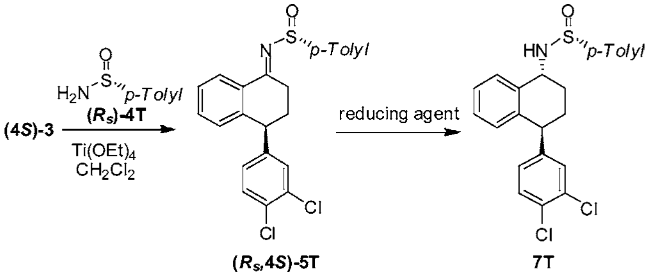

Table 2. **Selectivity in reduction of (R_s,4*S*)-5T**

entry	reducing reagent	solvent	reaction temp. (°C)	HPLC conv.[11]	selectivity[a] (*trans/cis*)
1	NaBH$_4$	MeOH	0	>99	13/87
2	BH$_3$-THF	THF	0	>99	98/2
3	9-BBN	THF	0	>99	>99/1

[a] Selectivity based on HPLC analysis after hydrolysis of **7T** to **1** with MeOH/HCl.

Reduction of **(R_s,4*S*)-5T** with sodium borohydride in methanol at 0 °C gave predominantly the undesired cis product (Table 2, entry 1). Both the borane−tetrahydrofuran complex and 9-BBN in THF gave the desired product in ≥98:2 *trans:cis* selectivity at 0−5 °C reaction temperature (Table 2, entries 2 and 3). However, this substrate **(R_s,4*S*)-5T** was not pursued further due to the difficulty in its preparation and the higher cost[15] associated with **(R_s)-4T**.

Sulfinyl imine **(R_s,4*S*)-5** gave similar undesired 13/87 *trans*-to-*cis* selectivity of **7** on reduction with sodium

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(11) Conversions were monitored by in-process HPLC methods: Zorbax SB-CN, 5μm, 4.6 mm × 150 mm column; mobile phase 0.2% H$_3$PO$_4$, 0.005 M sodium dodecyl sulfate/acetonitrile (60:40 isocratic); temperature, ambient; flow rate, 1.0 mL/min; injection volume, 10 μL; UV wavelength, 220 nm. Approximate retention times for **(4*S*)-3**, 20.8 min; **(R_s,4*S*)-5**, 29.6 min; **7**, 24.8 min; **1**, 11.5 min.

(12) (a) Annunziata, R.; Cinquini, M.; Cozzi, F. *J. Chem. Soc., Perkin Trans. I* **1982**, 341. (b) Hua, D. H.; Lagneau, N.; Wang, H.; Chen, J. *Tetrahedron: Asymmetry* **1995**, *6*, 349. (c) Hua, D. H.; Miao, S. W.; Chen, J. S.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4. (d) Hose, D. R. J.; Mahon, M. F.; Molloy, K. C.; Raynham, T.; Wills, M. *J. Chem. Soc., Perkin Trans. I* **1996**, 691. (e) Lu, Z.-H.; Bhongle, N.; Su, X.; Ribe, S.; Senanayake, C. H. *Tetrahedron Lett.* **2002**, *43*, 8617. (f) For diethylzinc reduction of preformed *N*-sulfinyl imine catalyzed by Ni(acac)$_2$ see: Xiao, X.; Wang, H.; Huang, G.; Yang, J.; Bian, X.; Qin, Y. *Org. Lett.* **2006**, *8*, 139.

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(14) Reaction was run in CH$_2$Cl$_2$ at 40−43 °C for ~18 h and afforded 28% isolated yield of **(R_s,4*S*)-5T**. ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 8.31 (dd, 1H, J = 1.6, 7.6 Hz), 7.74 (m, 2H), 7.35 (m, 5H), 7.19 (d, 1H, J = 2.4 Hz), 6.88 (m, 2H), 4.15 (dd, 1H, $J_{3a,4}$ = 4.8 Hz, $J_{3b,4}$ = 8.4 Hz), 3.44 (ddd, 1H, J = 4.0, 7.6, 13.2 Hz), 2.89 (ddd, 1H, J = 4.4, 9.6, 13.2 Hz), 2.42 (s, 3H), 2.32 (m, 1H,), 2.17 (m, 1H).

(15) (*R*)-*p*-Toluene sulfinamide is listed in the Aldrich 2006 catalogue at 0.5g/$59.40, whereas the (*S*)-isomer is listed at 5.0g/$126.50.

Table 3. **Selectivity in reduction of (R_s,4S)-5**

entry	reagent	solvent	reaction temp. (°C)	HPLC conv.[11] to **7**	selectivity[a] (*trans/cis*)
1	$NaBH_4$	MeOH	0	>99	13/87
2	BH_3-THF	THF	0	>99	98/2
3	9-BBN (0.5 M) in THF	THF	0−5	>99	>99/1
4	9-BBN (0.5 M) in THF	toluene/THF up to 2:1 (v/v)	0−5	>99	>99/1

[a] Selectivity based on HPLC analysis after hydrolysis of **7** to **1** with MeOH/HCl.

Table 4. **Yield and quality data of *trans*-norsertraline·HCl (1) from (4*S*)-3**

entry	(S)-tetralone **(4*S*)-3** input (kg)	(1R,4S)-**1** recrystallized (kg)	% overall yield from **(4*S*)-3** to **1**	HPLC A% purity	chiral purity[19] by HPLC (%)
1	0.05	0.031	55.0	99.85	99.98
2	2.30	1.25	48.3	99.67	99.97
3	4.11	2.57	55.9	99.76	99.95
average			53.1	99.76	99.97

borohydride in methanol (Table 3, entry 1). As with the **(R_s,4S)-5T** case, both boranes also gave ≥98/2 *trans*-to-*cis* selectivity of **7** (Table 3, entries 2 and 3). At temperatures higher than 5 °C, the trans selectivity deteriorated significantly, although an increase in the reaction rate was also apparent. After our work was completed, two independent groups reported pertinent communications involving the evaluation of a wide range of hydride reagents for asymmetric reduction of various *tert*-butylsulfinyl imine substrates.[16] Both groups observed a reversal of stereoselectivity when the reducing agent was changed from sodium borohydride to a sterically hindered L-Selectride in THF solvent. Their work confirmed the same phenomenon that we observed during our development work—a reversal of selectivity with different reducing agent/solvent combinations.[17] Sodium borohydride in MeOH predominantly gave cis product, whereas boranes in THF gave predominantly *trans*-**7** (Table 3).

During initial laboratory development, the toluene solution of imine **(R_s,4S)-5** was concentrated to dryness before dissolution with THF for the reduction with 9-BBN. However, at a larger scale in the pilot plant, the complete removal of solvent was not feasible. In order to telescope the two steps, the toluene extract of **(R_s,4S)-5** was azeotropically distilled to remove water. The reduction with 9-BBN was evaluated using a mixture of toluene and THF. To our surprise, when compared to THF-only as the reaction solvent, the rate and selectivity did not change when a 2:1 (v/v) mixture of toluene and THF was used (entry 4).

For the large-scale process, the toluene extract of **(R_s,4S)-5** was dried by azeotropic distillation, and a THF solution of 9-BBN (0.5 M) was added after cooling to 0 °C. The reaction was found to be slower at 0 °C or below but reasonably fast between 0 and 5 °C (2−3 h). Analysis of the reaction mixture for selectivity by nonchiral HPLC method[11] showed >99.5:0.5 *trans*-to-*cis* ratio.

Primary amines can be easily liberated from sulfinamide products by treatment with methanolic acid.[18] Thus, **7** was treated with a solution of 4M HCl in methanol, prepared by mixing 36% concentrated aqueous HCl and methanol, at 0 °C to yield crude product **1**. After removing the methanol and THF by distillation at reduced pressure, the product was free-based with aqueous sodium hydroxide and extracted into MTBE. The free base was converted back to the HCl salt after drying the MTBE solution azeotropically by treating with an anhydrous solution of HCl in MTBE. The crude product **1** was collected by filtration and recrystallized from ethanol/heptane to afford the API in >99.7 A% purity HPLC with >99.9% chiral purity.[19] The yield and input data from the lab and pilot-scale runs are tabulated in Table 4.

Conclusion

In summary, we have developed an effective and robust stereoselective process for the GMP synthesis of **1** in an overall yield of >50%. The process has been successfully telescoped to avoid the isolation of unstable intermediates. It involves two isolations, the crude and recrystallized API, **1**. In this process we have demonstrated the successful use of (R)-TBSA for selectively setting the desired stereochemistry at the amine center. The present route offers the potential for a scalable commercial process.

Experimental Section

General. All reagents were obtained from commercial suppliers and were used without further purification. Only anhydrous solvents were used for the reactions, and these were equally purchased from commercial suppliers. All the reactions were performed under nitrogen atmosphere. ^1H NMR and ^{13}C NMR were obtained from a Varian Mercury 400 spectrometer in deuterosolvents with TMS as an internal standard at room temperature. A Waters 2690 HPLC system equipped with Waters 2487 UV detector was used for in-process as well as chiral assays. The HPLC data were reported in area % and were not adjusted to weight %.

(1*R*,4*S*)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-ylamine HCl (Crude 1) from (*S*)-tetralone (4*S*)-3. (S)-Tetralone **(4*S*)-3** (4.11 kg, 14.1 mol) and (R)-*tert*-butylsulfinamide **(R_s)-4** (TBSA, 1.9 kg, 15.7 mol) were charged to a suitable reactor and dissolved in anhydrous THF

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(16) (a) Colyer, J. P.; Andersen, N. G.; Tedrow, J. S.; Soukup, T. S.; Faul, M. M. *J. Org. Chem.* **2006**, *71*, 6859. (b) Tanuwidjaja, J.; Peltier, H. M.; Ellman, J. A. *J. Org. Chem.* **2007**, *72*, 626.

(17) We observed a similar reversal of selectivity on our substrate **(R_s,4S)-5**, as reported by Andersen et al.[16] when sodium borohydride was used as reducing agent in methanol as compared to more sterically demanding 9-BBN in THF. Also, sodium borohydride in THF at 0 °C gave 95% conversion and reverse selectivity of 85/15 *trans/cis*. However, L-Selectride in THF at 0 °C gave >99% conversion and 1/99 ratio of *trans/cis*.

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(19) The chiral purity of **1** was analyzed using an HPLC method: Chiracel OD-H, 5μm, 4.6 cm × 25 cm column from Chiral Technology; mobile phase, hexane/ethanol/ethane sulfonic acid/H_2O, 95:5:0.05:0.01; flow rate of 0.8 mL/minute; ambient temperature; 220 nm wavelength. Approximate retention times for (1R,4S)-**1**, 39 min; for (1S,4S)-**1**, 36 min. In addition, this verified that no epimerization of the 4S center occurred during processing.

(29 L). Titanium ethoxide (31.6 kg, 27.7 mol, 20 wt % solution in ethanol) was added, and the mixture was heated to 70 °C for 20−24h. The reaction was monitored by HPLC.[11] After reaction completion, the mixture was cooled to 22 °C and added to a solution of 24 wt % aq NaCl (∼60 L). The slurry was diluted with THF (20 L), filtered, and washed 2× with THF (10 L). The mother liquor and washes were concentrated to a minimum volume. The aqueous phase was extracted with toluene (30 L) and toluene/ethyl acetate (2:1 v/v, 30 L), and the combined organic phases were washed with aq NaCl (7 L) followed by water (4 L). The organic phase was concentrated to half volume (∼40 L) under vacuum.

A purified sample from the crude product **(R_s,4*S*)-5** was analyzed: mp 104 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.23 (dd, 1H, $J = 7.9$, 0.9 Hz), 7.38 (ddd, 1H, $J = 14.7$, 7.3, 1.5 Hz), 7.37 (d, 1H, $J = 8.4$ Hz), 7.33 (d, 1H, $J = 7.7$ Hz), 7.17 (d, 1H, $J = 1.8$ Hz), 6.93 (d, 1H, $J = 7.7$ Hz), 6.89 (dd, 1H, $J = 8.4$, 2.2 Hz), 4.18 (dd, 1H, $J = 7.3$, 4.8 Hz), 3.36 (ddd, 1H, $J = 17.5$, 8.8, 4.4 Hz), 2.93 (ddd, 1H, $J = 17.6$, 8.3, 4.2 Hz), 2.33 (m, 1H), 2.15 (m, 1H), 1.34 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 144.2, 142.7, 132.6, 130.8, 130.7, 129.7, 128.1, 127.6, 127.4, 57.8, 44.3, 31.1, 29.4, 22.8. HRMS calcd for $C_{20}H_{21}Cl_2NOS$ 394.0799, found 394.0767.

The toluene solution of **(R_s,4*S*)-5** was diluted with THF (12 L) and cooled to −5 to −10 °C. 9-Borabicyclononane (9-BBN, 36.3 kg, 20.3 mol as 0.5 M solution in THF) was added dropwise over 2−3 h and stirred at 0−5 °C until reaction completion to give **7**. HCl (4 N)/methanol (8 L) was added to the mixture and stirred until the hydrolysis reaction was complete to give **1** (3−4 h). **Caution!** Hydrogen gas is generated and caution must be taken to properly ventilate this flammable gas. After neutralization with 6 N aqueous NaOH (15 kg) to ∼pH 8, the mixture was distilled to remove THF and methanol. The residue (aqueous phase) was extracted twice with MTBE (2 × 16 L). The organic phase was then washed with water and concentrated. After cooling to 0 °C, 2 N HCl in MTBE (5.4 kg) was then added slowly and the product precipitated as the HCl salt. The slurry was filtered and washed with MTBE (2 × 8 L). The product was dried under vacuum at 45 °C to afford 3.73 kg of crude product **1**.

A purified sample of the crude product sulfinamide **7** after reduction was analyzed: mp 152−154 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.58 (d, 1H, $J = 7.7$ Hz), 7.29 (m, 2H), 7.18 (br t, 1H, $J = 7.5$ Hz), 7.09 (d, 1H, $J = 1.8$ Hz), 6.87 (d, 1H, $J = 7.7$ Hz), 6.80 (dd, 1H, $J = 8.3$, 2.0 Hz), 4.65 (dd, 1H, $J = 4.4$, 4.4 Hz), 4.15 (t, 1H, $J = 5.5$ Hz), 3.30 (d, 1H, $J = 3.7$ Hz), 2.35 (m, 1H), 1.95 (m, 1H), 1.85 (m, 1H), 1.75 (m, 1H), 1.23 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 138.4, 138.0, 132.6, 130.8, 130.6, 130.5, 129.8, 128.3, 127.9, 55.8, 53.3, 44.0, 28.2, 27.7, 22.9. HRMS calcd for $C_{20}H_{23}Cl_2NOS$ 396.0956, found 396.0968.

Recrystallization of Crude (1*R*,4*S*)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-ylamine HCl (1). Crude (1*R*,4*S*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-ylamine HCl (3.63 kg) was charged to a suitable reactor, and denatured ethanol (5% methanol, 128 L) was added. The mixture was heated to reflux and polish-filtered. The volume was then reduced to 50% via distillation and cooled to 50 °C (crystallization occurred during the distillation). Heptane (80 L) was added to the slurry to further crystallize the product. The slurry was cooled slowly to 0 to −5 °C. The product was isolated by filtration, and the cake was washed with ethanol/heptane (1/1 v/v, 2 × 5.7 L), followed by hexane (6 L). The wet cake was dried under vacuum at 45 °C to afford 2.57 kg of **1** in 56% overall yield from (*S*)-tetralone **(4*S*)-3**. The HPLC purity of **1** was 99.65A% and chiral purity[19] was >99.9%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.81−1.93 (m, 2H), 2.12−2.21 (m, 1H), 2.28−2.36 (m, 1H), 4.28 (t, 1H, $J = 6.8$ Hz), 4.59 (br s, 1H), 6.84 (d, 1H, $J = 7.6$ Hz), 7.05 (dd, 1H, $J = 8.4$, 1.6 Hz), 7.25 (t, 1H, $J = 7.6$ Hz), 7.32 (t, 1H, $J = 7.6$ Hz), 7.37 (d, 1H, $J = 1.6$ Hz), 7.56 (d, 1H, $J = 8.4$ Hz), 7.76 (d, 1H, $J = 7.2$ Hz), 8.80 (br s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.4, 138.9, 133.6, 131.0, 130.5, 130.4, 130.1, 129.0, 128.9, 128.4, 128.2, 126.8, 47.9, 43.1, 27.8, 25.2. Anal. Calcd for $C_{16}H_{15}Cl_2N$: C, 58.47; H, 4.91; N, 4.26; Cl, 32.36. Found: C, 58.44; H, 4.79; N, 4.21; Cl, 32.53.

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Supporting Information Available

^{1}H NMR and ^{13}C NMR spectra for **(R_s,4*S*)-5**, **7**, and **1** as well as chiral HPLC assay of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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